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I-01: *Nurul Azrin Abd Rahman* A population pharmacokinetic/pharmacodynamic (PK/PD) model of the investigational antimalarial drug Artefenomel in a Plasmodium vivax Volunteer-Infection Study

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Introduction: *Plasmodium vivax,* one of the five species of malaria parasites that infect humans, puts approximately 2.5 billion people at risk [1] and causes an estimated 7.5 million infections a year [2]. Artefenomel, an investigational antimalarial, was tested at a subtherapeutic dose in healthy volunteers infected with *P.vivax* blood-stage parasites.

Objectives:

- Develop a population PK/PD model describing the time course of parasitemia with the PK and parasitemia profiles observed in the infected volunteers.
- Use the model to establish the minimum effective dose of artefenomel required to clear *P. vivax* parasites in patients.

Methods: Eight healthy subjects were inoculated intravenously with ~680 viable *P. vivax* parasites and were administered a single oral dose of 200 mg artefenomel 10 days later. Parasitemia was monitored twice a day for 4 days after inoculation until drug administration, at 4, 8, 12, 16, 24, 30, 36, 48, 60, 72, 84, 96, 108 hours after drug administration and then three times per week until 28 days after inoculation. A rich PK profile was acquired in each volunteer. To enrich the PK/PD dataset from this study, the PK profiles of another study in which artefenomel was tested at three doses in healthy volunteers infected with *P. falciparum* (another species of plasmodium) were added, as well as parasitemia observations prior to drug administration from another *P. vivax* study testing another compound. To develop the PK/PD model, a two stage approach was used. First a PK model was built. One-, two- and three-compartment disposition models were tested. First- and zero-order absorption models, with or without lag time as well as linear, saturable and mixed linear and saturable elimination models were evaluated. The individual PK parameter estimates were used as regression parameters for the subsequent PD modelling stage. Different PD models were explored to link drug concentrations with parasite clearance. Finally, simulations were performed with the final PK/PD model to determine the minimal dose that is necessary to clear all parasites in patients. The minimum effective dose was defined as the lowest dose that resulted in at least a total parasite reduction ratio (PRR_{total}) of 9 log_{10} unit.

Results: A three-compartment PK disposition model with first-order absorption, a lag time and linear elimination adequately described the PK data. Body weight was incorporated as an allometric function on clearance and volume of distribution parameters and found to improve the fit significantly. Dose was also found to be a significant covariate, resulting in a decreased clearance with increasing doses. Artefenomel-dependent parasite killing rate was well described by a sigmoid E_{max} model. The estimated maximum parasite killing rate (E_{max}) was 0.158 h^{-1}. The artefenomel plasma concentration that resulted in 50% of the maximum effect (EC_{50}) was determined to be 0.65 ng/mL. The PK/PD model predicted a minimum inhibitory concentration (MIC) of 0.61 ng/mL, and a minimum parasiticidal concentration at which the parasite killing rate was equal to 90% of its maximum (MPC_{90}) of 0.81 ng/mL. A log_{10} parasite reduction ratio over 48 hours (PRR_{48}) was estimated to be 2.17, with a corresponding parasite clearance half-life ($PCt_{½}$) of 6.64 h. The minimum single dose that resulted in log_{10} PRR_{total} >9 was 300 mg (13.4, 95% CI: 3 – 35.9).

Conclusions: The model adequately characterized the PK/PD of artefenomel in a *P. vivax* Volunteer Infection Study. It was then used to estimate the minimum effective dose to clear *P. vivax* parasites in patients. As artefenomel lacks activity against latent liver stage parasites (hypnozoites) it would need to be combined with a drug such as primaquine or tafenoquine to reliably cure *P. vivax* malaria.

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I-02: *Mahmoud Abdelwahab* Clofazimine population pharmacokinetics in South African patients with drug resistant tuberculosis

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Objectives: Clofazimine is a key component of the short regimen for drug-resistant tuberculosis (TB) but there is currently no evidence base for the standard 100 mg daily dose of clofazimine in widespread use. A model-based approach that can account for the unusual PK characteristics of clofazimine and predict individual exposures for linkage to clinical outcome data is required to inform dose optimization. We present a model to describe the population PK of clofazimine, and characterize covariate effects on PK variability, in a large cohort of South African patients with drug resistant TB.

Methods: Adult drug-resistant TB patients with or without HIV co-infection were enrolled in a prospective, observational cohort study (PROBeX). At recruitment, participants were on drug-resistant TB therapy (usually including clofazimine at a dose of 100 mg daily); follow-up was for 24 months, and included PK visits at months 1, 2 and 6 after study entry with a single sample collected approximately 6-12 hours after the previous dose (time reported by the participant). A subset of participants underwent intensive sampling at month 2 with blood draws pre- and 1, 2, 3, 4, 5, 6, 8, and 24 hours post-observed dose. Plasma clofazimine concentrations were measured using a validated LC-MS/MS assay with 0.00781 mg/L as the lower limit of quantification. Clofazimine plasma concentrations are available for 81 participants, 22 of whom contributed rich PK samples. PK data were analysed using NONMEM 7.4 with FOCE-I; PsN was used for model run execution and R software was used for data preparation. xpose4 and Pirana were used for post-processing results.

Results: Data from the intensive PK-sub study (22-participants & 186 observations) were used to develop the population PK model. No steady-state assumption was made and all doses since treatment initiation were captured. Eleven participants were male and 9 HIV-infected. Median weight was 55.2 kg (IQR 48.4-63.9), fat-free mass 47.3 kg (IQR 38.7-47.6) and fat mass 7.6 kg (IQR 21.1-7.36) and fat mass by sex; females: 22.7 kg (15.0-31.5), males: 7.29 kg (4.93-7.68). The median the duration on clofazimine at the intensive PK visit was 71 days (IQR 62-80). There were no concentrations below the limit of quantification (BLQ). A two-compartment disposition model with first-order elimination and transit compartment absorption fitted the data well (with no separate estimate for absorption rate constant). Female participants had lower exposure on visual plots, and we tried to explain this difference using body composition via allometric scaling as opposed to sex per se. The best size descriptors for scaling of disposition parameters were total body weight (WT) for central clearance (CL) and inter-compartmental clearance (Q), fat-free mass (FFM) for central compartment volume (Vc) and fat mass (FAT) for the peripheral compartment (Vp). To overcome instability of Vp parameters, we added a weakly-informative Bayesian prior on Vp based on a previous report of clofazimine in healthy volunteers and leprosy patients.[1] The prior was log-normally distributed with typical values of 3960 L and ~70% uncertainty. In the final model the typical (median values of WT, FAT and FFM) value of CL was 9.25 L/hr, Vc 1090 L, Q 13.8 L/h, and

Vp 7259 L. Based on these values, the typical terminal half-life was derived to be ~40 days (~76 days for a typical female and 31 days for a typical male).

Conclusions: Our model characterized PK of clofazimine in South African patients with drug-resistant tuberculosis. Our results are physiologically plausible and consistent with the (limited) information available on clofazimine PK, i.e., its long terminal half-life and accumulation in fat cells. The difference in exposure between males and females is ascribed to differences in body size and composition. The female participants in our cohort had a higher proportion of body fat, and thus a larger peripheral volume of distribution when compared to males. This extends the terminal half-life of the drug in females and prolongs the number of repeated daily doses necessary to achieve steady state. Because the PK profiles observed in this study were not at steady state, but the drug was still accumulating, females in our study have lower concentrations. Furthermore, the model can be used to simulate different scenarios for loading and maintenance dosing to reduce the time needed to achieve steady state.

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I-03: *Khaled Abduljalil* Integrating a tumour Growth inhibition Model within a Physiologically-Based Pharmacokinetic Model to predict Erlotinib tumour concentrations in Mice

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Objectives: Erlotinib is a tyrosine kinase inhibitor that exerts its action intracellularly. Integrating a dynamic tumour growth inhibition model within a physiologically-based pharmacokinetic (PBPK) model provides improved insight into the drug kinetics within the target tissue. The objective of this work is to link a dynamic tumour model with a PBPK model in mouse and predict local erlotinib concentrations at the site of action and to predict changes in tumour volume after modifying the dosing regimen.

Methods: A compound file for erlotinib was built within the Simcyp Mouse Simulator V18 that includes a permeability-limited tumour model. Published parameter values for erlotinib absorption and clearance [1] as well as tissue-to-plasma partition ratio (Kp) for brain, liver, kidney, heart and lung [2] were used during model building. Other tissues Kps were predicted within the simulator [3] and scaled by 5 to match the reported overall distribution volume [1]. The passive permeability (PS) and fraction unbound for the tumour tissue was optimized to describe the reported tumour homogenate concentration after the first dose of 100 mg/kg [1]. The Simeoni model was used to describe the natural growth of the tumour in the absence of the drug using published parameters [1]. Tumour growth inhibition (TGI) effect after pulsed dosing of 100mg/kg/day was assumed to have a linear inhibition rate (k2) on the tumour growth using the predicted intracellular free drug concentration. The k2 value was estimated using reported TGI data for the 100mg/kg dosing schedule. The TGI model was used to predict tumour volume after continuous administration of 6.25 and 25 mg/kg/day erlotinib and compared to observations [1].

Results: Predicted plasma concentrations after multiple doses of 100mg/kg match observations [1] reasonably well. Tumour exposure was best described if intracellular fu was set to plasma fu (0.06). Estimated parameters for the final model parameters were 0.5 ml/min/ml of tumour volume, and 0.64 1/uM*day for PS and k2, respectively. The final model was able to predict tumour volume inhibition after both 6.25 and 25 mg/kg adequately. PBPK Predicted vs observed [1] tumour volume (mL3) for 100, 25 and 6.25 mg/kg dose at the end of the dosing (on day 16) were 0.17 (vs 0.14), 0.36 (vs 0.35) and 0.51 (vs 0.66) %, respectively.

Conclusions: PBPK models offer an approach to investigate the drug exposure in the total tumour tissue and the tumour intracellular compartment following systemic dosing. The ability to predict the pharmacologically active drug concentration within the tumour can facilitate understanding of the molecular mechanism of drug action and help to optimise study design.

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I-04: *Anson Abraham* Lack of pre-clinical target pharmacology: How to predict first-in-human trial dose(s) and inform clinical trial design?

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Introduction: During development of biologic drugs such as monoclonal antibodies (mAb), a major challenge can be posed by the lack of homology between human and non-human primate or murine target protein/receptor, thus limiting the utility of preclinical studies for FIH dose selection in some cases. Furthermore, *in-vivo* abundance and turnover of human target/protein is typically unknown during the early stages of drug discovery and development. In oncology, such challenges often lead to a very low FIH starting dose, resulting in sub-therapeutic drug exposures for many patients with life-threatening diseases. For such targets in oncology, a FIH clinical study design informed by PKPD analysis, is outlined.

Objectives:

For a mAb drug with lack of pre-clinical cross-reactivity:

- Predict a safe starting FIH dose
- Outline a dose-escalation clinical study design
- Predict the highest clinical dose to ensure proof of pharmacology

Methods:

The proposed pharmacology-based model consists of membrane-bound and soluble forms of the therapeutic target. The model included zero-order synthesis of membrane target, first-order formation of soluble target from the membrane target and first-order degradation of the soluble target. The PK of the mAb drug was characterized using a two-compartment linear PK model. For simulations, population level fixed and random effect parameters of pembrolizumab were taken as representative of a typical mAb [1]. The model allowed binding of mAb to both, membrane and soluble forms of the target. The only pharmacological information available for the target was binding affinity (K_D) of drug to the human target and soluble target concentrations (10-24 ng/mL) measured in human serum. A wide range of turnover rates for membrane (5-100 /day) and soluble targets (0.01-0.2 /day) were considered for simulations [2].

A multiple dosing regimen with a 21-day dosing interval was adopted for all simulations. For informing the starting FIH dose and highest clinical dose, simulations for membrane target occupancy profiles were conducted for a range of doses (3 mg to 2400 mg) using distinct combinations of membrane target concentrations and target turnover rates considering variabilities wherein inter-individual variabilities (log-normal distribution) were assigned to PK and system parameters.

For dose escalation, accelerated titration design (ATD) with 1 patient per dose level until adequate target engagement (i.e., required for pharmacological effects), followed by a transition to a more conventional

modified toxicity probability interval (mTPI) design was planned. The ATD to mTPI transition dose was informed using the model by predicting the dose required for >75% target engagement.

All simulations were conducted using “ubiquity Ver 1.0.0” package [3] in R (version 3.4.3).

Results: Using the model, a starting FIH dose of 3 mg was predicted to achieve <50% target occupancy at PK C_{max}. By using measured soluble target concentrations and exploring a range of turnover rates [2], the simulation space was constrained to a distinct set of nine potential scenarios with respect to target occupancy. These nine scenarios included specific combinations of membrane target concentrations (0.06, 1, 10 nM) and target turnover half-life (0.1, 1, 16 h). If target turnover half-life was 0.1h and baseline target concentration was either 1 nM or 10 nM, then membrane target occupancy at all clinically feasible doses could not be sustained over a 21-day dosing interval. For a target with rapid turnover half-life of 0.1h and 21-day dosing interval, the membrane target expression had to be low *i.e.*<= 0.06 nM to achieve >75% target occupancy at ≥700 mg mAb dose. For the remaining scenarios, >75% membrane target occupancy could always be achieved by >=1600 mg mAb dose over a 21-day dosing interval, thus informing the highest clinical dose. Simulations predicted approximately 80% membrane target occupancy at the 100 mg dose C_{trough} suggesting that the ATD to mTPI transition could occur at this dose.

Conclusions: In conclusion, a systems pharmacology model was used to address the issue of lack of pre-clinical pharmacology data. Given the unknowns related to the target pharmacology, these model-based results guided the initial clinical design, which would be updated with emerging clinical data. This work shows how FIH clinical study design can be informed in cases of limited pre-clinical pharmacology and PK-PD data.

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I-05: *Ahmad Abuhelwa* Population pharmacokinetic and pharmacodynamic modelling of the therapeutic and adverse effects of ketamine in patients with treatment-refractory depression

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Introduction:

Major depressive disorders present a major clinical challenge with current antidepressant treatment achieving remission in only approximately 30% of patients [1]. Several recent trials suggested that a subanaesthetic dose of ketamine could provide a significant antidepressant effect in patients with depression (e.g.[2, 3]) and most studies have given ketamine at a fixed dose (0.5 mg/kg). A recently reported dose-titration pilot study evaluated low doses of ketamine administered across multiple routes of administration (IV, SC, IM) in patients with treatment refractory depression [4]. This analysis uses the data reported in by Loo et al. [4] to characterize the population PK-PD relationships for the effect of ketamine on the Montgomery–Asberg Depression Rating Scale (MADRS scores) and cardiovascular side effects of blood pressure and heart rate.

Objectives:

The objectives of this analysis were to:

- Develop population pharmacokinetic/pharmacodynamic (PK/PD) models that can effectively describe ketamine and norketamine pharmacokinetic and pharmacodynamic relationships for MADRS scores, blood pressure and heart rate after intravenous (IV), subcutaneous (SC), and intramuscular (IM) administration of ketamine in patients with treatment-refractory depression.
- Identify covariates that are predictive for the PK/PD of ketamine.
- Present the PKPD models as a web page application to facilitate interactive decision support of the use of ketamine for treatment of depression.

Methods:

Pharmacokinetic and pharmacodynamic data were collected from an active placebo-controlled pilot study in which 21 treatment-refractory depressed participants received ketamine (dose titration 0.1-0.5 mg/kg) by three routes of drug administration (IV, SC, IM) or midazolam (control treatment) in a multiple crossover design. Model development was conducted in a step-wise manner. The sequential 2-stage approach was used for development of both the metabolite PK model and the PD models using the final pharmacokinetic model [5]. Model development employed non-linear mixed effect modelling using NONMEM [6]. The final PK/PD models of ketamine, MADRS, blood pressure, and heart rate were implemented as a web application with user-friendly interface to facilitate communication of model results and allow for interactive decision support of the use of ketamine for treatment of depression.

Results:

The concentration-time data for ketamine and norketamine were adequately described using two-compartment models with first-order absorption after SC and IM administration. The model indicated that the bioavailability of ketamine after IM and SC is ~64%. Allometric scaling of body weight on all clearance and volume of distribution parameters for both ketamine and norketamine resulted in a significant improvement in the model fit. The delay in the concentration-response relationship for MADRS scores was best described using a turnover model, while for blood pressure and heart rate immediate effect model best described the data. For all PD effects, models of ketamine alone were superior to models with norketamine concentration linked to an effect. The estimated EC_{50} from the MDRDS score, blood pressure, and heart rate PKPD models were 0.439, 321, and 7580 ng/ml, respectively.

Conclusion:

PKPD models simulations suggest that a low-dose sustained release subcutaneous injection is a promising method of ketamine administration as the antidepressant effect and remission criteria can be achieved at low plasma concentrations (small EC_{50}) while maintaining plasma concentration far below the EC_{50} for blood pressure and heart rate, and hence reducing the associated side effects. The shiny web application of the population PKPD models herein can be used as a practical tool for optimizing the antidepressant - side effects trade-off.

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I-06: *Ahmed Aliyu Abulfathi* External validation of a para-aminosalicylic acid population pharmacokinetics model using the ncappc R package

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Introduction: Para-aminosalicylic acid (PAS) is one of the essential add-on Group C medicines recommended by the World Health Organisation for the treatment of multi-drug resistant tuberculosis[1]. Compared to the salt formulations of PAS, the granular-release formulation (PASER) is expected to be better tolerated[2]. There is limited information on the pharmacokinetics (PK) of this now widely available formulation. De Kock *et al* developed a one-compartment disposition model with 3-transit absorption compartments in series to describe the population PK of the granular-release formulation of PAS in South African patients with multi-drug or extensively drug resistant tuberculosis[2]. Understanding the dose-exposure and exposure-response relationships of high-doses of PASER are critical for its optimisation.

Objectives: To externally validate a previously published PAS population PK model[2] using the *ncappc* R package[3].

Methods: We used the final parameter estimates from the PAS population PK model developed by de Kock *et al*[2] and applied this model to a separate data set obtained in a similar population[4]. Nonlinear mixed effects modeling (NONMEM) software version 7.4.3 was used[5]. R, an open-source statistical software[6] was used to implement the *ncappc* R package[3]. The de Kock *et al* model[2] was used to simulate concentration-time profiles of each individual 1000 times through Perl-Speaks-NONMEM (PsN)[7]. Non-compartmental analysis (NCA) metrics such as peak plasma concentrations (C_{max}) and area under the concentration-time curve from time zero to the time of last measured concentration (AUC_{last}), were estimated from both observed and simulated datasets. The estimated observed and simulated NCA metrics were compared graphically. Additionally, PsN and Xpose[8] were used to create visual predictive checks and standard goodness-of-fit plots.

Results: The visual predictive checks showed that de Kock *et al* PAS population PK model[2] describes the external data[4] reasonably well. However, the goodness-of-fit plots showed a systematic deviation between observed concentrations and population predictions. This deviation was compensated by the between-subject variability as shown in the observed versus individual prediction plot. The median C_{max} of the observed dataset fell outside the histogram of 95% non-parametric prediction interval (npi) of the simulated datasets. Similarly, the median AUC_{last} of the observed dataset fell outside the histogram of the 95% npi of the simulated datasets. These findings suggest the model[2] needs optimisation.

Conclusions: Our findings suggest the inability of a PAS population PK model[2] to adequately simulate the concentration-time profile of an external dataset[4]. On average, the model was under-predicting PAS plasma concentrations. There is a need for the current model to be optimised with pooled PASER

datasets[2,4] before using the improved model for simulation studies evaluating target attainment with novel dosing strategies with PASER.

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I-07: *Oliver Ackaert* Characterizing exposure of apalutamide and its active metabolite, N-desmethyl-apalutamide, in healthy and castration-resistant prostate cancer subjects

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Objectives: Apalutamide is an androgen receptor inhibitor approved for treatment of high-risk non-metastatic castration-resistant prostate cancer (NM-CRPC) subjects [1,2]. The objective of this population pharmacokinetics (PK) analysis was to characterize the time course of plasma concentrations of apalutamide and its active metabolite N-desmethyl apalutamide following single and repeat oral dosing.

Methods: Plasma concentration data of apalutamide and N-desmethyl-apalutamide from 1092 subjects (3 single-dose studies in healthy male subjects and 4 multiple-dose once daily studies in CRPC and NM-CRPC subjects) were pooled for a population PK analysis using a non-linear mixed effect modelling approach. A covariate analysis was conducted to quantify the impact of intrinsic and extrinsic factors on the PK of apalutamide and N-desmethyl apalutamide.

Results: Apalutamide pharmacokinetics were adequately described with an open linear two-compartment disposition model with a time-dependent apparent clearance and lagged first-order absorption. The apparent total clearance of apalutamide was composed of a constant, not inducible, clearance and an inducible clearance that increased over time until achieving steady-state after the continuous once daily dosing of apalutamide. The apparent total clearance of apalutamide increased according to a first order process with an induction half-life of 18 days from 1.31 L/h after first dose to 2.04 L/h at steady-state, consistent with auto-induction of apalutamide's own metabolism. The formation of the metabolite N-desmethyl apalutamide was assumed to be equal to apalutamide elimination. N-desmethyl apalutamide pharmacokinetics were described with an open linear two-compartment disposition model with the assumption of linear elimination from the central compartment. After 4 weeks of treatment, more than 95% of steady state exposure of apalutamide and N-desmethyl-apalutamide is reached. At steady-state, the elimination half-life of apalutamide and its metabolite was 4.2 and 4.6 days, respectively. At 240 mg of apalutamide per day, apalutamide and N-desmethyl-apalutamide exposure exhibited a 5.3 and 85.2-fold accumulation in plasma, respectively. In addition, apalutamide administration once daily results in relative constant steady state apalutamide and N-desmethyl apalutamide plasma concentration with 1.4- fold and negligible fluctuation over the dosing interval, respectively. Within the range of covariate values evaluated using a stepwise covariate modeling approach, only health status (healthy vs. patients), body weight and albumin concentration were statistically associated with the exposure of apalutamide or N-desmethyl-apalutamide and the effect was small (<25%).

Conclusions: The PK of apalutamide and N-desmethyl-apalutamide was adequately described simultaneously using one combined model. None of the investigated covariates has a discernible and or clinically relevant impact on the apalutamide or N-desmethyl-apalutamide PK.

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I-08: *Bambang Adiwijaya* Component score models of HAMD were more predictive than total score models

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Objectives: SAGE-217 is a potent investigational GABAA receptor modulator at both synaptic and extrasynaptic receptor subtypes, and is currently being studied in patients with psychiatric disorders, including major depressive disorder (MDD) and postpartum depression. In a pivotal, double-blind, placebo-controlled clinical trial of 89 patients with moderate to severe MDD, administration for 14 days with SAGE-217 was associated with a statistically significant mean reduction in the Hamilton Rating Scale for Depression (HAMD) 17-Item total score. The objective of this analysis was to evaluate alternative models of HAMD total scores and their predictions of alternative treatment durations, with emphasis on the comparison of prediction accuracy of models that quantify total score directly (TS method) to models that quantify each of the 17 component scores (CS method).

Methods: Baseline (Day 0 [D0]) and on-treatment HAMD assessments on Days 1-7, and 14 from 89 patients (44 placebo, 45 SAGE-217) were used to evaluate alternative methods. Two mixed-effect models were tested: Model 1 (primary): HAMD~ cumulative concentration (log-transformed), and Model 2 (secondary): HAMD ~ time (log-transformed). Regression estimates were corrected by the placebo effects in each timepoint. In the TS method, HAMD total scores were modeled as continuous variables. In the CS method, HAMD component scores were modeled as ordered categorical variables.
Prediction accuracy was assessed by comparing root mean square error (RMSE) of observed and predicted HAMD total score in the test set, from the model estimated from the training set. Three cases of training/test sets were evaluated: 1) training: D0-7, test: D14; 2) training: D0-6, test: D7 & D14; and 3) training: 80%, test: 20% (5-fold cross-validation). Comparisons of TS and CS methods were performed by evaluating the model comparisons from the same training/test sets.

Results: Alternative methods to model HAMD scores were evaluated by comparing prediction accuracy for TS and CS methods using multiple model covariates and training/test conditions. Compared to the TS method, the CS method demonstrated higher accuracy in all conditions. The RMSE difference of HAMD1 total scores between TS and CS method was highest for Case 1 (training: D0-7, test: D14), with Model 1 RMSE of 4.67 and 4.16 for TS method and CS method, respectively. The RMSE difference was not as large for Case 3 (5-fold cross-validation), with Model 1 RMSE of 3.50 and 3.35 for TS and CS method, respectively. Evaluation of the predictions showed that TS method predicted a few scores that were less than zero (zero is the lower bound of the HAMD scores), while CS method predicted all nonnegative scores. Detailed evaluation of the model predictions in a few example subjects showed the benefits of CS method in providing accurate lower bounds to each component of HAMD score, resulting in more accurate predictions. Model predicted that the optimal treatment duration of SAGE-217 in MDD was 14 days.

Conclusions: HAMD scores in patients with MDD were predicted more accurately by quantifying each component of HAMD scores than by quantifying HAMD total scores directly. The results may permit more accurate study planning during clinical development.

I-09: *Jae Eun Ahn* Longitudinal Model-Based Meta-Analysis for Liver Biomarkers and Biopsy Endpoints in Patients with Non-Alcoholic Fatty Liver Disease

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Objectives:

Non-Alcoholic Fatty Liver Disease (NAFLD) is defined by excessive hepatic fat accumulation (steatosis, defined as a liver fat content greater than 5%) in the absence of significant alcohol consumption, autoimmune, viral, metabolic disorders, or drug induced liver disease [1]. Non-Alcoholic Steatohepatitis (NASH) is a clinical and histological subset of NAFLD that is associated with increased all-cause mortality, cirrhosis and end-stage liver disease, increased cardiovascular mortality, and increased incidence of both liver related and non-liver related cancers [2]. Currently, there are no medicines approved to treat NAFLD and NASH and clinical trials for several therapeutic agents in NASH patients are ongoing. Through model-based meta-analysis (MBMA), the following objectives were identified: 1) to understand the relationship between changes in plasma biomarkers and biopsy related endpoints, and 2) to quantify the effects of different therapeutic agents providing quantitative criteria to inform NASH clinical development strategies.

Methods:

A literature search was performed according to the following PICOS criteria [3]. Study populations (P) were NAFL and NASH patients with or without type 2 diabetes mellitus, fibrosis, and metabolic syndrome. Interventions (I) included but were not limited to pioglitazone, metformin, exercise, vitamin E, diet, lifestyle modification, ursodeoxycholic acid, liraglutide, pentoxifylline, bariatric surgery, and rosiglitazone as well as new investigational drugs. Placebo or standard of care (typically diet and exercise) served as comparators (C). The outcomes (O) of interest included circulating biomarkers such as alanine aminotransferase (ALT), aspartate aminotransferase, gamma glutamyl transferase, and alkaline phosphatase, and also liver fat, fibrosis grading, NAFLD Activity Score (NAS), and responders. Either placebo or active controlled studies (S) were included. The search databases included OVID MEDLINE® 1946-07Sep2018, OVID MEDLINE® In-process and Epub Ahead of Print, BIOSIS Previews 1969 to 2018 Week 40, Embase 1974-06Sep2018, Scopus®, and ClinicalTrials.gov (https://clinicaltrials.gov/). R (version 3.4.1) was used for data cleaning, modification, and plotting. NONMEM (version 7.4, ICON Development Solution, Gaithersburg, MD) was used for estimation. For biomarkers, the following structural model was applied for % change from baseline measures (Y), as reported or imputed using the reported baseline and change from baseline measures:

$$Y_{ijk} = -Pmax\cdot(1-\exp(-0.693/ET50\cdot time_k)-Trt_h+\eta_i+\eta_{ij}+\varepsilon_{ijk}$$

where Y_{ijk} denotes observation at i^{th} study, j^{th} arm, and k^{th} time; Pmax, maximum placebo or control response; ET50, the time for reaching a half Pmax; Trt_h, treatment effects specific for h^{th} drug class; η_i, inter-study random effect; η_{ij}, inter-arm level random effect, nested within the study; ε_{ijk}, residual variability, weighted according to the sample size of arm.

Results:

Following the literature search and critical review, 198 studies were included in the final NASH MBMA data set among which 173 publications reported ALT, and 22 studies reported liver fat measured by MRI. Biopsy endpoints such as NAS (either total or sub scores) and fibrosis were reported in 45 and 49 studies, respectively. A longitudinal model for ALT estimated a Pmax of 23.7 % (RSE 5.63 %) with ET50 of 12.4 weeks (11.8%) could be achieved by the control. Trt_h were characterized, and estimated to vary between an additional 3.85% (RSE 55.5 %) and 19.4% (RSE 9.24%) reduction relative to control. Liver fat data did not show any parametric trend in the control groups; however, overall changes varied between a 56% reduction to a 7% increase. The relationships between liver fat content and NAS or liver fat and fibrosis remain unclear, as the quantity of data informing this relationship is sparse. Responder definitions were heterogeneous among different studies and further characterization and grouping are ongoing.

Conclusions: Literature data were constructed for NAFLD/NASH disease area and the longitudinal MBMA was performed. While the preliminary modelling results provide some quantitative criteria to benchmark/compare the treatment effect of interest versus other agents, further discussion and additional data would be necessary to properly identify the relationship between the biomarkers and clinical endpoints from the literature data.

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I-10: *Maurice Ahsman* A mechanism-based population K-PD model for long-term testosterone inhibition in prostate cancer patients under intermittent androgen deprivation therapy

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Objectives: Intermittent androgen deprivation therapy (iADT) is a treatment option for selected subpopulations of prostate cancer (PCa) patients that can prevent or delay disease progression and development of castration resistant prostate cancer (CRPCa). It can also reduce risk and severity of side effects associated with chemical castration in PCa patients. The aim of this investigation was to derive a mechanism-based population model for testosterone in PCa patients undergoing long term iADT during active treatment and recovery phases, to predict PSA response in stable and relapsing patients.

Methods: One of the earliest comprehensively documented clinical trials on iADT was reported more than a decade ago [1]. In this study, PCa patients showing PSA relapse after previous radiation therapy started iADT treatment under a pre-defined titration scheme, with a 32 week treatment cycle followed by an off-drug period. Repeated PSA recurrence above a threshold re-initiated active treatment, until PSA returned to below the target level. 72 patients underwent one to five active treatment cycles during a period of up to six years, in which testosterone and PSA levels were monitored continuously every three months. A K-PD model for long-term testosterone inhibition and recovery via GNRH-receptor downregulation was developed, based on a recently reported testosterone-PSA model for Leuproline [2], under Monte-Carlo importance sampling (IMPMAP) in NONMEM.

Results: The model could successfully describe testosterone inhibition during and after each active treatment cycle on population and individual patient level. Precision of model predicted testosterone response decreased approximately three-fold after the first active cycle, but remained constant during subsequent cycles. Model accuracy was equally adequate during each cycle. Some disease progression-related aspects of long-term iADT in the population, originally reported as clinical observations [1], were quantified from the data by model inference: Pre-treatment testosterone concentration for the population at baseline was 11.5 nmol/L and a first-order constant of 0.097 h^{-1} was derived for long-term decrease of endogenous testosterone production, visible after treatment recovery at the end of each cycle. However, the median testosterone nadir during active treatment remained constant (0.13 nmol/L) for patients remaining in the trial. A non-normal distribution of individual estimates (EBE's) for testosterone production decrease was observed and a negative Box-Cox parameter for this could be identified. In addition, the return rate of testosterone concentrations after the end of active treatment cycles was approximately 60% lower after cycle 2-5, compared to the wash-out phase after cycle 1.
For a small sub-population of 12 patients designated as PSA relapsers, slightly higher testosterone levels at the nadir of cycle 1 and 2 were observed compared to stable patients, which indicates that the individual nadir estimates may be predictive for development of long-term PCa resistance to castration, but a bi-modal distribution for this could not be derived using the $MIX option in NONMEM. From model-derived parameters, obtained by fitting to the data reported from cycle 1 and 2, the response during subsequent active cycles 3-5 could be adequately predicted.

Conclusions: A mechanism based K-PD population was developed that can describe and predict the long-term testosterone response under iADT in this patient population, including some typical aspects of receptor down regulation and post-recovery decay in testosterone production.

In future, this model may be used to explain and predict the long-term disease progression as reflected by PSA response in the same PCa patient population.

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I-11: *Marie Alexandre* Modeling viral rebound in HIV therapeutic vaccine studies

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Introduction: HIV therapeutic vaccines are currently developed with the objective of long-term viral control in the absence of anti-retroviral treatment (ART). To evaluate their efficacy, supervised treatment interruptions (STIs) are often used. Modeling biomarkers before and after STI in HIV-vaccinated individual is needed to gain a deeper understanding of mechanisms of action of vaccines.

Objectives: We aim at modeling viral load rebound in HIV-infected patients after HIV prime-boost vaccination during ART cessation. We investigate which mechanistic model, based on ordinary differential equation (ODE), is best to model the variability of the viral rebound induced by reservoir reactivation.

Methods: Five mechanistic models were studied to describe the viral rebound and CD4+ T cells count dynamics: (1)-(2) 2 and 3 compartments ODE systems featuring uninfected CD4+ T cells, productively infected CD4+ T cells and viruses concentration, respectively with and without proportional relation between infected cells and viruses, (3) 4 ODE system also considering quiescent CD4+ T cells, (4) 5 ODE system also considering immune response by means of effector and precursor immune cells and (5) 5 ODE system introducing eclipse phase and non-producing virions. Practical and theoretical identifiability as well as sensibility analysis were performed to evaluate these models. Parameter estimations were done using the SAEM (Stochastic Approximation of Expectation-Maximization) algorithm as implemented in Monolix. Finally AIC criteria, quality of prediction using cross-validation leave-one-out and external data validation were used as comparison criteria.

Results: Models were evaluated on HIV therapeutic vaccine trial VRI02 ANRS 149 LIGHT, a double-blinded phase II trial including ninety-eight chronic HIV patients with CD4+ T cells counts ≥ 600 cells/µL and HIV RNA < 50 copies/mL for at least 6 months previous to the study and whose nadir CD4 ≥ 300 cells/µL while on ART. Patients were randomized (2:1) to receive either GTU-MultiHIV B at week 0, 4 and 12 followed by LIPO-5 vaccine at week 20 and 24, or vaccine placebos. Prime-boost vaccination strategy was followed by STI at week 36 until 48 and resumption of ART after week 48. Viral load and CD4+ T cells dynamics of the sixty-seven patients of the control group of the ILIADE clinical trial were then considered as external validation sample to evaluate the models (1-5) quality of prediction. In this trial 24 weeks on ART is followed by therapy cessation at week 24 until week 120 and a follow up until week 168, for patients with CD4 cells count above 350 cells/µL. Practical identifiability was achieved by fixing, when needed, some of the parameters of the models. Overall, in most patients, adjustment and prediction where satisfactory, but simple model (2-3) failed to describe specific viral rebound trajectories, such as delayed viral rebound. The best model, which is a model with 5 ODE, has an AIC decreased by about 10% compared to other models. In term of prediction on the ILIADE dataset, we have a good agreement between observations and predictions. Assuming the measurement error similar between LIGHT and ILIADE datasets, we find that about 95% of the observation for CD4 T cell count and 90% of the observation for viral load count are accurately predicted. For the latter, this is lower than the expected nominal value of 95% but no particular trend indicating a model misspecification was detected. We explain most of this inconsistency by the fact that the model assumes perfect adherence.

Conclusions: Although increasing the number of parameters to estimate makes the estimation less identifiable and lead to the necessity of fixing parameters, we demonstrate that ODE models with higher number of compartments are more flexible to adjust viral rebound and CD4 T cell count data and show good prediction abilities on external dataset.

I-12: *Joachim Almquist* Estimation of equipotent doses of the oral selective glucocorticoid receptor modulator (oSGRM) AZD9567 and prednisolone based on ex vivo TNFa inhibition after LPS stimulation

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Introduction:

AZD9567 is an oral selective glucocorticoid receptor modulator (oSGRM) aimed for the treatment of inflammatory disease [1]. It has been designed to deliver similar efficacy to oral steroids such as prednisolone, but to differentiate on safety.

Here, we present a model-based approach to estimate equipotent doses of AZD9567 and prednisolone in terms of equally large ex vivo inhibition of the anti-inflammatory biomarker TNFα. The resulting equipotency relationship makes it possible to translate doses of one compound into the other based on their anti-inflammatory effect.

Objectives:

The objective was to estimate an equipotent dose relationship between AZD9567 and prednisolone with respect to ex vivo TNFα inhibition. It is particularly interesting to estimate the dose of AZD9567 equipotent to the commonly used 20 mg prednisolone. Key intermediate steps towards this goal are to develop two popPK models, one for each compound, and to develop a joint TNFα PD model for both compounds.

Methods:

Models were based on clinical data from a SAD and a MAD study, which include measurements of plasma concentration of the respective compound and concentrations of the cytokine TNFα as released in response to an ex vivo whole blood lipopolysaccharide (LPS) stimulation [2].

Nonlinear mixed effect PKPD modeling was done sequentially, fixing both fixed and random effects of the PK models before fitting the PD model. The PD model contained both common and compound-specific parameters and was fitted for both compounds simultaneously. All models were estimated with NONMEM 7.3.0 using the FOCE method [3].

Dose-response curves for each compound were determined by simulation. The response was defined as the average inhibition of TNFα over 24 h following 5 consecutive daily doses. Confidence intervals for the equipotent dose relationship were determined by simultaneously accounting for the uncertainty in the dose-response of each compound.

Results:

A two-compartment model with first order absorption and a lag time was used to describe the PK of AZD9567. The dominant phase was associated with a half-life of 4.4 h. Since the PK was not dose proportional, the oral dose was used in a linear covariate model for the relative bioavailability.

Due to nonlinear plasma protein binding of prednisolone, a static model was first set up to convert total concentrations into unbound concentrations. This model showed that the unbound fraction goes from 6% in the limit of low concentrations to 38% in the high limit. Subsequently, a two-compartment model with a transit compartment approximation [4] was used to describe the PK of unbound prednisolone. The dominant phase was associated with a half-life of 1.9 h.

TNFα inhibition was modeled by an inhibitory Imax-model with sigmoidicity parameter, but in which the driving concentration was a weighted sum of the plasma concentration and the concentration in an effect compartment. Since the weighting parameter was estimated from data, this model had the ability to revert into a direct response model or into an effect compartment model, or to adopt an intermediate setting. The estimate of the weighting parameter (the plasma proportion) was 22%, thus favoring the effect compartment as the main PD driver. The estimate of IC_{50} for total AZD9567 was 765 nM (95% CI of 610 – 920 nM). Given an unbound fraction 0.637%, this corresponds to a IC_{50} of 4.87 nM for unbound AZD9567. The estimate of IC_{50} for unbound prednisolone was 17.0 nM (95% CI of 13.5 – 20.4 nM). Considering unbound concentrations, AZD9567 is a more potent inhibitor of TNFα release than prednisolone.

Simulated doses-response curves for AZD9567 and prednisolone were compared to identify equal levels of TNFα inhibition. For example, it was estimated that a dose of 40 mg AZD9567 (95% CI 29 – 54 mg) was equipotent to 20 mg prednisolone, with both doses resulting in an average TNFα inhibition of 43%. When performed over the whole range of studied doses, such comparisons defined the full equipotency relationship. The full relationship is nonlinear and there is no simple formula such as a factor that relates the equipotent doses.

Conclusion:

An equipotency relationship between AZD9567 and prednisolone was estimated using PKPD modeling of the anti-inflammatory biomarker TNFα. Not only is this relationship a critical component of a dose selection strategy with respect to efficacy, but it also provides a common reference system that will facilitate future assessment of safety biomarkers.

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I-13: *Jokha AL-Qassabi* Predicting the Fraction Unbound (fu) and Plasma Drug Clearance Based on Known Changes in Albumin and Alpha1-Acid Glycoprotein Levels at Varying Degrees of Renal Impairment

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Introduction/Objectives: Renal impairment (RI) leads to physiological changes that can affect the pharmacokinetics (PK) of drugs [1]. These changes, besides the reduced glomerular filtration rate (GFR), include reductions in the activity of hepatic drug metabolising enzymes and plasma protein binding (and hence fraction unbound (fu))[1]. The latter can be due to alteration in proteins levels (mainly human serum albumin (HSA) and α_1-acid glycoprotein (AAG))[2]. The main objectives of this study were to develop (1) a model that can predict the (fu) based on known changes in the levels of (HSA and AAG) in various degrees of RI for 23 drugs and, (2) a model that can predict the clearance (CL) using the (fu) model for 14 drugs in different stages of RI. The overall aim of this study was to examine the importance of (fu) in determining the changes in the (PK) for various drugs at varying degree of RI, when accounting for (GFR), (fu), and metabolic enzyme activity (CYP enzymes). This attempt hopefully will help in understanding the role of protein binding and more importantly, it might help to explain some of the variability seen with drug exposure in RI population.

Method: A list of renal impairment pharmacokinetics studies was collected, where fu of a drug was reported as a measured value. Total drugs that were found with a measured fu were 23 drugs. Beside this, information on protein binding, pka values, compound type, fraction eliminated or fe, metabolism via CYP enzymes (fm if reported), total clearance and renal clearance if reported, bioavailability, route of administration, dose of the drug given, the study group and the number of patients was also collected. The same list of drugs was used for the prediction of total clearance, renal clearance as well as non-renal clearance of the drugs at different stages of renal impairment. Nine drugs were excluded from this list as there was either no information on fe, or renal clearance, or no information on their metabolic clearance or the fraction metabolised at varying degree of RI. 4 models were developed using data from the list of dedicated renal impairment studies.

The equation used for calculating the HSA for a given GFR is as follow(Model1):

Equation 1

y=0.00005x^2-0.0004x+3.9875

Where y represents the HSA in g/dL, and x is the glomerular filtration rate in mL/min.1.73m^2.

The equation used for calculating the AAG for a given GFR is as follow (Model2):

Equation 2

y=-0.0031x2 + 0.3239x + 20.143

Where y represents the AAG in µmol/ L, and x is the glomerular filtration rate in mL/min.1.73m2.

Model3:

Equation 3

$fui=1/(1+((1-fu)*[P]i)/([P]*fu))$

Where, fu_i is the individual fraction unbound in the renal impairment patient, fu is the fraction unbound in healthy individual, $[P]_i$ is the concentration of either HSA or AAG in renal impaired patient and [P] is the concentration of either HSA or AAG in healthy individuals.

Model 4:

Equation 4: CLr Predictions:

$CLr_{mild} = (CLr_{HV}*((GFR_{mild}*fu_{mild}) / (GFR_{HV}*fu_{HV})))$

$CLr_{moderate} =(CLr_{HV}*((GFR_{moderate}*fu_{moderate})/ (GFR_{HV}*fu_{HV})))$

$CLr_{Severe} = (CLr_{HV}*((GFR_{severe}*fu_{Severe}) / (GFR_{HV}*fu_{HV}))$

Equation 5: CLnr Predictions:

$CLnrPred_{(mild)}= (((Clnr_{HV}*fmCYPn*\text{fraction of CYPn activity in mild}) *(fu_{mild}/fu_{HV})$

$CLnrPred_{(moderate)}= (((Clnr_{HV}*fmCYPn*\text{fraction of CYPn activity in moderate}) *(fu_{moderate}/fu_{HV})$

$CLnrPred_{(Severe)}= (((Clnr_{HV}*fmCYPn*\text{fraction of CYPn activity in severe}) *(fu_{severe}/fu_{HV})$

Equation 6: Clt Prediction:

$Clt_{mild} = Clr_{mild} + Clnr_{mild}$

$Clt_{moderate} = Clr_{moderate} + Clnr_{moderate}$

$Clt_{Severe} = Clr_{severe} + Clnr_{severe}$

Results: The results showed that the (fu) model performed well when compared with those reported within clinical studies as the predicted values of 23 drugs were within 2-fold of observations as well as the (CL) model estimation. Predictions of (fu) (AFE=0.96, AAFE=1.27) and (CL) (AFE=0.65, AAFE=1.78) based on HSA seems to be better than predictions of (fu) (AFE=0.69, AAFE=1.48) and (CL) (AFE=0.53, AAFE=1.98) based on AAG.

Conclusion: The statistical models proposed in this study for fu and CL seems to be predictive of the clinical data. In the absence of measured protein levels this model can be of use. Clearance and plasma protein binding predictions showed superior performance for HSA substrate drugs as compared to AAG, as more data was available to inform the HSA binding model

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I-14: *Hesham Al-Sallami* The use of a Bayesian dosing tool to optimise enoxaparin treatment: a pilot clinical study

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Objectives: Enoxaparin is a widely used anticoagulant in the treatment of thrombosis. Due to its narrow therapeutic window, monitoring of enoxaparin therapy is warranted in the clinical setting especially for patients who are at the extrema of body weight or have renal impairment.[1] A pilot study showed that clinicians do not find current dosing guidelines credible for patients at the cut-points of dose banding based on body weight (> 90 kg) or renal function (CLcr < 30 mL/min).[2] It has been proposed that model-based [3,4] dose-individualisation may result in improved attainment of the treatment target and subsequently better patient outcomes. Bayesian forecasting dosing methods employ the use of a dose-response model and a Bayesian maximum a posteriori (MAP) function in conjunction with patient response in order to estimate individual model parameters. A dosing tool (TCIWorks) was evaluated previously and found to have a higher probability in achieving target anti-Xa when compared to standard dosing.[5] Thus, based on predefined acceptable exposure levels, the dose for each patient can be optimised accordingly. Previously, an enoxaparin concentration target was identified as a peak (approx. 5 hours post-dose) anti-Xa concentration of > 500 IU/L and a trough (approx. 11 hours post-dose) anti-Xa concentration of < 500 IU/L. [1]

The objectives of this study was to compare individualised enoxaparin dosing against standard dosing in a prospective clinical feasibility trial.

Methods: Adult patients admitted to Dunedin Hospital, New Zealand, who were likely to receive treatment doses of enoxaparin for at least 48 hours were studied in a randomised, double-blind, parallel group clinical feasibility study. Patients were randomly assigned to either a TCIWorks-guided individualised dosing regimen or a standard treatment. The amount of the first dose was at the discretion of the prescribing doctor and followed standard enoxaparin dosing protocols. Subsequent doses were calculated using TCIWorks to achieve a peak anti-Xa concentration of > 500 IU/L and a trough anti-Xa concentration of < 500 IU/L. The adjusted dose was communicated blindly to a medical collaborator who possessed a stratified randomisation sequence and implemented dose changes. Patients in the control group received the same dose as prescribed whereas patients in the individualised group received an adjusted dose.

The two treatment groups were compared in terms of the incidence of bleeding or bruising events. Patients were followed up for 30 days following discharge from hospital for evidence of revascularisation or re-thrombosis.

Results: Twenty-two patients were recruited, 10 in the standard group and 12 in the individualised group. There were no differences in the demographic and medical information between the two groups. The median duration of enoxaparin treatment while in hospital was 3.7 days.

A total of eight patients (38%), 3 in the standard group and 5 in the individualised group, did not achieve the anti-Xa target after the first dose and an adjusted dose was estimated using TCIWorks. Doses were adjusted in all five patients in the individualised group. Three of these patients required two or more dose adjustments in order to reach target anti-Xa concentration.

A total of four safety events, all minor bleeding or bruising, occurred during enoxaparin treatment. Three events occurred in the standard dosing group and one event occurred in the individualised group. Both bruising events occurred in patients whose dose was recommended to be reduced to meet anti-Xa treatment target. There were no recurrent thromboembolic events in either arm during follow-up.

The trial was found to be feasible logistically and the time between the first and subsequent doses was adequate to measure anti-Xa concentration and calculate subsequent doses. However, acute coronary syndrome patients, who make up the bulk of enoxaparin treatment users in the acute setting, were often found to be not suitable for recruitment as enoxaparin treatment in this patient group is often short and is ceased once surgical revascularisation is achieved.

Conclusion: In this feasibility study, standard dosing of enoxaparin which is based on body weight and creatinine clearance was compared to individualised dosing where the patient's response in addition to their covariates were used to inform dose selection. Suboptimal anti-Xa concentration was noted in 38% of patients following standard dosing. An adequately powered clinical trial is required in order to make statistically significant inferences.

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I-15: *Vincent Aranzana-Climent* Use of a semi-mechanistic PK-PD model to quantify the combination effect of polymyxin B and minocycline against polymyxin-resistant Acinetobacter baumannii

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Objectives:

Acinetobacter baumannii is one of the most difficult to treat multi-drug resistant (MDR) pathogens responsible for opportunistic nosocomial infections all over the world [1]. It can cause a broad range of infections, the deadliest being ventilator-associated pneumonia and bloodstream infections [2], and has the ability to become resistant to a wide variety of drugs [3]. In face of these resistances, neglected and disused antibiotics like polymyxins (colistin and polymyxin B) may be used, especially in combination with other antibiotics, as the last line of defence against MDR *A. baumannii* [4]. In a preliminary checkerboard screening study (data not shown), polymyxin B (PMB) and minocycline (MIN) combination was shown to be synergistic on polymyxin-resistant *A. baumannii* clinical isolates.

To further investigate this synergistic combination, a polymyxin-resistant clinical isolate (CR17) was selected to be thoroughly studied through development of a semi-mechanistic pharmacokinetic-pharmacodynamic (PK/PD) model.

The main objective of this study was to investigate the determinants of the PMB + MIN synergy against CR17 observed in checkerboard experiments

Methods:

A polymyxin-resistant *A. baumannii* clinical isolate CR17 (MIC: PMB 8 mg/L; MIN 4 mg/L) was studied [5].

Heteroresistance to PMB and MIN was evaluated by plating a high inoculum (~109 CFU/mL) on plates containing 8 x MIC of drug (resistant subpopulation) and on drug free plates (total population) and counting after 24h at 37°C.

Fitness cost was evaluated by inoculating a 96 well plate with ~106CFU/mL of bacteria that grew on drug-free and drug-containing plates and reading OD at 600nm over 24h.This enabled calculation of a growth rate constant as described earlier [6].

Single drug and combination time-kill experiments (TKE) with determination of total bacterial count at 0, 3, 8, 24 and 30h at concentrations ranging from 1/16 to 4 x MIC for MIN and from 1/128 to 1 x MIC for PMB. Simultaneously, population analysis profiles (PAPs) were performed by culture and bacterial count on PMB-containing (8 x MIC) plates.

A mechanistic bacterial life cycle model based on results of heteroresistance and fitness cost experiments was built. For single drug effect model multiple PK/PD models taken from literature [7] were tested and the interaction between the two drugs was explored using the "Global PharmacoDynamic Interaction model (GPDI)" [8].

Analysis was performed using NONMEM v7.4.3 with Laplacian algorithm [9], PsN [10] and R [11].

Results:

CR17 did not exhibit heteroresistance to MIN but to PMB (mean frequency: 5.07 *10-6, n=6).

No fitness cost was found, mean growth rate for colonies that grew on drug-free plates was 1.105 h-1 (n=11) and 1.092 h-1 (n=11) for colonies that grew on plates containing 8 x MIC of PMB.

A total of 253 TKE were performed. In single drug TKE, no effect was observed at concentrations <1 x MIC MIN while at concentrations >= 1 x MIC a concentration-independent effect was observed, with complete bacterial killing at 30h. PMB alone exhibited a fast concentration-dependent effect followed by regrowth at all tested concentrations. When combining MIN and PMB, total bacterial killing at 30h was observed for concentrations as low as 1/4 x MIC MIN + 1/16 x MIC PMB.

Data were adequately described by a model including a phenotypic switch to resting [12] form at high bacterial concentrations, two subpopulations (PMB-susceptible and PMB-resistant), a sigmoidal Emax effect of MIN, a slope power effect model of PMB and adaptive resistance to PMB of both subpopulations. Synergy consisted of PMB increasing MIN killing of both subpopulations, and MIN increasing PMB killing of the susceptible subpopulation. Simulations showed that while significantly improving the fit to data, the potentiation effect of MIN on PMB could be accounted for a marginal part of the total effect, while the potentiation effect of PMB on MIN was essential to the observed effect.

Conclusions:

Combining MIN and PMB *in vitro* proved to be efficient against a polymyxin-resistant *A. baumannii* clinical isolate. The developed PK-PD model enabled us to quantify the synergistic effect between MIN and PMB.

This study could serve as a proof of concept that using targeted experiments to inform model building and then use advanced PK/PD models built on combination TKE+PAPs data is a good methodology to gain insights on the *in vitro* PK/PD of antibiotic combinations.

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I-16: *Million Arefayene* Population Pharmacokinetics (PK) and pharmacodynamics (PD) Modeling of anti-avß6 integrin Antibody (BG00011)

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Introduction:

Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease caused by progressive scarring in the lungs tissue [1]. To date, there is no known curative therapy for IPF patients [2]. BG00011 is first-in-class humanized IgG1 monoclonal antibody that blocks αvβ6 integrin, which is highly upregulated in IPF patients and responsible for activation of latent transforming growth factor-beta (TGF-β), a key regulator of IPF. BG00011 is currently being investigated in phase 2B clinical trial.

Objectives:

Understand impact of pre-defined predictors on BG00011 exposure and characterize relationship between BG11 exposure and PD modulation (ratio of phosphorylated-SMAD to total-SMAD proteins (pSMAD/tSMAD).

Methods:

The BG00011 serum concentration obtained from a single ascending dose healthy volunteer study and serum concentration and PD (the ratio of phosphorylated-SMAD to total-SMAD proteins (pSMAD/tSMAD)) obtained from a multiple ascending dose in IPF patients were used in development of PK and PK/PD model. One and two compartment models with linear and non-linear clearance were evaluated as base PK models. The AUC at steady state (AUC_{ss}) over the dosing interval after the last dose and the pSMAD/tSMAD percentage change from the baseline was used for development of PK/PD model using a naïve pool approach. The following steps were followed to achieve the objective: (1) exploratory PK data analyses were performed graphically, (2) base PK model structure was developed, (3) effect of body weight, gender and disease status were evaluated on PK parameters (4) PK/PD model for BG00011 was developed using the predicted exposure (AUC_{ss}) based upon the final PK model. PK and PK/PD models were developed sequentially using Monolix (Version 2018R1) and Phoenix (version 7.0), respectively. Parameter estimates with associated standard errors, diagnostic plots and visual predictive checks were used for model evaluation.

Results:

In total, 794 serum concentrations and 19 pSMAD/tSMAD ratio data from patients were included in the population analysis. The two-compartment model with first order absorption and combination of linear and nonlinear elimination model was identified as optimal with all parameters estimated with high precision [PK: CL (0.034), V_c (2.31), V_p (6.07), V_{max} (26.8), K_m (389); RSE% for all parameters < 25%]. The covariate analysis indicated that body weight, gender and disease status had no effect on PK parameters. The predictive ability of the model demonstrated that the median, 10^{th}, and 90^{th} percentiles of predictions well-captured the observed data in the evaluated dose range.

The relationship between BG00011 concentration and pSMAD/tSMAD ratio was best described by a direct response model with sigmoidal effect on pSMAD/tSMAD ratio mediated by BG00011 concentrations. The model-estimated I_{max} was 129.2 hr·mg/mL.

Conclusion:

The population PK/PD model adequately characterized BG00011 PK/PD in IPF patients. The nonspecific disposition component estimates (*CL, V_{ss}*) were consistent with results obtained for other IgG1 monoclonal antibodies [3]. Covariates on PK parameters are not expected to have any clinical impact at the proposed Phase 2B dose. The PK/PD model will be updated and used to support future dose and regimen selection.

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I-17: *Leticia Arrington* An R package for Automated Generation of Item Response Theory Model NONMEM Control File

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Introduction

Pharmacometrics Item response theory (IRT) models have been recognized as a valuable modeling approach for analyzing healthcare related composite assessments; it provides a natural framework to combine different outcomes from the same disease into a joint disease model. However, the implementation of Pharmacometrics IRT presents several technical challenges, e.g. it has many components increasing the risk of coding errors, IRT models contain large number of parameters that require initial estimates, and with many contributing data types to the elaborate model diagnostic. These challenges are especially hampering in a drug development setting where analysts need to be skilled in a wide area of techniques. There is a need to develop a tool that facilitates the implementation of Pharmacometrics IRT. Existing ready to use IRT-R packages are mainly focused on psychometrics with limited flexibility for modeling longitudinal data.

Objectives: The objective of this work was to develop a modeling tool in the form of an R package, called nmIRT, that streamline the implementation of Pharmacometrics IRT. The functionality of nmIRT is showcased using Parkinson's disease composite assessment data (i.e. MDS-UPDRS).

Methods: The nmIRT R package aims to streamline the implementation of Pharmacometrics IRT models. The overall package can be decomposed in two main components: the assembler, responsible for creating NONMEM-IRT model and the Inspector, responsible for the generation of diagnostic plots. The assembler allows the users to specify the desired structure of the IRT model and then generate the corresponding NONMEM code that can be ran in any NONMEM modeling and simulation platform. The calculation of initial values for the NONMEM code as well as the identifiability analysis will rely on existing IRT R-packages (e.g. mirt). Currently the types of data that are supported are ordered categorical and binary. Once the NONMEM-IRT model is fitted, the "Inspector" part of nmIRT will perform model diagnostic that include mirror plots, Item characteristic curves and residual correlation plots. Additional capabilities such as data checkout and the creation of a IRT model based directly from a provided data set are included in nmIRT package. The ability of the newly designed workflow to handle IRT model development was assessed using a Parkinson's disease model and data from Gottipati et al.

Results: The model assembler was able to generate the IRT model structure including all components required for estimation and simulation for ordered categorical and binary items and provided a default structure for the latent variable after execution of a few lines of code. The item parameter estimates were comparable between the manual IRT model and the autogenerated model from the nmIRT package. The model diagnostics provided information on item parameter fit and provided supportive evidence of the functionalities within the nmIRT package.

Conclusions:

The nmIRT model assembler first generation is able to expedite the IRT model development process by generating an editable IRT NONMEM control file for MDS-UPDRS scale for use in NONMEM with input from the user. While the current package internal predefined scale is MDS-UPDRS, the current package is able to handle datasets from other scales with categorical and binary data, which allows general use for other similar assessments.

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I-18: *Usman Arshad* A semi-mechanistic pharmacokinetic-pharmacodynamic model of 5-fluorouracil continuous infusion in gastrointestinal cancer patients

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Objectives: The study was aimed to develop a population pharmacokinetic model of 5-fluorouracil continuous infusion and a semi- mechanistic myelosuppression model to describe the relationship between 5-FU exposure and myelotoxicity. In addition, genetic and non-genetic covariates influencing 5-FU pharmacokinetics and myelotoxicity were explored.

Methods: Thirty gastrointestinal cancer patients received 650 or 1000 mg/m^2/day 5-FU for 5-days as continuous venous infusion. Fourteen patients were additionally infused with cisplatin 20 mg/m²/day. Plasma concentrations of 5-FU and its major metabolite 5-fluoro-5,6-dihydrouracil (5-FUH2) were quantified. Absolute leukocyte count (ALC) data was obtained once prior to and 2-3 times after the start of infusion until day 27. Covariate data included patient demographics such as age, weight, height, sex, body mass index, lean body weight, body surface area (BSA), alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, and albumin levels and information on dihydropyrimidine dehydrogenase (*DPYD),* thymidine synthase (*TS*), and methylene tetrahydrofolate reductase (*MTHFR*) genotypes. Pharmacokinetic parameters for 5-FU and 5-FUH2 were obtained by nonlinear mixed effect modeling using NONMEM. ALC data were described by a semi-mechanistic myelosuppression model driven by 5-FU plasma concentrations. Covariate evaluation was principally guided by physiological plausibility, decrease in objective function value and interindividual variability. Simulations were designed to assess the influence of respective *MTHFR* genotypes, cisplatin co-medication and dosing regimens by predicting the depth (ALC_{nadir}) and time (T_{nadir}) of lowest ALC and the recovery period (T_{rec}) for the reestablishment of ALC to its baseline value.

Results: Plasma concentration-time data were best described by a two-compartment model for 5-FU and one-compartment model for 5-FUH2. BSA and *MTHFR* genotype dependant total plasma clearance of 5-FU was 278 L/h for *MTHFR* 677CT or 677CC and 150 L/h for *MTHFR* 677TT genotype. 5-FU central and peripheral volumes of distribution were estimated to be 5.78 L and 39.6 L, respectively. Estimates for 5-FUH2 clearance and volume of distribution were 119 L/h and 91.9 L, respectively. A fractional deviation of 66% (L/h) per m^2 from the median BSA was observed for 5-FU and 5-FUH2 clearance. ALC over time was appropriately described by the semi-mechanistic myelosuppression model with three transit compartments accounting for a delay between drug administration and the observed toxicity [1]. Baseline leukocyte count ($Circ_0$) and mean leukocyte transit time (MTT) were estimated as 6.88×10^9/L and 280 h, respectively. A linear model adequately described the relationship between 5-FU exposure and myelosuppression. A higher degree of myelosuppression was observed in patients receiving additional cisplatin (slope=2.82 L/mg) as compared to patients receiving monotherapy (slope=1.12 L/mg). In addition to cisplatin co-medication, myelosuppression was demonstrated to be higher in subjects with *MTHFR* 677TT genotype due

to higher drug exposure. Similarly, a greater degree of toxicity attributable to 5-FU was predicted in virtual subjects receiving the doses of 5-FU suggested in FOLFIRINOX regimen in comparison to de Gramont regimen [2, 3]. For a more realistic prediction of myelosuppression, acquiring further data on combined drugs is essential.

Conclusions: 5-FU pharmacokinetics and pharmacodynamics were found to be influenced by hereditary (*MTHFR* genotype) and demographic (BSA) factors. It is desired to further elucidate the role of *MTHFR* C677T genotype in 5-FU disposition. Cisplatin co-medication was found to significantly aggravate myelotoxicity.

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I-19: *Muhammad Waqar Ashraf* Mechanistic model to characterize the pharmacokinetics and -dynamics of subcutaneous dexmedetomidine in healthy adult volunteers

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Objectives:

Dexmedetomidine is an α2-adrenoceptor agonist [1] that has been shown to be extremely useful in the management of intractable anxiety, stress and pain in palliative end-of-life care patients [2]. It provides an adequate therapeutic benefit of pharmacological dose-dependent sedation without any risk of ventilatory depression [3], while also avoiding the inconvenient side effects associated with opioids, benzodiazepines, antidepressants or antipsychotics [4]. Dexmedetomidine has also been reported to attenuate hemodynamic and endocrinal stress responses in humans [5]. The objectives of our study included: 1. The development of a population pharmacokinetic model to characterize the kinetic profile of intravenous (IV) and subcutaneously (SC) administered dexmedetomidine, 2. The development of a population pharmacokinetic-pharmacodynamic model to explain the inhibition of norepinephrine (NE) and epinephrine (E) production *in vivo* and, 3. The development of a population model to predict the effect of diminished NE release on heart rate (HR), mean arterial pressure (MAP), vigilance (VIG) and performance (PER).

Methods:

Data was gathered from an open two-period, crossover study with balanced randomization published previously [6]. Ten volunteers (aged 18 to 30 yrs) were given in 10 minutes 1 µg/kg dexmedetomidine either intravenously (IV) or subcutaneously (SC) on two occasions. Plasma dexmedetomidine concentrations were measured for 10 h after drug administration. In addition, the effects of dexmedetomidine on plasma catecholamine levels, vital signs and sedation were recorded. Nonlinear mixed effects modelling was performed with NONMEM software (version 7.4.1). First, IV and SC administration data was used to construct and validate a PK model for explaining dexmedetomidine disposition kinetics. One, two and three compartmental mammillary models were evaluated during the model development. Different absorption models were
tested to capture the trends in dexmedetomidine absorption after SC dosing. PK model was used further to develop a PD model to explain the inhibition of NE and E production caused by dexmedetomidine-induced sympatholysis. Finally, a direct effect model or an effect compartment model together with a sigmoidal Emax function was used to predict the effect of NE inhibition on other PD parameters.

Results:

A semi-mechanistic structural model was developed. A three-compartment (CMT) mammillary model was better than a two CMT model in explaining dexmedetomidine disposition kinetics [ΔOFV = -331 and -346, respectively]. Plausible parameter estimates [CL = 39 L/HR, V = 0.32 L, CL = 104 L, V = 76 L, CL = 312 L, V = 13.7 L] and visual

predictive checks (VPC) described model adequateness for the data. In the second stage, the absorption of dexmedetomidine after SC administration was captured by the addition of a fat CMT alongside depot. This assumption is supported by the high lipid solubility of dexmedetomidine (logP = 2.4). Rate constants for drug movement from the depot to SC fat layer (K,FAT), from the depot to central CMT (Ka,FAST) and from SC fat to central CMT (Ka,SLOW) were estimated. The model produced an adequate parameter estimates for the data [K,FAT = 1.9, Ka,FAST = 0.61 and Ka,SLOW = 0.083]. Next, an indirect response model was employed to explain dexmedetomidine-induced decrease in NE and E production. In the final stage, all other PD parameters that are dependent on the circulatory levels of NE and E were modelled using effect compartment model with sigmoidal EMAX function. The model parameter estimates were biologically plausible [C[50,NE] = 0.29, E[BASE,NE] = 0.80, K[OUT,SYN,NE] = 9.3, K[OUT,PER,NE] = 11, C[50,E] = 0.52, E[BASE,E] = 0.23, K[OUT,SYN,E] = 3.6] and the results were further evaluated with VPCs (Figure) and bootstrap resampling.

Conclusions:

The pharmacokinetic-pharmacodynamic model developed in this study adequately describes the pharmacokinetic profile of intravenous and subcutaneously administered dexmedetomidine in healthy human volunteers, along with accurately predicting the inhibition of norepinephrine and epinephrine production *in vivo* due to dexmedetomidine challenge, as well the inhibitory effect of reduced catecholamine production on heart rate, mean arterial pressure, vigilance and performance of the study subjects.

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I-20: *Magnus Åstrand* nonmem2R: An R-package for Visual Predictive Checks and Goodness-of-fit Plots

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Objectives:

nonmem2R is an open-source R-package, freely available on CRAN[1]. On top of the main functionality of the previous version, Visual Predictive Checks (VPC) plots and functions to extract parameter estimates from NONMEM[2] and PSN[3] generated output files, the functionality has been extended with Goodness-of-fit (GOF) plots.

Methods:

The plotting functionality in nonmem2R builds on the R-packages ggplot2[4] and as far as possible return ggplot-objects that can be further modified by adding ggplot formatting. The GOF functions use a default graphical setting to provide GOF's of similar appearance with a minimum input. Each GOF plot will have a red dashed reference line and blue solid lines are smoother's representing the actual data when applicable. The default setting can easily be modified to affect all GOF's within a script including captions text to indicate source script for each generated graph. The GOF function assume a data-frame as input as returned by e.g. read.table when reading a NONMEM $TABLE output file.

Results:

The package has a set of tailored functions to provide basic GOF plots for NONMEM generated output files.

- Basic.GOF4 will provide a summary GOF of population and individual predictions vs observations together with conditional weighted residuals (CWRES) untransformed as well as transformed by square root of the absolute value, both plotted vs TIME by default. The square root of the absolute value CWRES is indented to explore for a trends of heteroscedasticity.

- Basic.GOF6 provide the same set of graphs as basic.GOF4 with 2 additional GOF's for the distribution of CWRES by histogram and normal quantile plot.

- do.individual.GOF will provide GOF plots of PRED, IPRED and DV vs TIME with one panel per subject This will generate one page/plot per 20 subjects (default) and therefore this function is best used when exporting to a PDF.
- There are 4 tailored functions for doing GOF plots for ETA's: basic.eta.GOF, eta.cov.GOF, eta.cat.GOF, and eta.pairs.GOF. These functions identify all ETA's in the input data-frame and provides different types of GOF plots for these columns. All 4 functions will by default exclude ETA's which are constant i.e. when set as FIX in your NONMEM model and each ETA is scaled to unit variance.

All GOF's have arguments to change from the default setting, e.g. to have time after last dose (TAD), or any column in the input data-frame, on x-axis instead of TIME; exclude the loess smoother; or drop the reference line.

It is also possible to add ggplot formatting to each sub GOF before combining into one single graph, e.g. adding the ggplot function facet_wrap(~SEX) to basic.GOF4 will make each of the 4 GOF plots stratified by gender in two separate panels.

Along with the above tailored functions there are a set of GOF building blocks from simple x-y-GOF plots to histogram and normal quantile GOF plots. The GOF building block functions can be used together a set of GOF builders to define new tailored GOF's and maintain the graphical settings.

GOF plotting functions will by default add a caption in the bottom of the graph to indicate date when figure was generated together with the full path to the script. However, this require that the script name has been set.

Furthermore, all GOF functions make use of the control argument for formatting of e.g. lines, plot symbols, histogram bars, caption text. Axis labels are set according to a default dictionary for the most common NONMEM columns e.g. CWRES is by default labelled "Cond. weighted res" and TAD is by default labeled "Time since last dose(hrs)". The dictionary can be extended and or modified with e.g. "Time after first dose (days)" for the variable `TIME` in case the unit is days.

Conclusions:

With the addition of easy to use yet flexible functions for GOF plots nonmem2R now can produce the vast majority of graphics for model evaluation.

References:

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I-21: *Ioanna Athanasiadou* Hyperhydration effect on pharmacokinetic parameters of recombinant human erythropoietin in urine and serum doping control analysis

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Introduction/Objectives: Excessive fluid intake, i.e., hyperhydration may be adopted by athletes as a masking method during anti-doping sample collection to influence the excretion patterns of doping agents and, therefore, manipulate their detection [1]. The aim of this exploratory study was to assess the hyperhydration effect on serum and urinary pharmacokinetic (PK) profile and detection sensitivity of recombinant human erythropoietin (rHuEPO)in athletes [2].

Methods: Seven healthy physically active non-smoking Caucasian males were participated in a 31-day clinical study comprised a baseline (Days 0, 1–3, 8–10) and a drug phase (Days 15–17, 22–24, 29–31). Epoetin beta was administered subcutaneously at a single dose of 3000 IU on Days 15, 22 and 29. This provided a total of 259 blood samples. Hyperhydration was applied in the morning on three consecutive days (Days 1–3, 8–10, 22–24, 29–31), i.e., 0, 24 and 48 hours after first fluid ingestion (water and a commercial sports drink, 20 mL/kg BW). Population PK modeling was performed on the measured serum concentrations after rHuEPO administration using Monolix® software version 2018a (Lixoft, Batiment D, Antony, France), while non-compartmental analysis (NCA) PK analysis was performed on the measured serum and urinary EPO concentrations using the Phoenix® version 8.0 PK/PD software package (Certara, Princeton, NJ, USA). One and two compartment models together with various absorption models which included zero and first order, separately and combined, with and without lag time, as well as different error models were tested. Interindividual variability (IIV) was considered as univariate log-normal for all the parameters. Age and BW were tested as covariates on the parameters of the final model.

Results: Serum EPO concentration-time profiles were best described by a one compartment (1-CP) PK model with zero order absorption, parameterized as total clearance (CL), volume of distribution (V_d) and time for zero order absorption. An EPO constant baseline parameter, to account for the endogenous EPO concentration which is measured with the exogenously administered rHuEPO, was introduced. Delayed absorption was observed after hyperhydration and, therefore, lag time was introduced in the PK model. A multiplicative residual model error was used in all cases. No covariates were found to improve the base model, probably due to the small number of individuals enrolled in the study. Regarding the estimated PK(RSE%) parameters, apart from the observed delayed absorption, with T_{lag} 1.4(33.3) h and 0.7(31.3) h after water and sports drink hyperhydration, a trend for decreasing V_d from 63.1(27.2) L to 53.4(29.1) L and 24.7(37.2) L and increasing CL from 0.775(14.6) L/h to 2.22(40.8) L/h and 2.03(25.5) L/h after hyperhydration was observed, mainly after sports drink consumption. The respective IIV(RSE%) was 59.3(46.5) and 39.1 (76.3) for T_{lag} (water, sports drink hyperhydration), 67.1(29.9), 66.2(34.7) and 80.3(33.3) for V_d (baseline, water, sport drink hyperhydration), and 14.5(73.3), 98.2(33.5) and 63.1(29.9) for CL (baseline, water, sport drink hyperhydration). The residual error was less than 30% in all cases. No significant difference (P>0.05) due to hyperhydration for any of the serum PK parameters calculated by NCA was observed. Results showed no significant difference (P>0.05) on serum or urinary EPO concentrations under hyperhydration conditions. Renal excretion of endogenous and rHuEPO, as reflected on the urinary

cumulative amount, was increased approximately twice after hyperhydration and this supports the non-significant difference on the urinary concentrations.

Conclusions: Serum and urinary EPO concentration-time profiles remained unaffected after excessive fluid intake (water or sports drink). Serum and urinary PK parameters of a WADA prohibited substance were utilized for the first time in conjunction to the urinary concentration-time profiles as a tool for doping detection. NCA analysis was applied to calculate basic PK parameters, while compartmental PK modeling was necessary for the accurate estimation of EPO serum CL considering the existence of the endogenous EPO levels. Analysis of serum and urine samples was able to detect rHuEPO up to 72 hours after drug administration. The detection window of rHuEPO remained unaffected after water or sports drink ingestion. Hyperhydration had no effect on the detection sensitivity of EPO either in serum or urine samples.

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I-22: *Linda Aulin* Physiologically-based pharmacokinetic model to predict lung distribution of anti-infective agents

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Introduction: Bacterial respiratory tract infections (RTIs) are associated with high mortality and are the leading cause of infection-related death worldwide[1]. Substantial differences between plasma concentrations and concentrations in the lung may exist for antibiotics, which may require adaptation of dose regimens for RTIs to reach optimal efficacy and to prevent emergence of antimicrobial resistance. The pharmacologically relevant target sites of antibiotics in the lung are the epithelial lining fluid (ELF) and alveolar macrophages (AMs), as these represent the focus of extracellular and intracellular bacterial lung infections respectively. While the concentrations in the ELF and AMs can be determined using bronchoalveolar lavage (BAL) sampling, there are significant limitations to this invasive technique. One approach which has been used in several therapeutic areas, including anti-invectives, is to *in silico* predict drug concentrations for different tissues by the use of physiologically based pharmacokinetic (PBPK) models[2].

Objectives: Although PBPK models describing the lung have previously been developed, no model explicitly including the clinically relevant compartments for RTIs has been published. To this end we aimed to develop a PBPK model for drug distribution to clinically important lung compartments, such as the ELF and AMs, with particular focus on anti-infective agents, and to evaluate its predictive performance.

Methods: A whole body PBPK model was expanded with a detailed multi-compartmental model structure representing the lungs. The lung section of the model was permeability-limited, while the remaining tissues were implemented according to a perfusion-limited model. For the lung model, we considered both lungs separately and considered three different lung zones, thus accounting for the spatial differences in perfusion and volume within the lung. The ELF and AMs were explicitly included in the model, thereby allowing for concentration predictions for theses clinically relevant compartments. Active transport was considered for the alveolar epithelium and AMs. As a proof-of-concept, we focused on prediction of lung distribution of the commonly used fluoroquinolone antibiotics ciprofloxacin, moxifloxacin, grepafloxacin, and levofloxacin. The model was used for predicting concentrations in plasma, ELF, and AMs, and the model predictions were subsequently compared to clinical BAL pharmacokinetic studies.

Results:

The model predicted plasma concentrations were in agreement with the clinical data for all the fluoroquinolones, with mean absolute percentage errors (MAPE) ranging between 7.11 and 23.4%. ELF concentrations of ciprofloxacin and levofloxacin were well-predicted (MAPE 29.7% and 40.15% respectively). Concentrations for moxifloxacin and grepafloxacin concentrations in ELF were under-predicted (MAPE 70.4% and 82.2% respectively), which is likely associated with limitation in *in vitro* assays quantifying active transport. AM concentrations were predicted for levofloxacin, ciprofloxacin, and grepafloxacin with MAPEs of 20.5%, 58.3%, and 45.7% respectively. No AM concentration data was available for moxifloxacin.

Conclusions: The developed lung PBPK model allows prediction of lung distribution into ELF and AMs of antibiotics based on their physiochemical properties, and could be of interest to investigate the effect of specific pathological lung conditions on antibiotic lung disposition. The PBKP model could thus constitute a tool to aid in improving antibiotic treatment of RTIs for existing drugs, with the possibility to consider special populations and pathophysiological changes, and inform drug development.

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I-23: *Ahmad Rami Ayoun Alsoud* Simultaneous Assessment of Time-to-positivity and Colony-forming Unit in tuberculosis patients under high-dose rifampicin therapy

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Objectives:

Colony forming unit (CFU) counting on solid agar has been used for more than three decades to measure anti-tuberculosis (TB) drug activity in sputum samples before, during, and after treatment. *Mycobacterium tuberculosis* has been hypothesized to exist in three states: fast-, slow- and non-multiplying i.e. persisters. Studies have shown that CFU only detects fast- and slow-multiplying subpopulations [1]. An alternative biomarker, time-to-positivity (TTP) in liquid medium (Mycobacterial growth indicator tube; MGIT), has been developed. In comparison to CFU, TTP is more sensitive as it is known to be reflective of more TB subpopulations than only the fast and slow states. The relationship between the CFU and TTP is not well characterized. Describing this relationship could allow the prediction of one biomarker using prior knowledge of the other. This is especially useful as TTP is a cheaper and less labour-intensive biomarker when compared to CFU. Furthermore, taking into account the three mycobacterial subpopulations enables the capture of the non-multiplying 'persistent' population thought to be responsible for late TB relapse.

The objective of this paper was to identify the relationship between TTP and CFU in rifampicin-treated TB patients and to develop a framework for predicting one of the biomarkers using the data from the other.

Methods:

Clinical trial data was obtained from the PanACEA HIGHRIF1 trial where an escalating dosing of rifampicin starting with 10 mg/kg and up to 40 mg/kg was used [2]. The trial included 83 previously untreated subjects with uncomplicated pulmonary tuberculosis and treatment lasted for 14 days, of which the first 7 days with rifampicin monotherapy were used. Initially, a CFU sub-model was developed by applying the Multistate Tuberculosis Pharmacometric (MTP) model [3,4], which was linked to the PK model from *Svensson et al* [5] in order to incorporate drug exposure response. All MTP disease model parameters were fixed except for a patient-specific B_{max}, which controls the initial bacterial load and allows for the adjustment of the individual CFU baseline. Exposure-response relationships were evaluated on bacterial growth and killing of different bacterial sub-states. Subsequently, the CFU sub-model was linked to the TTP sub-model by *Svensson et al* [6] to generate the final CFU-TTP model. Initially, all parameters for this sub-model were fixed except the TTP B_{max}, which is a liquid culture-specific parameter that controls the bacterial growth in the MGIT tube, and a hazard scale parameter. Model selection and evaluation were done using the objective function value (OFV), parameter uncertainties and diagnostic plots e.g. visual predictive checks (VPC). All modeling and simulation were performed in NONMEM version 7.4 (ICON, Hanover, MD, USA) along with R statistical software version 3.5.1.

Results:

During model building, the CFU baseline parameter (patient-specific B_{max}) was estimated along with the inter-individual variability (IIV) in B_{max}. Moreover, drug effect on the fast-multiplying subpopulation was best described using an on-off effect for growth with no effect on its death rate. On the other hand, an E_{max} model was the best descriptor of the kill rate of the slow-multiplying (semi-dormant) subpopulation as well as the inclusion of IIV in the E_{max} parameter. As for the non-multiplying (persisters) subpopulation, a linear kill model with IIV in slope was selected. The liquid culture-specific TTP B_{max} and hazard scale parameters were also estimated during the CFU-TTP model building. Based on the aforementioned model evaluation tools, the final CFU-TTP model was shown to successfully predict the data.

Conclusions:

The CFU-TTP model was successfully developed using human clinical data. This model serves to link the two biomarkers CFU and TTP into one framework which further serves to predict one of the two biomarkers from the other in clinical trial simulations.

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I-24: *Geraldine Ayral* Straightforward dose adaptation simulations with Simulx, the simulator of the MonolixSuite

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Objectives: Therapeutic drug monitoring (TMD) is increasingly advocated in clinical practice. Most of the time, target concentration windows are established using retrospective studies [1]. To better assess the value of TMD, clinical trials are required. Simulation of clinical trials including TMD and dose adaptation can greatly help to better design those trials and maximize their probability of success.

However, the implementation of such simulation with standard simulation tools can be cumbersome, as it requires the user to run a first simulation, analyze the results and decide for a new dose, run a simulation again, etc. The procedure can be further complicated if the simulation and analysis are done with different applications.

We propose a doseAdaptation() function as an extension of the simulx function from the mlxR R package (http://simulx.webpopix.org/) for simulation (which is part of the MonolixSuite) to automatize the simulation of therapeutic drug monitoring and dose adaptation.

Methods: The doseAdaptation() function works as an extension of the simulx function, which permits to easily simulate clinical trials.

In addition to the usual simulx arguments needed to define a simulation (model, population parameters, number of individuals, covariates, outputs), the doseAdaptation() function requires the definition of an initial treatment and one or several adjustment rules:

- Initial treatment:
  - Dose
  - Inter-dose interval
- Rule(s):
  - The model variable on which the rule applies (for instance the drug concentration)
  - The type of the model variable (continuous or event)
  - The condition that should be checked (for instance the comparison of the measured concentration to a threshold)
  - The time point(s) at which the measurements are made and the condition is checked
  - How to adapt the dose if the condition is not met: by increasing/reducing the dose by a certain factor (multiplicative) or a certain value (additive)
  - The factor or value by which the dose should be increased or reduced

Results: The use of the doseAdaptation() function is shown on two examples.

In the first example, we simulate a clinical trial with dose-adaptation of everolimus. Everolimus is a promising candidate for TMD [2] as there is evidence for the relationship between exposure, safety and efficacy [3,4,5]. We reuse published models for the pharmacokinetics and exposure-toxicity relationship to develop a joint PK-TTE model taking into account the pharmacokinetics and the adverse events whose hazard is related to the exposure. The model is used to simulate a clinical trial with two arms: one where

dose adaptation (reduction) is only done if toxicity events appear, and one where dose adaptation is performed following therapeutic drug monitoring and adverse events. Using simulation replicates, the power of the study can be estimated for different numbers of patients per arm.

In the second example, we compare the sample size needed to achieve a given power for dose-controlled trials (arms are defined by a given dose) versus concentration-controlled trials (arms are defined by a given plasma concentration). As effect is usually related to the concentration or exposure, concentration-controlled trials are expected to have a higher power [6]. We investigate this hypothesis using a typical PK/PD model with Emax response.

Conclusion: The doseAdaptation() function allows to easily simulate dose adaptation following therapeutic drug monitoring by defining adaptation rules for continuous variables or events in a flexible and efficient way. This allows to explore “what if” questions or plan the design of clinical trials.

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I-25: *LE Ba Hai* Population pharmacokinetic model of sorafenib and application to a case report

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Introduction: High inter- (61-65%) and intra-individual (44-47%) variability in pharmacokinetics (PK) of sorafenib was observed during phase I studies, as well as in some population pharmacokinetic (pop-PK) studies, which could explain the unstable response and the unintended toxicities that occur in some patients under a recommended dosage of sorafenib [1-4]. Therefore, we aimed to develop a sorafenib pop-PK model based on a large population treated by sorafenib during a long period. This pop-PK model will be used to predict sorafenib plasma PK based on sparse therapeutic drug monitoring using Bayesian approach, then to explore the relationship between sorafenib plasma exposure and toxicity outcome in patients from La Timone hospital.

Method: Sparse PK data available from 267 patients treated with sorafenib between 2008 and 2018 in have been included in this multicentric study (10 French hospitals). The daily dosing of sorafenib doses ranged from 200 to 5200 mg in a b.i.d regimen. The PK data were analyzed using nonlinear mixed-effect modeling (NONMEM software version 7.3). Model evaluation was performed using standard goodness-of-fit plots, and simulation-based tools such as visual predictive check (VPC).

The final pop-PK model was applied to provide explanations for the onset of severe sorafenib-related toxicities in one patient, then to evaluate the rationale of the associated empirical dose reductions in this patient. The individual parameters were estimated using Bayesian method in NONMEM and used to simulate the exposure to sorafenib over the course of the treatment in R studio.

Results: All 1310 plasma concentrations came from the clinical routine practice and were collected at steady-state. The follow-up of patients lasted between 15 and 1997 days (5.5 years). A 1-compartment structural model with first-order absorption and linear elimination described the data satisfactorily. Bioavailability (F1) was found to vary as a function of the dose and to decline over time on sorafenib treatment, as described by the following equation: F1=(Fmax-(Fmax*DOSE^n)/(D50^n+DOSE^n))*exp(-lambda*TIME/720). Typical values (RSE %) of the final model parameters were as follows: clearance (CL) 4.91 L/h (4%), distribution volume (V) 177 L (12%), absorption rate constant (ka) 0.727 h^{-1} (28%). The high inter-patient variability was confirmed in this study with 46.5 % for CL (46.5%), V (73.2%) and ka (150%). The lack of information regarding the absorption phase and covariates such as food intake may account for the extremely large variability of ka.

Based on the final pop-PK model, the individual parameters of the patient were estimated and used to describe the PK of sorafenib over the course of the treatment. The steady-state AUC from 0 to 12h (AUC_{0-12}) post dose was calculated: values of 99.85, 82.83 and 57.70 mg*h/L were obtained with the dosages 800mg/24h, 400mg/24h and 200mg/24h respectively. These values are particularly high when compared to the mean AUC_{0-12} of 57.7±28.6 mg* h/L obtained in patients experiencing grade 3–4 adverse events in a previous study [4] and are consequently consistent with the observed severe toxicities. These results document the decision to continue reducing the sorafenib dose by expanding the time between doses with the 200mg dosage.

Conclusion and perspectives: The high unexplained inter-individual variability in our population could be partly explained by covariates that will need to be collected in further prospective studies. However, the established population model allows reliable prediction of pharmacokinetics based on Bayes estimation. The population model could be used in the context of therapeutic drug monitoring to support dose adjustments in patients.

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I-26: *Junjie Ding* Pharmacometric drug adherence approach and its application in a clinical setting

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Introduction: Adherence to medication is crucial for expected treatment outcomes. Poor adherence can result in sub-optimal drug exposure, thereby increasing the risk of treatment failure. Furthermore, poor adherence in many disease areas can cause resistance development, resulting in both patient specific and population health risks. Although a number of approaches have been developed to access treatment adherence in patients, many of them are not robust enough to be used as standard methods [1]. Population pharmacokinetic-based approaches [2,3], in which levels of drug and/or its metabolite are measured to assess the adherence, are objective approaches which should be able to identify if a patient has taken the medicine without asking the patient or counting tablets. However, the accuracy of these methods needs to be evaluated before application in a clinical setting.

Objectives: The aim of this project was to evaluate the predictive performance of two population pharmacokinetic-based approaches (the percentile and the Bayesian method) for adherence assessment in a clinical setting of malaria therapeutics.

Methods: A drug with first-order absorption and 1-compartment disposition kinetics was used as the basis for the simulation study and was assumed to be administered once daily for 3 days. Stochastic simulations (n=2,000) were performed for all possible dosing scenarios, from full adherence to complete non-adherence. Two different methods to evaluate adherence were investigate:

1. The percentile method, in which different cut-off concentrations (e.g. 5th percentile of predicted concentrations) were calculated based on the simulations from the full adherence scenario. A simulated concentration at time *t* below the generated cut-off value was considered as non-adherence to the treatment.
2. The Bayesian approach, in which the posterior probability was calculated at a given concentration according to conditional probability and the prior equiprobable probability. The most plausible dosing scenario of a given concentration at time *t*, is the one with the largest posterior probability among all scenarios.

The predictive performance of these methods was evaluated by assessing sensitivity, specificity, Youden's index, as well as by evaluating the receiver operating characteristic (ROC) curves. In addition, the impact on predictive performance of different magnitudes of inter-subject variability, and more complicated structure models were investigated. Finally, the best performing method was used to assess the adherence to an antimalarial drug in a programmatic setting in Africa.

Results: For the one-compartment disposition model, the highest Youdex's index as well as ROC AUC was observed at Tmax and were reduced with increasing time. The predictive performance of the Bayesian approach was similar to the percentile method when investigating the adherence of the last dose (assuming full adherence for the first two doses), but the percentile method was superior when investigating the adherence at all other dosing scenarios. Different magnitudes of inter-subject variability

had an impact on the predictive performance of both approaches, resulting in lower Youdex's index and ROC AUC in the event of higher variability. For the percentile method it was found that a higher percentile cut-off value (e.g., 20-30%) was preferred when the inter-subject variability was high (60%). Using a two-compartment disposition model resulted in the same findings and conclusions as that found with a one-compartment model. When applying the percentile method to a clinical trial of distributing seasonal antimalarial prophylactic therapy and collecting one drug concentration, the method predicted full adherence in less than 20% of the children.

Conclusions: The two population pharmacokinetic-based approaches investigated here, showed satisfactory predictive performances, but the percentile method was superior when investigating more than one missing dose. The percentile method was also successfully applied in a clinical trial setting of an antimalarial drug.

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I-27: *Vanessa Baier* Assessing the cholestatic potential of drugs using a physiology-based model of the bile acid metabolism

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Objectives: Cholestasis is a major clinical manifestation of drug induced liver injuries (DILI) characterized by an impaired bile flow. In consequence, bile acids (BAs) accumulate in the liver and other tissues ultimately leading to clinically diagnosable symptoms. BA metabolism is a systemic process that involves the interplay of multiple tissues along enterohepatic circulation including the gastrointestinal tract and the liver. Due to the many processes involved in BA distribution a mechanistic understanding of the events underlying drug-induced cholestasis is challenging to achieve [1]. Computational modelling bears the chance to significantly contribute to a comprehensive description of BA metabolism and its interplay with drugs. For this purpose, the ability of these models to compile existing knowledge in a mathematical representation, to simulate tissue concentration profiles which are experimentally inaccessible, and to formulate hypotheses to be specifically addressed in further experimental studies are of great use. We here present the application of a previously developed physiology-based bile acid (PBBA) model [2] for the quantification of the cholestatic risk of different known hepatotoxicants.

Methods: The PBBA model was based on well-established concepts from physiology-based pharmacokinetic (PBPK) modelling and built with the Open Systems Pharmacology Suite [3]. It was initially informed by clinical plasma BA measurements and subsequently used for the prediction of changes in body BA levels after drug administration in healthy individuals as well as in patients with a high-risk genotype [2]. In the presented approach, adaptation of the liver in response to repeated drug administration was investigated in a PBPK-informed *in vitro* assay setup with liver spheroids for 10 known hepatotoxicants [4]. For each compound, a simulated drug PK profile was used to determine *in vivo* drug exposures at liver tissue. These drug profiles were then transferred to *in vitro* assay concentrations in an assay with human liver spheroids to reproduce physiologically relevant drug levels for up to two weeks. It was thus possible to track changes in the expression of drug-ADME genes and to include this in the PBBA model.

Results: Transcriptomics were generated from liver spheroids reflecting the adaptation of liver tissue in the face of up to two weeks of drug exposure. The measured mRNA fold changes of CYP7A1, bile salt export pump (BSEP), and NTCP were dynamically integrated into the PBBA model to simulate the changes of BA levels in various tissues after drug administration. The drugs were then ranked according to the resulting average BA levels in different body compartments. In a complementary approach, plasma BA levels were measured from patients hospitalised after a DILI event and ranked according to their cholestatic risk. Using these clinical data for the overlapping set of drugs as a benchmark we identified the venous blood compartment in the PBBA model as the one showing the highest agreement with patient measurements. This correlation was higher than for the case of BSEP fold changes, which is frequently used as an experimental marker for cholestasis. We thus obtained a full ranking of all 10 investigated drugs with

respect to their cholestatic potential. In agreement with a previous study [5], the results suggest that plasma BA levels might not be representative for tissue BA levels where changes can be more severe than in the plasma.

Conclusions: Our results show that the contextualisation of specifically-generated *in vitro* data in the model provides mechanistic insights which would otherwise not have been accessible. PBPK modelling is particularly suited for such detailed analyses since it allows the integration of heterogenous *in vitro* and other preclinical data. The prospective design of an *in vitro* assay with physiologically relevant tissue concentrations simulated with drug-specific PBPK models significantly supported these analyses. It could be shown that the PBBA model with the contextualised assay data reveals better insight than for example simple *in vitro* transport assays of BSEP. Also, our model based-analyses enhance the mechanistic understanding of the occurrence of drug-induced cholestasis. Our approach could therefore in the future provide a platform for advanced preclinical testing in pharmaceutical development programs with lower incidence rates of cholestatic DILI as such enhancing patient safety and in consequence success rates in pharmaceutical development.

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I-28: *Pavel Balazki* A mechanistic model of gastric emptying of caloric liquids and solids for the use in physiologically-based pharmacokinetics models.

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Objectives: The rate of emptying of gastric contents into duodenum defines the availability of orally administered drugs for their absorption and, therefore, has a major impact on the pharmacokinetics (PK) of highly soluble and permeable substances (1). Physiologically-based (PB) PK models rely on correct description of gastric emptying (GE) to predict the bioavailability of drugs, as do models of glucose homeostasis, such as the PB Quantitative Systems Pharmacology (QSP) Diabetes Platform (2,3), when predicting appearance of glucose from ingested meals. The GE is controlled by various processes, whereby the caloric density of the contents seems to be the driving factor (1). Available GET models usually do not distinguish between the energy sources (carbohydrates (CHO), lipids, or proteins) and describe GE by non-mechanistic functions (Open Systems Pharmacology Suite (OSPS)) (4) or do not consider emptying of solids (5).

Our objective is to develop a mechanistic model of GE for solids and liquids that is able to describe the effects of different meal compositions and integrate it into the PB QSP Diabetes Platform.

Methods: The model of GE is based on the PBPK model of PK-Sim® as part of the OSPS, version 7.2 (4). Data on either gastric emptying or gastric retention of unabsorbable marker administered together with water (6–11), glucose (6,8,12–15), lipid (6), or protein (6,7) solutions, or liquid mixed meal (6,7,12,16,17) were used to define model structure and identify parameter values for GE of liquids. Transfer of solids was parametrized by fitting the model to GET data from (18,19). Only data gathered by the scintigraphy or magnetic resonance imaging methods were used.

Results: In the final model, the standard stomach representation as modeled in PK-Sim® was divided into proximal and distal parts. Approximately 1/3 of ingested liquid volume is applied directly to the distal part, whereas 2/3 are applied to the proximal part and transit to the distal part in exponential manner. From the distal part of the stomach, the liquid phase is released into the duodenum, where CHOs are absorbed (saturable transporter mediated uptake). Absorption of lipids and proteins is not modeled as it is probably negligible in duodenum. CHOs, lipids, and proteins in liquid phase (i.e., dissolved) have inhibitory effects on proximal-to-distal and distal-to-duodenal transfer rates, modeled using Hill-equations. Solids from the proximal part of the stomach are transferred to the distal part at a different rate than liquids, the same is true for the distal-to-duodenal transfer. Solids are digested and dissolved to liquid form in the duodenum.

GE of non-caloric liquids changes according to the different phases of the interdigestive migrating myoelectric complex (IMMC). To adequately describe GE of low-caloric liquid meals, transition into the quiescence phase of the IMMC from the fed state was implemented.

The model successfully describes patterns of GE of multicomponent liquid and solid mixed meals, with the majority of simulated points deviating less than 10% from the observed values. The GET model was integrated into the previously described PB QSP model of incretins (20) and parametrized with data from intraduodenal glucose infusion experiments. Coupling of the models resulted in good prediction of incretin hormones' response to oral glucose administration (data from (21)).

Conclusion: We present a refined mechanistic model of GE that incorporates the distinct effects of CHO, lipids, and proteins and explicitly considers liquid and solid phases of the administered meals. Such a model can significantly improve accuracy of generic drug bioavailability predictions when the influence of meal composition and different phases of the IMMC are investigated with PBPK modeling. As part of the PB QSP Diabetes Platform, the new GE model allows simulation of complex (sub sequential) meal patterns including a detailed characterization of glucose absorption and the dependent dynamics of incretin hormone secretion and subsequent insulin secretion.

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I-29: *Violeta Balbas-Martinez* Quantitative Systems Pharmacology model for the key Interleukins involved in Crohn's Disease

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Introduction:

Crohn's disease (CD) is a complex inflammatory bowel disease, which causes a functional impairment of the gut wall leading to abdominal pain, severe diarrhoea, fatigue, weight loss and malnutrition(1). The reported lack of effectiveness in the standard of care(2) together with the worldwide increase in CD incidence(3) require the application of techniques aiming to find new targets and therapeutic strategies. At this point, systems pharmacology (SP) modelling gains importance as the available knowledge can be integrated into a single computational model.

Objectives:

To develop a SP model in humans characterizing the dynamics of the main interleukins (ILs) involved in CD using previous modelling efforts as starting point(4–7), and incorporating new relevant molecular pathways in CD.

Methods:

We followed the six-stage workflow for robust application of SP modelling(8) to standardize the quantitative SP (QSP) model building: (i) identify main project goals; (ii) selection of species and literature search for blood levels to define their average profile in healthy subjects (HS) and CD patients; (iii) representation of model topology and parametrization of the interactions using data extraction and curation. ILs' kinetics were characterized by zero-or first-order synthesis (ksyn) and first-order degradation (kdeg). Constant levels for ILs and cells at the steady state (SS) of HS and CD were assumed for synthesis rate constant derivation. To parametrize the IL interactions (stimulation/inhibition of synthesis), different sub-models were tested using nls in R. Model selection was based on the akaike information criterion. As an example, IL12 parametrization and ODE building would be explained in detail, including the assumptions made. Ordinary differential equations (ODEs) were implemented in SimBiology®(MATLAB®vR2018b)(9) to mathematically describe the time course of the system components' levels in blood. Afterwards, (iv) 1000 stochastic simulations, where the ILs and cells initial conditions were randomly fixed from uniform distributions (between the literature reported ranges in CD) were run and evaluated by visual comparison of ILs concentration with their reported levels. Then, (v) the exposure to two doses of recombinant human IL10 (rhuIL10) from a clinical study was simulated(10). Finally, (vi) the next steps were defined.

Results:

A total of 21 species representative of the innate and adaptive immune response in CD were included. Those species were (i) activated macrophages, dendritic cells and CD4+ T cells, (ii) CD4+ T cells subtypes (Th2, Th1, Th17 and Treg), (iii) pro-inflammatory ILs (IFNg, TNFa, IL12, IL23, IL6, IL1b, IL17, IL22, IL18, IL4, IL2 and IL15) and (iv) regulatory ILs (IL10 and TGFb1). Individual graphical representations were generated per

IL, and subsequently, integrated into one single figure of the whole model providing a big picture of model structure.

The developed QSP model included 14 ODEs and 98 parameters. Generally, each IL kinetics is ruled by three key parameters: 'kdeg, 'ksyn' in the basal healthy state and 'ksyn' drived by antigen presenting cells stimulated in CD, which were modulated by other model components. ILs degradation parameters were obtained from the literature(11–13), whereas those referring to synthesis modulation were estimated using in vitro data. IL10, TGFb1 and IL6 presented larger differences in their levels when comparing HS with CD patients. TNFa, IFNg and IL12 were the most complex interleukins, with up to 8 interleukins regulating their synthesis.

We obtained a quantitative reproduction of CD showing the model performance accuracy. Radom values between the physiological range of the model components did not produce non-physiological SS levels for any of the ILs. Furthermore, the simulated exposure to rhuIL10 showed a reduction of IFNg, IL18 and TNFa towards HS at the lower dose which was in agreement with the general outcome of the clinical study.

Conclusions:

We present a QSP model for the main ILs involved in Crohn's disease. Not only is supported by a comprehensive repository summarizing the most relevant literature in the field, but also by a standardized methodology for QSP model building. This model proved to be promising for the *in silico* evaluation of potential therapeutic targets and the search for specific biomarkers. Finally, it can be expanded or reduced as demanded, leading to different quantitative model/s to address research gaps regarding CD.

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I-30: *Irina Baltcheva* ggPMX: an open-source R package for pharmacometric model diagnostic plots

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Introduction:

ggPMX is an open-source R package freely available on CRAN since April 2019. It builds on the R-package ggplot2 and provides a library of reproducible diagnostic plots needed for longitudinal population model building and validation. The package aims at providing a workflow that is consistent and efficient, resulting in high quality graphics ready-to-use in submission documents and publications. Intuitive functions and options allow for optimal figure customization and graphics stratification. ggPMX enables straightforward generation of PDF, Word or PNG output files that contain all diagnostic plots for keeping track of modeling results. The package is currently compatible with Monolix versions 2016 and 2018R1.

Methods:

ggPMX implementation uses object-oriented programming, which allows having code that is modular and easy to customize. The architecture consists of the following four components:

- **Reader** - reads model outputs from different sources (i.e. text files containing population parameters, model predictions, individual random effects, simulations and data-related inputs like covariates) and restructures these outputs into standard formats, which can be easily processed by the Generator.
- **Generator** - processes outputs from Reader and produces the diagnostic plots. A set of default plots is defined in a configuration file. The configuration file can be adapted, e.g., to have different configurations for different types of modeling activities (health authority submission, publication, internal report).
- **Controller** - serves as user interface. The user will call Generator functions via the Controller to produce either the default plots or customized versions.
- **Reporter** - generates sets of graphs and tables as individual PNG files and integrates them all into one single output document (Word or PDF) with annotations pointing to the locations of the individual PNG files. The report generation is based on Rmarkdown, which enables the user to create his own report template.

The most important task for the user is the Controller creation. This is the step where the user defines which model variable and which covariates to consider for the diagnostic session. All these settings can be defined manually, or can be automatically parsed from a Monolix project file (.mlxtran). Once the Controller is created, the user can display the graphs by calling pre-defined functions. The same syntax is used independently of the model structure or of the fitting software.

Results:

Using simple syntax, the toolbox produces various model diagnostics such as residual- and empirical Bayes estimate (EBE)-based plots, distribution plots, prediction- and simulation-based diagnostics (visual predictive checks). In addition, shrinkage and summary parameters table can be also produced. By default, the output file generated by the Reporter contains essential goodness-of-fit plots. However, these can be adapted to produce different sets of diagnostics as desired by the user, and any of the plots may be customized individually. The types of supported customizations include modifications of the graphical parameters, labels, and various stratifications by covariates.

Conclusions:

The ggPMX R package generates standard diagnostic plots for mixed effect models used in pharmacometric activities. The tool is built upon ggplot2 and currently supports models developed with Monolix 2016 and 2018R1. Future plans are to enhance ggPMX to support Monolix 2019, nlmixr and NONMEM outputs. ggPMX is now ready for inputs and enhancements by the pharmacometric community.

I-31: *Maddlie Bardol* Population pharmacokinetics of fentanyl in very preterm infants

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Objectives: The aim of this work was to develop a population pharmacokinetic model for a new formulation of fentanyl 5 µg/mL in preterm infants.

Methods: This PK study is part of a PK/PD/PG study designed to optimize fentanyl dosage for procedural pain in newborn preterm infants. 25 infants born with gestational age between 23.3 and 30.7 weeks were included. They received 0.5 µg/kg before skin-breaking procedures or 2 µg/kg before tracheal intubation. Physiologic parameters were monitored. The median gestational age and weight were 27 weeks and 0.85 kg, respectively. Population pharmacokinetic modelling was undertaken with NONMEM 7.4. One-, two- and three-compartment structural models were tested to define the basic structural model and size and age were tested as covariates. Body weight and postmenstrual age (PMA) were included in the model using an allometric weight scaling and a sigmoidal maturation function, respectively [1]. The value below the limit of quantification (12%) were included using the M3 method. The final model was validated using prediction corrected visual predictive check (PC-VPC).

Results: A two compartment model with allometric scaling and fixed maturation function adequately described fentanyl concentration in this specific population. The estimates of the PK parameters (standardized to 70 kg) were: Clearance (CL) = 55.7 L/h (CV 18%), central volume of distribution (V1)= 179 L (CV 15%) with an interindividual variability of 31% (CV 54%), peripheral volume of distribution (V2)= 83.9 L/h (CV 23%), and inter-compartmental clearance (Q)= 17.5 L/h (CV 19%). Allometric weight exponent fixed to 0.75 for clearances and 1 for volumes of distribution provided a good fit of the model and clearance was best described fixing parameters of the maturation function to values estimated from a previous study [2]. Global PK parameters CL and steady state volume of distribution (Vss) calculated for the studied population were 0.10 L/h and 3.2 L, respectively.

Conclusions: A semi-mechanistic population PK model has been developed that can adequately describe the fentanyl plasma concentration in preterm infants. CL in this population is affected by both PMA and weight. To our knowledge, this study is the first one to include change in organ maturation in a mechanistic model to describe the fentanyl clearance in a neonate cohort. Further analysis will be done to investigate the influence of the genotype on the PK, and the relationship between PK and analgesic effect evaluated using pain scales (PK/PD modelling).

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I-32: *Christian Bartels* Getting a better description of treatment effects for time to event data using PKPD modelling

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Introduction:

Exposure-response relations for time to event data are often analyzed with non-parametric (Kaplan Meier) or semi-parametric (Cox regression) methods. These methods have their limitations. Population pharmacokinetic–pharmacodynamic (PKPD) modelling can overcome some of the limitations.

Objectives:

- Using data from the CANTOS trial (Ridker 2017), evaluate the potential of PKPD modeling in characterizing the exposure-response relationship for time to event data relative to simpler non-parametric or semi-parametric methods.
- Use the PKPD model to estimate the efficacy of the drug when all patients had strictly adhered to treatment, i.e., assess the treatment method effectiveness estimand (Sheiner and Rubin, 1995).
- Position the PKPD estimate of the method effectiveness within statistical causal inference framework (Robins, 2000; Daniel, 2018; Rogers, 2019).

Methods:

We performed a series of exposure-response analyses for the CANTOS trial (Ridker 2017). The CANTOS trial studied anti-inflammatory therapy with Canakinumab for atherosclerotic disease, and involved 10,061 patients with previous myocardial infarction. The primary efficacy endpoint was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death (MACE). The analyses extended from non-parametric Kaplan-Meier estimates, over semi-parametric proportional hazard methods (linear Cox regression) towards more detailed characterizations using full parametric non-linear population PKPD models for time to first MACE event.

With both modeling approaches (linear Cox and non-linear PKPD), base models were first established that described the baseline hazard as well as baseline covariates. The base models were then expanded by evaluating different exposure-response relationships. For the PKPD models, direct and indirect models were considered. For the linear Cox models, different linear relationships were evaluated including step functions and linear splines.

The models were qualified for simulations based on plots of martingale residuals, visual predictive checks and precision of parameter estimates. In addition, the final model was positioned within a series of alternative models via comparisons of their diagnostic plots, their values of the objective function and their parameter estimates. Importantly, the alternative models included sensitivity analyses to assess potential selection/immortality biases.

Simulations based on the qualified model, corresponding to g-computation in terms of statistical causal inference, were used to assess method effectiveness.

Non-parametric and semi-parametric analyses have been implemented using the survival package in R. The parametric modeling was performed with NONMEM, using R to generate the model diagnostics.

Results:

The non-parametric and semi-parametric linear analyses provided strong evidence for exposure-response on clinical primary and secondary endpoints and gave an initial characterization of the shape of the exposure-response, which seemed to be non-linear.

Nevertheless, some limitations are inherent to these analyses:

1. It remains challenging to assess the shape of the exposure-response curves in a continuous manner, since non-linear shapes cannot be evaluated.
2. Longitudinal aspects are not being characterized such as the effect of missing a dose.
3. These models are not well suited for simulation purposes, e.g., to evaluate different dosing regimens.

Instead, the use of longitudinal non-linear population PKPD analyses gave a more detailed characterization of the exposure-response relationship by estimating EC50, the maximal possible response and by exploring time dependence of the clinical response, as well as incorporating all the dosing records.

Population PKPD modeling provided a framework for robust simulations giving the opportunity to explore further the dose-exposure-response relationship, to assess different dosing regimens and to estimate method effectiveness.

Conclusions:

Standard descriptions of time to event data using semi-parametric (Cox regression) models might be enough to characterize exposure response in most cases. Describing data in a more detailed longitudinal manner using parametric PKPD methods gives additional insights into shape of the exposure response, describes the progression of the clinical endpoints over time, and it enables simulations. . Simulations from the PKPD model adjusted for confounders correspond to g-computations and can provide valid statistical causal inference estimates of method effectiveness.

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I-33: *Roberta Bartolucci* Optimal design of paediatric clinical trials: the Macitentan case study

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Introduction: This work is focused on the use of Modeling and Simulation (M&S) techniques to optimize experimental protocols of paediatric clinical trials, using Macitentan as a case study. Macitentan has been approved for the treatment of pulmonary arterial hypertension (PAH) in adults, although PAH is a rare condition that can occur also in children [1]. A further investigation in the paediatric population is therefore required. However, paediatric clinical trials can have ethical and practical restrictions that need to be considered when the experimental protocol is defined and, for this reason, its optimization is required in order to maximize the information that can be exploited from collected data, minimizing the impact on patients [2]. M&S can help in this, for example, by looking for the optimal sampling schedule that can guarantee a certain level of precision for the parameter estimation.

Methods: A population PK model, describing the steady state kinetics of Macitentan and its metabolite in adults, was found in literature [3]. The model was translated to a paediatric population by a suitable scaling of the model parameters. To improve the model identifiability and then the optimization process, a constraint on the metabolism of Macitentan was applied, based on in vitro findings. Real data of age and weight of a paediatric population were collected from the public NHANES databases [4] and they were sampled to obtain a dataset of 40 subjects, from 2 to 6 years old, on which the protocol was optimized. The R package of PopED [5] was used to optimize the experimental protocol in terms of number of samples and sampling times. Different numbers of samples per patient were evaluated in order to select the minimum number that assures a certain level of precision in parameter estimation. The maximum value of the Relative Standard Error (RSE_max) calculated on the most important population parameters, such as volumes of distributions and elimination rates, was used for schedule comparison; a threshold of 20% was considered acceptable. For each scenario, PopED was used to optimize the sampling schedule with a Ds-optimality, that maximize the determinant of the Fisher Information Matrix (FIM), obtained only with a subset of the model parameters. Finally, each scenario was evaluated twice: i) without additional constraints; ii) with a more realistic design, forcing the algorithm to use the same sampling schedule for the two observations, i.e., Macitentan and its metabolite.

Results: In both scenarios (with and without the constraint on the sampling of Macitentan and its metabolite), it appears that for a small number of samples per patient the algorithm is unable to invert the covariance matrix and cannot perform the optimization with reliable results. As the number of samples increased, the estimated precision of the parameters increased accordingly; however, some of the selected time points resulted very close to each other or even coincident. Although sample replicates can increase the model estimation performance, especially when dealing with inter-individual variability, these schemes are not easily implementable in clinical practice. A second observation is that the RSE_max was systematically lower when the constraint was not applied (scenario 1). The RSE_max reached the 20% threshold with only 3 samples for each measured molecule (i.e., Macitentan and its metabolite), whereas more samples were needed in the case with the constraint on the sampling (scenario 2). However, scenario 2 was considered more clinically relevant. A third analysis was performed, fixing the sampling schedule for both the molecules at the one derived in scenario 1 for Macitentan. The optimization of the metabolite sampling schedule was considered less important, since its concentration profile at steady state is almost

constant between two consecutive drug administrations. In this case, the RSE_max reached intermediate values between those of the scenario 1 and 2, with 5 samples needed to reach the threshold.

Conclusion: The optimization of the experimental protocol is an important phase of the clinical studies, especially for paediatric populations. PopED applied on a scaled PK model can be used to compare different designs and find the sampling schedule that maximize data exploitation under different practical constraints.

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I-34: *Carla Bastida Fernández* Assessment of tapering strategies for intravenous tocilizumab in rheumatoid arthritis patients

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Introduction: Tocilizumab is a humanized monoclonal antibody approved for the treatment of rheumatoid arthritis (RA) that competitively inhibits interleukin 6 receptors [1]. In Europe, it is current practice to implement empirical dose tapering strategies in those patients showing sustained remission or low disease activity (LDA) [2] to avoid overtreatment, minimize side-effects and foster a reduction in costs. Another approach is the Therapeutic Drug Monitoring (TDM)-guided dose tapering, which has already been proven to be superior to empirical dose tapering in inflammatory bowel disease [3] and comparable in RA [4,5].

Objectives: Using modeling and simulation, the aim was to compare different dose tapering strategies for iv tocilizumab and assess the performance of these strategies by quantifying the percentage of patients who maintain in disease remission/LDA according to the Disease Activity in 28 joints (DAS28) score, as well as the reduction in direct drug-related costs.

Methods: A previously developed PKPD model for iv tocilizumab [6] was used for simulations. A total of four scenarios were evaluated on a simulated population of 5000 individuals. In all scenarios, the same initial dose was administered every 28 days for six consecutive months. After six months of treatment, different dose tapering strategies were considered:

- Scenario 1: Label dosing; Label-dosing was continued at 8 mg/kg every 28 days [1].
- Scenario 2: Mild Empirical dose tapering; In those individuals in disease remission/LDA a 25% dose reduction of the initial label dose was applied, resulting in 6 mg/kg every 28 days.
- Scenario 3: Intense Empirical dose tapering; In those individuals in disease remission/LDA a 50% dose reduction of the initial label dose was applied, leading to a final dosing of 4 mg/kg every 28 days.
- Scenario 4: TDM-guided dose tapering; If C_{trough} at six months was ≥5 µg/mL, a dose reduction was applied. This dose reduction was conducted using a model-based algorithm [7] in which subsequent doses were chosen to approach the steady-state target C_{trough} of 5(±1) µg/mL. This PK target was chosen based on literature [6,8]. Subsequent simulated doses for patients with a C_{trough}

The different strategies were primarily evaluated on the proportion of patients who maintain remission/LDA one year after the intervention. In addition, cost savings of direct drug costs were estimated.

All PKPD simulations and dose optimizations were performed with R [9], using the differential equation-solving R-packaged deSolve.

Results: After six months of treatment at the initial dose, 77.5% of the simulated population was in DAS28 remission/LDA and 79.7% showed serum drug concentrations ≥5 μg/mL.

The overall proportion of simulated patients in DAS28 remission/LDA after one year of the intervention was comparable between the mild empirical dose-tapering strategy and the TDM-guided dose tapering strategy (80.3% and 78.2%, respectively). The intense empirical dose-tapering strategy showed a lower overall percentage of patients in DAS28 remission/LDA (69.0%). Likewise, one-year flare rates were lower for the mild empirical dose tapering and TDM-guided tapering strategies (6.5% and 10.6%, respectively) compared to a 24.8% flare rate for the intense empirical dose-tapering strategy. There was also a difference between the cost-savings among the three tapering strategies (relative dose intensity was of 80.4%, 61.2% and 71.0% for the mild and intense empirical dose-tapering and the TDM-guided dose tapering strategies, respectively).

A lower variability in serum drug concentrations was observed for the TDM-guided strategy compared to the other tested scenarios. Within the empirical tapering strategies, higher simulated median serum drug concentrations were found in patients who kept in remission/LDA compared to those who lost response after tapering.

Conclusions: From the *in silico* study, we demonstrated that the TDM-guided strategy using model-based algorithms approach performed similarly to mild empirical dose tapering strategies in overall remission/LDA rates but proved to be superior in target achievement and cost-savings. Further studies are needed to test new dose tapering strategies for iv tocilizumab based on TDM using the developed algorithms as a tool to optimize patients' treatment in clinical practice.

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I-35: *Francesco Bellanti* Application of Model-Based Meta-Analysis to evaluate the relationship between early biomarker to late stage clinical endpoints for the development of anti-asthmatic drugs

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Introduction: A significant unmet medical need remains for severe asthmatics, a patient population defined as not well controlled on inhaled corticosteroids and/or other current standard of care and experiences clinically significant asthma exacerbations and associated with those ER visits and hospitalizations. The key challenge in the development of drug with improved clinical benefit in patients with severe asthma is to establish a robust clinical development plan from proof of concept studies through phase II/III. Such a development may benefit from the ability to translate of phase I/IIa clinical signal such as Forced Expiratory Volume (FEV1), to late stage (phase III/IV) clinical outcomes such as reductions in clinical asthma exacerbation rates. Model-based meta-analysis (MBMA) of relevant clinical trial data allows evaluating such a translational opportunity.

Objectives:

- To perform an MBMA of comparative effectiveness of biologics for the treatment of moderate to severe asthma
- To develop a joint MBMA model that relates early clinical well-established endpoints (FEV1) to late stage clinical outcomes (exacerbation rate)

Methods: The MBMA was based on a comprehensive database of summary clinical outcome efficacy data from randomized controlled trials in moderate to severe asthma [1]. FEV1 and exacerbation rate data were modelled simultaneously; differences in variances of mean endpoint values between studies were accounted for using appropriate weighing schemes. Different variance structures were used for FEV1 (Gaussian) and exacerbation rate (Poisson) endpoints. The treatment effect on both endpoints was modelled as a function of drug and dose, where endpoints effects were related using a scaling factor. The mean FEV1 and (log) exacerbation rate responses were described by the sum of the placebo response and drug effect. Given presumed non-Gaussian distribution of the placebo effect, this was modelled non-parametrically by estimating study, time and endpoint specific fixed effects. The effect of continuous covariates on endpoints was tested using power functions. All analyses were performed using R (version 3.4.2) typically applying functions gnls() and nlme().

Results: A total of 24 and 21 trials (all placebo controlled) and 660 and 108 observations were included for FEV1 and exacerbation rate, respectively. Exploratory data analysis indicated that an increased FEV1 (change from baseline) effect was related to a lower exacerbation rate. A joint MBMA model of FEV1 and exacerbation rate was developed based on the observed correlation. Drug-specific effects were shared between endpoints, and the scaling factor correlating the drug effect of FEV1 and exacerbation rate was estimated to be -0.872 (RSE of 2%). Baseline exacerbation rate and baseline eosinophil levels were found to significantly affect drug effect, with estimated exponents of 0.902 (RSE of 43.6%) and 0.419 (RSE of 26.9%), respectively. The joint MBMA model was externally validated using additional biologic data that were not part of the analysis data set. The results confirmed robustness and predictive ability of the developed framework. Model-based simulations were subsequently performed to evaluate comparative treatment effects of biologics for both FEV1 and exacerbation rate endpoints.

Conclusions: A joint MBMA model of drug effect on FEV1 and exacerbation rate was successfully developed using summary clinical outcome data from randomized controlled trials in moderate to severe asthma. This joint model may be used to provide early insights on expected late stage clinical response (exacerbation rate) for new drugs based on FEV1 response in early Phase I/IIa studies. As such, this predictive framework can support timely decisions (e.g. Go/noGo criteria, dose/regimen selection, and study design optimization) in the clinical development programs of biologics for the treatment of moderate to severe asthma.

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I-36: *Amina Bensalem* Nonlinear pharmacokinetics and concentration-effect relationship of rituximab in anti-neutrophil cytoplasmic antibody associated vasculitis

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Objectives: Rituximab is approved in patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV). Levels of antibodies to proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA) are correlated with disease activity, decrease with treatment [1], and may therefore be used as biomarkers of response. The objectives of this study were to investigate the pharmacokinetics of rituximab and the relationship between rituximab concentration and ANCA levels in AAV patients.

Methods: Ninety-two AAV patients from the RAVE trial (rituximab for ANCA- associated vasculitis) were assessed [2]. Blood samples were collected at baseline, at weeks 2, at month 1, 2, 4, 6, 9, 12, 15 and18, and every 6 months until the end of follow-up. Rituximab concentrations were measured using a validated enzyme-linked immunosorbent assay (ELISA) by Genentech. Concentrations were not available at months 12 and 15. Levels of both MPO-ANCA and PR3-ANCA were measured using an ELISA supplied by Euroimmun. Pharmacokinetics of rituximab was described using a semi-mechanistic model that included a latent target antigen turnover and allowed the estimation of both target-mediated elimination and non-specific elimination. Concentration-ANCA relationship was described using semi-mechanistic Friberg models [3] that included a blood compartment, where ANCA concentrations are measured, and a production compartment that was sensitive to rituximab treatment and to negative feedback by blood ANCA. These models included 0, 1, 2 or 3 transit compartments. Pharmacokinetic and PK-PD parameters were estimated using nonlinear mixed-effects models with Monolix Suite 2018R2.

Results: A two-compartment model including target-mediated elimination best described pharmacokinetic data. A Friberg model [3] with no transit compartment best described the concentration-autoantibody relationship. Mean (interindividual standard deviation) estimated systemic clearance and target-mediated elimination rate constant were 0.15 L/days (7.7 %) and, 20.10^{-6} $nmol^{-1}$ day^{-1}, respectively. Concentrations of rituximab leading to 50% decrease of ANCA input in patients with MPO-ANCA and PR3-ANCA were 37.5 mg/L (29.3%) and 21.1 mg/L (34.7%), respectively.

Conclusions: This study is the first to describe rituximab pharmacokinetics in AAV using population PK-PD modeling approach. A nonlinear target-mediated elimination of rituximab was detected. Concentration-ANCA levels relationship was well described by a Friberg model with no transit compartment. The potency of rituximab in depleting ANCA input was higher in patients with PR3-ANCA than in patients with MPO-ANCA.

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I-37: *Linnea Bergenholm* Predicting plasma and liver exposure in humans with a pharmacokinetic model for a GalNAc3-conjugated antisense oligonucleotide using sparse monkey data

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Objectives: Optimal design of first time in human studies mainly relies on preclinical data for predicting drug exposure and pharmacodynamic effects. We developed a triantennary N-acetyl galactosamine (GalNAc3)-conjugated antisense oligonucleotide (ASOs) targeting the mRNA encoding for a specific protein prevalent in hepatocytes for the treatment of non-alcoholic steatohepatitis (NASH). Previous data propose that effective doses and plasma clearance scale from mouse with a factor of 5-10 [1,2] and monkey pharmacokinetics scale 1:1 [1]. The objectives of this study were to i.) assess the feasibility to predict plasma and liver ASO concentrations using a generic model for the pharmacokinetics of a GalNAc3-conjugated ASO, and ii.) to combine with a model for the turnover and inhibition of target mRNA in the liver based on TG mouse data in order to predict human dose and liver exposure and mRNA knockdown in the clinic.

Methods: We assessed the performance of a pharmacokinetic (PK) model for the 2´-O-methoxyethyl (2´-MOE) GalNAc3-ASO ISIS 681257 [3] in predicting the plasma and liver exposure of our candidate compound, a Gen 2.5 cEt GalNAc-ASO, in a 12 weeks high dose tolerability study in non-human primates. The model was also expanded by incorporating mRNA knock-down using exposure-response data from a 2 weeks study with 5 dose levels in human transgenic mice, similar to previously described [4,5]. The final model was used to predict plasma and liver exposure and mRNA knock-down in humans and estimate the dose-response. In addition, the dose-response was predicted by an allometric scaling approach applying a factor 7, in line with previous data [1,2]. Main assumptions are that the PK translates 1:1 based on body weight between NHP and human, that the liver exposure to mRNA reduction in TG human translates to human and that the human TG mouse knockdown is at steady state.

Results: We show that the model predicts both plasma and liver exposure as well as the plasma accumulation profile expected with a half-life of 4 weeks in the NHP tolerability study. Saturation in liver uptake at high doses is accounted for in the NHP model. Furthermore, 80% mRNA knock-down was predicted at a dose of 5 mg/week both by this approach and by allometric scaling of mouse dose-response data applying a factor 7. The similarity in the dose prediction applying these two different methods builds confidence in the dose prediction.

Conclusions: This translational approach relies on the similarities in PK of ASOs within the same chemistry, and our results indicate that pharmacokinetic information and the mathematical model for 2´-MOE chemistry GalNac-ASOs applies to cEt chemistry GalNac-ASOs. The dose-exposure-response prediction may be used to design pre-clinical and clinical studies. Plasma target engagement biomarkers are required to link data between animal and human for early validation of the mRNA reduction in liver prior to liver biopsies.

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I-38: *Aliénor Bergès* Importance of Quantifying Neutropenia Risk Factors in Phase I Solid Malignancy Dose Finding; A Simulation Case

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Background

In Oncology drug development, the primary objective of most phase I clinical dose finding studies continues to be identification of a maximum tolerated dose (MTD): a dose/regimen found to have limited "dose-limiting toxicities (DLT)", in a small group of patients (typically ≤ 1 out of 6), over a finite period of time (usually 21-28 days following treatment). The scientific and statistical limitations of this approach are well-documented [1]. However, patient characteristics, such as cancer type, health status or prior anti-cancer therapy, may influence the MTD identified in these studies. We have previously reviewed the risk factors for neutrophil toxicity in cancer populations [2], a common DLT in phase I studies, and Lyman *et al.* have attempted to quantify risk of neutropenic complications in patients undergoing chemotherapy [3].

We present a simulation study to assess the effect of various degrees of patient's risk to dose-limiting neutropenic complications (represented by severe or febrile neutropenia (SN/FB)) on the MTD of a theoretical anti-cancer agent.

Methods

We used a logistic regression model that includes i) background risk , ii) patient's risk prior to treatment and based on the patient's specific risk factors *Xi=1,2,...m* and iii) dose-related drug effect toxicity.

*Logit(pSN/FB) = a + b1 * X1 + ... + bm * Xm + C * DOSE*

The probability of neutropenia (*pSN/FB*) was calculated from *Logit(pSN/FB)* and binary individual SN/FB events (DV=1 if presence or DV=0 if absence) were generated according to a binomial distribution given *pSN/FB* and a sample size per group. The binomial distribution led to natural variability in the toxicity for a given dose, in a given patient among the simulations.

The simulations were generated based on a typical dose escalation study design: 5 dose levels (0.1, 1, 3, 6 and 9 mg) and 6 patients per dose group. Four scenarios were selected, based on drug toxicity and patient's risk prior to treatment:

- Low and high-toxicity drug, with a parameter value such as *pSN/FB* at the top dose was associated to 0.5 and 0.9 respectively;
- Low and high-risk population, with a combination of risk factors *Xi* such as *pSN/FB* prior to treatment was associated to 0.05 and 0.25 respectively. The risk factors and their regression coefficient values *bi* were obtained from the risk model from Lyman *et al*. [3]

For each study, 1000 replicates were simulated to obtain the predictive distribution of MTD values. The simulations were performed in R software (version 3.5.1). Count of SN/FB events was calculated from the

simulated individual SN/FB events per dose group, and MTD was determine per study using the operational definition.

Results

Based on Lyman model [3], we simulated two sets of patient's characteristics; one associated with the low-risk population (age <65 years, breast tumor, no prior chemotherapy, normal white blood cell and normal liver enzymes) and one associated with the high-risk population (age ≥65 years, small-cell lung cancer, prior chemotherapy, low white blood cell and elevated liver enzymes).

The distributions of MTD values were significantly different between the low and the high-risk populations. For the low-toxicity drug, the most likely MTD was at the high doses (9 mg and above) in the low-risk population, and at the low doses (0.1 and 1 mg) in the high-risk population. For the high-toxicity drug, the most likely MTDs in low-risk population and high-risk population were up to 6 mg and up to 1 mg respectively.

Additional simulations using other risk models from literature are planned to investigate the MTD impact for other risk factors and/or other degrees of correlation. In addition, trials combining low and high-risk patients would give a more representative Phase I patients population.

Conclusion

Those simulations including baseline patient's risks, reveal a clear shift in the MTD distributions between the low and high-risk populations, irrespective of the level of drug toxicity. Although those simulated cases are the extreme SN/FB predicted risks, they illustrate the importance of accounting for risk factors in the MTD concept, determination and application for dose finding.

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I-39: *Martin Bergstrand* Caplacizumab Dosing Rational in aTTP Patients Supported by Mechanism Based PKPD Modelling

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Objectives: To describe the interplay between caplacizumab concentrations and its target, von Willebrand factor antigen (vWF:Ag) following treatment in different adult populations. The developed model should be utilized for simulations of what-if scenarios to support the dosing regimen.

Methods: The analysis was based on data from ten phase I to III studies [1-10] of caplacizumab in healthy volunteers (n=100), patients undergoing percutaneous coronary intervention (PCI) (n=225) and patients with acquired thrombotic thrombocytopenic purpura (aTTP, an orphan disease) (n=216), with a total of 3629 PK and 6295 PD observations. The majority of the aTTP patients received plasma exchange (PE) and immunosuppressant treatment as standard of care. A wide range of dose levels, treatment and PE schedules was represented in data. Data following both i.v and s.c administration was included.

The Population PKPD analysis was conducted by nonlinear mixed-effects modelling using NONMEM, version 7.3.0. The model was developed stepwise. Initially, a subset of the data set including data in healthy volunteers and PCI patients was used for the model development. Subsequently, the model was updated to describe the specific characteristics related to the aTTP disease status and standard of care, PE, in the subset of the data set with aTTP patients. The effects of age, sex, race, blood group, body weight, creatinine clearance, and concomitant treatment were evaluated based on graphical evaluation by means of stratified prediction corrected visual predictive checks and univariate evaluation in NONMEM.

Simulations were performed using the final model for aTTP patients to evaluate the effect of change in doses, patient bodyweight, need for dose adjustment in paediatric patients etc.

Result: The interaction between caplacizumab and vWF:Ag was adequately described by a full target-mediated drug disposition model. The model included a two-compartment drug disposition model with a parallel slow and fast first-order absorption processes and first-order linear elimination of the free drug. The model described the formation of drug-vWF complexes with the ability to form both dimers and trimers. The production and maturation of vWF were described by transit compartments and storage of vWF in a pool compartment, mimicking the storage in the Weibel-Palade bodies in the endothelium and subsequent rapid release and elimination of free vWF. The half-life of free vWF was fixed to the literature value 16 hours [11-14]. A dual feedback mechanism was included, stimulating the production rate and release of vWF from the pool when vWF decreased below the subject's baseline level.

For aTTP patients, disease progression was captured as a transient increase in vWF:Ag over time and the effect of PE was described as parallel removal of free vWF, free drug and drug-vWF complex. The population typical total elimination rate under PE was estimated to be 3.7-fold higher for free drug, 3.5-fold higher for free vWF and 1.7-fold higher for the drug-vWF complex.

Body weight was allometrically included in the model (fixed exponents) and creatinine clearance was identified as a statistically significant covariate with a minor reduction in CL for patients with CRCL below the median CRCL (100 ml/min) in aTTP patients.

The model was successfully applied to simulate what-if scenarios to support the dosing regimen, dosing in special populations and how to handle missed doses. Simulations were also performed to inform the dosing regimen in paediatric patients and to predict the PKPD behaviour in Japanese aTTP patients based on differences in body size. Simulations were also conducted to learn more about the impact of baseline vWF:Ag concentrations as well as the effect of the PE schedules in terms of timing, intensity, and duration.

Conclusions: A semi-mechanistic population PKPD model was developed to describe the interaction between caplacizumab and vWF (based on observations of vWF:Ag). The model adequately described the drug-vWF complex interaction over time, including disease progression in aTTP patients and the effects governed by PE treatment. The model has successfully been applied to increase the understanding of the PKPD interplay between caplacizumab and vWF in the target population and by the use of simulations supported the dosing rational in both adult and paediatric patients and allowed bridging to Japanese aTTP patients.

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I-40: *Jan Berkhout* Application of population PK/PD modeling and simulation to inform the design of a dose-finding study in patients with schizophrenia

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Objectives:

TAK-831 is a highly selective and potent inhibitor of d-amino acid oxidase (DAAO), an enzyme that degrades d-serine and is highly expressed in glia and neurons within the mammalian brain[1,2]. Inhibition of DAAO increases levels of d-serine, a co-agonist of *N*-methyl-d-aspartate (NMDA) glutamate receptors, and may improve NMDA-dependent glutamatergic hypofunction[1], such as in cerebellar ataxia and schizophrenia. Clinical studies were performed to assess safety, pharmacokinetics (PK), pharmacodynamics (PD), and brain enzyme occupancy (EO) in healthy volunteers. TAK-831 is being developed for the treatment of Friedreich ataxia (FRDA) and as an adjunctive therapy for negative symptoms of schizophrenia.

The aim of this work was to describe the relationship of TAK-831 plasma PK with plasma d-serine, TAK-831 in cerebrospinal fluid (CSF), and CSF d-serine time courses. In addition, the TAK-831 plasma exposure versus brain EO was described. Simulations were performed to provide insights into the TAK-831 PK/PD relationships and inform dose selection for a dose-finding study in two proof-of-concept (POC) studies in patients with schizophrenia or FRDA.

Methods:

PK and PD d-serine data from 4 phase 1 studies of TAK-831 given as a single daily oral dose (10 to 1200 mg) or as multiple daily oral doses (30 to 400 mg) were pooled for analysis. A population PK model was developed using a 3-compartment model with 6 transit compartments to account for the observed differences in the absorption profile of TAK-831 given as an oral suspension or as a tablet and with or without food. The population PK/PD analyses were performed by means of nonlinear mixed effects models using NONMEM (v.7.3) and PsN (v4.6). An indirect response model was used to describe the inhibitory effect of TAK-831 on d-serine production in both plasma and CSF. A direct response model was used for linking TAK-831 plasma PK to brain EO.

Results:

A total of 149 healthy subjects with 2495 PK and 2270 PD observations were included for model building. The established models well described the PK/PD relationships among TAK-831 exposure, brain EO, and downstream d-serine increases in plasma and CSF. Brain EO and CSF d-serine levels reached a plateau, with reduced interindividual variability at the highest doses tested; the sustained CSF d-serine elevation during 24 h supported a once-daily dosing regimen. On the basis of the simulations, the highest dose associated with the maximum d-serine increase and 2 lower doses were recommended for a phase 2 POC study to fully describe the PK/PD relationships and subsequently understand how this relates to clinical benefit in the patient population.

Conclusions:

This integrated PK/PD and PK/EO modeling analyses provided the quantitative basis for model-informed dose selection in early clinical development. It was found that daily dosing of TAK-831 resulted in an exposure-dependent d-serine increases, with CSF steady-state levels remaining constant over 24 h.

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I-41: *Julie Bertrand* Model-based approach for group sequential and adaptive designs in parallel and cross-over bioequivalence studies

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Introduction: Bioequivalence (BE) studies are performed to compare pharmacokinetics (PK) of drug formulations. Traditionally, the two one-sided test (TOST) is performed using estimates of AUC and Cmax obtained by non-compartmental analysis (NCA). Assumptions on the expected variability of AUC and Cmax are needed for sample size calculation. In case of uncertainty, it has been recently proposed to perform two-stage studies considering group sequential and adaptive designs [1]. In a previous work [2], we proposed a model-based TOST as an alternative to NCA-based TOST.

Objectives: To extend model-based statistical approaches for BE assessment to two-stage group sequential and adaptive designs and evaluate them by clinical trial simulation.

Methods: Group sequential design, with fixed number of subjects at each stage, and adaptive design, with interim sample size re-estimation, were developed for model-based TOST using the Pocock method [3] and the standard combination test [1], respectively. We evaluated parallel and cross-over rich sampling PK designs. We generated, under H_0 and H_1 hypothesis, 500 simulated data sets for each scenario and design. The parameters of the nonlinear mixed effect models were estimated using Monolix software and asymptotic standard errors were used. Total sample size, type I error and power were compared between single-stage, group sequential and adaptive two-stage designs.

Results: We implemented, in R, two-stage parallel and cross-over BE designs using model-based approach with tests on the treatment effect. The expected Population Fisher Information Matrix was used to compute the number of subjects needed at the second stage of adaptive designs [4]. Clinical trial simulations illustrated the good properties of the approach with preserved type I errors. Total sample sizes were generally reduced when two-stage design was performed with no loss of power compared to single-stage design. The benefit was even more striking with adaptive design when a higher variability was assumed at the planning stage than the one actually obtained from the first stage.

Conclusions: We showed that BE assessment using two-stage designs is feasible using model-based approach, which is an extension of these designs for NCA BE [1]. Further extensions are needed for sparse design where asymptotic standard errors can be too small [2].

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I-42: *Robert Bies* On the Multilemma of reproducibility: Stochastic or Deterministic or Stochastic and Deterministic

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Objectives

The current scientific publishing landscape has been plagued with problems concerning reproducibility, recently discussed by Munafo et. al in [1]. A simplistic definition of reproducibility in this context would relate to the ability to duplicate a set of results, whether computational or experimental within a similar experimental environment by a different individual at another site. Specifically focusing on pharmacometrics and in particular quantitative systems pharmacology modeling, the issue relates to a failure to identify and differentiate between stochastic and deterministic systems, consequently risking the replacement of causality with probability. This affects all aspects of the problem from the development of the model itself, to the interconnection of different models qualitatively and ultimately to the reproducibility of the outcomes of these models. This is demonstrated especially remarkably in chaotic non-linear dynamic models [2], where initial solutions and model behavior are intertwined. In the current study, we depict these concepts within reproducibility using specific chaotic non-linear dynamic models. We perform simulation studies and statistical tests to demonstrate significant variability in final states (tumor burden) due to slight changes in critical controlling parameters.

Methods

We examined three models of tumor immune interactions:

1. The Kuznetsov's model (a mathematical representation of cytotoxic T lymphocyte response to the growth of immunogenic tumor) [3],
2. The Kirschner-Panetta [4] model (model which explores the role of cytokines in the disease dynamics as well as addresses the topics of long-term tumor recurrence and short-term tumor oscillations) and
3. The Mehmet model (which models the interactive nature between tumor cells, healthy tissue and activated immune system cells) [5].

Two analyses were performed to demonstrate the issue of irreproducibility of results due to the inherent nature of the model system. In the first analysis, for each model, two virtual samples (for number of patients, n=200 and 1000) of tumor burden were generated of different patients. The tumor burden was in turn calculated by creating a virtual sample of parameter values such that mean of this sample is equal to the nominal value provided in [3-5] and %CV is equal to 30%. The two samples only differed in the value of seed number. These two samples were then compared using Wilcoxon rank sum test. In the second analysis, for all three models, the first analysis (for n = 200) was repeated 100 times and the number of times the calculated p-value was below the level of significance was noted.

Results

We compared the tumor burden of two samples generated. Since the sample of tumor burden produced by the parameters generated from a normal distribution were not normally distributed the Wilcoxon rank sum test was used to compare the two. A p value of 0.0039, 0.011 and 0.0220 was obtained for Kuznetsov, Kirschner Panetta and Mehmet model respectively, for an unpaired two-sided test for the null hypothesis that the difference between the two samples arises from a distribution with zero median against the alternate that the difference arises from a distribution with a non-zero median. Based on the result of the test, at the default 5% level of significance the p value indicates that the test rejects null hypothesis, indicating that the two samples might be significantly different.

Conclusions

Multiple pharmacodynamic systems exhibit chaotic behavior (cardiovascular, CNS, metabolic). Hence, we should exercise caution in analytical tools and summary statistics when handling these kind of systems since they may be prone to irreproducibility due to inherent nature of the model system. If a nonlinear dynamic model exhibits chaotic behavior, even for a densely sampled data a small change in parameter values or initial cell count can cause significant change; this leads to failure of experiment or irreproducibility. Many irreproducibility problems are encountered in various disciplines e.g. social psychology; it is advisable to consider if nonlinear dynamical analysis can provide a plausible interpretation.

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I-43: *Bruno Bieth* Optimal Scheduling of Bevacizumab and Pemetrexed/Cisplatin Dosing in Non-Small Cell Lung Cancer

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Introduction: Bevacizumab-pemetrexed/cisplatin (BEV-PEM/CIS) combination therapy has been shown to be an effective first line therapy for non-small cell lung cancer (NSCLC) in Phase III clinical trial [1]. PEM and CIS disrupt DNA synthesis in rapidly dividing cells – eventually leading to cell death [2], [3]. BEV is an antiangiogenic that disrupts neovascular growth in rapidly growing tissues such as tumors. Counter-intuitively, in the process of disrupting neovascular growth, BEV induces a transient period where perfusion, and consequently drug delivery, is improved. Currently, BEV is administered concomitantly with PEM and CIS. However, previous studies have observed that sequential scheduling of BEV-PEM/CIS, i.e. administering BEV several days before PEM/CIS, improves the efficacy of BEV-PEM/CIS combination therapy in NSCLC [4]. This is thought to be an effect of aligning BEV peak efficacy with PEM and CIS peak exposure.

Objectives: In this study, we used a large dataset generated from xenograft NSCLC tumor-bearing mice in Imbs *et al.* 2017 to validate and subsequently fit a previously published semi-mechanistic PKPD model of tumor growth vs. BEV-PEM/CIS exposure [5]. We then used relevant literature values to scale the model fit to describe tumor growth vs. BEV-PEM/CIS pharmacokinetics in humans. Lastly, we used Monte Carlo (MC) simulations to derive the optimal scheduling of BEV-PEM/CIS sequential dosing in humans.

Methods: PK models and parameter estimates for BEV, PEM and CIS were adapted from literature values [6]–[8]. Competing PKPD models were written as NLME and parameter estimates were obtained using the SAEM algorithm as implemented in Monolix 2018R2. Competing structural models were evaluated using Bayesian information criteria, precision of parameter estimates (as defined by RSE%), inspection of search stability, and visual predictive checks. Correlation between random effects were evaluated using correlation plots of the full posterior distribution of random effects, as well as Pearson correlation tests with a threshold of $P < 0.01$. Scaling of PK model parameters to humans was done by substituting mouse PK parameter estimates with values from the literature [9-11]. The PD portion of the model was then scaled by using literature estimates of human NSCLC tumor growth parameters [12]. After adapting the model to make predictions in humans, 1000 MC simulations were performed in R 3.4.4 using the mlxR package to estimate the optimal scheduling of sequential BEV-PEM/CIS in humans [13].

Results: Using the final semi-mechanistic model, we predicted that the optimal scheduling gap in mice is 2.0 days, which is consistent with findings in previous preclinical studies [4]. We observed little to no inter-individual variability in the estimated optimal gap. Based on simulations from the PKPD model, the optimal scheduling gap in BEV-PEM/CIS was estimated at 1.2 days in humans. Administrating BEV-PEM/CIS at a 1.2 day gap rather than concomitantly improved therapy efficacy (defined as relative tumor volume reduction) by 106% over 67 days of treatment. Finally, our results suggest that the efficacy loss in scheduling BEV-

PEM/CIS at too great of a gap is much less than the efficacy loss in scheduling BEV-PEM/CIS at too short of a gap.

Conclusion: These findings support a growing body of evidence suggesting that the efficacy of BEV-PEM/CIS would greatly improve if scheduling was optimized. Using mathematical modeling to explore a range of practical scheduling regimens allowed us to estimate the optimal scheduling gap in sequential BEV-PEM/CIS in both humans and mice without the considerable time and resource investment required to conduct a suite of *in vivo* experiments. The developed structural model can be used in future systems pharmacology modeling of tumor growth and response vs. antiangiogenic-antiproliferative combination therapy.

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I-44: *Roberto Bizzotto* Conditional linear mixed-effect modelling of HbA1c and fasting glucose in diabetic patients shows that progression rates for the two variables are different: an IMI DIRECT study

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Objectives: Research on personalization of treatment for type 2 diabetes (T2D) requires the study of the individual rate of disease progression, corrected for treatment and weight changes. Glycated hemoglobin (HbA1c) has been used as a marker of glucose tolerance deterioration, as it is considered to reflect the average glycaemia over the last two to three months. Fasting plasma glucose (FPG) is another important marker of glucose tolerance. However, the relationship between progression of HbA1c and FPG has not been studied. The aim of this work is the description of both HbA1c and FPG progression rates and the analysis of the differences in their individual values. A conditional linear mixed-effect model (Model C) is used for this purpose, as it is a tool for characterizing individual longitudinal patterns while minimizing the potential bias introduced by assumptions on and shrinkage of cross-sectional effects [1].

Methods: White European T2D patients enrolled within 24 months from diagnosis, treated only with lifestyle change or metformin until baseline visit, and with HbA1c <60 mmol/mol within previous 3 months, were recruited in the DIRECT multi-center study (*N*=736). HbA1c and FPG concentrations were collected at months 0, 9, 18, 27 (HbA1c only) and 36 after start of the study. Mixed-meal tolerance tests (MMTT) were performed at 0, 18 and 36 months. The Model C orthogonal longitudinal and cross-sectional components of the data were computed. The longitudinal components of HbA1c and FPG data were described as proportional functions of time, with normally distributed slopes describing underlying progression. As a term of comparison, the original untransformed HbA1c data were modelled as well, using linear time effects with normally (Model N) or uniformly distributed intercepts (Model U). Additive linear effects of the changes in BMI and in standardized dosage of the antidiabetic treatments were included in all models. Medications were considered effective when started at least 30 days before the HbA1c measurement, and 6 days before FPG measurement. Modelling was performed with MonolixSuite2016 R1.

Results: Model N produced 20% η-shrinkage of the individual estimates of HbA1c intercept. The HbA1c slope estimates of Model U or Model C were equal, and different from the slope estimates from Model N (mean absolute deviation = 0.32 mmol mol^{-1} y^{-1}). Estimated slope was 0.70±1.33 mmol mol^{-1} y^{-1} (median±SD) (with median r.s.e. = 17%) for HbA1c and 0.22±0.27 mmol L^{-1} y^{-1} (12%) for FPG. BMI effect was 1.4 mmol mol^{-1} kg^{-1} m^2 (8%) for HbA1c and 0.228 mmol L^{-1} kg^{-1} m^2 (10%) for FPG. Linear correlation between individual slopes of HbA1c and FPG was 0.70. The number of subjects with positive FPG slopes was higher than that with positive HbA1c slopes (p<10-6, McNemar test). To understand this discrepancy, two groups of patients with discordant slopes were selected: group FPG+HbA1c- with FPG slope above the median and HbA1c slope below the median, and group FPG-HbA1c+ with FPG slope below the median and HbA1c slope above the median. The HbA1c and FPG trajectories were discordant in the two groups, as expected. The trajectories of mean incremental glucose during MMTT mirrored those of HbA1c and were discordant with FPG. The trajectories of mean absolute MMTT glucose were similar in the two groups and

discordant with those of HbA1c and FPG. Group FPG+HbA1c- had robust baseline β-cell function but decreasing standardized fasting insulin secretion rate [2] and increasing HOMA insulin resistance. Group FPG-HbA1c+ was relatively β-cell deficient at baseline and had a fall over time in potentiation ratio [2] and rate sensitivity. Changes over time of cholesterol, LDL and triglycerides concentrations were correlated with those of insulin resistance and β-cell function.

Conclusions: Underlying progression of HbA1c and FPG were analyzed in T2D patients of recent diagnosis. Potential spurious correlations between the individual estimates of progression (slope) and baseline (intercept) were avoided using conditional modelling or, equivalently, uniformly distributed individual intercepts. On average, progression was faster for FPG than for HbA1c. The difference could not be explained in terms of mean glycaemia during the MMTT. Temporal trajectories of β-cell function and insulin sensitivity, together with lipid profiles, provided a possible explanation for the differences in the individual progression of HbA1c and FPG.

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I-45: *Irina Bondareva* Population pharmacokinetics of levetiracetam (LEV) in preterm neonates with seizures based on sparse therapeutic drug monitoring (TDM) data

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Introduction: Premature infants have a high risk of developing neonatal seizures [1]. Levetiracetam is a second-generation broad spectrum antiepileptic drug (AED). Routine TDM of LEV is unnecessary due to its favourable pharmacokinetic (PK) profile: linear pharmacokinetics, predictable dose-concentration relationship, wide therapeutic index, minimal side effects, and unlikely clinically significant drug-drug PK interactions [2]. However, significant and rapid changes in pharmacokinetics may occur in neonates, and LEV pharmacokinetics in neonates appears to be highly variable, which makes neonates a special population for TDM use [3, 4].

Objectives:

- Determine the influence of clinically relevant covariates on interindividual variability of PK parameters for intravenously (IV) administered LEV-monotherapy for the treatment of seizures in preterm neonates
- Develop a population model of LEV pharmacokinetics from sparse TDM data of preterm neonates with seizures

Methods: TDM data were routinely collected in the neonatal intensive care unit. LEV daily doses (18.5 – 51, median = 30 mg/kg/24 h) were administered by IV infusion bid. For this PK analysis, demographic and clinical characteristics as well as LEV administration details and measured concentrations were retrieved from patients' records retrospectively. Blood samples were collected at predose (trough levels) and at the end of 30 min IV infusion (peak levels) at different treatment days, each included subject had 2 – 14 (median = 4) LEV levels. LEV concentrations were measured by high performance liquid chromatography. PK analysis was performed using the Pmetrics software based on the one-compartment model and TDM measurements (peak-trough strategy) of 31 preterm neonates who received IV LEV-monotherapy. Repeated TDM data of 25 preterm neonates were used to estimate the model predictability taking into account change in body weight and maturation process.

Results: All included subjects had a gestational age (GA) 22 – 32, median = 26 wk; at blood probe, post-conceptual age (PCA) was 24.4 – 38.3, median = 34.5 wk; weight 0.62 - 2.4, median = 1.4 kg; the glomerular filtration rate (GFR) estimated using the Schwartz equation (the coefficient was set to 0.33) 8.6 – 38.3, median = 18.6 ml/min/1.73 m^2. The geometric means (min - max) of predose and peak LEV concentrations were 8.8 (4 – 19.4) and 16.3 (8.4 – 63.3) µg/ml, respectively. The majority of neonates (more than 90%) had serum trough levels above 6 µg/ml. The median values for total body clearance and elimination serum half-life (T1/2) of LEV were 1.6 ml/min/kg and 14.6 hours, respectively, with interindividual CV > 50%. In average, clearance and GFR increased, and T1/2 decreased with increasing GA. The GFR was strongly correlated with the PCA, and in most patients with repeated measures during the first two months, the GFR increased with post-natal age. For 33 weeks of GA/PCA considered as a cut-off for the capacity of drug renal elimination, the mean elimination serum half-life of LEV was statistically significant higher for less versus more than 33 weeks group (p=0.023). The regression analysis revealed that total body weight at dosing significantly influenced the LEV pharmacokinetics, and GFR significantly influenced LEV elimination.

Conclusion: Despite a small number of studied patients and narrow patient population which included subjects with relatively normal renal function, the results demonstrated that extremely premature and premature newborns, in whom extensive pharmacokinetic changes occur over the first months after birth, require monitoring of their LEV therapy. Bayesian approach for LEV concentration prediction based on minimum sampling steady-state or non-steady-state TDM data appear to be useful. This is especially important, because in preterm neonates, their PK parameters changed significantly during the first months of life and often before steady-state was reached. Bayesian feedback adaptive control and population modeling can improve LEV dosage adjustment for this patient group during the first few months of life.

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I-46: *Guillaume Bonnefois* A new computational approach to match control subjects to renal impaired patients in pharmacokinetic studies

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Introduction: Most of drugs that are likely to be administered to patients with renal impairment should be investigated in this population to assess the effects of this condition on the pharmacokinetics (PK) and to provide appropriate dosing recommendations, if necessary.

These PK studies would generally include the enrollment of control subjects who should match the renal patients with respect to age, gender, race, weight or body mass index (BMI). However, based on existing regulatory guidance documents and literature, there is no well-established "matching" methodology that would ensure appropriate comparability in terms of demographics, while taking into considerations the recruitment challenges for the control subjects [1-4].

Various strategies are applied for the matching procedure [5]: one approach, referred to as "mean matching", would consist in recruiting a single cohort of control subjects about equal size of each renal impairment cohort that would match the mean characteristics of the patients. A flexibility is usually allowed for age and BMI parameters, but these limits are somewhat arbitrary (*e.g.*, mean age ±10 years, mean BMI ±20%). Another approach consists in a "one-to-one pairing" of the prospective control subject to the renal patient. Again, certain flexibility may be allowed for age and BMI parameters. In that case, each category of renal impairment (*e.g*., mild, moderate and severe) would have its own control [5].

One of the current challenges with the above methods is to ensure a similar distribution of demographics between patient cohorts and control subjects.

Objectives: The objectives of the work were to address this challenge by:

- Applying statistical concepts to propose a more robust and quantitative matching approach that would limit bias in the PK comparison;
- Developing a new computational platform to guide clinicians and to facilitate the selection of the control subjects.

Methods: This work relies on the demographic characteristics' distribution of the patient cohorts. For the mean matching approach, a three-step process was developed. In the first step, the normality of demographics of each patient group was assessed. In the second step, the mean and standard deviation (SD) were calculated and the statistical differences between the means of the three patient groups were investigated using the Levene and Anova tests. A non-significant statistically difference implied pooling the three groups together. Otherwise, the control group should be matched according to the three separate patient groups. Using an empirical rule, *i.e.* proportion of patients within 1-, 2-, and 3 SD of the mean or 68.27%, 95%, 99%, respectively, the third step enabled to well distribute the variables of the control group to attain similar patient distributions.

In the one-to-one pairing strategy, a two-step iterative process was established. For each demographic characteristics and each renal impaired group, the empirical distribution was firstly estimated by a non-parametric method: the kernel density estimation [6,7]. Thereafter, this empirical probability density

function was divided in two or more parts according to the total number of renal impaired patients. The corresponding intervals and densities were calculated to obtain the number of control subjects within each interval. These methods were then implemented into a web-site application, which was developed using R-Shiny [8, 9].

Results: A computational approach was developed to implement both updated matching strategies through the Shiny application. Demographics variables can be tested such as age, BMI, or gender to develop an integrated tool that would be convenient for clinicians. The creatinine clearance or the glomerular filtration rate of each patient can be calculated (*e.g*. using Cockcroft-Gault, Modification of Diet in Renal Disease, or other equations) to automatically classify this patient within the three patient cohorts, if necessary.

Conclusions: An R-Shiny application was developed through a user-friendly interface. This tool provides a quantitative assessment of control subjects to facilitate and guide the selection of these subjects. The tool may require further validation to confirm its practical application to a renal impairment studies using real patient datasets.

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I-47: *Elisa Borella* Development of a Target-Mediated Drug Disposition Model for the Prediction of Target Occupancy of MEN1112, an Anti Bst1/CD157 Humanized Antibody for the Treatment of Acute Myeloid Leukaemia

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Objectives: The pharmacokinetics of MEN1112, a humanized de-fucosylated monoclonal IgG1 antibody directed against human Bst1/CD157, has been described in relapsed/refractory (R/R) acute myeloid leukaemia (AML) patients. Under the assumption that the degree of target engagement at the site of action drives clinical response, the aim of the present work was to develop a mechanistic target-mediated drug disposition (TMDD) model [1] to provide an *in silico* projection of receptor occupancy (RO) in peripheral blood (PB) and bone marrow (BM) under different dosing schedules supporting dose selection for next clinical trials.

Methods: Circulating free MEN1112 serum concentrations from R/R AML patients subjects from FIH study [2] after multiple intravenous administration at five escalating doses of MEN1112 injected weekly were used for model building. The quasi-steady state (QSS) approximation of the general TMDD model [3-5] was implemented. NONMEM VII was used to develop the model. Model performances were evaluated through changes in Objective Function, GoF plots and VPCs. The next step was to project RO at the target site (i.e. bone marrow) under two major data limitations: neither the target concentration in BM is known, nor the partition coefficient between BM and plasma. Assumptions regarding the similarity between target and plasma MEN1112 concentrations were considered conscientiously, and the results from such analysis served as the rationale to design the different scenarios of a simulation study consisting on evaluating RO assuming different ratios of target concentration between BM and plasma: (1) receptor density in BM to be equal to the estimate obtained from serum data (R0), and (2) receptor density in BM to be 30, 50, 100 and 200 % higher than R0 (most plausible scenarios given that the majority of patients had baseline leukopenia).

Results: A TMDD model using the QSS approximation including inter-patient variability on initial target density and additive residual error provided a very good description of the individual profiles, and all parameters were estimated with high precision [relative standard errors (RSE) < 20%]. Sensitivity analysis showed that MEN1112 concentration vs time profiles are sensitive to changes in main parameters related to TMDD kinetics, supporting parameter identifiability. The estimate of the drug-receptor dissociation constant resembles very well the result obtained from *in vitro* binding experiments, supporting the mechanistic nature of the model. RO in peripheral blood was predicted to be 50 and 75% at steady-state concentrations of MEN1112 at the highest doses explored so far. Lower doses were associated with RO lower than 30%. At Cmax median RO in BM, assuming receptor density 50, 100 and 200% greater than R0, is predicted to be ≥ 75% at the next dose levels according to the dose escalation. With respect to Cmin, median RO ≥ 75% was obtained only for the highest planned dose in the escalation in all simulation scenarios.

Conclusions: In conclusion, this pharmacometric evaluation has integrated all information available (in a comprehensive and mechanistic quantitative way). It therefore allows to rational discuss about potential

receptor occupancy in next clinical trials, as well as to suggest design characteristics improving the understanding of drug response and making less uncertain the outcome of future clinical trials.

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I-48: *Agnieszka Borsuk-De Moor* The influence of age and body weight on pharmacokinetics and pharmacodynamics of dexmedetomidine in rabbits

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Introduction: Dexmedetomidine (DEX) is a relatively new sedative agent with a growing use in the pediatric population. However, limited data exist concerning the influence of age on the pharmacokinetics of DEX and the data regarding age influence on DEX pharmacodynamics is lacking. Studies in laboratory conditions offer decreasing of the error related to the inter-subject variability by developing PK/PD model in laboratory animals with each animal serving as its own control.

Objectives: The aim of this study was to develop population pharmacokinetic (PK) and pharmacodynamic (PD) model of dexmedetomidine in rabbits and investigate the relationship between model parameters and age and weight of rabbits. Another aim was to investigate the linearity of pharmacokinetics of the drug in the examined dose range.

Methods: 18 New Zealand white rabbits were investigated during this prospective, cross-over study. Dexmedetomidine was administered as a single bolus injection in the following doses: 25 µg/kg, 35 µg/kg, 50 µg/kg, 75 µg/kg, 100 µg/kg, 140 µg/kg, 150 µg/kg, 200 µg/kg, 250 µg/kg and 300 µg/kg, with three rabbits per each dose. Specified dose of the drug was given to the same animal at 3 subsequent stages of age development at median ages of 44 (n=14), 79 (n=12) and 192 (n=14) days. To determine dexmedetomidine pharmacokinetics, 7 blood samples were taken from each animal. Pedal withdrawal reflex was the PD response measured to assess the degree of sedation. Nonlinear mixed effects modelling was used for the population PK/PD analysis.

Results: Dexmedetomidine pharmacokinetics was described by two-compartment model. Interindividual variability was estimated for CL, V1 and V2. Since the animals were examined at different occasions, the inclusion of interoccasion variability in individual parameters was tested and estimated for CL in the final model. Pharmacodynamic response was modeled by logistic regression in relation to the apparent drug concentration in the effect compartment (biophase) with interindividual variability estimated for biophase distribution rate constant. Age was identified as a significant covariate affecting the clearance. The typical value of elimination clearance was 0.057 L/min and was higher in younger rabbits compared to older animals. The estimated volumes of distribution of the central and peripheral compartment were 0.53 L and 0.89 L, respectively, and the estimated intercompartmental clearance was 0.08 L/min. Interindividual and interoccasion variability of parameters were below 36 %. The pharmacokinetics of dexmedetomidine was linear in the examined concentration range. The age-related changes in pharmacodynamics were not detected.

Conclusions: The results suggest that younger rabbits will have lower dexmedetomidine concentrations and shorter duration of anaesthesia for the same doses of dexmedetomidine per kg of body weight than older animals.

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I-49: *Thomas Bouillon* Model predictive control with Bayesian updates (MPC) is more robust to model misspecification, compared to standard Bayesian control (sEBE) for Therapeutic Drug Management (TDM). Investigation in a cohort of 315 patients receiving tacrolimus during the fi

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Objectives: Model qualification (transfer between populations), treatment of interoccasion variability (IOV) and downweighing of observations are relevant issues in TDM [1]. MPC, a technique derived from process control theory, could help relax the requirement for a "perfect" model: if the "states" of the model can be frequently updated, MPC is relatively robust against model misspecification. As a proof of concept for MPC in TDM, we evaluated predictive ability for tacrolimus concentrations between physicians, MPC and sEBE, using both a model trained on the evaluation dataset and a (misspecified) model trained on a different dataset.

Methods: Model building was performed independently on two datasets: (A) 100 patients with a rich profile of 10 samples over 12 h at d7 post-transplant [2], and (B) 315 patients with daily trough samples 0-14 days post-transplant [3]. As the intended use of the models was to inform TDM, no extensive covariate search was performed. Monolix2018R2 was used [4].

The models were implemented in TDMore, a framework for model based dose adaptation and simulation currently under development. Dataset B was used for prospective evaluation. sEBE was performed on all available concentration measurements at each respective time. MPC performs piece-wise estimation. For the first measurement, the individual parameters are obtained as with sEBE, using the population typical values and population IIV as prior. Predicted ODE compartment states at the observation time and corresponding individual parameters are then stored in memory. For the subsequent measurement, the prediction starts at the previously stored ODE compartment states. EBE for this measurement only is performed using the previous individual parameters and population IIV as prior, the latter being a heuristic decision to allow for sufficient flexibility during future updates.

Predictive performance was characterized as IPRED/DV, and summarized as fraction within a target range between 0.88 to 1.11 corresponding to the target range for tacrolimus at our institution immediately after transplantation (12-15mcg/L)). To evaluate physician-based dosing, it was assumed that physicians predict their chosen doses will hit the target of 13.5 mcg/L. Since (mis)prediction of future samples translates inversely into dosing decisions, an inference regarding dose adjustments can be made (underprediction -> overdosing and vice versa).

Results: Model building on Dataset A identified a 2-cpt model with lagged oral absorption (Model A). CYP3A5 and Weight were included as covariates. Model building on dataset B (trough levels only) identified a 1cpt model with saturable increase of the elimination rate over the observation period (Model B). This implies that Model A is misspecified, as it does not capture this trend. Prospective evaluation is summarized in Table 1 (d2, d4 and d10 after transplant).

Table 1: Probability of target attainment (PTA) and 95% binomial proportion confidence interval.

Day	Method	Underpred.	PTA	Overpred.
2	sEBE model A	26 (22-31)	26 (21-31)	48 (42-53)
2	MPC model A	26 (22-31)	26 (21-31)	48 (42-53)
2	**Physician**	**60 (55-66)**	**16 (12-20)**	**24 (19-29)**
2	sEBE model B	33 (27-38)	30 (25-36)	37 (31-42)
2	MPC model B	33 (27-38)	30 (25-36)	37 (31-42)
4	sEBE model A	22 (18-27)	26 (21-31)	52 (46-57)
4	MPC model A	31 (26-36)	34 (29-39)	35 (29-40)
4	**Physician**	**35 (29-40)**	**29 (24-34)**	**37 (31-42)**
4	sEBE model B	37 (32-43)	37 (32-43)	25 (20-30)
4	MPC model B	44 (38-49)	35 (30-40)	21 (17-26)
10	sEBE model A	8.3 (5-12)	25 (19-30)	67 (61-73)
10	MPC model A	23 (18-28)	43 (37-49)	34 (28-40)
10	**Physician**	**7.5 (4.3-11)**	**22 (17-27)**	**71 (65-76)**
10	sEBE model B	27 (22-33)	42 (36-48)	31 (25-36)
10	MPC model B	27 (22-33)	45 (39-51)	28 (22-33)

Model predictions outperform physician predictions in almost all cases, except using misspecified model A with sEBE. Since the procedure for MPC and sEBE does not differ for the first observation, target attainment is identical on day 2. On later days, sEBE and MPC perform equally well using model B. Using misspecified model A, MPC performs as well as when using model B, and outperforms sEBE.

Conclusions: These results are preliminary and require confirmation with simulated and historical datasets. However, in the case of perhaps inevitable model misspecification in real world situations, MPC is a viable alternative to sEBE. Specifically for tacrolimus during the first 14d after renal transplantation, MPC outperforms physicians regardless of model misspecification.

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I-50: *Marion Bouillon-Pichault* Model-based meta-analysis of efficacy and safety of anti-PD1 compounds in melanoma

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Objectives: Several immuno-oncology (IO) agents are currently approved for the treatment of melanoma. Phase 3 clinical trials to date have compared different treatments to one another, but between trial comparisons are not possible due to differences in trial design and population characteristics. Given these challenges, an evaluation of IO and non-IO therapies across clinical trials in melanoma would be informative.

Our objective was to develop a modeling framework to quantify the landscape of available treatments in melanoma to enable the positioning of new assets in clinical development. This framework would include both efficacy and safety and would quantify the impact of important covariate effects and population characteristics (eg, PD-L1 expression, performance score, line of treatment) across trials.

Methods: The analysis database was made of publicly available summary-level results from clinical trials investigating the efficacy (overall response rate – ORR) and safety (incidence of all grade 3+ adverse events [AEs]) of approved and investigational anti-PD1 and anti-CTLA4 agents in melanoma and their comparators. Four different monotherapy or combination treatments were included in the database. These data were used to quantify the efficacy, safety, and covariate effects of different therapeutic classes (anti-PD1, anti-CTLA4, anti-PD1 + anti-CTLA4 combination, and chemotherapy [no BRAF or MEK inhibitors]) using a non-linear mixed effects model-based meta-analysis approach (MBMA) (1).

Results: A general empirical MBMA was established linking ORR and incidence of AEs with received drug class; the residual variability was weighted by the square root of the number of patients in the trial arm to account for summary data precision (1). The model passed the goodness of fit plots diagnostics. The MBMA estimated that the efficacy of anti-PD1 compounds, both in monotherapy and in combination with anti-CTLA4, was higher in the PD-L1–positive population. The efficacy of all drug classes evaluated increased with the percentage of patients with the highest performance score (Eastern Cooperative Oncology Group [ECOG] performance status of 0) in the population. Anti-PD1 was the drug class associated with the lower incidence of AEs and no covariate effect was quantified with this analysis.

Conclusions: We used an MBMA to estimate the efficacy and safety of IO and non-IO drug classes in melanoma and quantified the impact of PD-L1 expression and ECOG performance score on efficacy. This MBMA can be used to simulate head-to-head comparisons between compounds in development and currently available IO therapies in melanoma prior to conducting a clinical trial.

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I-51: *Muriel Boulton* What is the proportion of abiraterone acetate effect on radiographic Progression-Free-Survival (rPFS) explained by Prostate-Specific Antigen (PSA) kinetics in metastatic castration-resistant prostate cancer (mCRPC)?

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Introduction: Prostate cancer, and more specifically metastatic castration-resistant prostate cancer (mCRPC), is a common cancer in men worldwide. Abiraterone acetate (AA) plus prednisone (P) is currently one of the standard regimens for treatment of patients with mCRPC. Prostate-specific antigen (PSA) plays an important role in the diagnosis, monitoring and management of prostate cancer. It was previously reported that PSA metrics (e.g., PSA doubling time, time to PSA progression) were highly associated with overall survival following AAP treatment [1].

Objectives: We aimed to evaluate the predictive performance of PSA kinetics in explaining the AA effect on radiographic Progression-Free-Survival (rPFS) in mCRPC subjects.

Methods: Data from two phase 3 studies investigating the efficacy of AAP in mCRPC patients pre-treated with chemotherapy (AA-COU-301 study, N=789) or chemotherapy naïve (AA-COU-302 study, N=750) were combined. In both studies, patients were randomized to AAP or placebo plus prednisone. As an initial step, rPFS data from the placebo subjects were analysed to identify the parametric form of the time to event model as well as key prognostic factors allowing to differentiate the background rPFS risk between naïve and pre-treated populations [2]. In a second step, a joint modelling approach was applied to characterize the relationship between longitudinal PSA levels (referred to as current PSA) and rPFS [3]. A mechanistic model with treatment-sensitive and treatment-resistant cells was used to describe the PSA levels. The mechanistic PSA model was then combined with the rPFS model with current PSA, using an exponential function, as link on the baseline hazard. The SAEM algorithm as implemented in NONMEM 7.3 was used for parameter estimation [4]. The predictive performance of the joint model was assessed through stochastic simulations of rPFS [5]. The final model was used to estimate the proportion of treatment effect explained by PSA kinetics [6].

Results: An accelerated failure time model with a log-normal distribution for rPFS described the placebo data best. The covariate analysis identified four prognostic factors (baseline lactose dehydrogenase (LDH), number of prior cytotoxic chemotherapy, bone metastases only at entry and baseline albumin) allowing to fully characterize the rPFS risk difference between chemotherapy naïve and pre-treated populations in the placebo group. For each unit increase of baseline LDH (log10) or number of prior cytotoxic chemotherapy (0-2), the survival time decreased by 65% and 15%, respectively. If only bone metastases were present and for each unit increase of baseline albumin, the survival time increased by 30% and 35%, respectively.

The mechanistic model for PSA, assuming the treatments inhibit treatment-sensitive cell proliferation, characterized the PSA levels adequately for both treatments and patient populations. Current PSA improved the rPFS predictive performance for the placebo subjects in both studies. The joint model reasonably captured rPFS in the chemotherapy pre-treated patients randomized to AAP, while it underestimated rPFS in the chemotherapy naïve patients allocated to AAP. Other functions linking PSA with rPFS hazard, such as combined baseline PSA and PSA change from baseline, were investigated but they

failed to improve model performance for the AAP group in both studies. The proportion of the overall AA effect on rPFS explained by current PSA was estimated to be 60% and 30% in the chemotherapy pre-treated and naïve populations respectively.

Conclusions: PSA kinetics explained a significant proportion of overall AA effect on rPFS in mCRPC patients treated with AAP. The predictive performance of PSA kinetics on rPFS in mCRCP patients treated with AAP was dependent on the previous administration of chemotherapy. Our conclusions are limited by the retrospective nature of our analysis and the absence of an AA-only arm in the AA-COU-301 and AA-COU-302 studies.

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I-52: *Ari Brekkan Viggosson* Model based support to biosimilarity assessment planning – A case study of pegfilgrastim

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Introduction/Objectives

Pegfilgrastim (PG) is a recombinant pegylated granulocyte colony stimulating factor (GCSF) used in the treatment of chemotherapy induced neutropenia and febrile neutropenia (FN) [1]. PG induces the maturation, proliferation and survival of neutrophil precursors resulting in an increase in absolute neutrophil count (ANC) [2]. Administration of PG is associated with a high treatment cost which can be mitigated by the approval of biosimilar versions of the drug. However, the first approvals of biosimilar PG are very recent and reasons for the difficulties related to development of biosimilar PG were explored using model-based simulation in this work. The aim of this work was twofold: to develop a population PK/PD model for PG and ANC using the data from three PG formulations tested in a clinical trial [3] and to perform sensitivity simulations with the model to elucidate exposure sensitivity of PG and ANC to differences in delivered dose, EC50 and baseline ANC levels.

Methods

Data from a three way cross over clinical study (N=174) of a potential biosimilar and 2 batches of Reference product (Neulasta®) was used for model building. An integrated bidirectional PK/PD model coupling PG concentrations and ANC was developed. The main modelling focus was to describe absorption and elimination mechanisms in the model, both of which were believed to be relatively complex. The PD model was a neutrophil kinetic model based on previous publications with all system parameters apart from ANC baseline fixed to literature values [4-6]. PG induced neutrophil proliferation, maturation and expansion of central volume (as a margination effect) through Emax effects. Covariate influence was assessed using FREM [7].

A biosimilarity trial was simulated using the model comparing hypothetical reference and test PG products. The system was evaluated by adding dose and potency (by perturbation of EC50) differences between the two administered products. Further, the influence of ANC baseline was evaluated. The power to conclude PK and PD similarity based on areas under the PG concentration and ANC curves from 0 to 312 hours (AUC and AUEC, respectively) was calculated for the simulated scenarios by comparing the geometric mean ratios of AUC and AUEC between the two products. The expected statistical power to conclude PK and PD similarity was calculated as the percentage of simulated studies that demonstrated equivalence according to traditional bioequivalence criteria.

Results

The final PK model was a one-compartment model with sequential zero- and first-order absorption and parallel ANC-dependent and non-specific saturable elimination. Non-specific saturable elimination was the primary elimination pathway identified based on the data at hand (single dose data). ANC mediated

elimination accounted for 50% of the elimination rate at the highest PG concentrations. FREM revealed that tested covariates could explain only a small degree (2%) of the variability in either AUC or Cmax.

Simulations of a two-way biosimilarity trial with the model indicated PK sensitivity and PD insensitivity to differences in delivered doses between the reference and test PG products. With a 2% delivered dose difference the difference in AUC was approximately 8% while a 10% dose difference resulted in an AUC difference of >50%. AUECs were less impacted by differences in delivered doses. A potency difference of up to 50% did not impact AUC or AUEC to a large degree.

The power to conclude PK similarity was impacted by differences in delivered doses between the products. A sample size of ~200 individuals was needed to conclude PK similarity with a 2% dose difference between the test and reference products. The power to conclude PD similarity was unaffected by differences in delivered dose amounts between a reference and test product. The power to conclude PK and PD similarity was relatively unaffected with EC50 differences up to 50%, but for larger EC50 differences between the reference and test products the power to conclude PD similarity was ~0%.

Conclusions

A well performing semi-mechanistic population PKPD model was developed to describe PG and ANC disposition. The model was used, by means of simulations, to determine the sensitivity of PK and PD to differences in delivered doses and potency and the results show a very high sensitivity of the PK parameters to changes in the amount of PG delivered to the circulation.

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I-53: *Astrid Broeker* Parameter uncertainty in small datasets – evaluation approaches at their limit

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Objectives: Small patient or subject numbers in pharmacometric analyses possess various restrictions such as higher uncertainty of population parameter estimates, in particular for interindividual variability. Yet, 'small-n' studies appear regularly in pilot studies or when specific research questions are addressed and therefore conclusions based on small datasets need to be reliable. This requests assessment of parameter uncertainty, for which various approaches are known, but many come with restrictions, especially regarding small datasets [1]. The aim of this study was (i) to compare techniques of parameter uncertainty evaluation in small datasets, and (ii) to provide guidance on how to assess parameter uncertainty in small datasets.

Methods: Simulation scenarios based on two-compartment pharmacokinetic models were implemented in NONMEM® 7.4.1 with different dataset sizes (n=5-100 subjects, n=10 samples per subject). Parameter uncertainty was determined by bootstrap, sampling importance resampling (SIR), log-likelihood profiling (LLP) and standard errors derived from the variance covariance matrix (SE) using R 3.5.2 and PsN 4.7.0. Stochastic simulations and estimations (SSE) were used to define a reference parameter uncertainty of the simulation examples. The 0-95% confidence intervals (CI) (median and 90% CI of all CIs across n=100 simulations) and the coverage were compared. A real data example (n = 11 subjects, [2]) was evaluated using bootstrap, SIR, LLP and SE and the 0-95% CI of all methods were compared.

Results: Parameter uncertainty of the simulation examples was assessed by bootstrap, SIR, LLP and SE and compared to SSE results. The 95% CI's of all methods were in good alignment with the SSE for the structural parameters and provided similar results even in very small datasets (n=5 subjects). However, uncertainty of interindividual variabilities (IIVs) was captured much worse, especially in these very small datasets. Bootstrap and SE underestimated the 95% CI for small datasets, while LLP in median overestimated the 95% CI. SIR results were sensitive to the proposal distribution and tended to underestimate parameter uncertainties of the IIVs in case the variance covariance matrix was used as proposal, while (arbitrarily) inflated proposal distributions led to overestimation.

In a second step, we evaluated providing LLP results as input to SIR, which resulted in best alignment of median 95% CI and SSE 95% CI. For example, 95% coverage of IIV of clearance was 85% for SIR and 91% for LLP in a small dataset scenario (n=10 subjects) and 82% and 90% in the respective very small dataset scenario (n=5 subjects), respectively. Bootstrap and SE coverage was lower and also poor for several structural parameters in small datasets, whereas LLP showed coverage rates closest to 95% across the investigated scenarios. A similar pattern of parameter uncertainties assessed by all methods for structural parameters was observed in the real data example.

Conclusions: Bootstrap and SE were least appropriate to evaluate parameter uncertainty, especially regarding IIVs in small datasets. LLP provided robust and conservative parameter uncertainty estimation but tended to overestimate the uncertainty of IIV parameters in very small datasets. SIR can benefit from rational proposal distributions, which might be provided by LLPs and led to most accurate estimations of parameter uncertainties in small datasets.

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I-54: *Vincent Buchheit* Data scientists for improving efficiency and quality of quantitative clinical pharmacology analyses

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Objective: For 12 years now, Roche has a group of Clinical Pharmacology Data Scientist (CPDS) embedded within the Clinical Pharmacometric (PMx) group. The added values of the CPDS to the conduction of PMx activities have been highlighted at previous PAGE meetings in 2013 [1] and 2016 [2]. The objective of this abstract is to describe the expansion of the CPDS role to all the different types of Quantitative clinical Pharmacology activities over the last few years and highlight how it further improved efficiency and quality of the quantitative clinical pharmacology analyses.

Methods: The Clinical Pharmacology (CP) group at Roche pRED consists of clinical pharmacologists, pharmacometricians, disease modelers and CPDS. All those roles have a similar objective which to help clinical project teams take the right decisions to transform molecules into medicines for patients. In order to do so, different type of quantitative analyses are conducted ranging from graphical analysis, non-compartmental analysis (NCA), population PKPD analysis to disease modeling. The CPDS's main accountability is to enable those analyses and ensure full data traceability and reproducibility.

Results: Over the last few years, we have established a group of 7 CPDS, which supports activities at study, project and disease levels. The diversity of the CPDS's tasks is constantly increasing. The main task remains the creation of data set ready for analysis (using data from different sources, different formats) that are evaluated using whenever applicable previously developed models to identify and fix data inconsistencies (PAGE 2013 [1]). Then it evolves with the data exploration by producing fit-for-purpose graphics to currently perform simulations, conduct NCA, produce outputs for reports, deliver interactive tools for simulation or data exploration, prepare submission-ready data files. In addition [JS{1] to their increasing contribution to the conduction of quantitative clinical pharmacology analyses, the CPDS are also driving the following two recent initiatives to improve efficiency and quality of those analyses:

- Improve Information Technology (IT) environment: in collaboration with IT colleagues, the team delivered a fully validated repository, to ensure complete traceability and reproducibility of all PMx activities. This new platform allows scientists to perform their daily work, in a secured validated and versioning control environment. It combines a global, secure file repository with a robust and versatile modeling management interface for tools like NONMEM®, SAS®, R, PsN.
- Enable data access before database lock: in an attempt to gain critical time especially during submission periods, a new process has been put in place to streamline fillings activities and enable pharmacometricians to start the development of PMx models prior to database lock to gain few weeks to few months.

With usually a Master degree in computational science and engineering, a CPDS brings flexibility and efficiency in the analysis process, increase the quality of the deliverables and also ensure full traceability and reproducibility. Based on our experience, a CPDS free up time of the quantitative clinical pharmacology scientists allowing for more scientific activities to be conducted. The most significant improvement is in the reduction of the time between clinical database lock and dataset ready for analysis which is usually around 70%.

Conclusions: Having data scientists fully embedded in a clinical pharmacology department allow to maximize efficiency and quality of the quantitative clinical pharmacology analyses.

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I-55: *Núria Buil Bruna* Can monocyte counts predict future drug-induced neutropenia toxicities?

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Objectives:

Neutropenia is a common dose-limiting toxicity in oncology patients following either chemotherapy, radiotherapy or targeted therapies. Such toxicity risks severe complications and can cause dose reductions/interruptions or delay in starting a new cycle of treatment, potentially worsening treatment outcome. It has been suggested that the monocyte count either at baseline [1] or the rate of decline after start of treatment [2:4] could be a predictor of future neutropenia events. However, to the best of our knowledge, there has not been a systematic multivariate assessment of monocyte features as early predictors of neutropenia. The purpose of this work is to produce a classifier for safety monitoring to predict subjects at risk of developing neutropenia in their next visit.

Methods:

A total of 880 absolute neutrophil counts (ANC) and absolute monocyte counts (AMC) (obtained in average every 4 days) were available from 73 patients. Out of these 73, 15% (11 patients) experienced neutropenia at least grade 3 (ANC≤1 x 10^9 cells/L). Observations after first neutropenia event were excluded.

Three modelling approaches were compared to predict neutropenia: 1) univariate cut-offs 2) multivariate decision trees 3) other machine learning algorithms (support vector machines linear and radial, random forest and stochastic gradient boosting). The analysis was performed in R using the caret package. Neutropenia status at each visit was modelled using predictors derived from ANC and AMC from previous visits. Derived predictors were: baseline cell counts, cell counts from the three previous visits and slope between visits. To evaluate the predictive capability of AMC, models were assessed with and without AMC predictors. We assessed the predictive performance of each model via Monte Carlo cross-validation (n=100) using precision and recall on the hold-out datasets.

Due to the imbalanced nature of the data, the following approaches were used; 1) neutropenia events in train datasets were up-sampled to 50% prevalence; 2) the probability threshold for classifier cut-offs were investigated as hyperparameters using a separate bootstrap cross-validation (n=100) 3) the F2-score (a measure of precision and recall, weighing recall higher than precision) was used to optimise hyperparameters.

Results:

All models significantly improved cross-validation performance when AMC features were included. The three top models were multivariate decision trees (F2-score = 0.61, precision=0.39, recall=0.71, specificity = 0.8), support vector machine (F2-score = 0.58, precision=0.32, recall=0.73, specificity = 0.68), and stochastic gradient boosting (F2-score = 0.55, precision=0.54, recall=0.56, specificity = 0.90). The univariate cut-off model was outperformed by all algorithms. The multivariate decision tree was therefore selected. The most impactful feature in the decision tree was the change in AMC from baseline in the visit prior to

observed neutropenia followed by the corresponding ANC. Interestingly, baseline AMC and ANC were found not to increase predictive performance of the decision tree classifier.

Conclusions:

We have demonstrated AMC significantly improve performance in predicting neutropenia. However, our results show that obtaining predictions with good operating characteristics for use in the clinic can be challenging, even when correlated variables have been identified. Although the more advanced machine learning algorithms provided the potential for improved performance, they come with additional practical and regulatory hurdles to implement due to the software requirement. The easy implementation of a decision tree may be a useful tool for clinicians to guide monitoring time of ANC in those patients with high risk of neutropenia. These findings require external validation with a larger dataset.

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I-56: *David Busse* Analysis of target-site distribution of meropenem in morbidly obese and non-obese patients using nonlinear mixed-effects modelling

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Objectives: Meropenem (MER), a broad-spectrum β-lactam antibiotic, is frequently used for the treatment of soft tissue infections, e.g. after surgery. Although obesity has been identified as a risk factor for surgical site infections [1], a quantitative evaluation of its pharmacokinetics (PK) in obese patients is lacking as of date. Nonlinear mixed-effects (NLME) PK analyses of MER in obese patients have been performed previously but none was based on observations providing insights into tissue distribution. The aim of this analysis was to characterise tissue distribution by developing a MER NLME PK model based on concentrations both in plasma and interstitial space fluid (ISF) of subcutaneous (s.c.) adipose tissue.

Methods: The dataset originated from 15 obese (BMI=38.1-81.5 kg/m^2) and 15 non-obese patients (BMI=20.5-27.1 kg/m^2) treated with 1000 mg MER (30-min i.v.) for infection prophylaxis prior to abdominal surgery. Rich sampling data were available over 8 h in plasma (n=269) and via microdialysis in the ISF of s.c. adipose tissue (n=322). NLME model development was performed in NONMEM® 7.3 using the integrated plasma and micro-/retrodialysis modelling approach [2,3]. Model adequacy was assessed by plausibility and precision of parameter estimates, goodness-of-fit (GOF) plots and visual predictive checks.

Results: Two three-compartment models adequately described MER PK in obese and non-obese patients and yielded precise parameter estimates: (i) a mammillary model with bi-directional distribution between the central and peripheral compartments, and (ii) a catenary model with a chain of two peripheral compartments (ISF attributed to the first peripheral compartment). Parameter estimates of clearance (10.9 and 11.0 L/h, respectively) and total volume of distribution (19.8 L for both models) were similar for both models. Interindividual variability (IIV) was estimated on parameters associated with the central and ISF compartment. For instance, IIV for intercompartmental clearance between the central and ISF-associated compartment (Q_1) was 51.0 and 44.6 %CV and for volume of the ISF compartment (V_2) 44.9 and 36.6 %CV for the catenary and mammillary model, respectively. Individual parameter estimates of Q_1 and V_2 were related to body size descriptors (adjusted, lean and total body weight) with correlation coefficients of 0.83 – 0.87 (catenary model) and 0.67 – 0.76 (mammillary model). Based on predictive performance (Akaike information criterion and plots of conditional weighted residuals versus population-predicted concentrations) the catenary model was favoured over the mammillary model.

Conclusions: An NLME PK model was successfully developed to describe concentration-time profiles of MER in obese and non-obese populations. The slightly better predictive performance of a catenary compared to a mammillary PK model could indicate further distribution into more remote tissues such as into intra-abdominal adipose tissues. These tissues have been described as less perfused compared to subcutaneous fat tissue which could explain the delayed distribution via the ISF compartment [4]. To further investigate the remote tissue hypothesis generated via the NLME approach, a physiologically-based

PK approach is planned to be applied. Additionally, a covariate analysis will be performed to explore differences in PK parameters between the two patient populations based on both structural models.

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I-57: *Antonio Cabal* Using multiscale mechanism based mathematical modeling to address many of the challenges associated with the estimation of local lung concentration after inhaled drug delivery

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Background/Objectives: Mathematical modeling can help provide otherwise unavailable information on of the local drug concentration in target tissues of the lung for multiple species. The aims of this work were to use the physicochemical properties and the drug delivery details as input to implement the following objectives:

- Multiscale mechanism-based integrated computational platform developed to provide mechanistic insights into key complex species-specific physiological-based processes associated with pulmonary drug delivery.
- Model qualification using existing lung and systemic data from the literature.
- Effect of breathing patterns on lung deposition and PK.
- Translation of systemic and lung PK from preclinical species to humans using in-silico lung platform.
- Effect of physicochemical properties on lung selectivity.
- Coupling of the systemic and lung PK to their associated local effects.

Methods: Five different mathematical modules were integrated in the platform: deposition, dissolution, transport, distribution, and effect. The inhaled modeled particles will be deposited [1] into three main regions of the respiratory tract: the upper tract, tracheobronchial region, and pulmonary region. Once deposited in the different lung regions a dissolution module accounts for the particles dissolving [2] in the surface lining fluid while simultaneously being cleared from the airway region (generation 0 to 15) due to the action of the mucociliary escalator. The dissolved drug partitions into seven different lung tissue compartments before reaching the systemic circulation [3]. A PBPK module [4] accounts for the drug distribution, partition throughout the body, and elimination. A mechanism specific PD module was used to account for the effect of corticosteroids and inhale soluble guanylate cyclases. The model was qualified using deposition fraction (DF) and PK data from diverse compounds in rats, dogs, and humans. For each case, the input data for the model included the drug physicochemical properties while the PK clearance parameter was either estimated based on the data or used from literature, if available. Single dose data then was used to test the agreement of the model with the observed PK profile in the systemic circulation for rats, dogs, and humans

Results: A translational strategy from rats to humans was done using the exact same compound specific physicochemical properties, allometrically scaled clearance, and the species specific dose delivery information. Good agreement was obtained between the predicted PK and the systemic concentrations for rat, dogs, and humans for the compounds tested after a single inhaled dose. The lung concentrations predicted were at least two orders of magnitude higher than the corresponding systemic concentration during the drug terminal decay phase. PD predictions were in agreement with available data.

Conclusion: The lung modeling platform presented here provided an in-silico option to overcome many of the challenges related to the estimation of the local drug concentration in the lungs. It was qualified using existing inhaled literature deposition data and systemic PK data for multiple species (rat, dog, human). This platform demonstrated the ability to make PK/PD translation between species using the exact same

compound specific physicochemical properties with allometrically scaled clearance underlining the value of this tool as a translational platform to make accurate human projections from preclinical observations.

Acknowledgement: This work was supported by multidisciplinary teams at MSD and CFDRC.

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I-58: *Unai Caballero* Pharmacodynamic modelling to evaluate the in vitro activity of amphotericin B against Candida auris

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Objectives: *Candida auris* is an emerging multidrug-resistant yeast that causes invasive candidiasis. It is associated with high mortality rates, up to 40%, and the control and treatment of hospital outbreaks are challenging due to difficulties in identification, persistence in the environment and reduced sensitivity to first-line antifungal agents. Most isolates show resistance to azoles and echinochandins, whereas with amphotericin B variable results have been reported [1]. Despite the importance of a complete characterization of the antifungal susceptibility of *C. auris*, there is a lack of studies regarding PK/PD modelling. The aim of this study was to develop a PK/PD model that characterized the in vitro activity of amphotericin B against *C. auris*.

Methods: In vitro static time-kill curves experiments were performed in microtitre plates in RPMI-1640 medium with six *C. auris* clinical blood isolates (Hospital La Fe, Valencia, Spain). Inoculum size ranged from 1 to 5 x 10^5 CFU/mL, amphotericin B concentrations ranged from 0.25 to 4 mg/L and samples for viable counts were taken at 0, 2, 4, 6, 8, 24 and 48 hours [2]. Colony forming units (CFU) counts over time for each drug concentration and isolate were simultaneously modelled in NONMEM v7.4 with first order conditional estimation method. Residual variability was modelled with an additive model and an exponential model was used to describe inter-individual variability in model parameters. The first-rate order constant for growth (k_{growth}) and natural death rate (k_{death}) of the fungal system were estimated in the absence of drug. The estimated values were later fixed when analysing drug-exposure data. Due to the multiresistant profile of *C. auris*, several models that tried to explain reduced drug sensitivity were tested [3]. Precision of parameter estimates, goodness of fit plots, changes in objective function value and performance of visual predicted checks were evaluated to assess model performance.

Results: A mixture model that included a sensitive (S) subpopulation and a non-growing drug-resistant (R) fungal subpopulation with a first- order transfer rate constant from S to R (k_{SR}) best described the experimental data. The effect of amphotericin B, which increased the killing rate of the sensitive subpopulation, was described by an E_{max} sigmoidal function. The typical values and relative standard errors were E_{max}=1,43 h^{-1} (1,03%), EC_{50}= 2,94 mg/L (%2,87%), Hill Factor=2,7 (3,87%) . Amphotericin B showed concentration-dependent fungicidal activity.

Conclusions: The model successfully described the activity of amphotericin B against *C. auris* in vitro and provides more information about the antifungal susceptibility of a newly discovered multiresistant species. To date, this is the first study that has modelled amphotericin time-kill data against *C. auris* with a semi-mechanistic approach. PK/PD modelling of in vitro data might help in the design of dosing regimens that optimize fungal killing and minimize antifungal resistance.

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I-59: *Elisa Calvier* Alirocumab population pharmacokinetics in Chinese patients using priors

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Objectives:

Alirocumab is a fully human monoclonal antibody directed against Proprotein Convertase Subtilisin Kexin type 9 (PCSK9), which is mainly expressed in the liver. PCSK9 directly binds to LDL-R (LDL-Receptor) and promotes LDL-R internalization and degradation. By blocking PCSK9 mediated regulation of LDL-R, alirocumab lowers serum LDL-C levels in a dose-dependent manner. Clinical studies did not evidence any impact of ethnicity on the pharmacokinetics of alirocumab. PRALUENT® (alirocumab) is currently approved in more than 60 countries worldwide, including Japan, Hong Kong and Taiwan, but not yet in China. Therefore, the objectives were to:

- Qualify a population pharmacokinetic (popPK) model for alirocumab in the Chinese population.
- Compare alirocumab exposure parameters between Chinese and non-Chinese patients

Methods:

A popPK model for total alirocumab (i.e., free and bound to PCSK9) previously developed on pooled clinical data of phase I, II and III studies (n patients ≈ 3000, mostly Caucasians) [1] was used for the analysis of a pooled dataset from phase I and III studies in Chinese patients (n = 68) using NONMEM prior's subroutine [2,3]. Chinese healthy volunteers (n=28) received a 75, 150 or 300mg single subcutaneous (SC) dose and Chinese high cardiovascular risk patients with hypercholesterolemia on background statin therapy (n=40) received an SC 75mg dose every 2 weeks (Q2W) over 24 weeks, with a possible up-titration to 150mg Q2W at week 12. The popPK model was a 2 compartment-model with a first order absorption rate and bioavailability (i.e., SC administration), a linear as well as a non-linear (i.e., Michaelis-Menten equation) clearance. Four covariates were included: weight and statin co-administration on clearance, age on peripheral volume of distribution and free-PCSK9 on the Michaelis–Menten constant. Informative priors were first only used on bioavailability (structurally unidentifiable parameter). No priors were used for the remainder of the parameters. Informative priors were then iteratively added on parameters that were not precisely estimated or to stabilize minimization. Model validation included goodness of fit plots, bootstrap (n samples =1000), VPC (n simulations = 100) with stratification on dose and clinical study and derivation of quality criteria using in house-tools [4]. The quality criteria were namely the average fold error (AFE), the root mean squared error (rmse%) and the mean prediction error (mpe%) expressed as percentage of mean concentrations. Finally, the qualified model was used to derive alirocumab individual Cmax and $AUC_{0\text{-}336h}$ at steady state in Chinese patients with statins as add-on therapy receiving a 75mg dose Q2W (n=36). These parameters were compared with those previously found in non-Chinese patients under the same dosing regimen: Caucasians/Blacks (n= 317) and non-Chinese Asians (n=14).

Results:

Informative priors on all model parameters (population PK, covariate, inter-individual variability and residual error parameters) were required for model stability and precision of parameter estimates.

Parameter estimates in the Chinese population were close to those previously found in non-Chinese, with a maximal difference of -10 % on the variance of the Michaelis-Menten constant. Individual and population predictions were in good agreement with observations and did not reveal any trends with observed concentrations or time. The AFE, rmse% and mpe% were, respectively, 1.56, 60.7% and 9.58% for population and 1.17, 25.9% and 3.49% for individual predictions. For all model parameters, mean estimates obtained in the final model were very close to the bootstrap values estimated from the 987 successful runs and were always included in the [2.5th - 97.5th] range. The VPCs showed that, whatever the study and the dosing regimen, a large majority of the observed concentrations were included in the range [5th-95th percentiles]. A median Cmax value of 6.27 mg/L and a median $AUC_{0\text{-}336h}$ value of 1650 mg.h/L at steady state for the dose of 75 mg as add-on therapy to statins were predicted. These values are close to those reported in non-Chinese patients (Cmax of 7.20 and 7.20 mg/L and $AUC_{0\text{-}336h}$ of 1870 and 1880 mg.h/L in Caucasians/Blacks and non-Chinese Asians respectively).

Conclusions: A popPK model for alirocumab in the Chinese population was qualified and allowed for the estimation of individual Cmax and $AUC_{0\text{-}336h}$ at steady state. These exposure parameters were close to those reported in the non-Chinese population.

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I-60: *Tim Cardilin* Tumor Static Exposure for anticancer combinations in early drug discovery

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Objectives: Examine how the Tumor Static Exposure (TSE) concept can help guide early drug discovery, particularly for combination treatments with two or more drugs.

Methods: TSE is a model-based prediction of the necessary exposure to a drug or combination of drugs that results in tumor shrinkage. TSE has been derived as an important quantity for single-agent treatments as well as combinations of drugs, and combinations involving radiation treatment [1-3]. When a population approach such as mixed-effects modeling is used, TSE predictions can be made to ensure tumor shrinkage not only for the median, but for a larger percentage of the population. Several published examples are given in order to highlight how TSE is:

1) Defined and can be derived for a given model

2) Used to assess synergy and optimize combination treatments

3) Used to understand between-subject variability

4) Useful when translating results from animals to humans

Results: TSE can be derived from a quantitative tumor model based on a steady-state condition where the growth rate of tumor cells is equal to the kill rate induced by one or multiple anti-cancer agents. TSE is then computed using the estimated parameter values from the model, which results in a point, curve, or surface consisting of all exposure combinations that result in tumor stasis. Exposure combination above TSE will lead to tumor shrinkage, whereas exposure combinations below TSE lead to tumor growth. The first example shows a TSE curve for combinations of cetuximab, an EGFR-inhibitor, and cisplatin [1]. TSE and mixed-effects modeling are used together to predict the necessary exposure to achieve tumor regression for 90% of the population. The second example involves combinations of radiation and a radiosensitizing agent [2]. The associated TSE curves consists of all combinations of daily radiation doses and radiosensitizer concentrations that will lead to tumor shrinkage. A strong synergistic effect is seen via a pronounced curvature of the associated TSE curve. TSE is also used to show that an optimal combination of radiation and radiosensitizer could significantly reduce the total exposure and consequently reduce toxicity. Such techniques could be useful when selecting candidates to move forward within an early discovery setting. The third example involves radiation and a different radiosensitizing agent [3]. A heat map is generated that shows the net tumor growth/shrinkage rates associated with different combinations of radiation and radiosensitizer. In particular, the TSE curve is given as a special case when the net growth rate is zero. Such a heat map allows combinations to be evaluated at greater exposure levels when the tumor is required to shrink at a certain rate. The translational potential of TSE is also explored by allometric scaling of the system parameters.

Conclusions: The three examples illustrate that TSE is a useful concept that can be derived and used for a variety of tumor models. TSE has a clear biological interpretation as the combinations of drug exposures that are sufficient to achieve tumor shrinkage. TSE can be used to assess the synergy of a combination, to optimize combination treatments, and can also help with translational efforts. TSE could be particularly useful when selecting drug candidates in early drug discovery.

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I-61: *Fernando Carreño* Population Pharmacokinetic Modeling of Quetiapine Lipid Core Nanocapsules in a Neurodevelopmental Animal Model of Schizophrenia

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Introduction: High variability in chronic SCZ response to treatment may be partially related to blood-brain barrier (BBB) dysfunction caused by the disease and consequent alterations on antipsychotic drug transport to the central nervous system (CNS)[1]. Therefore, we developed lipid-core nanocapsules (LNC) aiming to improve drug targeting to the brain[2].

Objectives: In the current study we aim developing a populational pharmacokinetic (popPK) model capable of describing changes in plasma and brain pharmacokinetics after administration of quetiapine (QTP) solution (FQ) or encapsulated in lipid core nanocapsules (QLNC) to naïve and schizophrenia-phenotyped (SPR) rats, increasing the understanding of the role of this drug delivery system in brain drug disposition.

Methods: Study approved by CEUA/UFRGS (#31001). QLNC (1 mg/mL) were obtained by nanoprecipitation and presented average size of 166 ± 39 nm, low polydispersity index (< 0.15) and high encapsulation efficiency (93.0 ± 1.4%). Wistar pregnant dams (GD15) received a single 4 mg/kg i.v. *bolus* dose of poly(i:c) or saline (naïve offspring) and SCZ-like deficits in the adult offspring (PND75) were accessed by pre-pulse inhibition of the startle response (PPI) in comparison to the naïve offspring. Model building was based on experimental data from venous blood (total plasma), venous microdialysis (unbound plasma) and hippocampus and medium prefrontal cortex microdialysis (unbound brain concentrations) obtained after the administration of single i.v. bolus dose of FQ (10 mg/Kg) or QLNC (5 mg/Kg) to naïve and SPR rats. Data were analyzed with nonlinear mixed effect modeling in NONMEM, version 7.4. The first order conditional estimation method with interaction (FOCE INTER) was used for all analysis. The overall aim was to estimate plasma and brain pharmacokinetic parameters, and the protein binding simultaneously.

Results: A two-compartment model was identifiable both in blood and in the brain after administration of FQ formulation to naïve and SPR rats. The *in vivo* unbound fraction of QTP was estimated to be 24% (RSE: 12%). Bi-directional transport of QTP across the BBB parametrized as CL_{in} and CL_{out} sufficiently described the data. Stepwise covariate model (SCM) revealed that the brain distribution of QTP was significantly affected by the disease status and is correlated with the PPI behavioral test results. SPR animals presented a significant reduction in the rate of BBB transport (CL_{in}: 0.019 L/h/kg; RSE: 16 % and CL_{out}: 0.017 L/h/kg; RSE: 7 %) in comparison to naïve animals (CL_{in}: 0.045 L/h/kg; RSE: 10 % and CL_{out}: 0.023 L/h/kg; RSE: 14 %). The model for FQ formulation was expanded to describe different features of the QLNC formulation (plasma and tissue release from the nanocarrier, including an estimate for the fraction of the dose associated to the interface of the polymeric shell that is released as a burst after the administration of the nanocarrier). The final model describes two *in vivo* QTP release processes from the nanocarrier in plasma ($Krel_{BURST}$: 0.261 h^{-1}; RSE: 4% and $Krel_{SLOW:}$ 0.47x10^{-3} h^{-1}; RSE: 25%). The significant decrease in brain exposure in SPR rats was reverted by drug nanoencapsulation, showing that LNC facilitates QTP distribution to brain interstitial space by carrying the drug into the brain and other tissues ($CL_{in,nano}$: 0.067 L/h/kg; RSE: 11%).

Conclusion: A simultaneous modeling of total and unbound plasma and unbound brain concentrations allowed the quantification of rate and extent of QTP brain distribution from FQ and QLNC formulations in naïve and SPR rats. The present model-based approach is useful to better understand the potential of LCN for drug delivery to the brain, opening the opportunity to use this approach to improve SCZ-treatment limited response rates.

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I-62: *Jantine Brussee* Model-based dose optimization of ivermectin to achieve equivalent exposure coverage in children and adults

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Objectives: Soil-transmitted helminthiasis is a neglected tropical disease mostly affecting the poorest and most deprived communities in tropical and sub-tropical areas, and approximately 1.5 billion people are infected worldwide [1]. Although the broad-spectrum antiparasitic drug ivermectin is commonly used to treat various helminth infections, including soil-transmitted helminthiasis, doses associated with consistent exposure in children 2–12 years of age and adults are unknown. Ivermectin is not approved in children weighing

Methods: Ivermectin PK data was collected in 80 pre-school-aged children (2–5 years), 120 school-aged children (6–12 years) [2], and eleven adults [3] with *Trichuris trichiura* infections in Côte d'Ivoire following a dense sampling scheme and using the dried blood spot technique. Pre-schoolers (2–5 years) were randomized to receive 100 or 200 µg/kg, school-aged children were randomized to receive 200, 400, or 600 µg/kg, and adults received 200 µg/kg ivermectin. A population PK model was developed (NONMEM 7.4) and a systematic covariate analysis was performed to explain part of the inter-individual variability in the estimated PK parameters. The model was evaluated using goodness-of-fit plots, a bootstrap analysis (n=500), and visual predictive checks (n=1000).
Different dosing scenarios were simulated with (a) the current dose of 200 µg/kg, rounded to whole 3-mg tablets, (b) an increased weight-based dose, and (c) an increased dose based on height. Different cut-off points for body weight and height in children in scenarios (b) and (c) were evaluated, to achieve equivalent exposure coverage in children and adults, with a target exposure within the 80–125% range of the median adult exposure observed with a 200 µg/kg ivermectin dose.

Results: A two-compartmental PK model was developed to describe ivermectin PK in children and adults, and included two transit compartments to account for a delay in absorption, with a mean transit time (MTT) of 3.14 h (median, 90% confidence interval (90% CI) 1.61–6.43 h). A typical individual of 18 kg had a clearance of 5.98 L/h, and clearance was found to increase with body weight. Clearance per kilogram bodyweight in pre-school-aged children was similar to that in school-aged children with median values of 0.346 (90% CI 0.12–0.73) L/h/kg and 0.352 (0.17–0.69) L/h/kg, respectively.
In adults, clearance per kilogram bodyweight was significantly lower (0.199 (0.10–0.31) L/h/kg). Consequently, administration of 200 µg/kg ivermectin is associated with a ~30% lower exposure in children compared to adults. Simulations indicate that an increased dose of 250 and 300 µg/kg would be needed in school-aged children and pre-school-aged children, respectively, to achieve equivalent exposure coverage in children and adults. Alternatively, we also provide a height-based dosing schedule, as height is easier to measure than body weight in settings with poor infrastructure.

Conclusions: We report the first dosing strategy for the widely-used drug ivermectin that is associated with equivalent exposure coverage in children and adults. An additional study is warranted to establish the safety of the recommended higher dose in pre-school-aged children, and the efficacy of appropriate doses against helminth infections in children.

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I-63: *Blesson Chacko* Why patients may not benefit from effective oncology drugs

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Objectives: To show that patients may not always benefit from an effective treatment through competing risks analysis of simulated data. To qualify the parametric models with simulation-based informative graphical displays.

Methods: 200 studies were repeatedly simulated while varying sample size (100 to 1000) and magnitude (γ=0,0.2,…,2) of binary covariate influence (exposure above and below median) on event of interest (response). Exposure influence on a competing event (dropout due to adverse events) was fixed in order to increase the dropout hazard by a factor of 2.7 for exposure above the median. The end of the observation period varied randomly between two months and two years. Response and dropout times were simulated using a Weibull hazard function with a 7-fold higher baseline hazard rate for response than for dropout.

The exposure effect on response **rate** in all simulated studies was investigated by the cause-specific hazard (CSH) approach using the standard Cox proportional hazard (Cox-PH) method. The exposure effect on the response **risk** in all simulated studies was investigated by the sub-distribution hazard (SDH) approach which evaluates the influence of exposure on the cumulative incidence function (CIF). Exposure effects on the SDH were analysed with the semi-parametric Fine-Gray method [1] and by directly modelling the CIF with a modified three-parameter logistic hazard function and a generalised odds-rate link function under the constraint that the asymptotes of CIFs for the competing events must add up to one [2]. A patient population is said to have benefitted if a significant exposure effect could be found on response **risk** in the presence of competing events.

Results: A significant ($p<0.05$) exposure effect on response **rate** was found in 53 of 200 simulated studies with 100 patients and γ=0.4 using the Cox-PH methodology (median hazard ratio, HR, of 1.9 and 90 percentiles ranging from 1.7 to 2.6). However, a significant exposure effect on response **risk** was found in only 16 of 200 studies with 100 patients and γ=0.4 using the Fine-Gray approach, despite only an average of 18% (+/- 4%) of patients dropping out. This indicates that a significant exposure effect on response **rate** does not always correspond to a beneficial effect for the patient population.

This finding was confirmed when the sample size of otherwise identical studies was increased to 1000, in which case a significant exposure effect on response **rate** was found in all studies (HR [90%] = 1.49 [1.3-1.7]). Whereas only 78 of 200 studies showed a significant exposure effect on response **risk**. Thus, lack of statistical power was not obscuring the possible benefit of a patient population.

Discussion: The simple binary exposure covariate can be replaced by a continuous covariate and the simulations yield a similar conclusion. Our definition of patient benefit is simplistic by claiming that absence of dropout alone paves the way to therapeutic benefit. A novel method to address goodness-of-fit with the model-derived and data-driven CIFs facilitates visual model qualification.

Conclusions: Treatment effectiveness and patient benefit can be evaluated at the same time by dealing with dropout as a competing risk and not as a case of right-censoring. It became clear, that under a range of conditions, treatment effects identified by their HR failed to translate into patient benefit.

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I-64: *Dong Woo Chae* Predictive model of postoperative nausea and vomiting in patients treated with Fentanyl-based intravenous patient controlled analgesia

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Introduction: Postoperative nausea and vomiting (PONV) is often ranked by patients as one of the most undesirable postoperative outcomes [1]. While PONV is typically self-limited, it can lead to unanticipated admissions [2] and postoperative complications. Risk factors of PONV have been studied extensively, and two of the most well-known risk scores in adults have been proposed by Apfel [3] and Koivuranta [4]. Female gender, history of motion sickness or PONV, non-smoking, and the use of postoperative opioids appear to be the most robust risk factors. While more elaborate models have been proposed, difficulty in their implementation seems to have limited their widespread use. Regarding postoperative opioids, there is evidence that there exists a strong dose-response relationship between postoperative opioid dose and PONV [5]. With increased use of postoperative patient controlled analgesia (PCA), accurate prediction of Fentanyl's nausea promoting effect would contribute to better patient management.

Objectives:

- Develop a predictive model of postoperative nausea and vomiting (PONV) and identify its risk factors.
- Investigate the time-varying effects of the risk factors.
- Develop a web application that facilitates the use of the predictive model.

Methods: Data from 22,144 postoperative patients who underwent general anesthesia and treated with intravenous Fentanyl based PCA were retrospectively collected from electronic medical records of two hospitals located in Seoul, South Korea. The dataset was randomly split into training and test sets in a ratio of 8:2. A stepwise logistic regression was performed on the training dataset to select the most significant covariates. This process was repeated 100 times with different random seeds, whereupon the frequency of each covariate inclusion was calculated. Using only those covariates that were selected in more than 95% of the resampled datasets, a multivariate logistic regression model predicting the incidence of PONV within 48 postoperative hours was built. Since effects of different types of surgery are often confounded by peculiarities of the hospitals, surgeons, and the treating physician, we also built an alternative mixed effects model that treated surgery type as a random effect. Non-linearity of the continuous covariates was explored in this step. Finally, the time-varying effects of the selected covariates were examined by performing multivariate logistic regressions for PONV occurring within 0~6 h, 6~12 h, 12~18 h, 18~24 h, and 24~48 h postoperative time periods. A web application that interactively outputs the probability of PONV was developed based on the final model using RShiny.

Results: As with previous studies, female gender, history of motion sickness and PONV, and non-smoking were identified as significant risk factors. In addition, the following covariates were found statistically significant: DM, ASA class, cancer surgery, laparoscopic surgery, use of total IV anesthesia (TIVA), postoperative pain severity, and use of postoperative Tramadol. A strong dose-response relationship between Fentanyl mg/kghr and PONV was found. The nausea-promoting effect of Fentanyl seems to be

alleviated when ketorolac is added to the PCA regimen. The parameter estimates acquired from a mixed effects model yielded similar results, and the standard deviation of the random variability incurred by different surgery types in a logit scale was estimated as 0.65. Time varying effects of the selected covariates were quantified and visualized using a rectangular grid with each axis representing the covariates and the time bins.

Conclusions: Our findings successfully identified factors associated with both increased and decreased risks of PONV. The magnitude of random variability due to different surgery types was identified using a mixed effects modelling technique, and the time varying effects of the selected covariates examined. An interactive web application developed using the predictive model is expected to improve clinician's accessibility and facilitate its use in the clinic.

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I-65: *Anne Chain* A Model Based Meta-Analysis of second generation antipsychotics for the treatment of Schizophrenia

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Objectives: This analysis aimed to develop a Model Based Meta-Analysis (MBMA)comparator model to provide a quantitative framework for the comparison and benchmarking of second generation antipsychotics (SGA) used for the treatment of schizophrenia under clinical development. Specific objectives include development of a network MBMA model describing the change from baseline of the total positive and negative symptom score (PANSS) with SGAs. As secondary objectives, MBMA will also be developed for only describing the positive and negative subscale scores.

Methods: A systemic literature review was conducted from the Quantify Schizophrenia Database, a schizophrenia literature database that consists of publicly available summary-level safety and efficacy data from trials investigating first- and second-generation antipsychotics. The database included 267 randomized controlled trials with approximately 60,000 patients. The database comprised of a source database that maintained the sources of information as well as a clinical outcomes database that contained information on trial, treatment, patient characteristics, efficacy and safety results of the trials.

Pre-specified list of inclusion/exclusion criteria, i.e. double-blind, sponsor- or investigator-initiated registration trials in adult patients with a typical disease duration of 1 years after the diagnosis of a first psychotic break up to ~20 years with a trial duration of 4-12 weeks, was used to select the final analysis dataset for the MBMA of sGAs. Model development, evaluation and simulations were performed using R 3.4.2. The models were developed using the generalized nonlinear least squares (gnls) function in R. Placebo response was described using non-parametric method to adjust for trial-to-trial variability. Drug effect was estimated using parametric method and dose-response was assessed where possible using an Emax model. Model appropriateness was assessed using diagnostic plots and covariates were graphically explored. Treatment effect estimates with associated 95% confidence intervals for each drug were derived from 10000 simulations with parameter values sampled from the multivariate normal variance-covariance matrix of the estimates.

Results: The selected analysis dataset contained monotherapy data from 33 trials of 10 oral SGAs as well as haloperidol for acute schizophrenia that either has forced dose titration or no dose titration. Long-acting or injectable formulations of SGAs were excluded. The models describing total PANSS score, positive and negative subscales were able to capture the data well and treatment effect was identified for each drug and dose-response relationship was obtained for lurasidone, risperidone and paliperidone. Age and black race were identified as significant covariates in the model. Treatment effects based on simulations using the MBMA model were obtained.

Conclusions: MBMA models for total PANSS, positive subscale and negative subscale scores of sGAs were successfully developed. Model estimated treatment effects provide a quantitative framework for benchmarking new investigational compounds in schizophrenia under clinical development.

I-66: *Anna Chan Kwong* Bridging studies: handling covariates models using the Prior approach

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Introduction/Objectives:

The PRIOR function in NONMEM stabilizes model estimates toward prior estimates by adding a penalty function on the objective function [1,2]: it enables the modelling of sparse data. However, covariate inclusion using this function requires further exploration.

We propose two strategies to handle covariates when modelling sparse data using the PRIOR function in NONMEM: first, to test the significance of a covariate already identified in the previous dataset (from which the prior parameters were estimated), second, to identify the covariates of the sparse dataset. We illustrate these approaches with the case example of a subcutaneously administered antibody.

Methods:

Two datasets were used for the analysis:

- Dataset A (previous data): rich data from two clinical trials (36 healthy volunteers, 546 samples; 18 patients, 154 samples)
- Dataset B (new data): sparse data from one clinical trial (216 patients, 1171 samples)

Population pharmacokinetic (PopPK) analysis was run with NONMEM® version 7.4.1. Covariate inclusion was performed with the Stepwise Covariate Modelling (SCM) tool implemented in Perl Speaks NONMEM (PSN)®[3] (forward inclusion: α=0.05, backward deletion: α=0.001). Age, weight, creatinine clearance, Glomerular Filtration Rate (GFR) and sex were tested as potential covariates.

Model A was built on dataset A.

Model AB was built on the pool of datasets A and B, to be used as a reference.

Dataset B was analysed using model A as prior in the PRIOR function, with two strategies for handling covariates:

1. Assessment of the significance of the covariate included in the previous model. Model A without covariate and Model A with covariate were both fitted on dataset B with informative PRIOR on all parameters. The two models were compared using the Likelihood Ratio Test (α=0.001). The sum of the weights of the prior estimates of each model was normalized to 1 in order to get comparable objective function values.
2. Search for new covariates. Model A without covariate was fitted on dataset B with informative PRIOR only on the parameters that needed to be stabilized. This model was then used as a base for SCM on the parameters estimated without prior information.

Covariates that were found statistically significant using strategies 1 and 2 (on dataset B) were compared to those of Model AB (on dataset A and B)

Results:

Model A and Model AB were monocompartmental with a first order absorption and a linear elimination, with interindividual variability estimated on all parameters (and a correlation between clearance and volume interindividual variability). Model A included the effect of age on clearance. Model AB included the effect of age, GFR and weight on clearance, and the effect of weight on volume. The relationship between clearance and age in Model AB was described by a piece-wise linear function ("hockey-stick").

The results of the two strategies to handle covariates on dataset B are presented below:

1. Assessment of the significance of the covariate included in the previous model. A drop of 7 points in objective function was found between Model A with or without covariate fitted on dataset B with informative PRIOR on all parameters, meaning that the covariate of Model A was not significant on dataset B.
2. Search for new covariates. As dataset B alone was sufficiently informative to estimate clearance and volume and their interindividual variability, the covariate search was done on these parameters. Informative PRIOR were implemented only on the absorption rate constant. The following covariates were included: GFR and weight on clearance, and weight on volume.

With both strategies, the covariate age that was included on clearance in both Model A and AB was not found to be statistically significant. This could be explained by the large difference in age distribution between Datasets A and B (median [range] of 36 [19-77] and 68 [44-85] respectively) together with an impact of age on clearance only across the "young" subjects, assessed by the piece-wise relation between age and clearance in Model AB.

Except for this covariate, the second strategy found the same covariates as Model AB.

Conclusions:

In this case example, the significant covariates found by the two strategies on the sparse dataset using the PRIOR function were consistent with those of the model of reference.

To generalize our results, this approach should be performed on simulations and challenged on other molecules and on datasets of different sizes.

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I-67: *Christophe Chassagnole* A precision dosing application for docetaxel in metastatic prostate cancer

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Introduction: The therapeutic window of chemotherapy drugs is commonly established at a population level and patient dose selection is often simply scaled with Body Surface Area (BSA). Due to large inter-individual physiological variability in term of ADME, this leads to a significant number of patients being under or over-dosed. While a limited number of precision dosing techniques exist to tailor patient-specific treatment, they typically require costly additional PK tests which severely restrict their use in clinical practice.

Objectives: Focusing on docetaxel for advanced metastatic prostate cancer, we have developed a demonstrator for precision dosing which requires a single weekly classical blood test in the first chemotherapy cycle. It will fit within the current clinical practice to improve patient outcome at low cost.

Methods: This tool was developed using publicly available data from the comparator arm of a phase III clinical trial for metastatic hormone-resistant prostate cancer (clinical trial number NCT00617669). This cohort includes 412 patients who were treated with docetaxel between 2008 and 2011 in cycles of 21 days with weekly blood tests in the first cycle.

A population PK/PD model for docetaxel and leukocyte population was assembled based on the literature [1, 2]. Individual patient parameters including docetaxel Area Under the Curve (AUC) were estimated by calibrating this model with weekly measured blood cell counts using a Bayesian approach. Survival and toxicity Cox models were developed using estimated PK/PD parameters as well as biomarker levels. They allowed estimations of gains in prognostic as well as toxicity risks associated with modifying patient dose after the first chemotherapy cycle.

These models were made available through a web application which supports clinicians in their decision to update patient dose. In a typical *in-situ* scenario, the patient would receive a first cycle of chemotherapy based on standard BSA-guided dose. Before administering the second dose, the clinician would enter the results of their patient's weekly blood tests in the app, which they would then use to estimate prognostic gains and toxicity risks associated with dose changes. This would help them make an informed dose selection for the second cycle. All subsequent doses would be kept identical unless severe toxicity is observed.

Results: Concordance levels of the order of 0.7 were obtained for the survival and toxicity models, with significant predictive variables including docetaxel AUC, age, patient protein and enzyme levels as well as Prostate Specific Antigen (PSA).

Patients with low estimated hematologic toxicity (neutrophil count not dropping under 0.5 billion/L) presented a median overall survival time of 480 days, against 625 days for patients with higher hematologic toxicity. Patients with low estimated docetaxel AUC (

Conclusion: We have developed a precision dosing app for docetaxel in metastatic prostate cancer which requires a single weekly classical blood test in the first chemotherapy cycle. This app will work as a decision support tool for clinicians, assisting them in adapting docetaxel dose to the patient from the second treatment cycle onwards. That has the potential to significantly improve patient outcome at low cost without disrupting current clinical practice.

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I-68: *Estelle Chasseloup* Use of mixture models in pharmacometric model-based analysis of confirmatory trials: part II – control of the type I error with real placebo data

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Objectives Controlling the type I error of the clinical trials designed to evidence drug efficacy is critical during drug development, to avoid unnecessary and unethical studies. To analyse the results of such proof-of-concept (POC) studies, non-linear mixed-effect models (NLMEM) are a good alternative to the classical approaches and are increasingly recommended. NLMEM are very efficient in terms of power for the POC studies[1,2], but inflated type I error rate, as a consequence of model misspecifications, is a main drawback. In this work, we used real data to compare both the type I error rate and the bias in drug effect estimates, together with their sensitivity to model misspecifications, for two NLMEM-based approaches: the standard approach, and a new approach using mixture models called individual model averaging (IMA)[3].

Methods Two real data set were used: pain score from patients with neuropathic pain receiving placebo[4,5], and the severity test ADAS-Cog from the natural history of patients with Alzheimer's disease[6]. The type I error rate was computed as the frequency with which there is a significant improvement in the model's likelihood, according to the likelihood ratio test (LRT; =0.05), by allowing different predictions based on the randomized treatment. By randomly (1:1) assigning patients in the above studies (n=800 for the ADAS-Cog data, and n=230 for the pain data) to "drug" and "placebo" treatment, we created data sets where any significant drug effect is known to be a false positive. Repeating the process of random assignment and analysis for significant drug effect many times (n=1000) for each placebo-drug model combination, statistics of the type I error were obtained.

For each combination in the standard approach, the base (only placebo effect) and the full (placebo and drug effect) models were compared. In the IMA approach, two submodels (placebo and placebo+drug effect) were present in both the base and the full model. In the base model, the probability for each subject to be described by one of the two models was 0.5. In the full model, the association between the treatment and the probability of a submodel allocation was estimated, using the treatment as a covariate.

Results The results showed that the IMA approach had a better type I error control than the standard approach, both on the pain and the ADAS-Cog data. 32 placebo-drug model combinations were tested on the pain data, and 110 on the ADAS-Cog data. For the pain data, the type I error rate of the standard approach was (minimum, 25^{th}, 50^{th}, 75^{th} percentile, maximum) 6.2, 41.8, 96.3, 100.0,100.0; and 2.5, 4.2, 4.9, 5.6, 6.3, for the IMA approach. For the ADAS-Cog data, the type I error was 3.6, 8.8, 26.4, 100.0, 100.0, and 0.3, 2.2, 3.5, 4.2, 5.8, for the standard and the IMA approach respectively. In terms of bias in the drug effect estimates, the IMA showed no bias, whereas in the standard approach the bias was frequently present.

Conclusion The results showed that the IMA approach has a better type I error control and less biased drug effect estimates than the standard approach. The IMA approach was more robust towards

misspecifications in the placebo model. Using IMA to analyse confirmatory trials seems a promising method to address the drawbacks of the standard NLME approach.

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I-69: *Jonathan Chauvin* Novel user-friendly applications for dose individualization of sunitinib and imatinib

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Objectives: Therapeutic drug monitoring (TMD) and dose individualization can contribute to increased benefits for patients by augmenting the efficacy and/or decreasing the risk of toxicity. TMD is especially interesting for drugs exhibiting a highly variable exposure between patients and a small therapeutic window. Target therapeutic windows are usually defined for the steady-state through concentration of repeated dosing regimens and a single drug concentration measurement is made.

For a number of drugs, such as Kinase Inhibitors [1] or Animoglycosides [2], clear relationships between exposure and treatment outcome have been established, thus allowing for the definition of target exposure values.

While dose individualization has been more and more advocated over the years, the lack of dedicated, user-friendly and reliable decision-support software hampers its use on a large scale in hospital care. We present dose-recommendation tools for two TKIs (sunitinib and imatinib) and the results of their retrospective application on TMD hospital data.

Methods: The dose adaptation procedure is divided in two steps: first we determine the pharmacokinetic parameters of the patient (such as volume and clearance) and second we use these parameters to perform simulations of alternative doses. For the first step, we integrate the information from a population PK model (usually a literature model revalidated and adjusted on internal data), the patient covariates if relevant (age, weight, …) and the TMD drug concentration measurement(s) to calculate the conditional probability distribution of the individual parameters. For the second step, simulations of the trough concentration after new doses taking into account the operational constraints (such as available tablet doses) are performed using the estimated individual parameters. The dose most likely to reach the target is selected.

This procedure has been implemented within two applications: one for sunitinib and one for imatinib. The applications share the same calculation engine as the MonolixSuite, which is widely used for population PK/PD modeling. They have been developed in collaboration with clinical pharmacologists to fit to the practical needs in hospitals.

Results: The interface is meant to be usable by non-modelers such as clinicians. The interface allows to enter:

- the current treatment (dose, inter-dose interval and treatment start day)
- the date and time of the last dose
- the date and time of the measurement
- the patient covariates (if relevant and available)
- patient ID
- user ID

The application returns a dose recommendation as well as the drug concentration profile (and its uncertainty) with the current dose and with the proposed dose. A report is generated automatically based on a template and the entered information is saved to an audit trail local data base. The two applications are currently experimentally used in routine in 3 hospitals in France.

To evaluate in advance the proportion of the patients that would benefit from sunitinib dose individualization, we have applied our dose-recommendation application to the TMD (without adaptation) data base of the Cochin Hospital (Paris, France). The data base records around 900 PK measures for 233 cancer patients. For only 16% of the patients the application recommended to maintain the standard dose, while for 67% the recommended dose was below the standard and for the remaining 17% above.

Conclusions: The developed dose-recommendation applications permit to use all the available information in a rigorous mathematical framework to suggest the dose most likely to reach the therapeutic target. In addition, estimating the individual parameters gives more flexibility for the logistics: the measurement does not need to be at the trough and the steady-state does not need to be reached, as the steady-state concentration at through can be calculated from the individual parameters.

The retrospective study on past sunitinib data shows the need for TMD and dose adaptation. The routine use of the dose adaptation applications will allow a more precise assessment of the benefits. In addition, the dose adaptation on sunitinib is expected to reduce the overall cost of the treatment as the average recommended dose is smaller than the standard dose.

The presented applications are easy to use and currently tested in several hospitals. Applications for further types of drugs (everolimus, vancomycin, …) are in test phase or under development.

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I-70: *Alexia Chauzy* Semi-mechanistic pharmacodynamics modeling of aztreonam-avibactam combination to understand its antimicrobial activity against multidrug-resistant Gram-negative bacteria

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Objectives: Aztreonam-avibactam (ATM-AVI) is a promising β-lactam-β-lactamase inhibitor combination to treat serious infections caused by multi-drug resistant (MDR) pathogens including those producing metallo-β-lactamases (MBLs). Three distinct effects have been previously characterized for AVI [1]: inhibition of β-lactamases, proper bactericidal effect and enhancement of ATM bactericidal activity. The aim of this study was to investigate the individual contribution of each of the three AVI effects using a semi-mechanistic PK-PD modeling approach.

Methods: ATM MICs were determined both in the absence and in presence of AVI at different concentrations (from 0.004 to 32 mg/L) for four MDR *Enterobacteriaceae* with different β-lactamase profiles. For static time-kill studies, ATM concentrations were set at 0.25, 0.5, 1, 2 and 4 times the MIC in combination with different AVI concentrations ranging from 0 to 8 mg/L. The effect of AVI alone was also evaluated. The fraction of pre-existing resistant bacteria was determined by culturing the initial inoculum onto agar plates supplemented with ATM-AVI at concentrations of 1 to 16 times the ATM MIC in combination with 4 mg/L AVI. In order to take into account ATM degradation by β-lactamases, the actual concentrations of ATM and AVI were determined by LC-MS/MS. ATM bactericidal effect and the three different effects of AVI were estimated using NONMEM 7.4 [2]. Simulations using the final model were then conducted in order to evaluate the impact of the three AVI effects separately at clinical range of ATM and AVI concentrations.

Results: A common structural model with two sub-populations, slightly different from the one previously developed by Sy et al. for ATM-AVI [3] and ceftazidime-AVI [4], was applied for all strains. There was no transformation between bacterial states, and the fraction of resistant bacteria was fixed at the value determined experimentally. ATM bactericidal effect was modeled as an increase in the killing rate for both subpopulations, according to a sigmoidal E_{max} model with a higher EC_{50} for the resistant state explaining regrowth. In addition, the three previously reported effects of AVI [1] could be well characterized by the PK-PD model. Bacterial counts impacted on ATM degradation according to an exponential function and the prevention of degradation by AVI was modeled according to a fractional inhibitory E_{max} model, except for *E. coli* strain for which no ATM degradation was observed even in the absence of AVI. AVI bactericidal effect was characterized by a sigmoidal E_{max} model affecting the susceptible subpopulation. And, the enhancement of ATM bactericidal activity by AVI was modeled as a decrease of ATM EC_{50} with increasing AVI concentrations using a bi-exponential function. According to the simulation results, among the three AVI effects, the enhancing effect was the most important, leading to a percentage of maximum effect close to 100% whatever the strain. On the other hand, the inhibitory effect of AVI poorly contributed to total effect resulting in bacterial response similar to that for ATM alone

Conclusions: Even though AVI prevented ATM degradation, model predicted that the combined bactericidal activity was mostly explained by the enhancement of ATM effect within concentrations currently used in the clinic for ATM alone and AVI in the combination with CAZ. Therefore, when selecting a β-lactamase

inhibitor for combination with a β-lactam, its capability to enhance the β-lactam activity should be considered in addition to the spectrum of β-lactamases inhibited.

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I-71: *Viji Chelliah* Mechanistic models of cancer-immune cycle and immunotherapies

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Introduction: Immuno-oncology (IO), where treatments mobilize a patient's immune system to fight cancer and provide lasting therapeutic benefit, is the fastest developing area of oncology. New therapies are being aimed at targeting different stages of the cancer-immunity cycle [1], which involves a dynamic system of non-linear interactions between cellular and molecular players of the immune system and tumour. The design of an effective cancer immunotherapy is complicated by various factors, including a potentially immunosuppressive tumour microenvironment, immune-modulating effects of conventional treatments and therapy-related toxicities. Quantitative and mechanistic understanding of this system is crucial to unravel these complexities where the application of the Quantitative Systems Pharmacology (QSP) approach becomes inevitable for diverse clinical decision making in IO drug discovery and development.

This work was carried out as a part of Certara's QSP IO Simulator Consortium Project [2], which aims to develop a mechanistic model of cancer-immune system dynamics through which combinations of different cancer therapies, different dose regimens and biomarkers in a virtual patient population can be tested.

Objectives: The aim of the present work was to conduct a comprehensive survey of IO literature-based models and to translate this to a QSP map of IO mechanisms. Hence, the study was focused on 1) to survey and integrate the knowledge from IO literature-based, 2) to understand the extent of cancer-immunity system dynamics that are captured by these models, and 3) to objectively compare the gaps where the growing awareness (from experimental/clinical and omics data) on cancer-immune system dynamics have not been well characterized or captured in the models.

Methods: We systematically surveyed 136 published mechanistic models describing various components of cancer-immune system dynamics, and immunotherapies. Information regarding the following topics were captured from the model papers: 1) the purpose for which the model was developed, 2) model variables (cell-types, cytokines, growth-factors, cell-surface receptors and other molecular signatures) and their interactions, 3) treatment types (mono, or in combination), 4) study type (preclinical/clinical data) and 5) the biomarkers used for model validation.

Results and Conclusions: We distill and discuss several example models that have grown in complexity by incorporating the advances in cancer-immune biology. We then integrated the mechanisms described in different models and developed a unified QSP map, which was implemented in the Certara QSP Platform which provided an illustration of the extent of cancer-immune system dynamics that have been mechanistically well characterized and quantitatively studied.

Even though there were several overlapping models that describe the same aspect of cancer-immunity cycle, the level of granularity in describing the underlying mechanisms differed between models, and together they cover a vast majority of cell-types and molecular signatures involved in the cancer-immune system biology. The 136 literature-based models describes the mechanisms involving 15 different cells types (includes cancer cells, immune cells and stromal cells) and 36 molecular signatures (includes cytokines, chemokines, cell-surface receptors, growth factors and intra-cellular molecules), applied to predict different treatment scenarios (with both immunotherapy and non-immunotherapy agents). This

comprehensive analysis of literature models of the cancer-immunity cycle allowed us to identify gaps in knowledge incorporation in models and where new interventions are needed to be applied.

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I-72: *Lu Chen* Bioavailability and the Variability of Posaconazole Exposure in Healthy Volunteers Using a Population Pharmacokinetic Analysis

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Objectives: Posaconazole is a broad-spectrum, systemic triazole antifungal drug and is widely used for prophylaxis and treatment of invasive fungal disease [1]. Exposure upon administration of the first released formulation, posaconazole suspension, showed high inter-individual pharmacokinetic variability due to erratic absorption [2,3], which can lead to an insufficient exposure and treatment failure. Intravenous posaconazole was subsequently released in response to the potential limitation of the oral suspension [4]. This allows us to establish the oral bioavailability. Our aim is to determine for the first time the absolute oral bioavailability of posaconazole suspension and quantify inter-individual variability of posaconazole pharmacokinetics in healthy volunteers.

Methods: Two healthy volunteer studies were conducted at Radboud university medical center, our analysis included 220 measurements from 20 subjects receiving posaconazole suspension at steady state [5], and 80 measurements from 8 subjects after a single dose of intravenous posaconazole 300 mg. In the intravenous posaconazole dataset, blood samples were collected throughout a 48 h period at 11 pre-defined time points (0.75, 1, 1.25, 1.5, 2, 4, 8, 12, 24, 48 h) after dosing.

NONMEM 7.3 was used to characterize the pharmacokinetics of posaconazole suspension and injection in a healthy adult population. The first-order conditional estimation method with interaction was used during model development. One, two and three compartment models with linear elimination were investigated. First-order absorption (with and without absorption lag time) and a multiple dose transit compartment models were investigated to describe the absorption of posaconazole suspension. For the estimation of bioavailability, a logit transformation was applied to ensure the estimate remained between 0 and 1. Inter-individual variability terms were tested on all pharmacokinetic parameters using log-normal distributions, with the exception of inter-individual variability in bioavailability, which was modeled with a normal distribution in the logit domain. Proportional, additive, and combined additive and proportional residual error models were evaluated. Two covariates, age and weight were investigated on clearance, volume of central and peripheral compartment, which were tested using linear and exponential relationships.

Visual predictive checks based on 1000 simulations were performed for model validation and a bootstrap procedure based on 1000 resampled datasets was used to further test the robustness of the final model.

Results: A two-compartment model with a lag time followed by first-order absorption and a first-order elimination best described the pharmacokinetic profiles of oral and iv posaconazole. The absolute bioavailability of posaconazole suspension was estimated to be 46.3% (residual standard error [RSE], 11.8%). The clearance was 5.9 L/h (RSE, 9.6%) and the lag time was 1.8 h (RSE, 3.3%).

The inter-individual variability for clearance, central volume and peripheral volume were 37.7% (RSE, 11.9%), 29.6% (RSE, 17%) and 101.0% (RSE, 35.9%), respectively. Inter-individual variability on bioavailability could not be identified. A proportional residual error model was used and the goodness-of-fit

plots indicated an acceptable model fit. None of the tested covariates was statistically significant in our analysis. The visual predictive checks indicated a good predictive performance, with acceptable agreement between the observations and model-simulated confidence intervals for the 5th, 50th, and 95th percentiles. Parameter estimates from bootstrap were close to those obtained from the original data set, suggests the parameter estimation in the final model is accurate and the model is with no misspecification.

Conclusions: This analysis is the first to quantify absolute bioavailability of the posaconazole suspension as 46.3%, which is slightly lower than the 54% reported for a delayed-release tablet [6]. The investigation of the bioavailability of the posaconazole suspension in various patient populations is part of further investigation.

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I-73: *Maxwell Tawanda Chirehwa* Population pharmacokinetics of cycloserine dosed as terizidone in drug-resistant tuberculosis patients

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Objectives: Cycloserine or its structural analogue terizidone which consists of two molecules of cycloserine (1), is a key drug recommended by WHO in long treatment regimens for multidrug-resistant tuberculosis (MDR-TB) (2). Considering the neurotoxicity associated with the use of cycloserine, and the relative weakness of many of the second-line anti-TB drugs, data defining target cycloserine exposures is needed. We describe (a) the population pharmacokinetics of cycloserine dosed as terizidone and (b) the distribution of the percentage of time the concentration is above the MIC (%Time$_{>MIC}$) within a 24-hour dosing interval.

Methods: We recruited adult patients on treatment for MDR-TB at two hospitals in South Africa. During the study period, the standard MDR-TB treatment regimen consisted of moxifloxacin, kanamycin, pyrazinamide, cycloserine dosed as terizidone (dosed by weight band), ethambutol, and ethionamide or high-dose isoniazid. Blood samples were collected pre-dose and at 2, 4, 6, 8, and 10 hours post-dose, and in 9 of 133 participants additional samples were collected at 12, 24, and 26 hours post-dose. We quantified plasma concentrations of cycloserine using a validated LC/MS/MS assay and interpreted using nonlinear mixed-effects modelling in NONMEM version 7.4.2. Assuming two molecules of cycloserine for each molecule of terizidone, the dose of terizidone was converted to an equivalent dose of cycloserine, adjusting for molecular weight. We evaluated one- and two-compartment disposition models with first-order absorption (with or without a delay) and elimination. We included allometric scaling in the base model, and considered the effect of other physiologically plausible covariates including creatinine clearance (CrCL, calculated using the Cockroft-Gault formula). We determined baseline sputum MICs using Sensititre MYCOTB MIC plates and calculated the proportion of patients with %Time$_{>MIC}$ of at least 30% (3), assuming a lung cavity-to-serum penetration ratio of 0.09 (4).

Results: 927 plasma samples were available from 166 pharmacokinetic profiles. The median weight and fat-free mass were 47 kg (range: 30 – 85) and 40.7 kg (24.1 – 58.9), respectively. A one-compartment disposition model with first-order absorption (after a delay described by a chain of transit compartments) and elimination best described the pharmacokinetics of cycloserine. The parameter estimates of the final model were: CL/F (0.832 L/h), V/F (23.3 L), Ka (0.836 h^{-1}), MTT (0.565 h). The model could detect two clearance pathways, non-renal and renal, with the latter being modulated by CrCL and accounting for approximately 50% of elimination. The predicted CrCL was adjusted to a median weight of 47 kg and its effect was included in the model relative to the median CrCL of 100 mL/min (5). Allometric scaling was included on both pathways and on the volume of distribution using FFM (52 points drop in OFV). Between-subject variability was supported on CL/F, and between-occasion variability was included on Ka, MTT, and F. MIC values (median [range]: 16 [2, 32] mg/L) were available for 103 patients. While the median plasma trough concentration (18 mg/L, range: 3 – 41 mg/L) was predicted to be above the MIC of 82% of the

patients, the %Time$_{>MIC}$ in the lungs was >30% in 2/103 patients (MIC was 2 and 4 mg/L, respectively) and zero in the rest of the cohort.

Conclusions: To our knowledge, this is the largest population pharmacokinetic study describing cycloserine dosed as terizidone. Cycloserine pharmacokinetics was best described by a one-compartment disposition model with first-order absorption and elimination. The estimated proportion of cycloserine eliminated via the renal pathway (50%) is lower than the range previously reported of 60-70% (6).

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I-74: *Siri Kalyan Chirumamilla* Application of physiologically-based pharmacokinetic model to mechanistically predict increased tumour uptake of paclitaxel in cancer patients

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Objectives: Tubulin targeting drugs such as paclitaxel exert their effect intracellularly within tumor, thus sufficient intracellular drug concentrations are essential for a pharmacological response, and thus the ability to predict the concentrations of drug at site of action has the potential to improve dose and dosage regimen finding. This study aimed to build a PBPK model extended with a tissue composition based permeability limited tumor model to (a) gain a mechanistic understanding of the paclitaxel distribution in tumor and (b) to predict clinical tumor exposure in breast cancer patients.

Methods: The permeability-limited tumor model available within the Simcyp Simulator V18 that integrates data on tumor composition and drug physiochemical properties was used. The model assumes that unbound drug is in equilibrium between the vascular and interstitial compartments and drug movement between the interstitial and intracellular space is via passive permeability (PS). Total tumor concentration is dependent on the concentration dependent nonlinear drug binding to target protein, neutral lipids, neutral phospholipids in the intracellular space, albumin in the interstitial and vascular spaces. A RES-Paclitaxel file which was developed in Simcyp Simulator using the Sim–Cancer population and verified with the clinical studies PK data at doses 80 mg/m^2, 135 mg/m^2 and 175 mg/m^{2}was used. Clinical tumor physiological parameters such as volume, blood flow and tissue composition are defined using published data (Default values for tumor model in Simcyp Simulator V18), the published Intracellular tubulin concentration[1] and tubulin-binding affinity [2] determined in cell cultures were used. The PS for the tumour was calculated using passive intrinsic permeability (Ptrans0) predicted from Simcyp ADAM Mechanistic Permeability (MechPeff) model and surface area of tumour calculated from cell volume based calculations.

Results: Consistent with clinical data, where 4-70 fold higher drug concentration are measured in tumor biopsy compared to plasma taken at ~ 20 hours after initiation of a 3 hour 175 mg/m^2 i.v. infusion in six previously untreated locally advanced breast cancer patients[3], the model predicts a 28.9 – 76.8 fold higher tumor exposure relative to plasma at 20 hours in six female patients. A 48.5 fold change in the fraction unbound in the intracellular space was observed, indicating concentration dependent nonlinear binding of paclitaxel to tubulin, and from sensitivity analysis, drug accumulation in tumour was found to be highly sensitive to the tubulin concentration, therefore inter-individual difference in the tubulin concentrations could be one of the reasons for observed variability in drug accumulation in tumour.

Conclusions: This model is useful to mechanistically understand the distribution of drugs in tumour tissues and to investigate the sensitivity of the model to key tumour attributes, including target concentration, blood flow and interstitial pH that may contribute to variability in drug exposure and treatment response. A similar modelling approach may be used to predict the tumor exposure of other small molecule anticancer drugs from their plasma concentration and physicochemical properties.

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I-75: *Palang Chotsiri* Mechanistic modelling of primaquine pharmacokinetics, gametocyte clearance, and mosquito infectivity

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Objective: Primaquine is the only antimalarial drug targeting the sexual stage of *Plasmodium falciparum*, gametocytes, which are responsible for the transmission of malaria. WHO suggests to add a single low dose of primaquine (0.25 mg/kg) to the normal artemisinin-based combination therapy (ACT) in order to reduce malaria transmission in low transmission areas [1]. However, the mechanism of gametocyte reduction and the reduction of malaria transmission after primaquine administration is still unknown. This study aimed to characterize the pharmacokinetic properties of primaquine and its metabolite, carboxyprimaquine, and to develop a mechanistic model for gametocyte clearance in patients and link this model to mosquito infectivity.

Methods: Eighty-one G6PD normal males with uncomplicated *falciparum* malaria with a detectable gametocytemia received a standard dose of dihydroartemisinin-piperaquine (DHA-PQ) [2]. In addition, each patient was randomly assigned to receive a single low dose of primaquine on day one (placebo, n = 16; 0.0625 mg/kg, n = 16; 0.125 mg/kg, n = 17; 0.25 mg/kg, n = 15; or 0.5 mg/kg, n = 17). Primaquine and carboxyprimaquine concentrations, gametocytemia, and mosquito infectivity were quantified. Pharmacokinetic and pharmacodynamic properties of primaquine were investigated using nonlinear mixed-effects modelling (NONMEM v.7.4).

Results: Primaquine and carboxyprimaquine plasma concentration-time profiles were modelled simultaneously using a linear drug-metabolite model, assuming 100% conversion of parent drug to metabolite. The absorption properties of primaquine were explained by a transit-compartment absorption model (n = 6) with an estimated fraction of a first-pass metabolism. A mechanistic model of gametocyte maturation was implemented as the pharmacodynamic model, consisting of five gametocyte compartments (G_I – G_V) representing the five gametocyte development stages. The first four stages (G_I – G_{IV}) represents undetectable immature and sequestered gametocytes, and the fifth stage (G_V) represents the observed circulating gametocytes. Transit rates between these gametocyte stages were fixed to two days, based on literature values. The co-administered antimalarial combination therapy (DHA-PQ) was assumed to be highly effective against asexual blood stage parasites, resulting in no additional gametocyte proliferation after start of treatment. Higher primaquine doses were associated with a higher gametocyte clearance, described by an E_{MAX} relationship between primaquine concentrations and gametocyte death

rate. The substantially delayed gametocyte killing effect of primaquine was characterized using a series of transit-compartments and an effect compartment. A combined E_{MAX} function, based on gametocyte density and primaquine concentrations, was used to explain the observed probability of mosquito infectivity.

Conclusion: The pharmacokinetic properties of primaquine and caboxyprimaquine were described successfully by a simultaneous drug-metabolite model. A mechanistic pharmacodynamic model quantified the relationship between primaquine exposure and gametocyte killing, resulting in increased killing of the sexual parasites at higher doses of primaquine. Both gametocyte density and primaquine exposure determined the probability of mosquito infectivity. Thus, the developed model described the pharmacokinetic properties of primaquine and its transmission blocking effects, demonstrating highly effective transmission blocking properties by a direct gametocyte killing effect and an additional drug effect most likely due to its sterilizing effects on the sexual form of the parasite.

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I-76: *Emmanuelle Comets* Conditional non-parametric bootstrap for non-linear mixed effect models

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Introduction: Standard errors of estimation (SE) measure the precision of estimation for the parameters in a statistical model. A commonly used approach in non-linear mixed effect models (NLMEM) is to use the inverse of the Fisher information matrix to derive the SE. How well this asymptotic approximation holds in practice is a matter of debate, and alternative approaches have been proposed such as log-likelihood profiling and bootstrap methods.

Bootstrap approaches have been extended to NLMEM by considering the different levels of variability involved at the individual and population level. They include the case bootstrap, resampling individuals, the non-parametric bootstrap, which resamples residuals within and across individuals and the parametric bootstrap, resampling from a distribution. Thai et al. have investigated their properties in NLMEM for different numbers of subjects in sparse or rich designs, and found contrasted results [1]. A question arising was whether it would be possible to improve the correction of the residuals, performed before resampling to compound for shrinkage, to benefit from the non-parametric bootstrap's ability to maintain the structure of the original dataset, while being less dependent on model assumptions than the parametric bootstrap.

In the present work, we propose an alternative non-parametric bootstrap, resampling from the conditional distribution of the individual parameters, and evaluate it in a simple framework.

Methods: A general bootstrap algorithm consists in creating bootstrapped datasets through resampling, fitting a model to the data, and storing the parameter estimates from each replicate to form a bootstrap distribution of the parameters. We implemented four bootstrap approaches: case, parametric, non-parametric [1], and conditional non-parametric bootstrap. In this new approach, instead of correcting the estimated random effects for shrinkage, we sample random effects within a set of 100 samples from the conditional distribution [2].

The bootstrap approaches were evaluated in a simulation study, using a one-compartment model, simplifying the model developed to describe the pharmacokinetics of valproic acid in children in [3]. Both single dose and SS profiles were simulated, and the design included 100 subjects with 6 sampling times, which were obtained by optimal design using PFIM [4].

The bootstraps and the asymptotic method were compared in terms of bias, standard errors (SE) and coverage rate of the 95% confidence interval for all parameter estimates. We used the SAEM algorithm implemented in R in the saemix package [5,6], as well as the MlxConnectors library, interfacing with Monolix [7], for comparison.

Results: In the single dose scenario, all methods provided unbiased estimates of the fixed parameters and of the variabilities, with the exception of the conditional non-parametric bootstrap which underestimated the variability of clearance and volume of distribution. All methods yielded biased estimations of the SE for

at least some of the parameters, although the absolute difference was actually small, and again, the conditional non-parametric bootstrap showed more bias than the non-parametric bootstrap. In the steady-state scenario, biases appeared also for the bootstrap estimates of the parameters themselves, and were more pronounced for the SEs. The single-dose simulation was run in MlxConnectors and showed qualitatively similar results.

Conclusions: Using samples from the conditional distribution in the non-parametric bootstrap increased the bias on bootstrap estimates of both parameters and SE, compared to the standard non-parametric bootstrap. We chose a simple scenario with linear pharmacokinetics for this first evaluation, as a method needs to perform well in simple settings before we use it in more complex conditions. Unfortunately none of the bootstraps, including our new proposal, clearly improves over the asymptotic method, and in particular they are unable to correct for estimation bias in the asymptotic method.

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I-77: *Valerie Cosson* Target-mediated drug disposition model of RG6206 (RO7239361), an anti-myostatin adnectin-IgG1-Fc-fusion protein, with positive feedback on myostatin endogenous production in healthy adults but not in boys with Duchenne Muscular Dystrophy

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Objectives: RG6206 (RO7239361) is a fully human anti-myostatin adnectin-IgG1-Fc-fusion protein that binds to and neutralizes the biological activity of myostatin, a protein that prevents muscle cell growth and differentiation. This blockade is expected to lead to larger and stronger muscles in human. The compound is currently in development for the treatment of patients with Duchenne Muscular Dystrophy (DMD). The objectives of the analysis are to describe the PK of RG6206 and the PKPD relationship between total RG6206 and free myostatin serum concentrations in healthy adults (HVs) and DMD patients using the population approach.

Methods: Blood samples for RG6206 and myostatin analysis were collected in two studies after subcutaneous administration: a single and multiple ascending dose study in HVs and a multiple ascending dose study in DMD boys. In total data from 109 HVs and 43 DMD boys were included in this analysis. Both total RG6206 and free myostatin serum concentrations were fitted together using the quasi-steady-state approximation of the full target-mediated drug disposition (TMDD) model [1-3]. HVs and DMD patient data were modelled separately since the bioanalytical methods for measurement of free myostatin were different. All models were developed using non-linear mixed-effects modelling implemented in NONMEM V7.4.0 [4].

Results: Total RG6206 and free myostatin serum concentrations in HVs were well characterized by the TMDD model. The PK was described with a one-compartment model with linear absorption and elimination. A positive feedback control was added on the myostatin endogenous production to describe the rebound of the free myostatin concentrations after the end of the treatment. It is known that increasing levels of active myostatin protein down-regulate its own expression [5,6] and an up-regulation can therefore be expected in case of inhibition of myostatin activity. The BSV on CL/F and V/F were moderate (<29%), and the BSV on Ka was large (83%). The BSV on PKPD parameters were 36% for Ksyn (myostatin production rate), 37% for Kint (RG6206-Myostatin complex degradation rate) and 53% for Kin (moderator production rate). Body weight was found to have a significant effect on CL/F and V/F with exponents fixed to the allometric values, 0.75 for CL/F and 1 for V/F. When the free myostatin is saturated, the half-life of RG6206 is estimated at ~14 days.

In DMD boys, the PK was described by the same model as in HVs but with an additional weight effect on Ka to capture the slower absorption observed with increasing weight. The population CL/F and V/F parameters and their associated weight effect were fixed in DMD boys to those estimated in HVs to ensure PK continuity between the two populations. The limitation of the PD sampling scheme and the absence of sampling after the end of treatment prevented the estimation of all TMDD parameters so Kss and Kint were fixed to those estimated in HVs. Contrary to HVs, the positive feedback control on the myostatin synthesis was not present in DMD boys. The reason is unknown, but does not seem to be due to the sampling scheme since this feedback estimated in HVs should lead to a slow increase of the free myostatin trough levels under treatment and that was not observed in DMD boys. BSV on CL/F and V/F were moderate

(<30%) while BSV on Ka and Ksyn were large 60 and 80% respectively. The body weight effect on CL/F and V/F of RG6206 in DMD boys could be well captured by the allometric coefficients used in the HVs model. The simulations show that the PK and PD steady states were reached after ~12 and 6 weeks, respectively, of QW administration of RG6206 to DMD boys weighing 16 to 46 kg. At steady-state, RG6206 maintains a reduction in free myostatin from baseline of ~77, 92 and 97% over the dosing interval with the weekly 4, 12.5 and 35 mg dose, respectively.

Conclusions: The PK of RG6206 and its effect on the free myostatin in HVs were accurately described by a model based on the TMDD concept with a positive feedback on the synthesis of myostatin. In DMD boys, a similar PKPD model structure as in adult HVs could accurately described the data however no positive feedback was needed.

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I-78: *Perrine Courlet* Influence of drug-drug interactions on population pharmacokinetics of atorvastatin and its active metabolite ortho-OH-atorvastatin in people living with HIV.

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Objectives:

Antiretroviral treatments (ARTs) have transformed HIV infection from a deadly disease to a chronic condition. People living with HIV (PLWH) are aging, experience age-related physiological changes and comorbidities, such as cardiovascular diseases. Atorvastatin is a widely prescribed lipid-lowering agent, predominantly metabolized by cytochrome (CYP) 3A4 into two major active metabolites: *ortho*-hydroxy (*o*-OH-atorvastatin) and *para*-hydroxy atorvastatin (*p*-OH-atorvastatin) (1, 2). The organic anion transporter protein (OATP1B1/1B3) regulates the entry of atorvastatin in the liver (3). Protease inhibitors are expected to substantially increase atorvastatin exposure by inhibition of its entry in the liver and its further biostransformation, potentially leading to serious side effects such as rhabdomyolysis. The aims of this study were to describe the pharmacokinetic profile of atorvastatin and *o*-OH-atorvastatin, to identify influencing factors and to evaluate drug-drug interactions (DDIs) with ARTs.

Methods:

Atorvastatin pharmacokinetic assessment involved rich (clinicaltrials.gov, NCT03515772) and sparse sampling studies (SHCS #815). The population pharmacokinetic analysis was performed using NONMEM®, with full PK profiles (87 atorvastatin concentrations) collected in eight PLWH, and then adding 79 atorvastatin concentrations from 55 PLWH. After removal of unreliable *o*-OH-atorvastatin concentrations (37% of metabolite data), 110 metabolite concentrations were available for model development. Plasma concentrations were converted into their molar equivalents. A stepwise procedure with sequential addition of the metabolite was used to find the model that adequately fit the data. For identifiability issues, the volume of distribution of atorvastatin and its metabolite were assumed to be equal. The correlation between parent drug and metabolite concentration measurements was tested using the L2 function. The influence of age, body weight and comedications on *o*-OH-atorvastatin formation rate was quantified.

Results:

A two-compartment model with first-order absorption and elimination best described atorvastatin pharmacokinetics, although variability was very high, notably during the absorption phase. During the analysis of rich pharmacokinetic data, absorption rate constant was estimated at 3.06 h^{-1} with high between-subject variability (BSV, 778%) and was fixed to this value for subsequent model development. *o*-OH-atorvastatin concentrations were described by adding one compartment and by assuming linear metabolism from atorvastatin. When combining all data, atorvastatin apparent clearance was 232 Lh^{-1} with a BSV of 105%. Atorvastatin apparent central volume of distribution was 3300 L (BSV 100%), apparent peripheral volume of distribution 830 L, and intercompartmental clearance 116 L/h. *o*-OH-atorvastatin

metabolic rate constant (k_{23}) was 0.265 h^{-1} with a BSV of 76%, and apparent clearance of the metabolite 1430 $L.h^{-1}$. K_{23} was reduced by 56% in PLWH treated with CYP3A4 inhibitors (*i.e.* boosted protease inhibitors and boosted integrase inhibitors) and explained 15% of the variability on k_{23}. Conversely, the presence of a CYP3A4 inducer (*i.e* efavirenz) increased k_{23} by 22% but this association did not reached statistical significance due to the lack of data (8% of atorvastatin concentrations). Finally, age was associated with a non-significant decrease of 8% of k_{23} for a 70-year patient compared to a 50-year patient. The narrow age interquartile range (58-71 years) might have compromised our power to detect an effect of age.

Conclusions:

The present study showed an important inter-individual variability in atorvastatin pharmacokinetics of which a large proportion remained unexplained after inclusion of covariates. The influence of protease inhibitors on atorvastatin clearance highlights the importance of a personalized dosage adjustment in PLWH treated with boosted ARTs. This pharmacokinetic model allows the establishment of dosages recommendations, thereby providing the most efficient and safest patient's care.

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I-79: *Sinziana Cristea* Untangling maturation functions for kidney transporters using a combined population pharmacokinetics and physiology-based pharmacokinetics approach

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Objectives: Active secretion by renal transporters, largely contributes to the elimination of drugs that are substrates for these transporters, however, there is limited information regarding the maturation of their expression and activity throughout the paediatric age-range[1]. This information could lead to more accurate clearance (CL) predictions for drugs that are renally actively secreted and, ultimately, to improved pediatric drug development. Therefore, we aim to combine population PK and PBPK approaches to characterize the maturation of the organic anion transporters 1 and 3 system (OATs), throughout the paediatric age range, using clavulanic acid and amoxicillin as a probe drugs.

Methods: Individual post-hoc CL values for clavulanic acid and amoxicillin were obtained from a population pharmacokinetics (PK) model published by De Cock *et al.*[4]. This model was based on data collected in 50 critically ill children with ages between 0.08 and 15 years (median of 2.6 years), admitted at the paediatric intensive care unit of the Ghent University Hospital in Belgium[4]. Both compounds were co-administered in a fixed ratio to all patients.
The major route of elimination for clavulanic acid is glomerular filtration (GF)[3] and for amoxicillin a combination between GF and active tubular secretion by OATs[2]. A published physiology-based PK (PBPK) sub-model describing renal clearance (CL)[5] was used in combination with the individual post-hoc CL estimates of the two compounds to derive individual intrinsic CL of OATs ($CL_{int,T}$), for which a maturation profile throughout the studied pediatric age-range was estimated. To fit the individual post-hoc CL estimates of both compounds, we first derived the typical CL values using the PBPK renal sub-model and then estimated inter-individual variability (IIV) separately for CL through GF (clavulanic acid) and for CL through active tubular secretion (amoxicillin). The parameters in the renal PBPK sub-model rely on published equations that describe the age-related changes of system-specific parameters (i.e., GF rate[6], renal blood flow[7], kidney weight (Simcyp v18), serum albumin concentrations[7]), of drug-specific parameters (i.e., fraction unbound) and the combination parameter (i.e., $CL_{int,T}$).
The post-hoc CL estimates of clavulanic acid were fitted with the PBPK sub-model including only GF and estimating IIV. In critically ill children CL was found to be augmented[4], therefore, a residual CL term was included, which may account for secondary routes of elimination or the disease status of the patients. The augmented CL through GF was assumed to yield a similar increase in amoxicillin CL as well. The post-hoc CL estimates of amoxicillin were fitted using the PBPK renal sub-model including both augmented GF and active tubular secretion. While fixing the established age-related changes of the system-specific parameters, we estimated the typical $CL_{int,T}$ value and IIV of active tubular secretion. We quantified the maturation profile of OATs by exploring available covariates such as age, postmenstrual age and weight in exponential or sigmoidal relationships on individual $CL_{int,T}$ estimates in a simultaneous fit.

Results: We found that the maturation profile of the OATs was best described by a sigmoid Emax relationship between $CL_{int,T}$ and PMA, for children between 0.08 and 15 years of age. $CL_{int,T}$ was estimated to be 31 ml/h/g kidney in a 15-year-old. At birth, the activity of the OATs is absent (i.e., $CL_{int,T}$ is 0) and reaches half of the maximum capacity of a 15-year-old at 8 months of age (PMA = 74.9 weeks with RSE% of 3%). The median contribution of active tubular secretion to amoxicillin renal CL for the studied pediatric population is 33% (range: 12% - 56%).
CL of clavulanic acid was estimated to be 2-fold higher than the expected CL based on GF in a healthy pediatric population. This is in line with previous findings showing increase in CL in critically ill children[4].

Conclusions: We are the first to use a combined population PK and PBPK approach to quantify a maturation function for the *in vivo* active tubular secretion CL throughout a broad paediatric age-range. In the future, the contribution of age-related changes in transporters' protein expression and activity, and number of proximal tubule cells per gram kidney to the *in vivo* $CL_{int,T}$ could be further disentangled.

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I-80: *Salvatore D'Agate* Population Pharmacokinetics and Dosing Recommendation of Aciclovir in Term and Pre-term Neonates with or without renal dysfunction

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Objectives: Herpes simplex virus (HSV) infection is uncommon amongst neonates, with an overall incidence of 9.6 cases per 100,000 live births in 2006 in the US.[1] Aciclovir is in many regards the prototypic agent against HSV infections. Currently, the doses of aciclovir IV for infusion in neonates is calculated based on body weight. Renal excretion is the major route of elimination of aciclovir and is dependent, in part, on active tubular secretion. Therefore, patients with impaired renal function require an appropriately modified dose, according to the degree of impairment. Limited attention has been given to the potential implications of immature renal function or to renal dysfunction due to the disease itself.[2, 3] The ultimate goal of this analysis was therefore 1) to characterise the population pharmacokinetics of aciclovir after IV administration to neonatal patients with or without suspected systemic infection and 2) to simulate the effect of variable renal function on the exposure to aciclovir taking into account the contribution of maturation (prematurity) and body weight on drug disposition.

Methods: A population pharmacokinetic model was developed using the data previously published by Sampson and colleagues.[4] Initially, model development was aimed at identifying an alternative parameterisation to disentangle the effect of size, maturation and organ function on clearance. In addition, we evaluated the role of disease on drug disposition by treating suspected systemic infection as a covariate factor. General model building criteria were applied to ensure that the appropriate structural PK model could be identified first. Final measures of model performance included visual predictive checks, bootstrapping, normalised prediction discrepancy error NPDE and mirror plots.

Using clinical trial simulations and extrapolation principles, a virtual patient cohort was created to explore the implications of age, body weight and renal function on aciclovir exposure. Relevant baseline characteristics along with a range of scenarios describing variable renal function, as defined by creatinine clearance were generated for the purposes of the analysis. Different dosing regimens were tested and compared to the currently recommended doses for patients aged 0 to 6 months. AUC, C_{max} and $T>IC_{90}$ values were derived and summarised. Simulation results were compared to exposure data in adults with variable renal function and newbors with renal dysfunction from previous publications.[5]

Results: Aciclovir exposure in neonatal patients was described by a 1-compartment model, with interindividual variability on disposition parameters and a proportional and additive error model. CL and V estimates were 0.31 (CI95% 0.11-1.91) L/h and 3.07 (CI95% 0.95-18.33) L, respectively. Covariates included in the final model were body weight, post-menstrual age and creatinine clearance on clearance and body weight and disease state on volume of distribution. Clinical trial simulations showed that alternative doses and dosing regimens may need to be considered when renal function is significantly reduced. Adjustments are suggested to the total daily dose whilst maintaining the dosing interval to a twice-daily regimen.

Conclusion: A suitable model parameterisation was identified, which discriminates between the changes in drug disposition associated with developmental growth, maturation, disease and organ function. Body weight and disease (systemic infection) were found to be statistically significant covariates on volume of distribution, whereas body weight, PMA, and CLCr had a significant effect on aciclovir clearance.

While there is no definitive consensus about the impact of confounding in creatinine clearance in newborns, our analysis shows dosing adjustment may be required to ensure patients are not treated sub-optimally. Simulated profiles show that systemic exposure to aciclovir can be achieved that are comparable levels to those observed in adults with renal impairment.

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I-81: *Kim Dao* Pharmacokinetic Profile of Sultiame in Healthy Volunteers with In Vitro Characterization of Its Uptake by Red Blood Cells

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Objectives:

Sultiame (Ospolot®), an inhibitor of carbonic anhydrase, is a first choice treatment in selected countries for *benign epilepsy with centrotemporal spikes*, an epileptic syndrome of childhood. Its pharmacokinetic (PK) profile was scarcely studied in humans. Linear disposition is reported by the manufacturer, with a half-life imprecisely described ("between 2 and 16 h"), while no values for volume of distribution (V) and clearance (CL) are published. It represents a suitable candidate for paediatric formulation optimization, as the current coated tablets of 50 or 200 mg allow neither precise and adapted dosing, nor convenient administration to young children. In that context, a pilot study aiming at specifying sultiame's PK characteristics was conducted. Preliminary results indicated a marked affinity for erythrocytes, attributed to sultiame binding to erythrocytes carbonic anhydrase. A secondary aim was then defined to characterize sultiame exchanges between plasma and erythrocytes.

Methods:

Single oral doses of 50, 100 and 200 mg of sultiame (Ospolot®) were administered in open-label during periods 1, 2 and 3 respectively, at 3-4 weeks intervals in four healthy volunteers. On each period, serial plasma, whole blood and urine samples were collected. A validated high performance liquid chromatography with mass spectrometry method was used for the quantification of sultiame.

An *in vitro* spiking experiment was also performed to further characterize sultiame exchanges between plasma and erythrocytes observed *in vivo*.

PK parameters were evaluated using standard non-compartmental calculations as well as non-linear mixed effect modelling (NONMEM®) accounting for saturable uptake by red blood cells. A three-compartment model was implemented, incorporating a saturable ligand to receptor binding parametrized in terms of constants of association (k_{on}) and dissociation (k_{off}), and ligand maximal specific binding capacity (B_{tot}), along with CL, plasma V (V_p), erythrocytes V (V_{ery}) and renal extraction fraction (Q_{Ren}). Variability was set onto CL, V_p, B_{tot} and Q_{Ren}. Predicted amounts of sultiame (mg) A_a in the absorption compartment, A_p in plasma, A_{ery} in erythrocytes and A_{ren} in urine were respectively computed over time according to the following differential equations:

$$dA_a/dt = - k_a \cdot A_a$$

$$dA_p/dt = k_a \cdot A_a - k_e \cdot A_p - k_{on} \cdot A_p \cdot (B_{tot} - A_{ery}) + k_{off} \cdot A_{ery}$$

$$dA_{ery}/dt = k_{on} \cdot A_p \cdot (B_{tot} - A_{ery}) - k_{off} \cdot A_{ery}$$

$dA_{ren}/dt = k_e \cdot A_p \cdot Q_{ren}$

Results:

The plasma concentration results showed striking non-linear disposition of sultiame, with tenfold increases in concentrations while doses were only doubled. Conversely, whole blood concentrations increased less than dose-proportionally and remained much higher than plasma concentrations. Very quick uptake of sultiame into erythrocytes was observed both *in vivo* and *in vitro.* Minimal efflux from erythrocytes was confirmed *in vitro*. Non-compartmental calculations indicated non-linearity in apparent CL (CL/F) between doses, suggesting a saturation process. Geometric means (CV%) for half-life in plasma were 50.8 (CV: 62%), 90.9 (19%) and 40 (31%) h after a dose of 50, 100 and 200 mg respectively, whereas half-lives in whole blood were much longer with means of 313 (23%), 233 (16%) and 253 (21%) h.

The final population parameters and BSV were: plasma CL = 11 L/h (28%), V_c = 56.3 L (9.3%), V_{ery} = 2.93 L, k_{on} = 0.949 mg/h, k_{off} = 0.796 h-1, B_{tot} = 97.1 mg (12%), Q_{Ren} = 0.247 (15%). Additive error on erythrocytes concentrations was 0.012 mg/L, and proportional residual errors of 56%, 26% and 43 % respectively for plasma, erythrocytes and urine concentrations. The quality of model fitting was good, based on usual diagnostic tests, showing that our model adequately captured the nonlinear behavior of sultiame disposition.

Conclusions:

We described sultiame's PK profile in detail for the first time, including estimations of CL and V. Plasma-to-blood concentration ratio revealed a strong affinity of the drug for erythrocytes. The remarkable ability of our simple saturable binding model to fit plasma, erythrocyte and urine concentrations is consistent with a strong affinity of sultiame for carbonic anhydrase, abundant in erythrocytes. Further studies should consider this peculiarity, which will affect the interpretation of therapeutic drug concentration monitoring, considered for sultiame dosage adjustment in patients.

I-82: *Mailys De Sousa Mendes* Transporter inhibition: modelling in-vitro Transwell assays

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Objectives:

Transporter inhibition can have an impact on the disposition of a drug as well as on its safety and efficacy. Being able to have reliable estimates of inhibition parameters for use in PBPK models is key to evaluating the DDI potential. However, the conventional analysis of the standard in vitro inhibition assays makes several assumptions that can impact the quality of the *in-vivo* prediction. For example, it assumes that sink conditions are maintained, which can be difficult to achieve experimentally, especially for highly permeable compounds. Moreover, it is sometimes challenging to robustly distinguish between the passive permeability of the substrate from the active transport. It also assumes that the driving concentration for the transporter inhibition is the nominal concentration. In addition, for efflux transporters the intracellular concentration typically perpetrates the inhibition. It has been shown for the substrates that using modelling to estimate the intracellular concentration decreases the inter-laboratory variability and tends to give lower and more consistent Km estimates [1]. The similar conclusions were recently made for inhibition parameters [2] and could explain the overestimation of Ki values frequently observed. We developed a model that mechanistically describes the efflux transport across Caco-2 cells for digoxin and quinidine, two P-gp substrates. The $Ki_{P\text{-}gp}$ value for quinidine was also estimate using the *in-vitro* drug-drug interaction (DDI) with digoxin.

Methods:

In-vitro assays

Data for the bidirectional transport of quinidine and digoxin across Caco-2 monolayers were previously generated [3]. Briefly, Caco-2 cells were seeded at a density of 1 x 10^5 cells/well onto 12-well Transwell® inserts and grown for 23±1 days prior to permeability experiments. Experiments were performed at 37°C, with apical and basolateral volumes of 0.5 and 1.5 mL, respectively, and was stirred at 450 rpm (calibrated plate shaker (BMG LabTechnologies GmbH, Offenburg, Germany). The basolateral and apical compartment were buffered to a pH of 7.4. Digoxin disposition was characterised at concentrations of 0.059, 1, 10, and 100 µM. Quinidine disposition was characterised at concentrations of 0.001, 0.05, 1, 10, and 100 µM. Samples were collected at 5,15,25,50,80, and 120 min for both. For the DDI assays, concentrations of 0.059 µM vs 100 µM, 0.059 µM vs 10 µM and 0.02 µM vs 50 µM for digoxin and quinidine, respectively were used and samples were collected at 5, 15, 25, and 50 min. Sampling of A-B experiments was conducted by moving the Transwell insert to a new well containing blank buffer and retaining the previous well, thereby representing complete removal of drug from basolateral buffer. Sampling of B-A experiments was conducted by removal of 400 µl of apical buffer and replacement with an equal volume of blank buffer.

Data analysis (modelling)

A mechanistic model was developed in R software (version 3.5.1) and included 3 compartments, representing apical and basolateral media in addition to the cell monolayer for the substrate and the inhibitor. No assumption about sink conditions was done and the passive diffusion (CL_{PD}) was estimated.

The driving concentration for P-gp as well as the perpetrating concentration for P-gp inhibition was assumed to be the intracellular concentration. The impact of sampling on the concentrations measured was accounted for in the model.

Results:

The model was able to describe the disposition of digoxin and quinidine alone, and digoxin disposition in presence of quinidine .The geometric mean fold error (GMFE) between observed and model predicted digoxin concentrations was 1.29 and the geometric fold bias (GMFB) was 1.15. For quinidine, the GMFE was 1.16 and GMFB was 1.002. And finally the GMFE was 1.18 and GMFB was 1.06. Digoxin Km, J_{max} and CL_{PD} were estimated to 18 µM (relative standard error (RSE%): 41%), 252.8 pmol/min (RSE%: 34%), and 41 x 10^{-6} cm/sec (RSE%: 3%) respectively. Quinidine Km, J_{max}, CL_{PD} and Ki were estimated to 0.278 µM (RSE%: 44%), 11.3 pmol/min (RSE%: 37%), 201.2 x 10^{-6} cm/sec (RSE%: 6%) and 3.45 µM (RSE%: 21%) respectively.

Conclusions:

The model was able to estimate J_{max}, Km, and CL_{PD} for digoxin and quinidine with reasonable accuracy. The present data set would have not allowed to estimate a $Ki_{P\text{-}gp}$ value using the conventional approach, however we were able to estimate a $Ki_{P\text{-}gp}$ value for quinidine.

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I-83: *Eva Maria del Amo Paez* Pharmacokinetics after intravitreal injection of a new anti-angiogenic therapeutic compound in rabbit eyes

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Introduction and objectives:
Proliferative diabetic retinopathy (PDR) is the more advanced form of diabetic retinopathy disease, with formation of new retinal vessels and oedema, at the back of the eye, that may lead to vision loss and scarring of the retina. An endogenous molecule of the eye, opticin, has potential therapeutic value as an anti-angiogenic agent inhibiting the formation of new blood vessels (1). It is an extracellular glycoprotein that binds to collagen fibrils in the vitreous, gel-like substance that occupies the space inside the eye between the lens and the retina. The objective of this study was to investigate the pharmacokinetic (PK) profile of exogenous opticin injected into the vitreous of rabbit eyes.

Methods:
In vivo PK studies were carried out with eighteen New Zealand rabbits that received an intravitreal injection in both eyes with 40 µg of human opticin (50 µl). Eyes were enucleated at different time points: 5 h, 24 h, 72 h, 7 days, 14 days, 28 days (n=5-6). The vitreous was extracted and the free and bound forms of human opticin were measured in the supernatant and in the collagen-containing pellet respectively. The measurement were done by mass spectrometry using selected reaction monitoring. Additionally, the concentration of free and bound endogenous opticin in rabbit vitreous were also measured using the same method at the same time points. The basal concentrations of both endogenous forms were also obtained from nine uninjected rabbit eyes.
The concentration profiles of the human opticin were analysed by Nonlinear Mixed Effects (Monolix software®) using a one compartmental model. The interplay between the exogenous and endogenous opticin in the vitreous was also investigated.

Results:
The injected free human opticin presented a first-order elimination profile with an intravitreal volume of distribution of 3.18 ml, clearance of 0.022 ml/h and half-life of 4 days, whereas the bound human opticin had a longer half-life of 7.5 days.
Regarding the endogenous opticin, the concentrations of the free form (in the vitreous supernatant) was relatively constant during the whole time profile, 19 nM (0.67 µg/ml) (n=5 per time point) and similar to the basal levels in the uninjected rabbit eyes, 17 nM (0.60 µg/ml) (n=9). Assuming that the elimination rate constant of the free rabbit opticin is similar to the one for human (0.168 days-1), the rabbit opticin synthesis rate was calculated as 0.15 µg of opticin/day. The basal bound endogenous opticin was 1.12 nM (0.04 µg /ml, n=9). The injected human opticin reached concentration 20-fold greater than free rabbit opticin, with an apparent partial replacement of the bound rabbit opticin by the human one. This effect was reversed as the human opticin was cleared from the eye.

Conclusions:
Free opticin presents a similar half-life to the antiangiogenic therapeutic drug, aflibercept (Eylea®), while

the bound form has a longer half-life, binding to the collagen fibrils and possible some other inner ocular tissue sites. Reversible displacement of the natural bound opticin was observed and the apparent synthesis rate of the endogenous opticin was calculated for the first time.

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I-84: *Francesca Del Bene* Intratympanic drug administration: a challenge for PK modelling

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Objectives: A number of drugs are administered in the intratympanic space, e.g. for the treatment of sudden onset neurosensorial hearing loss, Ménière's disease, or autoimmune ear diseases [1,2]. Intratympanic (IT) drug delivery refers to drug administration in the middle ear beyond the tympanum with these main objectives: maximize the delivery in the site of interest; minimize systemic exposure and side effects [2,3,4]. After systemic administration, drug distribution to the inner ear would be limited by the blood–labyrinth barrier (BLB), physiologically similar to the blood–brain barrier [3,5], leading to low bioavailability (~<5%) [1]. IT administration enables the drug to bypass the BLB and access directly the inner ear: the drug diffuses from the middle ear across the round window membrane (RWM), located at the end of the scale tympani (separating the middle from the inner ear and protecting the inner ear) [6,7]. Factors such as the permeability of RWM to drugs, diffusion and clearance mechanisms affect perilymph drug levels responsible for efficacy. Animal studies show high variability in perilymph drug levels after RWM applications [1]. Evaluation of pharmacokinetics (PK) after IT administration is challenging due to difficulty in accessing the inner ear and its limited size [8,9]. Therefore, the development of a model to predict inner ear and systemic PK following local administration would support dosing regimen selection and study design in both preclinical and clinical settings: the objective of the present work was to review modelling approaches proposed in the literature.

Methods: A literature search was performed in PubMed and Google Scholar (keywords: intratympanic pharmacokinetic; intratympanic model; intratympanic administration; inner ear administration). Additional articles were selected among the references of those initially found. Exclusion criteria were: (i) no full text available; (ii) focus on administration routes other than IT; (iii) no relevant information on PK after IT administration and no modelling approach described. Current capabilities of the main tools for physiological based (PB) PK modelling (GastroPlus, PKSim, and Symcip [10,11,12]) were investigated.

Results: A total of 39 papers were found; 10 were discarded because of (i), 8 because of (ii), 7 because of (iii). No examples of empirical compartmental models for IT administration were found, neither in preclinical nor clinical setting. PB models of the guinea pig, mouse, and human ear were developed and implemented in the computer simulation software FluidSim by Washington University [13,14]. This tool simulates solute movements in fluid and tissue spaces of the cochlea and vestibular systems; elimination to systemic circulation is considered [8,13,15,16,17]. In the preclinical setting, the FluidSim model has been applied to explore perilymph PK both after systemic and local administration [15,16,17,18]. In Ménière's disease and idiopathic sudden sensorineural hearing loss patients, inner ear drug concentrations after IT administration were computed and associated with hearing changes, and risk of hearing loss and deafness [19,20]. Furthermore, in [21] mathematical equations to quantify the permeability coefficient through the RWM based on drugs' physicochemical properties were obtained. State-of-the-art PBPK tools such as GastroPlus, PKSim, and Symcip do not include a description of the ear and do not allow simulation of IT administration.

Conclusions: Literature search results highlighted a knowledge gap about PK after IT administration. The physiological structure of the ear is complex and extrapolation from animal to humans is not easy: animals

like guinea pigs are used in preclinical studies, however anatomical differences with humans should be considered. Furthermore, data collection in the inner ear is challenging both in animals and (especially) in humans [8,9], because of its invasiveness and of possible cerebrospinal fluid contamination. Empirical approaches have not been attempted yet, however simple compartmental PK models and deconvolution techniques (to separate the intratympanic component of systemic absorption) might be coupled to describe drugs' PK after IT administration and scale across species. A PB model of the ear for different species is currently available, however well-defined criteria for parameters selection and integration of a whole-body description for systemic exposure prediction are still open challenges.

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I-85: *Laurence Del Frari* Population modelling and simulations of binimetinib pharmacokinetics in subjects with hepatic impairment to explore optimal dosing regimen using total and unbound binimetinib exposures

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Objectives: Binimetinib is a potent and selective inhibitor of MEK 1 and MEK 2. Binimetinib is indicated for use in combination with encorafenib for the treatment of adult patients with unresectable or metastatic melanoma, with BRAF V600 mutation. Binimetinib is mainly eliminated through hepatic metabolism mediated by multiple enzymes. A population pharmacokinetic (popPK) modelling approach was used to identify optimal binimetinib dose and/or dosing regimens in patients with hepatic impairment (HI) based on the objective of exposure matching to non-impaired subjects. Data from a phase 1 clinical study with subjects with hepatic impairment (Study CMEK162A2104) were used.

Methods: The clinical study was a Phase 1, multicenter, open-label, single-dose study to assess the PK of binimetinib in healthy subjects with mild, moderate, and severe HI, with a normal hepatic function control group. 27 subjects were enrolled in four groups (5-6 subjects per HI group, based on Child-Pugh (CP) scores). PK samples were collected from pre-dose to 120 hours after dosing. An additional blood sample for the determination of unbound plasma concentration was collected at 1 hour after dosing. A popPK model previously developed for binimetinib [1] was used as a starting point to assess the PK of binimetinib in healthy subjects with HI. Since subjects with normal hepatic function were matched to subjects with HI with respect to their age, gender and body weight, the covariate analysis focused on the impact of HI severity. Monte Carlo simulations were performed for each HI group (250 virtual subjects per group) to explore total and unbound binimetinib exposures for the following regimens: 15 mg, 30 mg, and 45 mg twice a day (BID) as well as 15 mg three times a day (TID). Normal distribution for unbound fraction within each HI group were used to generate 250 values. Descriptive steady state statistics and box plots of simulated maximum concentration (Cmax), minimum concentration (Cmin), average concentration (Cave) and area under the concentration-time curve during 24 hours (AUC) are provided for total and unbound binimetinib.

Results: The effect of hepatic impairment on binimetinib apparent oral plasma clearance (CL/F) was evaluated based on National Cancer Institute Organ Dysfunction Working Group (NCIODWG) and CP classifications:

- Healthy subjects and subjects with mild hepatic impairment had comparable CL/F using either NCIODWG or CP classifications.
- Subjects with moderate and severe hepatic impairment had comparable CL/F. Their typical values were about half the value estimated in subjects with normal hepatic function using either NCIODWG or CP classifications.

Based upon the distribution of total binimetinib concentrations following administration of 15 mg TID or 30 mg BID, subjects with moderate and severe HI based were predicted to have similar exposures (i.e., AUC, Cmin, Cave and Cmax) relative to healthy subjects and subjects with mild HI receiving 45 mg BID. Exposure unbound metrics were also predicted to compare impaired groups with non impaired subjects. Similar results were obtained using both NCIODWG and CP classifications of hepatic impairment.

Conclusions: The proposed popPK modelling and simulations predict optimal binimetinib dose and dosing regimen in patients with various degrees of HI based upon both total and unbound binimetinib exposures. This approach can be used to support dose selection in the patient population with unresectable or metastatic melanoma, with BRAF V600 mutation.

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I-86: *Oleg Demin Jr* Investigation of dose response behavior of bispecific T-cell engaging antibodies using quantitative systems pharmacology modeling

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Objectives: A lot of bispecific T-cell engaging antibodies are in preclinical and clinical development for the treatment of various types of cancers. Kinetics of bispecific therapeutic antibody bound with its targets (trimer complex) is more complex than simple monospecific antibody bound with one target. Theoretically, the dependence of concentration of trimer complex on dose is bell-shaped. The aim of this work is to investigate dose response behavior of bispecific T-cell engaging antibodies under physiological conditions on the basis of B-cell acute lymphoblastic leukemia (B-ALL) treatment with blinatumomab, CD19/CD3 bispecific T-cell engaging antibody.

Methods: Developed QSP model consist of three parts: (1) physiologically-based pharmacokinetic (PBPK) model of blinatumomab including binding to target receptors – CD3 on T cells and CD19 on leukemic cells; (2) dynamics of normal cells (CD20 positive and CD20 negative B cell precursors, neutrophils, platelets) and leukemic cells during B-ALL progression without treatment; (3) specific lysis of CD19+ cells (both normal and leukemic cells) by CD3+ T cells in presence of blinatumomab. Model describes immunological synapse between CD3+ T cells and CD19+ cells, and formation of trimer complex of blinatumomab with CD3 and CD19 in synapse. Parameters of the model were identified on the basis of published in vitro and in vivo data on healthy subjects and adult relapse/refractory B-ALL patients, but not clinical data. Blinatumomab clinical data including pharmacokinetics and pharmacodynamics was used to validate the model. Also, in vitro data was used to implement variability in specific lysis of CD19+ cells in presence of blinatumomab.

Results: PBPK part of the model was able to reproduce clinical PK data on blinatumomab without fitting of clinical pharmacokinetics data. Pharmacodynamics of blinatumomab was validated against data on dynamics of CD19+ cells in blood of B-ALL patients. Model shows that there is no response at doses up to 8 ug/m^2/day, which is correspond to clinical data [1]. Duration of CD19+ cell depletion to the level below 1 cell per microliter was varied from 0.5 to 21 days for responders in the model as in clinical trials [2,3]. The threshold for activation of specific lysis in presence of blinatumomab was 253 nmol/L (corresponds to 38 trimer complexes in synapse) for CD4 T cells and 103 nmol/L (corresponds to 16 trimer complexes in synapse) for CD8 T cells. The decrease in concentration of trimer complex (bell-shaped behavior) can be observed only at doses starting from 10^6 ug/m^2/day, which correspond to steady state concentration in plasma - 47 ug/mL, whereas concentration of blinatumomab in plasma after administration of approved dose is about 700 pg/mL.

Conclusions: Developed model is able to reproduce pharmacokinetics and pharmacodynamics data of blinatumomab without fitting of clinical data. Model shows that threshold for activation of specific lysis of CD19+ cells in presence of blinatumomab is very low and bell shaped dose response can be observed only at very high non-physiological doses of blinatumomab.

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I-87: *Laure Deyme* Optimizing FOLFIRINOX regimen in pancreatic adenocarcinoma using a 5FU-PKPD model of neutropenia including G-CSF rescue

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Objectives: Pancreatic adenocarcinoma is one of the most lethal human malignancies and a major health issue. FOLFIRINOX regimen is commonly used in colorectal cancer. Recently, Conroy et al. have shown that FOLFIRINOX is the most efficient regimen in pancreatic cancer. However, this polychemotherapy causes significant and dose-limiting toxic effects leading to empirical dose-reduction, postponement of the forthcoming courses and sometimes treatment discontinuation. The first aim of our study is to describe the PK of each drug included in FOLFIRINOX regimen and to establish dose-concentration-toxicity relationships for haematological and categorical adverse effects. Second, we aim to perform in silico simulation to define the optimal FOLFIRINOX administration protocol (i.e., dosing, scheduling, sequencing) for a maximal benefit to risk ratio.

Methods: As a first step, a multicenter retrospective study was performed. Data from 75 patients with pancreatic adenocarcinoma and 566 courses of FOLFIRINOX (varying doses of each drug according to toxicities) were collected. The dataset contained 596 absolute neutrophil count observations. Patients have often been supplemented with Granulocyte-Colony Stimulating Factor (G-CSF) or pegylated G-CSF (PEG G-CSF) to prevent neutropenia.

The pharmacokinetics of 5-fluorouracil (5FU) was simulated using the population PK model from Terret et al[1]. The PD model for neutropenia was modified from Friberg et al. (2002)[2]. The PKPD model of G-CSF and PEG G-CSF has been added on the Friberg model with effects on proliferation and maturation processes of proliferative cells in bone marrow as described by Pastor et al (2013)[3]. The effect of 5FU chemotherapy has been described with power function (Edrug = slope * Cdrug ^ beta). Five parameters (slope, maximal effect of GCSF on proliferation ($E_{max}1$) and on maturation ($E_{max}2$), value of free concentration of GSF eliciting 50% of the maximal effect on proliferation ($EC_{50}1$) and on maturation ($EC_{50}2$)) have been estimated using Matlab 2018b. Next, the model has been used to simulate alternative administration protocols of 5-FU and G-CSF targeting lesser use of G-CSF and lesser toxicity.

Results: The pharmacokinetic profile of 5FU was simulated with a two-compartments model and Michaelis-Menten elimination[1] including body surface area as covariate on the maximum rate of elimination (Vmax). The individual PD parameters were estimated. The baseline value of circulating cells was fixed to the observation before the beginning of treatment and PK parameters of drugs (5FU and G-CSF) were fixed. For one patient with nine absolute neutrophil count observations, eight courses of FOLFIRINOX with different doses and six courses of four or five administrations of G-CSF, the following values were obtained: slope = 1.2 L/µg, $E_{max}1$=2.87, $EC_{50}1$=0.21 µg/L, $E_{max}2$=2.79 and $EC_{50}2$=0.22 µg/L. Several administration protocols were simulated to compare the effect on neutropenia: increasing/decreasing the duration of 5FU perfusion, with/without G-CSF. The PKPD model predicted a better tolerance with a longer duration of 5FU perfusion and in presence of G-CSF.

Conclusion: This preliminary modelling work shows that PKPD modelling can be a useful tool to optimize administration protocol of chemotherapy and G-CSF in FOLFIRINOX regimen. To achieve our goal, effects of oxaliplatin and SN38 will be considered. Furthermore, a Hidden Markov chain Model will be developed to describe major categorical adverse effects (such as peripheral neuropathy and digestive toxicities) in order to find a new FOLFIRINOX regimen that would be more efficient while maintaining all limiting toxicities in an acceptable range.

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I-88: *Sofie Dhaese* The use of optimal experimental design to inform a clinical trial on non-linearity of piperacillin clearance in critically ill patients.

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Objectives: Evidence on the linearity of piperacillin clearance at therapeutic plasma concentrations in patients in conflicting [1–5]. Non-linearity in piperacillin clearance impacts the optimal dosing regimen and this is particularly relevant given the recent introduction of continuous as opposed to intermittent infusion of beta-lactam antibiotics in several ICU's worldwide[3,6].

The aim of this study was to revisit the evidence on the (non-)linearity of piperacillin clearance using clinical trial simulations. For this, the type I error rate and power for detecting non-linear piperacillin CL of published clinical trials on piperacillin PKs was evaluated. The difference between non-parametric (NPAG) vs. parametric parameter estimation in type I error rate and power was also investigated. Based on the same principles, an optimal experimental trial design was developed to inform a clinical-trial on non-linearity of piperacillin clearance.

Methods: Piperacillin PK profiles were simulated according to the design of different published studies on piperacillin PK in patients (i.e. same number of patients, number of observations, mode of administration, doses, sampling times, etc.). For these simulations, the PopPK model by Landersdorfer *et al*[1],on piperacillin PKs in healthy volunteers, served as the true model. Cohorts of patients with non-linear piperacillin PKs were simulated according to the final parameter estimates by Landersdorfer (H_1). In parallel, cohorts with linear PKs were simulated by fixing the V_{max}estimate to zero (H_0). Two nested models, a two-compartment linear model and a two-compartment model with parallel linear / non-linear elimination, were fitted to the simulated datasets. The likelihood ratio testat the 5% level of significance was used to compare both models.

The type I error rate and power were approximated by the frequency of significant LRT in the simulated datasets without non-linear (H0) and with non-linear piperacillin CL (H1), respectively. In addition, a type I error calibration was implemented and the statistical power was calculated with this calibrated chi-square value in order to obtain the power of a specific study design corresponding to a type I error rate ≤ 5%[7].

The accuracy of $K_m$and V_{max}estimates was assessed by the percentage of times the estimated values for both $K_m$and V_{max}fell within a two-fold range (i.e. -50%; +100%) of the original mean $K_m$and V_{max}estimations reported by Landersdorfer, *et al*[1].

Parameter estimation was performed using the NPAG estimation routine as implemented in Pmetrics (Version 1.5.2; Laboratory of Applied Pharmacokinetics, Los Angeles, CA, USA) and the FOCE-I algorithm in NONMEM (Version 7.3; GloboMax LLC, Hanover, MD, USA).

Results: Six published piperacillin PopPK models were selected from the literature of which three[4,5,8]described linear clearance of piperacillin while the other three[3,9,10]described non-linear clearance of piperacillin. The number of patients per study ranged between 8 and 50 and the number of observations per patient ranged between 6 and 27.

The type I error rate was between 1.4% and 26% with NPAG and between 1.9% and 75% with FOCE-I. The calibrated power of the study designs was between 5.1% and 97.1% with NPAG and between 0.2% and 47.9% with FOCE-I. None of the NPAG estimates for $K_m$and V_{max}fell within a two-fold range of the true $K_m$and V_{max}values used for simulation, not even in the study with high calibrated power[8]. For FOCE-I, accuracy was also low except for the study with high calibrated power [8]where 16.4% of estimates were within the 2-fold range. Our proposed study design (based on 10 patients) resulted in a type I error rate of 3.0%, a power of 100% with 47% of parameter estimates within 2-fold of the values used for simulation. When NPAG was used instead of FOCE-I, the type I error rate increased to 12% without significantly affecting power. Remarkably, both for Vmax and Km parameter estimates were always higher than 2-fold the value used for simulation.

Conclusions: Published studies evaluating the non-linear pharmacokinetics of piperacillin were poorly powered and likely resulted in in-accurate estimates for $V_{max}$and K_m. An optimal experimental design to study piperacillin non-linearity is proposed. Further work is necessary to study the influence of the estimation algorithm on the statistical inference in the context of the differentiation between linear and non-linear PKs in clinical trials with patients.

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I-89: *Richard Dimelow* PK Precision Estimation to support the Design of a Pediatric Study of Belimumab Administered Subcutaneously

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Objectives:

Belimumab (BENLYSTA) is a monoclonal antibody that binds to the B-lymphocyte stimulator protein and is currently approved for the treatment of active systemic lupus erythematosus (SLE) in adults. To address unmet needs in childhood-onset SLE (cSLE), a study in a paediatric population with active cSLE is planned to investigate the safety, pharmacokinetics and pharmacodynamics following sub-cutaneous (SC) administration (study 200908). It is a regulatory requirement that the study must be prospectively powered to target a 95% confidence interval (CI) within 60% to 140% of the geometric mean estimate for clearance (CL) and volume of distribution (V) with at least 80% power [1]. The objective of this analysis was to confirm that study 200908, with proposed subject number (N=24) and sampling times, was sufficiently powered to meet this condition.

Methods:

A simulation / re-estimation approach was performed to investigate the precision to which CL and V can be estimated. The precision estimation for the PK focused only on data from the mandatory Part A of study 200908 (12 weeks Part A plus 40-week extension phase with additional PK samples) and therefore provide a conservative estimate of the precision. In the simulation scenario 24 subjects between 5 and 17 years will receive 200 mg belimumab SC every week for 12 weeks, with subjects less than 30 kg receiving 200 mg once every two weeks. Pre-dose PK samples will be taken on weeks 1, 2, 4, 8 and 12, followed by an 8-week washout sample. A paediatric population PK model previously developed for IV administration (study BEL114055) was combined with the SC absorption component in adults [2], and the resulting model used to simulate 2000 trial outcomes. Several 1-compartmental models, all with fat-free mass (FFM) as the body size covariate on CL and V, were fitted to each trial simulation. In each case the covariance matrix for parameter precision was used to calculate the 95% CI in CL and V [1]. The probability that the 95% CI was within 60% to 140% of the geometric mean or median estimate (defined as the power) was calculated. The impact of a 25% drop-out rate was investigated by repeating the model-fitting on simulated datasets containing only 18 subjects. The results were benchmarked against a theoretical “best-case” design with rich PK sampling scheme, enabling accurate individual PK parameters to be obtained through non-compartmental analysis (NCA).

Results:

Both CL and V can be estimated with 100% power (CI = 60% to 140%) providing the FFM exponents on CL and V are fixed at their allometric theoretical values 0.75 and 1.0 respectively for all subjects. The power remains high (95% for both CL and V) when measured against the more stringent definition of precision (CI = 80% to 120%). The power (CI = 60% to 140%) drops off significantly when the FFM exponent on CL (power = 36%) and V (power = 22%) are estimated. Applying a prior probability distribution on the FFM exponents (0.75 ± 0.1 for CL, 1.0 ± 0.1 for V) as part of the parameter estimation reverses this drop in performance, recovering 100% power (CI = 60% to 140%) in both the CL and V estimates, although the power is still somewhat below 80% when benchmarked against the higher level of precision (CI = 80% to 120%). For a

rich sampling scheme with NCA derived CL and V for each subject, at least 10 subjects per trial would be required to estimate CL and V with 80% power (CI = 60% to 140%). This is a theoretical "best-case" outcome but given the sparse PK sampling requirements for study 200908 (to minimize patient burden) 15 subjects (but not 12) are sufficient to estimate CL and V with a population PK approach to the required level of precision. The study design should therefore be robust against a drop-out rate of at least 25% (N=18).

Conclusions:

- The paediatric study 200908 (N=24, sparse PK sampling) is sufficiently powered to estimate CL and V directly form the data providing the FFM exponent is fixed at 0.75 (on CL) and 1.0 (on V) or providing a prior likelihood about these is included.
- A 25% drop-out rate (N=18) can be accommodated with minimal loss of power.
- By comparison, a rich PK sampling scheme enabling NCA derived PK parameters for each subject would only require 10 subjects to estimate CL and V with 80% power. This is the smallest possible sample size to meet the precision criteria for the paediatric population if patient burden were not of concern.

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II-01: *Åsa Kragh* Population pharmacokinetic analysis of PT010, an inhaled triple fixed-dose combination product, in patients with chronic obstructive pulmonary disease

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Introduction: PT010 is a triple fixed-dose combination, with budesonide (B/BD), glycopyrronium (G/GP) and formoterol (FF), formulated using co-suspension delivery technology in a pressurized metered dose inhaler (MDI) [1], developed for the inhaled treatment of chronic obstructive pulmonary disease (COPD).

Objectives: To evaluate the population pharmacokinetic (popPK) properties of PT010, and the impact of covariates on each of its components, in patients with COPD.

Methods: Pharmacokinetic (PK) data from 9 clinical studies, in subjects with mild to very severe COPD, were included in the analysis. Each study contained data on one or more of the following triple-, dual- and mono products (i) PT010, (ii) BFF MDI, (iii) GFF MDI (Bevespi Aerosphere® [2]), (iv) BD MDI, (v) GP MDI, and (vi) FF MDI. In total, 3930 samples from 220 subjects were included in the analysis of BD, 7612 samples from 481 subjects were included in the analysis of GP, and 10277 samples from 652 subjects were included in the analysis of FF.

Different structural base models were investigated, and the following covariates were considered: age, body weight, absolute estimated glomerular filtration rate (eGFR), sex, smoking status, COPD severity, and formulation effects of products (ii)-(vi) versus (i) on relative bioavailability (Frel).

Simulations were conducted to assess the impact of identified covariates on AUC, Cmax, and Cmin, during BID dosing of the planned market dosage form of PT010 (BD/GP/FF: 320[160]/18/9.6 µg) at steady state.

Results:

Budesonide
The final popPK model for BD was a 3-compartment model with first-order absorption, including body weight as covariate on the inter-compartmental clearance parameters (Qp1/F and Qp2/F), and age as covariate on clearance (CL/F).

All evaluated covariates had a minor impact on Cmax, Cmin, and/or AUC of BD. The “worst case” combination of covariates (selected to obtain the highest Cmax/AUC) are low body weight and high age. Considering the 10th percentiles of body weight and age in the BD data set (57.6 kg; 74 years), the change in median Cmax, Cmin, and AUC at steady state, relative to the typical individual, was predicted to be approximately 7%, -5%, and 7%, respectively. These differences were not considered clinically relevant.

Glycopyrronium
The final popPK model for GP was a 2-compartment model with first-order absorption. Covariates included in the final model were absolute eGFR on CL/F, body weight on the volumes of distribution (Vc/F and Vp/F) and Q/F, and smoking status on the absorption rate constant (ka) and Frel.

Absolute eGFR was the covariate that had the greatest impact on Cmax, Cmin, and AUC of GP. The “worst case” combination of covariates are low body weight, low absolute eGFR, and former smoker. Considering the 10th percentiles of body weight and absolute eGFR in the GP data set (57.6 kg; 63.7 mL/min), the increase in median Cmax, Cmin, and AUC at steady state, relative to the typical individual, was predicted to be approximately 21%, 30%, and 29%, respectively. These differences were expected since GP is renally cleared to a large extent, and they were not considered clinically relevant.

Formoterol
The final popPK model for FF was a 2-compartment model with first-order absorption. Important covariates included in the final model were body weight on CL/F and Vc/F, smoking status on ka and CL/F, and COPD severity on ka. Other covariates included in the final model were formulation effects for BFF MDI, GFF MDI, and FF MDI on Frel (higher relative to PT010). The formulation effects were relatively small (<16% increase) and not considered clinically relevant.

Body weight was the covariate that increased Cmax, Cmin, and AUC the most. The “worst case” combination of covariates are low body weight, mild or moderate COPD, and former smoker. Considering the 10th percentile of body weight in the FF data set (58.0 kg), the increase in median Cmax, Cmin, and AUC at steady state, relative the typical individual, was predicted to be approximately 24%, 26%, and 23%, respectively. These differences were not considered clinically relevant.

Conclusions: The popPK properties of PT010, in patients with COPD, were thoroughly evaluated and none of the identified covariate effects were deemed clinically relevant.

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II-02: *Markus Krauß* Mice with human livers improve First-in-Human prediction of pharmacokinetics

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Objectives:

Over the last years, a new technology allowed the creation of chimeric mice with a humanized liver consisting of human hepatocytes surrounded by phagocytic, vascular and biliary murine sourced cells. Chimeric mice with a humanized liver can be used to predict human ADME characteristics of new chemical entities such as overall clearance and elimination mechanisms to improve nonclinical to clinical translation. Data from such mice might be helpful especially in cases where *in vitro* to *in vivo* extrapolation (IVIVE) is challenging and classic allometric scaling with wildtype nonclinical species results in a wide prediction interval. In a retrospective meta-analysis using in-house data from First-in-Human (FiH) studies, we compared the predicted human clearance and area under curve (AUC) as well as the shape of human pharmacokinetic (PK) profiles based on data from chimeric mice with those predictions from wildtype nonclinical species.

Methods:

Several drugs were incorporated in the analysis where FiH data were available for intravenous administration. Total clearances in humans were predicted by a single-species allometric scaling approach from data obtained in chimeric mice with humanized liver (FRG® knockout mice, Yecuris Corporation). Results were compared to clearance prediction using classical allometric scaling from wildtype nonclinical species and observed clearance in humans. For selected compounds prediction of concentration-time profiles in humans was also performed with single-species scaling using a compartmental modeling approach. Resulting PK parameters such as AUC as well as the shape of predicted concentration-time profiles were compared with human experimental data and predictions from wildtype nonclinical species.

Results:

Overall, superior prediction of human clearance was achieved after single-species allometric scaling using data from chimeric mice. For seven out of ten compounds human clearance prediction was within a twofold range. In comparison, applying classical allometric scaling prediction for six out of ten was within a twofold range. In addition, in three projects human PK was predicted from chimeric mice data using a two compartment model, where a broad AUC interval was predicted from nonclinical species due to interspecies differences. Resulting predictions were at least as good as from the nonclinical species that predicted best the observed human data, especially regarding AUC, but also the PK profile. Notably, the nonclinical species best predicting human PK differed in the three projects.

Conclusions:

The presented results demonstrate that single-species-scaling from chimeric mice with humanized liver predicts human clearance quite well and can also lead to valuable prediction of human pharmacokinetics in general. Especially in projects where a broad range of human CL based on wildtype nonclinical species was predicted and when IVIVE is challenging, chimeric mice clearly strengthen human ADME and PK prediction.

Therefore, chimeric mice with a humanized liver can expand the toolbox to improve prediction of human ADME properties, especially by further derivation of mass balance data and information about potential human metabolites. Such data can then be incorporated into mechanistic modeling approaches to further improve predictivity of human PK in future early drug development programs.

II-03: *Rukmini Kumar* Quantitative Systems Pharmacology (QSP) tools to aid in model development and communication: Vantage QSP Modeling Tools (VQM-Tools)

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Introduction: Quantitative Systems Pharmacology (QSP) models connect physiological mechanisms at the cellular and organ level, to responses at the patient and population level. Tool development in QSP is vital to 1) improve efficiencies in model development, 2) provide a framework to capture model design aspects and decisions, and 3) provide a way to communicate the multiple constraints that are incorporated as part of robust QSP model development.

Objectives:

- Develop tools to aid and accelerate the QSP model development
- Develop tools that explicitly assimilate model design features by visualizing modelling constraints and enable effective communication with all non-modeling stakeholders
- Show application of VQM-Tools in the development of the Vantage Rheumatoid Arthritis QSP model

Methods: "Reference Virtual Subjects" are a key milestone in QSP model development (Stage 4,[1]) that capture baseline characteristics of patients and show an “average” (or a range of) response to perturbations (such as treatment). QSP models develop Virtual Subjects that are simultaneously consistent with 1) understanding of physiology and the interactions amongst species (summarized in model equations), 2) model rate constants being within ranges identified from basic science literature (‘bottom-up’ constraints) and 3) model dynamics spanning ranges identified from clinical literature for various perturbations (‘top-down’ constraints). In addition, modelers may need to keep track of constraints such as correlations among parameters, relationships across perturbations, maintenance of steady-state dynamics etc.

Need: Implementation of Virtual Subjects in the model requires exploring plausible parameter ranges, performing parameter sensitivity analysis and defining ranges in multi-dimensional parameter spaces that are consistent with the constraints of physiological feasibility and observed clinical behaviours.

Solution: Vantage QSP Modelling tools (VQM-Tools) have been developed (using Matlab) to:

- Define and visualize response range for Virtual Subjects: VQM-Tools provide a framework that lets the user define and visualize physiological, clinical and modeling constraints and tested repeatedly in the iterative process of creating Virtual Subjects.
- Develop Virtual Cohort: Modelers carry out systematic sensitivity analysis in VQM-Tools that helps in understanding the most and least sensitive parameters. Based on model design requirements, physiological uncertainties and inferences from sensitivity analysis, VQM-Tools are used to vary key subsets of parameters to create feasible Virtual Cohorts.
- Develop Virtual Population: Feasible parametrizations from Virtual Cohort are carried over for development into Virtual Population. Multiple approaches are used in VQM-Tools to develop VPops including those reported in previous literature [2,3]

Results: We illustrate the use of VQM-Tools for Vantage RA QSP model development. This model connects the pathophysiology of Rheumatoid Arthritis with the observed population behaviour in clinical trials using standard therapies (RA-BEAM [4] and RA-PREMIER [5]).

VQM-Tools was used to consolidate RA constraints in a single framework to visualize the effect of model parameterization on alignment with constraints. Further the results of selected Parameter Sensitivity analysis and estimation of free/under-constrained parameters for calibrating reference Virtual Subjects are shown. A Virtual Cohort that spans the range of baseline disease characteristics (in terms of cell densities, cytokine concentrations and disease scores) and response to treatment (methotrexate and anti-TNF-alpha) have been created and visualized using these tools.

Conclusions: VQM-Tools helped accelerate development of the Vantage RA model, and provided accessible visualizations of the model constraints for communication to external stakeholders from various non-modeling disciplines. Once tool development is complete, VQM-Tools will be made available for public use.

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II-04: *Hanna Kunina* Diabetes progression modelling of competing risks of long-term complications and mortality using Swedish registry data

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Objectives: Type 2 diabetes mellitus (T2D) is a group of metabolic diseases that are associated with long-term damage to and failure of various organs [1]. Recent evidence suggests that the risk of long-term complications for patients suffering from T2D may vary, depending on the presence and severity of comorbidities [2]. T2D is associated with disabling and life-threatening micro- and macrovascular complications, and diseases e.g. chronic kidney disease (CKD) and cardiovascular disease (CVD) are of paramount interest [3]. The aim of this project was to develop a multistate model for competing risks analysis using data from the Swedish National Diabetes Registry (NDR) and characterize the impact of covariates on the competing risks.

Methods: The NDR coverage is approximately 90% of patients with diabetes in Sweden and contains ~360,000 patients. All adult patients with T2D, registered in NDR 2005-2013, without prior events of CKD and CVD, with record of key covariates (e.g. glycated haemoglobin - HbA1c, body mass index - BMI, sex, systolic blood pressure - SBP) were included in our study. In total, 78,951 patients with 603,308 observations were included. To describe disease progression, a multistate, competing risks model with five clinical states was used [4]. All subjects started from the initial state having T2D without comorbidities and moved towards the terminal state (death), either through intermediate states (CVD, CKD, or the dyad state, CVD+CKD) or directly. The Renal Association Guide [5] and presence of stroke or ischemic heart disease was used to define CKD and CVD, respectively. Cumulative hazards were used to describe the transition intensities between the different states, based on mean transit times (MTTs) through the states [4]. Due to limited and non-regular observations, MTTs were subject to interval censoring. Several hypotheses were tested: 1) risk of CVD is independent of CKD, 2) risk of CKD is independent of CVD and 3) mortality is independent of CVD, CKD and dyad state. Model building was conducted using the likelihood ratio test and visual predictive check. Data management and exploration was performed using R V3.5.1. and the model fitting and evaluation was performed with NONMEM V7.4.3 and PsN.

Results: A disease progression model, taking into account being in any of five different states and competing risks of transitions between these states, was developed. By definition, all individuals started in the initial state with T2D without comorbidities, and the probability of staying in this state declined non-linearly over time. All mortality transitions were implemented using the Gompertz-Makeham formula, adjusted for the Swedish mortality rate and estimating a shift of age for the current state transition. The mortality risk was dependent on state and the initial state was estimated to be equal to a 10.5-year younger population than the standardized, while the mortality risk of the CVD, CKD and the dyad state were estimated to be equal to a 2.5-year, 1.3-year and 8.6-year older population. Thus, comorbidities reduce the expected life-span. The transition intensity to CKD was time-constant and dependent on baseline BMI, baseline SBP and age. The risk of developing CKD was 75% higher if preceded by CVD. The transition intensity to CVD was time-varying with higher risk the first 10 years and dependent on baseline BMI, baseline HbA1c and age. The risk of developing CVD was 70% higher if preceded by CKD. The 5-year risk moved 13% out of the initial state and distributed it between CVD, CKD and death (9%, 2.5% and 1.5%, respectively). A challenge with these large data were model evaluation, and data was thus splitted into several parts and simulated separately for creation of VPCs.

Conclusions: A multi-state model for competing risks analysis of T2D long-term complications was successfully developed. This model adequately described the diabetic disease progression in the Swedish patient population. The magnitude of estimated covariate effects on MTTs was reasonable and meaningful. Future work involves model validation and assessment the treatment impact on the risk of comorbidities and mortality through changes in covariates.

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II-05: *Sofiene Laarif* Quantitative modeling of inter-lesion and inter-organ variability of tumor size

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Objectives: In metastatic cancer, the growth and drug-induced shrinkage of individual tumor lesions may be highly dependent on the microenvironment of the hosting organ, and individual lesions may contribute differently to overall disease progression and survival. Lesions within the same organ may be more likely to evolve and respond in a similar manner than lesions from different organs. In the traditional analysis of tumor response to treatment, an overall measurement of patient tumor burden is used, i.e. the sum of the longest diameters (SLD) of up to 5 lesions (RECIST criteria v 1.1). Information of the impact of individual lesion dynamics on the outcome is hence ignored. The aim of this analysis was to develop population models to better understand and characterize the differences in tumor dynamics between lesions and between metastatic site.

Methods: The dataset consisted of lesion measurement data from 183 subjects with metastatic HER2-negative breast cancer receiving docetaxel at the dose of 100 mg/m^2 on the first day of three-week treatment cycles. The treatment continued until disease progression as assessed by RECIST criteria (v 1.0) [1] or an intolerable toxicity was reached. The dataset included up to 10 lesions per individual which were followed up to 145 weeks (median 32 weeks). A kinetic/pharmacodynamic (K/PD) function was driving the effect in a tumor growth inhibition model [2] that characterizes both lesion growth and drug-induced lesion shrinkage. Inter-lesion (ILV), inter-organ (IORV), and inter-individual variability (IIV) were explored in lesion baseline, growth rate and drug-induced shrinkage parameters. Logistic regression models were developed to describe the observed dropout from lesion measurements and the appearance of new lesions. Evaluated predictors included SLD or lesion size, disease progression (defined as 20% increase in SLD from nadir or the appearance of a new lesion), number of total lesions, number of metastatic organs and treatment duration.

Results: In the study population, metastasis were located in 11 different morphological locations of the body. Liver (50% of patients), lymph nodes (46%) and lungs (26%) were the most frequent metastatic sites. The median number of lesions per subject was 3 (range: 1-10). Lesions showed diverse profiles of shrinkage and growth during the study, but were more similar within an organ than between organs.

The lesion model included a baseline value typical for the organ, along with IIV shared across all organs (28 %CV), and ILV that ranged from similar magnitude (kidney, soft tissue) and up to three times higher (pelvis) compared to the IIV. For growth rate, the model included IIV and IORV of similar magnitudes (~80 %CV). The drug-induced shrinkage rate was almost twice as high for liver compared to the other organs.

The probability to dropout from tumor size measurements increased with the appearance of a new lesion, 20% increase from SLD nadir, and treatment duration. The probability of a new lesion increased with a large tumor size at baseline, a large number of lesions at baseline and treatment duration.

The dropout model was applied for visual predictive checks. These demonstrated the models' capability to adequately describe the typical trend and variability of lesion shrinkage and regrowth.

Conclusion: Inter-lesion, inter-organ, and inter-individual differences were well captured by the developed lesion model. This modeling approach, separating different levels of variability, has the potential to provide a better understanding of drug effect in different organs, and may be used to tailor treatments based on lesion location, lesion size and early lesion response. In a next step, the lesion model and the new lesion appearance model will be applied to explore relationships to survival.

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II-06: *Jennifer Lang* Combining physiologically-based-pharmacokinetic modelling and a Bayesian method for prediction of ivabradine oral absorption and drug-drug interactions

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Introduction: Ivabradine (I_f currents inhibitor) is indicated in stable chronic angina and heart failure. Ivabradine and its main metabolite (S18982) are both substrates of the metabolic enzyme CYP3A4, but nonlinear pharmacokinetics (PK) of S18982 was attributed to the efflux transporter P-gp in the intestine. The interplay between P-gp and CYP3A4 is often cited in the literature but in silico characterisation of this complex process is still not unequivocally successful. Combination of physiologically-based-pharmacokinetic (PBPK) and population PK modelling enables to take advantage of both top-down and bottom-up [1]. Underlying physiological structure of PBPK modelling allows investigation of the complex interplay between active transport and metabolism occurring in the gastrointestinal tract whereas the population approach provides more robustness and statistical power to the PBPK model development [2].

Objectives: The main objective is to model the interplay between P-gp and CYP3A4 using the example of ivabradine. To this end, PK after intravenous (IV) administration was described using a PBPK model and drug-specific parameter estimates were refined by means of a Bayesian method. Subsequently, the whole-body PBPK (WB-PBPK) model complexity was reduced by using the lumping method proposed by Dokoumetzidis and Aarons [3]. Finally, model prediction of oral drug absorption was evaluated against clinical data from Phase-I studies and drug-drug interaction studies with CYP3A4 and/or P-gp inhibitors.

Methods: A WB-PBPK model (n=14 organ tissues [4]) was used to describe ivabradine disposition in Phase-I clinical data in healthy male volunteers [5]. Drug-specific parameters were either measured in *in vitro* systems (e.g. permeability in Caco-2 cells, CYP3A4 metabolism in human liver microsomes) or predicted (i.e. blood-to-tissue partition coefficients by Rodgers and Rowland's method [6]) and used as informative priors in statistical analyses. A global sensitivity analysis was performed to identify drug-specific parameters that significantly influence prediction of systemic drug exposure. The Bayesian estimation method using MCMC was carried out in NONMEM v7.4. Parameter posterior distributions were updated using a Gibbs sampling method and convergence of parameter posterior distributions was verified by using the Gelman-Rubin test. Using the lumping method, reduction of the WB-PBPK model was investigated in order to facilitate further analyses (e.g. parent-metabolite relationship, oral absorption…). The disposition model was then linked to a gut model to account for drug absorption and model predictive performance was assessed using four clinical studies (following ivabradine dosing alone or co-administered with ketoconazole) [7].

Results: The sensitivity analysis identified importance of the blood-to-tissue partition coefficient for muscle (Kb_{muscle}) and the hepatic intrinsic clearance ($CLint_{hep}$) on systemic drug exposure for both parent and metabolite and were thus updated using the Bayesian method. The MCMC chains were well sampled and parameter posterior distributions reached convergence. Therefore the population-PBPK model described successfully ivabradine PK following IV administration. Model reduction from 14 to 8 compartments demonstrated that lumping allowed similar model performance and did not affect plasma prediction of drug disposition. A peripheral compartment comprised of skin, adipose tissue, bones and rest of body and a splanchnic compartment including spleen, pancreas, stomach wall and intestinal serosa were redefined.

The reduced PBPK model linked to a gut model adequately described ivabradine oral absorption, metabolite formation and the magnitude of intestinal and hepatic CYP3A4 inhibition by ketoconazole.

Conclusions: Combining physiological structure of PBPK models with parameter refinement using clinical data allows the investigation of complex physiological mechanisms for which *in vitro* or clinical data might be sparse. This integrated population-PBPK method was satisfactorily applied to ivabradine in healthy volunteers and is useful for predicting drug exposure or drug-drug interaction risk in different populations (e.g. the elderly or children).

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II-07: *Silvia Maria Lavezzi* Pharmacokinetic Models for Drug and Metabolites Including First Pass Effects: A Priori and A Posteriori Identifiability Analysis

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Objectives: Joint pharmacokinetic (PK) modelling of a parent drug and its metabolites is fundamental to evaluate absorption, distribution, metabolization, and elimination of all analytes. This is particularly relevant when metabolites are formed during first pass through the liver and may be pharmacologically active or lead to toxicity episodes. Different joint drug-metabolites PK models have been proposed in the literature: in our study, a priori and a posteriori identifiability analyses were performed on published models including first passage through the liver [1,2].

Methods: Three models were evaluated: Model 1, with one depot per analyte [1]; Model 2, with a single depot and different absorption rates for each analyte [1]; Model 3, with a single depot and absorption rate to a liver compartment [2].
A priori identifiability was explored (similarly to [3]), via DAISY [4], assuming the drug is given intravenously (IV) and orally, and parent responses to both IV and oral administration are available, while two metabolites are measured after oral administration only.
A posteriori identifiability was explored via bootstrap analysis in NONMEM 7.4.3 (FOCE method), fixing a priori non-identifiable parameters. 500 bootstrap datasets were obtained from a re-scaled dataset of a real case study involving two metabolites.

Results: None of these models were a priori identifiable unless prior knowledge on some parameters was assumed. All models were a priori identifiable after fixing metabolites volumes (or clearances), one parameter for parent drug distribution/elimination, and one parameter for drug absorption.
For a posteriori identifiability analysis, metabolites volumes (Vm1, Vm2), bioavailability (F), and intercompartmental drug clearance (Q) were fixed. In particular, Vm1 and Vm2 were set equal either to 1 (scenario i) or to drug central volume, i.e. Vm1=Vm2=V (scenario ii).
- *Model 1*: During bootstrap, 75% and 83% of runs failed to converge in scenario i and ii, respectively. In both scenarios, fixed effect and inter-individual variability (IIV) for fraction of metabolite 2 absorbed (Fm2) did not change from their initial estimates and a high IIV on fraction of drug metabolized to metabolite 2 (FMm2) was estimated with low precision. In scenario ii, also a high IIV on total fraction metabolized (FM) was estimated with poor precision, as well as both fixed effect and IIV for absorption rate constant.
- *Model 2*: 63% and 56% of runs failed to converge in scenario i and ii, respectively. In scenario i, metabolite 2 clearance (CLm2), FM, and IIV on FMm2 estimates displayed low precision. In scenario ii, IIV on FM and FMm2 was high on average and poorly estimated.
- *Model 3*: 39% and 52% of runs failed to converge in scenario i and ii, respectively. In scenario i, all parameters were estimated with reasonable precision, except for FM; IIV on this parameter was fairly high. In scenario ii, this IIV term became higher (on average) and was estimated with low precision.
For all models, estimation issues were rarer in scenario i (Vm1=Vm2=1) compared to scenario ii (Vm1=Vm2=V).
Among common parameters, V and metabolite 1 clearance (CLm1) were on average consistently estimated (i.e. with similar bootstrap medians) across models but not across scenarios. Parent drug clearance (CL) and peripheral volume of distribution (Vp) were consistently estimated across both models and scenarios.

Conclusions: A priori identifiability analysis helps detecting parameters that are non-identifiable in practice: this is a necessary but not sufficient requirement for a posteriori identifiability. A priori identifiability analysis performed on three PK models for a parent compound and two metabolites including first pass effects demonstrated structural over-parametrization. Even after fixing non-identifiable parameters, practical identification issues were still highlighted by the bootstrap analysis (especially for fractions of drug metabolized). This means that additional information would be needed to obtain reliable model estimates. Despite a posteriori identifiability results are dataset-dependent, it is of some interest that Model 3 showed the lowest rates of failed runs, and, when successfully estimated, reasonable precisions for almost all parameters.

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II-08: *Jean Lavigne* Population Pharmacokinetics of Piperacillin-Tazobactam Extended Infusions in Paediatric Population

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Introduction: Sepsis is one of the leading cause of morbidity and mortality in infants and children.[1,2] Sepsis treatment depends on early, effective antibiotic therapy,[3,4] but therapeutic efficacy is increasingly challenged by antibiotic resistance.[5] Piperacillin-tazobactam efficacy depends on achieving appropriate drug concentrations in the body. Similar to other β-lactam antibiotics, piperacillin exerts bactericidal activity in a time-dependent manner.[6] Consequently, piperacillin is most effective when the free (unbound to plasma protein) drug concentration exceeds the pathogen's minimal inhibitory concentration (MIC) for at least 50% of dosing interval (50% *f*T > MIC).[6] Time over MIC is therefore the pharmacodynamic (PD) parameter serving as a surrogate target for efficacy.[6]

Objectives: The objectives of the current analysis were 1) to describe the population pharmacokinetics (PK) of piperacillin-tazobactam, 2) to establish extended-infusion piperacillin-tazobactam dosing recommendations in infants and young children 2 months to 6 years of age with normal renal function for the treatment of sepsis caused by bacteria with decreased susceptibility to piperacillin-tazobactam, and 3) to provide dosing recommendations according to different levels of antibiotic susceptibility.

Methods: Piperacillin-tazobactam is a combination with a fixed ratio of 8:1. This was a single-center prospective pharmacokinetic study. Piperacillin-tazobactam was administrated intravenously (IV) with a dose of 80 mg/kg of piperacillin every 6 hours infused over 2 hours for infants 2 to 5 months old, and 90 mg/kg of piperacillin every 8 hours infused over 4 hours for children 6 months to 6 years of age. A total of 79 children with 165 and 163 samples of piperacillin and tazobactam, respectively, were included in the analysis. Population PK analysis was performed using nonlinear mixed effect[7] and sources of variability (body weight, sex, age, race, ethnicity, markers of liver/kidney function, concomitant medication, hospital unit) were explored using a stepwise covariate analysis[8]. Simulations were performed to support dosing of piperacillin-tazobactam in children. For different dosing regimens, we estimated the probability of target attainment (PTA) over a range of MICs from 4 to 32 mg/L. The pharmacodynamic (PD) target was defined as free piperacillin concentrations above the MIC for ≥ 50% of the dosing interval. A PTA ≥ 90% was defined as optimal.

Results: Both piperacillin and tazobactam were best described with a 2 compartment PK model with linear elimination. Weight (WT), albumin (ALB) and concomitant furosemide use were significant covariates in the piperacillin PK model. Typical clearance (CL), distribution clearance (CLd), central volume of distribution (Vc) and peripheral volume of distribution (Vp) were 4.53 L/h, 133 L/h, 2.19 L, and 2.00 L, respectively [for child with WT of 11.4 kg, ALB of 29 g/L and not taking furosemide as concomitant medication]. Typical CL, CLd, Vc, and Vp of tazobactam were 2.88 L/h, 1.04 L, 8.10 L/h and 1.66 L, respectively [for child with WT of 11.4 kg, and ALB of 29 g/L]. Piperacillin and tazobactam elimination half-life were 0.646 and 0.744 h, respectively. Simulations were done using MICs of 4, 8, 16 and 32 mg/L in 3 age groups: 2-11 months, 12-23 months, and 2-6 years. PTAs increased as age increased. Among the tested dosing regimens, 100

mg/kg/dose every 4h infused over 2h reached the optimal PD target at MICs of 4 mg/L and 8 mg/L in all age groups and PTAs at MICs of 16 mg/L and 32 mg/L were 85% and 60-69%, respectively.

Conclusions: Both piperacillin and tazobactam exposure were affected by weight. Concomitant furosemide use increased piperacillin exposure possibly due to competition of tubular secretion. The recommended piperacillin dosing is 100 mg/kg IV over 2 h at every 4 h.

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II-09: *Jacob Leander* Development of a population pharmacokinetic model of verinurad used for simulations of various dosing scenarios in different populations

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Objectives: Verinurad (also known as RDEA3170) is a novel URAT1 inhibitor currently in Phase II development for treatment of chronic kidney disease (CKD). Verinurad lowers serum uric acid (risk factor for CKD [1]), by inhibiting reabsorption of uric acid in proximal tubule [2]. Verinurad as mono therapy or combined with a xanthine oxidase inhibitor has been shown to lower serum uric acid in patients with recurrent gout and/or asymptomatic hyperuricemia [3][4][5][6].

In recent studies, verinurad has been administered as an oral extended release formulation that has higher bioavailability and no effect of food compared to the oral modified release formulation that was used in the Phase II studies in gout. In addition to difference in formulation, renal function and Asian origin has previously been identified to impact verinurad exposure [6][7].

The objective of this work was to integrate pharmacokinetic data from relevant verinurad studies and to build a fit-for-purpose population pharmacokinetic (popPK) model of verinurad capable of predicting exposure for the two formulations in different populations.

Methods: In total 12398 verinurad plasma concentration samples from 419 subjects (299 non-Asians and 120 Asians) were obtained from 12 studies (8 Phase I and 4 Phase II). Three of the studies included gout patients (n=144), one study included patients with albuminuria (n=27), one study was a renal impairment study (n=31), and 7 studies were done in healthy volunteers (n=217). The modified release formulation was used in 8 studies (n=316) while the extended release formulation was used in 4 studies (n=123). Renal function ranged from 12 to 138 mL/min in the pooled population. Subjects with at least one measurable PK concentration were included in the analysis.

Covariates included in the analysis were: renal function (estimated glomerular filtration rate (eGFR) using the CKD-EPI formula [9]), Asian origin, formulation, food status, body weight, and gout. The popPK model of verinurad was developed using non-linear mixed effect modelling as implemented in NONMEM 7.3.0 [10]. Covariates were investigated in a stepwise fashion as implemented in PsN 4.4.8 [11].

Results: The pharmacokinetics of verinurad was adequately described by two-compartmental linear disposition model. The absorption phase of verinurad required a complex absorption model with three parameters, of which formulation and food (for the modified release) was found to be highly significant covariates on the zero-order duration parameter D1. Additional covariates in the final model included eGFR, Asian origin, and body weight.

Simulations show that the typical Asian subject has a 1.45-fold higher AUC compared to a non-Asian subject after correcting for renal function and body weight. Subjects with moderate renal impairment (eGFR = 60 mL/min) were estimated to have 1.25-fold higher AUC compared with subjects with normal renal function (eGFR = 90 mL/min), while subjects with low body weight (60 kg) were estimated to have 1.47-fold higher exposure compared to those with high body weight (100 kg).

Conclusions: A population pharmacokinetic model was developed for verinurad, based on the wide range of data integrated from several studies (different patient populations and drug formulations). This allowed to simulate various dosing scenarios and was valuable to support dose selection during verinurad clinical development program.

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II-10: *Donghwan Lee* Effect of Pharmacokinetic Model Misspecification on Antibiotic Probability of Target Attainment Predicted by Monte Carlo Simulation

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Objectives: Many population pharmacokinetic (PK) models have been developed for an antibiotic, and the structures of such models are very diverse. The first aim of this study was to compare the predictability of efficacy by MCS between a true one-compartment model and a true two-compartment model for doripenem. The second aim was to explore how we can identify the usefulness of a one-compartment model when the PK/PD indices between three mis-specified one-compartments models and a true two-compartment model are compared.

Methods: The reported two-compartment model parameters of two doripenem studies and a vancomycin study were used to generate 200 virtual concentration-time profiles for each study. Sparse and dense sampling designs were selected to build the one- and two-compartment models, respectively, for the drugs. We conducted 10,000-subject simulations with the newly constructed PK models. The probability of target attainment for the PK/PD indices were compared between the one- and two-compartment models of the same drug, applying the clinical breakpoint distribution of minimum inhibitory concentration (MIC)s.

Results: The simulated concentration-time profiles well-reproduced the original data. In addition, the PTAs were similar between the one- and two-compartment models when infusion time and MIC were the same in the doripenem studies. For vancomycin simulations, the maximum difference was 65.9% between a mis-specified one-compartment model and the true two-compartment model.

Conclusions: This study explored the PK/PD indices of antibiotics using one- and two-compartment models built with the same cohort; however, with different sampling designs. When a one-compartment model was established with the sparse sampling data from a two-compartment model simulation, the probability of target attainment when evaluated by $fT_{>MIC}$ was similar to that of the two-compartment model. When a mis-specified one-compartment model was established using the sparse sampling data from a two-compartment model simulation, the probability of target attainment when evaluated by AUC/MIC significantly differed form that of the two-compartment model. For drugs that are commonly known to follow the two-compartment model, when a one-compartment model is developed through PK studies, the model must satisfy the following three conditions to be useful: 1. A review of the residual based diagnostic plots including the residuals vs. time plot and residuals vs. population model-prediction plot; 2. The distribution of the observation and predictions should be compared to the visual predictive check; and 3. The range of the sampling times should be wide enough based on the expected half-life, which is dependent on the drug and the condition of the patient.

II-11: *Woo Yul Lee* Population pharmacokinetics of recombinant coagulation factor VIII in Korean hemophila A patients

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Objectives: Although several population pharmacokinetic (PK) models for recombinant coagulation factor VIII are presently available, no such model has been developed in Korean population. Population PK (PPK) model, however, has many applications if developed, one important example of which is therapeutic drug monitoring (TDM) which is widely used for patient care. In TDM, PPK model is used as a basis to estimate individual PK parameters to be used to find an optimal individual dose. Thus, PPK model is a key to monitoring and controlling drug concentrations, particularly useful for drugs with a narrow therapeutic window or wide interindividual variation. In the case of hemophilia patients who have little or no endogenous coagulation factor VIII, the use of TDM based on PPK model is further important as maintaining factor VIII concentrations above a certain effective level with an exogenous coagulation factor VIII given regularly is crucial for them to avoid suffering from life-threatening bleeding tendency.

In this respect, our study aims to develop a population PK model of recombinant coagulation Factor VIII and investigate its relationship with covariates such as age, body weight and Von Willebrand Factor (VWF) in Korean patients with hemophilia A, with an expectation of improving their quality of life and possibly saving medical expenses given the high price of recombinant factor VIII preparations.

Methods: Data were acquired from a prospectively designed coagulation factor VIII PK study conducted by Korea Hemophilia Foundation in 2018. In total, after a brief infusion of factor VIII, 85 samples from 21 subjects with hemophilia A were used for analysis. The severity of hemophilia was classified into 3 categories according to the baseline concentration of coagulation factor VIII (1 mild, 2 moderate, 18 severe). Age ranged from 9 to 75yr, with the median value being 26 yr. Body weight ranged from 27.5 to 110 kg, with the median value being 66 kg. The concentration of VWF ranged from 71.7 to 229 IU/dl, with the median value being 116.7 IU/dl. Based on theory-based allometry [1,2], body weight was incorporated into the volume of distribution (V) linearly and into clearance (CL) with a power function. Significant relationships of covariates with PK parameters were initially explored using R and then formally tested using stepwise covariate model building. All analyses were performed using R ver 3.5.2 and NONMEM ver 7.3.

Results: One compartment model with 1st order elimination described the data. Results showed that CL (dL/hr) of factor VIII decreased by 0.53% per one year increase in age and it also decreased with the increase of VWF concentration. The typical parameter estimates evaluated at the median body weight (66kg) were 44.04 dL for V, 2.977 dL/hr for CL and 2.33 IU/dL for coagulation factor VIII baseline concentration. The inter-individual variabilities (CV%) were 12.3% for CL, 18.1% for V and 94.9% for baseline factor VIII concentration. The proportional residual error (CV%) was estimated to be 15.1%. Our model successively described the time course of observed coagulation factor VIII concentrations.

Conclusions: One compartment model competently described our data although two compartment models are more commonly suggested by previous studies. This could be due to small sample size and sparse

sampling points of our data. Nevertheless, these preliminary results demonstrated that clearance of recombinant coagulation factor VIII in Korean hemophilia A patient is negatively influenced by age and the concentration of VWF binding with coagulation factor VIII, where the former relation was as shown by previous PK studies. Given a small sample size used in current study, further work in a larger patient population would be needed to generalize the results.

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II-12: *Soyoung Lee* Population Pharmacokinetic Analysis for Novel Acid Pump Antagonist DWP14012

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Objectives: DWP14012 is a novel potassium-competitive acid blocker, which reversibly binds to H+, K+-ATPase without acid activation [1]. As expected to show better therapeutic effect for gastroesophageal reflux disease and gastric ulcer, DWP14012 has been under development. Since its exposure shows more than dose proportional manner across 10 to 320 mg dose range, predicting pharmacokinetic profile of DWP14012 is needed. The current study aims to construct a population pharmacokinetic model for DWP14012 in healthy Korean subject.

Methods: A population pharmacokinetic model for DWP14012 was developed by using a nonlinear mixed-effects method in NONMEM (version 7.4). A total of 860 plasma DWP14012 concentration from a phase 1 single ascending dose pharmacokinetic study (n=48), which included 10, 20, 40, 80, 160, 320 mg dose group, were used to construct base model. One or two compartment models with first order or zero order absorption with or without lag time were assessed to identify the best describing absorption profile of DWP14012. In addition, first order elimination or Michaelis Menten elimination were evaluated to determine appropriate DWP14012 pharmacokinetic profile. The model performance was evaluated with basic goodness-of-fit diagnostics and visual predictive checks. Simulations were performed investigating multiple dosing scenario, such as 20 mg, 40 mg, 80 mg daily administration of DWP14012 for 7 days. The peak concentration (C_{max}) and minimum concentration (C_{min}) of DWP14012 were evaluated for each of the multiple dosing scenarios.

Results: The pharmacokinetic characteristics of DWP14012 were well described with a two-compartment non-linear pharmacokinetic model with first-order absorption and lag time with proportional residual error. Non-linear pharmacokinetic properties were explained by Michaelis Menten elimination. The typical estimates of absorption constant (Ka), central volume of distribution (V2), peripheral volume of distribution (V3), intercompartmental clearance (Q), and lag time was 0.128 h^{-1}, 107 L, 702 L, 54.8 L/h, and 0.238 h, respectively. The typical value of maximum rate (V_{max}) and Michaelis constant (K_m) was estimated to 6.29 L/h and 38.1 μg/L, respectively. The inter-individual variability (CV%) of V2, Ka, and V_{max} was 114.2 %, 17.2 %, and 30.0 %, respectively. Model evaluation by visual predictive checks suggested that the proposed model was adequate and robust with good precision. The simulation results of median C_{max} in 20 mg, 40 mg, 80 mg group was 13.24 μg/L, 32.53 μg/L, and 94.65 μg/L, respectively. The simulation results of median C_{min} in 20 mg, 40 mg, 80 mg group was 1.84 μg/L, 4.42 μg/L, and 14.41 μg/L, respectively.

Conclusions: The population pharmacokinetic model for DWP14012 was well developed to predict the multiple dose administration of DWP14012. Further model refinement using patient data can be utilized to improve the dosing regimen in patient group with gastroesophageal reflux disease and gastric ulcer.

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II-13: *Hyun A Lee* A mechanism-based pharmacokinetic/pharmacodynamic model to evaluate the mutual relationships between YH4808, a novel K+-competitive acid blocker, and intragastric pH in humans

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Introduction: YH4808 is a highly potent, selective and reversible potassium-competitive acid blocker of the H+/K+-ATPase under development to treat gastric acid-related diseases. The pharmacokinetics of YH4808 was dose-proportional in humans after a single oral dose at 30-800 mg. However, the systemic exposure to YH4808 decreased after multiple oral administrations, particularly at higher doses (200 and 400 mg) [1]. The reduced solubility of YH4808 caused by elevated intragastric pH after treatment with YH4808 was suggested as the main cause of the reduced exposure. This hypothesis was supported by a physiologically-based pharmacokinetic modeling and simulation analysis [2].

Objectives: To develop a pharmacokinetic and pharmacodynamic model to quantitatively evaluate the mutual relationships between the plasma concentrations of YH4808 and the time course of intragastric pH after single and multiple oral administration in humans.

Methods: The plasma concentrations of YH4808 and intragastric pH profiles obtained from healthy subjects who received a single (30-800 mg) or multiple (100-400 mg) oral doses or their matching placebos (intragastric pH only) were pooled and a pharmacokinetic and pharmacodynamic model was developed simultaneously using the first-order conditional estimation with interaction (FOCE-I) method implemented in NONMEM version 7.3 (ICON Development Solutions, Ellicott City, MD, USA). The effects of the covariates (i.e., age, body weight and height) were also evaluated and tested. The final model was qualified based on the precision of parameter estimates, diagnostic plots and visual predictive check plots.

Results: We pooled 1627 plasma concentrations and 1846 intragastric pH points from 80 subjects (56 and 24 for single and multiple dose studies, respectively), aged 20-41 years and weighing 53.5-87.2 kg. A two-compartment pharmacokinetic model with lagged first-order absorption model and a sigmoid maximum effect model linked with an effect compartment best described the observed YH4808 plasma concentrations and intragastric pH profiles over 24-hour period after YH4808 dosing, respectively. To address changes in intragastric pH over time affecting the plasma concentration of YH4808, we introduced a feedback path such that increased intragastric pH decreases the relative bioavailability of YH4808. The intragastric pH profiles at baseline exhibited a circadian rhythm, which was well described by a four-harmonic function in the pharmacodynamic model. No covariates significantly affected the pharmacokinetic or pharmacodynamic parameters of YH4808. The typical values of E_{max} or the maximum effect and EC_{50} or the drug concentration that produces half of E_{max} were 6.9 (95% confidence interval (CI): 6.6-7.3) and 206.4 ng/mL (95% CI: 201.3-211.5 ng/mL), respectively. The interindividual variability of E_{max} and EC_{50} was 19.6% (95% CI: 16.2-23.1%) and 3.5% (95% CI: -3.0-10.1%), respectively.

Conclusions: We developed a pharmacokinetic and pharmacodynamic model that adequately described quantitative mutual relationships between the plasma concentrations of YH4808 and the time course of intragastric pH after single and multiple oral administrations in humans. Our analysis provides mechanistic

insight into the relationship between the exposure to YH4808 and intragastric pH, which will allow for devising optimal dosing regimens for YH4808 in future clinical studies.

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II-14: *So Jin Lee* The new era of pharmacokinetic/pharmacodynamic modeling and simulation in drug development in Korea

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Introduction: As Korean pharmaceutical industry is reaching the golden era of drug discovery due to increased investments in R&D and government funds over the past decade, the need for a more efficient tool for the quantitative analysis has emerged. The traditional academia-based platform was no longer feasible to provide pharmacometric consultancy services to domestic pharmaceutical companies with evolving demand for higher quality services. Accordingly, the first pharmacometric analysis company in South Korea was launched in 2016 from the previous academia-based research institution, Pharmacometrics Institute for Practical Education & Training (PIPET) through academia-industry collaboration. The pharmacometric analysis project experiences were gathered and evaluated to show the changing landscape of the use of pharmacokinetic/pharmacodynamic modeling and simulation in drug development in Korea.

Objectives:

- Assess the pharmacometric analysis experiences in Korea
- Evaluate the characteristics of the pharmacometric consultancy projects over time from the academia-based to the current platform
- Identify the current trends of pharmacometric consultancy in Korea and identify unique local needs
- Assess the impact of the application of modeling and simulation techniques in drug development in Korea
- Identify an area of development to trail future demands

Methods: PK/PD modeling and simulation project lists and its experiences (2014-2018) were gathered; academia-based platform, PIPET, experiences (2014-2016), and current new platform, Q-fitter, experiences (2016-2018). The data analysis and graphing were done using Microsoft Excel. The project experiences were classified by categories, such as purpose, drug development stages, therapeutic areas, types of outsourcing companies. Each category results were ranked from highest to lowest to identify the most sought-after characteristics by clients. Project characteristics were compared between academia-based and current company-based era. With a current platform, a yearly comparison was made to observe differences in pharmacometric project characteristics between 2017 and 2018.

Results: Based on the assessment, we observed a steep increase in the number of projects per year and the expansion of the scope of analysis services. The number of projects completed increased by 240% from the previous platform to current. Also, on a current platform, the demand for PK/PD analysis increased consistently over the years, as high as 275% per year. The pool of outsourcing client expanded including domestic CRO and US bioventure from domestic pharmaceutical companies and biotech companies, a major client still consisting of 80% of the total. The most important goal of PK/PD analysis in Korean pharmaceutical industry was the prediction of first-in-human dose followed by optimization of efficacious doses and dose regimens (specific scenario-based). Consistently, greater than 90% of the projects focus on the translational step from preclinical to clinical, and clinical phases. Previously, oncology (~27%) and

immunology (~27%) were the top therapeutic areas to use PK/PD analysis. With the transition, we observed increased use in oncologic drugs (~31%), but also a broader application in other therapeutic areas was seen, such as rare diseases and vaccines. Continuous use of a model-based approach for the monoclonal antibodies for oncology and immunology drugs were observed. The PK/PD analysis results were mainly used to support internal decision-making, supplement the regulatory submission and aid the process of out-licensing deals. Additionally, more complex systems pharmacology models and drug-drug interaction predictions were on demand from the industry.

Conclusions: Current transition of the pharmacometic analysis-providing platform and its project experiences indicate that the pharmacometrics environment in Korea is rapidly evolving. The model-based drug development is becoming one of the essential tools for successful drug development in Korea, and awareness is increasing. Through the assessments, we were able to identify the most important goal of the analysis, therapeutic areas of focus, and key trends of PK/PD analysis in Korea, as well as areas of improvement. The continued increase in the use of pharmacometrics is expected in Korea pharmaceutical industry, thus it is necessary to establish further strategic development goals to take the analysis services to the next level.

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II-15: *Anja Lehmann* Toxicokinetic modelling of hepatotoxic pyrrolizidine alkaloids: a combined in silico, in vitro and in vivo approach

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Introduction/Objective: Pyrrolizidine alkaloids (PAs) are a class of secondary metabolites in plants of which some are highly hepatotoxic, genotoxic, and carcinogenic [1]. Humans are exposed to PAs via intake of herbal supplements or medicines, and via contamination of foodstuffs such as tea, honey, and spices [2]. The combination of PAs with cytochrome P450 enzyme-inducing compounds, e.g. the drug phenobarbital, has been shown to dramatically increase PA toxicity [3]. Our aim was to develop a specifically tailored physiologically-based toxicokinetic (PBTK) model for PAs that includes the necessary detailed representation of PA metabolism to predict hepatic interactions.

Methods: In contrast to most pharmaceutical compounds, PAs are not well characterized in terms of their physico-chemical/biochemical properties. Kinetic data is sparse due to general efforts towards reduction of animal testing in chemical risk assessment. To overcome this sparse data situation, we used a combined *in silico*, *in vitro*, and *in vivo* approach for PBTK model development. We performed *in vitro* assays to determine lipophilicity, transcellular permeability (Caco-2), and metabolic clearance in mouse, rat, and human liver microsomes. *In vivo* metabolic clearance was predicted via *in vitro* to *in vivo* extrapolation. *In silico* methods were applied to predict ionization (SPARC v2018), plasma protein binding (GastroPlus v9.5), and tissue distribution [4]. We implemented the PBTK model in R based on the *RxODE* (v0.7.2-1) package [5] and inferred parameters via Maximum Likelihood Estimation and the Delayed Rejection Adaptive Metropolis algorithm [6].

Results: Retrorsine was identified as suitable PA for model development, since mouse and rat *in vivo* data (i.p. or i.v. administration) are available. The data include measurements of retrorsine and selected metabolites (protein adducts, DNA adducts, glutathione conjugates) in plasma, liver, urine or bile [7-10]. With regard to PBTK model development, we have specifically tailored the liver compartment by adapting the extended clearance model [11]. The adaption includes a representation of basic PA toxification and detoxification pathways. This allows to discriminate between metabolic and transport-related clearance, and makes the PBTK model well-suited to predict hepatic interactions of PAs. Determination of retrorsine metabolic clearance in liver microsomes revealed inter-species differences: metabolic clearance was more than 3-fold higher in rat compared to mouse and human. For all species, retrorsine depletion in liver microsomes followed a biexponential pattern. We explained and modelled this pattern mechanistically via end-product inhibition of the metabolic activity. Transcellular permeability of retrorsine in Caco-2 cells was determined to be $5.52 \cdot 10^{-6}$ $cm \cdot s^{-1}$, which we use to predict oral absorption profiles.

Conclusions: Our research underpins highly relevant interactions between medical and foodborne compounds that should be considered in both drug dosing and food safety risk assessment, respectively. On the example of PA hepatic interactions, we demonstrate that translational toxicology is an efficient tool

for the development of PBTK models, especially in sparse data situations. Next steps include the extrapolation of the PBTK model to humans and simulating real-life consumer exposure scenarios.

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II-16: *Rory Leisegang* Establishing evidence for improved outcomes for HIV+ patients receiving antiretroviral drugs through home delivery

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Objectives: Establishing evidence for interventions that may improve patient care, using data routinely available in electronic healthcare records (EHR), is important. Delivery of chronic medication by courier to a patient's home (home refill) is an emerging intervention and should be considered within differentiated service delivery (DSD) models [1] and may improve adherence. Home-based antiretroviral therapy (ART), which included clinical management, laboratory monitoring, and antiretroviral (ARV) delivery has been shown to be effective in a systematic review [2]; only one study has looked purely at ARV delivery and found improved outcomes, but numbers were limited and the study was conducted in a high-income country setting only [3]. In this analyses, we compared various outcomes in patients from a large cohort in South Africa, who either collected ARV refills at their local pharmacy (self-refill) or received ARV refills at home via courier (home-refill) during the course of the study.

Methods: We conducted a retrospective cohort analysis of ART naïve HIV-infected adults in AFA who initiated first line NNRTI based ART regimen between January 2002 and July 2013. The primary endpoint was all-cause mortality; secondary endpoints included viral load (VL) suppression, CD4+ cell (CD4) response (cells/µl), and hospitalization events. Statistical analyses included nonlinear mixed-effects models, survival analyses, baseline (propensity-score) models, and time-updated (marginal structural) models (MSM).

Results: 40,939 patients, contributing over 66,000 years of follow-up were evaluated. group. Home-refill (versus self-refill) was associated with improved survival (adjusted hazard ratio = 0.90 [95% CI: 0.84-0.96], p-value for log-rank test < 0.001) after adjusting for baseline differences; CD4 response and VL suppression rates were also superior for home-refill. Moreover, in patients who switched from self-refill to home refill ARVs during the course of their treatment (either routinely or on request), CD4 response and VL suppression rates all improved after switching together with survival (after adjusting for time-updated differences up to the point of switching). Finally, patients doing worse (lower CD4, higher VL) on self-refill were more likely to switch to home refill and this impacted comparison of hospitalization rates between the group and established the need for MSMs to evaluate the true impact on survival.

Conclusions: Using routinely-collected real-world data, we established evidence for home refill chronic ARVs (via courier) being associated with improved clinical, immunological, and virologic outcomes compared to self-refill in patients with HIV. Home refill offers a promising additional option to the growing chronic disease models and should facilitate the UNAIDS 90-90-90 targets [4] for HIV in resource-poor and resource-rich settings alike, where barriers to care impact ARV adherence.

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II-17: *Giulia Lestini* Handling dropouts in longitudinal observational studies – an illustration of a workflow from data preparation to model building and model diagnostics in Alzheimer's disease

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Objectives: Longitudinal observational studies collecting cognitive data can be used to model Alzheimer's disease progression. Those models cannot be evaluated using standard simulation-based diagnostics given the high dropouts rates as commonly observed in observational studies, even if dropouts happen "at random" [1]. A solution is to develop a dropout model that can be used to adjust the simulation part of simulation-based diagnostics. Here, we present a workflow on how to handle dropouts in these type of studies – from data preparation to model building and diagnostics of the "time to dropout" model.

Methods: Our work is based on longitudinal data collected from three cohort studies (ROS, MAP and MARS) of memory and aging at the Rush Alzheimer's Disease Center. For the purpose of our analysis we consider a cut-off at 8 years and we define as dropouts those individuals with their last cognitive assessment occurring before year 8. Individuals who have assessments up to 8 years or beyond, are right-censored at 8 years. We propose to model the dropout times using time-to-event analysis with interval censoring. The rationale for this methodology is that the dropout can occur at any time between two subsequent visits. Since visits are not all scheduled at the same time, we stochastically impute the end of the censoring interval based on the information available from the other subjects.
In order to have a first insight about the shape of the dropout baseline hazard, and on the possible relationship between the hazard and some covariates of interest, such as baseline age and baseline cognitive score, we analyse the data using a Cox proportional hazard model, without or with covariates. We then move to parametric modelling, in order to expand the model by accounting for the nonlinearity of the hazard. Baseline covariates are also tested. Time-independent and time-varying Martingales residuals and Kaplan-Meier of the Martingale (predicted cumulative hazard) [2] are produced to assess the quality of the models.

Results: There are 2194 subjects in this analysis data set with 1124 dropping out before year 8. The algorithm that stochastically imputes the end of the censoring interval for a subject who drops out considers records from all subjects with visits in the time range of the last visit of the dropout subject (plus or minus 6 months) and having a follow-up visit. These records are used to derive the respective time intervals "delta" between the selected visits and their subsequent ones. From this set of intervals one delta time is randomly sampled and used to define the right-end of the interval during which the dropout time occurred. This stochastic imputation takes into account the possible differences in time intervals between visits occurring earlier and later during the study. Graphical analysis is used to check unbiased imputation of the right-end time interval.
The cumulative hazard obtained from the Cox proportional hazard model suggests that the hazard of dropping out in the first year and a half is almost zero, and then it constantly increases over time, which translates into fitting an exponential function or a generalized exponential function, such as the Weibull, or a log-logistic function, when moving to parametric modelling.
All parametric models tested show some misfit in the diagnostic plots, with the log-logistic function providing the best fit. When baseline covariates are included additively into this model, the systematic trend observed in the smooth regression line of Martingale residuals disappears, suggesting that the effect of the covariates on the hazard is appropriately specified in the model.

The Kaplan-Meier plot of the Martingale of this model now overlays the shape of an exponential distribution of mean 1 as expected.

Conclusions: This analysis provides a workflow on how to handle dropouts before actually modelling the outcome of interest. Although other algorithms of interval imputation could be used, the one we implemented provides a good approximation of the end of the censoring interval for dropout subjects, allowing for interval censoring time to single event modelling.

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II-18: *Yisheng Li* A semi-mechanistic dose-finding design in oncology using pharmacokinetic/pharmacodynamic modeling

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Objectives: While a number of phase I dose-finding designs in oncology exist, the commonly used ones are either algorithmic or empirical model-based. Other statistical designs that incorporate pharmacokinetic (PK) data mainly focus on summary PK information. We aim to: 1) propose an extended framework for modeling the dose-toxicity relationship, by incorporating dynamic PK and pharmacodynamic (PD) information; and 2) apply this modeling framework in the design of phase I trials.

Methods: We propose to jointly model the PK, latent PD, and dose-limiting toxicity (DLT) outcomes by using dynamic PK/PD modeling as well as modeling of the relationship between a latent cumulative pharmacologic effect and a binary DLT outcome. This modeling framework naturally incorporates the information on the impact of dose, schedule and method of administration (e.g., drug formulation and route of administration) on toxicity. The resulting design is an extension of the existing designs that make use of pre-specified summary PK information (such as the area under the concentration-time curve [AUC] or maximum serum concentration [Cmax]). We conduct extensive simulation studies to evaluate the performance of the proposed design and compare it with the existing designs. The performance of each design is summarized by the percentage of correct selection of the maximum tolerated dose (MTD), average number of patients allocated at the MTD, and average probability of patient experiencing DLT, in the simulations.

Results: Our simulation studies show, with moderate departure from the hypothesized mechanism of the drug action, that the performance of the proposed design on average improves upon those of the common designs, including the continual reassessment method (CRM), Bayesian optimal interval (BOIN) design, modified toxicity probability interval (mTPI) method, and a design called PKLOGIT that models the effect of the AUC on toxicity. In case of considerable departure from the underlying drug effect mechanism, the performance of the proposed design is shown to be comparable to that of the other designs. We illustrate the proposed design by applying it to the setting of a phase I trial of a γ-secretase inhibitor in metastatic or locally advanced solid tumors. We also provide an R package to implement the proposed design.

Conclusions: The proposed design improves upon the existing designs. The proposed joint modeling framework may be considered promising for use in other settings of early phase oncology trial designs as well.

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II-19: *Patrick Lilienthal* Mathematical modeling of RBC count dynamics after blood loss

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Introduction:

The production of red blood cells (RBCs) in humans is an individual complex process. Our main interest lies in the regeneration of RBCs after a blood loss. The deeper understanding of this regeneration process could have an important impact for personalized clinical decision support in the case of polycythemia vera (PV). PV is a slow-growing type of blood cancer, where especially the production of RBCs is increased. The principal treatment targeting the symptoms of PV is bloodletting (phlebotomy), at regular intervals that are based on personal experiences of the physicians. Due to the complexity of the process, reduction to the most essential features concerning the application is crucial for the development of a model usable in clinical practice.

Objectives:

- Development of a novel simple compartment model for RBC regeneration usable in clinical practice
- Model verification and estimation of characteristic variables for personalization of the model using clinical data

Methods:

In [1] a three compartment model was developed covering the most essential aspects of RBC regeneration after a blood loss in healthy human adults. The essential biological feedback mechanism by erythropoetin (EPO) was included indirectly by a negative feedback expression. Individual aspects of the underlying dynamics are covered by two amplification variables: BETA for the overall cell maturation and GAMMA for the reaction to a blood loss.

The experimental data used in this study were obtained in 2008 in [2]. Here the recovery time of total hemoglobin mass (tHb) after a blood donation in healthy adult was investigated. Therefore, tHb before and after 1-unit (erythrocyte concentrate) standard blood donation was evaluated in 29 male, healthy volunteers (30 +- 10 years, 181 +-7 cm, 76.6 +- 11.2 kg). The use of tHb data ensures a much higher precision than hematocrit (Hct) measurements routinely used in clinical practice. Numerical evaluation was performed on 24 data sets, as five sets were excluded due to unreasonable outliers in the data or a bad initial guess of an initial value.

Both nonlinear mixed-effects estimation and point estimation methods were applied to investigate the model dynamics. First, a nonlinear mixed-effects estimation for the two variables was performed using NONMEM (version 7.4, first-order conditional estimation method with interaction) in combination with PsN

software (version 4.4.0; Uppsala Pharmacometrics, Uppsala, Sweden). We used an exponential model for inter-individual variability (diagonal OMEGA matrix) and an additive model for residual variability. Secondly, for point estimation, using the available data and the derived model, parameter estimation problems with a least-squares objective were solved with a multiple shooting based Gauß-Newton algorithm coded in the PAREMERA software and an adaptive, error-controlled backward differentiation formulae (BDF) method for integration coded in the software DAESOL, both included in the experimental design package VPLAN [3] developed at the University of Heidelberg.

Results:

Using the nonlinear mixed-effects estimation, the fixed effects of the variable BETA was estimated as 1.02 +- 0.151, the inter-individual variance as 0.294 +- 0.125. For GAMMA, the fixed effect was estimated as 0.46 +- 0.0651 with an inter-individual variance of 0.346 +- 0.148. The high inter-individual variances of more than 40% for the even quite homogeneous population (male, healthy, non-smokers) suggest the use of point estimation methods. Point estimation lead to a very good fit based on average values for R^2 of 0.86 +- 0.11. Average values for BETA and GAMMA were 1.519 +- 0.751 and 0.555 +- 0.215, respectively.

Conclusions:

A three compartment model with a negative feedback for erythropoiesis was developed. Essential physiological properties were captured in the model, which could be shown with the application of the RBC regeneration after a blood donation. In this early phase, point estimation methods might be more suitable than population estimation approaches due to heterogenous and sparse data from pathological cases. Point estimation without regularization was successful in most of the cases and can be improved with additional initial information about the subject. Next steps are the evaluation of the model on data for multiple blood donation cycles and extention of the model to PV patients.

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II-20: *Dan Liu* Investigating Impacts of Model Parameters Correlations in Global Sensitivity Analysis: Determining the most influential parameters of a Minimal PBPK Model of Midazolam

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Objectives: Sensitivity analysis has been widely used to identify the most influential model parameters affecting pre-specified model outputs. In local sensitivity analysis (LSA) usually parameters are scanned in one or two dimensions while keeping all the rest of model parameters fixed. However, global sensitivity analysis (GSA) allows simultaneously evaluating the relative contributions of each individual parameter to the model output variance by varying all parameters over the entire intended parameter space. Hence the sensitivity or influence of a parameter to model output in GSA is measured without fixing values of all the rest input parameters. This allows ranking the importance of parameters considering their uncertainty and influence on the variation of outputs. GSA is gaining attention in the PBPK modelling and systems biology and pharmacology [1-4]. GAS can provide information about the model structure or driving mechanisms for physiology or biological responses. We present an application of three GSA methods, namely Morris, Sobol, and extended Sobol method to a minimal-PBPK (mPBPK) model of Midazolam. The primary aim is to identify the most influential model parameters affecting the pharmacokinetic (PK) properties of interest. We also investigated the effect of ignoring correlations of model parameters on their rankings. Despite known correlations between biological and drug parameters, they are rarely considered in conduct of GSA when the probability of various parameter values are commonly considered independent of the probability of other parameter values.

Methods: Midazolam, a BCS class II drug that has been widely used in anaesthesia due to its favourable safety profile, and rapid anxiolytic effect or as preanesthetic medication for children [5, 6]. Morris, Sobol, and extended Sobol methods were used to determine the most influential model parameters for the intended PK properties, *i.e.* C_{max}, T_{max}, and AUC, of an mPBPK model of Midazolam given orally. Morris and Sobol are GSA methods designed for models where the model parameters are not correlated [7]. Nevertheless, exSobol method is designed to handle a model with correlated model parameters [8]. The influential parameters were determined using these three GSA methods independently. Subsequently, influential parameters picked up by Morris and Sobol methods were compared to those by exSobol to explore how considering correlations could affect appropriately identifying and ranking influential model parameters. System parameters, such as body weight (BW), blood flow rate, tissue volume, tissue to plasma partition coefficient, enzyme abundance, etc., and their correlations were considered in this study.

Results: The exSobol method suggests, V_{ss} (volume of distribution at steady-state), F_g (fraction scape gut wall metabolism), enzyme abundance of CYP3A4 and CYP3A5, and BW, are the most important parameters determining C_{max}; k_a and V_{ss} are identified as the most significant parameters determining T_{max}; enzyme abundance of CYP3A5, CYP3A4, F_g, V_{liver} (the liver volume), and f_a (fraction absorbed into enterocytes), have significant impact on AUC. Compared to exSobol, different sets or ranking of influential parameters were identified by Morris and Sobol due to lack of consideration of parameters correlation, which underestimated the effect of V_{liver} and the impact of UGT1A4 Abundance on the Midazolam AUC. Further, the qualitative Morris screening was as informative of the quantitative Sobol method, if a lack of correlation of parameters was considered or correlations could be ignored.

Conclusions: Knowing Midazolam's physicochemical, metabolism and plasma/blood binding properties the determined ranking by exSobol are as expected. Without considering parameters correlation, GSA methods such as Morris and Sobol, can provide biased assessment of their influence on the model outputs of interest. A major weakness of GSA methods assuming independent input parameters is that unrealistic parameter combinations are more likely to be produced due to independent random sampling. Therefore, GSA results should be carefully used when using Morris and Sobol methods or when there are uncertainties around the model parameters correlations. It is important to bear in mind that GSA methods can only provide information about the explored 'model' rather than the reality it intends to represent. In other words, if a model mis-specifies the reality or inadequately represent it then the provided GSA outcomes can be either biased or incorrect.

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II-21: *Feiyan Liu* Modeling inflammatory biomarker dynamics during clinical challenge studies with lipopolysaccharide

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Objectives:

Sepsis is a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs. It is associated with high mortality and is typically treated with a broad-coverage antibiotic treatment. Sepsis is characterized by uncontrolled excessive production of pro- and anti-inflammatory cytokines, where tumor necrosis factor (TNF-α) and interleukin-6 (IL-6) are key pro-inflammatory mediators [1]. The immune response is typically triggered by activation of pathogen recognition receptors such as the Toll-like receptor 4 (TLR4) by lipopolysaccharide (LPS). Clinical challenge studies where LPS is administered to healthy volunteers to induce an inflammatory response are relevant to characterize immune response biomarker response profiles associated with TLR4 activation, although these studies should not be seen as a model for sepsis. Quantitative understanding of inflammatory biomarker dynamics during infection and sepsis is relevant to monitor disease progression and treatment response but remains currently poorly understood. We aimed to develop a dynamic model of immune biomarker for IL-6, IL-8, TNF-α and C-reactive protein (CRP) dynamics after administration of LPS to help quantitative interpretation of clinical sepsis biomarker studies.

Methods:

Previously reported LPS concentration-time profiles in healthy volunteers were used to obtain insight in the pharmacokinetics of LPS [2]. Data from a previously conducted clinical LPS challenge study in healthy male volunteers (3 cohorts of 8 subjects, LPS:placebo=6:2) who received a single ascending low dose of LPS (0.5, 1.0 or 2.0 ng/kg) was used to study the kinetics of inflammatory biomarkers [3]. For each volunteer, multiple blood samples were obtained prior to LPS injection and within 24 h after dosing, cytokines (IL-6, IL-8, TNFα) and C-reactive protein (CRP) were measured in plasma to investigate the *in vivo* inflammatory response. Vital signs were assessed by measurement of temperature, heart rate and blood pressure.

For LPS concentration-time profiles we evaluated different compartmental models. For the pharmacodynamic models we aimed to use indirect response models in combination with transit models to account for the delay between receptor activation and release of inflammatory biomarkers. Linear, exponential, power, Hill and E_{max} functions were tested to investigate the relationship between LPS and inflammatory markers. A prediction-corrected visual predictive check was used to evaluate model fit. Parameter precision was evaluated using bootstrap analysis. All diagnostic procedures were implemented by using PsN and all models were fitted in NONMEM version 7.3 using the First Order Conditional Estimation method.

Results:

A one-compartment PK model with first-order elimination was used to capture the time-concentration profile of LPS. Clearance (CL) and volume of distribution (V) were estimated to be 46.2 L/h and 6.62 L, respectively.

The LPS exposure-response relationship for IL-6, IL-8 and TNFα in relation to LPS exposure was described using an indirect response model in combination with a transit model to account for the delay in TLR4 signal transduction. The baseline value for IL-6, IL-8 and TNFα were estimated to 6.00, 6.40 and 3.31 pg/mL, respectively. Mean transfer time (MTT) within transit compartments were 2.38, 2.76 and 2.20 h^{-1}, respectively. Slope factor between LPS and cytokines concentration were 4.73, 3.96 and 5.81, respectively. This model was then linked to a second LPS indirect response model to describe the relationship between IL-6 induced changes in CRP, with a baseline of 1.12 mg/L, an MTT of 10.4 h^{-1}, a slope factor of 1.48, and an induction rate constant of 0.03 h^{-1}. The final model described the observed concentration-time profiles accurately with no major model misspecification and with good predictive performance.

Conclusions:

We developed a model describing the dynamic relationship between LPS exposure, IL-6, IL-8 and TNF-α, and between IL-6 and CRP. The model can be used as a basis to quantitatively interpret inflammatory biomarker kinetics in patients with sepsis to guide treatment strategies.

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II-22: *Carolina Llanos-Paez* Implementation of event time distribution as a random effect in time-to-event analysis

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Introduction: Different distributions of event times considered in time-to-event (TTE) analysis are well documented. These distributions include the exponential, Weibull, Gompertz, among others [1]. It has been reported that event times can be generated following any of those distributions by using a random variable with uniform distribution [2]. Including this random variable on the distribution of the event time may help to perform TTE analysis using the Full Random Effect Modelling (FREM) approach [3], and therefore take into account correlation between covariates without affecting parameter estimates as well as handle potential missing covariates.

Objectives: To perform TTE analysis adding a random effect on the event time to take into account correlation between covariates by using the FREM approach.

Methods: Single event times according to an exponential distribution (constant hazard) were repeatedly (n=100) simulated for 1,000 subjects and thereafter used to perform TTE analysis using: i) the random variable (RV) approach [2] and ii) the standard (STD) parametric modelling approach. Estimation properties of the two approaches were compared at different proportions of censored data (0%, 20%, 50% and 80%) using both constant hazard and Weibull models. Further estimation of covariate effects was performed using the RV model with the FREM approach (RV_FREM) and the STD model. Comparison between models were assessed in terms of their objective function value (OFV), parameter estimates and using the stochastic simulation and estimation (sse) tool to obtain the relative standard error (RSE) of estimates. In addition, a real data set (that was used previously to perform a published TTE analysis [4]) was used in this study to assess the significance of different covariates (treatment-group with digoxin (n=105) or placebo-group (n=112), sex, age, body weight and creatinine clearance) on the time of conversion to sinus rhythm in patients with acute atrial fibrillation using the FREM approach. All analysis and data simulation were performed using NONMEM® software v.7.4.3 with an Intel® FORTRAN compiler and PsN version 4.8.9.

Results: The same OFV and similar parameter estimates were obtained for the RV and STD model. The hazard estimate [RSE%] for a constant hazard for the RV/STD model was: 0.93/0.93 h^{-1} [0.34%/0.32%] (0% censored patients), 0.94/0.94 h^{-1} [0.37%/0.37%] (20% censored subjects), 0.96/0.95 h^{-1} [0.49%/0.50%] (50% censored subjects), and 0.98/0.98 h^{-1} [0.69%/0.70%] (80% censored subjects). The scale and shape parameter estimates for a Weibull distribution for the RV and STD model were similarly close. When a covariate effect was considered in both models, STD/RV_FREM, the ΔOFV (base model vs. model with covariate effect included) for the i) constant hazard was: 658/1,093 (0% censored subjects); 761/666 (20% censored subjects); 674/516 (50% censored subjects); 385/307 (80% censored subjects); ii) Weibull distribution was: 945/1,092 (0% censored subjects); 947/662 (20% censored subjects); 761/502 (50% censored subjects); 408/279 (80% censored subjects). Parameter estimates for the STD/RV models when using the real data set for the constant hazard was a hazard of 0.04/0.04 h^{-1}; and for the Weibull distribution were a scale of 0.03/0.03 h^{-1} and shape parameter of 0.67/0.66. The ΔOFV (base model vs. model with all covariates included at the same time) for the STD/RV_FREM considering a constant hazard was 26/8 and considering a Weibull distribution was 21/8.

Conclusion: A random variable affecting the event time was incorporated in a TTE analysis using both simulated and real data sets**.** This allows the use of the FREM approach to perform TTE analysis. It may also allow other extension to standard TTE analysis, such as additional diagnostics, possibility to explore different distributions of the event time. Results from the real data set using the RV approach are comparable to the original model. While the present results are encouraging, further analysis is warranted, especially in the way of handling the censored data when using this additional random effect.

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II-23: *Rasmus Jansson Löfmark* Translational pharmacokinetic-pharmacodynamic modelling predicts human exposure target engagement

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Introduction/Objectives: Pre-clinical data and predictive translational modelling are extensively used in support of candidate drugs taken into the clinic. This includes the prediction of human dose commonly anchored upon an understanding of the level of target modulation required to drive efficacy in an animal model or using clinical competitor data. A fundamental part in the human dose prediction is to have a solid prediction of human exposure-response for target engagement. Given the big leap in extrapolation from non-clinical data to clinic, this step in translation can be associated with uncertainties.

There are publications focusing on best practice [1-4], efficacy and pharmacokinetic pharmacodynamic translation of individual compounds [5,6]. But based on our knowledge there are very few publications reporting an analysis that evaluates multiple compounds, targets and therapy areas. Despite the implementation in pharma of model based solutions to predict human dose and exposure-response for target engagement, it is perhaps surprising that there are relatively few publications reporting an analysis that evaluates the pre-clinical to clinical translation at a cross therapy level. This work presents such an analysis looking across the AstraZeneca portfolio and examines how pre-clinical data / models translates to clinical pharmacodynamic/target engagement response.

Methods: A retrospective analysis of internal data across oncology, respiratory and cardiovascular renal or metabolism therapy areas was done. Inclusion of a compound for evaluation were driven by (1) the availability of sufficient clinical data to enable a derivation of exposure-response relationship, (2) the same biomarker measured both in the animal model used and the clinic. The compiled dataset composed of 19 small molecule drugs with various drug targets, mode of action, receptor types and biomarkers. The majority of pre-clinical pharmacokinetic-pharmacodynamic datasets were either analyzed by direct exposure response models or by indirect turnover models. For the pre-clinical dataset, a naïve data pool data analysis was deemed sufficient in most cases to retrieve exposure-response relationships. For the translation, interspecies differences in plasma protein binding, affinity for the target receptor and time delays were also considered.

Results: For those projects that had clinical data available to enable back translation of a target engagement biomarker, 83% of the compounds showed an exposure response relationship that translated within 2-fold. The 50^{th} (5^{th}, 95^{th}) percentile of the ratio between predicted exposure response to measured was 1.1 (0.55; 3.1). For those compounds that deviated, there was a trend of a binary deviation suggesting that biological or experimental assumptions were flawed.

Conclusions: This exercise demonstrates that applying translational pharmacokinetic-pharmacodynamic modelling can predict human exposure-response in the majority of cases. It also provides the modeller with some quantitative understanding of the confidence to predict human exposure-response for taget engagement. Additionally, it suggests that miss-predictions in translations could be due to flawed biological or experimental assumptions rather than technical miss specifications in the PKPD modelling process.

Attrition in the clinic continues to be dominated by lack of efficacy, and therefore, much work is still required to improve the translation and prediction of human drug efficacy, linking target modulation to effects on disease biology.

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II-24: *Aurelie Lombard* Tumour size measurements: impact of inter-operator variability on model-based drug effect evaluation

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Objectives: Being readily available during oncology clinical trials, tumour size (TS) measurements are commonly used as a biomarker for drug efficacy. Indeed, TS represents a key variable of the treatment phase of a study that determines disease progression and consequently, whether patients will stay on treatment for another cycle. Variability in TS measurements could lead to drug effect misinterpretation and therefore affect patient's performance within the trial. Although inter-observer variability has been investigated in the past [1], there is limited knowledge available about its impact on response-to-treatment assessment using modelling approaches despite their use to determine patient benefit during clinical trials. Here, we explore the inter-operator variability of tumour size measurements in a selected population of a phase III clinical trial and its impact on model-based drug effect evaluation at individual lesion level.

Methods: TS measurements (longest individual lesion diameter) were obtained from a randomized phase III clinical trial [2] where metastatic non-small cell lung cancer patients were treated with cisplatin alone or in combination with gemcitabine. 122 lesions from 62 patients (out of 522) were selected according to imaging methods (Computed Tomography-scan) and based on the availability of two lesion measurements of the same CT-scan at each time point; measurement 1 (M1), performed at the hospital; measurement 2 (M2), performed at the centralised centre. Firstly, a graphical exploration was performed to identify trends within TS kinetics. The correlation between M1 and M2 was investigated by using linear regression and the relative error ratios (RER) were derived. Secondly, a tumour growth inhibition (TGI) model was applied separately to the M1 and the M2 data (NONMEM 7.3, FOCE I). The correlation between M1 and M2 individual estimates of TS at baseline and the drug effect estimate were assessed by using linear regression. The relative error ratios of population parameter estimates were also derived.

Results: We found three different patterns by visually comparing M1 and M2 measurements: (i) M1 and M2 were similar over time (23%) and so no impact will be observed on drug effect assessment; (ii) M1 and M2 were different but follow the same trend (42%) and the lack of agreement would mostly affect estimation of the tumour size at baseline; (iii) M1 and M2 were different and did not follow the same trend (35%) and the discrepancies would directly affect drug efficacy evaluation. The linear regression analysis showed that M1 and M2 of the same lesion were correlated with an r^2=0.72; however, a higher correlation would have been expected, as M1 and M2 are based on the same "true value" and the variability only relies on the operator. The RERs of M1 compared to M2 were widely distributed from -91.7% and 1,200.0%. Extreme ratios were mostly observed when one radiologist (e.g. at the hospital) measured a tumour which was considered to be non-existent by the other radiologist (e.g. at the centralised centre). The 1st and the 3rd quantiles were distributed from -13.4% to 28.5%, close to the 15% variation observed by Hopper et al. [1]. The analysis of the TGI model parameters showed that the correlation between M1 and M2 individual estimates of TS at baseline was comparable to the raw measurements (r^2 = 0.71), contrary to the individual estimates of drug effect, which appeared not to be correlated (r^2 = 0.27). However, M1 and M2 population parameters were similar (less than 15% variation), indicating that interpretation of outcomes for a typical patient will be close.

Conclusion: This analysis revealed that the operator is an important variable to consider which can induce a wide variability in tumour size measurements. This could affect the model-based interpretation of drug response, especially at the individual level, as no correlation was observed between M1 and M2 drug effect estimates. However, drug-response interpretation for a typical patient will be similar as population parameters were comparable; suggesting that the global evaluation of drug efficacy by modelling approaches might not be affected.

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II-25: *Dominik Lott* Prediction of exposure and effect on total lymphocyte count following long-term treatment of healthy subjects and lupus patients with the selective S1P1 receptor modulator cenerimod

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Objectives: Development of a population model describing the pharmacokinetics (PK) and pharmacodynamics (PD), i.e., effect on total lymphocyte count, of the selective sphingosine-1-phosphate 1 ($S1P_1$) receptor modulator cenerimod [1], including effects of demographics and differences between healthy subjects and systemic lupus erythematosus (SLE) patients. Assessment of attainment of steady-state conditions with a terminal half-life of up to 22 days [2]. Prediction of incidence of low total lymphocyte counts, a safety parameter.

Methods: Data from four Phase 1 studies in healthy subjects [2] and one Phase 2 study in SLE patients [3] were pooled for analysis. These included single-dose administration of 1 to 25 mg and multiple-dose administration of 0.5 to 4 mg cenerimod once daily (o.d.). The modelling data set comprised 2393 cenerimod concentration and 1906 total lymphocyte count measurements from 110 (64 healthy, 46 with SLE) and 130 (67 healthy, 63 with SLE) subjects, respectively. PK/PD model development was conducted sequentially using nonlinear-mixed effects modelling techniques. Parameters were estimated using SAEM in Monolix 2018R2 [4]. Age, body weight, body mass index, fat mass, food intake, and effect of disease were investigated in covariate analyses for their impact on model parameters.

Results: The PK of cenerimod were well described by a 3-compartment model with estimates of 121, 196, and 306 L for apparent volumes of distribution of the central compartment and peripheral compartments, respectively, and a low apparent clearance of 1.42 L/h. Body weight was added as a covariate on all volumes of distribution, inter-compartmental flows, and drug clearance with covariate coefficients fixed to allometric coefficients [5]. Presence of food was identified to delay cenerimod absorption by 0.9 h and to slightly decrease the rate of absorption by 15%. There was no evidence for differences in PK between healthy subjects and SLE patients.

Model-based simulations of cenerimod administration o.d. for 365 days showed that 90, 95, and 99% of the exposure after 365 days is reached after 49, 75, and 134 days, respectively, compared to 85% on Day 35. Exposure to cenerimod is predicted to be 20% lower and 37% higher in subjects with a body weight of 100 and 50 kg, respectively, compared to the population-typical subject (75 kg). Food intake had no relevant effect on the exposure to cenerimod.

The model that characterized the relationship between cenerimod concentration and total lymphocyte count best was an indirect-effect I_{max} model with I_{max} proportional to the estimated baseline total lymphocyte count. A periodic function was used to describe the variation in total lymphocyte count (circadian rhythm) over the course of a day. Maximum drug effect (I_{max}) and concentration at half-maximum effect (IC_{50}) were estimated as 92.3% and 25.6 ng/mL, respectively. In covariate analyses, as expected due to disease, SLE patients were identified to have a lower total lymphocyte count at baseline (1.63×10^9/L) than healthy subjects (1.96×10^9/L).

Simulations predicted average total lymphocyte count decreases from baseline to Day 35 of 66.9 and 77.5% for o.d. doses of 2 and 4 mg, respectively. The respective decreases on Day 365 were 69.7 and 79.5%, suggesting that the maximum PD effect is essentially achieved after 35 days of treatment.

Total lymphocyte counts below 0.5 and 0.2×10^9/L were predicted to increase with dose and to be higher with a lower total lymphocyte count at baseline. Following o.d. doses of 2 mg for 365 days, the model predicted that 0.4 and 0.6% of healthy subjects and SLE patients, respectively, would experience total lymphocyte counts below 0.2×10^9/L at least once with 4 predose measurements at 3, 6, 9, and 12 months.

Conclusions: Relevant demographic differences were limited to body weight. Predicted changes in exposure and effect on total lymphocyte count beyond 35 days of o.d. cenerimod administration are negligible. This indicates that long-term administration for, e.g., 365 days, should not result in drug exposure substantially different from that observed in completed Phase 1 and Phase 2 studies. Due to the drug's long half-life the *in silico* model of long-term treatment scenarios that have yet to be clinically tested proved to be useful. The model provides a robust basis to support planning of late-phase studies and answering of questions from health authorities via model-based simulations.

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II-26: *Qiang Lu* Population Pharmacokinetic Meta-Analysis of Dupilumab in Adult Atopic Dermatitis Patients, Asthma Patients, and Healthy Subjects

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Objectives: Dupilumab is a human monoclonal antibody of the IgG4 subclass that binds to the IL-4Rα subunit and inhibits IL-4 and IL-13 signaling which are key proximal drivers of type 2 inflammation [1]. Dupilumab has demonstrated significant clinical efficacy in multiple type 2 inflammatory diseases, namely atopic dermatitis (AD), asthma, and chronic rhinosinusitis with nasal polyposis (CRSwNP). Taking into account the similarity in PK profiles across adult healthy subjects (HV), AD and asthma populations, a Pop PK base model developed based upon data pooled from these populations holds great potential to characterize the pharmacokinetic profile of dupilumab across multiple type 2 inflammatory disease populations. Therefore, this meta-analysis aimed to develop and qualify a global Pop PK base model for dupilumab in adult HVs and AD and asthma patients.

Methods: Concentrations of functional dupilumab in serum from 20 Phase 1, 2 and 3 studies were used. These included Phase 1 studies in HV after a single intravenous (IV) or subcutaneous (SC) administration of dupilumab and Phase 2 and 3 studies in AD and asthma patients after repeated SC administration of dupilumab once every week (qw), two weeks (q2w), or four weeks (q4w), were included for the Pop PK base model development. Based on the similarity in dupilumab PK profiles between adult HV, asthma and AD populations, the base model structure of a previously developed asthma Pop PK model (two-compartment model with parallel linear and Michaelis-Menten [M-M] elimination)[2] served as the starting point. Given the well characterized body weight effect on dupilumab PK in previous AD and asthma Pop PK models [2, 3], the relationship between body weight and selected PK parameters was evaluated in the current analysis using forward selection followed by a backward elimination procedure.

Results: Final model development dataset included 30557 dupilumab concentrations from 4056 subjects consisting of 202 HV, 1839 AD patients, and 2015 asthma patients (including 69 adolescents) across a wide dose range of 100 mg q4w to 300 mg qw. The PK of dupilumab was well described by a 2-compartment model with first order absorption kinetics and parallel linear and nonlinear M-M elimination. The precision of PK parameter estimates from this global base model was high throughout (%RSE < 40%). Notably, key PK parameter estimates (e.g. bioavailability of 60.9%, distribution volume at steady-state (V_{ss}) of 4.37 L, linear clearance of 0.12 L/day) were consistent with those from prior AD and asthma Pop PK models [2, 3]. Similar to prior AD and asthma models, weight was included as a covariate in the final Pop PK base model, where volume of central compartment (V_2), maximum target-mediated rate of elimination (V_{max}), and linear elimination rate constant (K_e) were significantly related to body weight with higher V_2, V_{max}, and K_e in patients with higher body weight. After inclusion of weight effect, inter-individual variability estimates for key PK parameters (i.e. K_e, V_2 and V_{max}) decreased approximately 4.0% – 6.21% compared to the base model. Moreover, model-simulated PK profiles were in good agreement with observed PK profiles (including the target-mediated elimination phase) in AD and asthma populations, supporting the predictability of this base model for other type 2 inflammatory disease populations (e.g. CRSwNP).

Conclusions: A population pharmacokinetic meta-analysis was performed to develop a Pop PK base model, which described the PK of functional dupilumab in HVs and AD and asthma patients across a wide SC dose range of 100 mg q4w to 300 mg qw. Consistent with the prior AD and asthma Pop PK models, weight

exerted a notable effect explaining between-subject variability of steady-state exposure of functional dupilumab concentration in AD and asthma patients. This Pop PK base model, which is based on a large dataset derived from 3 different populations, may serve as a robust starting point for predictions of dupilumab concentrations or subsequent Pop PK analyses in other populations with type 2 inflammatory disease.

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II-27: *Inga Ludwig* A Quantitative Approach to Assess Similarity of Adult and Pediatric Efficacy to Support Full or Partial Extrapolation in Pediatric Drug Development

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Objectives:

Recruitment of patients into pediatric studies is difficult and slow, hence fully powered pivotal trials are prohibitive.

For indications and drugs where the disease progression in children is similar to that in adults, and where the pharmacology of the drug is similar to that in adults, one may fully extrapolate efficacy from adults to children. It suffices to demonstrate that the selected pediatric dose provides comparable plasma concentrations as the registered adult dose, and to demonstrate adequate safety.

Often, there is not yet enough evidence to apply full extrapolation, and one may want to apply a partial extrapolation approach. Here, one needs to collect some efficacy data in children to demonstrate that the adult and the pediatric efficacy are similar. However, for ethical and practical reasons one wants to avoid large studies in children, and one often cannot include a comparator group.

The goal then is to demonstrate similarity between adult and pediatric efficacy. We use the adult data set to develop an exposure-response model for the clinical outcome. Such a model accounts for exposure and baseline risk factors. The model is used to predict the clinical outcome of the children, conditional on their observed exposures and covariates. These predicted outcomes are then compared with the observed outcomes in children, to validate that the adult model is adequate to predict pediatric efficacy.

The objective of this paper is to develop quantitative methods to compare such predicted with observed outcomes, and to understand the operating characteristics of these methods via simulations. The operating characteristic should improve with increasing sample size.

Methods:

For continuous or time to event data, we generate a prediction distribution for each of the n children in the pediatric data set from an adult model via simulations. These individual prediction distributions will differ from child to child according to the observed exposures and covariates. If P1 is the prediction distribution for the outcome of child 1, and Y1 is the corresponding observed outcome, then P1(Y1) should be approximately uniformly distributed on the interval [0,1]. Applying this approach to all children provides n uniformly distributed data points.

Note that the prediction distributions may differ between the children, because they are obtained conditionally on the observed exposures, covariates, and censoring times.

We apply a Cramer von Mises goodness of fit test to check whether the data are uniformly distributed. The Cramer von Mises test statistic measures the distance between the empirical distribution function based on the P1(Y1), ... Pn(Yn) from a uniform distribution function. If the adult model is a good predictor, then the true distribution of the Pj(Yj) is close to a uniform one, and the Cramer von Mises test statistics should be

close to zero. One can use the well-known asymptotic distribution of this test statistic (see [1], [2], and [3]) to obtain a (one-sided) asymptotic confidence interval for deviation from uniformity.

Note that the confidence intervals defined here are closely related and applicable VPCs and the normalized prediction distribution errors (NPDE) as discussed in [6] and earlier by [4] and [5]. In our case, each pediatric subject only contributes one observation Pj(Yj) and hence the issue of decorrelation does not apply.

Results:

Our simulations show that proposed approach works well. This is true when using the asymptotic confidence interval for deviation from uniformity, as well as when using a corresponding bootstrap version. The bootstrap confidence interval has slightly better coverage probabilities for small data sets.

In simulation scenarios where the adult and children data were generated from the same distribution, the confidence intervals get narrower and approach zero when increasing the pediatric sample size to a very large n. In scenarios where the children data were generated from a different distribution, our simulations demonstrate that the width of the confidence interval will not reduce to zero with increasing sample size n. The results were comparable when using completely artificial data, or when simulations were based on real data examples.

Conclusions:

Our simulations demonstrate that the proposed approach for model validation works well. The outcome of the simulations is as expected. The coverage probability of the CI is as desired.

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II-28: *Ulrich Ruben Luecht* Physiologically based pharmacokinetic modeling approach to assess drug-drug interactions (DDI) between psychopharmaceuticals – focus on mirtazapine and venlafaxine

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Introduction: In clinical and ambulatory care, drugs are often combined to improve the efficacy of the therapy. Especially the combination of psychopharmaceutical drugs can increase the success of the antidepressant or antipsychotic treatment. The problem of adding a drug is that it might influence the other medication, causing an increase or decrease of the others' plasma concentrations. Particularly the inhibition of enzymes like cytochrome P450 (CYP) oxygenases provokes higher risks for toxic side effects. By using physiologically based pharmacokinetic modelling the possible extent of an interaction can be predicted. These model approaches may state if a dose reduction or a substitution of a drug is useful to decrease the potential risk for negative side effects.

Objectives:

- Creation of a drug-drug interaction physiologically based pharmacokinetic model for pharmacokinetic interaction between mirtazapine and venlafaxine
- Comparison of the model's predicted area under the curve (AUC) to the results of the SCHOLZ Databank's multi drug drug interaction (MDDI) tool
- Investigations to evaluate the utility of dose adjustments or substitutions

Methods: For the PBPK-model, samples were collected in the context of a therapeutic drug monitoring (TDM) study [1]. Whole blood was collected from 82 elderly patients via dried blood spot method. The blood concentrations of four psychopharmaceutics - the tetracyclic antidepressant mirtazapine, the atypical antipsychotic risperidone and the selective serotonine reuptake inhibitor citalopram and its eutomer escitalopram - were measured by using liquid chromatography and mass spectrometry detection.

The subjects' medication plans were analyzed using the software SCHOLZ Databank. This software is a tool to execute medication analyses and to detect medication problems like cumulative side effects or drug interactions. SCHOLZ Databank allows the optimization of the patients' therapy including substitutions of comparable drugs or dose adjustments [2]. The most frequently displayed pharmacokinetic interaction was between mirtazapine as a substrate of CYP 2D6 and the noradrenaline and serotonine reuptake inhibitor venlafaxine, which inhibits [3] mirtazapine's metabolism (n=14).

Models for mirtazapine and venlafaxine are created based on their bio- and physicochemical properties using PK-Sim® (BayerAG, Leverkusen, Germany). Evaluation of the models was done by comparison to literature values [4, 5]. Afterwards, both models are combined in an interaction simulation. Plasma concentrations from TDM are used to evaluate the predictability of the interaction model.

Results: If mirtazapine is combined with venlafaxine, there is no measurable change in the AUC of mirtazapine's plasma concentration curve in the PBPK-interaction model. So, the model, which is validated with TDM data, shows no clinically relevant interaction. SCHOLZ Databank's MDDI calculator predicts an 8-% higher exposure which is not clinically relevant as well.

Conclusion: In order to better evaluate clinical relevance of DDI there is a need for more clinical research. In addition, more clinical data in the routine setting should be collected including for example renal function and pharmacogenetic data.

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II-29: *Nicolas Luyckx* Improving the performances of clinical trial simulations in Simulo using compiled code

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SGS Exprimo

Objectives:

In R, dynamic linked models (DLL's) have been proved to increase the speed of repetitive tasks, such as clinical trial simulations (CTS). Since its first release in 2012, ordinary differential equations (ODE's) in Simulo have always been specified with pure R code and solved using the package deSolve [1]. Recently, an attempt to use a compiled version of the drug model has been developed. Additionally, improvements allowing to reduce the number of interruptions during the solver integration routine have been considered and implemented. To quantify the gain of performance in Simulo, we evaluated execution times of four different drug models and study designs.

Methods:

Two main modifications have been implemented resulting in a new version of Simulo:

1) Model structural equations are now defined in C code. For backwards compatibility purposes and for user comfortability, a Java-based converter was developed to translate any ODE and structural model equation from R into C code. Given that the syntax of those programming languages is very similar when defining drug model equations, the translation algorithm complexity was rather limited. Unit tests validated the conversion and usual R mathematical symbols, operators as well as functions used in pharmacometrics can be interpreted automatically.

2) The way observations were handled was also completely reviewed. They can now be either of type 'solver output' or 'event-based'. With the first type of observations, values are directly transmitted to the solver. Consequently, the integration routine automatically determines itself when to store data and it results in less interruptions. With the second type, the solver is more often stopped to execute the 'event-variability' section and to trigger conditional events.

For an objective comparison, four different Simulo study implementations were used to benchmark Simulo Expert 7.2 [2], the latest version in production that includes parallel execution features, against Simulo 8.0, the new compiled version prototype. Each model selected for the evaluation explored specific features that can have a different effect on the speed. The Integrated Glucose Insulin (IGI) model [3] contains control mechanism between ODE's. The Viral Kinetic (VK) model [4] exhibits compartments that can have very different scales in their amount values. A PKPD Sunitinib model [5] including interrupting events has been implemented and used to assess conditional events. A PKPD Sunitinib with overall survival model [6] [7] examines longer simulation periods.

In each case, 20 replicates of 500 subjects were simulated with parallelization over 8 CPUs in both Simulo versions. The full time of simulation (setup, execution and result concatenation) has been used for the comparison.

Results:

Details about model specificities and execution times in each Simulo version are summarized in Table 1.

Table 1 - Comparison of model features and speed improvement

Model	Integrated Glucose Insulin (IGI) model	Viral Kinetic (VK) model	Sunitinib PKPD with conditional events	Sunitinib PD with survival runs
Description	Glucose Insulin model with control mechanisms	2-cpt PK model + Viral kinetic model	2-cpt PK model + Platelet count (PC) model	Modeling of biomarkers + tumour growth inhibition + survival model in GIST treatment
Number of ode's	9	6	9	9
Absolute tol. / Relative tol.	1E-6 / 1E-6	1E-6 / 1E-6	1E-6 / 1E-6	1E-8 / 1E-8
Simulation length	8 weeks	2 days	36 weeks	104 weeks
Number of doses	56	10	168	~500
Number of observations	20	400	36	~100
Number of observed variables	2	5	3	23
Interrupting events	/	/	Every day (suspend dosing if PC too low)	Every hour
Runtime in 7.2	2258s	614s	2421s	1254s
Runtime in 8.0	134s	111s	327s	253s
Speed improvement	17x	5.5x	7.5x	5x

IGI, VK, Sunitinib PKPD with conditional events and Sunitinib PKPD with survival runs respectively 17, 5.5, 7.5 and 5 times faster than the reference Simulo Expert 7.2. On overall, the speed increase tends to be higher for complex studies containing a high number of ODE's and/or observations.

Conclusions:

The compiled version shows a significant increase on the simulation time varying from a 5 to 17 fold factor in the Simulo studies used in the benchmark. This version allows to provide faster simulations results evaluating complex clinical study designs and to help take early decisions during drug development process. The integrated Liveview takes also benefit from this speed improvement, making Simulo more convenient to work with as standalone application while exploring your drug model.

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II-30: *Yassine Kamal Lyauk* Dose Finding in Clinical Development of 60 FDA-Approved Drugs Compared to the Learning versus Confirming Paradigm

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Introduction

The highest prevailing reason for non-approval of new molecular entity (NME) applications by the US Food and Drug Administration (FDA) between 2000 and 2012 was uncertainty regarding the adequacy of proposed marketing dose(s) [1]. Furthermore, post-marketing changes to the label dosage have occurred in 21% and 18.2% of FDA-approved drugs in the period of 1980 to 1999 [2] and 2000 to 2014 [3], respectively. These reports highlight the importance of dose finding and benefit-risk assessment for obtaining and maintaining regulatory drug approval.
We have characterized the dose finding process in the clinical development of drugs recently approved by the FDA and compared our findings to concepts rooted in Lewis B. Sheiner's *Learning versus Confirming* paradigm [4]. Central in this paradigm are two learn-confirm cycles, with the first cycle confirming the efficacy of the highest tolerable dose of the drug in a small patient trial. In the second cycle, an adequately designed dose-ranging trial informs the dose for which benefit-risk is to be confirmed in a large study.

Objectives

- To investigate the clinical development paths, dose-ranging trial design, and dose-exposure response characterization, which formed the basis for label dose identification in drug development programs.
- To compare these to the concepts of Learning and Confirming.

Methods

60 drugs approved by the FDA between February 2015 and February 2017 were included for review following search of approval packages on the Drugs@FDA website [5]. All information available from the published FDA reviews was used to identify clinical trials relevant for dose finding. Clinical development programs were categorized based on initiation in healthy volunteers or in patients, and clinical trials were classified as *exploratory* or *confirmatory*. The number of doses studied in each of these stages was summarized, distinguishing between exploratory first-in-patient (FIP) trials and exploratory post-FIP trial(s). For exploratory dose-ranging trials, both the number of doses and dose range was summarized. Lastly, any information available regarding assessment of dose-exposure-response in FDA approval packages was retrieved.

Results

In terms of clinical development paths, 89% of development programs included several doses in the FIP trial, 43% proceeded directly from the FIP trial to confirmatory trials, and 52% included multiple doses in confirmatory development. The number of doses in exploratory development was found to be significantly higher for development programs with a single dose in confirmatory development compared to programs with multiple doses (median 6 vs. 4, $p = 0.004$). The median ratio of the number of doses in exploratory to confirmatory development was 2:1 for programs initiated in healthy volunteers and 5:1 for programs

initiated in patients. Only 20% of dose-ranging trials included at least four investigational drug doses over an at least 10-fold dose range. Lastly, in a third of approval packages, no dose-response or exposure-response evaluation was identified, and model-based dose-exposure-response was alluded to in only two of 60 approval packages.

Conclusions

Results indicate that i) in many cases confirmatory development leans more towards learning than confirming as multiple doses are commonly included in this stage, questioning sponsors' certainty of drug benefit/risk when initiating confirmatory development, ii) learning in dose-ranging trials may often be limited due to the low number of doses and dose range included, the latter presumably affecting the extent to which model-based analysis can be meaningfully applied and iii) dose-exposure-response appears to be robustly assessed in only a minority of clinical drug development programs, suggesting there may be room left for optimizing the benefit-risk profile of confirmatory/marketed dose(s).

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II-31: *Sreenath M Krishnan* A combined population kinetic-pharmacodynamic-overall survival model for docetaxel and paclitaxel in the treatment of HER2–negative metastatic breast cancer patients

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Introduction: Population modelling is increasingly used for describing tumor responses to anticancer treatments and different model-derived tumor metrics have been suggested as predictors of overall survival (OS) [1,2]. Bender et al. [3] developed a novel semi-mechanistic population kinetic/pharmacodynamic (KPD) model to characterize tumor growth in HER2–negative metastatic breast cancer patients receiving either docetaxel or paclitaxel treatment. Since the study populations were comparable in terms of cancer type, tumor baseline and patient characteristics, the analysis was here extended by developing a combined model for tumor response for the two taxanes, and tumor size metrics and time-course of tumor size, were explored as predictors of OS.

Objectives: The aims of this study were (*a*) to develop a combined tumor size model of docetaxel and paclitaxel in HER2- metastatic breast cancer patients, and (*b*) to investigate predictors including time-dependent covariates, such as tumor size ratio (TSR) and tumor time-course, for overall survival.

Methods:

Tumor data: The combined dataset consisted of tumor response from 185 patients receiving docetaxel treatment (100 mg/m2 infused over 1 hour on day 1 of each 3-week cycle) and 219 patients treated with paclitaxel (90 mg/m2 of paclitaxel infused over 1 hour on days 1, 8, and 15 every 4 weeks). Patients were HER2- metastatic breast cancer women with a median age of 55 years (range 27–85 years). The tumor size was followed for a maximum of 2.8 years (median=0.6 years) and the survival data was collected for a maximum of 4.8 years (median=2.2 years).

Tumor model: The tumor model developed by Bender et al. [3], was applied to fit the combined dataset and evaluated for shared tumor-related parameters between docetaxel and paclitaxel treated patient populations.

OS model*:* Parametric time-to-event (TTE) models with different probability density functions such as exponential, Weibull, Gompertz, log-normal and log-logistic functions were evaluated for describing the observed survival data. A joint model of tumor-OS was applied for investigating the predictors of OS [4]. The tested predictors were

- Patient baseline characteristics:
  - Age
  - Tumor baseline
- Tumor model parameters, and tumor model metrics:
  - Model-predicted tumor time-course (TS(t))
  - Time-varying relative change in tumor size (rTS(t))
  - Tumor size ratio week 6 and week 8 (TSRw6 & TSRw8)
  - Derivative of TS(t)

- Log-transformed growth rate (log(k_g))
- Time-to-tumor-growth (TTG)

Covariates were investigated as time-varying until the time of tumor nadir (TTG), until w6 and w8 occurred (TSR) or until the last tumor size observation (derivative of TS(t)). NONMEM 7.4.3 software was used for model development.

Results: The tumor model consisted of six compartments mimicking tumor quiescence, drug–resistance, and tumor drug–sensitivity. The total observed tumor size is represented as the sum of all 6 compartments. All tumor-related parameters could be shared between the docetaxel and paclitaxel datasets, without causing an apparent deterioration in the model fit, while tumor shrinkage was drug-specific. The model described the data from both drugs well and the uncertainty of the estimated parameters were acceptable.

A parametric TTE model with a Weibull distribution described the observed OS data the best. In univariate analysis, baseline tumor size, derivative of TS(t), tumor time-course (log transformed), TSRw6, and TTG were significant predictors of survival for both docetaxel and paclitaxel treatment. After the best predictor, baseline tumor size, was included, the derivative of TS(t) was the most significant predictor and included in the final OS model. No other predictor improved the model fit further.

Conclusion: The combined model for HER2- breast cancer patients, incorporating tumor shrinkage, tumor quiescence, and tumor regrowth upon resistance to taxane drug exposures, described the individual time-courses well. The results from OS analysis indicated that a large tumor baseline ($\beta_{baseline}$ = 0.004 mm^{-1}) and higher tumor burden at dropout from study ($\beta_{derivative}$ = 0.01 mm^{-1}) were associated with poorer survival. The developed models, with shared tumor-related and OS parameters, may support development of other drugs in this indication.

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II-32: *Guangda Ma* Evaluating the influence of genotype on warfarin dose predictions made using a theory-based PKPD model.

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Objectives:

Warfarin continues to be the mainstay of oral anticoagulation therapy, however, a narrow therapeutic range poses a barrier to safe and effective therapy. Published evidence suggests that current methods to predict warfarin maintenance dose requirements are biased at the extremes [2]. In contrast, Bayesian dose forecasting using a theory-based warfarin PKPD model can achieve unbiased and precise dose predictions across a full range of clinical doses [3].

Despite the association between genotype and warfarin dose requirements, current evidence is not sufficiently robust to support clinical benefits of genotype-guided warfarin therapy [4-6]. Bayesian dose forecasting may overcome the need for prior genotype data [7]. A theory-based PKPD model for warfarin that accounts for the influence of genotype on warfarin PKPD can be used to evaluate this[8].

Objective 1: External Evaluation
Evaluate the predictive performance of the theory-based model against an external, clinically derived dataset and evaluate whether genotype knowledge influences model predictive performance.

Objective 2: Simulation-Estimation
Use simulation and estimation techniques to evaluate whether genotype knowledge influences the predictive performance and potential clinical utility of Bayesian forecasting using the theory-based model.

Methods:

Estimation and simulation was performed using NONMEM 7.4.1.

External Evaluation
The external evaluation dataset consisted of 138 individuals which has been previously used to evaluate an empirical warfarin dosing model [9]. The model was used to predict the maintenance dose needed to achieve the observed stable INR given the full dosing and INR history for each individual. The model predicted maintenance dose was compared with that clinically observed.

Simulation-Estimation

Bayesian dose individualisation using the model was evaluated using a simulation-estimation procedure. A virtual study population (*n*=1000) was created by sampling sex, weight, CYP4F2, CYP2C9, and VKORC1 genotypes as covariates. Following initial dose individualisation based upon each individuals' covariates and population parameters (days 1-3), INR measurements on days 3, 7, 10, 14, 21, 28, 35, 42, 49, and 56 were then used successively to individualise daily warfarin doses.

The predictive performance of the model was evaluated using measures of bias (mean prediction error, ME) and imprecision (root mean square error, RMSE). Clinical utility was evaluated using the percentage of time within the therapeutic range (INR 2.0-3.0) during days 4-14 (TTR_{4-14}), and 15-28 (TTR_{15-28}).

Influence of Genotype
To evaluate the influence of genotype, the simulation-estimation and external evaluation investigations were conducted using a genotype-guided model and compared to a genotype-missing model.

Results:

External Evaluation

External evaluation of the genotype-guided and genotype-missing models was unbiased and precise over the actual dose range of 0.75-11 mg/day. Improvements in predictive performance following the addition of genotype knowledge were not apparent:

Genotype	ME	2.5%ile	97.5%ile	RMSE
Yes	0.115	-0.91	-0.53	0.58
Missing	0.08	-0.93	-0.56	0.54

Simulation-Estimation
Based on covariates alone the model predictions were initially biased and imprecise, however, unbiased and precise dose predictions across the simulated range of doses (0.77-27 mg/day) were achieved as time progressed and more INR measurements and dose adjustments were made:

INR and Doses	Genotype	ME	2.5%ile	97.5%ile	RMSE
Day 3 (one INR & dose adjustment)	Yes	-0.76	-7.01	1.8	2.42
	Missing	-0.77	-7.55	2.09	2.62
Day 21 (five INRs & dose adjustments)	Yes	-0.15	-2.45	1.23	0.99
	Missing	-0.16	-2.74	1.25	1.04
Day 56 (ten INRs & dose adjustments)	Yes	-0.02	-1.06	0.79	0.45
	Missing	0.0004	-1.11	0.80	0.51

Measures of predictive performance were similar for the genotype guided and genotype missing simulations across the entire simulated dose range.

The time within the therapeutic range with genotype-guided dosing (TTR_{4-14}: 29%; TTR_{15-28}: 69%) was similar to genotype-missing dosing (TTR_{4-14}: 30%; TTR_{15-28}: 69%).

Conclusions:

Unbiased and precise warfarin dose predictions were achieved using the theory-based PKPD model based on external evaluation. Genotypes as covariates did not improve the predictions. The simulated use of genotype information is consistent with the small effects observed in clinical trials but without the bias associated with empirical dosing algorithms.

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II-33: *Panos Macheras* On the unphysical hypotheses in pharmacokinetics and oral drug absorption:Time to utilize instantaneous rate coefficients instead of rate constants

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Objectives: i) examine the homogeneity hypothesis using Monte Carlo simulations for a reaction and a diffusional process, which take place in Euclidean and fractal media ii) re-consider the flip-flop kinetics assuming that an instantaneous rate coefficient and not a rate constant governs the input kinetics for a one-compartment model of drug disposition iii) re-consider the extent of drug absorption using an in vivo reaction limited model of drug dissolution with integer and non-integer stoichiometry values published recently [1].

Methods:

i) Diffusional processes and reactions in homogenous-heterogeneous media.

Diffusional processes were examined in homogeneous and fractal environments. For the homogeneous case a random walker is placed at a randomly chosen lattice site [2, 3] and then performs random walks. For the heterogeneous case, random walks on the percolation fractal were studied. The reaction of type A+B->0 was examined on homogeneous and fractal spaces.

ii) Flip-flop kinetics with time varying absorption rate coefficient.

Kinetics are tested for one compartment model under scenarios where the absorption rate is time-dependent either following a power function or a Weibull distribution function [4].

iii) Classical or fractal kinetics in a reaction-limited in vivo model of drug dissolution.

Simulations were carried out using the *in vivo* reaction limited model of drug dissolution [1]. Two drugs with different solubilities were considered. The fraction of dose absorbed was calculated as a function of drug dose assuming integer and non-integer values for the stoichiometry of drug dissolution/reaction.

Results:

i) Diffusional processes and reactions in homogenous-heterogeneous media.

We observed straight lines with different slopes when the mean squared displacement of the random walker was plotted relative to time for the homogenous and the fractal case. We further found a profound slowing down of the reactions in fractals as compared to homogeneous spaces. The environmental heterogeneity leads to increased fluctuations of the measurable quantities. At all times the standard

deviation for the A+B->0 reaction on a fractal was found to be considerable higher than the homogeneous environment.

ii) Flip-flop kinetics with time varying absorption rate coefficient.

We observed that higher time exponent values of the power-model lead not only to higher C_{max} but also to a change of the shape of the curve that retains a steeper drop for higher exponents. Similarly, when Weibull function is used, larger time exponents leads to higher C_{max} and a change of the steepness of the C-t curve. The fitting of one compartment model retaining either constant or time-dependent absorption rate coefficients for three compounds known to exhibit flip-flop kinetics [5-7] showed that ka vs ke relationship may be time dependent.

iii) Classical or fractal kinetics in a reaction-limited in vivo model of drug dissolution.

In all cases studied the low values of the fraction absorbed was found to be linked with the backward constant in comparison with the dissolution/rate constant [1]. The fraction of dose absorbed is higher for the stoichiometry integer values. Ascending and descending limbs for the higher stoichiometries were observed. For both drugs, the fraction absorbed for the lower values of stoichiometry exhibit a non-dependency on dose profile.

Conclusions:

Our work revealed that the processes are slowed down in heterogeneous media; besides, the environmental heterogeneity leads to increased fluctuations of the measurable quantities. These findings explain high variability in measurements in understirred biomedia e.g. intrathecal space, gastrointestinal fluids [8,9]. Similarly, incorporation of time-dependent absorption rate coefficients showed that the simulated concentration-time profiles resemble the classical curves but the exact shape of the curve is dependent on the value of the time exponent of the input function. Fitting of PK data further underlined that the rate limiting process is time dependent and as such identification of flip-flop behavior can be misinterpreted. Finally, the profile of the fraction of dose absorbed as a function of dose, assuming different stoichiometries, revealed i) that the shape of the profile is affected by the solubility of drug and the stoichiometry of the dissolution/reaction, and ii) that higher profiles are observed for higher stoichiometries.

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II-34: *Paolo Magni* Artificial intelligence and machine learning: just a hype or a new opportunity for pharmacometrics?

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Objectives:
Artificial Intelligence (AI) in drug development has attracted a growing interest [1]. AI deals with computer systems able to perform human-like tasks or solve complex problems. Machine Learning (ML) is a subfield of AI whose aim is to learn from data in order to find hidden patterns that could be exploited for classification or clustering purpose. ML is further categorized into supervised, unsupervised and reinforcement learning (RL), according to the type of learning procedure on labelled (i.e., with known classes), unlabelled data or with a reward/penalty schema. Among the plethora of ML techniques, Deep Learning (DL), which exploits deep neural networks architectures, has recently outperformed previously developed methods in different tasks. The adoption of AI/ML techniques is well established during both drug discovery [2,3] and patient recruitment process [4,5]. However, ML and AI are also spreading in other drug development phases, historically supported by pharmacometrics and modelling approaches.

In this work, we provide an overview of the AI/ML applications in pharmacometrics, with the aim of understanding how AI/ML can support, substitute or be integrated with model-based approaches and trying to clarify their effective role in this field.

Methods:
We performed a literature review and we tried to classify the different contributions. Four main pharmacometric tasks, that have been approached by AI/ML, were identified in the literature: i) model building and covariate selection; ii) PK/PD parameters prediction; iii) Time-To-Event (TTE) analysis; iv) therapy optimization.
For each topic, the most significant works are reported.

Results:
1) Genetic Algorithm approaches and Stochastic Approximation for Model Building Algorithm (SAMBA) were proposed to select the best combination of structural features, covariates effects and random effects in [6-11] and [12], respectively. Moreover, automatic covariate selection has be performed exploiting Gene Expression Programming [13] or Multivariate Adaptive Regression Splines [14].

2) Artificial neural networks (ANN) were used to make PK/PD predictions: in [15] an ANN was trained to estimate the plasma concentrations of a drug in a given population, with performances comparable to those obtaining by classical NLME models with NONMEM.

3) In TTE analysis several ML techniques, such as Random Survival Forest, Support-Vector Machine, one-layer ANN and DL were used in place of the standard Cox Proportional Hazard model to discover non-linear relationships between covariates and risk [16, 17].

4) RL methods are successfully applied to therapy optimization. In [18-20], they are used to find an optimized treatment strategy that can balance drug efficacy and toxicity for a single patient, or the entire

trial group, and the dose amount is decided by an agent that evaluates the patient status (i.e., tumor size, neutropenia level), obtained from model simulations.

Conclusions:
Despite AI and ML methodologies are not novel approaches and are well established in other fields or phases of drug development, they have recently raised interest in pharmacometrics. From our analysis, it emerges the contribution that the adoption of AI/ML methods could have to support different tasks. For example, in the automation of the model building process they could be a more efficient and valid alternative to the standard forward-addition/backward-elimination approaches, even if an user (subjective) evaluation of the selection steps remains essential. They are also promising for therapy optimization, especially in the perspective of personalized medicine. In other circumstances, however, they cannot substitute a model-based strategy and their data-driven approach is in contrast to the current pharmacometrician efforts towards the building of more mechanistic models. In conclusion, AI/ML methods could be successfully exploited in pharmacometrics and their capabilities should be assessed for further tasks such model-based meta-analysis, but only after a careful and critical evaluation of the characteristic of the investigated problem and an assessment of their real applicability.

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II-35: *Mats Magnusson* Population PK and PASI exposure-response modelling for Certolizumab pegol in patients with chronic plaque psoriasis

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Objectives: The overall objective of this analysis was to develop a population pharmacokinetic (PK) model to describe the PK characteristics of certolizumab pegol (CZP) in subjects with moderate to severe chronic plaque psoriasis (PSO) and to describe the exposure-response relationship between CZP and the PSO efficacy variable Psoriasis Area and Severity Index (PASI)[1].

Methods: The data for the model development originated from plasma concentrations of CZP and PASI observations from three Phase 3 clinical studies combining data from 834 subjects with PSO. In the three Phase 3 trials, subjects were randomized at baseline to treatment with either CZP 200 mg dosing every 2 weeks (Q2W) (loading dose of CZP 400 mg at Weeks 0, 2 and 4), CZP 400 mg Q2W or placebo (PBO). CZP was dosed subcutaneously. Subjects with an inadequate PASI response (PASI50 or PASI75 non-responders) at Week 16 were transitioned to different CZP treatments. Data up to Week 48 were included in the population PK analysis and up to Week 16 for the exposure-response analysis. The starting point for the population PK model was a population PK model developed for the rheumatoid arthritis population. PASI was treated as a continuous variable. Since there is both an upper and a lower bound of the PASI scale a logit-transformation was used. The development of a structural model for PASI was guided by a graphical analysis. The exposure-response model included a component to describe the PASI baseline observations, a placebo effect component, a drug effect component, and a component describing the time-course of PASI response. The covariates tested included demographics, anti-CZP antibodies, region, disease duration and prior biologic therapy. Nonlinear mixed effects modelling was conducted with NONMEM v 7.3.0.

Results:
PK characteristics of CZP in patients with PSO were well described by a one compartment model with first-order absorption and a first order elimination from the central compartment. No deviation form dose proportionality could be identified. Consistent with CZP PK knowledge, in PSO subjects both apparent clearance and apparent volume of distribution increase with body weight with heavier subjects achieving lower CZP plasma concentration. The presence of anti-CZP antibodies increases the apparent clearance.

The relationship between CZP exposure and PASI was described with an indirect response model where a placebo effect could result in both an increase or a decrease in PASI, and where a sigmoidal maximum effect model inhibiting the production of the response described the relationship between the individually predicted CZP plasma concentrations at the time of the pharmacodynamic observations and PASI response. The exposure-response model was parametrized to estimate an EC90 (CZP concentration resulting in 90% inhibition of the PASI production rate) as the two dose regimens tested were at the top of the dose-exposure-response curve. The Emax was estimated to be almost 100% and the typical value for EC90 was 11.1 µg/mL. The typical value for PASI t1/2 was 22.5 days leading to a time to maximum response of 16 weeks in the typical subjects, which matches with the clinical observed data. The covariate analysis revealed that body weight was a significant covariate of PASI half-life with heavier subjects taking longer to achieve maximum response. There were other statistically significant covariates such as region on PASI half-life or baseline PASI, and baseline PASI on maximum effect, but none were deemed to be clinically relevant.

Conclusions:
The proposed models were able to characterize the PK and the exposure response of CZP versus PASI in subjects with moderate to severe chronic plaque PSO. The two tested regimens were at the top of the dose-concentration-response curve.

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II-36: *Corinna Maier* Quantifying the uncertainty: informative decision-support in individualised chemotherapy

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Objectives:

A major aspect of therapeutic drug or biomarker monitoring (TDM) is to combine monitoring data with prior knowledge for model-based predictions of individualised therapy. These predictions are used to identify patients at risk for toxic or subtherapeutic concentrations and to give recommendations for subsequent dose adaptations. Bayesian forecasting tools typically only use the most probable model parameters for predicting therapy outcome without quantifying the associated prediction uncertainties, which include essential information about the probabilities of possible outcomes. A particularly critical example in which TDM could be beneficial is cytotoxic chemotherapy with neutropenia as the most frequent dose-limiting side effect. Bone marrow toxicity can expose patients to life-threatening infections, but also serves as surrogate for efficacy. It is therefore appealing to use neutrophil counts as a biomarker to guide individualised dosing [1]. For neutrophil guided dose selection, the neutropenia time-course for clinically possible dosing regimens must be predicted based on patient-specific neutrophil counts.

Methods:

Bayesian forecasting typically uses maximum a-posteriori (MAP) estimation, which determines the mode of the posterior distribution, i.e. the most probable parameters given patient-specific data. Such an analysis was e.g. performed in some prior work to control neutropenia [2]. In our study, data assimilation (DA) methods are presented which enable a comprehensive uncertainty quantification by deriving the full posterior distribution, namely the Sampling Importance Resampling (SIR) algorithm, the Metropolis-Hastings (MH) algorithm and the particle filter (PF). We systematically compare the properties of these fully Bayesian approaches with a local (normal) approximation and MAP estimation in terms of the accuracy of point estimates, the quality of uncertainty quantification and computational efficiency. We also investigate the benefits of deriving the full posterior distribution for informed decision support in the context of chemotherapy-induced neutropenia. For these purposes, we performed simulation studies in which we combined prior knowledge from clinical studies for the anticancer drugs docetaxel [3] and paclitaxel [4] with simulated patient data.

Results:

We identified that MAP estimation has several limitations for model-informed precision dosing, since it provides only a point estimate without quantification of associated uncertainties. In addition, the MAP parameter estimate depends on the parametrisation of the model, e.g. log-transformation, and the predicted outcome does not necessarily correspond to the most probable outcome. We also observed that a local (normal) approximation to the shape of the posterior distribution could yield misleading results, e.g. underestimation of the risk of severe neutropenia, which can have serious consequences and is highly undesirable in a high-risk environment. The fully Bayesian approaches provided increased accuracy of point

estimates compared to MAP estimation and a comprehensive uncertainty quantification. The full posterior distribution also enables probabilistic statements about all possible outcomes for a patient, e.g. the probability of all neutropenia grades 0-4 or of possible recovery days. The particle filter additionally provides a sequential framework for efficient processing of monitoring data during ongoing treatment: Data does notneed to be stored for future analysis and the implementation of inter-occasion variability is facilitated as the information of previous occasions is already encoded in the current posterior distribution.

Conclusions:

Fully Bayesian methods offer crucial advantages over MAP estimation for TDM. They provide more accurate point estimates, a comprehensive uncertainty quantification and probabilistic statements about different possible outcomes, all of which are important aspects for decision makingin clinical care. Dose selection can then be based on the simultaneously available risk of toxic as well as of subtherapeutic regimes in order to find an effective as well as safe dose for the individual patient. Therefore, fully Bayesian approaches have the potential to improve patient care in various therapeutic areas. As new digital monitoring devices enable the frequent and non-invasive collection of patient data during treatment, sequential approaches to TDM will offer attractive opportunities in future.

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II-37: *Victor Mangas-Sanjuan* Population Pharmacokinetic and exposure-efficacy Markov modelling of enzymatic activity in Gaucher disease patients treated with enzyme replacement therapy

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Objectives: The aim of this study is (i) to develop a population pharmacokinetic model of enzyme activity in Gaucher disease type I (GD1) patients after intravenous (IV) administration of enzyme replacement therapy (ERT) and, (ii) to establish an exposure-efficacy relationship for a categorical outcome in order to propose dose adjustments according to patient covariate values

Methods: A prospective follow-up, semi-experimental multicentre study was conducted in four public hospitals from June 2010 to December 2017. Continuous glucocerebrosidase activity (GBA1) observations were collected 10 and 75 minutes pre- and post-administration, respectively, during therapeutic drug monitoring (TDM) up to one year after the patient's enrolment. GBA1 observations in leukocyte and monocyte were available for the analysis. The efficacy dataset consisted of categorical data of infiltration of Gaucher cells in the bone marrow collected every 12 months during seven years of treatment, with grades 1, 2 and 3, based on the number of infiltrated Gaucher cells. GBA1 in leukocytes and monocytes were described with compartmental models parameterized in apparent volumes of distribution, and first-order distribution and elimination clearances. A zero-order synthesis (k0) of GBA was also considered in order to physiologically describe the endogenous production of GBA in humans. Between subject variability (IIV) on pharmacokinetic (PK) model parameters was modeled exponentially, and residual variability was described with an additive model on the logarithmic scale. The covariate analysis was carried out by the stepwise covariate modelling (SCM). The significance of potential covariates was systematically evaluated in a stepwise forward selection (ΔOFV <3.84 points, $p<0.05$) one at a time. Model evaluation was performed through prediction-corrected visual predictive checks and bootstrap analysis. Logistic regression models using a discrete-time Markov model (DTMM) was performed. The efficacy data were treated as ordered categorical data, and through a fist-order Markov element.

Results: A total number of 18 individuals with 180 GBA1 in leucocytes and monocytes observations were included in the PK analysis. The base population PK model contains a two concatenated compartments to describe GBA1 observations in leucocytes and monocytes, respectively. The structural model assumes a zero-order endogenous production of GBA1 to describe a constant synthesis of the endogenous enzyme. A first-order distribution of GBA1 from leucocytes into monocytes and a first-order elimination process of GBA1 from monocytes properly modelled GBA1 profiles. An exponential time-dependency effect on CL1 statistically improved the description of the data ($p<0.01$), demonstrating a roughly 10% decrease over time in CL1 after 3 months of ERT. A total of 14 individuals with 68 observations of efficacy after ERT administration were included for the analysis during 7 cycles of treatment. Pharmacodynamics (PD) measurements of 4 patients from the PK study could not be collected. The final exposure-efficacy model was a longitudinal logistic regression model with a first-order Markov element[1], where the probability of improving efficacy outcome raised from 7% (grade 3 to 2) and 16% (grade 2 to 1) to 20% and 38%, respectively. An Emax model (1.24 U/kg) best described the dose effect with exponential IIV (129%)

included on EC50 parameter. Inclusion of averaged steady-state concentrations in plasma or monocyte provided slightly worse results in terms of OFV and model stability.

Conclusions: In conclusion, a population pharmacokinetic model has been developed and successfully qualified to explain the leukokycte and monocyte GBA1-time profiles following intravenous administration of ERT in GD1 patients. A dose-efficacy relationship, measured as infiltrated Gaucher cells in bone marrow scale adequately predicts the pharmacodynamic outcome along treatment cycles using a first-order Markov dependency. The information obtained from this study could be of high clinical relevance in ERT individualization in GD1 patients as it can lead to anticipate these decisions regarding clinical response and optimal dosing strategy.

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II-38: *Nicolás Marco Ariño* Pharmacodynamic modelling of pupil diameter after noxious stimulus in patients undergoing surgery

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Objectives: Movement is an extensively characterised response to noxious stimulus. However, its applicability to assess intraoperative pain has limitations due to the effect of anaesthesia in the response. Previous research has shown that pupil reflex, an indicator of anesthetic depth, could also predict movement after noxious stimuli[1,2]. The objective of this project is to characterise the effect of remifentanil and potentially propofol on the pupil size over the time course of the operation and to evaluate the pupil size as a predictor of response to movement after anaesthetic and/or nociceptive stimulus, thus enabling anaesthesiologists to optimise dosing during surgery.

Methods: Patients undergoing gynaecological, hysteroscopic and urinary incontinence surgery were recruited for the study. Exclusion criteria included ocular diseases, prescription of drugs affecting the size or reflex of the pupil and morbid obesity (IMC> 35). Pupil diameter was measured multiple times before and after surgery using the AlgiScan (Neurolight, IDMED™) hand-held pupillometer which was also used to delivered a 60 mA tetanic stimulus during 5 seconds in the forearm of the patient. Movement response to the stimulus was evaluated in a categorical scale ranging from 0 (absence) to 3 (strong movement) by the physicians. Propofol and remifentanil concentrations in plasma and effect site were predicted using previously validated PK models. Data were analysed using NONMEM 7.3.

Results: Eighty-seven patients participated in the study (3 males and 84 females) each having a median of 5 (range 3 to 7) measures of pupil size after noxious stimulation during surgery. The first measure was performed in the presence of propofol (1152 observations) and the rest in the presence of propofol and remifentanil (9271 observations). No data from basal pupil size in the absence of anaesthesia was available due to the impossibility to perform the procedure in awake subjects. The median pre-stimulus pupil diameter in the presence of propofol was 4.02mm. A two compartment indirect response model accurately described the effect of the noxious stimulus on the pupil size over the time course of the records (before, during and after perturbation). In this model the administration of the tetanic stimulus modulates a nociceptive compartment whose synthesis and degradation rates are governed by a KSD1 parameter ($0.492 s^{-1}$). The amount in the nociceptive compartment subsequently controls the turnover of the pupil diameter. The pharmacodynamics effects of propofol and remifentanil were sequentially evaluated. The effect of propofol in the pupil size could not be assessed due to the lack of baseline pupil measurements but the pupil diameter in the presence of propofol was estimated in 3.77mm. Remifentanil reduced pupil diameter by modulating the turnover of the nociceptive compartment with an IC50 of 0.481ng/ml and the pupil size with an IC50 of 2.78ng/ml. Precision of the parameter was estimated accurately (RSE <25%) although high inter-individual variability was observed. Model performance was based on goodness of fit plots and visual predictive checks.

Conclusions: A semi-mechanistic pharmacodyamic model to describe the pupil size after a noxious stimulus in the presence of propofol and remifentanil was successfully implemented. Assessment of covariates

affecting the model parameters would be performed to reduce the unexplained variability. This model will be further developed to incorporate the movement response

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II-39: *Fatima Zahra Marok* Physiologically-based pharmacokinetic modeling of DPYD substrate 5-fluorouracil and its prodrug capecitabine

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Introduction: The intravenously administered cytotoxic drug 5-fluorouracil (5-FU) and its oral prodrug capecitabine (CCB) are used as first line agents for the treatment of colorectal cancer, one of the most common tumor types today [1]. Dihydopyrimidine dehydrogenase (DPD) is the rate-limiting enzyme in the transformation of 5-FU, CCB and further fluoropyrimidine based drugs [3]. Polymorphisms in DPYD, the gene encoding for DPD, lead to a genotype dependent enzyme activity which can increase the occurrence of 5-FU and CCB related adverse drug effects leading to life-threatening toxicities [4]. The general use of fluoropyrimidine analogues in the anticancer therapy is broad and thus, it is important to understand the impact of drug-gene and drug-food interactions, to optimize dosing recommendations and consequently limit the occurrence of adverse drug effects.

Objectives:

- To build a physiologically-based pharmacokinetic (PBPK) model for CCB, 5-FU and their respective metabolites 5'-desoxy-5-fluorocytidine (DFCR), 5'-desoxy-5-fluorouridine (DFUR), 5,6-dihydrofluorouracil (DHFU), α-fluoro-β-ureidopropionicacid (FUPA) and α-fluoro-β-alanine (FBAL)
- To predict drug-food-interactions (DFIs) for CCB
- To predict drug-gene-interactions (DGIs) of all compounds for the clinically relevant DPYD gene variants c.1905+ 1G>A (DPYD*2A), c.1679T>G, c.2846A>T and c.1129-5923C>G
- To develop dose recommendations for various DGI combinations

Methods: PBPK model development was performed with PK-Sim® and MoBi® (version 7.4.0) as part of the Open Systems Pharmacology Suite [6]. Data for model development were extracted from literature, including physicochemical parameters and plasma concentration-time profiles for all compounds and for various DPYD genotypes. Data were separated in an internal and an external dataset for model development and evaluation, respectively. Additionally, an uracil (U) model was developed and used for the evaluation of the genotype implementation, where the enzyme activity of genetic variants of DPYD are described through the ratio of U and its first metabolite dihydrouracil (DHU). The final models were used for dose optimization. For this purpose, exposure of 300 mg/m^2 5-FU as the area under the plasma concentration-time curve (AUC) at steady-state was simulated as reference value. Exposure were simulated for different DPYD genotypes at steady-state adapting the dose stepwise until matching exposure compared to wildtype was reached.

Results: Nine whole-body PBPK models for CCB, 5-FU and their five metabolites, as well as U and DHU were developed. The compiled data consists of 12 CCB studies (dose range 1260-2372 mg as Xeloda® tablet in 183 patients), 21 5-FU studies (250-1134 mg as bolus injection, continuous infusion or peroral solution in 226 patients) and two peroral U studies (as peroral solutions in 42 patients). The models precisely predict the PK of CCB and 5-FU in wildtype patients and heterozygous patients for the gene variant *2A for fed and fasted patients. Predicted and observed AUC ratio of fed versus fasted was 1.23 for CCB. Additionally, mean

predicted to observed AUC values for fed and wildtype individuals show ratios of 1.0 and 1.1 (range 0.73 – 1.87) for CCB and 5-FU, those of the remaining metabolites as well as the DHU/U ratios lie within the two-fold acceptance limits. Dose recommendations were derived for combinations of hetero- and homozygous variants of the four relevant polymorphisms as well as under fasted or fed conditions. For example, model predicts a dose reduction of 35% for DPYD*2A heterozygous variants compared to 50% which is recommended by the current CPIC guideline [5].

Conclusion: A comprehensive set of PBPK models for CCB, 5-FU and their respective metabolites were successfully developed. The models capture the important impact of drug-food and drug-gene interactions and can play an important role in decreasing the occurrence of potential life threatening adverse drug effects by deriving alternative dosing regimens for DPYD deficient patients.

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II-40: *Frederico Martins* Application of Physiologically Based Pharmacokinetic (PBPK) Modelling to Support First in Human dose selection.

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Objectives: GLPG1205 is a novel, potent and selective antagonist of G protein-coupled receptor 84 (GPR84), activated by medium chain fatty acids. It is more than 100 fold selective for GPR84 over 123 other GPCRs, including free fatty acid homologs. Physiologically based pharmacokinetic (PBPK) modelling is a key component in the movement toward *in vitro*-based risk assessment, providing a tool to integrate diverse experimental data and mechanistic information to relate in vitro effective concentrations to equivalent human exposures [1]. The objective of the work was to compare the predictive performance of allometric model (AM) with a (PBPK) model to predict clearance, area under the concentration-time curve (AUC) and maximum concentration (C_{max}) and T_{max} (time to maximum concentration), following administration of single oral doses to healthy human volunteers.

Methods: A whole-body PBPK model of GLPG1205 was established with PK-Sim® modelling software (Version 7.3.0) [2]. Physicochemical parameters incorporated from experimental data were logP = 2.38, pka= 1.34, thermodynamic solubility pH 7.4 = 5.18 µg/mL, f_u=0.029, the absorption rate was determined *in vitro* by Caco-2 permeability and clearance from *in vitro* human hepatocytes. The volume of distribution was calculated based on Poulin & Theil model [3]. Allometric scaling of clearance and volume of distribution obtained from a single dose study in monkeys was performed. Data from a first-in-human volunteer study were used for performance verification and model refinement. Pharmacokinetic (PK) parameters (AUC, C_{max}, T_{max}) were calculated using PKsim (version 7.3). Overall prediction performance was evaluated based on performance indicators (Absolute average fold error-AAFE).

Results: A PBPK model was developed for GLPG1205 to describe the tissue-specific absorption, distribution, metabolism, and excretion. Model based simulations of GLPG1205 plasma concentrations in humans showed that T_{max} was attained in 2-4 hr, with dose proportional increase in C_{max} and AUC over 10 to 600 mg single dose . The PBPK model was able to predict the prolonged elimination half-life (observed 32±12hr, predicted 47±20hr) against 3.7 hr of classical allometry . Predictions with the PBPK model showed 0.5 to 2-fold prediction error compared to 4 to 10-fold prediction error with allometric scaling, compared to observed clinical data.

Conclusions: Allometric model entails scaling of clearance and volume of distribution and resulted in a lower accuracy in human PK prediction than PBPK model, which include the mechanistic parametrization of biologic processes. This case study is an example of *in vitro* to *in vivo* extrapolation (IVIVE) approach for PBPK model development. While Allometric and PBPK models may at times be comparable, PBPK is of particular value for drugs with scaling challenges due to poor ADME properties.

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II-41: *Paolo Mazzei* Prospective Evaluation of a Model-Based approach to select Phase 1 Dosing Regimen for MEN1309/OBT076, a novel antibody drug conjugate (ADC) targeting Ly75 antigen for the treatment of CD205-positive metastatic solid tumours and Non-Hodgkin lymphoma

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Objectives: The aim of this work is to prospectively evaluate the model-based approach used to select Phase 1 study dosing regimen for MEN1309/OBT076, a novel antibody drug conjugate (ADC) targeting Ly75 antigen, with the observed clinical PK and safety data emerging during the ongoing first-in-human (FIH) SHUTTLE-01 study in patients with CD205-positive metastatic solid tumours and Relapsed/Refractory (R/R) Non-Hodgkin Lymphoma (NHL).

Methods: First, a population PK model was developed based on preclinical PK data from 3 toxicological studies in cynomolgus monkeys. Monkey plasma concentration–time data were modelled, and PK parameters appropriately scaled to derive human PK parameters. Second, toxicokinetic (TK) data (i.e. absolute neutrophils counts, ANC) from these studies were used to describe MEN1309/OBT076 neutropenic effects in cynomolgus monkeys and, once appropriately scaled, to predict onset and recovery of hematologic toxicity in human. Third, a translational PK/PD model was established to quantitatively express the relationship between MEN1309/OBT076 plasma concentration and tumour volume in nude mice bearing orthotopic HPAF-II tumours. MATLAB, R and NONMEM VII were used to perform the analyses. Using the previously established translational strategy, an appropriate dosing schedule for the FIH study was proposed. Finally, model-projected PK and safety profile in human for MEN1309/OBT076 have been compared to PK and safety data from the ongoing FIH study in an interim PK/PD analysis to verify the goodness and adequacy of model predictions.

Results: A two compartment PK model with linear and saturable elimination best described preclinical PK data. An exponent of 1 was used to scale clearance and intercompartmental clearance. The neutropenia model structure developed by Friberg et al. [1] was applied for MEN1309/OBT076-associated neutropenia in cynomolgus monkeys. The estimated drug-related parameters in cynomolgus monkeys, together with the scaled PK model and the typical system-related parameters in human [1], were used to scale up to human the Friberg model and to predict the time course of myelosuppression in patients. The semi-mechanistic model developed by Simeoni et al. [2] was applied to model tumour growth inhibition data from xenograft experiments. The threshold concentration for tumour eradication was derived and used as a reference concentration for achieving a significant activity in human. According to the predictions of the developed translational exposure–efficacy and safety modelling framework, a starting dose in human of 0.05 mg/kg was considered to provide an adequate safety margin. Moreover, the PK/PD model predictions supported an accelerated titration design (ATD) from 0.05 mg/kg to 6.4 mg/kg. Finally, median and 90% prediction intervals (PI) of fully-scaled simulated MEN1309/OBT076 concentration-time profiles and ANC-time profiles in human were compared against observed data in patients from FIH study. In general, observed values were well distributed around median predictions and the extent of inter-individual variability was well represented by the 90% PI.

Conclusions: A translational strategy developed from preclinical data proved to be a valuable tool for the selection of the dose of a FIH study of a novel ADC. Good agreement between the model-based predictions and the clinical PK and safety data collected from the ongoing Phase 1 study shown in a subsequent model validation analysis confirmed the adequacy of the followed approach.

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II-42: *Mark Meerson* Quantitative systems pharmacology model of key intraneuronal pathways regulating toxic protein accumulation in Alzheimer's disease

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Objectives: Alzheimer's disease (AD) is a complex neurodegenerative disorder, its pathogenesis mechanism is still debated and there is no effective treatment or prevention therapy. Apart from the accumulation of protein aggregates there are many intracellular processes altered in AD brain, which are related to Aβ and tau pathology, and are believed to be the cause or contributors to toxicity. They include, for example, protein degradation and secretion machinery and lipid metabolism, as demonstrated by changes in specific biomarkers in AD pathology. Although some of these cellular pathways [1], as well as, e.g. amyloid or tau pathology progression have been modelled previously, there is a lack of insights in the quantitative aspects of their interactions in pathology and health. Quantitative systems pharmacology (QSP) provides a quantitative framework to study the interaction of complex disease mechanisms.
The objective of this study was to develop a QSP model describing the key neuronal processes observed to be affected in AD and potentially influencing, or significantly influenced by, tau and Aβ pathology. The model is aimed at describing both, baselines of target variables in healthy human brain and their dynamics during disease progression.

Methods: The proposed model describes several neuronal processes in human brain disturbed in AD by means of ordinary differential equations (ODEs). Based on a literature review, several pathways interacting with Aβ and tau accumulation were selected: protein degradation (via autophagic-lysosomal system, ALS, and cytoplasmic proteolytic systems), protein secretion (via exosome secretion), as well as sphingolipid and cholesterol metabolism.
Protein degradation and secretion were described using a mechanistic approach, which allows for calibration to quantitative data (e.g. [2]) and comparison with in vitro data. Most of the important regulatory hubs (e. g. mTOR in the ALS) were described by algebraic functions, which were derived using a quasi-steady state (QSS) assumption and are dependent on various cellular components. The model includes activating and inhibiting interactions between variables and functions, allowing for the reflection of complexity of cellular metabolic regulation. Here, we purposefully focused on the dynamics of dysregulation of neuronal homeostasis during AD pathology describing several drivers of the dysregulation, including (but not limited to) Abeta and Tau protein pathology, in terms of explicit functions derived from published data.
Calibration of the model was carried out using public domain data on baseline concentrations of different metabolites and vesicle content in human brain tissues. The model was validated on in vivo clinical data sets and in vitro data for interventions into different cellular pathways.

Results: The model correctly describes the baseline concentrations of cellular components in healthy human brain. Steady-state levels of 87% of variables in brain compartment were compared to published quantitative data. 77% of them match data within 2-fold range and 80% of these variables in turn match the data within 20% error. Comparing model simulations to data for pharmacological treatments we show that cellular responses to various compounds (e.g., rapamycin, vinblastine, ACAT inhibitors) are described correctly by the model, demonstrating that our model captures complex interactions between cellular pathways.
Finally, the model is able to reproduce the dysregulation of different cellular pathways in AD compared to healthy subjects. In particular, the model matches observed biomarkers indicating impairment of protein

degradation and secretion, demonstrating that the model correctly captures the age-dependent breakdown of protein degradation and secretion machinery and its exacerbation by amyloid and tau pathology in AD.

Conclusions: The model describes key AD-related cellular processes and we showed that it matches levels of different cellular components in healthy subjects, as well as key pathway interactions and dysregulation in AD. The model can be used as a mechanistic description of processes driving initial accumulation of toxic proteins in AD and of the feedback mechanisms leading to further development of AD progression. In future work, it should be integrated with dynamic models of amyloid and tau pathology to explore their interactions during disease progression. The model provides a quantitative framework for hypothesis generation and testing in biomedical research and drug development for AD.

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II-43: *Christophe Meille* Combining BLRM and safety PKPD models to improve decision making in a phase I dose escalation study: case study of PCA062, an antibody drug conjugate targeting P-Cadherin

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Introduction

The Bayesian Logistic Regression Model (BLRM) is a well-defined statistical method for analyzing the relationship between dose and dose limiting toxicities (DLT) for dose escalation phase I studies. Semi-physiological PKPD models can describe longitudinal PD markers such as platelet counts. In this work, BLRM and PKPD models were used to support decision making during dose escalation and the prediction of maximum tolerated dose (MTD) for PCA062, an antibody drug conjugate (ADC) targeting P-Cadherin. PCA062 is an ADC containing the toxic payload emtansine (DM1), which has thrombocytopenia as an expected toxicity.

Objective

The objective of this work is to demonstrate how a PKPD model, developed for a specific toxicity (i.e., thrombocytopenia and/or platelet count decrease) may be combined with approaches such as BLRM, improve the decision making in a phase I dose escalation study when compared to only using DLT information alone.

Methods

PCA062 was administered by infusion (in mg/kg) every two weeks (Q2W). Ten dose levels ranging from 0.4mg/kg to 5.0mg/kg (Q2W) were tested during the dose escalation. Parallel evaluation of the BLRM and PKPD models' predictions was conducted. The BLRM uses a two parameter logistic model to describe the dose-DLT relationship, where DLT is a binary outcome describing the occurrence of specific toxicities in patients (e.g., CTCAE grade 3 or higher). The prior distribution for the BLRM parameters was derived using preclinical data in monkeys. The probability of DLT and the risk that a given dose level exceeds the true MTD are estimated based on the posterior distribution of the model parameters. The safety PKPD model was introduced to support prediction of MTD after 29 patients had been treated in seven different dose levels. The PK model structure is a two compartmental model with linear elimination. The thrombocytopenia model from Bender et al. was adapted to describe platelet counts. The population thrombocytopenia PKPD model of PCA062 was developed from the clinical study data (n=29 , total number of platelets observations = 256). By using the estimated individual patient parameters, thrombocytopenia toxicity rates at different dose levels were simulated with the PKPD model. Estimation of parameters was done applying non-linear mixed effect modelling with Monolix 2016.

Results

Up to a dose level of 3.6mg/kg, both BLRM and PKPD modeling predicted a similar toxicity probability. Only the PKPD modeling approach accurately predicted the thrombocytopenia toxicity rates for unexplored dose ranges (>3.6mg/kg Q2W) suggesting 3.6mg/kg Q2W as a potential MTD for PCA062. However, when including all patient data up to 5.0mg/kg into the BLRM method both methods predicted comparable

results. With the data from the 5mg/kg patients, the projected toxicity rates at 5mg/kg from the BLRM is 34.2% (95% CI 13.9 to 61.1), and the PKPD model is 31.7% (95% CI 18.1 to 48.1). Without the data from the 5mg/kg patients, the projected toxicity rates at 5mg/kg from the BLRM is 20.1% (95% CI 5.8 to 43.7), and the PKPD model is 37.8% (95% CI 20.5 to 57.7).

Conclusion

The BLRM and PKPD models were used during the decision to declare the MTD, with the PKPD model complementing the results from the BLRM. Using a semi-physiological PKPD model is relevant when the safety profile of a drug can be anticipated; in this case, PCA062 is anticipated to cause thrombocytopenia. While the BLRM incorporates all types of toxicities considered as DLTs as a binary outcome, the PKPD model describes only the platelet count observations, but as a longitudinal continuous measurement. Combining the BLRM model predictions with the a PKPD model can improve decision making in dose escalation studies. For the PCA062 phase I study, the PKPD model of thrombocytopenia was projecting a higher risk of thrombocytopenia DLT than overall risk of DLT from the BLRM method. Longitudinal measurement of a safety PD marker can be used to develop a PKPD model to supplement the BLRM results and have a significant impact on the decision making with respect to selecting an optimal dose for further development.

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II-44: *Nicola Melillo* Global sensitivity analysis of a physiologically based pulmonary absorption model

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Objectives: We performed a global sensitivity analysis (GSA) on an in-house physiologically based pulmonary absorption model for rats [1]. Physiological models are characterized by uncertainty and variability in the model parameters. It follows that the predicted metrics are uncertain (or variable) too [2]. As highlighted by the regulatory agencies, to improve the knowledge on the model, it is important to assess how much each parameter, with its variation, impacts on the model output variation. This can be achieved performing a GSA [3]. Here, we performed two types of GSA: *inter-compounds* and *intra-compound*. The aim of *inter-compounds* GSA is to understand what are the parameters that mostly influence the variability of the model predictions between different drugs. Instead, the aim of the *intra-compound* GSA is to understand how much the uncertainty associated with the parameters of a given drug impacts the model output uncertainty.

Methods: GSA methods consider each parameter X_i as a random variable, with associated a certain probability distribution [2]. Thus, the model output Y is a random variable too. For each X_i, variance based GSA derives two sensitivity indices from the decomposition of the variance (V) of Y: the main effect (S_i) and total effect ($S_{T,i}$). Both S_i and $S_{T,i}$ are always included in [0,1]. The higher S_i and $S_{T,i}$ are, the more X_i is important in explaining $V(Y)$. Instead, $S_{T,i}$=0 means that X_i is not influent on $V(Y)$ [2].

In the *inter-compounds* GSA, drug related parameters are considered distributed into a range of values that includes all the compound of interest [4, 5]. All the parameters distributions were considered uniform within these ranges. The considered model outputs were the fraction absorbed (f_a) and the lung-tissue AUC. We performed two GSA, one for highly soluble and the other one for poorly soluble compounds. The criterion used to divide compounds into these two classes resembles the one for orally administered compounds [6]. A dose number for inhaled compounds was defined ($D_{0,inh}$) and it was used to distinguish highly and poorly soluble compounds.

We performed the *intra-compound* GSA on the absorption model coupled with a PBPK distribution model [7], for three internal compounds of interest. The parameter ranges of variation were defined equal to ±30% of the mean values, except for the active and passive permeabilities across lung tissues and for the blood to plasma ratio, that were considered equal to ±70% and ±10%, respectively. The considered outputs of interest were the lung tissue and plasma AUC.

Results: Concerning *inter-compounds* GSA, for highly soluble compounds, the parameter that mostly explain the f_a variability is $D_{0,inh}$ (S_T≈0.9) while for poorly soluble compounds are the mass median aerodynamic diameter (MMAD) and $D_{0,inh}$ (S_T≈0.33 and 0.40, respectively). For lung AUC, the most important parameters for highly soluble compounds are the lung tissue binding (LTB) and both passive and active permeabilities (S_T≈0.6, 0.6 and 0.2, respectively). For poorly soluble compounds, in addition to LTB and the permeabilities, $D_{0,inh}$ and MMAD (S_T≈0.45 and 0.2, respectively) are also important. In the *intra-compound* GSA, for all the considered compounds, the lung AUC variance is mainly explained by the passive

permeability variation (S_T>0.5). The most important parameter for plasma AUC of the first internal compound is the extraction ratio (S_T≈0.5), for the second one are the B:P, the dose and the rat weight (all S_T≈0.25) and finally, for the third one are the dose, the rat weight and B:P (S_T≈0.3, 0.2 and 0.25, respectively).

Conclusions: In the *inter-compounds* GSA, for highly soluble compounds, the most important parameters in explaining $V(f_a)$ are related with the dissolution process, while those for lung AUC variability, with drug retention in the lungs. With respect to highly soluble compounds, poorly soluble compounds have higher impact of parameters related with the dissolution process in explaining the lung AUC variability. In the *intra-compound* GSA was highlighted that the uncertainty related with the lung AUC is mainly explained by the passive permeability, while that of the plasma AUC by parameters related with drug distribution and metabolism. The *inter-compounds* GSA helps in understanding the model general behaviour in the whole parameters space, while the *intra-compound* GSA helps in identifying what parameters should be more precisely known to reduce the model output uncertainty.

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II-45: *France Mentré* New version of PFIM for optimal design in nonlinear mixed effects models using R S4

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Introduction: Nonlinear mixed effect models are increasingly used for the analysis of longitudinal studies in drug development. Using the Fisher Information Matrix (FIM) to optimize the design of these studies is an efficient alternative to clinical trial simulation. PFIM 4.0 [1] is one of the R program devoted to the design evaluation and optimisation. S4 is an object-oriented programming language which can offer several advantages compared to the traditional programming [2].

Objectives: To program in R S4 language, a new version of PFIM in order to increase its simplicity of use, its comprehensibility and its modularity.

Methods: PFIM was re-programmed from scratch in R S4 language, according to a top-down approach. The conception of the new PFIM is based on multiple classes and inheritances, which can be represented as a class diagram, with PFIM as a central object. The different programmed classes and objects are conceived to be easily used or modified for programmers and users of PFIM. The FIM is evaluated by first order linearisation of the model [3], as in PFIM 4.0. Under given design constraints and based on the D-criterion, the design is optimised using a multiplicative algorithm [4] which is a new feature as compared to PFIM 4.0. Several tests and examples were performed during the new PFIM programming process. The examples were composed of models with one or two responses (e.g. PK/PD model), expressed as analytical solutions or as ordinary differential equations. The results were compared to those obtained with PFIM 4.0.

Results: The new PFIM, by its conception, is different from PFIM 4.0. First, the use of the program is closer to most of R packages than PFIM 4.0. For the different tested examples, the evaluated FIM is consistent with the one obtained with PFIM 4.0. The different elements of a project as the model, the design (evaluated or optimized), the evaluated FIM and predicted standard errors (SE) of parameters can be stored as objects. Moreover, the project can be easily saved and reloaded. Design optimisation through the multiplicative algorithm allows to optimize the number of arms, measuring times and doses simultaneously. After performing design evaluation and/or optimisation, the results are displayed in a summary, with the different elements that could be manipulated in R

Conclusions: There is a need to increase the use of model based optimal design approaches, as it can anticipate 'fatal' studies. The new version of PFIM fulfill some needs by its usability. Nevertheless, this PFIM version is not final: some features implemented in PFIM 4.0. have to be also implemented in the new PFIM (e.g. Fedorov-Wynn and Simplex algorithms for design optimisation, Bayesian FIM to give shrinkage predictions [5], discrete covariates and Wald test power predictions [6]). The perspectives are also to implement new features such as alternative methods to evaluate the FIM (e.g. MC/AGQ [7]) for discrete response models. It should also be of interest to increase the interoperability with estimation parameter software tools, as aimed by the DDMoRe project.

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II-46: *Matilde Merino-Sanjuán* Impact of ABC gene single nucleotide polymorphisms in population pharmacokinetic of capecitabine and its metabolites 5'-deoxy-5-fluorouridine (5'-DFUR) 5-fluorouracil (5-FU) in patients with colorectal cancer

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Objectives: The aim of this study was (i) to assess the pharmacokinetics (PK) of capecitabine and its metabolites 5'-deoxy-5-fluorouridine (5'-DFUR) and 5-fluorouracil (5-FU) in a population of colorectal cancer patients, and (ii) to analyze whether single nucleotide polymorphisms in the ABC transporter gene may explain inter-individual variability of pharmacokinetic parameters.

Methods: A prospective observational post-authorization study between February 2015 and August 2016 was carried out in the Doctor Peset University Hospital of Valencia in patients with colorectal cancer. Capecitabine was administered in different schedules with doses between 850-1250 mg/m^2 orally twice a day. Three blood samples were obtained at 1h, 2h and 3h post-administration and the plasma concentrations were determined by high-performance liquid chromatography (HPLC) [1]. Capecitabine and its metabolites plasma levels were described with compartmental models parameterized in first order rate constant, apparent volumes of distribution, and first-order distribution and elimination clearances. Several models to describe the possible delay in absorption were assessed. Model parameters were estimated using Monolix® (Suite-2018R1) [2]. The subject inter-individual variability (IIV) on pharmacokinetic (PK) parameters was modeled exponentially, and residual variability was described proportionally with one residual error for each analyte. Relationship between individual pharmacokinetic parameters (IPK) and covariates such as: polymorphisms of the ABC gene with prevalence higher than 20% in the population, age, sex, body surface, bilirubin, creatinine, creatinine clearance, and concomitant oxaliplatin therapy, were assessed using forward inclusion and backward elimination criteria manually. The predictive performance of the model was evaluated using a visual predictive check (VPC) based on 500 simulated replicates of the development dataset. Parameter precision was evaluated through relative standard error and non-parametric 95% confidence intervals.

Results: 48 patients were included in our study in which 432 plasma samples were collected, 12.7% (55/432) below the limit of quantification (BLQ). Different strategies were followed to account for BLQ (M1, M3, M4 and M6) [3-4] The methodology best described the experimental data in terms of parameter precision and stability was the M1 method, which discards BLQ data and applies extended least squares to the remaining observations. The absorption process was described by a first order process with absorption lag time (0.28 h). The clearance values of capecitabine, 5'-DFUR and 5-FU were 294, 26,8 and 8,97 L/h, respectively. The apparent volume of distribution of capecitabine (V2) was 449 L, while V3 (5'-DFUR) and V4 (5FU) were fixed at 1L. A statistical relationship (p-value) between IPK and 85 covariates (78 polymorphism and 7 biochemical, treatment-related and demographic covariates) was performed. From the total statistically significant covariates (36), highly-correlated covariates were removed for model evaluation (28). Each relationship was incorporated manually in the model. The final model incorporates the following covariates: oxaliplatin with absorption lag time, rs6720173 with clearance of 5'-DFUR and

rs2271862 with clearance of 5-FU. A reduction of 14%, 19%, and 66% in the IIV of each parameter was estimated when base and final parameter estimates were compared.

Conclusions: A population pharmacokinetic model which allows to describe concentrations of capecitabine and its metabolites in plasma has been developed, showing the effect of ABC gene single nucleotide polymorphisms rs6720173 and rs2271862 on clearance of metabolites of capecitabine in patients with colorectal cancer.

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II-47: *Danica Michalickova* Pharmacokinetics of phenobarbital in neonates on extracorporeal membrane oxygenation

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Objectives: Phenobarbital is one of most frequently used anticonvulsive drugs in pediatric patients undergoing extracorporeal membrane oxygenation (ECMO). The use of ECMO is associated with significant changes in drug pharmacokinetics (PK) [1]. The aim of this study was to characterize the PK of phenobarbital in neonates on ECMO.

Methods: Data from therapeutic drug monitoring (TDM) were available from 13 (6 female, 7 male) neonates (median (IQR), body weight (BW): 3.62 (2.65-3.80) kg; postnatal age (PNA): 13 (5-21) days; gestational age: 38 (38-41) weeks) receiving veno-venous (VV) or veno-arterial (VA) ECMO, yielding 5 phenobarbital concentrations before ECMO, 31 during ECMO, and 19 concentrations after ECMO. The median loading dose of phenobarbital was 7.5 (8.5-16) mg/kg, while the median maintenance dose was 6.9 (4.5-8.5) mg/kg/day. Phenobarbital levels ranged between 2.8 and 56.4 mg/L.

Population PK analysis was performed using NONMEM 7.3.0 [2]. For the structural model, one and two compartment models were tested. Log-normally distributed inter-individual variability terms were tested on each PK parameter. Proportional, additive and combination error models were tested for the residual error model. To disentangle the impact of maturation from other disease related and treatment related covariates, maturation functions for clearance (CL) and volume of distribution (Vd) were obtained from a previously published model in patients with an overlapping age-range [3].

The following covariates were evaluated: laboratory values, concomitant therapy, and ECMO therapy (on/off, duration, modality (VV, VA), speed, flow, change of circuit, time after start and stop of ECMO). Covariates were included based on a forward inclusion and backward deletion ($p<0.05$ and $p<0.01$, respectively). Additional criteria for covariate selection were relative standard error (RSE) of the estimates, physiological plausibility, and absence of bias in goodness-of-fit (GOF) plots. The final model was validated using normalized prediction distribution errors (NPDE) [4].

Results: In a one-compartment model, CL and Vd for a typical neonate of median birth BW (3.21 kg) at median PNA (13 days) off ECMO were 0.0096 L/h (RSE = 11%)) and 2.72 L (16%), respectively. The coefficients of variation for inter-individual variability (IIV) for CL and Vd were 29.4 % (26%) and 45.3 % (17%), respectively. A proportional error with a coefficient of variation of 4.41% (32%) provided the best description of the residual variability.

The maturation function could accurately describe the observed concentrations before ECMO start, as indicated by the lack of bias in GOF plots. During ECMO, CL was found to be increased and this increase was time-dependent. Over the 12-day period observed in this study, the relationship between CL and time since

the start of ECMO was best described by a linear function. Furthermore, phenobarbital CL reduced after decannulation compared to CL during ECMO, with an initial decrease, followed by an increase according to the maturation fucntion. Changes in Vd during ECMO could not be identified, possibly due to sparse data collection shortly after the start of ECMO, that would prevent the estimation of changes in this timeframe. The predictive properties of other tested variables were not statistically significant.

The distribution of the NPDEs in this dataset had a mean of -0.0799 and variance = 1.034. Neither of these values were significantly different from the expected values of 0 and 1, respectively. No bias could be observed in NPDE over time and versus the predicted concentration in plots stratified for before, during and after ECMO.

Conclusions: Continuously decreasing phenobarbital exposure in patients during ECMO treatment, resulting from the time-dependent increases in phenobarbital CL, may increase the risk of therapeutic failure over time. Hence, these results strongly indicate a need for regular and repeated TDM measurements for phenobarbital in neonates on ECMO.

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II-48: *Robin Michelet* A workflow for application of the general pharmacodynamic interaction model on high-throughput combinatorial data in order to identify, quantify and characterise drug combinations that can overcome multi-drug-resistance

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Background:

Antimicrobial resistance is one of the key challenges in the current global healthcare system [1]. As new antibiotics are lacking, combinations of existing drugs can help to treat multi-drug-resistant (MDR) bacterial infections. In order to detect synergistic combinations between antibiotics, human-use (non-antibiotic) drugs and other compounds (e.g. food additives), we previously combined ~3000 compound pairs and assessed their interaction in three Gram-negative species [2]. In the current work, a robust workflow to quantitatively characterise these interactions using the General PharmacoDynamic Interaction (GPDI) model [3] is presented. Using this approach, not only the magnitude but also directionality of an interaction between two or more compounds can be elucidated, possibly identifying interesting combinations for further non-/clinical development.

Methods:

A model selection & evaluation workflow was established using R (v. 3.4.4) and RStudio (v. 1.1.447). In step 1, linear, power and E_{MAX}-type models were fitted to single concentration-effect data, after which their parameters were fixed and all possible interaction parameters for all possible model combinations were estimated (113 interaction model types). Parameter estimation was performed by ELS regression using the Nelder-Mead and BFGS algorithm. Parameter precision was assessed using the diagonal of the Fisher Information Matrix (calculated from the Hessian outputted by the last successful algorithm). For the best model combination, all parameters were estimated again and the model next evaluated. Model selection was based on the precision of parameter estimates (discarding models with parameter imprecision >50% RSE) and the AIC (penalty of 2 points per parameter). Model evaluation was performed by comparing the model to the experimental data, for which >15% deviation from observed effect, or no overlap with the 95% confidence interval of the t-distribution estimated from the data, were considered significant deviations. Per combination, the best model was then used to simulate a response surface, which was compared to the Bliss Independence surface [4], in order to visualise the interaction. The parameters of the GPDI model were then used to assess the magnitude and direction of the interaction in order to inform hypotheses about the interaction mechanism and select interesting candidates for further development.

Results:

A dataset [2] consisting of extended-dose data (8x8 checkerboard experiments, 242 drug combinations in susceptible Gram negative strains and 7 synergistic combinations in a set of 6 *E.coli* and *K. pneumoniae* MDR clinical isolates) was first analysed using the developed workflow. In general, the GPDI model described the experimental data well and identified similar synergies and antagonisms as conventional response-surface analyses suggested. Furthermore, using the estimated interaction parameters, the nature of the interactions and putative perpetrator and victim drugs could be identified. Indeed, 28.3% of the observed interactions were mono-directional synergistic, 24.1% mono-directional antagonistic, 13.6% bi-directional synergistic, 2.2% bi-directional antagonistic and 30.4% asymmetric. In the clinical isolates, strong synergies between colistin and macrolide drugs (strong decrease of macrolide EC_{50} in function of colistin concentration) and between colistin and loperamide (strong decrease of loperamide EC_{50} or increase in E_{max} in function of colistin concentration, depending on the strain) were characterised. Weaker synergies were quantified between doxycycline and procaine (bi-directional effect), and vanillin and spectinomycin (only for *E. coli*).

Conclusions:

A robust workflow was set up to apply the GPDI model to high-throughput data and select the most fitting model structure per combination. In this way, promising combination candidates could be identified and their interaction quantitatively described. This workflow can now be applied on the larger dataset consisting of 3000 combinations to identify the complete set of promising candidates. These combinations can be further investigated and pushed towards pre-clinical testing and eventual clinical application. Furthermore, clustering approaches could be applied to the generated model repository in order to group interactions according to their intensity and directionality to inform mechanistic hypothesis generation.

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II-49: *Iris Minichmayr* Impact of genetic variants of UGT1A1 on myelosuppression during irinotecan therapy

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Objectives: The topoisomerase inhibitor irinotecan (CPT-11) is a valuable treatment option primarily for colorectal cancer [1]. It is bioactivated by hydrolysis into its more potent metabolite SN-38, which is further metabolised by uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1) to the inactive compound SN-38-glucuronide (SN-38-G). Common adverse reactions associated with irinotecan therapy include diarrhoea, leukopenia and neutropenia. The risk of these toxicities increases with genetic variants associated with reduced UGT enzyme activity, particularly in patients who are homozygous for the UGT1A1*28 allele. To avoid complications from neutropenia, a reduction of the initial dose by 30% if greater than 250 mg/m^2 has been recommended for *28 homozygotes [2]. The objective of this analysis was to integrate several model sources to enable predictions of the pharmacokinetics (PK) of irinotecan and its metabolites as well as of myelosuppression, with the ultimate goal to illustrate the impact of genetic variants of UGT1A1 on neutropenia following treatment with conventional and pharmacogenomics (PGx)-based dosing of irinotecan.

Methods: A multicompartmental PK model [3] was used to predict plasma concentrations of CPT-11 (number of individuals n_{ID}=109), SN-38 (n_{ID}=109) and SN-38-G (n_{ID}=83) in patients with solid tumours. The model was extended with information describing the influence of the UGT1A1 genotype on the clearance of SN-38 (35.7% reduction in poor metabolisers) [4]. Furthermore, body surface area (BSA) was included as a covariate on the distribution and elimination parameters of all three entities. SN-38-induced myelosuppression was described based on a semi-mechanistic PK/pharmacodynamic (PD) model [5] and parameters were estimated for neutropenia driven by SN-38 (n_{ID}=20). Stochastic simulations (n=100) were performed based on a population (n=200) spanning BSA values of 1.45-2.35 m^2 to illustrate the potential impact of UGT1A1 genotype (wildtype versus UGT1A1*28) and dosing (350 mg/m^2 versus 245 mg/m^2 over 90 minutes) on myelosuppression. For this purpose, the occurrence of grade 4 neutropenia according to the National Cancer Institute-Common Toxicity Criteria (absolute neutrophil counts ANC<0.5 · 10^9 cells/L) was assessed during a period of 25 days (assuming 1 measurement of neutrophils/day). Population PK modelling and simulations were executed by PsN version 4.8.9 (https://uupharmacometrics.github.io/PsN/) using NONMEM7.3 [6, 7]. Statistical and graphical analyses were conducted using R 3.4.3 (CRAN.R-project.org).

Results: The semi-mechanistic PK/PD model adequately predicted neutropenia driven by SN-38. The drug effect on neutrophils was modelled using a linear function (slope · conc; slope=26.8 μM^{-1}). System-related parameters were in the range of previously published values (neutrophil baseline: 5.58 · 10^9 cells/L, mean transit time: 92.8 h) [5]. Simulations suggested a marked effect of patients' genotype on the occurrence of grade 4 neutropenia: Following a single dose of 350 mg/m^2 irinotecan, 52.0% (median) of individuals with wildtype-genotype displayed grade 4 neutropenia (95% prediction interval PI_{95}=42.0-61.6%); the corresponding proportion in individuals with UGT1A1*28 genotype was 67.0% (PI_{95}=59.5-76.5%). Given a dose reduced by 30% (245 mg/m^2), a markedly lower proportion of individuals with UGT1A1*28 genotype displayed grade 4 neutropenia (median 48.5%; PI_{95}=41.0-60.5%).

Conclusions:

Simulations with a population pharmacokinetic model describing the PK of irinotecan and its metabolites as well as myelosuppression during irinotecan therapy suggested that genetic variants associated with reduced UGT1A1 enzyme activity increase the risk of severe neutropenia in agreement with clinical observations. The model will be extended to include also the risk of diarrhoea. Furthermore, the model may serve to inform the design of future clinical trials investigating the benefit of PGx-based dosing to improve the safety and efficacy of irinotecan therapy, particularly in patients with aberrant genotypes.

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II-50: *Jonathan Mochel* A Physiologically-Based Pharmacokinetic (PBPK) Model for the Prediction of Levodopa (L-dopa) Disposition in Plasma and Various Brain Compartments Across Species

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Objectives:

Levodopa, also known as L-dopa or L-3,4-dihydroxyphenylalanine, is the current standard of care for the treatment of Parkinson's disease (PD) [1]. Symptoms of PD are associated with the loss of dopaminergic neurons in the central nervous system (CNS). Unlike dopamine (DA), L-dopa can readily cross the blood-brain-barrier (BBB) and be converted to DA by decarboxylases. However, prediction of target site concentrations for L-dopa is complex, and direct measurements of human brain concentrations are highly restricted for ethical reasons. Therefore, alternative methods that can robustly predict human brain concentrations of L-dopa based on *in silico* approaches are critically needed.The objective of this study was to develop a translational CNS PBPK model to enable predictions of L-dopa disposition in the brain across species.

Methods:

In this study, we developed a PBPK model of L-dopa disposition kinetics in rats and dogs using the generic PBPK model structure from [2]. The model combined a plasma PK and a CNS PBPK module consisting of brain microvessels (MV), brain extracellular fluid (ECF), intracellular fluid (ICF), and multiple cerebrospinal fluid compartments. This model also considered transcellular and paracellular passive diffusion as well as active transport to account for drug transport across the BBB and the blood-cerebrospinal fluid barrier (BCSFB). Literature values were used for system-specific parameters ofrats [2,3] and dogs [4] for all relevant CNS compartments [2,3]. Missing parameter values in dogs were estimated using linear interpolation of brain weight for scaling. For drug-specific parameters , the BBB transmembrane permeability was evaluated using the computed aqueous diffusivity coefficient of L-dopa. Asymmetric transport factors (AF, at the BBB and BCSFB with influx and/or efflux, [2]) were estimated using the fraction of unbound drug concentrations based on the plasma and brain ECF profiles for rats [5]. The same dataset [5] was also used to estimate the L-dopa binding factor value (BF, [2]) by fitting a NLME model in Monolix 2018 R2. L-dopa levels in plasma were used as input to the CNS PBPK model. Parameter estimates for the plasma module were estimated from literature data from rats [6,7] and dogs [8,9] using the SAEM algorithm implemented in Monolix 2018 R2.

Results:

A 2-compartment disposition model with 1^{st}-order elimination was found to best describe the disposition kinetics of L-dopa in plasma in rats and dogs. Structural identifiability of the model parameters was further confirmed using sensitivity analyses, the estimated correlation of the random effects (< 0.10) and the accurate precision of the final parameters (RSE < 30%). For the CNS PBPK module, the simulated time-course of L-dopa concentrations in the brain ECF was compared to available literature data [6], using

estimate of the symmetric mean absolute percentage error (SMAPE) for quantification. Results from our simulations (SMAPE = 24%) confirmed that the CNS PBPK model could predict L-dopa concentration-time profiles in the ECF with minimal prediction error.

Conclusions:

These preliminary data are encouraging as they support the ability of the CNS PBPK model to predict L-dopa disposition in the brain ECF in preclinical species. Additional efforts are warranted to further demonstrate the performances of the model in predicting L-dopa distribution in other compartments (*in vivo* data from dogs are pending). This contribution will be significant as it is expected to provide a mechanistic mathematical platform for modeling the transport, distribution and effect of L-dopa in the CNS.

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II-51: *Daniel Moj* Biotest's Pentaglobin® in adults and neonates (term and preterm) – A PBPK approach

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Introduction: Pentaglobin® is a polyclonal intravenous immunoglobulin preparation consisting of 12% immunoglobulin M (IgM), 12% immunoglobulin A (IgA), and 76% immunoglobulin G (IgG) that is applied (i) as adjuvant therapy to the treatment of severe bacterial infections and (ii) as immunoglobulin substitution for immunosuppressed patients and during severe secondary antibody deficiency syndrome. So far, no physiologically-based pharmacokinetic model of Pentaglobin® has been developed to virtually assess its pharmacokinetics (PK) following single and multiple doses of Pentaglobin® in adults and neonates (term and preterm).

Objectives: 1. Describe the maturation of IgM, IgA, and IgG for term and preterm neonates.
2. Develop PBPK models to describe and predict the concentration-time profiles of IgM, IgA, and IgG in adults following single and multiple Pentaglobin® doses.
3. Use the maturation data and the developed PBPK models to predict the concentration-time profiles of IgM, IgA, and IgG in term and preterm neonates following various Pentaglobin® dosing schedules.
4. Employ the maturation data and the final PBPK models to assess the C_{max} and C_{trough} values for IgM, IgA, and IgG following daily doses of 5 mL Pentaglobin®/kg body weight (bw)/day for adults and neonates (term and preterm).

Methods: Maturation data for IgM, IgA, and IgG was gathered from various sources in the literature [e.g. 1-3]. Data for the development of the adult PBPK models for IgM, IgA, and IgG comprised Phase I (age = 32.0 ± 7.13 years, n = 21) and Phase II (age = 70.8 ± 12.0 years, n = 11) with 1492 concentration-time points [4,5]. The data for the evaluation of the predicted neonate concentration curves (no IgA data available) consisted of clinical trial data from 2 internal (n = 11 - 22) and 3 published Pentaglobin® studies (n = 34, gestational age = 28.6 – 31.8 weeks) [6,7]. Adult PBPK models were developed in a step-wise manner in which the available datasets were split into an internal (development) and external (qualification) dataset. IgM, IgA, and IgG maturations were described using Berkeley Madonna 8.3.18. PK-Sim and MoBi (Open Systems Pharmacology Suite 7.3.0) and R 3.5.2 were used for PBPK modelling and simulation. GetData Graph Digitizer version 2.26.0.20 was used to digitize data when necessary.

Results: The maturations of IgM and IgA were best described using a Michaelis-Menten model with baseline parameter, while IgG was best described with an additional linear model (first 3 months after birth). At the date of birth, the typical term (preterm) neonate shows IgM, IgA, and IgG baseline concentrations of 0.13 (0.06), 9.7 (3.6) and 0.04 (0.005) g/L, respectively. The final IgM, IgA, and IgG models described the adult PK data very well and predicted the IgM and IgG PK in neonates successfully with a mean C_{max} prediction error ($C_{max,pred}/C_{max,obs}$) of 11%. Following multiple doses of 5 mL Pentaglobin®/kg bw/day, model-based simulations suggest a 18% higher baseline-corrected C_{max} in neonates in comparison to adults for IgM and IgA, whereas the baseline-corrected IgG C_{max} is 31% higher in the neonates. The results for the baseline-corrected C_{trough} are comparable.

Conclusions: When developing IgM-, IgA-, or IgG-based drugs for neonates, the maturations of these immunoglobulins must be taken into consideration. The developed PBPK models were able to describe and predict the PK of IgM, IgA, and IgG in adults and neonates, however, in order to evaluate the correctness of

the subsequent model-based simulations, more PK data of IgM, IgA, and IgG in neonates is needed. The developed PBPK models my serve as future tools to support the development of IgM-, IgA-, and IgG-based drugs.

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II-52: *Camille Riff* Population Pharmacokinetics of Rituximab in patients with Chronic Lymphocytic Leukemia

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Introduction: Rituximab is a chimeric human/mouse immunoglobulin G1 (IgG1) monoclonal antibody that binds specifically to the CD20 antigen present on the surface of normal and neoplastic B-lymphocytes and results in B-cell depletion. The pharmacokinetics (PK) of rituximab is characterized by a large variability, which could affect the clinical response to rituximab. In elderly patients, the influence of target-antigen burden (lymphocyte turnover) is expected to be different compared to younger patients [1]. A randomized, open-label, multicenter phase 3 trial was conducted to evaluate rituximab maintenance following an induction with rituximab in elderly patients with chronic lymphocytic leukemia (CLL). Binet staging system was used to classify CLL and to guide the initiation of treatment. This study enrolled treatment-naïve and fit patients aged 65 years or older with an active Binet stage B or C chronic lymphocytic leukemia requiring treatment.

Objectives: The objective of this analysis was to develop a population pharmacokinetic (PopPK) model for rituximab administered in elderly patients with CLL and to assess relationships between Pop PK parameters and potential individual factors of variability.

Methods: Included patients (CLL 2007 SA) [2] received induction treatment consisting of four monthly courses of full FCR (fludarabine, cyclophosphamide, rituximab) with two additional rituximab doses on day 14 of cycles 1 and 2. Rituximab was administered at a dose of 375 mg/m^2 intravenously on day 0 of cycle 1 and subsequently at 500 mg/m^2. Through and peak rituximab concentrations were determined before and after each rituximab infusion. Additional pharmacokinetic samples were collected one week after the first infusion and at the end of the induction phase during response assessment. The potential covariates collected included demographics characteristics (weight, age, sex, body mass index and body surface area), biological factors (baseline serum albumin concentration and lymphocyte count), and Binet stage. The population pharmacokinetic model was implemented using Monolix software version 2018R2 (Lixoft®, Antony, France).

Results: A total of 591 rituximab concentrations from 69 patients (25 women, age ranging from 64 to 86 years, weight from 39 to 121 kg) were available. The semi-mechanistic model including two compartments with linear and nonlinear target-mediated elimination. A significant correlation (r = 0.81) was found between linear clearance and the central volume of distribution. Age significantly influenced the central and the peripheral volume of distribution while Binet stage significantly influenced the production rate constant of target antigen. Lymphocyte count had no influence on rituximab PK. The mean PK parameter estimates (interindividual standard deviation) were linear clearance CL = 0.32 L/d (80.9%) central volume of distribution V_1 = 5.41 L (57.5%) intercompartment clearance Q = 1.03 L/d, peripheral volume of distribution V_2 = 7.73 L (70.8%), zero-order production rate constant of target antigen kin = 0.001 nmol/d (50.9%), first-order rate constant of rituximab-independent death latent target antigen kout = 1.60 x 10^{-4} d^{-1},mean maturation time MMT = 19.7 d and rituximab target-mediated elimination rate constant kdeg = 6.70 $nmol^{-1}.d^{-1}$(89.9%), respectively.

Conclusions and perspectives: A popPK model was developed and validated for rituximab in elderly patients with chronic lymphocytic leukemia. This is the first description of the rituximab PK in this population showing the nonlinear elimination of rituximab. The next step of this study will be to quantify the impact of baseline lymphocyte counts on concentration-response relationship, and prognosis in elderly patients with CLL treated with standard doses of rituximab, and to propose an optimize regimen for rituximab treatment in this population.

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II-53: *Anna Mueller-Schoell* Model-informed precision dosing for tamoxifen therapy in breast cancer patients: Comparison of different target attainment metrics

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Objectives: In 2011, Madlensky et al. [1] established an efficacy threshold for endoxifen, (ENDX), the active metabolite of tamoxifen (TAM). Minimum concentrations at steady state ($C_{SS,min\ ENDX}$) >5.97 ng/mL were associated with a 26% lower breast cancer (BC) recurrence rate. Six years later, de Vries Schultink et al. [2] developed the Antiestrogenic Activity Score (AAS), considering TAM, its three major metabolites (including ENDX) and their respective antiestrogenic potencies. Based on the same dataset, a relation between AAS ≥1798 and a 31% lower BC recurrence rate compared to AAS <1798 was identified. Still, current therapeutic drug monitoring approaches use the ENDX threshold as target attainment (TA) metric [3]. The presented simulation study aimed to investigate the impact of using the AAS vs. the ENDX threshold as TA metric on dose selection in model-informed precision dosing. Individual TAM doses could range between 5 and 120 mg (all once-daily (q.d.)), considering available tablet formulations and maximum reported doses in TAM dose escalation trials [4]. Differences in dose selection were investigated for the population as whole and for genotype-predicted CYP2D6 normal, intermediate and poor metabolisers (gNM, gIM, gPM), respectively. For the genotype-to-phenotype classification based on patients' CYP2D6 activity scores (AS), we used the most recent Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and tamoxifen therapy (gNM: AS ≥1.5, gIM: AS=0.5-1.0, gPM: AS=0) [5].

Methods: A previously developed NLME-PBPK model of TAM and its three major metabolites [6] was used to simulate TAM treatment in 10.000 virtual BC patients. Covariates (age and CYP2D6 AS) in the virtual population were generated to represent the respective frequencies observed in a pooled database of 6 clinical studies [7]. In the first simulation step, virtual patients received CYP2D6 phenotype-adjusted initial doses (gNM: 20 mg, gIM: 40 mg, gPM: 60 mg; all q.d.). In step 2, virtual minimum concentrations of TAM and its three major metabolites were measured after 2, 4 and 6 weeks of treatment. $C_{SS,min\ ENDX}$ and AAS at 6 months were predicted for each virtual patient for the full dose range by Bayesian Forecasting (BF), considering patient covariates, prior knowledge (model parameters) and virtually measured concentrations of (1) TAM and ENDX in the ENDX-guided dosing group and (2) TAM and its three major metabolites in the AAS-guided dosing group. The lowest respective doses required for TA according to (1) the ENDX ($C_{SS,min\ ENDX}$ >5.97 ng/mL) or (2) the AAS (AAS>1798) threshold were selected as adjusted individual doses for each patient. Finally, the predictive performance of BF using either TA metric was assessed by calculating "true" TA at 6 months according to both (1) and (2), using the respective doses selected in step 2 and PK parameters chosen in step 1. Covariates and PK parameters of patients with different doses selected in (1) and (2) were further investigated. Modelling and simulation were performed using NONMEM (v.7.3), pre- and post-processing was conducted in R (v.3.4.4).

Results: In 76% of patients, the same doses were selected with either TA metric used, while in 24% of patients, different doses were selected (23.2% of gNM, 19.1% of gIM and 61.7% of gPM). For 21.9% of all gNM, a higher dose in the AAS vs. the ENDX group was selected, for 9.94% of all gIM, a higher dose, and for 9.21% of all gIM, a lower dose. For 61.5% of all PM, a lower dose in the AAS vs. the ENDX group was

selected. Among patients with different dose selections, 98.9% of gNM, 92.2% of gIM and 88.3% of gPM reached at least one target in the AAS group, while 77.2% of gNM, 85.3% of gIM and 100% of gPM reached at least one target in the ENDX group. gNM with high apparent formation to and clearance of the ENDX-precursor metabolite N-desmethyltamoxifen (NDMT) were at highest risk for selection of a too low dose in ENDX-guided dosing.

Conclusions: In this simulation study, more than three out of four patients received the same dose regardless of the TA metric used. In patients with different dose selections, dose selection according to the AAS target seemed preferable for gNM and gIM, while dose selection according to the ENDX target was better for gPM. A vulnerable subpopulation with high apparent NDMT formation capacity and eliminating clearance was discovered and the clinical relevance of this finding should be further investigated.

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II-54: *Flora Musuamba Tshinanu* Dose optimization based on control and system theory: Case of Meropenem

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Objectives: Thanks to mathematical modeling, clinical pharmacology is an interesting and promising field of application of control and system theory [1]. Examples reported in the literature include the automated anesthesia [1,2] and the artificial pancreas [3]. They all involve closed-loop control strategies based on a control system which continually adjusts the drug infusion rate. This contribution focuses on treatments given by constant intravenous infusion at regular intervals and aims to provide guidelines (decision-making aid) for drug dosing based on relevant patient's characteristics (covariates) and on any other practical condition (target exposure for efficacy, dosing interval, infusion time, price, etc.). The results were exemplified by a case study for which numerical results were reported: meropenem, an antibiotic used for treating severe sepsis (see e.g. [4,5], and [6] and references therein), for which there is currently a lack of consensus regarding the optimal dosing [5–8]. The available dosing optimization methods for this antibiotic are based on iterative Monte Carlo simulations for different dosing regimens and modes of administration (see e.g. [9,10]) and carry some limitations [1].

Methods: Two approaches (open-loop methods) are considered. The analysis presented here is intended to be general and applicable to any pharmacological system described by a linear time-invariant state-space model with a one-dimensional input corresponding to the drug administration. In the first method, the analytical expression of the output trajectories, i.e. systemic and infection-site (if these concentrations are described) concentrations, is obtained and used to provide a closed-form formula designed to compute the dosing regimen, given the selected practical conditions (target concentration, dosing interval and infusion time). The second method is a finite time horizon optimal control approach which consists in minimizing a cost function corresponding to the L2-norm of the input function and quantifying in some way the total administrated drug. The constraints of the optimal control problem are the differential equations describing the dynamic of the system, the lower bound of the (systemic or infection-site) concentration trajectory and a particular structure of the input function (rate of infusion). The rate of infusion is supposed to be constant, but not necessarily to have the same value on different intervals

Results: A system analysis of standard population pharmacokinetic models proved that such models are nonnegative and stable. A standard transfer function approach yielded the analytical expression of the concentration trajectories. Due to system stability, the concentration trajectory converges to an asymptotic equilibrium trajectory: the pharmacokinetic steady-state (or plateau). The system response exponentially converges towards this asymptotic behaviour. By solving the appropriate equations, a closed-form formula was produced to compute the dose such that ctrough (at steady-state, either in the site of infection or in the plasma) is equal to a given target concentration. Consequently, the steady-state concentration is above this lower bound. For different practical conditions (dosing interval and infusion time), the settling time was considered to be the time required for the output to reach and remain within a pre-specified error band around the desired trajectory (work in progress). Then, an optimal control approach was applied on the discretized model. The Karush-Kuhn-Tucker optimality conditions produced the discrete-time minimum principle. Numerical results confirmed in some way the previously established formula as an optimal dosing

(on the average patient). In fact, it turned out, after implementations for the studied drug (meropenem), that the dosing suggested by the Karush-Kuhn-Tucker conditions converges numerically toward the maintenance dose computed by the first method.

Conclusions: A standard input-output analysis led us to obtain the analytical expression of the concentration trajectories and the steady-state response for the exposure to a drug administrated by intermittent iv infusion. A formula was derived to compute the dose needed to maintain the steady-state concentration trajectory above a given lower bound and was confirmed by an optimal control approach. The reported drug dosing strategies were numerically implemented for meropenem and showed satisfactory robust and reliable results.

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II-55: *Tadakatsu Nakamura* A Model-Based Meta-Analysis (MBMA) of Efficacy of Different Drugs for Postmenopausal Vasomotor-Symptoms

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Objectives: Model-based meta-analysis (MBMA) allows to compare the clinical outcomes with different drugs that have not been compared directly using published aggregate data from many clinical studies. By modelling the response as a parametric function of time, MBMA allows the integration of information from trials of different durations and with different sampling time-points. The aim of this analysis was to develop a MBMA model for postmenopausal hot flush 1) to characterize the placebo and drug response, and 2) to provide a quantitative comparison of drugs which are currently developed as well as used for the treatment of vasomotor-symptoms (VMS).

Methods: Literature was searched in the public databases to extract data of clinical trials on drugs for postmenopausal VMS, including estradiol (oral estrogen, transdermal estrogen), conjugated estrogens/bazedoxifene (Duavee), paroxetine, gabapentin and neurokinin 3 receptor (NK3R) antagonists (fezolinetant, pavinetant, NT-814). Included studies were double-blind, randomized controlled trials that evaluated the efficacy in the reduction of moderate to severe hot flush frequency and set the criteria of a minimum of 7 hot flushes per day at baseline. For hot flush frequency, longitudinal MBMA was developed using a placebo and drug response (exploring Emax dose-response) models incorporating covariate effects. Simulation was performed to compare the treatment effects of the drugs included in this analysis. Model development and simulation were performed using NONMEM 7.3.

Results: Thirty three trials in 32 articles, involving 11,543 women, were included in the analysis. Our developed model indicated that the placebo and drug responses for hot flushes increased in a time-dependent manner. As a placebo run-in period is generally set to reduce the placebo response in clinical study, the effect of placebo run-in period was explored and identified as a covariate for the placebo response. The estimated placebo responses were smaller in the trials with placebo run-in period than without it (-3.7 vs -5.6 as change from baseline at 12 weeks). For the effect of estrogen (both oral and transdermal), which are current standard therapy for VMS, Emax dose-response model were implemented with a common Emax value and different ED50 values, but dose-response model was not identified for other drugs. Comparing the estimated drug effects, the change from placebo of daily hot flush frequency at 12 weeks for oral estrogen (1.0 mg), transdermal estrogen (0.050 mg), Duavee, paroxetine, gabapentin and NK3R antagonists were -3.9, -4.6, -3.3, -1.5, -3.0 and -6.3 per day, respectively, and time to achieve the decrease of 2 hot flushes per day from placebo (clinically relevant change) were within 4, 3, 4, 6, 1 and 1 weeks, respectively. Change from baseline of daily hot flush frequency were also presented in time-course plot to compare the drug effects and its response rate.

Conclusions: We performed a MBMA for the efficacy of different drugs which are under development as well as used for VMS. The developed model was found to describe adequately the time course of hot flushes reduction after administration of placebo and drugs. Our model also indicated that setting placebo run-in period in clinical trials decreased the placebo response. This is the first time to implement placebo run-in period into placebo response and characterize the Emax dose-response of estrogen for hot flush in meta analysis. This analysis provided a quantitative framework for comparison of treatment effects of VMS drugs.

II-56: *Ricardo Nalda-Molina* Evaluation of the predictive performance and the model adequacy of four population pharmacokinetic models of adalimumab in patients with inflammatory bowel disease.

Ricardo Nalda-Molina
University of Miguel Hernandez de Elche

Objectives:

To evaluate the predictive performance and adequacy of four population pharmacokinetic models (PopPK) of adalimumab in adult patients diagnosed of inflammatory bowel disease (IBD).

Material and methods:

A retrospective observational study was performed, with the following inclusion criteria: Adult patients with ulcerative colitis or Crohn's disease treated with adalimumab, with at least one trough concentracion (TC) between 2014 and 2018 were included. Four different pharmacokinetic models were evaluated: FDA, 2008 (Mod-A)[1], Ternant et al, 2015 (Mod-B)[2], Sharma et al, 2015 (Mod-C)[3] and Berends et al, 2018 (Mod-D)[4]. The models were implemented in NONMEM® v7.3.

The individual and population predictions of adalimumab concentrations were estimated from the four PopPK models, by calculating the empirical bayesian of estimates (EBEs). Two different data sets were created from the original dataset to evaluate the model adequacy and predictive performance; 1) DATASET-1: To evaluate the model adequacy, all the patients and TC were included, and their population predictions were compared with the observed TC; 2) DATASET-2: To assess the predictive performance, only the patients with two or more TC were included. Only the first TC of these patients were used to estimate the EBE, and the individual prediction that were left out were compared with the observed TCs.

To validate these models, bias and precision of estimated concentrations were calculated as the mean predictive error (MPE) and the mean square predictive error (MSPE) in the population, respectively.

Results:

In the DATASET-1, 171 patients and 245 TCs were included. The mean values (95% CI) of weight, basal albumin and TC were: 69.5 kg (43.5-100), 3.82 g/dL (2.53 : 4.70) and 5.70 mg/L (0.1 : 13.5), respectively. In the DATASET-2, 55 patients and 74 TCs were included. The mean values (95% CI) of weight, basal albumin and TC were 68.9 kg (49.5 : 89.6), 3.77 g/dL (2.24 : 4.74) and 6.93 mg/L (0.505 : 17.74), respectively. 5.85% of patients in DATASET-1 and 3.64% in DATASET-2 developed antibodies anti-adalimumab.

The bias (95% CI) of the predictions for the model adequacy and predictive performance were: Mod-A: -5.26 (-5.95 : -4.57) and -0.906 (-1.99 : 0.175); Mod-B: -2.88 (-3.47 : -2.29) and -0.666 (-1.71 : 0.376); Mod-C: -3.71 (-4.34 : -3.01) and -2.84 (-3.95 : -1.72); Mod-D: -3.06 (-3.66 : -2.46) and -1.77 (-2.89 : -0.643), respectively.

The precision (95% CI) of the predictions for the model adequacy and predictive performance were: Mod-A: 7.61 (6.80 : 8.42) and 4.80 (2.97 : 6.63), Mod-B: 5.52 (4.88 : 6.16) and 4.59 (2.83 : 6.35), Mod-C: 6.26 (5.52 : 7.00) and 5.63 (4.22 : 7.04); Mod-D: 5.67 (4.92 : 6.41) and 5.20 (3.56 : 6.85), respectively.

Conclusions:

The evaluation of the adequacy of the four adalimumab PopPK models in IBD patients shows that all the four models overestimate adalimumab concentrations in the population with a statistic significance<0.05, although Mod-B had a better bias and precision, (i.e. closer to zero). The evaluation of the predictive performance, shows again an overestimation of the adalimumab TC, and MOD-B showed a better prediction performance of the TCs.

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II-57: *Srividya Neelakantan* Population Pharmacokinetic/Pharmacodynamic Modeling of PF-06480605, an Anti-TL1A Antibody, in Healthy Subjects and Ulcerative Colitis Patients

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Objectives: The tumor necrosis factor(TNF)-like ligand 1A(TL1A)/ Death Receptor 3 (DR3) pathway has been implicated in the regulation of pathogenic helper T lymphocyte (Th) subsets 1, 2, and 17, respectively (Th1, Th2, and Th17), T cells and in natural killer (NK) and natural killer T (NKT) cell responses. The TL1A expression on antigen presenting cells (monocytes, macrophages, dendritic cells) and DR3 expression on effector cells (ILC2, T-cells, NK and NK-T cells) is highly dependent on pro-inflammatory conditions. Significant literature data in nonclinical species and humans implicate TL1A in the pathophysiology of inflammatory bowel disease (IBD). PF-06480605 is a fully human neutralizing antibody against TL1A which is expected to neutralize the binding and subsequent signaling of TL1A to its functional receptor DR3 and is currently being developed for the treatment of IBD.

The objectives of the analysis were to characterize the pharmacokinetics (PK) and pharmacodynamics (PD, serum total sTL1A) of PF-06480605; and identify covariates of interest to explain the inter-individual variability.

Methods: The PK and PD of PF-06480605 were analyzed in two studies: a Phase 1, randomized, double-blind, placebo-controlled, single and multiple dose escalating study in healthy subjects as well as a Phase 2a multicenter, single arm (non-placebo controlled), two-stage study in subjects with moderate to severe Ulcerative Colitis (UC). Both intravenous (IV) and subcutaneous (SC) routes of administration were tested in the Phase 1 study. The Phase 2a study evaluated PF-06480605 500 mg IV administered every 2 weeks for a total of 7 doses. Serum PF-06480605 concentrations and the serum total TL1A data were characterized jointly using a target mediated drug disposition model with Michaelis-Menten (MM) approximation. Covariate analyses were performed to identify intrinsic and extrinsic factors that explain the inter-individual variability in the PK of PF-06480605. Body weight, age, baseline albumin, and gender were explored as potentially influential covariates on the linear clearance (CL) of PF-06480605. Body weight was tested as a covariate to explain the inter-individual variability in the central volume of distribution (V1). Goodness of fit plots, visual predictive check (VPC) and nonparametric bootstrap were performed on the base and final models to evaluate the model performance.

Results: The PK of PF-06480605 after single and multiple IV or SC dosing in healthy subjects and UC patients were adequately described by a 2-compartment model with additional target-mediated clearance with MM approximation. The population PK/PD analysis indicated that PF-06480605 displayed the attributes of a typical IgG monoclonal antibody with a long terminal half-life of ~20 days. The CL was slow with an estimate of 0.00754 L/hr, while the inter-compartmental clearance was 0.00521 L/day. The central and peripheral volumes of distribution were 3.03 L and 1.64 L, respectively.

Body weight was identified as an important covariate on the CL of PF-06480605 with a power exponent of about 0.7.

The results from the VPCs as well as the goodness of fit plots indicate that the population PK/PD model adequately described both the PF-06480605 and total sTL1A concentrations.

Conclusions: The target mediated drug disposition model with MM approximation adequately described the serum PK and total sTL1A following PF-06480605 administration. Covariates were identified that explained the inter-individual variability in PK.

II-58: *Ida Netterberg* The tumor time-course predicts the overall survival in non-small cell lung cancer patients treated with atezolizumab in a large Phase I study: an evaluation of using different censoring times

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Objectives: Atezolizumab (an immunooncology checkpoint inhibitor) was administered to 88 non-small cell lung cancer (NSCLC) patients in the phase I, dose-escalation study PCD4989g [1]. The patients received doses of 1-20 mg/kg or a fixed dose of 1200 mg. A large number of biomarkers were studied in this study, which opened up opportunities to explore biomarker relationships with tumor size (TS) and overall survival (OS). TS together with atezolizumab concentrations and biomarker concentrations (e.g. Interleukin 18, IL-18, and interferon-inducible T-cell alpha, I-TAC) were measured longitudinally. Based on these data we previously developed a pharmacokinetic (PK)-TS-IL-18 model, where the drug area under the curve (AUC) and model-predicted relative change from IL-18 baseline at day 21 ($RCFB_{IL\text{-}18,d21}$) were identified as predictors of TS changes [2]. A large $RCFB_{IL\text{-}18,d21}$ predicted a prolonged suppression of tumor growth, which is in line with a slower apparent growth rate and longer survival [3]. The aim of this study was to evaluate the potential of early biomarker effects, i.e. IL-18 and I-TAC, together with other model-derived metrics (i.e. PK and TS related) and baseline covariates, as predictors of OS in the same population. Since patients may be exposed to other anticancer drug treatment after atezolizumab treatment stopped, it was also investigated what impact the duration of the follow-up time has on the inclusion of predictors.

Methods: Five different distributions were evaluated to describe the baseline hazard for three different censoring times, i.e. (i) all available data (AAD, 69 deaths), (ii) censored 2 years after start of treatment (C2YASOT, 54 deaths) and (iii) censored 5 months after last dose (C5MALD, 28 deaths), using time-to-event modelling. The median time to death in the full data set (AAD) was 1.4 years and the follow-up times ranged from 16 days to 5.2 years (AAD), 2 years (C2YASOT) and 4.7 years (C5MALD). Baseline covariates (n=32) were evaluated in a stepwise covariate modelling (SCM) procedure for each of the three censoring times. Thereafter, PK, biomarker and TS model-derived variables were evaluated on top of the baseline covariates. Lastly, all added covariates were excluded one by one in a backward deletion step to arrive at a final model. A p-value of 0.05 was used for statistical significance in both forward and backward steps. The analysis was performed by joining the OS model with the PK-TS-IL18 model in a population PK parameter and data approach [4] in NONMEM 7.4.

Results: The baseline hazard functions were best described by the exponential (AAD and C2YASOT) and Gompertz (C5MALD) distributions. A summary of the included covariates at the different steps in the analysis is presented below. None of the evaluated IL-18 or I-TAC variables, or atezolizumab AUC, added predictive value on top of the baseline covariates, while all TS related variables resulted in p-values

AAD[1]	C2YASOT[1]	C5MALD[1]	AAD[2]	C2YASOT[2]	C5MALD[2]	AAD[3]	C2YASOT[3]	C5MALD[3]
LYM	NLR	NLR				LYM	NLR	NLR
ALP	ALP	ALP	RCFB-TS(t)	TSR6	TSR12	ALP	TSR6	ALP

PD-L1 SMK	race	RCFB-TS(t)	race
PD-L1	SMK		AST
	AST		TSR12

Included covariates: [1]Baseline (SCM), [2]Model-derived and [3]Final model
LYM: lymphocyte count; ALP: alkaline phosphatase; PD-L1: programmed death-ligand 1 expression; NLR: neutrophil/lymphocyte ratio; SMK: smoking status; RCFB-TS(t): relative change from baseline tumor size time course; tumor size ratio week 6; TSR12: tumor size ratio week 12

Conclusions: Relationships between the tumor time-course and OS were established based on early Phase I study data in a large cohort of patients with NSCLC, regardless of censoring time. However, although IL-18 was used as a predictor of tumor size changes, the biomarker was not directly a predictor of OS. The included covariates (both baseline and model-derived) varied slightly dependent on the censoring time, but those selected were in general correlated.

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II-59: *Bernard Ngara* A Semi-mechanistic population pharmacokinetic model quantifying hair concentrations of ritonavir-boosted atazanavir. A study of HIV infected Zimbabweans adolescents.

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Introduction: An estimated 36.9 million people were living with Human Immunodeficiency Virus (HIV) worldwide in 2017. Of these approximately 3.0 million were children and adolescents under 20 years of age [1]. Zimbabwe has a prevalence of 13.3%, with 1.3 million people living with HIV including, 77,000 children and adolescents [2]. Adolescence experience higher levels of non-adherence to treatment of HIV [3]. Measuring drug concentration in hair promises to be reliable method for assessing exposure to antiretroviral drugs due to accumulation from plasma [4]. Modelling and simulation approach are necessary to explore the usefulness of quantifying drug concentrations in hair for the benefit of measuring long term adherence. Drug plasma measurements cannot reliably be used for adherence monitoring especially in settings where patients took the drugs only towards clinic visits.

Objectives:

- To develop a pharmacokinetic model based on drug concentrations quantified in the hair
- To identify population characteristics associated with variability in ritonavir-boosted concentrations in hair

Materials and methods: Data used in model development and validation was obtained from a study conducted in Zimbabwean adolescents on HIV treatment for at least one month[3]. Participants were randomised to the intervention or control study arms. Hair samples and other data variables were collected at enrolment and three months follow-up. The structural model was characterised using a two-compartmental model structure, which included an output compartment to predict measurements observed from the hair compartment. A generalised nonlinear model was fit using ADVAN13 in NONMEM 7.3 [5]. Previously published models describing population pharmacokinetics of as atazanavir or ritonavir in plasma were utilised, and parameter estimates were fixed to literature values [4], [5]. Then the fraction of the drug that accumulated in hair was estimated while the hair volume of distribution was fixed to unit for both drugs. Stepwise covariate modelling strategy was used for covariate selection in PsN [8]. Model assessment was done using goodness of fit plots in Xpose4 [8].

Results: Our findings showed that there is 16% and 18% of the respective atazanavir and ritonavir concentrations in hair relative to steady-state trough plasma concentrations. At follow-up event, we estimated an increase of 30% and 42% in concentrations of the respective atazanavir and ritonavir concentrations that accumulated in hair compared with accumulation at enrolment. A unit increase in self-reported adherence measured was associated with a 2% increase for both atazanavir and ritonavir concentrations in hair. Thinner participants had 54% higher hair concentrations while overweight had 21% lower compared to normal weight participants. Adolescents receiving care from fellow siblings had atazanavir concentrations of at least 54% less compared to receiving care from mature guardians. Participants in the control arm and those in earlier stages of disease progression had volume of distribution for atazanavir concentrations 53% higher and for ritonavir concentrations 37% less compared to their counterparts.

Conclusion: The work demonstrated methods for hair quantitative pharmacology, to compliment efforts working towards establishing point of care methods based on quantifying drug in hair. Hair collection is easy, analysis is cheap and samples can be transported without biohazardous precautions and cold chain. Drug concentrations in hair provide information on drug exposure and adherence, predicts virologic treatment outcome, and segmental analysis tells us drug exposure at different time points. Most important determinants of increased concentrations in hair were monitoring at follow up event, body weight and care. Measuring ART levels in hair promises to be more accurate and feasibly accomplished. It is crucial to perform follow-up work which involves establishing the relationship between hair pharmacokinetic parameters and a measure of treatment response such as viral loads. Additionally, comparing the predictive accuracy for exposure-response models when exposure is based on either plasma or hair drug concentrations is also to check.

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II-60: *Laurent Nguyen* Pharmacokinetic time-dependency and covariates modelling of Isatuximab monoclonal antibody in multiple myeloma patients: analysis from pooled phase I/II & phase III studies

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Introduction Multiple Myeloma (MM) is a malignant disease characterized by clonal proliferation of plasma cells in the bone marrow and the production of excessive amounts of abnormal proteins, the so-called Myeloma proteins (M-prot). The M-prot are usually monoclonal immunoglobulins of type G (IgG) and less frequently other Ig types or free-light chains. Isatuximab (ISA) is a humanized monoclonal antibody of IgG1 isotype that selectively targets the CD38 antigen overexpressed in malignant plasma cells [1]. A full clinical development program of Isatuximab as monotherapy or in combination therapy is on-going.

Objective: The aim of this work was to characterize the time-dependent PK of free ISA concentrations and to investigate the sources of PK variability from a pooled dataset of phases I/II & phase III clinical studies.

Methods: A total of 476 MM patients treated as single agent or in combination with Pomalidomide/Dexamethasone were analysed. Isatuximab was administered as intravenous infusion over various dosing regimens (QW and/or Q2W at doses ranging from 1 to 20 mg/kg). The population PK analysis was performed using SAEM algorithm for nonlinear mixed-effects model implemented in MONOLIX software (version 2018R1). Several structural PK models including linear and/or non-linear elimination pathways with different time-varying clearance functions were tested. The influence of many baseline demographic and pathophysiological covariates was investigated following univariate and multivariate analyses based on likelihood ratio test and Wald test. Qualification of the population PK model was performed using goodness-of-fit plots and visual predictive checks.

Results: ISA PK was best described by a two-compartment model with parallel linear and nonlinear (Michaelis Menten) elimination and time-varying linear clearance function. At the recommended therapeutic dose, the linear elimination pathway was the main contributor to the total clearance indicating that the target receptor was saturated.

Linear clearance was found to be related to the type of Myeloma (IgG vs non IgG), beta2-microglobulin and body weight while central volume of distribution was found to be related to body weight, gender, formulation and Race (Asian vs others). Myeloma type has the most meaningful impact: patients producing monoclonal IgG (IgG myeloma) demonstrated higher linear clearance than patients secreting other types of immunoglobulins or free-light chains (non-IgG myeloma). In average, a two-fold lower exposure at steady-state was predicted in IgG myeloma compared to non-IgG myeloma. Other covariates retained in the final model showed limited to moderate effect with a maximal variation less than ±30% at steady state exposure compared to the median value. There was no effect of age, renal or liver function impairment.

Linear clearance change over the treatment course was modeled as a sigmoidal Emax function. For a typical patient, the linear clearance decreases 50% from its initial value over the first 8 weeks of treatment. The decrease in clearance was slower in IgG myeloma compared to non-IgG myeloma patients. On average, the linear clearance reaches quasi-steady state after 4 weeks and 10 weeks of treatment in non-IgG myeloma and IgG myeloma patients, respectively.

Conclusion: The type of myeloma proteins production was the main contributor to explain ISA PK variability: faster clearance in IgG myeloma patients is likely due to the competition between high concentration of disease-produced IgG M-protein secreted by myeloma cells and Isatuximab undergoing lower FcRn recycling. Time-varying clearance of ISA was well characterized on a large set of data. As already shown with other therapeutic monoclonal antibodies in oncology [2-3], the decrease of clearance over time might be partly explained by an inflammatory status reduction associated with lowering of protein turnover due to treatment efficacy. Supporting this hypothesis, a close correlation was established between time-varying clearance and clinical response rate. Further development of the current model is warranted to include the mutual interplay between PK change over time and the clinical response measured by longitudinal PD biomarkers evolution (M-Prot).

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II-61: *Laura Zwep* Hierarchical group LASSO with random effects: identification of high-dimensional omics-drug interactions predictive of treatment response in patient-derived tumor growth data

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Objectives:

High-dimensional molecular profiling technologies ('omics') including genomics and transcriptomics are rapidly emerging as promising approach to personalize drug treatments. The development and implementation of statistical methodologies to identify predictors for treatment response using high-dimensional omics data in the context of pharmacometric models is therefore becoming increasingly important.

LASSO variable selection has been implemented for non-linear mixed effect PK-PD models [1] and for high-dimensional linear mixed effect models [2]. However, one important aspect not yet included in these models is the consideration of hierarchical interaction terms [3], which can be used to identify predictor interactions within or across omics datasets, or drug treatment-omics interactions.

In the current study we first develop a tumor growth inhibition model for a large dataset of patient-derived tumor growth data. We subsequently implement a linear mixed model extension of the hierarchical group LASSO to facilitate identification of high-dimensional predictors including interactions from a multi-omics dataset derived from tumor biopsies.

Methods:

Data: We demonstrate our methodological contribution using a large dataset of tumor growth curves derived from patient-derived xenograft (PDX) experiments. A total of 3276 tumor growth profiles was generated from 174 unique patient-derived tumors for which 54 anti-cancer drug treatments were evaluated as monotherapy or in combination [4]. For each tumor biopsy, high-dimensional transcriptomics (RNA) and copy number variations (CN) data was generated at baseline.

Tumor growth inhibition model: A nonlinear mixed effect tumor growth model was implemented in NONMEM using ordinary differential equations [5]. The model included parameters for tumor growth rate (KG), and the treatment-specific parameters for drug effect (KD) and a time-dependent resistance development term (KR).

Hierarchical group LASSO implementation: The hierarchical group LASSO technique [3] was used to assess the relation of the drug-specific outcome metrics (KD or KR) with respect to omics-predictors (RNA and/or CN), the treatments, and their two-way interactions; resulting in the simultaneous analysis of over one million effects. The penalty parameter for the LASSO was obtained using 5-fold cross-validation. To reflect compound symmetry-dependence between PDX data derived from the same tumor, we have extended the method of high-dimensional regularized interactions with a random intercept term [2], combining both techniques through iterative Expectation-Maximization.

Results:

Tumor growth inhibition model: The predictions of the tumor growth model were visually inspected. Curves with less than 5 observations and biased fits were removed by putting a threshold on the absolute error and the covariance between the individual predictions (IPRED) and the measured tumor volume. The KD and KR of 2899 PDX tumor growth curves showed a good fit and were included in the second part of the analysis.

Hierarchical group LASSO implementation: Our extended algorithm could successfully estimate a linear random intercept in the hierarchical group LASSO. We identified multiple interactions between drugs and CN variations affecting KD. For the treatments with LGH447, encorafenib and dacarbazine we identified interactions with specific CN variations. Positive interaction effects, such as the interaction between encorafenib and the gene HSF2BP show that tumors with a higher CN in HSF2BP have a better treatment response . A positive intra-tumor correlation of 0.2 was estimated, confirming that some tumors are more receptive to drug treatments than others.

Conclusions:

We implemented and applied the modelling of predictor interactions with the LASSO for extracting drug-response biomarkers and demonstrate the relevance of this method to identify interactions in high-dimensional omics datasets. The positive intratumor correlation shows the benefit of the proposed random effect extension. Our two-step approach allows many types of outcomes derived in the first step to be coupled to high-dimensional LASSO analysis in the second step. The linear mixed model extension allows modeling of dependent data such as encountered in repeated measurements. To this end, our approach is generalizable to a wide variety of applications in pharmacometrics where identification of predictors from high-dimensional datasets is required.

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II-62: *Joakim Nyberg* Implicit and efficient handling of missing covariate information using full random effects modelling

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Introduction: Covariates are observable predictors that are included in models to reduce the unexplained variability. The identification and estimation of the coefficients for covariates can be done in many different ways but a common challenge with all methods is how to handle missing covariates. There are many ways to handle missing covariates and the choice of method depends on if the data are missing at random or not [1]. A common approach within the field of population pharmacokinetics and pharmacodynamics is to use median imputation.

In the present paper we will compare the ability to handle missing covariate information of a new full model covariate estimation method - the full random effect model (FREM) approach [2]. In this method the covariates are treated as observed data points and are modelled as random effects instead of being treated as error free explanatory variables. Since missing covariates are handled as any missing dependent variable, i.e. simply just not included in the analysis, FREM implicitly handles missingness. However, the analysis is still implicitly informed by the missing covariate information through the correlation to other covariates and dependent variables as the variance-covariance matrix of all parameters and covariates are estimated for the whole population.

The FREM approach to handle missing covariate information is compared to the more traditional full fixed effects modelling (FFEM) [3] approach with median imputation. In the FFEM approach, the covariates are treated as independent, error free predictors, which are associated to the model parameters through estimated fixed effects parameters.

Objectives: To investigate missing covariate data properties with the FREM approach compared to the traditional FFEM approach with median imputation.

Methods: A previously developed model [4] (bi-exponential model with drifting baseline, parameterized with 6 parameters; BASE, BASESL, BP, HLKOFF, HLKON and PLMAX with SEX, birth length (BL) and birth weight (BW) as covariates on all parameters, to describe the height-for-age Z-score in children (0-15 years) in low and middle income countries, was used to investigate estimation properties with different missing covariate patterns. Observed covariates and realized design (~8 samples/per child) from an Indian cohort (n=6626) was used to sample individuals with complete covariate information. The FFEM model was used to simulate 1000 datasets with 1000 children in each dataset with different levels of missing covariate information at random; 0%, 10%, 30%, 70% and 90%. A FREM model and a FFEM model were used to re-estimate the model given the simulated datasets, and bias and precision were computed and visualized. Missing covariates were imputed using the median value in the FFEM models. With FREM, missing covariates were treated as missing data and handled implicitly.

Results: Overall, the FREM approach did not exhibit any bias in the estimated covariate coefficients, even with 90% missing covariate information. In contrast, median imputation using FFEM resulted in increasingly biased coefficients with increasing degree of missing information. For example, the sd normalized coefficient bias for BW on BASE with FFEM and FREM, at 90% missing covariate information, were 3.47 versus 0.01 respectively. Precision was affected (decreasing precision with increasing percentage missing)

for both for FFEM and FREM but with more pronounced imprecision with the FFEM approach. In, SEX on HLKOFF, for example, the sd of the normalized coefficient at 10% missing covariate information were 0.046 with FREM against 0.169 with FFEM.

Conclusions: The FREM approach handled the missing covariate information more efficiently than the FFEM approach with median imputation, making it a promising tool for situations with large amount of missing covariate data, for example when bridging between studies from different development phases.

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II-63: *Boram Ohk* Population pharmacokinetic analysis of tacrolimus: The role of integrative pharmacogenetics and pharmacometabolomics

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Objectives:

Tacrolimus has a narrow therapeutic range while it shows large inter-individual variability(IIV) in its pharmacokinetics(PK) [1]. Several studies have been conducted to find out the factors contributing to IIV in Tacrolimus PK, and many studies have consistently shown that the CYP3A5 polymorphism is a significant covariate in tacrolimus clearance [2-4]. Here, we aimed to deepen the understanding of the IIV of Tacrolimus PK using population pharmacokinetic modeling by taking into account the CYP3A5 polymorphism and the metabolites identified from untargeted metabolic profiles [5].

Methods:

Data were obtained from clinical trial, involving 29 healthy subjects. At screening, CYP3A5 genotype of subjects was determined by polymerase chain reaction-restriction fragment length polymorphism assay. The number of subjects with CYP3A5 *1/*1, *1/*3, and *3/*3 were 3, 11, and 15, respectively. For CYP3A5 polymorphism, subjects was divided into two groups (*1/*1 or *1/*3, *3/*3) for analysis. For untargeted metabolic analysis, urine samples were collected over a 24-hours period before pre-dose and after post-dose, respectively. All subjects received 0.075 mg/kg of oral tacrolimus as a single dose in fasting condition. Sequential blood samples (6 ml per sample) were collected just before (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, and 72 h after oral drug administration. Tacrolimus blood concentrations were determined by ultra-performance of the liquid chromatography-tandem mass spectrometry. A total of 406 tacrolimus concentrations were used to develop population PK model. The final PK model was validated using bootstrap and visual predictive check.

Results:

The mean age of a total of 29 subjects were 23.4 years old. The mean height, weight and BMI were 174.7 cm, 67.1 kg, and 21.9 kg/m2, respectively. A 2-compartment model with first-order absorption after a lag time provided the best fit from healthy subjects. Estimates of the population PK parameter were as follows; $CL_{CYP3A5*3/*3}$, 9.4 L/h; Vc, 16 L; Vp, 361 L/h; Ka, 0.53 h-1; ALAG, 0.39 h-1; Q, 26 L/h. CYP3A5*1 and hydroxycotinine were found to be significant covariates for the CL of tacrolimus(CL/F=9.4×(2.03,if CYP3A5*1)×?(hydroxycotinine/10.95)?^1.65). Median values of the parameter estimates and their 95% CIs from bootstrapping were very similar to the population mean estimates from the final model The visual predictive check (VPC) was performed and the result exhibited the acceptable predictive performance of the final model.

Conclusions:

In this study, we performed a population PK modeling to investigate that the endogenous metabolites could provide additional information to genetic data for explaining variability of the tacrolimus PK. As a result, we confirmed that CYP3A5 genotype explained a part of variability in tacrolimus CL/F, and hydroxycotinine intensity additionally account for some of variability, which was unexplained by CYP3A5 genotype. This result shows that integrating pharmacogenomics and pharmacometabolomics into PK could provide the valuable information in explaining the variability of PK parameters and predicting individual PK parameters.

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II-64: *Andrés Olivares-Morales* Bayesian pharmacokinetic (PK) and pharmacodynamic (PD) modelling of the qEEG response to a selective GABAA a5 receptor modulator in rats to inform its use as a translational biomarker

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Objectives: RO1 is a small molecule, selective $GABA_A$ α5 receptor positive allosteric modulator under development for the treatment Neuro-psychiatric disorders. Quantitative electroencephalography (qEEG) has previously shown utility as a biomarker for related compounds (Benzodiazepines). Here we investigate the pharmacokinetics (PK) and pharmacodynamics (PD) relationship of the qEEG modulation by RO1 and diazepam (DZP) in Wistar Rats using a previously published mechanism-based PK/PD model [1] in the context of a Bayesian framework.

Methods: Rats (n=12 per cohort) were surgically implanted with EEG electrodes 2 weeks prior to the compound administration. RO1 (10 mg/kg), DZP (2 mg/kg) and vehicle were administered intravenously as five-minute infusions. Blood samples were obtained from all the animals and plasma samples were analyzed for RO1 and DZP with a qualified analytical method using LC-MS/MS. In addition, EEG was recorded after drug administration over a period of 17 h in the freely moving rats during dark cycles. The PK and PD data (fronto-central wake EEG beta-band amplitude, at 20 - 30 Hz) for each treatment were analyzed in NONMEM 7.3 using a Bayesian approach. Compartmental models were fit to the PK data, whereas the PD data was fitted to a mechanism-based model previously described for other $GABA_A$ modulators by Visser et al [1]. For the Bayesian analysis, informative priors were derived from exploratory analysis of the PK (RO1 and DZP) and PD (vehicle) data. Additional priors were derived from the work of Visser et al. [1] for the drug-independent elements of the PK/PD model (i.e., parameters **A**, ***b*** and **d**). Markov chain Monte Carlo (MCMC) analysis was conducted by initiating two chains for each compound ($1x10^6$ iterations each). The first part of each chain was discarded as a burn-in phase while the second part was kept and split into two. To assess the model convergence, multi-chain diagnostics (total 4 chains) were used as described by Gelman and Rubin [2]. Visual inspection of the MCMC chains and calculation of the potential scale reduction factor (Rhat) and effective sample size (Neff) for each parameter was implemented in R version 3.4.4 (https://cran.r-project.org/)using the latest versions of the “coda” and “MCMCpack” packages.

Results: In total 11 and 9 animals had evaluable PK samples for RO1 and DZP, respectively, whereas clean EEG recordings were obtained from 9, 7 and 10 rats for RO1, DZP and vehicle, respectively. The PK of RO1 and DZP were best described by a 3-compartment model, whereas the baseline qEEG data of the vehicle was best described by a cosine function. Using the Bayesian approach and prior information, all the PK and PD parameters models converged successfully (Rhat <1.1) and the posterior distributions, means and credible intervals (CI) were within acceptable limits. In addition, the mechanism-based PK/PD model provided reliable estimates for both RO1 and DZP’s potency and efficacy (K_{pd} and $E_{pd,}$ respectively). In addition, the estimates for DZP (K_{pd} =22 [CI: 18- 27] ng/mL and E_{pd} = 0.49 [CI: 0.44 - 0.54]) were in line with the previously reported values for DZP in rats [1].

Conclusions: A PK/PD relationship for qEEG modulation by RO1 and DZP was established in rats using a Bayesian approach, allowing the fit of complex models to limited data with the use of prior information. This approach facilitated a full PK/PD modelling without the need for a two stage PK/PD assessments,

where parameters are generally fixed. Finally, this study contributes towards the establishment of qEEG as a translational biomarker for use in the potential clinical development of RO1.

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II-65: *Sean Oosterholt* Model-based optimisation of N-acetylcysteine for the treatment of paracetamol overdose

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Introduction: Paracetamol is the commonest drug taken in overdose in the United Kingdom, accounting for 48% of all poisoning admissions to hospital and an estimated 100–200 deaths per year. The recommended dosing regimen for treating acetaminophen (APAP) overdose consists of an intravenous dose of N-acetylcysteine (NAC) 150mg/kg over 60 minutes, then 50mg/kg over 4 hours and finally 100mg/kg over 16 hours. Empirical evidence suggests that this protocol is both effective and safe, but increased incidence of cases in which patients taking massive overdoses (> 30 g APAP) have had poor outcome seems to highlight the need of a stoichiometric basis for the current regimen. We critically evaluate the current nomogram and explore the correlation between APAP overdose and NAC regimens using modelling and simulation.

Methods: A population pharmacokinetic modelling approach was used to characterise the disposition of APAP and NAC. Published literature was used for the APAP model, NAC model building was based on digitized profiles of three studies published in literature. Model parameters were subsequently used to simulate both moieties according to the available clinical information (overdose time, overdose amount and NAC treatment) and explore the implications of variable exposure to NAC on treatment outcome in a cohort of 28 patients, who were admitted and treated for paracetamol overdose at a tertiary London hospital. Ethics approval was obtained for the review and analysis of the data. NONMEM version 7.3 and PsN version 4.6.0 were used for the modelling and simulation, R version 3.5.1 (2018-07-02) was used for statistical and graphical summaries.

Results: A review of the clinical records showed that eight (28.6%) patients reported opioid co-ingestion, and eleven (39.3%) of overdoses were staggered. The reported ingested dose was 12g (IQR: 8-21g, maximum 56g). The median plasma paracetamol concentration at presentation was 50.9mg/L (18.55-101.025mg/L, maximum 305.2mg/L). All patients received N-acetylcysteine, with a median dose of 22.9g (IQR: 19.8-30.7g), whereas six (21.4%) patients had additional NAC infusions beyond 21-hours of treatment. Despite prompt intervention, twelve patients (42.9%) developed an ALT rise above the upper limit of normal, with 6 (21.4%) above 1000IU/L, and 5 (17.9%) of patients had an INR rise to >1.3. Simulated APAP and NAC profiles shed further light on the limitations of the nomogram for APAP intoxication lack of a stoichiometric basis for the current NAC regimen. Furthermore, the slope of the correlation between APAP and NAC exposure was found to be -0.02 and 0.09 for C_{max} and AUC respectively.

Conclusion: NAC remains an important measure for the prevention of severe hepatic damage following APAP overdose. Current NAC therapy recommendations have been effective, but evolving insight from pharmacokinetic modelling and simulation demonstrates that its regimen can be optimised. Most importantly, simulations make clear that a revised nomogram is needed to ensure appropriate clinical management of acute overdose.

II-66: *Fernando Ortega* Developing a head and neck cancer model to assess the effect of radiotherapy on tumour growth inhibition and regrowth

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Introduction:

We have previously developed agent-based tumour models that successfully replicate and predict the effect of irradiation on tumour growth inhibition in a number of preclinical studies [1, 2]. These studies utilize different irradiation doses and regimes as well as combination with therapeutic agents with disparate mechanism of action. The primary outcome measure of these models was tumour size over time up to 1-2 months. Having achieved the translation of pre-clinical models for small molecules [3], we have considered how this radiotherapy model could be translated into a clinical setting to support development decision making.

Objectives:

Develop an enhanced model of radiotherapy treatment that is capable of predicting tumour shrinkage and regrowth in squamous cell carcinoma head and neck tumours in humans.

Methods:

Analysis of historical data from clinical trials in head and neck cancer [4,5] showed that *i*) the initial rate sum of longest diameter (SLD) shrinkage depends on the SLD before treatment where the largest initial SLD the faster the initial tumour shrinkage rate *ii*) the magnitude of the tumour shrinkage can not only be explained by depletion of the proliferative layer of the tumour *iii*) a significant proportion of tumours remained suppressed for years following treatment.

Results:

We used these findings to update and adapt the mathematical model to the clinical setting as well as to calibrate the model to describe the behaviour of head and neck tumours treated with radiotherapy alone. We assumed that the mechanism of action of radiotherapy at the cell cycle level is unaltered between preclinical and clinical model, i.e. only proliferative cell layer is depleted by DNA damage production. However, we hypothesized that the integrity of the growing layer plays a role in preventing the necrotic core from being degraded by biological or physical processes. Therefore, the death of viable cells leading to depletion of the growing layer indirectly contributes to the overall tumour size shrinkage through enhanced erosion of or leakage from the necrotic core.

The other major challenge was to develop a mechanism to reflect the wide variation in time to regrowth post-treatment. Literature evidence [6,7] suggested that this regrowth can be explained by variation in cellular doubling time and we were able to calibrate our modelled cell population using a distribution of doubling times that enabled the model to accurately predict regrowth profiles from literature.

Conclusions:

We were able to extend our mathematical model from a tool that explained and predicted the effect of radiotherapy on tumour growth inhibition in the preclinical space to one that describes both tumour growth inhibition and regrowth in the clinical space. We have used this model as the basis to predict the effects of different radiotherapy regimens as well as combinations with other therapeutic agents in a clinical setting. Thus, we have developed a platform that enables us to predict in head and neck the effect of radiotherapy alone or in combination with other procedures on tumour shrinkage and locoregional control. This approach can also be implemented to model other tumour types.

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II-67: *Taniya Paiboonvong* Development of physiologically based pharmacokinetic model of sitafloxacin in plasma and epithelial lining fluid

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Objectives: Alveolar epithelial lining fluid (ELF) has been suggested as an important site of lower respiratory tract infections caused by extracellular pathogens. Therefore, the drug concentrations in ELF has been demonstrated more relevant than the concentrations in plasma for predicting therapeutic efficacy. Most of the fluoroquinolones have been studied for determining the degree of lung penetration, and the overall results showed that they could achieve the higher ELF concentrations than in serum or plasma [1, 2]. However, there are still limited data of drug penetration in critically ill patients. Sitafloxacin, a new broad-spectrum fluoroquinolone antimicrobial agent, has been approved for oral formulation for treatment of pneumonia in Thailand since 2011. Oral sitafloxacin was rapidly absorbed and widely distributed into various tissues. Pharmacokinetics of sitafloxacin were demonstrated with linear plasma pharmacokinetics that maximum plasma concentration (Cmax) and area under concentration-time curve (AUC) were increased in dose proportion ranging from 25 mg to 500 mg [3-5]. The objective of this study was to develop physiologically based pharmacokinetic (PBPK) modeling approach to predict concentrations of sitafloxacin in ELF.

Methods: The PBPK model was constructed and evaluated using plasma and ELF concentrations obtained from 12 critically ill patients with pneumonia after oral sitafloxacin single dose 200 mg administration during 0.5-2, 3-4, 5-6, and 7-9 h. Sitafloxacin concentrations were determined using liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay. The concentrations in ELF were calculated using plasma concentration * fraction unbound in plasma calculated from albumin level in each subject. The concentrations in ELF were assumed to be free drug. The plasma pharmacokinetic parameters described by one-compartment model with first-order absorption were used in conjunction with lung compartment for developing simple PBPK model using Stella software version 9.1.4. Tissue to plasma distribution coefficients (Kp) were determined from the ratio of ELF and plasma concentrations (Kp = CELF/CPlasma). The PBPK model was evaluated by root-mean-square error (RMSE) between concentrations predicted by the model and the concentrations actually observed in ELF. The different dosage regimens were simulated to create sitafloxacin concentration-time profiles in ELF.

Results: The concentrations in ELF had variation with different sampling times. The mean ± SD of Cmax was 1.07± 0.93 µg/mL. Accounting for physiology, the parameters included blood flow (Q), and volume of lung compartment were inputted into the model. The PBPK model can be used to predict the pharmacokinetic behavior of sitafloxacin in agreement with observed data (RMSE of 0.54). From the modelling and simulation, sitafloxacin penetrated into ELF and accumulated with the dose proportion at steady state. Stimulation with the dose of 200 mg, 300 mg, 400, mg, and 500 mg q 12 h, the Cmax of sitafloxacin in ELF at steady state were 0.8 µg/mL, 1.20 µg/mL, 1.61 µg/mL, and 2.01 µg/mL, respectively.

Conclusion: The PBPK modeling of sitafloxacin are acceptable to predict sitafloxacin concentrations in ELF in critically ill patients with pneumonia. This findings provided the useful information for further development of population PK/PD modelling to predict the optimal dosage regimen of sitafloxacin.

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II-68: *Semra Palic* Neopterin dynamics in pediatric patients after miltefosine treatment of visceral leishmaniasis

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Introduction/Objectives
Visceral leishmaniasis (VL) is the most severe form of the neglected tropical disease leishmaniasis affecting internal organs such as spleen, liver and the bone marrow. If left untreated, VL is lethal within months. In East Africa, the pediatric population appears particularly vulnerable for this infection (1). *Leishmania* parasites are known to invade macrophages of the host, persuading the rise in anti-inflammatory cytokines to foster disease progression. Activated macrophages produce neopterin, a pteridine that has served as a marker of immune activation in various pathologies for decades (2). Recently, neopterin was also shown to be increased in patients suffering from VL, where it could potentially function as predictor of relapse (3). The main objective of the present study was to develop an integrated pharmacokinetic-pharmacodynamic (PK-PD) model to characterize the neopterin response to miltefosine treatment of pediatric VL.

Methods
Pediatric East African VL patients from two trials investigating miltefosine monotherapy were included in the current analysis. Twenty one patients (age 7-11) were treated with the conventional linear weight based miltefosine regimen (median 2.4 mg/kg/day) (4), while thirty patients (age 4-12) were treated with an allometric weight based dosing regimen (median 3.2 mg/kg/day) (5). Individual PK parameters from a previously developed population PK model of miltefosine (6) were used to link with neopterin PD. In total 562 neopterin plasma concentrations (analyzed using an ELISA assay, Demeditec Diagnostics GmbH) were available. All samples were measured in duplicates, and average values were used for this population analysis. Data were analyzed using the first-order conditional estimation with interaction (FOCE+I) estimation method in NONMEM (version 7.3.0, Globomax, USA) using Pirana as interface (version 2.9.6).

Results
Neopterin pharmacodynamics were characterized using a turnover model. Given that neopterin is an endogenous marker, also present in plasma of healthy individuals, two modes of neopterin production were included in our model. Normal neopterin production, and VL-specific production were estimated in combination with neopterin elimination. VL specific production was modelled to be influence by miltefosine exposure (cumulative AUC) by a second-order inactivation rate constant. The turnover time, which corresponds to the mean residence time of neopterin, was estimated at 29 days (relative standard error (RSE) 14%). The typical neopterin increase at baseline due to the disease was 77.4 nmol/L, but was variable among patients (between subject variability (BSV) 35%, RSE 19%), while the healthy neopterin steady-state to which neopterin returned after treatment in this patient population was estimated at 19.4 nmol/L (RSE 13%). However, literature reports a healthy standard reference for neopterin in various other patient populations at 10 nmol/L (7), but none of the patients in this cohort recovered to endogenous values. Moreover, during follow-up neopterin plasma levels increased again in a subset of patients. To identify these individuals, a mixture model was used, which indicated a subpopulation (30%, RSE 17%) for whom a zero-order regrowth rate during follow-up could be estimated at 0.0157 disease unit/day (RSE 12%).

Conclusion

We developed an integrated PK-PD model using a latent disease variable and an underlying endogenous turnover model to elucidate the relationship of miltefosine pharmacokinetics with neopterin dynamics and VL-driven change in neopterin production. Future analyses will focus on identifying predictors for the neopterin increases during follow-up. Finally, this model will further be used to explore neopterin as a potential biomarker of disease relapse in patients who suffered from VL.

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II-69: *Robert Palmér* A novel joint modelling approach to estimating treatment effects on COPD exacerbations in the presence of differential discontinuations

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Introduction: COPD clinical trials aimed at evaluating long-term treatment effects on exacerbations often suffer from a high rate of patient discontinuations. Discontinuations imply a loss of information and should ideally be considered in the statistical evaluation of study results, particularly if the discontinuations are related to disease severity or treatment and become unequally divided between treatment groups (differential discontinuations).

Objectives: In this work, we aimed to quantify the association between COPD exacerbation and discontinuation risks, and to evaluate the impact of this association on exacerbation treatment effect estimates, using a joint frailty model approach.

Methods: A joint frailty model[1] describing the hazards of recurrent episodes of exacerbations and early discontinuations was developed using the R-package *frailtypack*. The two risk processes were coupled using a gamma distributed shared random effect (*frailty*), where the effect of the *frailty* in the discontinuation hazard is scaled using an association parameter (α):

$r_{ex,ij}(t|u_i) = Y_i(t) * u_i * r_0(t) * \exp(\mathbf{x}'_{ex,ij} \cdot \boldsymbol{\beta}_{ex})$
$\lambda_{ed,i}(t|u_i) = (u_i)^{\alpha} * \lambda_0(t) * \exp(\mathbf{x}'_{ed,i} \cdot \boldsymbol{\beta}_{ed})$

Here, $r_{ex,ij}$ and $\lambda_{ed,i}$ are the patient-specific hazards for recurrent exacerbations and early discontinuation, respectively. The variable u_i denotes the *frailty* for patient i, and the $\mathbf{x}$s and $\boldsymbol{\beta}$s are the covariates (e.g. treatments) and their related regression coefficients. r_0 and λ_0 denote the population baseline hazards and Y_i is the at-risk process for patient i.

The importance of modelling the association when estimating exacerbation treatment effects was first investigated using simulated data from the joint frailty model. The data included two treatment groups (control and active) and was simulated assuming (1) different discontinuation and exacerbation rates, (2) different frailty variances, and (3) different associations strengths (α) between the two risk processes. Treatment effect estimates of the joint frailty model were compared to those of conventional and simpler statistical models, such as the negative binomial and shared frailty model[1]. Since models like the negative binomial model estimates rate ratios rather than hazard ratios, constant baseline hazards were used in the simulations to allow for a fairer comparison.

The joint frailty model was then applied to data from five randomized controlled Phase III-IV trials in patients with moderate to severe COPD[2,3,4,5,6], and the same comparison to simpler models was made. Early discontinuations were defined as any discontinuation of investigational product before the predefined end of study, irrespective of reason.

Results: Simulations showed that simpler statistical models produce biased treatment effect estimates in the presence of differential discontinuations and a discontinuation-exacerbation association ($\alpha \neq 0$). In

scenarios with a 2-fold higher discontinuation risk in the control group and a positive risk association (α = 0.5-1.5, *frailty* variance = 1.7), a true treatment effect of 40% exacerbation risk reduction (hazard/rate ratio = 0.6) was underestimated by 4-8 percentage points (hazard/rate ratio = 0.64-0.68) if ignoring the association in the statistical analysis. The joint frailty model produced less biased results (1-2 percentage points).

When analyzing the clinical trial data, significant ($p<0.00001$) and similar (α = 0.83-1.69) associations between exacerbations and discontinuations were found in all trials. The differences in treatment effect estimates between the joint frailty model and simpler models ranged from 1-11 percentage points. More than 5 percentage points differences between models were seen in the studies with the largest differences (>1.5-fold) in discontinuation rates between treatment groups. With the joint frailty model, we also saw up to 10% relative improvements in treatment effect standard errors in several of the trials.

Conclusions: We have found a significant association between early discontinuation and exacerbation risks in five Phase III-IV COPD clinical trials and show that this association may cause bias when estimating exacerbation treatment effects if discontinuations are unequally divided between treatment arms. The use of a joint frailty modelling approach can reduce bias and improve precision in treatment effect estimates in the presence of differential discontinuations.

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II-70: *Hyeonsoo Park* A population pharmacokinetic model of Glimepiride(Amaryl®)

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Objectives: Glimepiride is an oral hypoglycemic agent used to treat type II diabetes mellitus (T2DM). Glimepiride directly stimulates insulin secretion and induces insulin receptor expression[1]. Hypoglycemia is a commonly reported side effect, and elucidation of a dose-response relationship would contribute to its prevention. In a previous study, H.-Y. Yun et al, constructed a PK-PD model based on the relationship between glimepiride and blood glucose.[2] In this study, glimepiride concentration, insulin concentration and blood sugar were measured in 6 healthy adult korean subjects and PK-PD model was constructed based on these results. In this regard, we have initiated a study to develop a population PK-PD model of glimepiride to investigate PK-PD relationship of the drug and the associated influencing factors. As part of the final PK-PD model, this presentation was to report on a PK model developed so far.

Methods:24 healthy male volunteers between the age of 19 and 55 with body weight over 55 kg were recruited. The subjects were given multiple doses of glimepiride 4 mg, QD for 7 days. Blood samples were collected for 48 hours after the last dose from which glimepiride concentrations were analyzed. Blood sugar was measured up to 24 hours after dose. Based on the collected drug concentration data, nonlinear mixed effect modeling was carried out using NONMEM software version 7.3. Covariate search was carried out using age, weight, alcohol uptake, smoking history, and caffeine intake as covariate candidates. To do so, stepwise covariate model building was implemented with likelihood ratio test at significance levels of $p < 0.01$ for forward selection and $p < 0.001$ for subsequent backward deletion. Inter-occasion variability(IOV) as well as inter-individual variability (IIV) was incorporated and correlations among random effects implemented using $OMEGA BLOCK. Exploratory data analysis was carried out using R software version 3.3.3.

Results:A two-compartment disposition model parameterized by central volume of distribution (Vc), peripheral volume of distribution (Vp), clearance (CL), and inter-compartmental clearance (Q), with zero-order absorption[2] was selected as the base structural model. Covariate search yielded age as a significant covariate of Vp. The estimates of Vc, Vp, CL, and Q were 9.45 L, 16.03 L, 4.429 L/h, and 1.41 L/h, respectively. The variance estimates of IIV of Vp, CL, and Q in the coefficient of variation (CV) scale were 54.18%, 26.62%, and 85.5%, respectively. IOV of Vc and CL were 53.86% and 11.93%, respectively. Residual error variability was best described by a proportional error model, yielding residual error variance of 32.94% (CV). Relative standard errors of all parameters were less than 30%, indicating the reliability of model parameters. Our model well described the observed concentration-time profile.

Conclusions: This preliminary work demonstrates that only the age-Vp relationship has significant influence on glimepiride PK while substantial variability (> 50% CV) still remains unexplained in IIV of Vp and Q and IOV of Vc.. Such unexplained high variability was conjectured to be related with a small number of subjects used here. Thus, in the future, to develop a model that better characterizes glimepiride PK, more analyses in a larger patient population possibly with a more diverse covariate distribution will be needed.

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II-71: *Christophe Passot* A kinetic-pharmacodynamic model of palbociclib reveals an influence of body weight on neutropenia onset.

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Objectives: Palbociclib is a cyclin-dependent kinase 4/6 inhibitor labeled for the treatment of estrogenreceptor positive (ER+) and human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer (mBC), in combination with endocrine therapy. The starting posology is 125 mg once daily for 21 days followed by 7 days off treatment, without adaptation according to patient's weight. The onset of neutropenia during the three first cycles may lead to dose reduction or treatment discontinuation for more than 7 days. Identification of covariates influencing dose-limiting neutropenia may lead to dose individualization at treatment initiation. In this study using real-world data, we aimed at describing the relationship between palbociclib dosage and absolute neutrophil count (ANC) and at assessing the interindividual variability.

Methods: Data from patients treated with palbociclib during the year 2017 in the Integrative Center for Oncology in Nantes-Angers (France) were collected retrospectively in medical records. Palbociclib dose and administration days as well as ANC were collected throughout the three first treatment cycles. Demographic (age, body weight) and biologic (creatinine, urea, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and total bilirubin) data were collected at baseline. The relationship between palbociclib treatment and ANC was described with a population kinetic-pharmacodynamic (K-PD) [1] model using Monolix 2018R2 software (Lixoft, Orsay, France). Demographic and biologic data mentioned above were tested as covariates on K-PD parameters.

Results: Data were collected for 56 mBCpatients. The median age was 63 y.o. (range 29-88) and the medium body weight was 62 kg (range 35-103). Three cycles of palbociclib were administered in 43 patients, 2 cycles in 8 patients and 1 cycle in 5 patients. A total of 540 ANC were available with a median of 8 ANC for each patient. Absolute neutrophil counts were described using a semi-mechanistic Friberg model [2]. Briefly, the model consists of a proliferating progenitors compartment, three transit compartments where neutrophils mature and a compartment of circulating neutrophils. The effect of palbociclib on progenitors proliferation rate was described with an inhibitory Emax model. The values (interindividual variability) of estimated population parameters were: the elimination rate constant from the virtual compartment KDE=0.11 $days^{-1}$ (-), the maximum effect Emax=0.65 (-), the infusion rate from virtual compartment that leads to 50% inhibition of neutrophils proliferation constant EDK_{50}=256 $mg.day^{-1}$ (0.34), the baseline ANC value $Circ_0$=3.97 G/L (0.33), the feedback parameter γ=0.15 (-) and the mean transit time MTT= 3.12 days (0.342). Body weight significantly increased EDK_{50} (β_{WT}=0.736, Δ-2log likelihood=-6.77, p=0.009).

Conclusions: This work is to our knowledge the first reporting a semi-mechanistic K-PD model developed to describe myelosuppression in human. The influence of body weight on palbociclib EDK_{50} may be related to CL and/or EC_{50} [2]. An influence of weight on clearance of palbociclib has been previously reported [3]. Measurement of palbociclib concentrations in future studies could allow determining if weight also influence EC_{50}. The present study suggests that dose adaptation at treatment initiation according to body weight may allow a decrease of the incidence of onset of neutropenia.

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II-72: *Nathalie Perdaems* Translational PK-RO modelling for a mAb to predict the outcome of the first in human study

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Objectives: In preclinical development, monkey is the reference species to predict the pharmacokinetics (PK) of monoclonal antibodies (mAb) in human. Allometric scaling can beused to transpose the PK model from monkeys to support the first in human (FIH) study in healthy volunteers.

Methods: A population PK model was built in monkeys, using data for a mAb, from a pharmacological study after single administration of 3 doses after iv (0.1, 1 and 10 mg/kg) and 1 dose after sc (1 mg/kg). Ten cynomolgus monkeys with a total of 78 plasma concentrations were included in the model. NONMEM version 7.3 was used for the population analysis.

Allometric scaling was used to transpose the population PK model in human and predict plasma concentrations for the FIH study. Allometric scaling factors were 0.85 for clearance, 1 for volume and -0.25 for the absorption constant after sc administration [1] [2] [3].

An *ex vivo* PK/PD relationship between the concentration and the receptor occupancy (RO) in human cells was used to predict the RO in the FIH study (3 experiments with 2 or 3 replicates were performed with 16 levels of concentrations from 0 to 10000 ng/mL). Phoenix WinNonlin version 6.4 was used to describe this relationship.

This approach allowed to justify the doses planned in the FIH study and the predicted concentrations and the predicted RO were compared to the observed one.

Results: The population PK model developed in monkeys allowed to well describe plasma concentrations of the mAb after the iv and sc administration. The model structure for the PK modelling in monkeys was a 2-compartment model with 3 elimination pathways (2 linear clearances (CL and CLADA describing ADA-related drug elimination) and a non-linear clearance) with no covariate. All the parameters were well estimated (RSE < ~40 %), except the intercompartmental clearance and the concentration at half the maximum rate of elimination (Vmax) (Km) with RSE < 85 %. Interindividual varibility (IIV) was estimated on the volume of the central compartment (VC) and a proportional error model (31.6 %) best described the residual error.

Allometric scaling were used for CL, Q, volumes (VC and volume of the peripheral compartment (VP)) Vmax and Ka. The monkey parameters were used for the bioavailability (F) after sc administration and Km for the human predictions. ADA-related clearance was not considered in the transposition.

The *ex vivo* PK/PD relationship was described using an inhibitory effect sigmoïd model (WNL5 classical PD model 107) relying the log-transformed concentrations and the percentage of normalized free receptors.

Observed concentrations are available for the first doses of the FIH study and were consistent with predictions.

Also the *ex vivo* PK/PD relationship allowed to predict the *in vivo* RO in human (less than 20 % for the first dose and less than 100 % for the second dose).

Conclusions: A population PK model in monkeys was built and the use of allometric scaling for clearances (including Vmax), volumes and Ka allowed to well predict plasma concentrations in human for a mAb and associated receptor occupancy.

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II-73: *Carlos Perez-Ruixo* Exposure-response relationships of the efficacy and safety of apalutamide (APA) in men with non-metastatic castration-resistant prostate cancer (nmCRPC)

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Objectives: Apalutamide (APA; ERLEADA®), an orally administered selective androgen receptor inhibitor,[1] is approved for the treatment of men with non-metastatic castration-resistant prostate cancer (nmCRPC) based on the pivotal phase 3 clinical study SPARTAN, which studied apalutamide plus androgen deprivation therapy (ADT).[2] We sought to understand the relationship between exposure to APA and its active metabolite N-desmethyl-apalutamide (N-APA) and selected clinical efficacy and safety endpoints to support APA dosing recommendations in men with high risk nmCRPC.

Methods: Data from 1207 subjects (806 APA 240 mg and 401 placebo) in the SPARTAN study were included in the exposure-response (ER) analysis. Using a population PK model developed in NONMEM® software,[3] exposures of APA and N-APA were quantified as the area under the concentration–time curve at steady state ($AUC_{0\text{-}24h,ss}$) at the average daily dose received up to the day of metastastic progression or adverse event. Univariate and multivariate Cox regression models evaluated the relationships between APA and N-APA $AUC_{0\text{-}24h,ss}$ and the primary outcome of the study, metastatis free survival (MFS) and were adjusted by pre-specified stratification factors (prostate-specific antigen doubling time, bone-sparing agent use, locoregional disease status) and other potential prognostic factors (age, ECOG performance status). In the multivariate Cox regression analysis, the impact of apalutamide and N-desmethyl-apalutamide exposure on MFS, was assessed by the hazard ratio (HR) and its 95% confidence interval (CI). Univariate and multivariate logistic regression models assessed the relationship between APA and N-APA $AUC_{0\text{-}24h,ss}$ and common treatment emergent adverse events (TEAEs): fatigue, fall, skin rash, weight decrease, and arthralgia. The corresponding odds ratio (OR), 95% CI, χ^2 and p-values were calculated. Additionally, a sensitivity analysis was conducted by including and excluding placebo subjects in the exposure-safety analysis.

Results: Both the univariate and multivariate Cox regression showed no statistically significant relationship between MFS, APA, and N-APA when categorized by quartiles of exposure (median $AUC_{0\text{-}24h,ss}$ of 78.1, 98.8, 116.1, and 143.5 µg·h/mL for quartiles 1, 2, 3 and 4, respectively) or when used as a continuous variable ($AUC_{0\text{-}24h,ss}$ range of 13.8 to 280µg·h/mL), suggesting that differences in APA and N-APA exposure within the range observed in SPARTAN are not associated with clinically relevant differences in MFS.

The univariate and multivariate logistic regression analysis demonstrated that within the exposure range observed in men treated with APA, the exposure-TEAEs relationship was statistically significant for skin rash and weight decrease. Using Li's method, APA exposure explained 57% and 38.8% of the effect on rash and weight decrease, respectively.[4]

Conclusions: The exposure-response analyses demonstrated that differences in APA and N-APA exposure with a starting dose of 240-mg daily are not expected to be associated with clinically relevant differences in MFS in men with nmCRPC. The exposure-safety analysis supports the dose reductions to 180 or 120 mg/day in subjects who experienced AEs, such as rash.

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II-74: *Soumya Perinparajah* Pharmacodynamics of rituximab on B cells in paediatric post-HSCT patients with EBV

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Introduction/Objectives: Rituximab is a chimeric IgG-1 monoclonal antibody that interacts with the CD20 protein on the surface of B cells, targeting them for cell lysis. It is given for a range of conditions including B cell lymphomas and leukaemias but is licensed for adults only, given on an off-label basis to children. Due to its mechanism of action, rituximab is used for Epstein Barr virus (EBV), which is commonly reactivated after haematopoietic stem cell transplantation (HSCT) and is the leading cause of post-transplant lymphoproliferative disease (PTLD). In immunocompetent hosts, EBV is controlled by cytotoxic T cells but reduced immune surveillance in immunocompromised post-HSCT patients leads to an outgrowth of EBV-transformed cells.

The current study aims to identify the pharmacodynamics of rituximab in children with EBV post-HSCT to optimise the dose.

Methods: Retrospective electronic data were collected from children who underwent HSCT at a tertiary paediatric hospital between 2005 and 2017, and were prescribed rituximab for EBV post-HSCT. Intravenous infusions of rituximab were administered at a dose of 375 mg/m^2 weekly for either one week on a conservative regimen or four weeks on a pre-emptive regimen. Plasma concentrations of rituximab were not available, but CD19$^+$ B cell counts were available before and after treatment with rituximab.

Time to CD19$^+$ B cell reconstitution was compared between patients given a single dose or four doses of rituximab using the survival and survminer packages in R (version 3.5.1).

A kinetic-pharmacodynamic (K-PD) turnover model, previously constructed and described by Pan et al [1], was applied in NONMEM® (version 7.4.3). Rituximab was assumed to be eliminated by first-order kinetics.

Results: 683 measurements of CD19$^+$ B cell counts were available from 55 children who received rituximab for EBV post-HSCT. Observations (n=317) with a CD19$^+$ B cell count below the lower limit of quantification (LOQ) were assigned a count of 5x10^6/L (LOQ/2). The median age at HSCT was 2.96 years.

The median time to reconstitution was 292 days in patients administered a single dose of rituximab (n=39) and 768 days in patients administered four doses of rituximab (n=16). There was no significant difference in the fraction of patients achieving age-specific CD19$^+$ B cell reconstitution between the single-dose and four-dose groups (p value = 0.21), although the observed trend was for a slower rate of reconstitution for the four-dose group than for the single-dose group.

The K-PD model described the time course of CD19$^+$ B cells well following treatment with rituximab. The final parameter estimates were as follows; rituximab elimination rate 0.044 day^{-1}; production rate constant

was 6.95×10^6 cells/day; cell death rate 0.037 day^{-1}; E_{max} was 56.9 (fold increase in cell death rate) and ED_{50} was 40 mg. These were consistent with values reported in previous literature [1,2], with the exception of ED_{50} which was higher in the present study.

Conclusions: The model adequately describes $CD19^+$ B cell dynamics in response to rituximab. Refinements to the model are planned to include age [3] and size scaling, and exploration of the M3 method for LOQ handling. EBV viral loads will then be included to better understand the dynamics of viral inhibition in this population, and ultimately inform rituximab dosing.

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II-75: *Thomas Peyret* Development of a Quantitative Systems Pharmacology Model to Support Dosing of rhPTH(1-84), a Recombinant Human Parathyroid Hormone, in Adult Patients with Hypoparathyroidism

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Objectives: rhPTH(1-84), a full-length Recombinant Human Parathyroid Hormone, is approved in the US and Europe as an adjunct to calcium and active vitamin D to control hypocalcemia in patients with chronic hypoparathyroidism (hypoPT). rhPTH(1-84) is indicated for once daily (QD) dosing, and the dose is to be individualized to achieve a serum calcium level in the lower half of the normal range (target range). A quantitative systems pharmacology (QSP) model of integrated calcium homeostasis and bone remodeling[1] was originally adapted for patients with hypoPT by including 1) the concentration-time profiles of PTH, 2) oral intake of calcium and active vitamin D, and 3) by performing various adjustments on the parathyroid gland pool and the ability of the gland to grow in size and in capacity for secretion. The objective of this project was 1) to enhance the QSP model by integrating additional drug- and disease-specific components to further improve the predictive performance of the model, and 2) to perform simulations to ultimately determine the effects of QD and twice daily (BID) administrations of rhPTH(1-84) on serum calcium and urinary calcium excretion in patients with hypoPT.

Methods: Additional drug- and disease-specific components were integrated into the QSP model, and qualification was performed based on pharmacokinetic (PK) and pharmacodynamic (PD) data available in 135 adult subjects with hypoPT in five clinical studies including QD (25, 50, 100 µg) and BID (25 or 50 µg) regimens. Simulations were performed with the enhanced QSP model to predict concentration-time profiles of PTH, serum calcium, and urinary calcium excretion, as well as the probability of hypercalciuria (defined as 24-h urinary calcium above the normal range) following various QD and BID does of rhPTH(1-84) of total daily doses of 25 µg, 50 µg, and 100 µg as well as standard of care (SOC, calcium supplement+ active vitamin D).

Results: The following components were included in the QSP model to improve predictive performance: 1) an input function of PTH with subject- and occasion-specific rate of absorption and bioavailability originally derived with a population model to optimally characterize double absorption peak profiles of PTH, and 2) a refinement of the disease model (i.e., primary hypoPT) which included a lower renal reabsorption of calcium, believed to be due to hormone resistance in renal tubules where it promotes calcium reabsorption by PTH. The enhanced QSP model presented an adequate predictive performance of plasma PTH, serum calcium and urinary calcium excretion. Based on simulations in patients with partial PTH production (endogenous PTH levels ranging from 5.63 to 27.2 ng/mL), following various rhPTH(1-84) QD and BID doses, serum calcium concentrations are maintained within the target range similar to those from the SOC while urinary calcium excretion is reduced. The predicted percentage of hypercalciuria (>7.5mmol over 24 hours in males and >6.25mmol over 24 hours in females) for various rhPTH(1-84) QD and BID regimens are presented below.

- 100 µg QD, 30.6% and 40.8% for males and females, respectively.
- 50 µg QD, 45.0% and 57.0% for males and females, respectively.
- 25 µg QD, 62.2% and 74.4% for males and females, respectively.

- 50 µg BID, 12.4% and 19.4% for males and females, respectively.
- 25 µg BID, 28.6% and 39.6% for males and females, respectively.
- 12.5 µg BID, 50.8% and 63.6% for males and females, respectively

The frequency of hypercalciuria following rhPTH(1-84) QD and BID doses is predicted to be largely reduced compared to that following the SOC (predicted at 100% based on the current model).

Conclusions: An enhanced QSP model was developed and qualified using PK and PD data from a large number of patients with hypoPT. Based on the current model, both QD and BID dosing regimens of rhPTH(1-84) at daily doses from 25 µg to 100 µg markedly reduced urinary calcium excretion and the possibility of hypercalciuria while maintaining serum calcium level in target range as compared to the SOC. Patients with hypoPT treated with rhPTH(1-84) BID dosing regimens are predicted to have a lower likelihood of hypercalciuria than the QD dosing regimens. A clinical study is planned to confirm these findings.

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II-76: *Chiara Piana* Development of a translational pharmacokinetic-biomarker-efficacy model in mouse to support dose recommendation in human

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Objectives:

In the preclinical phase of oncology drug development, a common way to test the activity of a drug is by means of tumor xenograft experiments**.** Of particular interest is the possibility of integrating the drug-to-biomarker dynamics with the associated drug-to-tumor growth inhibition response. This would allow to predict tumor response from biomarker data, which would be a key in the translation from preclinical to clinical research. The aim of this analysis is to find a quantitative relationship between MEN1703 drug exposure or plasma/tumor partitioning coefficient and pharmacological effects as measured by biomarkers and tumor growth inhibition in MOLM16 leukemia (AML) cell line xenografts in mice. To address this aim, a predictive pharmacokinetic/pharmacodynamic (PK/PD) model, which integrates preclinical pharmacokinetic, biomarker and efficacy data has been developed.

Methods:

First, MEN1703 Pharmacokinetics (PK) model in mouse was developed using data both at single and multiple doses from four studies. Second, PK data in plasma and tumor from two studies were used to determine the relationship between MEN1703 concentrations in the two matrices, with biomarker data in tumor. Third, a model describing dynamics of S6 (Ser235/236) phosphorylation inhibition (%) in MOLM-16 xenograft was developed by using parameter estimates from the plasma-tumor PK model. Fourth, xenograft tumor growth and MEN1703 tumor growth inhibition data from four studies in mouse were modelled by means of the modified biomarker-driven TGI model developed by Simeoni et al.[1] and Sardu et al. [2]. All the analyses were performed using the NONMEM 7.3 computer program. Selection between models was based mainly on the goodness of fit and residual plots, and precision of parameter estimates expressed as coefficient of variation

Results:

Disposition of MEN1703 in mouse plasma was best described with a one compartment model with a linear elimination. Predicted plasma concentrations of MEN1703 were related with concentrations in tumor through a partition coefficient between plasma and tumour (kp ~10). The time course of biomarker pS6 (Ser235/236) inhibition was best described with a direct response model driven by MEN1703 concentrations in tumour. The IC_{50} and γ estimated values were 7360 ng/mL and 3.5, respectively. Data obtained from different TGI studies were fit separately due to high inter-study variability. The tumour growth in the absence of MEN1703 administration was well described by the model allowing for the switch from an exponential to a linear growth. With regards to the perturbed growth model, the Simeoni model captured well the tumor growth profiles and the effect of the anticancer treatment k_2 for all the studies which ranged from 0.016 to0.043 $\mu g^{-1} \cdot mL \cdot d^{-1}$. Standard goodness of fit, together with prediction-corrected

VPC were generated for each study. Overall, the models were able to well predict the observed tumor growth data.

Conclusions:

An integrated PK-biomarker-efficacy model for MEN1703 has been developed in mouse. This preclinical model-based framework in conjunction with a population PK model in human will be used to support dose selection in clinical trials.

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II-77: *Philippe Pierrillas* PK-PD modelling of C4 concentrations after administration of a FXR agonist in healthy volunteers and Hepatitis B patients

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Objectives: EYP001a is a modulator of the nuclear farnesoid X receptor (FXR) and part of the agonist family which was originally discovered for a therapy of non-alcoholic steato-hepatitis, primary biliary cholangitis and metabolic syndrome. It was also found to have anti-viral activity on Hepatitis B virus (HBV) [1].

The objective of this work was to develop a population Pharmacokinetic-Pharmacodynamic model (PK-PD) using biomarker data to assess the effect of EYP001a on bile acids pathway in both healthy volunteers and HBV infected patients.

Methods: Data from four phase 1 studies (including a 4-arm cross-over study to evaluate the impact of food intake and a potential nycthemeral rhythm and a drug-drug interaction study) conducted in healthy volunteers and HBV-infected patients were included in this analysis. Plasma samples from 180 individuals after single and repeated administrations of EYP001a at different dose levels (from 30 to 800 mg) and different dosing regimen (once a day and twice a day) and placebo were analysed for EYP001a and C4 concentrations (i.e. 7-alpha-hydroxy-4-cholesten-3-one, intermediate in the synthesis of bile acids from cholesterol located in the liver). A covariate analysis, using a stepwise approach, was performed to assess the impact of covariates and also to investigate the potential differences between healthy volunteers and HBV infected patients.

Parameters were estimated with the First-Order Conditional Estimation method with Interaction (FOCE-I method) implemented in NONMEM 7.3 (ICON) and model development was guided by residual- and simulation-based diagnostics.

Results: EYP001a PK was best described using a 2-compartment disposition model and an absorption phase modelled using 4 transit compartments. Relative bioavailability appeared to be nonlinear with time and dose: bioavailability decreases when dose increases after repeated administration. HBV infected patients were found to have a lower clearance (~25%) compared to healthy volunteers, and administration of EYP001a under fed condition decreased the absorption rate by a 2-fold factor but with a similar exposure.

C4 time-course in the placebo arm was modelled using a turn-over model and a cosine function was used to describe the nycthemeral rhythm of C4 production. EYP001a inhibitory effect was modelled using an effect compartment [2] and a steep sigmoidal function (coefficient of sigmoïdicity >2) on the C4 production.

Model evaluation by goodness-of-fit plots and Visual Predictive Checks, were satisfactory.

Simulations performed from the final population PK-PD model showed that administration of either 200 mg twice a day or 400 mg once a day would be suitable in order to reduce C4 plasma levels.

Conclusions: EYP001a and C4 concentrations were adequately described by the elaborated model and confirm the impact of EYP001a on bile acids pathway. This model might be expanded to safety aspects as

they will be available in order to assess the benefice-risk balance and better identify the recommended dosing regimen.

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II-78: *Nikhil Pillai* Single objective genetic algorithm based approach for optimal population pharmacokinetic/pharmacodynamics (PK/PD) model selection for tumor growth response

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Objectives:

Traditional approach to PK/PD model selection proceeds in a stepwise manner, first finding the best base structural model, and then searching for significant covariate relationships and statistical models. The stepwise approach ignores the interaction between structural, statistical and covariate effects; it involves a local search, is time consuming and is prone to errors as it involves manual editing of control streams. Thus, the model selected using the traditional stepwise approach may not be a globally optimal model. To overcome the issues faced by traditional approach one can use a global search algorithm. Genetic algorithm (GA) is one such method, which can help the modeler to find a global optimal model. The objective of this work is to develop a model, which best describes the dataset using single objective GA (SOGA) [1] and compare it to the model obtained using traditional approach.

Methods:

24 mice with established LNCaP xenograft tumors were randomized into four groups: control, vehicle treatment (5 intact mice); intact (not castrated) with diazepam treatment (5 mice), castrated mice with vehicle treatment (7 mice) and castrated mice receiving diazepam treatment (7 mice). Kinetics of tumor growth were modeled using nonlinear mixed effects modeling with NONMEM 7.4. First order conditional estimation with interaction was used for estimation purposes. While developing the model using traditional approach we used goodness of fit plots and objective function values for model selection and while developing the model using SOGA we used a fitness function to guide the model selection (eqn 1).

$$Fitness=-2LL+2*Npar+10*Pconvergence+10*Pcovariance \quad (1)$$

Where -2LL is the negative 2 log likelihood, Npar is the number of estimated parameters, Pconvergence is penalty for unsuccessful convergence and Pcovariance is a penalty for an unsuccessful covariance step.

While developing the model using traditional approaches the initial modelling focused on selecting a growth function capable of characterizing the tumor growth without intervention. Gompertz, Simeoni[2], Koch[3], logistic and exponential growth models were evaluated. Since there is a delay between drug treatment and tumor regression, a transit compartment model was used to describe the effect of drug on tumor. To analyze whether a particular intervention had a significant effect on the tumor growth, each intervention was tested using a stepwise addition and backward elimination strategy. In each growth model, combinations of four IIV model structures (none, additive, proportional, logarithmic) and three residual error structures (additive, proportional, additive+proportional) were tested.

Results:

The model selected using the traditional approach was the Simeoni model with an OFV value of 5135.724. This model had a proportional IIV on λ_0, λ_1, k_1, k_2 and a combined residual error model. The model selected using SOGA approach was the Koch model and had a fitness value of 4958, OFV value of 4922, had logarithmic IIV on λ_0, λ_1 and baseline tumor size. The treatment (intact) group had no IIV on k_1, proportional IIV on k_2. The model for castrated mice with vehicle treatment had logarithmic IIV on k_1, normal IIV on k_2. The model for castrated mice with drug treatment group had no IIV on k_1, proportional IIV on k_2 and a proportional residual error model was selected.

Conclusions:

SOGA was able to identify a model that had substantially lower OFV and fitness value compared to the model selected by traditional approach. SOGA automates the model development process and helps the researchers to focus on model evaluation, hypothesis testing and interpretation and application of resulting models rather than spending time on manual editing of control streams.

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II-79: *Vikram Prabhakar* QSP Model of Rheumatoid Arthritis, capturing range of clinical responses to Methotrexate and anti-TNF-a therapies

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Introduction:

Rheumatoid arthritis (RA) is an inflammatory, systemic autoimmune disorder affecting about 1-3% of global population, with over 2.3 million cases in the EU alone. QSP models are vital to understand patient response to existing and novel therapies. Multi-scale Quantitative Systems Pharmacology (QSP) models connect physiological mechanisms at the cellular and organ level, to responses at the patient and population level, and can therefore be used to predict clinical response of novel therapies.

We have developed an RA QSP model comprising multiple immune-cell types and cytokines of interest. The model simulates ACR & DAS-28 scores for an entrant population for two RA therapies – Methotrexate and anti-TNF-alpha therapies.

Objectives:

* Develop QSP model of RA, at appropriate physiological detail and scale, to address various questions of interest in drug development at both mechanistic and population level

* Use model to generate predictions of interest, such as: clinical outcomes for novel therapies, combinations of existing therapies, identifying sub-populations with greater response to therapies, and simulate and optimize novel trial designs

* Create a modular model design such that common immunological pathways are re-usable for auto immune diseases

Methods:

Model design, engineering, survey of published physiological and clinical data was carried out in accordance with standard QSP approaches[1]. An average, inflamed joint capturing the disease at steady-state (i.e., with no disease progression or episodic inflammation) is modelled.

Using Ordinary Differential Equations (ODEs), the model captures cellular lifecycle and interactions of Fibroblast like Synoviocytes (FLS), B cells, T cells and macrophages among other relevant cell types and relevant pro and anti-inflammatory cytokines (e.g., Il-6, TNF-alpha, TGF-beta). Reference virtual subjects are generated and calibrated to be average responders/non-responders to methotrexate (standard of care) and to anti-TNF-α therapy. Model parameters are constrained by clinical trial data **(top down constraints)** as well as by data from basic science literature **(bottom up constraints)**, e.g. proliferation and apoptosis rates of cells, cytokine secretion rates. ACR and DAS-28 scores in Virtual Populations are calibrated to match seminal trials for Methotrexate and anti-TNF-alpha therapies, namely Premier Study[2] and RA Beam[3].

To enable model repurposing to other autoimmune diseases, modular design approaches are used in setting up common immunological subsystems such as cell life-cycles and cytokine effects. This common

compartment structure is modelled to impact the site of inflammation in an appropriate way in each disease (e.g., site of inflammation is joint in RA, or Lamina Propria in Inflammatory Bowel Disease).

Results:

A QSP model capturing multiple physiological pathways of interest and response to specified therapies in RA was developed that can be used for clinical trial visualization, trial optimization, responder/non-responder identification etc. Reference virtual subjects in this model span a DAS-28 range from 5 to 7 at baseline and show a comparable response (reduction of disease severity) to the two therapies studied in the BEAM and Premier trials. Reference subjects corresponding to responder and non-responder to Methotrexate and anti-TNF-alpha therapies were generated. Sensitivity analysis of pathways was carried out to determine factors contributing to response.

Conclusions:

The Vantage RA-QSP model captures the physiology and clinical outcomes of RA, including response to Methotrexate and anti-TNF-alpha therapies[4]. Modular model design allows the model to be extended to other autoimmune disorders with similar pathophysiology by re-use of the core immunological components. Future efforts will add therapeutic pathways including anti-IL-6, anti-IL-17, JAK-inhibitors and anti-IL-23.

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II-80: *Sudeep Pradhan* Evaluation of study designs to test the intact nephron hypothesis

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Background: Methods to adjust doses of drugs that are renally cleared are based on the assumption of a linear relationship between renal drug clearance (CL_R) and glomerular filtration rate (GFR). The theory underpinning this practice is the Intact Nephron Hypothesis (INH) [1]. A recent review suggested that the INH might not be a suitable general model for renal drug clearance, particularly for drugs that are cleared primarily by active tubular processes where a non-linear relationship between CL_R and GFR might be expected [2]. To date, the study designs required to detect a deviation from the INH that might influence dose recommendations from renal drug studies have not been explored.

Objective: To evaluate the phase 1 study designs for pharmacokinetic studies in patients with renal impairment recommended by the European Medicines Agency (EMA) [3] and the United States Food and Drug Administration (FDA) [4] for the purpose of delineating a non-linear relationship between CL_R and GFR i.e., to test the INH.

Methods: The EMA and the FDA guidelines are essentially similar with main difference being recommended method for describing renal function i.e., using an exogenous marker for measured GFR (mGFR) and a serum creatinine based equation for estimating GFR (eGFR), respectively. Two models were proposed to describe the relationship between CL_R and GFR:

1. M1: a linear model (INH scenario)
   CL_R = THETA(1) * GFR

2. M2: a nonlinear model (non-INH scenario)
   CL_R = THETA(1) * GFR ^ THETA(2)

where, GFR is mGFR or eGFR for the EMA or the FDA guidelines, respectively; THETA(1) is a linear coefficient parameter and THETA(2) is an exponent parameter. The value of the nonlinear exponent was based on the work of [5].

This is a stochastic simulation estimation study. Virtual subjects were simulated with GFR values stratified to the 4 renal function groups as defined by the respective guidelines. The number of subjects for each simulated study was n = 4, 8, 12, 16, 20, 24, 32, 48, 72, 120, 240, 480, 1080; and they were equally distributed across the renal function groups. Simulations were performed assuming M2 as the “true model” i.e., a non-linear relationship between CL_R and GFR, using MATLAB (R2016b) to generate data sets. The simulated data sets were fitted to both the M1 and the M2 using NONMEM (version 7.3). Alpha error was calibrated to be 5% for every simulation setting. The preferred model for each simulated trial was based on the log likelihood ratio test. The simulation and estimation steps were repeated 1000 times for each of the designs tested. Power, relative standard error (RSE) and bias were calculated to evaluate the designs based on the EMA and the FDA guidelines.

Results: Study designs under the EMA guideline with ≥ 8 subjects had ≥ 80% power to correctly detect a non-linear relationship between CL_R and GFR. Under the FDA guidelines, ≥ 80% power was achieved only

with ≥ 24 subjects. The linear coefficient (THETA(1)) was well estimated when power was ≥ 80% for the designs under both the EMA (n ≥ 8) and the FDA (n ≥ 24) guidelines with a RSE of < 25%. The nonlinear exponent (THETA(2)) was poorly estimated (RSE ≤ 59%) for the designs under both the EMA and FDA guidelines, even when power was ≥ 80%. Of note all designs using eGFR (FDA) yielded a slight bias in the estimate of the nonlinear exponent which was not evident for the mGFR (EMA), where bias was < 20%.

Conclusions: The designs under EMA guideline would require fewer subjects to achieve ≥ 80% power to detect non-linear relationship between CL_R and GFR compared to those based on the FDA guideline. This was entirely predicated on the choice of method used to estimate renal function with eGFR being a poor choice compared to mGFR, the latter providing an unbiased measure of GFR [6]. Note however that precision of estimate of the nonlinear exponent was independent of the measure of GFR with a requirement of up to 72 subjects (across the 4 renal function groups) being required to achieve a RSE of < 25%. In essence, therefore, both guidelines perform equivalently for the limiting feature of the design (parameter precision). In conclusion, if the non-INH holds then neither guidelines, EMA guidelines (n=24) and FDA guidelines (n=24) would provide a precise estimate of the true relationship between CL_R and GFR.

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II-81: *Mélanie Prague* In Silico Clinical Trials for Evaluation of HIV Short-Cycle strategies

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Objectives: The challenge associated with lifelong combination antiretroviral treatments (cART) taken by HIV infected patients have motivated the development of strategies for therapeutic relief. The cART simplification reduces toxicity and drug costs, and improves patients' quality of life. Short-cycles treatment interruptions (SCT), in which patients take their treatment only few consecutive days in the week, have been shown as promising and are still under investigation. The PENTA Trial group investigated 5/7 designs (5 days on, 2 days off cART) in adolescents in the Breather trial. They showed a sustainable non-inferiority of virologic suppression compared to continuous cART [1]. The ANRS 170 QUATUOR is an ongoing trial investigating 4/7 designs and conclusions are yet to be drawn We propose a pipeline for computer-based simulations of trials which aim at quantifying and predicting *in silico* the effect of ongoing and future SCT in order to accelerate and personalize their development.

Methods: HIV viral load and CD4+ T cells count trajectories under treatment conditions were modelled using dynamical mechanistic models based on Ordinary Differential Equations [2,3]. Data from 2550 patients of the ANRS CO3 Aquitaine HIV cohort were used to estimate model parameters. Because longitudinal observations were sparse and prone to error measurement, we adopted a population mixed effects approach and supplemented it with information from *in vitro* assays. Of particular interest, we used Instantaneous Inhibitory potentials (IIP) of antiretroviral and cART to increase information [4]. Estimates of the *in vivo* cART effect were obtained from a populational statistical optimization approach using both NIMROD [5] and Monolix [6]. We generate pseudo subjects sampled with statistically controlled heterogeneity, for whom pseudo parameters are sampled from the estimated parameters distribution. Then, by predictions, we simulate *in silico* data of realistic SCT trials. Computer-based success of the SCT is evaluated regarding the distribution of the probability of detectable viral load (at level 1 and 50 copies/mL) and the distribution of the basic reproduction number R0 at 48 weeks in the *in silico* population. The R0 can be thought of as the number of d CD4+ T infected cells one infected cells generates on average over the course of its infectious period, in an otherwise uninfected CD4+ T cells population. If R0 is below 1 the infection will die out in the long run. Therefore, R0 provide additional mechanistic information on the computer-based probability of success of the SCT.

Results: We estimate that most of the investigated Efavirenz-based (EFV) cART will be potent enough to guarantee the success of 5/7 designs (5 days on, 2 days off cART). We can derive *in silico* the results of the Breather trial [7], which is a 5/7 design for EFV-based cART. Simulations predict 1% [0%; 11.9%] of virologic failure and show a mean R0 of 0.82 [0.63; 0.99]. The *in silico* and *in vivo* results were consistent as the 95% confidence interval included the true outcome (8.1% of 50 copies/mL virologic failure at 48 weeks). The investigation of 4/7 designs show that with the most potent cART (such as dolutegravir- or darunavir- based cART), viral suppression is likely to be sustained, simulations predict between 0% and 2% of virologic failure.

Conclusions: The computer-based approach correctly predicts the outcome of existing SCT trials. Moreover, it has the advantage to characterize mechanistic indicators, such as the R0, which provides alternative

outcome for the SCT success. Thus, our pipeline for *in silico* trials is a promising tool for accelerating the development of novel strategies based on existing cART. Finally, as a direct extension of the methodology, it is also a promising tool to investigate individual- and treatment- specific SCT.

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II-82: *Luna Prieto Garcia* Physiologically-based pharmacokinetic model for itraconazole and its metabolites: the importance of parameter sensitivity analysis

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Introduction: : Itraconazole has emerged as one of the best candidates to use as a standard CYP3A4 inhibitor in clinical drug-drug interaction (DDI) studies [1]. A physiologically based pharmacokinetic (PBPK) model for itraconazole is clearly beneficial for both DDI risk assessment and optimization of clinical trial design [2]. However, PBPK modeling for itraconazole using a 'bottom-up' approach is challenging. Not only due to complex saturable pharmacokinetics (PK) and presence of three metabolites exhibiting CYP3A4 inhibition, but also because discrepancies in reported in vitro data. Itraconazole and its metabolites are both substrates and inhibitors of CYP3A4 and the simulations of the plasma PK profiles are sensitive to all parameters included for both the parent and the metabolites. Therefore, the application of sensitivity analysis to the PBPK modeling is key to understand what factors that are of highest importance for the PK and DDI predictions.

Objectives:

- to perform a sensitivity analysis to assess the relative importance of the parameters into this complex model of a parent compound and two sequential metabolites in which all are substrates and inhibitors of the same enzyme.
- to provide a comprehensive 'bottom-up' PBPK model for itraconazole to increase the confidence in its DDI predictions.

Methods: The sensitivity analysis was done using two different local methods: the one-factor-at-a-time and the sensitivity index (SI) approach [4,5]. Input parameters were simultaneously experimentally determined for the parent and the metabolites. All generated data (in-vitro and in-vivo) were included in the model using Simcyp® software. To assess the performance of the model on simulating PK profiles a quantitative analysis was conducted according to previously established methods [5]. The difference factor ($f1$), which is a model-independent parameter, was applied for the comparison of the plasma concentration-time profiles of itraconazole, hydroxy-itraconazole (OH-ITZ) and keto-itraconazole (keto-ITZ). In addition, performance of the model was validated using pre-specified acceptance criteria against different dosing regimens and formulations for 18 DDI studies including midazolam and other CYP3A4 substrates.

Results: Sensitivity analysis was a key element for model development. It was crucial to guide decision-making on additional experimental resources to generate in vitro data that could be applied to the PBPK model development. The sensitivity analysis showed that the predicted area under the concentration- time curve (AUC) were more sensitive to plasma protein binding and enzyme kinetics compared to CYP3A4 inhibition. Overall, the PK profiles were predicted adequately, exhibiting $f1$ of 43%, 30%, and 52% for itraconazole, OH-ITZ, and keto-ITZ, respectively. The observed plasma concentration fell within the 90% prediction interval and accumulation over days was reasonably well captured by the model for all three compounds under all of the different conditions. In addition, clinical DDI studies with midazolam and other CYP3A4 substrates were successfully predicted within 2-fold error. Prediction precision and bias of DDI

expressed as geometric mean fold error were for the AUC and peak concentration, 1.06 and 0.96, respectively.

Conclusions: This model provides improved mechanistic understanding of the PK and DDI of itraconazole and its metabolites. The sensitivity analyses highlight the importance of having robust in vitro and in vivo data to enable complex model building. The predictive DDI risk capability of this model is improved compared with the Simcyp itraconazole library model [6] (100% vs. 80% predicted within 2-fold), showing no bias and good precision. Therefore, our observations suggest that this novel PBPK model built for itraconazole and two of its main metabolites can be successfully used to both evaluate DDI involving new victim compounds and to facilitate optimal study design.

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II-83: *Alicja Puszkiel* Population pharmacokinetic analysis of tamoxifen and its six metabolites in breast cancer patients: Quantification of the impact of genetic polymorphisms and co-medications on tamoxifen metabolism

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Objectives: Plasma levels of endoxifen (ENDO), the major active metabolite of tamoxifen (TAM), vary widely among individuals (1) which may explain the high inter-individual variability (IIV) in efficacy and toxicity observed in breast cancer patients (2). The aim of this study was to develop a population pharmacokinetic (PK) model for TAM and six of its metabolites in breast cancer patients and to investigate the impact of genetic polymorphisms and co-medications on TAM metabolism.

Methods: PK data for TAM and six metabolites (N-desmethyl TAM [NDT], 4-hydroxy-TAM [4-OHTAM], 4'-OHTAM, ENDO and Z'-ENDO) come from a prospective, multicenter, 3-year follow up study of 879 breast cancer patients initiating adjuvant TAM treatment (20 mg/day). Plasma samples were drawn 24 hours post-dose every 6 months over a 1.5-year period and co-medications at time of PK sampling were recorded. A validated UPLC-MS/MS method (3) was used to measure plasma concentrations of TAM and metabolites. Analysis of *CYP2D6*, *CYP3A4*, *CYP3A5*, *CYP2C19* and *CYP2B6* genetic polymorphisms was performed at study inclusion. Patients were assigned a CYP2D6 phenotype - poor (PM), intermediate (IM), normal (NM) or ultrarapid metaboliser (UM) - based on the presence of functional (*1), reduced function (*9, *10, *17, *41) or non-functional alleles (*4, *6, *7) and the number of gene copies (*5 or gene duplication). PK analysis was performed using non-linear mixed-effects modelling in NONMEM 7.4.1.

Results: Concentration-time data for TAM and six metabolites (n = 15,575 concentrations) were analysed simultaneously with a seven-compartment model. The absorption of TAM from depot compartment was described by a first-order rate constant k_a. Apparent volumes of distribution of the metabolites (V/*F*/*fm*) were not identifiable and were fixed to the value of V/*F* of TAM (966 L). The formation of primary or secondary metabolites and their subsequent elimination were described by first-order conversion (k) or elimination (k_e) rate constants, respectively. The IIV was included on several PK parameters according to an exponential model. Inclusion of off-diagonal covariance elements and inter-occasion variability improved the model fit. The base model was used to perform covariate analysis with significance levels of pNDT/ENDO. The estimates of $k_{NDT/ENDO}$ were 81% and 65% lower in PM and IM patients, respectively, and 51% higher in UM patients, compared to the estimate in NM patients. In addition, $k_{TAM/4\text{-}OHTAM}$ was decreased in both IM and PM patients by 30%. Patients with *CYP3A4*1/*22* or **22/*22* genotype had significantly lower $k_{TAM/NDT}$ (–12%) whereas patients with *CYP2B6*6/*6* genotype had significantly lower $k_{TAM/NOX\text{-}TAM}$ (–24%). Use of weak/moderate or potent CYP2D6 inhibitors decreased $k_{NDT/ENDO}$ in NM patients by –26% and –52%, respectively. In addition, the use of CYP2D6 inhibitors decreased $k_{NDT/ENDO}$ in UM patients (–71%) whereas they had no effect on $k_{NDT/ENDO}$ in IM and PM patients. Use of CYP2D6 inhibitors decreased $k_{TAM/4\text{-}OHTAM}$ by 12%. Finally, body weight had significant impact on $k_{e,NDT}$. The estimates (%RSE) of

the PK parameters of the final model were: $k_{TAM/NDT}$ = 7.8 x 10^{-3} h^{-1} (1.4%), IIV = 28% (3.8%), IOV = 29% (2.0%), $k_{TAM/4\text{-}OHTAM}$ = 5.3 x 10^{-5} h^{-1} (19%), IIV = 57% (3.1%), $k_{TAM/4'\text{-}OHTAM}$ = 6.0 x 10^{-8} h^{-1} (1.3%), IIV = 25% (3.5%), $k_{TAM/NOX\text{-}TAM}$ = 4.9 x 10^{-7} h^{-1} (2.2%), IIV = 47% (3.2%), $k_{NDT/ENDO,CYP2D6\ UM}$ = 8.0 x 10^{-4} h^{-1} (13%), $k_{NDT/ENDO,CYP2D6\ NM}$ = 5.3 x 10^{-4} h^{-1} (10%), IIV = 46% (3.4%), $k_{NDT/ENDO,CYP2D6\ IM}$ = 1.9 x 10^{-4} h^{-1} (11%), $k_{NDT/ENDO,CYP2D6\ PM}$ = 9.8 x 10^{-5} h^{-1} (14%), $k_{NDT/Z'\text{-}ENDO}$ = 3.9 x 10^{-7} h^{-1} (1.3%), $k_{4\text{-}OHTAM/ENDO}$ = 2.7 x 10^{-3} h^{-1} (18%), $k_{e,NDT}$ = 3.7 x 10^{-3} h^{-1} (3.1%) IIV = 48% (2.3%), $k_{e,ENDO}$ = 8.8 x 10^{-3} h^{-1} (9.4%), $k_{e,4'\text{-}OHTAM}$ = 1.9 x 10^{-6} h^{-1} *(fixed)*, $k_{e,NOX\text{-}TAM}$ = 3.0 x 10^{-6} h^{-1} *(fixed)*, $k_{e,Z'ENDO}$ = 1.0 x 10^{-5} h^{-1} *(fixed)*. The visual predictive check showed good agreement between observed and simulated concentrations which allowed for model validation. The developed model will be used to perform simulations of alternative dosing regimens for PM and IM patients who are at increased risk of subtherapeutic exposure to ENDO.

Conclusions: The developed model could be useful to establish recommendations for monitoring of plasma concentrations of ENDO and to individually adjust the dose if the correlation between ENDO exposure and therapeutic outcome is confirmed in prospective studies.

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II-84: *Rajith Rajoli* PBPK Modelling of Atovaquone Long-acting Injectable Formulations

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Background: Malaria remains a global health threat despite the improvement in controlling the spread of this disease. Although effective treatment and chemoprophylactic regimens are available, sub-optimal adherence to oral regimens results in sub-therapeutic plasma concentrations increasing the risk of failure (1). Atovaquone is a commonly used antimalarial for treatment and prophylaxis as part of a combination with proguanil, and target plasma concentrations for treatment and prevention have been identified (2). Recent application of long-acting injectable (LAI) drug delivery in other therapeutic areas such as schizophrenia, contraception and HIV has opened opportunities to simplify therapy, reduce drug costs and tackle adherence issues (3).

Objective: The aim of this study was to simulate the pharmacokinetics (PK) of a theoretical parenteral atovaquone LAI using physiologically-based pharmacokinetic (PBPK) modelling. Atovaquone PK was simulated across doses and release rates to achieve PK targets for treatment and prophylaxis as 4-weekly LAI administration.

Methods: Simulations were conducted in 100 healthy individuals (50% women, 18-60 years, 77 ± 19 kg (40-120 kg)) (4) using published anthropometric equations (5). A validated whole-body PBPK model for parenteral delivery was used in this study (6) and the PBPK model was constructed using Simbiology v 5.8 (MATLAB 2018a). The PBPK model was constructed using physicochemical and drug-specific parameters available from the literature. Initially, atovaquone simulations were qualified against observed data from a single oral dose in healthy adults (7). The PBPK model was assumed to be qualified if the mean simulated values i.e. the AUC, C_{max} and the plasma concentration time curve were within ± 50% from the mean observed values. Atovaquone LAI PK were simulated across a range of doses and release rates. For atovaquone LAI treatment and prophylaxis, target concentrations of 1.83 mg/L (2) and 0.2 mg/L (8) were considered as adequate target concentrations at the end of the 4-weekly dosing interval to identify the minimum dose and optimal release rate.

Results: The PK parameters of atovaquone oral PBPK model qualification were within the acceptable range, with the mean simulated vs. observed AUC_{last} (mg.h/L) – 351 ± 95 vs. 430 ± 103 (difference of -18.4%) and C_{max} (mg/L) – 3.7 ± 1.1 vs. 5.3 ± 1.59 (difference of -30.2%) values comparable. For a 4-weekly LAI, the administration of a LAI dose of 1500 mg with the release rate constants from 1.5×10^{-3} to 2.5×10^{-3} h^{-1} for treatment and a minimum dose of 200 mg with release rate constants from 1×10^{-3} to 3×10^{-3} h^{-1} for prophylaxis, was predicted to result in plasma concentrations above the defined target concentrations.

Conclusions: The PBPK model identified minimum dose and release characteristics for atovaquone, supporting rational development and streamlining the optimisation of future LAI formulations. Dosing suspensions containing over 300 mg/mL have been developed for other indications meaning that higher doses and longer exposures may be possible for atovaquone. Ultimately, the duration of achievable exposure will be dependent upon achievable drug loading and whether intramuscular or subcutaneous administration is preferred.

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II-85: *Chetan Rathi* Model-Informed selection of doses and sample size for a Phase 2a POC study of GSK3640254, a next generation HIV-1 maturation inhibitor

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Introduction: GSK3640254 (MI-254) is a next generation HIV maturation inhibitor (MI) that prevents maturation of HIV-1 virions by binding near a key structural element within the Gag polyprotein that is required for virion maturation and assembly. Prior validation of this target was demonstrated with bevirimat and GSK3532795 (MI-795) which were later terminated in Phase 2a for treatment-emergent resistance and Phase 2b studies for GI intolerability respectively. MI-254 has improved coverage of baseline Gag polymorphisms over the prior developmental MIs. The safety, tolerability, and PK of MI-254 was investigated following single (1 to 700 mg) and repeated daily (50 to 320 mg for two weeks) administration in a Phase 1 First Time In Human (FTIH) study (NCT03231943).

Objectives: The aim of this model-based analysis was to select a) doses and b) cohort size for a Phase 2a POC study (NCT03784079) to evaluate short term maximum HIV-1 RNA decline in monotherapy and to characterize Dose-Exposure-Response relationship.

Methods: To predict the anticipated individual decline in HIV-1 RNA over a wide range of possible doses for the POC study, a model-informed framework was developed using the exposure-response (ER) model for the POC study for MI-795, the in vitro potency distribution for MI-254, and the PK profile of MI-254. The ER model links the individual inhibitory quotient (IQ) (trough concentration divided by the individual protein binding adjusted EC90 (PBAEC90)) to the maximum decline in HIV-1 RNA following 10 days of MI once-daily monotherapy, the primary endpoint in the POC study. This ER relationship was characterized using an Emax model composed of the following parameters: Reduction in HIV-1 RNA from baseline (E), placebo HIV-1 RNA decline (E0), maximum HIV-1 RNA decline (Emax) and IQ50 all obtained from the MI-795 model and the individual IQ for MI-254. These individual IQ were obtained by predicting MI-254 trough concentrations using a PopPK model based on the FTIH data and sampling from the distribution of MI-254 PBAEC90 obtained from in vitro studies. These in vitro PBAEC90 are considered representative of the distribution of clinical PBAEC90 values based on experience with MI-795. Reduction in HIV-1 RNA (E) was simulated with both variability and uncertainty included on PK parameters and with variability on PBAEC90 for 1000 trials with 6 and 8 subjects per cohort for a wide range of doses (5 to 200 mg QD). %Emax was summarized in terms of 2.5th, 50th and 97.5th percentiles achieved in each trial for each dose level. Finally, % Emax was summarized in terms of 2.5th, 50th and 97.5th percentiles of the 1000 median values obtained in the previous step. The FTIH PK data were analyzed using non-linear mixed effects modeling implemented in NONMEM V7.3.0[1]. Clinical trial simulations were conducted using the mrgsolve package in R [2].

Results: A 2-compartment PK model with first order absorption and lag time adequately characterized the pharmacokinetics of MI-254 in healthy volunteers. The typical values of the model are as follows: clearance (CL/F, 7.99 L/h), volume of distributions (V2/F and V3/F, 197 and 81.8 L, respectively), inter-compartmental clearance (Q/F, 15.1 L/h) and first-order absorption rate constant (Ka, 0.912 h-1) with lag time (0.894 h). Inter-individual variability (IIV) for clearance, central volume of distribution and absorption rate constant ranged from 30.9 - 73.3% with uncertainty on PK and IIV parameters ranging from 5.9 - 34.6%. Based on simulated virtual trials for HIV-1 RNA decline, doses of 5 mg, 10 mg, 40mg, 100 mg and 200 mg were identified as doses providing ~30%, 50%, 80%, 90% and >=95% of maximum effect respectively. Simulations also suggested that increasing cohort size from 6 to 8 did not provide any additional benefits.

Conclusions: Model informed drug development (MIDD) approach provided an integrated pharmacometric framework in conjunction with historical clinical data to guide selection of doses and cohort size for the POC study. Simulation of virtual trials allowed a recommendation of 5 mg, 10 mg, 40 mg, 100 mg and 200 mg doses with a cohort size of 6 for the POC of GSK3640254 in HIV infected patients.

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II-86: *Michael Reed* Evaluation of competitive differentiation of novel therapies and the impact of patient variability on efficacy in a psoriasis QSP platform

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Introduction

Psoriasis is a chronic, debilitating autoimmune skin disease affecting ~2% of the population with itching, thickened, red scaly skin, and more rarely psoriatic arthritis. Despite several therapeutic options including topical agents and systemic therapies, there is widespread undertreatment due to lack or loss of response, safety concerns, and tolerability. Novel drugs (small molecules, new biologics) with fewer side-effects or more convenient dosing may help overcome these obstacles.

Objectives

Quantitative Systems Pharmacology (QSP) can provide insight into disease pathophysiology, help optimize the efficacy of novel therapies, and reduce the risk at various stages of drug development. The main objectives were to:

- Assess the potential of novel oral drugs and anti-cytokine antibodies in psoriasis.
- Compare efficacy to standard of care therapies, i.e., methotrexate, adalimumab, guselkumab, and secukinumab.
- Identify mechanistic drivers and impact of patient variability on treatment response.

Methods

We developed a mechanistic QSP model using algebraic and ordinary differential equations to represent the physiology of a single chronic psoriatic plaque (including keratinocytes, immune cells, cytokines, chemokines, and their regulation), drug pharmacokinetics, and clinical outcomes (PASI score). The model was designed and qualified in accordance with Rosa's Model Qualification Method [1]. Over 450 individual parameters were assessed from more than 2000 literature references to quantify cell numbers, lifecycle parameters, mediator production rates and their effects on cellular functions (e.g., EC50 and Emax), and the impact of therapies. The Psoriasis Platform was qualified using published clinical and histology data for four standard of care therapies (**Table 1**).

Table 1. Standard therapies dosing and outcomes used to qualify the Psoriasis Platform

Outcomes	Therapy	Dosing schedule	References
· PASI score & subscores · Reduction in cellular infiltration	Adalimumab (anti-TNFα)	80 mg SC once, then, after 1 week, 40 mg SC Q2W	[2-7]

Guselkumab (anti-IL-23)	100 mg SC at week 0, week 4, and Q8W thereafter	[3, 8-12]
Secukinumab (anti-IL-17)	300 mg SC at weeks 0, 1, 2, 3, and 4 followed by 300 mg SC Q4W	[13-17]
Methotrexate	15 mg oral weekly dose	[2, 18-22]

Research simulations provided insights into the potential efficacy of a novel orally delivered drug targetting the IL-17 pathway as well as novel anti-TNFα and IL-23 antibodies. Sensitivity analysis was used to determine pathways and drug characteristics critical for decreasing skin inflammation and improvement in the PASI clinical score. Alternate disease phenotypes were created to define best- and worst-case scenarios and to evaluate the impact of variability in key target-related pathways.

Results

Research using the Psoriasis QSP Platform predicted that targeting IL-17 pathways with a novel oral compound would be more efficacious than methotrexate in most disease phenotypes. Simulations in a moderate psoriasis virtual patient predicted that 20 mg QD of oral anti-IL-17 drug would reduce the PASI score by 49 to 64% after 4 weeks depending on its pharmacokinetic properties, compared to only 33% reduction with methotrexate. The novel anti-TNFα and anti-IL-23 antibodies were predicted to be very efficacious, achieving a PASI 90 clinical response in all virtual disease phenotypes tested, better than adalimumab, guselkumab, or secukinumab responses. Clinical efficacy was sensitive to skin immune cell infiltration (Th17 versus Th1/macrophages), and to drug distribution and bioavailability. Simulations confirmed that a short-term (4-weeks) Phase I clinical trial design is sufficient to demonstrate efficacy and competitive differentiation for the new therapies.

Conclusion

The Psoriasis QSP Platform was designed to quantitatively assess the clinical efficacy of novel therapeutics for moderate to severe psoriasis and reduce risk throughout the drug development process. Research in the Psoriasis Platform identified:

- Dosing regimens and pharmacokinetics constraints under which novel experimental drug would be superior to standard of care therapies
- IL-17 pathways as critical to disease pathophysiology and response to therapies in all virtual patient phenotypes evaluated
- Key uncertainties related to target expression and drug biodistribution in the skin
- A shorter trial duration sufficient to demonstrate efficacy while significantly reduced cost

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II-87: *Javier Reig-López* Validation of a Semi-mechanistic model with first-pass metabolism, two metabolic pathways and intestinal efflux transporter implemented in PhysPK biosimulation software.

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Objectives: The aim of this work is to validate model predictions from PhysPK biosimulation software using a previously published semi-mechanistic model by comparing exposure metrics (AUC and C_{max} values) previously generated in NONMEM with those obtained with PhysPK for each type of analyte: parent drug (PD), primary- (PM) and secondary-metabolite (SM).

Methods: A sample of 24 patients previously generated by Monte Carlo simulations in NONMEM 7.3 [1] was introduced in a parametric experiment wrote in EL language in PhysPK biosimulation software [2]. A previously semi-mechanistic model served as a basis for the analysis [3]. The study design was a single-dose study in 24 individuals receiving 100 mg of a drug. The dose is orally administered as a solid form (C8) and dissolution (E1) is considered limited by the solubility (S). The drug dissolved in lumen is either degraded or absorbed (E2). However, in this study the luminal degradation was fixed to zero. Moreover, the intestinal transit is considered as an operative absorption time (OAT1) fixed to 7h, allowing for passive diffusion, and the efflux activity was limited to 3h (OAT2). After drug absorption, the gut and liver partially metabolize the drug (E3-E6). This metabolism can be linear or non-linear, depending on the drug concentration related to K_M. Then, the drug is rapidly distributed in one compartment (C4) and slowly distributed (E7) in peripheral compartment (C5). The elimination of parent drug is by intestinal (E3 and E5) and hepatic (E4 and E6) metabolism, while both metabolites are eliminated by renal excretion (E8 and E9). The simulations were performed after a single dose administration. Different scenarios were explored: different degrees of inter-individual variability, dose levels and BCS class (II and IV).

Results: Individual plasma concentration-time profiles of PD, PM and SM were represented, showing the concordance between both softwares. Relative change in exposure metrics (AUC and C_{max}) were computed, considering NONMEM estimates as the reference value. Results showed that PD AUC values obtained with PhysPK biosimulation software were of the same magnitude order of those achieved with NONMEM. In general, PhysPK biosimulation software showed a relative change in PD, PM and SM AUC and C_{max} values which are in agreement with the predicted value from NONMEM. The 95% confidence interval of the relative changes ranged from -12.5 to 10.7 % in the worst scenario. No statistically significant bias were detected when high versus low doses were used or high versus low variability, which demonstrates the adequacy of the non-linear processes implemented in both environments.

Conclusions: PhysPK biosimulation software is useful for estimating the pharmacokinetic parameters of a complex pharmacokinetic model, since it allows obtaining pharmacokinetic profiles similar to those obtained using NONMEM. However, these evaluation studies must be continued in order to correctly conclude the validity of the software.

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II-88: *Isabel Reinecke* Levonorgestrel-Containing Contraceptives: Comparison of Daily Doses and Exposure for Various Routes of Administration by an Integrated Population Pharmacokinetic Analysis

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Introduction: Women can choose among a number of contraceptives and administration routes containing the progestin levonorgestrel. This hormone is used as a component in contraceptives because of its influence on at least 2 mechanisms in preventing pregnancy: ovulation inhibition and thickening of the cervical mucus. A direct comparison of levonorgestrel daily doses and exposure of these different products has not been made until recently [1]. Levonorgestrel-containing contraceptives administered orally or as an implant act mainly via their systemic levonorgestrel exposure, whereas levonorgestrel administered via an intrauterine system (IUS) is released directly into the uterine cavity, resulting in lower systemic levonorgestrel concentrations. All levonorgestrel-containing contraceptives included in this analysis are known to be safe and highly effective, despite the fact that they differ in administration route, daily levonorgestrel dose and systemic exposure. However, a comparison of daily dose and exposure would support decision making between products by health care providers and by the women themselves.

Objectives:

- Compare typical levonorgestrel exposure for 3 IUSs, 2 oral contraceptives, and an implant, by simulating the exposure for the same treatment duration with an integrated population PK (popPK) model.
- Compare absolute bioavailability and daily levonorgestrel doses by calculating in vivo release rates for the IUSs and implant based on the integrated popPK model.

Methods: For this analysis, data from 10 clinical pharmacology studies in healthy premenopausal women (n=3424) with 6 levonorgestrel-containing contraceptives, including iv data, were integrated: 3 intrauterine systems (IUSs; levonorgestrel [LNG]-IUS 20 [Mirena®], LNG-IUS 12 [Kyleena®], and LNG-IUS 8 [Jaydess®/Skyla®]); 2 oral contraceptives (the progestin-only pill [Microlut®/Norgeston®] and the combined oral contraceptive [Miranova®]); and a subdermal implant (Jadelle®). The integrated population PK analysis was performed by means of a nonlinear mixed-effects approach using NONMEM® software (Version 7.2.0). Simulations were performed using R software (version 3.2.0 or higher).

Results: The estimated released daily dose of levonorgestrel into the uterine cavity for LNG-IUS 20 decreased over the 5 years of period-of-use from 21.7 µg after 24 days to 10.7 µg after 5 years, for LNG-IUS 12 from 15.4 µg after 24 days to 7.59 µg after 5 years, and for LNG-IUS 8 (3 years period-of-use) from 13.4 µg after 24 days to 5.51 µg after 3 years. The estimated absolute bioavailability was close to 100% for all 3 IUSs. The estimated daily dose of the implant (5 years period-of-use) decreased from 53.0 µg after 24 days to 32.8 µg after 5 years. The absolute bioavailability was estimated to be 66.0%. Compared to that, the daily dose of the combined oral contraceptive was 100 µg, in combination with 20 µg ethinylestradiol (28-day cycle, i.e. 21 days on/7 days off), and of the progestin-only pill 30 µg (absolute bioavailability estimated at approximately 80% for both oral contraceptives). Thus, the highest daily dose is provided by the combined oral contraceptive, followed, in decreasing order, by the progestin-only pill and the implant (both

similar daily doses), and the IUSs LNG-IUS 20, LNG-IUS 12, and LNG-IUS 8. This is in line with the comparison of the estimated levonorgestrel exposure. The geometric mean of the average total levonorgestrel concentration at steady-state of the combined oral contraceptive was estimated to be 1676 ng/L whereas the geometric mean of the total levonorgestrel concentration of the LNG-IUS 8, the IUS with the lowest daily dose, decreased from 127 ng/L after 24 days to 58.1 ng/L after 3 years, which is only approximately 8 % and 3 %, respectively, of the average serum concentration of the combined oral contraceptive.

Conclusions: The integrated popPK analysis allowed a valid comparison of daily levonorgestrel doses and systemic exposure for 6 levonorgestrel-containing contraceptives which may support decision making between products by health care providers and by the women themselves. The analysis revealed that the combined oral contraceptive provided the highest daily levonorgestrel dose and led to the highest levonorgestrel exposure, whereas the IUSs, in particular LNG-IUS 8, provided the lowest daily levonorgestrel dose and led to the lowest systemic levonorgestrel exposure.

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II-89: *Dinko Rekic* Higher Febuxostat Exposure observed in Japanese Compared to Caucasian Subjects Independent of Bodyweight

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Objectives: Febuxostat is a xanthine oxidase inhibitor indicated for gout and hyperuricemia. Several clinical studies are completed or ongoing to investigate the effect of xanthine oxidase inhibitors and other uric acid lowering drugs on renal function in chronic kidney disease [1]. Xanthine oxidase inhibitors including febuxostat are titrated to a serum uric acid target in gout and hyperuricemia. Medical value of adjusting the dose of febuxostat to achieve a target serum uric acid for chronic kidney disease is unknown. This work investigates potential clinically relevant covariates for febuxostat dosing to support a fixed dose regimen in the chronic kidney disease indication.

Methods: Febuxostat plasma concentrations from 145 male subjects were obtained from 2 phase-2 studies in hyperuricemic/gout patients and 1 study in healthy volunteers. Subjects were administered febuxostat doses ranging from 10 to 80 mg. The pharmacokinetics of febuxostat were analyzed using non-linear mixed-effects modeling as implemented in NONMEM 7.3.0 [2]. The dataset consisted of racially diverse subjects, 40% being Japanese, 10% of unknown Asian origin, 39% Caucasian and 10% Black. Most subjects (n=92, 63%) had normal CrCL (90 mL/min), while 52 subjects (36%) had mild renal impairment (CrCL >60-<90) at baseline. Mean (±SD) bodyweight (BW) differed between Asian (78±12 kg) and Caucasian subjects (98±16 kg). The effect of disease state, BW, and time-dependent Creatinine clearance (CrCL) on febuxostat pharmacokinetics was investigated using stepwise covariate modeling as implemented in PsN 4.4.8 [3].

Results: Asian race (Japanese or of unknown Asian origin) was the only covariate resulting in potentially clinically important increase in febuxostat AUC (1.63-fold, 90%CI: [1.48;1.79]) compared to Caucasians. Difference in BW between Asian and Caucasian subjects did not explain the difference in febuxostat exposure. Febuxostat pharmacokinetics were well described by a 2-compartment model. Absorption was modeled as sequential first and zero order process with lag-time. Additive residual error was estimated separately for the absorption- and for the disposition phase on the log-scale.

Conclusions: In this pooled analysis of 3 studies, we show that Japanese subjects, or Asians of unknown origin, have 1.63-fold higher febuxostat exposure than Caucasians, independent of bodyweight or other investigated covariates. These findings may be of importance when selecting starting febuxostat doses in Asian patients.

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III-01: *Clémence Rigaux* An approach for reducing the sample sizes of pediatric trials in Type 2 Diabetes Mellitus: longitudinal analysis versus standard analyses

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Introduction: Since 2005, pharmaceutical companies have been required by the Food Drug Agency to complete formal safety and efficacy pediatric trials for 21 new non-insulin drugs under the Pediatric Research Equity Act. However, recruitment for pediatric trials in Type II Diabetes Mellitus (T2DM) is very challenging (1), necessitating new approaches for reducing the sample sizes of pediatric trials in T2DM. In this work we assessed if a longitudinal Non-Linear-Mixed-Effect (NLME) analysis of T2DM trial results could be more powerful and so require less patients than standard analyses. These standard analyses currently used are Last Observation Carried Forward (LOCF) + analysis of variance (ANOVA) analysis, and Mixed-effects Model Repeated Measures (MMRM) analysis, which is a repeated measures analysis including treatment-by-visit interaction effect and that accounts for missing data phenomenon. The longitudinal NLME analysis is expected to be more precise and more powerful than standard analyses as it includes information from all observed time points and as the difference between drugs could be summarized by only one drug effect parameter.

Objectives: to compare the power of MMRM analysis, LOCF + ANOVA analysis at end of study, and longitudinal NLME analysis in the assessment of results of a simulated T2DM trial.

Methods: Studies in T2DM were simulated, with glycated hemoglobin (Hba1c) as main endpoint, 24 weeks duration, 2 arms, 75 patients per arm, HbA1c measurements at week 0, 8, 12 and 24 as in standard clinical trials in T2DM, and assuming a mean placebo effect of -0.1% HbA1c and a mean treatment effect of -0.5% HbA1c. Hba1c change was modelled using 3 scenarios: 2 with a structured model of negative exponential progression with steady state reached at week 12 (A) or week 20 (B), and an unstructured (ie not coming from a mathematical model) scenario (C). Inter-individual-variability was accounted for. Dropout was also modeled, assuming a Missing At Random (MAR) phenomenon and a global dropout rate at week 24 of about 10%.

1000 trials were simulated and for each trial, statistical significance of a between-group difference in HbA1c change from baseline at week 24 was assessed, using the 3 types of analyses:

- LOCF + ANOVA at week 24
- MMRM approach, then computation of treatment difference at week 24
- Longitudinal NLME modelling, using a structured model of negative exponential shape, then prediction of treatment effect at week 24.

Then the power of each type of analysis was computed as the % of the 1000 trials with significant tests, and these powers were compared. Two types of power were computed: in case of bad convergence of an analysis for a trial, the test was considered either missing or non-significant.

Results: The LOCF + ANOVA analysis slightly under-estimated the magnitude of drug effect and was less powerful than the MMRM and NLME analyses in all scenarios (mean bias between +0.010 and +0.024 %HbA1c depending on the scenario, and power always < 78%). For structured scenarios A and B, similar power was observed between MMRM and NLME analyses (around 83% for scenario A and 85% for scenario

B depending on the method and type of power calculation), and for unstructured scenario C, NLME analysis was a little more powerful than MMRM (92% versus 88%) but was associated with a slight overestimation of magnitude of drug effect (mean biais -0.044 %HbA1c).

A slightly more precise estimation of the drug effect parameter was obtained with the NLME method compared to the two other methods (standard error ≤0.172 versus between 0.179 and 0.189 %HbA1c).

Further explorations showed that adding some HbA1c measurements at week 4 and 52 led to a gain in power for NLME compared to MMRM (gain ~+8% for scenarios B & C), and that the type 1 error was a little inflated for MMRM (9%) and for NLME (7 to 10%).

Conclusions: The longitudinal modelling analyses MMRM and NLME were more powerful than the LOCF + ANOVA analysis at week 24. The NLME analysis gave slightly more precise drug effect estimations than the 2 other methods. However, it tended to overestimate the magnitude of drug effect and it was more powerful than standard MMRM analysis only in some scenarios, with an increased gain in power in presence of additional time-points. These initial results suggest that NLME analyses may help to reduce the required sample sizes in T2DM pediatric studies, provided that sufficient HbA1c assessments are planned.

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III-02: *Matthew Riggs* M-EASE-1: A Modelling and simulation study conducted to further characterize the efficacy of low-dose Empagliflozin as Adjunctive to inSulin thErapy (M-EASE) in Type 1 Diabetes Mellitus

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Objectives: The objective of this modelling and simulation study was to further characterize the efficacy of empagliflozin (EMPA) 2.5 mg qd dose, independent of data from EASE-3 [1], a phase 3 study which investigated this dose. Specifically, this semi-mechanistic exposure-response modelling study (M-EASE-1) was performed to simulate two scenarios for placebo-corrected HbA1c change from baseline:

1) To assess the effect of insulin dose adjustment on HbA1c

2) To extrapolate the effect on HbA1c lowering in the study population of a 4 week phase 2 trial (EASE-1) [2] by simulating HbA1c lowering to 26 weeks

Methods: M-EASE-1 model development was informed by data from EASE-1 (4 weeks, EMPA 2.5, 10, 25 mg qd) and EASE-2 (52 weeks [1], EMPA 10 and 25 mg qd). Individual predictions of EMPA exposure were taken from a previous population PK analysis. The analysis was conducted in NONMEM Version 7.4 with the FOCEI routine. The exposure-response relationships between longitudinal HbA1c, total daily insulin dose (TDID) and mean daily glucose (MDG) measurements as functions of EMPA exposure at steady state ($AUC_{\tau,ss}$) were parametrically modelled in a step-wise fashion. First, TDID was estimated as a function of EMPA exposure. Next, MDG placebo data and thereafter, the effect of EMPA exposure and TDID on MDG were estimated. In a final step, the time course of HbA1c was estimated using individually derived MDG profiles. For internal and external model evaluation via visual predictive checks, 500 Monte Carlo simulation replicates were generated with parameter uncertainty based on both fixed and random effects. External model qualification, focused on an out of sample prediction using data from EASE-3.

For trial simulations, 500 Monte Carlo simulation trial replicates including inter-individual and residual variability as well as parameter uncertainty were created. The effect of insulin adjustment was based on random sampling from the full data set (EASE-1, -2 and -3 population) with 500 patients per dose group; simulating with and without an EMPA exposure effect on TDID (hypothetical stable insulin). The extrapolated HbA1c time course out to 26 weeks in EASE-1 was based on the study population and the treatment paradigm of this study (19 patients per dose group, 1 week stable insulin, then insulin titration).

Results: TDID was described using a direct response E_{max} function driven by $AUC_{\tau,ss}$. MDG was affected by three components, 1) EMPA exposure expressed as an E_{max} function 2) a linear time-dependent placebo effect, and 3) TDID profiles derived from the first model part. Lastly, changes in HbA1c were driven by changes in MDG predicted in the second step. Typical key population parameters (95% CI) were: Baseline HbA1c: 8.15% (8.09%, 8.21%); AUC_{50} for $TDID_{EASE\text{-}1}$: 110 (14.3, 836) nmol·h/L; E_{max} for $TDID_{EASE\text{-}1}$: 0.186 (0.145, 0.238); AUC_{50} for MDG: 370 (83.9, 1630) nmol·h/L; and E_{max} for MDG: 634 (534, 753) mg·day/dL. Inter-individual variability (CV %) for baseline TDID, E_{max} on TDID, baseline MDG and E_{max} on MDG were 32.0%, 86.0%, 9.51% and 27.8% respectively. The proportional and additive residual variability estimates (CV% and SD) were 15.6% and 0.0316 for TDID and 16.0% and 0.0316 for MDG, respectively. The

simulations performed for external qualification were consistent with EASE-3 results. The simulated median (95% CI) placebo-corrected HbA1c change from baseline at Week 26 for EMPA 2.5 mg qd was -0.29% (-0.40%, -0.10%) and -0.40% (-0.53%, -0.23%) with adjusted and stable insulin therapy, respectively. Simulations of the study population and treatment paradigm of EASE-1 (i.e. 19 patients) showed a median (95% CI) placebo-corrected HbA1c change from baseline at Week 26 of -0.26% (-0.62%, 0.08%) for patients receiving EMPA 2.5 mg qd.

Conclusions: The semi-mechanistic exposure-response model successfully predicted the time-course and dose-related changes of HbA1c for internal (EASE-1 and -2) and external (EASE-3) data.

M-EASE-1 illustrated how pharmacometric analyses can be utilized to simulate untested scenarios (insulin titration, longer treatment duration) to create further evidence of efficacy and substantiate clinical findings.

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III-03: *François Riglet* Bayesian individual dynamic predictions of biomarkers and risk of event in joint modelling (with uncertainty): a comparison between Stan, Monolix and NONMEM

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Objectives: Joint models of drug or biomarker kinetics and occurrence of event are increasingly used in drug development using nonlinear mixed effect model (NLMEM)[1]. Given a joint model, Bayesian individual prediction of biomarkers and probability of event can be performed for new patients at different landmark times i.e. different time of collection of the individual data[2,3]. Several software tools allow to perform these Bayesian individual dynamic predictions and to compute associated uncertainty. It has already been shown that Stan software is able to well predict the evolution of biomarkers and survival over time in a joint model[4]. This software uses MCMC-Hamiltonian Monte Carlo (HMC), a bayesian algorithm to obtain individual *a posteriori* distribution of parameters. Lately, this ability to generate individual predictions was incorporated in other software more often used in nonlinear mixed effect modelling such as Monolix2018R2 version, or NONMEM7.4 using MCMC-Metropolis Hasting (MH) algorithm[5]. MH allow to obtain individual dynamic predictions by drawing biomarker kinetic parameters from their conditional distribution of each subject, computed from the model population parameters and individual data available, and then extrapolated the individual survival probability.
The aim of the present study was to compare the abilities of three software used in nonlinear mixed effects modelling (Stan, Monolix, NONMEM) to perform Bayesian individual dynamic predictions, with uncertainty, of biomarker kinetics and risk of death using simulated data.

Methods: Simulations of biomarker and survival data were performed using a mechanistic joint model of prostate specific antigen (PSA) kinetics and risk of death in metastatic prostate cancer[3]. PSA was measured every 3 weeks for 2 years. The survival model was a Weibull proportional hazard model with association between the current PSA kinetics and survival. Two values for the strength of this association (β) were evaluated: low link (β=0.05) and high link (β=0.02). In addition, another simulation scenario of short survival, with a smaller Weibull scale parameter λ, was also evaluated. No other mechanism than death or the administrative end of the study (T_{end} = 2 years) were considered for dropout. For each scenario, one sample of N=200 'new' patients using R software were simulated. Several landmark times s={0, 6, 12 and 18} months were studied. For each individual of each scenario, using individual data until each time s, a posteriori distribution of PSA kinetic individual parameters was estimated with each software. True population parameters were used as fixed effects in Monolix2018R2 and NONMEM7.4 and as prior in Stan. L=200 samples of individual parameters were drawn from the posterior distribution and, for each sample, biomarker and risk of death predictions were computed, given the survival model, for a horizon time $t_h = T_{end} – (s+2)$ months. Median, 2.5% and 97.5% percentiles (to derive 95% prediction interval) were derived for each parameter, predicted biomarker and risk of death at each horizon time. Relative estimation errors were used to assess bias and imprecision (RMSE) of individual parameter estimates. Similarly, bias and imprecision were also evaluated on individual PSA kinetic predictions at each horizon time. Moreover, coverages of 95% prediction interval of PSA and risk of death were also evaluated.

Results: We obtained similar results with each software tool. At each landmark, estimations of individual parameters had small biases regardless of the software. Imprecision on individual parameters was rather high but were similar with all software and showed marked improvements with increasing landmark time. In terms of coverage, results were roughly comparable with each software and these software were able to

well predict individual PSA kinetics and survival during the follow-up. In term of computing time, Stan using HMC algorithm was faster than MH software in Monolix and NONMEM to obtain individual parameters, for every scenario and at every landmark time.

Conclusions: These findings suggest that Stan, Monolix2018R2, and NONMEM7.4 are able to characterize individual dynamic predictions of biomarkers and risk of event in joint modelling framework with correct uncertainty and hence could be useful in the context of individualized medicine.

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III-04: *Christer Rimmler* Evaluating the Influence of Cardiopulmonary Bypass on the Pharmacokinetics of Cefuroxime using PBPK and PopPK Models

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Objectives: There is a wide discrepancy describing the influence of a cardiopulmonary bypass (CPB) on drugs used during surgery (e.g. the perioperative antibiotic prophylaxis (PAP)). Despite existing guidelines and recommendations, there are important issues of uncertainty regarding the timing and dose before incision and the intraoperative follow-up administrations. In order to assess the influence of CPB, we analysed plasma samples collected from patients receiving cefuroxime during surgery.

Methods: We collected 278 plasma samples from 23 patients aged 45 to 82 years during cardiopulmonary bypass surgeries and at follow up on ICU. After induction of anesthesia, a dose of 1.5 g cefuroxime was administered intravenously. Another 1.5 g cefuroxime was given at start of the CPB and three further doses were administered at ICU every 6 hours. To identify relevant covariates, a PopPK model using NONMEM® was developed. To gain deeper insight in the physiological changes during surgery, triggered by the CPB, we included relevant changes in our previous PBPK model (System Pharmacology®) [1]. For beta-lactams, the relevant PD-target to achieve a maximal bactericidal effect is the free drug concentration exceeding the pathogens minimal inhibitory concentration (MIC) for 100% of the time during the dosing interval. To reach this target, it is advocated that the blood concentrations should also exceed the MIC by a factor of 2 to 5 [2]. Test pathogens for the definition of the MIC are *S. aureus* and *E. coli,* which are most relevant for surgical side infections. MIC values were taken from EUCAST Clinical Breakpoint Tables [3].

Results: Relevant covariates were the estimated glomerular filtration rate influencing the clearance and albumin influencing the rate of distribution. Furthermore, there is a high intraindividual variability in the clearance during the different occasions (before, during CPB and on ICU). The CPB itself has no significant influence, neither on clearance nor on volume of distribution. This finding could by confirmed by the CPB-PBPK-model. The large and rapid expansion of the blood pool with the extra volume through the CPB-system leads to a small drop of the plasma concentrations, which is negligible over the time. Therefore no relevant changes in the AUC or C_{min} occurred. According to PopPK or PBPK simulations using the described dosing regime, patients during surgery are well protected against *S. aureus*, whereas a protection against *E.coli* is not sufficient. Redosing at start of the CPB is necessary to cover the period of surgery. During the subsequent time on ICU, no sufficient protection is maintained for both pathogens. A bolus of 1 g cefuroxime in addition to continuous infusion of 0.5 g/h during the time of surgery results in an adequate protection for *E.coli* (0.5 g bolus for S.aureus), without increasing the total dose of cefuroxime.

Conclusion: Our results show that the kinetics of cefuroxime is influenced by age and kidney status, not by gender, BMI or the evaluated types of surgery [1]. The use of cefuroxime for perioperative prophylaxis to prevent staphylococcal surgical site infections appears to be reasonable. However, perioperative prophylaxis against *E.coli* in abdominal surgeries is not sufficient using the actual dosing regime. We recommend an alternative regimen with 1 g bolus loading dose and continuous infusion of 0.5 g per hour.

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III-05: *Viktor Rognås* Bounded Integer approach to model time-varying SOFA scores from patients with carbapenem resistant infections

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Objectives: A Bounded Integer [1,2] modeling approach can be used to model ordered categorical data when the number of categories becomes too cumbersome for a classical ordered categorical modeling approach. The aim was to explore the ability of the Bounded Integer modeling approach to elucidate if colistin exposure had any influence on how SOFA [3] (sequential organ failure assessment) score changed over time. The SOFA score is a composite score used to evaluate organ dysfunction. The score is structured as ordered categorical data with 25 categories, range 0–24, where 0 is considered normal organ function. Previous time-to-event analysis of the AIDA study data [4] indicates that higher SOFA scores correlate with a higher hazard of death.

Methods: The AIDA study contributed clinical data from 406 critically ill patients, ages 17–95 years (median 68 years). Recruited patients had bacterial infections that were carbapenem-resistant (MIC ≥ 2 mg/L), and colistin susceptible (MIC ≤ 2 mg/L). The study evaluated treatment with colistin + meropenem versus colistin alone. Colistin concentration measurements were available from 350 of the patients. SOFA scores were assessed by the study investigators at 4 time-points: onset of disease (before randomization), randomization (day 1), day 7 and day 14.

A Bounded Integer modeling approach was applied: The mean and standard deviation (SD) of a normally distributed latent variable was modeled as a function of predictors of interest, including interindividual random effects (additive for the mean, exponential for the SD). The fractional areas of the estimated distribution within each of 25 intervals given by the 24 quantile function values (1/25 to 24/25) of a standard normal distribution are taken to be the probability of the SOFA score.

Model development was performed using the software NONMEM 7.43 and PsN 4.8.8. For model evaluation and selection, improvements in the objective function value, goodness-of-fit (visual predictive checks, VPC) and reduction in the Pearson residual were used. Parameter estimation was done using a three-step method: A short iterative two-stage step to improve the initial estimates for the random effects, followed by a maximum likelihood estimation through a stochastic-approximation expectation-maximization step and finally an importance sampling step to achieve the likelihood value.

Covariates were explored on the mean parameter using stepwise covariate modeling (forward addition, $p<0.05$; backward deletion, $p<0.01$). The tested covariates included average colistin concentration up to 24 and 120 hours (after the first dose after randomization), treatment arm, age, time-varying serum albumin concentration, log-MIC values for meropenem/colistin, as well as time itself to describe disease progression.

Results: The typical estimated [MP1] [LF2] SOFA score at baseline was 6 (median observed was also 6), with a relative standard error (RSE) of 5%. The SD (z-scale) was estimated as 0.18 (RSE 5%). The mean and SD parameters had an interindividual standard deviation of 0.21 (RSE 6%) and 0.28 (RSE 46%), respectively. Significant covariates, after inclusion of disease progression (decreasing SOFA score with time), were average colistin concentration 24 hours after first dose after randomization (Hazard ratio (HR) in relation to a median patient: 1.05 [1.01 1.08] per mg/L increase), and log-MIC values for meropenem (HR: 1.08 [1.02 1.14] per log increase in MIC). Pearson residuals followed a N(0, 1) distribution for all time points. The VPC showed that the model adequately described the data.

Conclusions: The Bounded Integer modeling approach was successfully applied to SOFA score data. The model could characterize the reduction in SOFA score over 14 days for the typical patient, as well as the variability between patients. The model indicated that high colistin exposure was associated with a high SOFA score. This finding might be confounded by kidney function since both colistin concentration and SOFA score increase with reduced kidney function.

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III-06: *Federico Romano* Title: Predictive performance and translational value of a parasite growth dynamics model for the evaluation of anti-malarial drugs: a case study with mefloquine

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Objectives:

One of the most challenging aspects of the development of new antimalarial drugs and vaccines is the lack of suitable animal models that mimic the pathophysiological features of the infection. For this reason, a humanised NOD/SCID/IL2Rγ$^{-/-}$ mice model of malaria infection has been developed that allows evaluation of parasite clearance and recrudescence presented by Tacconi et al (2018) [4]. Recently, we have shown that these data can be parameterised into a drug-disease model, allowing the characterisation of the infection cycle of the parasite and prediction of the parasiticidal drug effect and time of recrudescence (Tacconi et al, 2018) [4]. The objective of the current investigation was to demonstrate the performance and translational value of the protozoa growth dynamics model to predict treatment response in humans. Mefloquine was used as a paradigm compound.

Methods:

Pre-clinical data were obtained from in vivo mice engrafted with human erythrocytes infected by *P. falciparum*. The experimental protocol consisted in the evaluation of the drug effect across a wide dose range. The experimental protocol was ethically reviewed and carried out in accordance with the European Directive 2010/63/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals. Initially, a compartmental transit model that reflects protozoal growth cycle, including replication and re-infection in absence of drugs was developed. Drug effect was then parameterised in terms of potency (IC50) on parameters describing the inhibition or growth, protozoal clearance or re-infection. The recrudescence of the parasite was predicted using a deterministic approach. Growth dynamics model parameter estimates were subsequently used in conjunction with mefloquine pharmacokinetic data at therapeutic dose levels to evaluate treatment effect in patients, as outlined in a previously published clinical trial by Reuter et al (2014) [1]. Simulations of the time course of parasitaemia were then performed taking relevant covariate factors into account, in particular, body weight and baseline parasitaemia. Model predictions were compared with the observed clinical study findings. The analysis was performed in NONMEM V7.3 [3], whereas data manipulation was performed using R V3.0.1 and R Studio user interface. Model performance was assessed based on graphical and statistical criteria (RSE), goodness of fit and visual predictive checks.

Results:

Our analysis provided a semi-mechanistic parameterisation of the protozoa growth cycle in the humanised mouse model. For mefloquine, the PK parameter estimates were 1.22L/h for clearance and 677L for the central volume of distribution. Estimates of drug potency and efficacy of mefloquine for K_{OUT}, which describes the clearance of human erythrocytes, and K_{DEATH}, which describes the degradation rate of merozoites were: $EC_{50}K_{OUT}$ (0.0119 mg/l), $E_{MAX}K_{OUT}$ (56.1), $EC_{50}K_{DEATH}$ (0.0036mg/l) and $E_{MAX}K_{DEATH}$ (22.8). Model predictions were in agreement with the observed effects of mefloquine at therapeutic doses in a clinical study by Looareesuwan et al (1999) [2], which resulted in a cure rate of 86%.

Conclusions:

In the present study, we have shown the performance and translational value of a semi-mechanistic model describing protozoa growth dynamics. Whilst the prediction of treatment response to mefloquine cannot be immediately generalised, our results illustrate the relevance of quantitative clinical pharmacology principles for the dose rationale and study design for novel antimalarial drugs.

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III-07: *Daniel Röshammar* Assessment of expected drug exposure relative maximum safety limits in early phase studies

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Introduction: During early phase drug development, such as in single or multiple ascending dose studies, drug exposure should not exceed the maximum exposure limits (normally established based on the observed toxicity in pre-clinical studies). Pharmacokinetic models are often used when designing such studies for predicting what doses will render exposure below the maximum exposure limits and for assessing whether to progress to the next dose level or not based on interim data analysis. However, there are various approaches to perform such simulations with regard to sources of uncertainty and exposure metrics of interest.

Objectives: In this work, we aim to evaluate different simulation strategies and explore the potential impact on decision making.

Methods: A single ascending dose study was simulated, using a two-compartment population PK model with first-order absorption and elimination. Doses of 1, 1.5, 3, 6 and 8 mmol were administered to 6 subjects per dose level. Drug concentrations in the central compartment were assessed up to 72h after dose. An interim analysis was performed after the 6 mmol dose level, whereby the model was updated and used to simulate into the next dose level of 8 mmol. The maximum exposure level was arbitrarily set at 1200 nM for the maximum concentration (Cmax) and 5500 nM*h for the area under the concentration to time curve up to 24h after dose (AUC). The study was simulated 300 times under each simulation strategy; 1.) without parameter uncertainty, 2.) with parameter uncertainty from the NONMEM covariance step (COV), and 3.) parameter uncertainty based on Sampling Importance Resampling (SIR) [1]. The expected proportion of study replicates and individuals exceeding the maximum exposure limits at the 8 mmol dose level was assessed for calculating:

1. The probability a subject may exceed exposure limits
2. The probability a study dose level may have average exposure exceeding limits

The stop criterion for not progressing to the 8 mmol dose level was a >5% risk of exceeding the exposure limit.

All simulations were performed in NONMEM version 7.3.0 installed on an Intel Xeon-based server and PsN 4.8.1. [2]. Post-processing of simulation results was performed using R version 3.3.3.

Results: The simulations showed that the choice of exposure metric, simulation strategy, and if to consider the mean exposure or individual exposure per dose level all influenced the decision if to progress to the 8 mmol dose level. There was less variability in the resulting decision between simulation strategies for the AUC than for the Cmax metric. However, whether assessing the exposure limit per subject or the average per dose level had greater impact on decision making for AUC than for Cmax. Based on AUC, progressing to the 8 mmol dose was supported with all simulation strategies when using the average exposure, but not with any simulation strategy when using individual exposure. For Cmax, the proceed/stop decision was the same for the average and individual exposure scenarios; stop at the 6 mmol dose level was only indicated when uncertainty was derived from the NONMEM COV.

In all cases the NONMEM COV was simulating wider distributions compared with SIR, and hence a greater proportion of cases were exceeding the exposure limits. This was most likely an effect of a poor covariance matrix from NONMEM due to the small amount of data simulated (only MATRIX=S successful), which was improved on by SIR.

As expected, the proportion of cases exceeding the exposure limits was much greater for individual subjects compared to for the average exposure per dose level. E.g. for the AUC exposure limit, the fraction of patients exceeding the limit was 13% compared to the fraction of studies where the mean exposure exceeding the limit was 2%.

Conclusions: This work shows that the simulation strategy may have impact when deciding whether to proceed to a next higher dose level or not based on available data during early phase trials. We recommend to clearly define upfront how the expected exposure will be assessed relative the maximum exposure limits when exploring the maximum dosing schedule. If of particular importance, different simulation strategies can be applied and subsequently the most conservative approach can be chosen.

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III-08: *Shimizu Ryosuke* Quantitative systems pharmacology modeling of thrombopoiesis and platelet life-cycle, and application for thrombocytopenia

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Objectives: Quantitative systems pharmacology (QSP) modeling provides mechanistic insight and contributes the comprehensive understanding of drug efficacy and effects of underlying disease. Platelets are produced by the hematopoietic stem cells via megakaryocytes in the bone marrow [1] and play a critical role in hemostasis. Thrombopoietin (TPO) which is produced in liver, is the most important humoral factor in the process of the proliferation and differentiation of megakaryocytes and regulates platelet production by binding with the TPO receptor. Thrombocytopenia (TCP) is developed by various diseases such as chronic liver disease (CLD) and chemotherapeutic treatment and increases the risk of bleeding. Platelet transfusion is the current standard of care for replenishment of platelets and TPO receptor agonists are also use for the treatment of TCP patients with CLD or Idiopathic thrombocytopenic purpura. Since thrombopoiesis and platelet life-cycle includes the complicated processes, understanding the process based on QSP modeling gives important information about prediction of platelet count profiles and the investigation of the most influential factors on the profiles for each disease. The objective of the study is to develop the platelet model for thrombopoiesis and platelet life-cycle based on physiological mechanism and clinical observations by QSP approach. The model was applied for thrombopoiesis of lusutrombopag, a TPO receptor agonist, in healthy subjects and the TCP patients with CLD.

Methods: A platelet model was constructed based on the scheme of thrombopoiesis and platelet life-cycle reported by Szilvassy [1] and Craig [2], and included the components of proliferation from progenitor cells, maturation from megakaryoblast to megakaryocyte and its reservoir, platelet production from megakaryocyte, platelet distribution to spleen and elimination, and effect of endogenous TPO.

The platelet model was used for simulation of platelet count profiles after administration of lusutrombopag in healthy subjects. In this simulation, the effects of TPO and lusutrombopag were considered to be additive on thrombopoiesis via TPO receptor. For simulation in thrombocytopenic patients with CLD, the mechanism of TCP was modeled and integrated to the platelet model since it has been reported that the major mechanisms for TCP in cirrhosis are decreases in production of TPO in the liver and splenic platelet sequestration [3]. All kinetic parameters related to thrombopoiesis, platelet life-cycle, and PK parameters of TPO and lusutrombopag were fixed to the clinical observations, published data, and calculated values from the clinical observations These simulations were performed using MATLAB®. The predictability was assessed visually against clinical trials of lusutrombopag (1,408 platelet counts from 78 healthy subjects and 3,526 platelet counts from 347 thrombocytopenic patients with CLD).

Results: The platelet model consists of 44 components. Visual inspection suggested that the platelet model could well describe the observed platelet profiles for healthy subjects after administration of lusutrombopag. In the prediction, maximum increase of platelet count and time to peak platelet count for the 14-day fixed dose of 2 mg were typically 23.3×10,000/μL and 16.6 days after first dose, respectively, which were consistent with those based on the observed data. The results suggest that the kinetic parameters of the model were reasonably set. In thrombocytopenic patients with CLD, the platelet count profiles well predicted by incorporating the mechanism of decreased production of TPO in the liver and platelet sequestration in spleen in the model (predicted maximum increase of platelet count and time to

peak platelet count for the 7-day fixed dose of 3 mg of 3.39×10,000/μL and 12.9 days after first dose, respectively).

Conclusions: The platelet model could adequately describe the platelet count profiles after administration of lusutrombopag for both healthy subjects and the thrombocytopenic patients with CLD. The platelet model constructed in this study is useful for understanding the process of thrombopoiesis and platelet life-cycle, the effect of TPO for platelet production, and pharmacodynamics of TPO agonist. In addition, the model would be applicable for predicting platelet count profiles in TCP driven by various diseases.

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III-10: *Tomohisa Saito* The evaluation of a population pharmacokinetic model of Tofogliflozin with the data from healthy volunteers and T2DM patients

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Objectives: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder and has serious impacts on our lives. Most existing drugs for treating T2DM aim to regulate blood glucose levels by directly enhancing insulin action. On the other hand, sodium-glucose co-transporter 2 (SGLT2) inhibitors increase urinary excretion of excess glucose by inhibiting renal glucose reabsorption via SGLT2 and reduce blood glucose levels without risk of hypoglycemia. Tofogliflozin that was discovered and synthesized by Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan) is one of the highly selective SGLT2 inhibitors administered orally for the treatment of T2DM patients [1] and was launched in Japan in 2014. We developed a population pharmacokinetic (PK) model to understand clinical pharmacology of tofogliflozin and to evaluate covariate effect on PK profile of tofogliflozin.

In addition, in order to evaluate the accuracy of parameters with real data, we used different types of evaluation methods to calculate prediction intervals of estimated parameters. A bootstrap method is a golden standard to evaluate the prediction intervals of the parameters and sampling importance resampling method has been in the rise to be used for the evaluation in recent years [2]. Therefore, we used these methods for the evaluation of prediction intervals for our actual concentration data.

Methods: Six clinical studies (CSG002JP, CSG003JP, CSG004JP, CSG006JP, CSG007JP, CSG010JP) were combined to prepare a dataset for the population analysis [3][4][5][6]. The dataset includes doses (range: 2.5 to 80 mg) and the following recruited subjects: 55 healthy volunteers, 9 patients with moderate hepatic impairment, 333 patients with T2DM, and 23 T2DM patients with moderate renal impairment. Full sampling has been done for the studies in healthy volunteers and some T2DM patients and trough sampling has been done for long term studies. A covariate search was performed using a Perl speaks NONMEM scm command [7] with stepwise forward and backward procedures.

After the model building, non-parametric bootstrap, parametric bootstrap and sampling importance resampling (SIR) methods were tested as the evaluation of parameter estimation using the tofogliflozin's data [2].

All analyses were performed using NONMEM® version 7.4.1 (ICON Developed Solutions, Ellicott City, Maryland) with a fortran compiler, gFORTRAN 4.6.0 and first order conditional estimation method with INTERACTION option was applied to estimate the population parameters.

Results: A three-compartment model with transit absorption compartments assuming a log-normal distribution well described the PK profile of tofogliflozin. The estimated population mean of CL/F, V_1/F, Q_2/F, V_2/F, V_3/F and MTT were 10.9 (L/h), 38.8 (L), 0.255 (L/h), 4.96 (L), 13.4 (L), and 24.2 (L), respectively. The inter individual variability of each parameter was less than 60%. No clinically relevant covariates were identified in the covariate search though food intake at administration of tofogliflozin and body weight were incorporated in the model as structural covariates before the search. Body weight was included with allometry function using the power of 0.75 for CL/F and 1 for V/F. Post-meal condition increased MTT by 231%.

The accuracy of the estimated parameters was assessed with some methods. The SIR method and the parametric bootstrap method showed almost the same prediction intervals of each parameters whereas the non-parametric bootstrap method showed a slightly wider interval. The computing time of the SIR method was about 1 day while that of the parametric bootstrap method was about 20 days. However, it takes 2 to 3 days to find the sophisticated setting of SIR method.

Conclusions: The final model well fitted with the observed data. We tested different types of evaluation methods for parameters and the SIR method using tofogliflozin concentration data showed reasonable results with shorter computing time even though the setting of the calculation was relatively complex.

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III-11: *Louis Sandra* A population pharmacokinetic model for propofol in (pre)term neonates and infants independently accounting for size, gestational age (GA) and postnatal age (PNA).

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Objectives: Propofol is frequently used for induction and maintenance of anesthesia and procedural sedation in (pre)term neonates and infants. Being a UGT1A9 and CYP2B6 substrate, maturational on top of scale effects have to be accounted for to describe its pharmacokinetics in this population. The current population PK models fall short in terms of suitability for extrapolation, plausibility and/or predictive capacity in the target population [1-3]. We would like to demonstrate that independently accounting for GA and PNA instead of aggregation of these metrics into postmenstrual age (PMA) improves the description of the pharmacokinetics of propofol in (pre)term neonates and infants.

Methods: An analysis dataset was compiled from 3 previously published studies (Allegaert 2007 [1], Smits 2016 [4] (PK unpublished), Sepulveda 2011 [5]). The dataset contains 837 arterial samples from 107 individual PK profiles (preterm: 53 (49.5%), neonate: 66 (61.7%)). Patients were aged from 0-2.0 years (median 0.022 years, GA 24.6-40.1 weeks, PNA 0-104 weeks) and weighed between 0.58-11.44 kg (median = 3.050 kg). 2 to 9 arterial blood samples per PK profile were available. A three-compartment model with bolus/infusion input and linear elimination, allometrically scaled parameters (fixed coefficients [7]) and a maturation term on elimination clearance was used to describe the concentration-time course of propofol. Investigated maturation terms, were: i) sigmoid Emax model based on PMA [3,6], ii) Richards's model [7] based on PMA, iii) i) + accelerated maturation after birth [6] and iv) a power model based on GA + asymptotic exponential model based on PNA. The analysis was performed using MONOLIX 2018R2 [8]. Objective function value (OFV) expressed as -2 log likelihood (-2LL), the Akaike information criterion (AIC), prediction corrected visual predictive checks (pcVPC) and standard errors of the parameters were used for judging goodness of fit/selection of models and covariate inclusion/deletion.

Results: The relevant models are displayed in Table 1. Separation of intrauterine and postnatal maturation yielded the lowest OFV. Since V1 negatively correlated with age, an effect of PNA on V1 was added to this model, which further improved the fit.

Table 1: Population parameters and OFVs

Model	**TV (RSE%, IIV)**						**Maturation parameters**	**OFV**	
All: fixed allometric coefficients	CL [L min^{-1} $70kg^{-1}$]	V1 [L $70kg^{-1}$]	Q2 [L min^{-1} $70kg^{-1}$]	V2 [L $70kg^{-1}$]	Q3 [L min^{-1} $70kg^{-1}$]	V3 [L $70kg^{-1}$]		-2LL	AIC
(**1**) Emax mat. based on PMA	1.63 (5.5, 0.462)	12.3 (10.3, 0.491)	4.21 (6.92, 0.352)	42.4 (3.52, 0.182)	0.502 (6.14, 0.421)	228 (7.94, 0.514)	PMA50 = 40.9 wks HILL = 8.25	93.52	123.52

(**2**) Emax mat. based on PMA + "acceleration term"	1.78 (5.21, 0.379)	12 (10.2, 0.464)	4.21 (6.49, 0.362)	42.1 (3.45, 0.18)	0.491 (6.31, 0.433)	217 (8.99, 0.58)	PMA50= 39.4 wks HILL= 5.87 FBmax[LS1] = 2.42 T1/2a = 0.765 wks	66.41	100.41
(**3**) intrauterine (GA) and postnatal (PNA) maturation	1.58 (4.96, 0.379)	12.2 (10.6, 0.502)	4.11 (6.08, 0.367)	42.2 (3.58, 0.214)	0.496 (6.42, 0.435)	233 (7.99, 0.49)	GMAX= 0.314 b=7.47 T1/2b = 4.69 wks	62.54	94.54
(**4**) (3) + effect of PNA on V1	1.56 (5.97, 0.38)	19.8 (8.18, 0.292)	4.16 (6.19, 0.367)	41.9 (3.94, 0.22)	0.511 (6.26, 0.436)	246 (8.14, 0.513)	GMAX= 0.334 b= 7.98 T1/2b= 4.43 wks betaV1= 0.718	43.92	77.92

All parameters of all models were scaled allometrically: (WT/70)^0.75 for clearances, (WT/70) for volumes. (**1**) Emax maturation model on clearance: MAT = PMA^HILL/(PMA50^HILL + PMA^HILL). (**2**) As (1) multiplied with BIRTH = (1+FBmax*(1-exp(-PNA*log(2)/T1/2a)))/(1+FBmax). (**3**) MAT = GMAX*(GA/38)^b + (1-GMAX)*(1-exp(-PNA*log(2)/T1/2b)). (**4**) Additional covariate effect of PNA on V1: exp(-PNA/52*betaV1).

Conclusions: Independently accounting for intrauterine (driven by GA) and postnatal (driven by PNA) maturation improves the description of propofol pharmacokinetics in a dataset with a relevant proportion of premature neonates. Accounting for the observed relationship of weight normalized V1 and PNA further improves the fit. However, it is more than likely that this "age" effect is caused by a change of body composition in this rapidly growing population. We would embrace efforts to extend the work of Al-Sallami et al [9] formalizing the estimation of fat free mass in children "down" into the neonatal population. In our opinion, the development of predictive equations accounting for developmental changes in postnatal body composition is crucial to improve the predictive properties of pharmacokinetic models in this variable and vulnerable population.

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III-12: *Marina Savelieva* Modeling decline in cognition to decline in function in Alzheimer's disease

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Introduction: Alzheimer's disease (AD) is a degenerative brain disease and the most common form of dementia. Current research is focusing on diagnosing the AD prior to clinical symptoms appearance [1]. The early stages of disease are defined clinically by the level of cognitive decline alone since functional decline is not apparent [2]. Recent studies suggested that progress of cognitive impairment is followed by subsequent decline in functional abilities [3]; however, the causal and temporal relationship between the two was uncharted. The irreversible nature of the disease makes the use of the neuropsychological tests that are sensitive to the first signs of cognitive decline essential, together with the development of adequate treatments for the early AD stages. On the other hand, demonstrating the benefits of pre-clinical AD treatments on functional impairment is inherently difficult [4]. To address this gap, we developed a disease progression model describing the dynamic relationship between cognitive and functional declines. The model also provides a promising tool for evidencing the value of future pre-clinical treatments in AD.

Objectives:

- Build a disease progression model for and to determine the temporal relationship between the cognitive and the functional declines in patients with Alzheimer's disease using a longitudinal mixed-effects model
- Evaluate the impact of the APOE4 genotype (carrier vs. non-carrier) on the dynamics of AD progression (i.e. cognition and function)

Methods: Longitudinal data of 659 patients diagnosed with AD dementia were sourced from the Alzheimer's disease neuroimaging initiative (ADNI) database and modeled in two steps using mixed-effects Emax models (R, version 3.4.3). A cognitive subscale, delayed word recall, of the Alzheimer disease assessment scale and a functional assessment questionnaire were selected as endpoints to characterize cognitive and functional declines, respectively. To evaluate the extent of the causality between cognition and function, individual parameter estimates derived from the cognitive decline model were used to partially drive and explain the functional decline. Furthermore, the impact of the APOE4 genotype status on the dynamics of AD progression as characterized by cognition and function was evaluated.

Results: Mixed-effects Emax models adequately quantified the individual and population disease trajectories as well as the relationship between cognitive and functional decline. While APOE4 carriers had a higher initial cognitive impairment than non-carriers, decline in function was similar between the two populations. The population-average time when patients reached their half of maximum cognitive decline proceeded the population-average time when they reached half of maximum functional decline.

Conclusions: The mixed-effects Emax models provide a tool to characterize the population- and individual-level AD progression and its dependence on patient-specific characteristics, e.g., APOE4 status. The analysis is also a first case study of a methodology to bridge dynamically the two outcomes sensitive in different

stages of (pre-)AD spectrum, thus provided a promising tool for evidencing the value of future pre-clinical treatments of AD.

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III-13: *Annika Schneider* A PBPK approach for simulating the effect of liver cirrhosis on drug PK

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Objectives:

Liver cirrhosis is a progressive disease which is associated with severe morphological and physiological changes. Those alterations are known to substantially affect drug pharmacokinetics (PK). Physiologically based pharmacokinetic (PBPK) modeling is a valuable tool to link knowledge on physiological changes in diseases and to predict their influence on drug PK. Currently, the suitability of PBPK models for the prediction of alterations in PK profiles of cirrhotic patients is still under discussion. Especially the common Child-Pugh grading system complicates model construction due to limited translatability of the classification rules into actual physiological parameters. The objective of the presented approach was to assess and refine a current PBPK model for liver cirrhosis. The improvement achieved with these physiological model extensions is exemplary shown for ascites and liver enzyme activity.

Methods:

Model implementation and simulations were performed using PK-Sim® as part of the Open Systems Pharmacology Suite [1] and the included MATLAB toolbox. As a starting point, an existing liver cirrhosis model [2] was used. This model includes changes in blood flows, plasma protein concentrations, hematocrit, liver enzyme activities and glomerular filtration rate. A comprehensive literature research was conducted to identify further physiological changes and their potential influence on drug PK.

Based on this literature research, ascites was additionally implemented into the PBPK framework. This was done by increasing the interstitial fluid of the large intestine. Tobramycin was chosen as a test compound due to its hydrophilicity and ability to enter the ascitic fluid [3]. Using predicted PK parameters like the volume of distribution, the correct model implementation as well as the sensitivity for the ascites volume were systematically evaluated. The generated information was implemented into the existing liver cirrhosis model and was used to generate in silico populations with different grades of liver cirrhosis.

Not only new physiological changes were added to the existing model, but also a continuous approach for altered liver enzyme activity was developed. To inform the influence of liver cirrhosis on four different CYP enzymes, data was compiled in a comprehensive literature search. The data was then used in a Markov chain Monte Carlo (MCMC) approach [4] to inform a function (and a corresponding prediction interval) that describes the loss of enzyme activity in relation to disease progression. As a marker for disease progression the Child-Pugh Score was used.

Results:

The literature analysis revealed several potential physiological changes that could have an impact on drug PK and are not yet included in the existing liver cirrhosis model. These changes relate to ascites, porto-systemic shunting, intestinal liver enzyme activity, transporter activities and sinusoidal capillarization. As one example, ascites was successfully integrated into the model. Simulations with the hydrophilic test

compound tobramycin revealed a strong correlation between the implemented ascites volume and the predicted volume of distribution. This is in line with data from literature [3].

The literature research on CYP1A2, CYP3A4, CYP2C19 and CYP2E1 activity in liver cirrhosis patients resulted in a dataset for each enzyme, showing continuous loss in activity on increasing Child Pugh Score. The functions resulting from the MCMC analysis show a decrease of activity throughout disease progression for all enzymes but with different slopes at different disease stages. This is in line with literature describing different CYP enzymes being differently affected in liver cirrhosis [5].

Conclusions:

In this study the impact of various pathophysiological alterations associated with liver cirrhosis was analyzed and implemented into a PBPK modeling framework. The changes like ascites and the liver enzyme activity, exemplary demonstrate the effect of an increased physiological level of detail compared to the already existing model. Hereby, continuous disease progression was taken into account while keeping the relation to the Child-Pugh grading system. In the future, this model will allow improved *in silico* trial simulations in cirrhotic patient cohorts and, thus, will be a helpful tool for the evaluation of drug efficacy and safety.

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III-14: *Rik Schoemaker* Performance of the SAEM and FOCEI algorithms in the open-source non-linear mixed effect modelling tool nlmixr

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Objectives:

nlmixr is a freely available open-source package for R [1] that does not depend on any commercial software, and is available on CRAN [2] and GitHub [3]. The package allows structural models to be implemented using a system of ordinary differential equations (ODEs), and allows fully flexible dosing definitions in terms of the type (e.g. bolus doses or infusions), the timing, the number of doses, and their amount, which can vary between individuals. nlmixr builds on RxODE [4], a fast and efficient R package for simulating nonlinear mixed effect models using ODEs, with rapid execution due to compilation in C. Comprehensive online documentation is available [5], and an nlmixr tutorial is in preparation. The package comes with its dedicated project manager shinyMixR [6] that runs in a web-browser, and is linked to xpose [7, 8] for graphical exploration and goodness of fit plots.

nlmixr implements a number of parameter estimation algorithms that can be accessed through a common model definition language. These algorithms currently comprise nlme [9], stochastic approximation expectation maximization (SAEM) [10], and first-order conditional estimation with interaction (FOCEI) [11]. Further algorithms and parallel computation are in active development.

For a new tool to be accepted by the pharmacometric modelling and simulation community, it is essential that its estimation algorithms can be demonstrated to perform well and provide results comparable to widely used standards. The question is, can one switch from another package to an nlmixr estimation algorithm and obtain similar results?

Methods:

Performances of the SAEM and FOCEI algorithms in nlmixr were compared to those found in the industry standards, Monolix [12] and NONMEM [11], using two scenarios: a simple model fit to 500 sparsely-sampled datasets, and a range of more complex compartmental models with linear and non-linear clearance fit to datasets with rich sampling.

Estimation with sparsely sampled data was investigated for a first-order absorption model with one-compartmental disposition and linear elimination. Single-dose data for 10,000 subjects were simulated, split into four equal-sized dose groups, and four time points were randomly sampled within the 24 hours after the dose. Using the bootstrap tool of PsN [13], 500 datasets containing 120 subjects each were resampled from these 10,000 subjects, stratified by dose so that 30 subjects in each resampled dataset received one of the four doses.

Each resampled dataset was then analysed using the same structural model that was used for simulation, using Monolix's SAEM algorithm, NONMEM's FOCEI algorithm, and nlmixr's SAEM and FOCEI algorithms, to allow a paired comparison for each simulated data set of the analysis outcomes.

Richly sampled profiles were simulated for 4 different dose levels of 30 subjects each, for a range of test models with one- or two-compartmental disposition, oral (first-order absorption), intravenous bolus, or intravenous infusion administration, with either linear or Michaelis-Menten clearance. Inter-individual variability was applied to all pharmacokinetic parameters. Data were simulated for a single administration with sampling over 72 hours (19 samples), seven repeated daily administrations, with 15 samples over 24 hours after the 4^{th} dose, 19 samples over 72 hours after the 7^{th} dose, and 5 trough samples, and the combined single and multiple dose profiles (58 samples). These combinations provided a total of 36 test cases. A similar set of models and data sets was previously used to compare NONMEM and Monolix [14].

Results:

Single-thread computational speed was higher for nlmixr/FOCEI compared to NONMEM, but lower for nlmixr/SAEM compared to Monolix. Estimation results obtained from nlmixr for FOCEI and SAEM matched corresponding output from NONMEM/FOCEI and Monolix/SAEM closely, both in terms of parameter estimates and associated standard errors, both for the repeated sparse data sets, and for the wide range of models and inputs with rich data sets.

Conclusions:

The FOCEI and SAEM algorithms in nlmixr provide near-identical results to those obtained from NONMEM and Monolix for the same models and data. These results indicate that nlmixr may provide a viable alternative to existing tools for pharmacometric parameter estimation.

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III-15: *Jérémy Seurat* Comparison of Phase I combination therapy designs by clinical trial simulations to evaluate early tumor shrinkage

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Objectives: In oncology, there is a growing interest in the use of combination therapies in early clinical trials, but most of the time only monotherapy data from each agent and no data from combination agents are available at early stage to evaluate trial design performances and optimize them. Literature evidences suggest that early tumor shrinkage (ETS) is a good predictor of overall survival [1]. The aim of this analysis was to compare in silico several combination designs of drug M with cetuximab (C) in the treatment of solid tumors and to define the appropriate dose of C, assuming dose M is fixed. The performances, type I error (α) and power, of several one-stage designs were compared to test the superiority of the combination C+M to C alone using modeling and simulation of exposure-tumor growth inhibition (TGI).

Methods: Clinical trial simulations were performed, using an exposure-TGI model [2]. The effect of C exposure on progression of tumor size was modeled as described in [3], following a dose of 500 mg/m^2 every 2 weeks (Q2W). Different combination effects of M and C (no effect/additive/synergistic) were explored, using a global pharmacodynamic model, assuming exposure independent effect of M [4]. 1, 2 and 4 arm designs, all composed of 60 patients in total were evaluated. For each treatment arm of the combination design described, 500 datasets with tumor sizes at baseline and weeks 2, 4, 6 and 8 were simulated. The data for all arms were fitted using SAEM algorithm in Monolix 2018R2 [5] to obtain individual ETS predictions at week 8 (ETS8). Comparison test were performed on predicted and observed ETS8 (with residual variability) between the different arms.
In the 1 arm design, 60 patients received C+M and individual ETS8 were compared to a 'reference' ETS8 for C only, using a one sample Wilcoxon test. Different historical values (wrong or reliable) for this reference ETS8 were used. Then, randomized trial with 2 arms, C and C+M, of 30 patients were simulated and ETS8 were compared using a two-sample Wilcoxon test. In the 4 arm designs, in addition to C_{500} and C_{500}+M, where dose of C is 500 mg/m^2 Q2W, two combination arms with lower dose of C: C_{400}+M and C_{200}+M were evaluated where each arm was composed of 15 patients. First, a global Kruskal-Wallis test was performed to compare the 4 arms. If the global test was significant, a Dunnett test was performed to test each combo arm to reference C alone.

Results: When the ETS8 reference value for C only is adequate, the 1 arm design has the maximum power (98% for additivity of M on C and 100% for synergy). There is, however, a strong inflation of α when no effect of M is simulated on top of C in case of a wrong historical reference: for instance, α is 34% if reference ETS8 is 14% lower than true one. With the 2 arm randomized design, the power of the Wilcoxon test is 69% in case of additivity assumption and 99% for synergy. The power is lower for the tests based on ETS8 computed from observations only (67% and 97%, respectively). With the 4 arm design, the power of the global test is 52% for additivity and 77% for synergy. With the Dunnett test, C_{500}+M was found better than C_{500}, with power of 26% for additivity and 65% for synergy. The superiority of a lower dose combo was respectively 13% and 52% with C_{400}+M, and respectively 5% and 19% with C_{200}+M. As expected, the power of 4 arms design, with a total number of 60 patients, is lower than the power of 2 arms design, but it allows to explore more aspects of the drugs combination.

Conclusions: This work highlights the strengths and weaknesses of the different early clinical combination designs in ETS, in the context where we have fixed dose of one already approved agent and different doses of another. The 1 arm design shows a better power of tests than 2 or 4 arms, but implies strong assumptions on the historical reference value, leading to strong inflation of type I error in case of under-estimated reference. Choosing a 2 or a 4 arms depends on the objective of the study: a 2 arms design is preferable than a 4 arms to reach a good power of statistical tests, but a 4 arms design allows a better understanding of the dose-exposure relationship and thus a better dose selection. An extension of this work is to perform model-based adaptive two-stage designs [6,7] using the Fisher Information Matrix to optimize the second stage of the study, where arms could also be added or dropped at the end of first stage.

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III-16: *Dmitry Shchelokov* Physiologically based pharmacokinetic modeling of anti-PD-1 therapeutic antibodies

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Introduction: Monoclonal antibodies (mAbs) are engineered immunoglobulins that have been used for several decades as therapeutic agents in immuno-oncology. Their protein nature and specific structure significantly influence pharmacokinetics (PK) behaviour. However, there is neither clear consensus nor guidance regarding how to model antibody biodistribution and choose the structure of empirical models for the better description of PK data. To address this issue, we developed a minimal physiologically based pharmacokinetic (PBPK) model of drug disposition and focused on a group of immune checkpoint inhibitors blocking the PD-1 receptor.

Objectives:

- To identify parameters of mAb uptake by endothelial cells on the basis of *in vitro* data
- To develop the PBPK model describing endogenous IgG biodistribution in healthy human
- To develop minimal PBPK model describing distribution of therapeutic mAbs and binding with PD-1 receptor

Methods: Computational model was presented in terms of ordinary differential equations (ODE) with reaction rates defined in accordance with mass action law. The model describes the main features of mAb disposition: intravenous administration, distribution within body fluids, fluid-phase uptake by endothelial cells, competition for neonatal Fc receptor (FcRn) binding with endogenous IgG in endosomal space, FcRn-dependent transcytosis and recycling by endothelial cells, degradation of unbound mAb within endothelial cells, convective and diffusive transfer across blood vessel wall, binding with PD-1 receptor expressed on the surface of T cells, internalization of mAb-PD-1 complex by T cells. Also, the model takes into account the valency of mAbs and describes surface binding of antigen and ternary complex formation [1]. The number of parameters was estimated on the basis of available published data, e.g., volumes of physiological compartments, blood and lymph flows, number of cells, levels of endogenous IgG in serum and lymph, etc [2]. To identify parameters related to antibody uptake, recycling, and degradation by endothelial cells, additional sub-model was developed and fitted against in vitro experimental data [3]. To select the values of the parameters we used the algorithm of fitting based on Hook-Jeeves method implemented in the DBSolve Optimum package which was used for the numerical solution of ODEs and visualization [4].

Results: Developed PBPK model was tested on a set of four anti-PD-1 monoclonal antibodies: nivolumab, pembrolizumab, MGA012, and TSR042. To this end, clinical findings were compared to model simulations performed under similar conditions (dose and schedule). Information on these therapeutics is available from the Food and Drug Administration biopharmaceutical reports or from ongoing clinical trials. Model adequately predicts the PK profile of all tested drugs, as well as target receptor occupancy in plasma and tumor, without any additional parameter fitting. The model shows 98% occupancy of PD-1 on T cells in tumor during treatment with an approved dose of nivolumab, whereas clinical data shows 85-97% PD-1 occupancy in the tumor [5]. It is important to note that no clinical data was used at the stage of the model calibration.

Conclusion: Pharmacokinetics of mAbs is presumably determined by their molecular size and structure (presence of Fc-domain), whereas antigen binding properties mostly affect target receptor occupancy and subsequent pharmacodynamic effect. However, more clinical data should be analyzed to test the predictive ability of the model. In conclusion, proposed minimal PBPK model offers an alternative approach to simulating pharmacokinetics of novel mAbs and may be used as a tool to select doses of antibodies for first-in-human studies.

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III-17: *Soyoung Shin* Novel population approach to establish in vitro-in vivo correlation for drugs with site-dependent absorption

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Objectives: In vitro-in vivo correlation (IVIVC) is a predictive mathematical approach to establish a relationship between an in vitro dissolution and in vivo pharmacokinetics for a modified-release formulation [1, 2]. However, conventional IVIVC approaches are only applicable to highly permeable drugs that do not need to consider complex absorption processes [3]. Therefore, this study aimed at establishing a novel IVIVC approach for drugs with site-dependent absorption process based on population pharmacokinetic modeling by using acyclovir as a model drug.

Methods: Sustained-release (SR) tablets containing 500 mg of acyclovir designed to present fast, medium, and slow drug release were prepared via the wet granulation method. Hydroxypropyl methylcellulose was used as a drug release rate modifier. The in vitro dissolution properties of the three SR tablets and an immediate-release (IR; 200 mg) tablet were evaluated by the paddle method. The in vivo pharmacokinetics were assessed following oral administration in Beagle dogs. A population pharmacokinetic model was developed to characterize the dissolution, time-dependent absorption, and systemic disposition of acyclovir. The population pharmacokinetic parameters were estimated by simultaneously fitting all the obtained in vivo plasma concentration-time profiles to the population pharmacokinetic model using S-ADAPT.

Results: The in vitro drug release profiles were best described by Michaelis-Menten kinetics. The developed population pharmacokinetic model was able to describe all the in vivo plasma concentration-time profiles of acyclovir following oral administration of acyclovir formulations and allowed predicting in vivo dissolution profiles of acyclovir. The dissolution parameters representing the in vitro and in vivo drug releases were correlated by linear regression to establish IVIVC. Finally, the plasma concentration-time profiles of acyclovir were adequately predicted by the developed IVIVC model from the in vitro dissolution data. Prediction errors for the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) by comparing the population pharmacokinetic model predictions with the in vivo observations were all within 9.7% and 10.6%, respectively, satisfying the FDA criteria [1]. The final population pharmacokinetics-based IVIVC model also allowed to predict the in vivo absorption rates of acyclovir following oral administration. Acyclovir absorption was predicted to achieve its maximum absorption rate at 0.6 h, and then gradually decrease to zero after 1.8 h, indicating the presence of an absorption window.

Conclusions: A level A IVIVC has been successfully established for a drug that has a narrow absorption window. The superior flexibility of the population pharmacokinetic approach enabled separating the dissolution and absorption processes and including factors affecting each process. The present approach provides a better understanding of the in vivo absorption for drugs that have limited absorption window and may be useful for their new formulation design and development.

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III-18: *Christian Siebel* Development of an adaptive dosing approach for doxorubicin in paediatric cancer patients

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Objectives: Anthracyclines, such as doxorubicin, are known for causing potentially irreversible cardiotoxicity. Paediatric cancer patients are at the highest risk to suffer from long-term cardiac side effects due to the generally long life expectancy of childhood cancer survivors. The reduction of variability in systemic therapy intensity (drug exposure and peak concentrations) holds promise to better balance tumour efficacy and the risk of cardiac toxicity. Dosing algorithms that reflect individual differences in pharmacokinetics are therefore needed. *A priori* dose adaptations that take into account relevant covariates might offer a possibility to reduce variability in particular during the first administration of the drug. A further attempt to reduce variability could be provided by adaptive drug administration based on a single or few drug concentration measurements and subsequent Bayesian estimation of individual pharmacokinetic parameters.

Methods: The impact of *a priori* dose adaptations based on a dosing formula derived from a published population pharmacokinetic model for doxorubicin in paediatric cancer patients was investigated [1]. The dosing formula takes into account individual body surface area and age which have been identified as predictive covariates during model building [2]. Hypothetical, dose-adjusted AUC was calculated using the proposed dosing formula and the *maximum a posteriori* clearance estimates from a paediatric patient population (94 children from the EPOC-MS-001-Doxo trial).The model-expected AUC of an 18-year-old boy with median demographics served as target for dose calculation. Dose-adjusted AUC values and the actual observed AUC values were normalised to the target AUC and compared with respect to bias (median prediction error), precision (median absolute prediction error) and the probability of target attainment. To assess the predictive power of the population pharmacokinetic model in a reduced sampling situation truncated datasets with 1 - 3 observations were generated based on the full dataset from the EPOC-MS-001-Doxo trial. Bayesian clearance estimates were computed in NONMEM version 7.3 (POSTHOC option with MAXEVAL = 0) [3] using the truncated datasets and the full dataset and compared. Bias, precision and the percentage of clearance values within 10 % and 20 % error range were calculated. Optimal sampling time points for 1 - 3 sample designs were identified based on Ds-optimality criteria using the optimal design software PopED [4]. Identification of optimal sampling times was performed based on data of the EPOC patient cohort as the EPOC population was considered to represent typical paediatric cancer patients.

Results: Using data from the EPOC population consideration of body surface area and age for dose calculation suggests to achieve a predefined target AUC without relevant bias (-2.5 %, 95 % CI -8 – 3 %). However, only a small decrease in precision between observed (21 %, 95 % CI 18 – 23 %) and dose-adjusted AUC values (17 %, 95 % CI 13 – 19 %) could be observed ($p < 0.01$, Wilcoxon signed rank test). The percentage of AUC attaining the range of 80 – 125 % around the target AUC was 58.5 % for observed and 69.1 % for dose-adjusted AUC values ($p > 0.05$, McNemar's chi-squared test). Bayesian forecasting of individual clearance seems to be sufficiently accurate and precise with median absolute prediction errors not higher than 13.1 % (95 % CI 9.5 – 17.5 %) for estimation based on a single observation. Exemplarily, for a treatment regimen with a 1 h infusion and a dose of 30 mg/m² (corresponding to the AIEOP-BFM ALL

2017 protocol) optimal sampling times for estimation of clearance were 8 h (1 sample design), 4 h + 16 h (2 sample design) and 1 h + 5 h + 23 h (3 sample design) after the start of infusion.

Conclusions: A standardised dosing concept that individualises doxorubicin doses based on body surface area and age seems to be beneficial given the current situation of diverse dosing strategies in particular for very young children. However, a relatively small reduction in variability of drug exposure can be expected with *a priori* dose adaptations. Bayesian forecasting suggests to allow accurate and precise prediction of individual clearance. Adaptive doxorubicin dosing based on the most informative sampling strategy might therefore provide a possibility to better control variability.

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III-19: *Iryna Sihinevich* Mathematical Modeling of Glucose Homeostasis in Morbidly Obese Diabetic Patients Undergoing Roux-en-Y Gastric Bypass Surgery: An IMI DIRECT Study

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Introduction/Objectives: Type 2 diabetes mellitus (T2DM) is a complex multifactorial disorder, impacted by several genetic and environmental factors. Overweight and obesity combined with an unhealthy diet and lack of physical activity are considered to be the strongest risk factors for developing T2DM [1]. For patients with severe obesity-related T2DM who could not achieve the recommended treatment targets otherwise, bariatric surgery can be considered an appropriate option [2]. After Roux-en-Y Gastric Bypass (RYGB) surgery a large number of diabetic patients demonstrate normalization of blood glucose levels and disappearance of diabetes symptoms within days, even before weight loss occurs [3,4]. To gain more insight into the underlying mechanisms, the main research goal was to develop a mathematical model that simultaneously describes individual changes in weight (WGT), fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) levels in morbidly obese diabetic patients over the first year after the bariatric surgery.

Methods: The model was developed using WGT, FPG, HbA1c and other data (n=78) from the prospective bariatric cohort (University of Lille, France) of the Diabetes Research on Patient Stratification (DIRECT) study [5]. This cohort consists of 79 patients with T2DM and severe obesity (BMI ≥ 35 kg/m^2 with comorbidities or BMI ≥ 40 kg/m^2) who underwent RYGB surgery. Plasma levels of biomarkers for T2DM as well as weight and other demographic and laboratory parameters were obtained at baseline and 1, 3 and 12 months after the surgery. The mathematical model was developed using the nonlinear mixed-effects (NLME) modeling approach implemented in NONMEM® (version 7.3.0) [6] using Pirana™ (version 2.9.5) as a modeling environment. Data analysis and visualization were performed in R (version 3.2.5) using RStudio (version 1.0.44).

Results: Individual changes in WGT, FPG and HbA1c levels after the bariatric surgery were well described using turnover models with zero-order production rates (kin) and first-order elimination rates (kout). Change in WGT was best described by a factor of 0.492 on kinWGT. Additional incorporation of a time-dependent long-term effect with an exponent of 0.0245 on kinWGT (49.9%CV IIV) allowed depicting different individual trajectories in the first year after the RYGB. Postsurgical changes in FPG were best described by a factor of 0.644 on kinFPG (26.5 %CV IIV). In addition, one month after the surgery the ratio of actual to baseline weight was a significant factor on the production rate of fasting plasma glucose (kinFPG) with a factor of 0.622 multiplied by the weight ratio. The formation of HbA1c from hemoglobin (Hb) was described by a second-order process dependent on Hb and FPG concentrations. The degradation of Hb and HbA1c was described by a first-order process assuming an erythrocyte half-life of 120 days. Overall, the developed model showed a very good descriptive performance of the individual time profiles and good precision of parameters estimates (relative standard error < 25%).

Conclusions: A mathematical model has been developed simultaneously describing individual changes in WGT, FPG and HbA1c occurring before and up to 12 months after the RYGB surgery. The initial effect of the surgery is possibly related to combined effects of caloric restriction, hormonal and metabolic changes (elevation of incretins, peptide YY, ghrelin levels and an increase in lipolysis [7] along with others) after

RYGB surgery and less dependent on the weight loss. Starting one month after the surgery, the biological system approaches new homeostasis, in which the variation in FPG and HbA1c seems to be mainly triggered by body weight changes. Next steps will be to investigate the effect of covariates and especially antidiabetic medication on FPG, HbA1c and body weight.

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III-20: *Florian Simon* A generic PBPK model for predicting the impact of inflammation on midazolam pharmacokinetics

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Objectives:

Systemic inflammation is known to impact drugs pharmacokinetics (PK) by different ways. In vitro tests have shown that exposure to some cytokines, e. g. interleukin(IL)-6, IL-1β or tumor necrosis factor (TNF)α, alters expression and activities of drug-metabolizing enzymes (DME) and drug-transporters in hepatic, intestinal or blood brain barrier (BBB) cell lines [1, 2]. Plasma binding proteins levels are also impacted by inflammatory response, resulting eventually in drug unbound fraction alteration [3]. Clinical studies have highlighted significant differences of PK profiles between patients with high or low systemic inflammation level [4]. These modifications could have clinical consequences and require dosing rate adaptations.

The aim of this work was to build a physiologically-based PK (PBPK) model to predict the impact of inflammation on drug PK. Since CYP3A4, one of the major DME, is strongly impacted by inflammation, midazolam was chosen as a probe for this study.

Methods:

In a previous study, we conducted RNA sequencing and activity tests on intestine and BBB cell lines to to select which DME and ABC transporters are the most impacted by inflammation.

Midazolam PBPK model was built using PK-sim 6.4. The inflammation model was calibrated using midazolam PK profiles after continuous infusion at four levels of CRP (10, 32, 100 and 300 mg/L) in a population of 83 critically ill children [5]. The relationship between CRP concentrations and CYP3A4 metabolic clearance was processed with Mobi 7.4. Metabolic CYP3A4 activity was described as a saturable process following Michaelis-Menten kinetics.

The model was externally validated using visual predictive checks (VPC). The data of 12 rheumatoid arthritis patients taking 0.03 mg/kg midazolam (oral route), before and after administration of sirukumab (an anti-IL-6 monoclonal antibody) [6] were compared to simulations for N = 1000 patients performed with PK-sim for different CRP concentrations (0.5 and 25.3 mg/L).

Results:

Among the different DME expressed in intestinal tissue, the expression and activity of majors CYPs P450 (including CYP3A4) are impaired by exposure to IL-6.

The severity of inflammation, assessed by the CRP level, was related to CYP3A4 metabolic activity by including a factor, kcrp, on the midazolam-metabolite formation rate equation : kcrp = 0.2+0.8*exp(-ln2/25*[CRP])

The VPCs were in good agreement with observations before (CRP = 25.3 mg/L) and after (CRP = 0.5 mg/L) sirukumab administration. Simulated AUCinf and Cmax are also comparable to the observed data.

Conclusions:

These findings suggest that midazolam PK could be predicted depending on the level of CRP. This model may be useful for adapting the dosing rate of CYP3A4 substrates and to avoid toxicities in case of high inflammatory response. This approach will be extended to other substrates of DMEs impacted by inflammatory response and to drugs with high protein binding in plasma (especially with alpha-1-acid glycoprotein). Effect of inflammation on drug-drug interactions will also be studied.

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III-21: *Noppaket Singkham* Pharmacogenetics-Based Population Pharmacokinetic Analysis for Dosing Optimization of Ritonavir-Boosted Atazanavir in Thai adult HIV-Infected Patients

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Objectives:

In Thailand, Ritonavir-Boosted Atazanavir (ATV/RTV) is a preferred protease inhibitor based-regimen for the treatment of HIV infection. The pharmacokinetics (PK) of ATV exhibit high interindividual variability that are influenced by patient characteristics and genetic factors. Single nucleotide polymorphisms (SNPs) of metabolizing enzymes, protein transporters, and gene regulation were found to be associated with PK of ATV/RTV.[1-4] There is evidence that Thai HIV-infected patients have a lower oral clearance of ATV (CL/F_{ATV}) compared to other ethnicities, leading to higher drug exposure.[5] Although non-genetic and genetic factors including *CYP3A5* and *NR1I2* polymorphisms had significant effect on CL/F_{ATV} in Caucasian, this information in Thai patients is limited. Thus, we aimed to characterize the population PK of ATV and RTV and identify potential factors influencing their disposition, taking into account the inhibition effect of RTV on ATV. Additionally, optimal dosage regimens for Thai HIV-infected patient were investigated.

Methods:

A total of 544 patients with 1464 concentrations of ATV and RTV were obtained from two clinical studies.[6-7] Thai adult HIV-infected patients receiving ATV/RTV-based regimen for their therapy (300/100 or 200/100 mg, once daily) were included in the analysis. Among all patients, 27 patients had intensive PK data (0, 1, 2, 4, 6, 8, 10, 12 and 24 h after dosing) and 517 patients had plasma trough concentrations. Genetic polymorphisms of *CYP3A5* 6986A>G, *ABCB1* 3435C>T, *ABCB1* 2677G>T, *SLCO1B1* 521T>C and *NR1I2* 63396C>T were genotyped. A population PK model was developed using the nonlinear mixed-effect modelling software (NONMEM®). The model of ATV and RTV was developed separately and then were incorporated to describe an interaction between drugs using sequential approach. One- and two-compartment models with the first-order absorption and elimination and a delay absorption with lag time or transit model were explored. The influence of covariates on PK parameters were analyzed using stepwise forward inclusion and backward deletion. The covariates included genetic factors (C*YP3A5* 6986A>G, *ABCB1* 3435C>T, *ABCB1* 2677G>T, *SLCO1B1* 521T>C and *NR1I2* 63396C>T) and clinical factors (age, sex, body weight, liver function test and using of tenofovir disoproxil fumarate). An effect of RTV concentrations on CL/F_{ATV} was determined with different inhibitory models. Monte Carlo simulations were conducted based on the final model to compare the probability of achieving the therapeutic range of ATV (C_{trough} 0.15-0.85 mg/L) under different dosing regimens and various covariates.

Results:

The PK of ATV and RTV were described by a one-compartment model with first-order absorption. The CL/F_{ATV} in the absence RTV was 7.39 L/h with interindividual variability (IIV) of 27.98%, apparent volume of distribution (V/F_{ATV}) was 76 L and absorption rate constant (ka_{ATV}) was 1.64 h^{-1}. The significant covariates for CL/F_{ATV} were *CYP3A5* 6986A>G and sex. Patients with *CYP3A5* 6986 GG (non-expressors) had a 7.3% lower CL/F_{ATV} than those with AA/AG genotype (expressors). The CL/F_{ATV} decreased by 10.5% for female compared with male patients. For RTV, the estimates of CL/F_{RTV} (IIV), V/F_{RTV} and ka_{RTV} were 8.46 L/h (30.3%), 58.3 L and 1.23 h^{-1}, respectively. The CL/F_{RTV} was influenced by body weight using allometric scaling and *CYP3A5* 6986A>G. The inhibition effect of RTV trough concentration on CL/F_{ATV} can be described by maximum effect model. The maximum inhibitory effect (Imax) of RTV was 66.7% and RTV concentration producing half of the maximal inhibition effect (IC50) was 0.561 mg/L. The simulation results showed that, more patients in the low dose of ATV/RTV (200/100 mg) group achieved target concentration (67.98%), whereas 36.21% of patients in the standard dose of ATV/RTV (300/100 mg) group had concentration exceed the target concentration (ATV C_{trough}>0.85 mg/L). For *CYP3A5* non-expressor patients receiving ATV/RTV 200/100 mg, the probabilities of achieving ATV target concentration were 62.74% and 71.31% in female and male patients, respectively.

Conclusions:

The population model was developed to describe PK of ATV/RTV in Thai adult HIV-infected patients. The results suggest an influence of *CYP3A5* 6986A>G and sex on CL/F_{ATV}. Simulations confirmed that a reduction of ATV dosage from 300 to 200 mg in combination with RTV 100 mg, once-daily was sufficient to achieve target concentration.

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III-22: *Jaydeep Sinha* Extension of the Janmahasatian fat-free mass model to account for ethnicity-related bias

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Objectives:

The *FFM* model developed by Janmahasatian et al. (FFM_{Jan}) [1] has been extensively used in clinical pharmacology studies. The FFM_{Jan} model was developed based on a linear relationship (Z_{Jan} *model*) between bioimpedance (*Z*) and body mass index (BMI) in a population that descended from European ancestry. Bioimpedance (*Z*) essentially reflects the body composition, which is known to vary widely between different ethnicities [2,3]. For example, at a fixed *BMI*, the estimated body fat percentage of Asian Indians was reported to be 7.6% (95% CI: 5.0% – 10.2%) higher on average than Europeans [2]. This indicates that that FFM_{Jan} that follows the European body composition pattern would be anticipated to over-estimate *FFM* in Asian Indians. A recent validation study by Srigiripura et al. [4] has reported that the FFM_{Jan} model over-predicted *FFM* in the Indian population when compared to the measured *FFM* data. Therefore, there is a need to extend the FFM_{Jan} model in order to account for inter-ethnic difference in the body composition. An extended model would incorporate ethnic specific parameters.

Objective-1: To derive an extended version of the *FFM* model (FFM_{Ext}) that would accommodate estimable ethnicity specific parameter(s).

Objective-2: To estimate the ethnic specific parameters for an Indian population ($FFM_{Ext(Ind)}$).

Methods:

Objective-1: In the proposed extended *FFM* model (FFM_{Ext}), the relationship between *Z* (Z_{Ext}) and *BMI* was relaxed to accommodate a non-linear relationship by incorporating a set of ethnic-specific composition parameters Ψ {ψ_1, ψ_2, ψ_3} to the coefficients of Z_{Jan} model. An extended equation for bioimpedance, Z_{Ext}, was developed and combined with the existing FFM_{Jan} model. By rearranging the equation, the final equation of FFM_{Ext} was obtained which contains body composition parameters Ψ {ψ_1, ψ_2, ψ_3}.

Objective-2: The Ψ parameters of the FFM_{Ext} model were estimated against predictions from a reference model that was developed specifically for the Indian population by Kulkarni et al. [5]. *FFM* (FFM_{Kul}) was simulated based on demographic data (age, sex, height, and weight) of 100 adult Indian medical patients. The Ψ parameters were estimated using NONMEM (version 7.3). Model selection was based on the likelihood ratio test (LRT). A visual plot of the reference FFM_{Kul} vs. the predicted ($FFM_{Ext(Ind)}$) data was used to evaluate the ($FFM_{Ext(Ind)}$) model.

Results:

Objective 1, the final equation of the FFM_{Ext} model was derived and is shown in Eq 1 and 2. When all values of Ψ = 1 the FFM_{Ext} equation simplifies to the existing FFM_{Jan} model.

For males:

FFM_{Ext} = 9270**WT* / [ψ_1*216**BMI* + ψ_2*6680**BMI* $^{(1-\psi 3)}$] (1)

For females:

FFM_{Ext} = 9270**WT* / [ψ_1*244**BMI* + ψ_2*8780**BMI* $^{(1-\psi 3)}$] (2)

In Objective 2, an initial comparison between the two models revealed that the FFM_{Jan} model over-predicted the reference model (FFM_{Kul}). The mean differences in prediction (FFM_{Kul} - FFM_{Jan}) [95% CI] were -1.9 [(-2.6) – (-1.2)] kg and 0.3 [(-0.2) – 0.9] kg in male and female subjects respectively, and the root mean squared errors (RMSE) were 3 kg and 1.6 kg in male and female respectively. The final $FFM_{Ext(Ind)}$ had two estimable ethnic-specific parameters (ψ_1 was estimated to be 0). Sex was identified as a significant covariate on ψ_2, which was the proportionality term, but not on ψ_3, the exponent. The estimates (%RSE) of ψ_2 were 0.77 (3.2%) and 0.70 (3.3%) for males for females respectively, and ψ_3 was 0.72 (1.3%). Note, for the Indian population the first term of the denominator drops as ψ_1 = 0. The final models of $FFM_{Ext(Ind)}$ have been shown in Eq 3 and 4.

For males: $FFM_{Ext(Ind)}$ = 9270**WT* / [0.77*6680**BMI* $^{0.28}$] (3)

For females: $FFM_{Ext(Ind)}$ = 9270**WT* / [0.70*8780**BMI* $^{0.28}$] (4)

Conclusions:

This work extends the Janmahasatian's *FFM* model to prediction of *FFM* in other populations by incorporating ethnicity specific correction factor(s). Importantly, the correction factor(s) can be directly estimated from bioimpedance (*Z*) measurements, and there is no need to measure *FFM* in the respective population, which has significant benefits for future clinical pharmacology studies.

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III-23: *Erik Sjögren* A PBPK Framework to Predict Drug Exposure in Malnourished Children

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Introduction: Protein energy malnutrition in children is a global health problem, particularly in developing countries. The effects of nutritional status on body composition and physiological functions may have implications for drug disposition and ultimately affect the clinical outcome in this already vulnerable population. Physiologically based pharmacokinetic (PBPK) modeling can be used to predict the effect of protein starvation as it links physiological changes to pharmacokinetic (PK) consequences. Still, the absence of detailed information on body composition and the scarce availability of controlled clinical trials in malnourished children, complicates the establishment and evaluation of a generic PBPK model in this population. However, by combining information on a) the differences in body composition between healthy and malnourished adults and b) the differences in physiology between healthy adults and children, a physiologically based bridge to a malnourished pediatric population can be made.

Objectives: To develop and evaluate a physiologically based translational framework for prediction of drug disposition and PK characteristics in children with severe protein energy malnutrition.

Methods: Changes to body composition and plasma protein concentrations due to protein energy malnutrition were derived for adults from the literature and implemented in PK-Sim® (v7.4.0) [1][2][3]. To accommodate the differences between a healthy and a malnourished adult population in PK-Sim, compiled physiological data were converted to a set of physiological scaling parameters. Based on the assumption that the physiological changes occurring in malnourished adults are similar to those occurring in children, the physiological scaling parameters were used to create a malnourished pediatric population from a healthy pediatric population. The healthy pediatric population had been generated using the population algorithm in PK-Sim® including maturation of biological systems, e.g., metabolic enzymes and plasma proteins.

Observed and simulated plasma concentration versus time profiles and PK parameters for three model drugs were compared to evaluate the performance of the suggested modelling approach and thereby to verify the appropriateness of the virtual malnourished pediatric population generated. PBPK models in PK-Sim® for the model drugs ciprofloxacin, caffeine and cefoxitin were either developed, based on drug specific information and a middle out modelling approach towards clinical data in healthy adults collected from the literature, or adopted from previous publications [4] [5] [6] [7] [8] [9]. All PBPK modelling and analyses were performed in PK-Sim®. Prediction error (PE) (predicted/observed) within the range of 0.5-2.0 were considered as adequate predictive performance.

Results: The drug models for ciprofloxacin, caffeine and cefoxitin were verified against clinical data from healthy adults. Plasma concentration-time profiles, as well as the inter individual variability, in malnourished children were well captured by the model predictions applying the suggested PBPK framework. Adequate predictions of model drug exposure were achieved for all investigated cases. The PE of AUC for ciprofloxacin in malnourished pediatric populations with an average age (years) of 0.5, 1, 2, 5 and 10 was 1.24, 0.95, 1.14, 1.25 and 0.71, respectively. For caffein and cefoxitin the PE of AUC was 0.57 and 1.17, respectively, in malnourished pediatric populations of an average age of 2.6 and 2.3 years,

respectively. The appropriateness of the derived physiological scaling parameters and the proposed physiologically based translational modeling strategy were supported by the results.

Conclusions: The results demonstrate that the proposed modelling strategy is appropriate for predictions of drug disposition and PK in malnourished children.

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III-24: *Eunjung Song* Selection of optimal study design based on the bioequivalence simulation study in highly variable drugs

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Objectives: Highly variable drugs (HVD) indicate drugs with within-subject standard deviation (S_{WR}) > 0.294. For HVD, bioequivalence tests are conducted with the reference-scaled average bioequivalence approach using $S_{WR.}$ Therefore, reference replicated bioequivalence study designs, such as partially replicated 3-way design (TRR, RTR, and RRT) or fully replicated 4-way design (TRTR and RTRT), are recommended to estimate $S_{WR.}$ However, it is difficult to decide which study design is the most efficient design between the designs. As an approach to solving this difficulty, the current study is planned to suggest an appropriate study design by comparing simulation results from various study designs including reference-replicated designs.

Methods: Given the population pharmacokinetic (PopPK) model with known parameters, a Monte Carlo simulation is performed to compare power for bioequivalence study designs for HVD. First, we generated simulation data from PopPK models with known parameters. In particular, we tried to have almost same total number of observations for each design to compare different study designs fairly. Second, we conducted bioequivalence tests for HVD according to reference-scaled average bioequivalence approach and mixed scaling approach. Then, we calculated power from the results of the tests for each study design. The procedure was performed by using SAS version 9.4.

Results: The power (%) in bioequivalence study was affected by the following factors: total number of observations, geometric mean ratio, covariance matrix structure for C_{max} or AUC. In detail, the S_{WR} of C_{max} or AUC was important factor increasing power. As the correlation within subjects decreases, the power for the study design tends to increase.

Conclusions: The covariance structure was a critical factor to reliably compare the power between the various bioequivalence study designs. From comparison of power for bioequivalence study designs under the proper covariance structure and appropriate parameters, we can select a study design which have the smallest the number of observations while maintaining pre-defined power.

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III-25: *Elena Soto* Population Pharmacokinetic (PopPK) Modelling and Simulation of Pregabalin to Support Dose Recommendation in Paediatric Patients 1 month to <4 years of Age with Partial Onset Seizures (POS)

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Introduction: Pregabalin is an alpha-2-delta ligand that has analgesic, anxiolytic, and anticonvulsant activity. It is approved for management of neuropathic pain (NeP) associated with diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, NeP associated with spinal cord injury, and as adjunctive therapy for the treatment of POS in patients 4 years of age and older. Pregabalin pharmacokinetics are linear and predictable and is primarily eliminated by renal excretion as unchanged drug.

A study to evaluate 2 pregabalin doses, administered three times daily (TID) as adjunctive therapy in patients 1 month to

Objectives:

To extend the current PopPK model for pregabalin to paediatric subjects 1 month to

To provide population pharmacokinetic simulations to support dosing recommendations for paediatric subjects 1 month to

Methods:

PopPK Model

Pharmacokinetic (PK) data from older paediatric (4 to 16 years of age) and adult patients, healthy volunteers and adults with renal impairment together with PK data from younger paediatric subjects (1 months to

The model previously described, consisting of a 1-compartment model with first-order elimination and absorption with a lag time [2], was applied to the current data using NONMEM 7.3 [3]. This base model included creatinine clearance (CrCL mL/min/1.73 m^2), body weight and sex as covariates for pregabalin apparent clearance (CL/F) and body weight and sex as covariates in pregabalin volume of distribution. It also included food status in absorption rate constant and lag time.

Simulations

Pregabalin PK profiles for subjects 1 month to

To account for renal maturation in infants, two simulation approaches were tested.

In Approach 1; for younger subjects scaled predictions of CrCL from glomerular filtration rate (GFR) estimates, derived utilising the equation described by Rhodin et al [4] were simulated. Pregabalin CL was then estimated based on the established relationship with CrCL.

In Approach 2, Rhodin's maturation equation [4] was included in the PopPK model to describe the renal maturation-related pregabalin CL/F in infants (

Paediatric demographics for simulations were bootstrapped from available study data (> 12 months of age) or created based on CDC Growth Charts [5].

Results:

A total of 1082 subjects including 358 paediatric (<=16 years of age) subjects and 724 adults contributing to 5562 plasma concentrations were included in the PopPK analysis. The youngest subject was 3 months old.

Data from patients

Simulations showed:

Pregabalin exposures for subjects 1 to

In Approach 1, the 12 mg/kg dose led to lower exposures in infants 1 to

For both approaches, the simulated average and maximum concentration at steady state in infants at the proposed maximal dose of 14 mg/kg/day did not exceed the adult exposures following the highest recommended dose in adults of 600 mg/day.

Conclusion:

The simulations demonstrated that pregabalin doses of 14 mg/kg/day administered TID in paediatric subjects 1 month to

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III-26: *Tomás Sou* Translational PK and PKPD modelling for the analysis of preclinical in-vitro and in-vivo studies to predict efficacious human dose of apramycin

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Objectives: Predictions of human dose for antibiotics are commonly based on 24h response in mouse infection models, ignoring the dynamics of bacterial growth and killing. Preclinical profiling has identified the aminoglycoside apramycin as a suitable candidate for development into a new human therapeutic. Apramycin has been shown to evade almost all mechanisms of clinically relevant aminoglycoside resistance. In this study, we applied translational pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PKPD) modelling to predict an efficacious human dose for apramycin using i) *in-vivo* data from a mouse thigh infection model, and (ii) *in-vitro* time-kill data, in combination with human PK predicted from allometric scaling and knowledge on earlier aminoglycosides.

Methods: PK models were fitted to the preclinical PK data of apramycin available from four different species (mouse, rat, guinea pig, and dog). The estimated PK parameters were allometrically scaled to obtain typical PK parameter values for humans. For antimicrobial efficacy, *in vitro* time-kill data from four *E. coli* strains were available and semi-mechanistic PKPD models were fitted to describe the killing of bacteria at various drug concentrations. Bacterial count data on *in-vivo* efficacy at 24h in the mouse thigh infection model, as well as information on natural growth rate without drug exposure, was available for the same four *E. coli* strains. The PK model for mouse, and the predicted PK in humans, were then connected to the final PKPD model to predict the growth and killing of bacteria in mice and in humans. A suitable human efficacious dose was derived through the classical approach based on 95% probability of target attainment (PTA), where the target is derived based on the response observed in mice, and, through a modelling approach based on the PKPD model developed from the *in-vitro* time-kill experiments.

Results: In the PK analysis, 1-compartment models described the plasma concentration-time profiles of the preclinical species. Based on allometric scaling, the typical values of clearance and volume of distribution in humans are expected to be 7.67 L/h and 21.2 L, respectively. These values are similar to the typical population PK parameters of the aminoglycoside gentamicin reported in the literature [1]. For *in-vivo* efficacy, the required fAUC/MIC targets for stasis and 1-log kill in the neutropenic mouse thigh infection model were 50 and 106, respectively. The PKPD model predicted the time-kill data well with strain specific differences in susceptibility, maximum bacterial load and the rate of resistance development. The human efficacious dose predicted from the PKPD-model and the 'classical' PK/PD target approach both supported an apramycin daily dose of 30 mg/kg/day for patients with a typical kidney function of 80 ml/min.

Conclusions: Translational PK and PKPD modelling was successfully applied to analyse the data on apramycin from *in-vitro* time-kill experiments. The estimated human efficacious dose aligned well with the

expected dose from *in-vivo* studies on apramycin. The agreement of the two methods support an anticipated efficacious dose of 30 mg/kg to be studied in patients.

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III-27: *Viktoria Stachanow* Does dried blood spot data enrich our understanding of hydrocortisone pharmacokinetics in paediatric patients with adrenal insufficiency?

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Objectives: Congenital adrenal hyperplasia (CAH) is a rare form of adrenal insufficiency leading to low or no biosynthesis of cortisol. Patients require a lifelong cortisol replacement therapy from birth. For paediatric patients hydrocortisone (HC, synthetic cortisol) is the recommended glucocorticoid [1]. HC has complex pharmacokinetics (PK) with saturable binding to corticosteroid-binding globulin (CBG), non-saturable binding to albumin and erythrocytes [2] and a dose-dependent oral bioavailability due to saturable absorption [3]. Dried blood spot (DBS) sampling is a sampling technique which is suitable for paediatric patients as it allows to collect full blood samples of small volumes (10–20 µL) for multiple times [4] and is therefore commonly used when monitoring the treatment of paediatric CAH patients. The objective of this analysis was to extend an established paediatric HC PK-model [5] with DBS data in order to improve the data density and to further understand and characterise the binding processes of cortisol, including binding to erythrocytes. The extended model is intended to be used to conduct simulations comparing different dosing regimens and thereby pave the way towards the optimisation of the cortisol replacement therapy in children.

Methods: A semi-mechanistic HC PK model that was based on adult plasma data from a phase I study for a novel HC formulation [6] has previously been reduced to a paediatric model using sparse paediatric plasma data from a phase III study in 24 patients with adrenal insufficiency [7]. In this phase III study cortisol plasma concentrations and DBS concentrations of cortisol and 15 other steroids, including the CAH biomarker 17α-hydroxyprogesterone (17-OHP), were collected. Additional DBS concentrations of cortisol and 14 further steroids were obtained from a follow-up study. The relation between plasma and DBS samples was characterised by a graphical evaluation using R (3.4.4). Finally, nonlinear mixed-effects modelling was applied using NONMEM 7.4 in order to extend the existing binding model, that included binding to CBG and albumin, with binding to erythrocytes and thereby informing the established HC model with DBS data.

Results: Plasma concentrations of cortisol were considerably higher than the corresponding DBS concentrations which were sampled at the same time points. The plasma/DBS cortisol concentration ratios ranged between 2 and 8 with similar inter- and intraindividual variability. The relation between the cortisol DBS concentrations and cortisol plasma concentrations showed nonlinear behaviour with plasma/DBS cortisol concentration ratios that decreased with increasing concentrations. The one-compartment model including plasma and DBS data incorporated nonlinear binding of cortisol to CBG, (equilibrium dissociation constant K_d= 9.71 nmol/L) as well as linear binding to albumin and to erythrocytes, described by linear non-specific binding parameters (NS_{alb}=6.48 and NS_{ery}=1.93, respectively). Goodness-of-fit plots showed that the plasma data were adequately described by the model while DBS concentrations were partly underpredicted at lower concentrations.

Conclusions: Observing that plasma concentrations are higher than DBS concentrations was expected since these differences in the concentrations of full blood and plasma samples are due to the removing of the cellular component, reflected in the haematocrit (Hct). However, we also observed very high plasma/DBS cortisol concentration ratios as well as high inter- and intraindividual variabilities. The nonlinear relation between DBS and plasma concentrations mirrors the nonlinear binding kinetics of cortisol to CBG, which potentially affects the binding of HC to erythrocytes. The next step in the model development is to optimise the model and its predictive performance for DBS data and to identify covariates such as individual Hct values and CBG concentrations for describing the substantial differences and variabilities between plasma and DBS concentrations that were identified in the graphical analysis.

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III-28: *Felix Stader* Physiologically based pharmacokinetic modelling to identify pharmacokinetic parameters driving age-related changes in drug exposure in the elderly

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Objectives:

Aging is characterized by physiological and biological changes, which can affect drug pharmacokinetics. Even though the use of medications is highly prevalent, clinical studies are rarely conducted in the elderly. To overcome the sparse clinical data, physiologically based pharmacokinetic (PBPK) modelling was utilized to perform virtual clinical trials across the entire adult lifespan to investigate the impact of adult age on drug pharmacokinetics.

Methods:

A whole-body PBPK model constructed in Matlab® 2017a was used [1]. Healthy, virtual individuals aged 20 to 99 years were generated considering age-dependent changes of anatomical and physiological parameters [2]. A structured literature search was performed to identify drugs whose PK have been studied in the elderly to validate the simulations with clinical data. Selected drugs included midazolam, metoprolol, amlodipine, rivaroxaban, repaglinide, atorvastatin, rosuvastatin and lisinopril. Input drug parameters were obtained from existing validated PBPK models, except for lisinopril [1, 3-8]. Tissue distribution of the amlodipine model was modified to be used in a whole-body PBPK model based on the observed volume of distribution from an iv study in healthy men [9]. Active hepatic drug transport was included in the repaglinide PBPK model based on published *in vitro* data [10]. The lisinopril PBPK model was developed combining published *in vitro* data (bottom-up approach) with available clinical clearance data (top-down approach).

PBPK models were verified in young adults (20-50 years) following the best practice approach [11]. After successful prediction in young adults, judged by visual inspection of concentration-time profiles and prediction of PK parameters within 2-fold of the observed data, we carried out simulations in elderly adults (>65 years) without any modification to the drug parameters. Simulations were matched as closely as possible to the published observed studies in terms of demographics, dosing regimen and number of subjects with 10 trials x n virtual subjects being simulated for each drug.

The final PBPK models were utilised to predict drug pharmacokinetics from 20 to 99 years in 500 virtual subjects (proportion of women: 0.5) in five years steps. The analysed PK parameters (Maximal concentration: C_{max}; time to maximal concentration: t_{max}; area under the curve: AUC; clearance: CL; volume of distribution: Vd; elimination half-life: $t_{1/2}$) were normalised to the youngest investigated age group (20-24 years).

Results:

The simulation of all eight drugs matched well the observed clinical data for young (20-50 years) and elderly (≥65 years) adults. The predicted AUC-ratio elderly:young adults was in close agreement to observed clinical data for midazolam (1.64 vs 1.96), metoprolol (1.20 vs 0.97), lisinopril (1.18 vs 1.24), amlodipine (1.31 vs 1.38), rivaroxaban (1.52 vs 1.52), repaglinide (1.62 vs 1.79), atorvastatin (1.32 vs 1.38) and rosuvastatin (1.24 vs 1.03). All other PK parameters were predicted within 2-fold of the observed data in young and elderly adults.

After successful model verification, the impact of adult age on the pharmacokinetics of the eight investigated drugs was examined. C_{max}, t_{max} and Vd were independent of adult age. In contrast, AUC and $t_{1/2}$ showed on average a progressive linear increase of 1.0% and 0.8% per year with age-related changes being more than expected from interindividual variability defined as the 1.25-fold interval from the age of 55 years. Accordingly, CL decreased linearly with a maximum 3.0-fold difference compared to young adults. Importantly, age-related changes for all investigated parameters were independent of gender.

Conclusions:

On a general rule, this study demonstrates that drug elimination rather than absorption or distribution drives age-related drug exposure changes in the elderly. For the first time, this study provides the scientific fundament for the 25-50% dose reduction used empirically by clinicians to treat elderly individuals [12] and shows principally that this dose reduction depends on the age-related decrease of liver weight, hepatic and renal blood flow as well as glomerular filtration rate and is independent of the drug. However, it needs to be emphasized that pharmacodynamic alterations and the presence of comorbidities should be considered when prescribing in the elderly.

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III-29: *Gabriel Stillemans* Simultaneous population pharmacokinetic modeling of darunavir and cobicistat in a cohort of HIV patients

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Objectives: Darunavir (DRV) is a widely used protease inhibitor in de novo or pretreated HIV patients, combined with a background regimen (usually two nucleoside reverse transcriptase inhibitors). It is coadministered with a pharmacoenhancer, either ritonavir (RTV) or cobicistat (COB) to increase DRV plasma exposure. DRV is characterized by a large pharmacokinetic (PK) variability, but the reasons for that variability have yet to be fully elucidated. Additionally, fewer PK studies are available for the more recently commercialized COB-boosted DRV. There is also an interest in evaluating the feasibility and safety of reduced doses or short cycle therapies such as weekends-off regimens in order to reduce costs and toxicity and to improve patient compliance. Our objective was to explore the PK of DRV and COB in a representative cohort of HIV patients using nonlinear mixed effects modeling and to determine the effect of covariates, including single nucleotide polymorphisms (SNPs), drug-drug interactions and clinical chemistry parameters.

Methods: The study was approved by the local ethics committee and was registered at ClinicalTrials.gov (NCT03101644). HIV-positive patients were prospectively recruited. For each participant, sparse blood samples for drug quantification were drawn at random post-intake times (one sample per visit and an average of 2.5 visits per participant), plus an additional sample for genotyping (*CYP3A4*22, CYP3A5*3*, and *ABCB1* 1199G>A and 3435C>T were determined). For all participants, clinical chemistry data, DDIs and demographic parameters were recorded. Simultaneous quantification of DRV, RTV and COB in plasma was performed using a validated UPLC-UV method [1]. NONMEM was used for population PK modeling. Runs were handled through PsN and Xpose was used for additional plotting. DRV and COB PK were first modeled separately, covariates were then added in a stepwise manner, and finally, a joint interaction model was evaluated. Goodness of fit was assessed using plots of predicted versus observed concentrations, plots of weighted residuals, as well as bias, imprecision and shrinkage of population parameters. For internal validation, visual (VPC) and numeric (NPC) predictive checks were performed based on 1000 simulations from the final model. Nonparametric bootstrapping was used to evaluate model stability and generate confidence intervals.

Results: 127 patients contributed to plasma PK sampling, for a total of 249 datapoints. RTV data was too sparse to be used (n = 18 subjects) and was discarded. DRV and COB PK were both adequately described by a one-compartment model with first-order absorption. DRV clearance (CL), volume of distribution (V) and absorption rate constant (ka) were 9.6 $l.h^{-1}$, 140 l and 0.38 h^{-1}, respectively, while COB CL, V and ka were 8.7 $l.h^{-1}$, 97 l and 0.86 h^{-1}. COB concentrations were found to inhibit DRV CL in a linear fashion ($r=0.47$, p-value<0.05) ; however, inclusion of this relationship in the joint model did not improve model fit. Higher levels of alpha-1 acid glycoprotein (AAG) were found to correlate with lower DRV CL, in accordance with previous studies [2,3] and was added as a covariate. Despite some borderline significant associations in univariate analysis, none of the other clinical or genetic covariates were retained in the final model as they did not significantly improve the fit. No apparent relationship could be described between PK parameters and HIV viral load, the main biomarker for evaluating treatment efficacy, in line with previous results [4]. VPC and NPC results were adequate. Still, parameters suffered from high shrinkage and high relative

standard errors, and bootstrap from the final model generated wide confidence intervals for parameter etas.

Conclusion: Population PK models were developed for DRV and COB. However, with such sparse data, accurate estimation of individual PK parameters proved difficult, limiting the applicability of this model (including its predictive power and ability to detect covariate relationships). The next step will be to enrich our model with dense PK data collected in a subset of participants, expand our panel of SNPs and perform extensive and rigorous internal and external validation of the model. We will also simulate the effect of alternate dose regimens on both PK and treatment outcomes.

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III-30: *Mark Stroh* Translation and Mechanistic Corroboration of the Preliminary Clinical Pharmacokinetics and Pharmacodynamics of a Masked, Tumor-Activated anti-PD-L1 Antibody with Systems Pharmacology

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Objectives:

Monoclonal antibodies (mAb) targeting the programmed cell death (PD-1) pathway have shown anticancer activity in different tumor types, though with associated toxicities especially in combination with other immuno-oncology agents [1]. Probody™ therapeutics (Pb-Tx) are mAb prodrugs designed to reduce on-target toxicities [2]. A mask inhibits antigen binding of the Pb-Tx in the periphery, and this mask can be removed by tumor-associated proteases to produce an active mAb. CX-072 is an anti-programmed cell death ligand 1 (PD-L1) Pb-Tx under clinical evaluation in cancer patients [3].

The study aim is to develop a quantitative systems pharmacology (QSP) model for CX-072 clinical translation and to compare predicted versus observed preliminary PK/PD from ongoing phase 1/2 study PROCLAIM-CX-072 (NCT03013491).

Methods:

A QSP model was developed, calibrated against monkey PK data, and used to project human PK/PD. Human and monkey PK samples were collected at prespecified times following CX-072 administration; plasma analytes included intact CX-072, activated CX-072 and the sum of intact and activated CX-072 (total CX-072). Receptor occupancy (RO) was estimated in cancer patients based upon levels of activated/unmasked CX-072 in postdose tumor biopsy lysates as measured by capillary electrophoresis immunoassay [4].

Models were implemented using KroneckerBio v. 0.5 (https://github.com/kroneckerbio) and expressed as a system of ordinary differential equations with the following form:

$$dx/dt=k+Ax+B\,(x\otimes x)$$

where k is a vector of 0th order rate constants, A is an n by n matrix of 1st order rate constants, and B is an n by n matrix of second order rate constants. Parameter estimation and simulations were performed using MATLAB v. 2015b (Mathworks, Natick MA).

Results:

The QSP Pb-Tx model was developed based on proposed mechanisms of Pb-Tx distribution, elimination, activation and binding. The QSP Pb-Tx model captures events both at the Pb-Tx- and compartmental-levels. Unique to the Pb-Tx, reversible breathing events and irreversible cleavage reactions are both captured in the model to yield multiple species that may interact with PD-L1 with differential

affinities. Common to other mAb pharmacology models [5], the multiple states of the Pb-Tx distribute to the plasma, peripheral, and tumor compartments.

The Pb-Tx QSP model was calibrated to intact and total CX-072 circulating levels following administration of CX-072 20, 60, and 200 mg/kg to cynomolgus monkeys. Preliminary human single-dose (SD) PK data following CX-072 0.03-30.0 mg/kg appeared consistent with QSP model predictions: CX-072 circulated predominantly as intact CX-072 (96% intact at 30 mg/kg) with no strong trending of intact CX-072 elimination kinetics with dose. In contrast to simulations for the Pb-Tx (intact CX-072), the parental mAb (CX-075) QSP model simulations suggest evidence of target mediated drug disposition (TMDD) as has been noted for other PD-L1 mAbs such as atezolizumab [6]. Preliminary tumor RO estimates were observed to be consistent with QSP predictions following CX-072 3 - 30 mg/kg.

Conclusions:

The CX-072 QSP model captures the determinants of Pb-Tx PK/PD and corroborates preliminary clinical PK/PD findings from PROCLAIM-CX-072: as designed, CX-072 circulates predominantly as intact CX-072 and likely is not strongly influenced by TMDD following CX-072 0.03 - 30 mg/kg SD.

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III-31: *Herbert Struemper* Population Pharmacokinetics of Belimumab Administered Intravenously in Children with Systemic Lupus Erythematosus

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Introduction

Belimumab (BENLYSTA) is a human IgG1λ monoclonal antibody that neutralizes B-lymphocyte stimulator protein (BLyS; also known as B-cell activating factor, BAFF) and is currently approved for the treatment of active systemic lupus erythematosus (SLE) in adults. To address the needs of pediatric patients with childhood-onset SLE (cSLE), the Phase 2, multicenter, randomized, double-blind trial BEL114055 (NCT01649765) evaluated the efficacy, safety, and pharmacokinetics (PK) of intravenous (IV) belimumab vs placebo, plus standard therapy, in pediatric patients 5-17 years of age with cSLE.

Objectives

- To characterize the population PK (popPK) of belimumab following IV administration in pediatric patients with cSLE and evaluate the potential effect of selected covariates on PK parameters.
- To compare belimumab exposure in pediatric patients with cSLE to exposure in adult SLE Phase 3 patients with IV administration.

Methods

Patients with cSLE were randomized to the weight-normalized belimumab dose of 10 mg/kg approved for adults or placebo, administered on Days 0, 14 and 28, and every 28 days thereafter for 52 weeks. PK data were provided by the 53 patients on active treatment, of which 20 patients were included in PK lead-in cohorts with more intense PK sampling (median 16.5 samples). Ten of the 53 subjects were in the younger age group (5-11 years of age). PK data were analyzed with a non-linear mixed effects modeling approach using NONMEM. Model development was guided by the previously developed popPK model for IV belimumab in adults [1]. Results using a MAXEVAL=0 approach on the adult model were compared with a revised popPK model with covariate effects updated for pediatrics, re-estimating all model parameters, then reducing the models with a variation of the full model approach [2]. Individual post-hoc parameters were used to derive steady-state PK profiles and exposure parameters (e.g. Cavg, average serum concentration over dosing interval), which were compared to the corresponding adult Phase 3 results.

Results

The resulting popPK model described pediatric belimumab PK in the form of a linear 2-compartment model with clearance from the central compartment (CL). The population estimates for central clearance, steady-state volume of distribution and terminal half-life were 158 mL/day, 3.5 L, and 16.3 days, respectively, in the overall pediatric population.
Fat-free mass (FFM) [3] best described the effects of body size on the PK.; estimates for allometric exponents were 0.691 for central/intercompartmental clearance and 0.944 for central/peripheral volumes of distribution (V1/V2). Age did not have a statistically significant effect on clearance after accounting for

body size effects. Additional covariate effects retained in the final model were baseline IgG, proteinuria, and estimated glomerular filtration rate on CL baseline white blood cell count on V1.

Belimumab Cavg exposures for the overall pediatric study and both pediatric age groups were similar to adult exposure at the 10 mg/kg dose level in Phase 3 trials; younger subjects had slightly lower exposures than the older subjects.

Conclusions

- The structure and parameters of the belimumab IV pediatric popPK model are consistent with those of the corresponding adult popPK model [1] after accounting for differences in body size and subject numbers.
- Enriched sampling in PK lead-in cohorts (n=20) together with sparse sampling in other subjects (n=33) supported estimation of popPK parameters with sufficient precision based on pediatric data only.
- The estimated allometric exponents on clearance and volume were consistent with values expected from allometric theory (0.75 and 1, respectively) when FFM was used, but lower when total body weight was used to characterize body size.
- Individual pediatric PK parameters predicted by the adult popPK model using the MAXEVAL=0 approach were appropriate, but the pediatric popPK model had superior simulation performance.
- Belimumab exposures were similar between pediatric and adults SLE subjects.
- These PK results support the approved adult IV dose of 10 mg/kg as an appropriate dose for pediatric patients with cSLE and that, other than weight-proportional dosing, no dose adjustments are required in the studied pediatric population.

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III-32: *Sabine Stuebler* Systems biology model of the mucosal immune system

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Objectives: Inflammatory bowel diseases (IBD), characterised by chronic inflammation of the gut tissue, are caused by autoimmunity of T cells against commensal bacteria. As the therapeutic outcome of the currently used treatment regimens (e.g. immunomodulatory small molecule drugs or monoclonal antibodies targeting TNF-a) differs highly between drugs and patients, a better understanding of the mucosal immune system in the context of chronic inflammation is highly desirable. The objective of this work was to mathematically describe the most important cellular processes of the intestinal immune system to provide a basis for the analysis of drug effects and inter-individual variability.

Methods: Through an extensive literature query we identified important processes of the (innate and adaptive) mucosal immune system on the cellular level and described them (i) using literature values as parameters, (ii) by fitting parameters to literature data from human, mouse or *in vitro* studies, or (iii) by assuming reasonable parameter ranges resulting in adequate model behaviour, where literature data were not available. These processes were then combined into an ODE model.

Results: The developed systems biology model included different subsets and activation states of dendritic cells, macrophages, neutrophils, T cells and bacteria, described as concentrations (cells/mL) in two tissues (lamina propria (LP) and mesenteric lymph node (MLN)): Dendritic cells enter the LP as quiescent cells and can be activated by pro-inflammatory cytokines and/or take up antigen and then migrate to a MLN. Macrophages enter the LP as pro-inflammatory cells and are subsequently deactivated [1], and can take up antigen. Neutrophils enter the LP as inflammatory cells. Their apoptosis triggers resolution of the infection by producing specialised pro-resolving mediators (SPM) and stimulating macrophages to produce SPM, which inhibit innate immune cell recruitment and stimulate further neutrophil apoptosis. Recruitment, activation and inactivation of dendritic cells, macrophages and neutrophils are dependent on cytokine concentrations, which were implemented as weighted sums of the cytokine-producing cells due to their short half-lives. Activation of naive and memory T cells (mainly in MLN) is based on the contact rate between T cells and antigen-presenting cells (mainly dendritic cells), limited by the available surface of both cell types and the contact duration. Subsequently there is proliferation and apoptosis [2,3] and differentiation (to T helper cell types 1, 2 and 17 and regulatory T cells) with specific functions via cytokine production. Regulatory T cells are also able to inhibit antigen-presenting cells via cell-cell contact. Epithelial barrier, mucus layer and bacteria in the lumen are described as change from baseline. Pathogenic bacteria, which compete with commensal bacteria for nutrients in the lumen, are able to cross the epithelial barrier, thereby destroying it and allowing commensal bacteria to follow. Once in the LP, bacteria are eliminated by phagocytic cells, limited by the maximal killing rate per phagocyte [4].

The model was able to reflect the main characteristics of the mucosal immune response to infection with an intracellular or extracellular bacterial pathogen or damage of the epithelial barrier: A sharp increase (peak at 16 h) of the neutrophil concentration was followed by an inflow of macrophages. Effector T cell concentrations increased with a delay (peak at day 8). Bacteria up to a threshold were eliminated, and subsequently all cell concentrations returned to baseline (resolution of the inflammation).

Conclusions: The proposed model is a systematic combination of available knowledge on the local gut immune effects related to IBD. It allows for the first time to include different known IBD predispositions and stimuli and thereby to generate a virtual population of IBD patients, defined by different parameter sets accounting for different predispositions leading to disease. After combining the systems biology model with drug-specific PK models, we aim to identify to what extent the inter-individual variability in treatment outcome is PK- and/or PD-related.

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III-33: *Suein Choi* contribution of trough concentration data for the evaluation of multiple-dose pharmacokinetics

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Objectives: In many clinical trial situations involving a multiple dose administration, the steady-state full pharmacokinetic (PK) study is emphasized to predict PK parameter while the trough samplings are only used for compliance check and often omitted for various reasons such as the inconvenience of the subjects and increase of total research budget. However, particularly for drug with long half-life, multiple dose full PK data obtained during a single inter-dose interval (II) after 3 half-lives may be insufficient to properly estimate the PK. In this study, using stochastic simulation and estimation method, we were to evaluate the contribution of trough concentration data for PK evaluation in such situations, and to obtain the most informative sampling timepoint with athe appropriate number of sampling

Methods: PK parameters and inter- and intra individual variation were obtained from the bioequivalence study data of amlodipine using nonlinear mixed effect modeling software NONMEM. Amlodipine PK model was assessed by goodness-of-fit plots and precision of parameters were evaluated by bootstrap analysis. Once amlodipine PK model was developed, stochastic simulation and estimation were performed using the predicted PK profile to evaluate the efficiencies of different trough sampling scenarios, which was performed just before the next daily dosing. Amlodipine PK profile was simulated with 64 different sampling scenarios and simulated data were generated 1000 times for each scenario. RSE (Relative standard error (%)) and the average relative bias (%) estimated for each scenario were evaluated to select the most effective scenario to predict the PK parameters with minimum effort.

Results: Amlodipine PK was well described by the 2-compartment PK model with first-order absorption followed by zero-order absorption with lag time and linear elimination. (Oral clearance(CL/F) = 36.4 L/hr, Central volume(Vc/F) = 1150 L, Peripheral volume(Vp/F) = 910 L, Intercomparmental clearance (Q/F) = 118 L/hr, Absorption rate constant of first-order absorption(Ka) = 0.563/hr, Lag time of first-order absorption (Alag1) = 0.51 hr, Lag time of zero-order absorption(Alag2) = 3.85 hr, Fraction amount for first-order absorption (F1) = 0.762, Absorption duration of zero-order absorption(D2) = 2.36 hr) Visual inspection including goodness-of-fit plots and bootstrap result showed that PK model and parameters were predicted adequately. Based on the estimated RSE and average relative bias value for each scenario, the result showed that, for one trough sampling, sampling at 48hr or 72hr are recommended (RSE(%) = 23.7%, average relative bias(%) = 3.8%). For two trough samplings, sampling at 48hr and 96hr is recommended (RSE(%) = 17.3%, average relative bias(%) = 2.1%). Adding trough sampling after 2 half-lives did not improve the prediction, and three times of trough sampling did not show significant improvement from two times of trough sampling when samplings were performed at adequate timepoint such 48hr and 96hr.

Conclusions: The results implied that there were more informative timepoints to estimate accurate PK parameters in the multiple dose studies. When this timepoint can be predicted at the stage of protocol development through similar approach, an efficient clinical trial can be conducted with minimized sample numbers for the drug.

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III-34: *Jesper Sundell* Pharmacokinetic variability of isoniazid, and its two major metabolites in patients co-infected with tuberculosis and HIV

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Objectives: Tuberculosis (TB) is the most common cause of death in HIV-infected individuals. Isoniazid in combination with rifampicin, pyrazinamide and ethambutol is used as first-line treatment to combat TB infection. Isoniazid primarily undergoes metabolic elimination resulting in formation of acetyl-isoniazid via polymorphic N-acetyltransferase 2 and isonicotinic acid via amidase metabolism of parent drug (1). Isoniazid-induced hepatotoxicity has been proposed to be a consequence of exposure to toxic metabolites (2, 3). Moreover, low exposure to isoniazid may result in treatment failure and resistance development. Hence, determination of clinical factors affecting the pharmacokinetics of isoniazid and its metabolites will benefit clinical outcome. We therefore aimed to investigate factors which influence the variability of isoniazid and its two major metabolites in patients co-infected with TB and HIV.

Methods: Concentration-time profiles with observations up to eight hours post dose were analysed using non-linear mixed effects modeling. Study participants were either on concomitant efavirenz-based antiretroviral therapy or HIV treatment naïve. Acetylator status was determined using a molar ratio of $AUC_{(acetyl\text{-}isoniazid,\ 0\text{-}8h)}/AUC_{(isoniazid,\ 0\text{-}8h)}$ with a cut off value of 0.9 (4). Isoniazid was assumed to be eliminated via either two or three pathways where two parallel pathways were responsible for the formation of acetyl-isoniazid and isonicotinic acid. Acetyl-isoniazid was assumed to be eliminated via two pathways where one resulted in the formation of isonicotinic acid.

Results: A total of 1247 observations of isoniazid, acetyl-isoniazid and isonicotinic acid from 63 TB/HIV co-infected patients were used for the present analysis. Isoniazid pharmacokinetics were most adequately described by a two-compartment disposition model with three elimination pathways. Acetyl-isoniazid and isonicotinic acid observations were fitted by one-compartment disposition models, respectively. Isoniazid clearance and fraction of isoniazid metabolized to acetyl-isoniazid were 2.5-fold higher in rapid acetylators compared to slow acetylators. Simultaneous treatment for HIV significantly increased acetyl-isoniazid and isonicotinic acid clearances by 56% and 77%, respectively. Relative bioavailability was 36% higher in females compared to males. Furthermore, isoniazid bioavailability was affected by CD4 cell count.

$AUC_{0\text{-}8h}$ for isoniazid, acetyl-isoniazid and isonicotinic acid was analysed stratified by acetylator status and study arm. Median $AUC_{0\text{-}8h}$ was 44% higher in HIV treatment naïve rapid acetylators compared to rapid acetylators on concomitant HIV therapy. No exposure difference was found between slow acetylators on concomitant HIV treatment or HIV treatment naïve. In the present cohort, 21% had isoniazid exposures below the recommended threshold. Among the rapid acetylators 6/10 were undertreated, out of which 3/3 rapid acetylators on concomitant efavirenz-based antiretroviral therapy had low exposures.

Conclusions: The pharmacokinetics of isoniazid were affected by acetylator status, HIV treatment, CD4 cell count and sex in the present cohort. Furthermore, the clearances of isoniazids two major metabolites were higher in patients on concomitant efavirenz-based antiretroviral therapy. Rapid acetylators on simultaneous HIV treatment had an increase in isoniazid clearance resulting in exposures below the

recommended threshold. A dose regimen based on NAT2 genotype and concomitant HIV treatment should be investigated.

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III-35: *Budi Octasari Susanto* Translational Model-Informed Selection of Tuberculosis Drug Combination Regimens for Early Clinical Development

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Objectives: There is still a gap between pre-clinical and clinical phase in tuberculosis (TB) drug development. New innovative tools are needed to streamline TB drug development. Since TB treatment contains several drugs, pharmacodynamic (PD) interactions can be a challenge for developing optimal regimens. Pre-clinical information about PD interactions needs to be used more optimally when designing early drug development clinical trials i.e. the so-called Early Bactericidal Activity (EBA) studies. The General Pharmacodynamic Interaction (GPDI) model is a novel model-based assessment of PD interactions [1], which has successfully been combined with the Multistate Tuberculosis Pharmacometric (MTP) model, a semi-mechanistic model developed to characterize drug effects on different growth states of the TB bacteria [2]. The MTP-GPDI approach has been used to identify PD interactions both *in vitro* [3] and *in vivo* [4], but no approach has yet been presented of how to predict human response given the identified pre-clinical interactions. A framework for clinical dose-response forecasting in EBA studies based on pre-clinical *in vitro* information using the MTP model has successfully been developed [5] but this far, only EBA studies after monotherapy have been predicted. The aim of this study was to develop a pre-clinical model-informed translational approach to guide dose selection of TB drug combinations in EBA trials using the MTP-GPDI model approach using rifampicin and isoniazid as an example.

Methods: Longitudinal colony-forming unit (CFU) data from rifampicin and isoniazid in different concentrations in monotherapy and combination based on *in vitro* static time-kill curve in *Mycobacterium tuberculosis* H37Rv strain were used to estimate exposure-response relationships as well as PD interactions at different mycobacterial growth states with the MTP-GPDI model approach [1-2]. The modelling of the *in vitro* data was performed using NONMEM 7.3. Clinical trial simulations of EBA studies were done using the final MTP models describing exposure-response in monotherapy with the GPDI model assessment of PD interactions coupled to the earlier developed model-informed MTP translational approach [5] with the earlier identified translational factors to account for differences between *in vitro* and human (post-antibiotic effects (PAE), mycobacterial susceptibility, bacterial growth phase and inoculum effect). To account for the change in drug concentration in humans and at the target site concentration, population plasma and epithelial lining fluid (ELF) pharmacokinetics of rifampicin [6-7] and isoniazid [8-9] were incorporated into the predictions. The simulations were performed using 'deSolve' package in R. The results of the predicted EBA trials were compared to different observed EBA trials in order to externally evaluate the approach against clinical data.

Results: Our MTP-GPDI model approach was able to predict $EBA_{0\text{-}2\ days}$, $EBA_{0\text{-}5\ days}$, and $EBA_{0\text{-}14\ days}$ from different EBA studies of rifampicin and isoniazid in monotherapy as well as isoniazid-rifampicin in combination. In addition, the GPDI model identified bidirectional antagonism with rifampicin and isoniazid being perpetrator on each other. Rifampicin acted as a perpetrator on isoniazid on the inhibition of fast-multiplying bacteria (F) growth, killing of F state and killing of slow-multiplying bacteria (S) state. On the other hand, isoniazid became the perpetrator on rifampicin only on the killing of F state. No interaction was identified on the killing of non-multiplying bacteria (N) state. The simulations demonstrated that increasing

the rifampicin dose will results in higher efficacy both in monotherapy as well as together with isoniazid. In contrast, the simulations showed that increasing the isoniazid dose will not give a significant improvement of the EBA in monotherapy and in combination. This finding indicated that maximum efficacy has reached for isoniazid in monotherapy and increasing isoniazid dose will not contribute to increase in efficacy for the combination.

Conclusions: The approach described in this study may help to inform decision making for dose selection and identification of optimal regimens in order to allow for early testing of drug combinations in TB clinical trials and contributing to closing the gap between pre-clinical and clinical drug development.

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III-36: *Hadi Taghvafard* Modeling (a)symmetry of concentration-effect curves

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Introduction: An important topic in quantitative pharmacology is modeling the shape of concentration-effect (E/[A]) curves, which relate the concentration of an agonist [A] to an observed functional effect E. Mathematical modeling of E/[A] data can allow us to classify agonists and receptors, design more selective and potent therapeutic agents, and better understand physiological functions [1]. Owing to the fact that all measures of system sensitivity or drug activity originate from E/[A] curves, it is of prime importance to find the mathematical functions which fit experimental data precisely. The shape of E/[A] curves can also provide insights into mechanisms of signal transduction.

Several mathematical equations have been postulated to describe E/[A] curves (see, e.g., [1, 2, 3, 4, 5]). One of the most important equations which has been extensively used in pharmacology to model E/[A] data is the Hill equation, which is symmetric, i.e., the inflection point is exactly the same as the mid-point of a concentration-effect curve. However, even standard models of receptor theory predict asymmetric E/[A] curves, which cannot be described by the Hill equation [3]. Therefore, there is a need for alternative equations to describe asymmetric E/[A] curves [1,3], which was the focus of the present study.

Methods: We propose two novel equations to describe E/[A] curves. The first equation is based on the exponential function and describes symmetric E/[A] curves. The second equation, being more general than the first one, can be applied to both symmetric and asymmetric curves.

The first equation has three parameters, while the second one has four parameters. In the second equation, there are two parameters which contribute to the asymmetry and slope of an E/[A] curve. We mathematically compare them to the Hill equation and the Richard equation [4] and explore how these new equations can be used for parameter fitting of E/[A] datasets.

Results: We propose the following equations:

E/[A] = a*(2/(1+e^-([A]^n/(K+[A]^n))) - 1), K,a,n>0 (1)

E/[A] = a*(2/(1+b^-([A]/(K+[A]))^n) - 1), K,a,n>0, b>=1 (2)

Comparing our two proposed equations with the conventional Hill equation, we have the following results:

- 1) Equation (1) is identical to the Hill equation for describing symmetric E/[A] curves. In this equation, parameters *K*, *a* and *n* correspond, respectively, to EC_{50}, E_{max} and the slope parameter in the Hill equation.
- 2) Equation (2) is applicable to both symmetric and asymmetric E/[A] curves, while the Hill equation is not a proper equation for describing asymmetric curves. In the Richards equation [5], there is only one parameter playing a crucial rule in the slope and asymmetry of an E/[A] curve [1]. However, in equation (2) there are two parameters, namely *b* and *n*, which make such changes.

Conclusions: We have proposed two new equations for modeling symmetrical and asymmetrical E/[A] curves, which may provide alternatives for the commonly-used Hill equation in pharmacokinetic-pharmacodynamic and systems pharmacology models.

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III-37: *Hiroyuki Takita* The dynamics of pharmacological effects aimed at gut wall: A framework for a nested-target-within-enterocyte (NTWE) model that accounts for turnover of target and cell

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Introduction: The gastrointestinal (GI) tract has been the focus of several potential therapeutic target linked to metabolic diseases, cancer, inflammatory disorders etc [1]. However, development drugs for such targets is challenging because of the complex and dynamic physiology of gut wall (e.g. the rapid turnover of the enterocytes [2]).

The enterocytes are produced in the crypt at the base of the villi in the intestine, and then migrate up the crypt-villous axis, where the turnover will be governed by apoptosis or shedding into the gut lumen at the tip of the villi. The average time from enterocyte generation to shedding is reported to be 3 and half days (range 1-7 days). This is much faster turnover cycle than other types of tissue cells. In addition, the turnover rate of the enterocyte is reduced to less than one day in some diseases such as untreated coeliac disease [3]. In the field of PK/PD modelling, turnover of target protein or drug dissociation rate constant from target protein (k_{off}) has been studied and considered as a rate limiting step of pharmacodynamics [4][5]. However, to the best of our knowledge, most of the models either ignored the turnover of the enterocytes itself or used a lumped cell-protein turnover, which could lead to a different PD effect in case enterocyte turnover is a rate limiting step. Moreover, these hybrid turnover functions cannot account for changes taking place in pathophysiology when disease affects part of the hybrid function.

Recently, we have shown that the nested-enzyme-within-enterocyte (NEWE) turnover model, which incorporates turnover for both enterocyte and metabolic enzyme, can capture the drug-drug interactions at gut wall in the presence of disease affecting cell turnover [6]. Here, we expanded the on the work and provide a general framework to investigate the impact of enterocyte turnover on dynamics of pharmacological effects on the gut wall under different conditions.

Objectives:

- l Develop a nested-target-within-enterocyte (NTWE) turnover model, which is a new theoretical PK/PD framework for pharmacological effects on gut wall in health and disease
- l Evaluate the impact of enterocyte turnover on time course of pharmacological effects on the GI tract through simulations in an array of realistic parameter ranges
- l Summarize information in the form of principles guiding the development of drugs for targets in the gut wall

Methods: The compartmental NTWE model consisted of the intestinal lumen, enterocyte, lamina propria, liver and central compartment. In the enterocyte compartment, drug association and dissociation with the PD target protein was described using binding rate constants. The degree of pharmacodynamics effect was assumed to be in proportion to the amount of target protein or drug-target protein complex. The turnover of enterocytes was expressed by initializing the parameters in the enterocyte compartment at the rate of enterocyte turnover. Representative values and probability distributions of parameters, such as turnover

rate of the enterocytes, turnover of target protein and binding kinetic constants, were obtained from the literature and used to inform the simulation study. The PD index, defined as the index of enterocyte turnover contribution on pharmacodynamics, was calculated as a ratio of the effect in the model considering enterocyte turnover and without considering enterocyte turnover.

Representative values for each parameter were defined based on their probability distributions. Parameters were randomly sampled to generate multiple parameter sets. Simulations were performed based on these parameter sets and results were analysed to evaluate the impact of enterocyte turnover on PD effect.

Results: When enterocyte lifespan was within the range observed in healthy volunteer (1-7 days), the reduction in PD index was observed when k_{off} was in the low range (0.003 h^{-1}, strong/irreversible target binding), and half-life of target protein was long (200 hours). More importantly, in case of diseased population, where enterocyte lifespan was shorter (0.25 days), a reduction was observed in PD index even at higher values of k_{off} (< 0.3 h^{-1}), which is in the range of reversible drug-target binding.

Conclusions: The contribution of enterocyte turnover should be incorporated into the mechanistic PK/PD model in the case of irreversible inhibition of target proteins particularly for disease states where enterocyte turnover rate is altered.

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III-38: *Lénaïg Tanneau* Evaluating potential link between liver enzyme abnormalities and bedaquiline exposure in multi-drug resistant tuberculosis patients

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Objectives: Bedaquiline (BDQ) is a drug indicated in the treatment of multidrug-resistant (MDR) tuberculosis (TB) as part of combination therapy [1]. Approved in 2012, it has shown ability to increase the cure rate and is now a prioritized component in MDR-TB regimens recommended by the WHO [2,3]. Despite its general well-tolerated profile, some risks are potentially associated with BDQ intake such as QT prolongation or hepatotoxicity. Our previous work focused on the relationship between bedaquiline or its main metabolite (M2) exposure and QT prolongation [4]. The aim of this analysis was to investigate a potential link between exposure of BDQ and/or M2 and elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels in MDR-TB patients using the approved BDQ dose.

Methods: Data were obtained from 2 phase IIb studies (C208 [5], C209 [1]) and were pooled to include a total of 335 patients treated with BDQ and 105 patients with placebo (PLC). Patients received BDQ (400mg q.d. for 2 weeks, then 200mg t.i.w.) or placebo for 24 weeks (or 8 weeks in stage 1 of C208) in combination with a background regimen of 5-7 anti-TB drugs. ALT and AST measurements were performed at day-1 and every 2 weeks in all patients of the placebo controlled C208 study and at day -1, week 2, 8 and 24 for patients in the open-label C209 study. Individual model-predicted pharmacokinetic variables were derived from a PK-model for BDQ and M2 previously established for these trials [8]. BDQ and M2 weekly average concentrations, time after start of treatment, and presence of background TB drugs were evaluated as covariates of the base transaminase levels. The impact of treatment group (PLC vs BDQ) was tested using C208 data only and the likelihood ratio test, with calibration for type 1 error using randomization test. Furthermore, a statistical analysis was performed on C208 data considering the highest on-treatment ALT/AST value per patient, either as continuous data or categorical data (graded to a 0-4 severity score, following the study protocol standards). A Wilcoxon rank sum test was used to compare the medians of the PLC group versus the BDQ group. A proportional odds model was used to describe the categorical data, analysing treatment group and BDQ/M2 exposures ($1/CL_{BDQ,i}$; $1/CL_{M2,i}$) as predictors.

Results: 5881 observations of ALT and AST levels were recorded at baseline (up to 48h before start of study treatment) and during the treatment period. ALT and AST data were fitted simultaneously with separate models but allowing correlations between random effects and residuals. A model with an effect of presence of background (BG) TB drugs and an Emax-shaped time dependency best described the data (ALT baseline of 20.1 UI/L [RSE 4%] decreased by 3.8 UI/L [RSE 19%] with BG effect and by maximally 0.74 UI/L [RSE 51%] with time, $T50_{ALT}$ of 0.25 weeks [RSE 101%]; AST baseline of 23.8 UI/L [RSE 2%] increased by 2 UI/L [RSE 27%] with BG effect and by maximally 2.8 UI/L [RSE 18%] with time, $T50_{AST}$ of 6.3 weeks [RSE 49%]).
Considering C208 data only, no significant difference between BDQ vs PLC groups ($p>0.1$) was found either in the expected on-treatment values of ALT and AST using the randomization test, or between the medians of maximal on-treatment values of ALT ($p=0.115$) and ALT ($p=0842$) using the Wilcoxon rank sum test, although for both analytes, the BDQ group had higher values (median of 21.5 UI/L and 34 UI/L in the PLC group vs 25 UI/L and 37 UI/L in the BDQ group for ALT and AST respectively). The difference between the BDQ and PLC groups in severity scores was not significant for AST ($P=0.38$) but was for ALT ($P<0.014$) with

higher ALT severity scores in the BDQ group (4 grade (G) 1 in the PLC group vs 6 G1, 6 G2 and 1 G4 in the BDQ group). However, no significant relationship with BDQ and M2 exposures could be identified.

Conclusions: Elevated transaminases have been labelled as a potential adverse reaction of BDQ treatment. Indeed, in C208/C209 studies, higher ALT and AST levels were observed in patients treated with BDQ compared to the C208 PLC group. However, our analyses could not correlate levels of BDQ or M2 with increased ALT or AST levels (i.e. no link was found to individual BDQ or M2 exposure metrics). Further analysis of confounding factors such as alcohol use or underlying hepatic disease may be interesting to fully describe the profile of ALT and AST levels.

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III-39: *Joel Tarning* Severe acute malnutrition results in lower exposure in children treated with artemether-lumefantrine for uncomplicated malaria

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Objectives: Young children (

Methods: This clinical trial was an open-labelled comparative intervention study of artemether-lumefantrine in 131 SAM and 266 non-SAM children, aged 6 to 59 months, with uncomplicated *falciparum* malaria. For each child, five capillary blood samples were collected in pre-specified time-windows. Lumefantrine capillary blood concentration-time data and time-to-malaria reinfection during the 42-days of follow-up were analysed using nonlinear mixed-effects modelling (NONMEM v7.3). Time-to-malaria reinfection was modelled using an interval-censoring time-to-event model. The lag-time between an emerging blood stage infection from the liver and the microscopy detection of malaria was accounted for by back-extrapolating the observed number of parasites at the time of microscopic detection with a fixed exponential parasite growth rate [2]. The *In vivo* minimum inhibitory concentration (MIC) of lumefantrine was estimated based on the individually predicted lumefantrine concentration at the start of the blood stage infection [3]. The final PK/PD model was used to simulate lumefantrine exposures and treatment outcomes in SAM and non-SAM children using alternative dosing strategies; (1) increased dosing, (2) intensified dosing, and (3) extended dosing regimens.

Results: Lumefantrine was described adequately by two transit-absorption compartments followed by two disposition compartments. The fraction of observed concentrations below the LLOQ were low (6.26%), but omitting the data (M1) resulted in misspecifications while imputations (M6) resulted in a good predictive performance. Allometrically scaled body weight and an enzymatic maturation effect were included in the PK model. All investigated indicators of malnutrition were highly correlated and had a significant impact on relative bioavailability of lumefantrine. MUAC resulted in the largest drop in objective function value (ΔOFV = -64.4) and was retained in the final model. The median bioavailability was reduced by 25.4% (95% CI: 21.3%, 27.1%) per 1 cm reduction of MUAC. Impact of malnutrition-associated indicators were investigated further using a full-covariate approach, supporting the impact of malnutrition. Risk of recurrent malaria was characterised successfully by an interval-censored time-to-event model with a sigmoid E_{MAX}-model describing the effect of lumefantrine. No covariates were found to have a significant impact in the model. The *in vivo* MIC of lumefantrine was estimated between 164 ng/mL and 182 ng/mL. Both the intensified and extended dosing regimens were able to increase the exposure to lumefantrine in SAM children to similar levels as that seen in non-SAM children receiving standard dosing, but resulted in a moderate improvement in protective efficacy. However, time above MIC should be highly correlated to therapeutic

efficacy since residual lumefantrine concentrations above the MIC value eliminate residual parasites in order to avoid recrudescent infections. Time above MIC in SAM children was increased to 9.81 (95% CI: 6.67, 50.8) days and 12.3 (95% CI: 8.10, 52.0) days after the intensified and extended dosing regimens, respectively, equivalent to that seen in non-SAM children after standard dosing (9.33 (95% CI: 6.60, 39.3) days).

Conclusions: Malnutrition had a significant impact on the absorption of lumefantrine, resulting in substantially lower drug exposure with increasing malnutrition. Research on altered dosing regimens should be considered for optimal treatment of malaria in malnourished children.

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III-40: *David Ternant* Revisiting target-mediated elimination of therapeutic antibodies: the irreversible binding approximation

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Objectives: The pharmacokinetics (PK) of therapeutic monoclonal antibodies (mAbs) often present a nonlinear elimination shape due to a target-mediated drug disposition (TMDD). The TMDD model [1] is however rarely used to described target-dependent PK of mAbs because necessitates rich databases with dense sampling strategies and measurements of free mAb, free target and mAb-target complexes. Usually, only mAb concentrations are available and nonlinear elimination is often described using a Michaelis-Menten model which relies on the assumption of constant antigen mass remaining constant during follow-up. The irreversible binding approximation described previously [2] was rarely used. A model describing irreversible binding where antigen is treated as a variable (IBLV) but was previsouly used with success to describe the PK of rituximab in chronic lymphocytic leukemia [3] and therefore deserves further investigation. This work aimed to investigate the relevance of IBLV on real mAb PK databases.

Methods: The IBLV approximation includes a second-order elimination term involving both mAb concentration and antigen mass amount. Being unavailable, antigen target amount is treated as a latent variable. To investigate the relevance of iIBLV approximation, the following mAb PK databases were revisited:

SPAXIM (infliximab in spondylarthropathies, N=26) [4],

IFX-CD (infliximab in Crohn's disease, N=133) [5],

LYSA-RTX (rituximab in non-hodgkin lymphoma, N=108) [6],

RTX-RA (rituximab in reumatoid arthritis, N=91) [7],

RADHER (trastuzumab in breast cancer, N=79) [8],

ORL-CTX (cetuximab in head and neck cancer, N=30) [9],

STIC-avastin (bevacizumab in colorectal cancer, N=130) [10],

LYMPHO (lymphoglobuline in kidney transplantation N=14) [11]

Several PK models were tested. They are made of a 2-compartment model with first-order transfer and elimination rates and target-mediated elimination (TLE) term as follows:

- 2C – linear 2-compartment model, with TLE = 0;

- 2C-MM – 2-compartment model with both linear and Michaelis-Menten elimination rates:

TLE = Vmax.Cc / (Km+Cc), where Vmax is maximum saturable elimination rate, Cc is mAb concentration in the central compartment and Km is Michaelis constant;

- 2C-IB-1 – 2 compartment model with second-order target-mediated elimination and latent target turnover:

TLE = - kon.Cc.L,

dL/dt = kin – kout.L – kon.Cc.L, L(0) = kin/kout

where kon is second-order mAb-target association and elimination rate constant, L is latent target amount variable, and kin and kout are zero-order input and first-order output of latent target amount, respectively;

- 2C-IB-2 – 2 compartment model with second-order target-mediated elimination and initial target amount :

TLE = - kon.Cc.L

dL/dt = - kon.Cc.L, L(0) = L0, where initial target amount is estimated

PK parameters were estimated using nonlinear mixed-effects modelling (Monolix Suite 2018R2, Lixoft, Antony, France).For each database the best model was determined using Akaike's information criterion.

Results: In all but one [9] databases, the published PK model was linear 2-compartment model without target-mediated elimination. Values of AIC of each model were for 2C, 2C-MM, 2C-IB-1, 2C-IB-2. The value of AIC of the best model was in bold:

Study	2C	2C-MM	2C-IB-1	2C-IB-2
SPAXIM	**4421.4**	4428.3	**4425.8**	4427.9
IFX-CD	6685.0	6691.4	**6672.4**	6679.7
LYSA-RTX	8106.7	8111.5	**8075.9**	8099.4
RTX-RA	**3409.9**	3425.8	3409.0	3410.1
RADHER	5378.0	**5309.9**	5365.8	5323.2
ORL-CTX	13096.7	**12697.6**	12709.7	12700.4
STIC-avastin	3828.7	**3804.9**	3817.2	3806.6
LYMPHO	1524.5	1536.9	1480.0	**1470.5**

Target-mediated elimination was detected in 6 of 8 databases and IBLV model were superior to Michaelis-Menten in 3 of 6 of nonlinear PK databases. Of note, nonlinearity was detected for infliximab in Crohn's disease for the first time.

Conclusions: Superiority of IBLV may be due to antigen mass which varies in time. This approximation should be considered in case of mAbs which present nonlinear PK.

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III-41: *Mita Thapar* Population pharmacokinetic analysis of MSB11022 following administration in healthy subjects and rheumatoid arthritis patients.

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Objectives:

The objectives of the present analysis were to develop a population (Pop) PK model to describe the PK of MSB11022, a biosimilar of adalimumab (Humira®), in healthy subjects (single dose study) and rheumatoid arthritis (RA) patients (48 weeks treatment period) and describe any potential differences in PK using formulation/product, health status, immunogenicity and standard demographics as covariates.

A total of 178 healthy subjects with available dosing information and sampling times that received a single dose of adalimumab (40 mg s.c.) contributed a total of 3350 post-dose concentration records (including the BLQs), an average of 19 observations per subject. A total of 285 RA patients with available dosing information and sampling times that received at least one dose of adalimumab (40 mg s.c. every other week upto week 48) contributed a total of 1819 post first-dose concentration records (including the BLQs), an average of 6 observations per subject.

Methods:

A Pop PK model in healthy subjects and RA patients was developed in two steps:

- In the first step, the model was developed to describe the MSB11022 PK in healthy subjects and the effects of formulation (citrate based vs modified buffer and stabilizer), demographics and immunogenicity as covariates were investigated;
- The predictive performance of this Pop PK model, built on healthy subject data, was evaluated by using the model and parameter estimates to predict MSB11022 concentrations and the predicted concentrations were compared to the actual observations from the RA patients;
- This Pop PK model developed in healthy subjects was updated by incorporating the data from RA patients and the influence of relevant intrinsic and extrinsic patient characteristics, including immunogenicity status and the product effect (MSB11022 vs Humira®) was evaluated. Other covariates considered to be evaluated were health status (healthy subjects versus RA patients), plasma albumin, CRCL and formulation on CL/F and Vc/F.

  The final Pop PK model was evaluated by performing a confidence interval visual predictive check (CIVPC)[1]. NONMEM® program version VII level 3.0 was used for all analyses using PDx-Pop (Version 5.2) as an interface.

Results:

- The PK of MSB11022 following single dose administration of both MSB11022 modified buffer and stabilizer and citrate based formulations in healthy subjects were well described by a two-

compartment model with first-order absorption and elimination. Neutralizing antibody (nAb) status and body weight were significant predictors of PK.

- In this model, nAb positive subjects had 1.6-fold higher estimated CL of MSB11022 compared to nAb negative subjects, reflecting the lower concentrations observed in nAb positive subjects.
- There was no difference in PK of MSB11022 between the two evaluated formulations.
- Predictive performance results showed that the Pop PK model obtained using data from healthy subjects described the observed data from RA patients fairly well.
- The PK of MSB11022 following a single and multiple dose administration of both MSB11022 formulations and Humira® in healthy subjects and in RA patients were well described by a two-compartment model with first-order absorption and elimination. Body weight, nAb status and albumin were significant predictors of PK.
- This final Pop PK model predicted 2.35-fold higher CL in nAb positive subjects compared to nAb negative subjects in the healthy subject and RA patient population in the present analysis.
- The Pop PK model did not identify any difference in PK between healthy subjects and RA patients and no difference in PK was identified between MSB11022 and Humira® products.

Conclusions:

- PK of adalimumab following single-dose administration in healthy volunteers and in RA patients were adequately described by a two-compartment model with first-order absorption and elimination.
- The presence of nAb, body weight and albumin were identified as significant covariates. The model estimated 2.35-fold higher clearance in nAb positive subjects compared to the nAb negative subjects.
- No treatment differences were identified in the main PK parameters (clearance and volume), indicating the PK similarity between the MSB11022 modified buffer and stabilizer and citrate based formulations in healthy subjects and no treatment differences were identified in the main PK parameters between MSB11022 and Humira® products in RA patients.

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III-42: *Anders Thorsted* Model-based translation from piglets to healthy volunteers: Prediction of TNF-α and IL-6 time-courses in human endotoxin challenge studies

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Objectives: Endotoxins (ETX), also known as lipopolysaccharides (LPS), are components in the plasma membrane of Gram-negative bacteria that lead to immune activation when administered to mammals. Consequently, ETX is widely utilized in studies into innate immune responses, both *in vitro* and in animals as well as *in vivo* in healthy volunteers. The purpose of the current work was to assess if a previously developed quantitative model based on studies in piglets could be used to predict the cytokine time-courses observed in ETX challenge studies in healthy volunteers.

Methods: A non-linear mixed effects model previously established the relation between infused ETX (*E. coli* O111:B4) in rates from 0.063 to 16.0 µg/kg/h, and the production of the cytokines tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) in a population of piglets (n=116, median body weight of 27 kg) [1]. The model described ETX kinetics with one compartment disposition and non-linear elimination (V_{max}, K_m, Vc), with the time-course stimulating the production of TNF-α, parameterized as a turn-over model (mean transit time MTT_{TNF} and baseline $S0_{TNF}$), through a sigmoidal Emax relationship (E_{max}, EC_{50}, γ) and incorporated tolerance. The time-courses of ETX and TNF-α both stimulated the production of IL-6, parameterized as a turn-over model with transit compartments (MTT_{IL6}, $S0_{IL6}$), through linear effect models ($E_{1,TNF}$, $E_{2,ETX}$).

Cytokine data were obtained from healthy volunteers (n=230, median body weight of 79 kg [2-8]) challenged with ETX as a bolus (0.4, 0.8, 1.0 and 2.0 ng/kg) or continuous infusion (1.0 ng/kg bolus followed by 1.0 ng/kg/h for three hours). Allometric scaling by body weight was applied to four parameters in the preclinical model (V_{max}, Vc, MTT_{TNF}, MTT_{IL6}) with fixed exponents of -0.25, 1.0, 0.25 and 0.25, respectively, while the typical cytokine baselines were allowed to differ between the species ($S0_{TNF}$, $S0_{IL6}$). In a second step, refinements were explored. For example, differences in the exposure-response relationships between ETX, TNF-α and IL-6 were evaluated, as doses differed substantially between piglets and healthy volunteers because humans are much more sensitive to ETX. Parameters were estimated with SAEM in NONMEM 7.4.3 and M3 was used to incorporate any samples below the limit of quantification. The focus of goodness of fit diagnostics was VPCs with acceptable overlap between the median observation and median simulation for each dose level.

Results: When refitting the cytokine baselines only, the observed human time-courses of TNF-α and IL-6 were both underpredicted. To refine the model, the potency parameter (EC_{50}) in the ETX-TNF-α exposure-response relationship was re-estimated, resulting in a human estimate of 31.5 ETX units/L (11% of the estimate for piglets) with an improvement in model fit (ΔOFV=-1777). This resulted in acceptable prediction of the median time-courses of TNF-α across all five dose groups (including combined bolus and infusion administration). For IL-6, additional modifications were required, as the relationship established for piglets resulted in underprediction of the effect in lower dose groups, and a prolonged stimulation in higher dose groups. The model for IL-6 was updated by re-estimating the contribution of TNF-α on IL-6 production

($E_{1,SLP}$) resulting in a slope of 11.5 (12 times the estimate for piglets, *ΔOFV*=-231), and tolerance was implemented in $E_{1,SLP}$, resulting in lower stimulation of IL-6 by TNF-α with time (half-life of 40 min, *ΔOFV*=-421).

Conclusions: Although species differences were apparent for some parameters, the preclinical model structure worked well to predict the median time-courses of TNF-α and IL-6 observed in healthy volunteers. Aside from allometric scaling and cytokine baselines, quantification of species differences in three parameters related to the ETX-TNF-α and TNF-α-IL-6 exposure-response relationships were required to fit the data well. This highlights the potential variations in how immune components affect each other at different ETX doses and between species, and the complexity of the innate immune response. Successful translational models can be of value by informing future study designs and for translating preclinical results to the clinic.

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III-43: *Tjokosela Tikiso* A pooled analysis of abacavir pharmacokinetics in HIV-infected African children: the effect of age, malnutrition, and common concomitant co-medications.

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Objectives: Abacavir given together with other antiretrovirals (ARV) such as efavirenz, lamivudine and lopinavir/ritonavir (4:1) are recommended as a component of 1st line antiretroviral treatment (ART) for infants and children below 12 years[1]. HIV is complicated by many conditions such as malnutrition and tuberculosis (TB) which require concomitant treatment and can potentially lead to drug-drug interaction. Abacavir is primarily metabolized by uridine diphosphate glucuronyltransferase and alcohol dehydrogenase, it is also a P-glycoprotein substrate. Knowledge of abacavir pharmacokinetics in children is limited. More data is required to characterise the impact of covariates on the pharmacokinetics of abacavir to better guide the management of children of various ages. Our objective is to conduct an in-depth population pharmacokinetics of abacavir to better characterize the differences in demographics, concomitant co-medications and other covariates.

Methods: A total of 229 HIV-infected African children from the studies ARROW[2] (n=41), CHAPAS[3] (n=29), DNDI[4] (n=84), and MATCH[5] (n=75) were used for pooled modelling analysis. The median age and weight of the pooled data was 0.79 (range, 0.14-12.78) years and 6.08 (range,2.5-30) kg respectively. The studies all included intensively sampled profiles on separate visits. Of the 229 children available for analysis, 183 were dosed twice daily while 46 were on daily dosing. 155 children were on concomitant lopinavir/ritonavir and 79 were on efavirenz. One hundred and six children received rifampicin-containing anti-TB treatment. Of these, 103 were on super-boosted lopinavir/ritonavir (1:1) and 3 on efavirenz. From the 229 children, 156 were malnourished, with weight-for-age z-score and height-for-age z-score below -2.0. Due to the combination of studies, the distributions of the covariates were unbalanced. NONMEM 7.4.3 with FOCE-I was used to develop a population pharmacokinetic model. PsN, Pirana and Xpose were used to facilitate modelling and model diagnostics[6]. Allometric scaling[7] was used to account for the effect of body size, using different predictors such as fat-free mass (FFM), fat mass and total weight. The effect of maturation[8] on clearance was tested as a potential covariate. Data below the limit of quantification was imputed with half the value of low limit of quantification, and only the first values in a series was retained in the analysis according to method M6 [9].

Results: Abacavir pharmacokinetics was best described by a two-compartment model with first-order elimination and transit compartment absorption. Allometric scaling with total body weight adjusted well for the effect of body size, after which maturation could be identified: clearance was predicted to reach half its mature value at around 3 months after birth and to be fully mature by around 2 years of age. The typical clearance in a child weighing 11-kg and co-treated with normal dose LPV/r (4:1) was estimated at 10.9 L/h. During co-administration of anti-TB treatment with lopinavir super-boosting (LPV/r 1:1), a 33%

decrease in bioavailability was found. A decreased clearance was observed in the malnourished HIV–infected children. Also, the first visit in MATCH (first-dose), had larger exposures due to lower clearance.

Conclusions: The proposed model successfully characterised the abacavir PK, including the effect of body weight and age. Abacavir exposure was significantly decreased by concomitant administration of rifampicin and super-boosted lopinavir**.** Clearance was significantly decreased in malnourished HIV-infected children. Exposure on the first dose was larger, possibly pointing towards induction of clearance over time on ART. Further investigation should address whether dosing adjustments are necessary to counteract the effect of drug-drug interaction and malnutrition.

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III-44: *Pauline Traynard* New library of double absorptions PK models for the MonolixSuite, application to veralipride pharmacokinetics

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Introduction:

Multiple peaks in plasma concentration-time curves are quite common, and can be explained by different physiological processes, such as enterohepatic recycling, delayed gastric emptying, or variability of absorption [1]. If not modelled properly, they can create difficulties in the estimation of PK parameters.

Modelling such profiles is sometimes attempted with mechanistic models that provide a physiological explanation, but they usually have the drawback of requiring many model parameters, which can cause poor accuracy of the estimates [2]. A simpler approach relies on multiple absorption models, assuming simultaneous or sequential inputs via parallel pathways.

We have developed a library of double absorption models implemented in the MonolixSuite that simplifies the selection and testing of different types of absorptions and delays.

We illustrate the performance of such models on an experimental data set for the pharmacokinetics of veralipride, a benzamide neuroleptic. Veralipride plasma concentrations exhibit double peaks after oral absorption [3], and site-specific absorption has been suggested to be the major mechanism [4]. Several modelling attempts for veralipride have been published that assume simultaneous absorptions or sequential absorption windows [3, 5], that showed the need to keep a reasonable number of parameters due to the small size of the dataset.

Methods:

The developed library of double absorption models allows to choose for each absorption a zero-order or first-order absorption process, and an optional delay with a lag time or transit compartments. The absorptions can be either simultaneous or sequential. Different number of compartmentsand linear and non-linear eliminations are available.

The library is used to easily test different hypotheses and find the appropriate model for the veralipride dataset.

The step-by-step modelling workflow set up with the MonolixSuite includes visualizing the data set to characterize the double peaks with Datxplore, exploring double absorptions model in Mlxplore, setting up and estimating a model in Monolix, assessing the uncertainty of the parameter estimates, and simulations of different models with Simulx to investigate the influence of the exact model on endpoints such as the AUC.

Results:

The model libraries in Monolix permit to easily fit stepwise the double peaks in the pharmacokinetics of veralipride, starting with a single absorption model, before moving to a delayed absorption model, to end

up with double delayed absorptions. Different hypotheses were tested for each process, and the possibility to estimate inter-individual variability was precisely assessed for each parameter. The final model shows a good predictive power, and we have verified with a convergence assessment (i.e several runs from different initial values) that there is no over-parameterization.

Simulations of the model with Simulx were made to assess the variability in a large population and showed that the double peaks phenomenon strongly affects relevant endpoints such as the AUC or the time spent in a therapeutic window.

Conclusions:

The MonolixSuite and the new double absorption library allow an efficient modeling and diagnosis of the double peaks, as shown with the example of veralipride pharmacokinetics.

The double absorption model library has been made available in the 2019R1 MonolixSuite release.

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III-45: *Carlos Traynor* Towards personalised medicine in Non-Small Cell Lung Cancer: design of a forecasting model of disease-progression to overall survival.

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Objectives: Lung cancer is the second most common cancer and the leading cause of cancer related death worldwide. In the UK, 46388 new cases were diagnosed and 35620 people died of lung cancer in 2016 [1]. Recently, new tailored therapies directed at the underlying molecular cause are being added to the battery of available anti-cancer drugs. Next-generation sequencing (NGS) is a technique based on modified DNA microarrays, a high-throughput technology that measures thousands of gene expressions in a single experiment in different individuals. The aim of this project is to use non-small cell lung cancer (NSCLC) patient data from a bespoke database to model and predict disease progression (DP) and overall survival (OS) and to further evaluate the association between biomarkers (related to NGS) and clinical outcome. To this end, we have developed mctte an open-source R package, freely available on GitHub [2], which allows fitting stochastic state-space models applied to time-to-event data. It builds upon recent developments in Bayesian software and uses Stan [3] for parameter estimation.

Methods: The data obtained from The Cancer Genome Atlas (TCGA) [4] comprise the clinical outcomes for 495 NSCLC patients, overall survival or time-to-death and disease progression or time-to-recurrence. Disease progression is evaluated by an increase in cancerous lesions or the appearance of metastasis. The data also include clinical covariates and 20431 NGS measurement. To model the course of NSCLC we propose an absorbing Markov Chain with disease progression as a transient state and death as an absorbing state. The model is a proportional Markov time-to-event model that accommodates censoring, allows covariate effects and assumes that baseline hazards of stable to deceased, and recurred to deceased are related through a proportional hazard ratio on the transition.

Results: Age has a higher risk for non-specific cancer death, while stage has a higher risk for related cancer events. Smoke might be easily misinterpreted while smoking people have a higher risk of contract lung cancer, the clinical outcome may differ depending on cancer subtype. The results for NGS are more informative to prognostic biomarkers: MYL7, RGL3 and MPRIP are related to cytoskeleton remodelling and actin binding, but with opposite hazard ratios in the present study. PDCHA3 and FMN1 are related to cadherin and cell adhesion. VAV2 is related to EGFR signalling.

Conclusions: The novelty in this study includes the development of a mechanistic model of disease progression from clinical, genomic and survival data, for lung squamous cell lung carcinoma. This study showed that the hazards of lung cancer-specific events are associated with genomic variables related to actionable mutations that are expected to predict the effect of therapy. The design of a forecasting model of disease progression combined with treatment effects may be used to select patients, thereby, advancing towards personalised therapies.

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III-46: *Iñaki F. Trocóniz* A modelling platform for onco-immunological drugs in early drug development

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Objectives: Humanised mouse models are widely used for preclinical evaluation of immuno-oncological (IO) drugs [1]. However, tumour response from these models is highly variable and dependent on the donor properties, potentially masking interpretation of drug effects. The objective of this work was to propose a mathematical framework to quantitatively assess (i) the *in vivo* effect of different therapeutic strategies during early preclinical development and (ii) the variability associated to these experimental settings to support drug development.

Methods: Longitudinal tumour volume from 22 different studies performed in established HCC827 xenograft tumour model were available. Briefly, NSG mice were implanted subcutaneously with 10^7 HCC827 tumour cells. When tumours reached a predefined volume (~300mm^3), a single intraperitoneal (IP) dose of human IgG (n=160) or a single intravenous dose of expanded human T cells (dose ranging between 2 to 4x10^6) was intravenously administered. After T cell administration, mice were left untreated (n=229) or were treated with weekly IP injections of different IO compounds under research for 4 weeks (n=769). In total, tumour growth data after administration of T cells from 9 different donors, and 6 different IO drugs was collected. In addition, pharmacokinetic data from all drugs was available. A stepwise population modelling approach was followed using NONMEM 7.3 and FOCEI algorithm: (i) tumour growth modelling in the absence of perturbation (Tcells or drug administration) was first characterised, (ii) T cell effect modelling was developed and finally (iii) treatment effect modelling was implemented. Additional levels of variability above inter-animal variability (IAV), i.e. inter-study variability (ISV) and/or inter-donor variability (IDV), were explored.

Results: The unperturbed tumour growth model proposed by Simeoni et al [2] enabled a satisfactory characterization of tumour data in absence of treatment, with an adequate parameter precision (relative standard errors, RSE, below 10%) and low inter-animal variability (IAV, below 25%). In addition, low inter-study variability at initial tumour burden was detected (ca. 20%) explaining half of the IAV at this level. Regarding the T cell model, a simeoni-like structure -where administered T cells trigger tumour cell death through a series of transit compartments- provided a better overall characterisation over alternative models, and was thus selected as final T cell model. Due to the lack of T cells measurements, T cells were assumed to engraft and remain constant over time at the administered dose. An efficacy parameter (K_{Tcell}) value of 0.013 (10^6 cells*day)$^{-1}$ with a relatively high associated IAV of 105% was estimated with high precision (RSE <10%). A relatively large inter-study variability (50 %) was identified explaining around 20 % of the variability estimated on K_{Tcell}. Unfortunately, using donor information instead of study information did not provide a better model performance or variability explanation, probably due to the lower number of donors compared to the number of studies and the high intrinsic IAV. Finally, and in agreement with the known biology, drug effects were introduced implemented in the model increasing T cells activity (i.e. no drug effect in the absence of T cell administration). For all drug candidates except one, a non-linear drug effect model (EMAX model) provided a better description than the linear relationship. Additional IAV could

not be identified at this step. Overall, a good characterisation of all treatment scenarios was achieved using the common T cell model structured and estimating drug-specific parameters (E_{MAX} and EC_{50}).

Conclusions: A quantitative framework has been developed to describe the effects of different onco-immunological treatments during early preclinical development using a common model structure. This methodology enables the ranking and comparison of different IO drug candidates, together with the quantification of the different sources of variability, thus facilitating data interpretation. Moreover, the identification of drug-specific parameters opens the possibility to explore potential *in vitro-in vivo* correlations that could be used to predict *in vivo* drug efficacy from *in vitro* experiments, as well as to extrapolate preclinical results to human scenarios.

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III-47: *Denise Tuerk* Physiologically-based pharmacokinetic modeling of the CYP2C8 perpetrator trimethoprim

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Introduction: Trimethoprim is applied alone or in combination with sulfamethoxazole to treat bacterial infections by inhibition of bacterial folic acid metabolism. Trimethoprim is a weak cytochrome P450 (CYP) 2C8 inhibitor and an inhibitor of multidrug and toxin extrusion (MATE) 1 and MATE2-K [1]. As trimethoprim is one of the most commonly prescribed antibiotics [2], the investigation of its drug-drug interaction (DDI) potential is clinically very relevant. If trimethoprim is co-administered with the CYP2C8 substrates repaglinide or pioglitazone, it increases the area under the curve (AUC) of those drugs by 61% and 42%, respectively [3,4]. In addition, during administration of trimethoprim an increase of serum creatinine was reported, probably due to inhibition of tubular secretion of creatinine [5]. Physiologically-based pharmacokinetic (PBPK) modeling is a valuable tool to quantitatively describe and predict the pharmacokinetics of trimethoprim and the effect of trimethoprim co-administration on the pharmacokinetics of victim drugs or endogenous substances.

Objectives:

- To build and evaluate a whole-body PBPK model of trimethoprim.

Methods: A whole-body PBPK model of trimethoprim was developed using the modeling software PK-Sim® and MoBi® (Version 7.4.0) [6]. Drug-dependent parameters (e.g. lipophilicity, solubility, acid dissociation constant) and plasma concentration-time profiles of 17 clinical studies of trimethoprim (intravenous and oral administration, dosing range 100 - 400 mg, single- and multiple dosing, individual and mean profiles) as well as fraction excreted to urine measurements were obtained from literature. The gathered plasma concentration-time profiles were divided into an internal (6 studies) and an external data set (11 studies), which were used for model building and model evaluation, respectively. Parameters that could not be informed from literature were optimized using the studies of the internal dataset. Model evaluation was performed by comparison of predicted to observed plasma concentration-time profiles, AUC values and maximum plasma concentrations (C_{max}) of the external data set. As a quantitative measure of the model performance, the mean relative deviation (MRD) between predicted and observed values was calculated for all observed plasma concentrations. An MRD value below 2 signifies an adequate prediction. Furthermore, the quality of the model was characterized by AUC ratios (AUC predicted / AUC observed), C_{max} ratios (C_{max} predicted / C_{max} observed) and the calculation of geometric mean fold absolute deviation (GMFE) values.

Results: The final trimethoprim model applies transport via P-glycoprotein, an unspecific hepatic clearance process, tubular secretion via MATE1 and MATE2-K and passive glomerular filtration. The studies of the internal and external data sets are well described and predicted, with 98% of all simulated plasma concentrations within the two-fold acceptance limits compared to observed values. The MRD over all trimethoprim studies is 1.65. AUC ratios and C_{max} ratios show low GMFEs of 1.15 (range 1.04-1.39, n=17) and of 1.10 (range 1.01-1.34, n=17), respectively.

Conclusion: A whole-body PBPK model of trimethoprim has been successfully established. The model precisely describes and predicts plasma concentration-time profiles and fractions excreted to urine of

trimethoprim over a wide dosing range. As a future application, the model can be coupled with CYP2C8 and MATE victim drugs, to investigate the DDI potential of new drugs or to predict the trimethoprim pharmacokinetics in vulnerable populations.

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III-48: *Sami Ullah* Population pharmacokinetics of cefepime in critically ill patients with and without impaired renal function

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Introduction

Pathophysiological changes in ICU patients with severe infections lead to a high pharmacokinetic variability (1) and risk of improper exposure to antibiotics. While inter-individual pharmacokinetic differences have been explored for cefepime (2), less information is available on intra-individual variability during the treatment. Especially in critically ill subjects, such variability might be of relevance since a stable exposure to antibiotics is endangered due to unstable renal function, concomitant medication, fluid resuscitation and further disease-/treatment-related factors. Consequently, ambiguities on the choice of optimum dosing regimens for drugs with a rather narrow therapeutic window, such as cefepime (2, 3), result. To individualize cefepime dosing during the treatment, predictors of pharmacokinetic parameters may be useful. Recently, Jonckheere et al. (3) concluded that Cockcroft-Gault creatinine clearance (eCRCL) might be a better predictor of cefepime clearance than measured creatinine clearance (mCRCL). This finding is challenged by the invalidity of eCRCL in presence of unstable creatinine kinetics (4) and potential confounding by components of the equation (body weight, sex and serum creatinine concentrations). Therefore, it is unclear whether eCRCL should be employed to predict time-dependent changes of cefepime clearance and whether intra-individual variability poses a clinically relevant risk to treatment efficacy.

Objectives:

- To evaluate inter- and intra-individual variability of cefepime pharmacokinetics in critically ill subjects.
- To evaluate eCRCL as a predictor of intra-individual changes in cefepime clearance during treatment.

Methods:

A total of 15 critically ill patients (median age and body weight of 62 [range 22-94] years and 71 [45-120] kg) treated in a medical-surgical ICU were enrolled after approval by the local ethics committee and informed consent from patients or legal representatives. Five patients received intravenous hemodialysis throughout the four study days. Cefepime was administered as 30-min intravenous infusions (median dose 2g) twice daily as per local guidelines. Post-dose plasma samples (median 12, 6, 7, 6 per subject on days 1 to 4) were obtained on four consecutive days and cefepime concentrations were quantified via validated HPLC (5). A compartmental model was developed using NONMEM 7.4.3 (6), whereas different models were compared in terms of changes in objective function value (dOFV), unexplained variability and goodness of fit. Changes in clearance (CL) and central volume of distribution (V1) throughout the treatment course were explored via random (intra-individual variability) and fixed effects (systematic changes in parameters). For patients on dialysis, CL and V1 were estimated separately. Based on the base model, the influence of

covariates (age, weight, sex, height, BMI, urea, serum creatinine, 24 hours urine creatinine and the corresponding mCRCL observed once daily) on cefepime clearance was evaluated. Assuming Cockcroft-Gault creatinine clearance might represent relationships to body weight, sex and baseline kidney function, a covariate model with eCRCL calculated on each treatment day was compared to a model comprising solely eCRCL obtained at study start.

Results:

387 plasma concentrations (median 61 mg/L [range 0.6-848 mg/L]) were available for analysis. A two-compartment model with linear elimination best described cefepime concentrations in dialysis and non-dialysis patients. While inclusion of eCRCL estimated for each individual day relevantly improved the model (dOFV -9, IIV reduced by 36%, IOV increased by 1.4%), no model improvement was observed for mCRCL (dOFV -0.1, IIV reduced by 2%, IOV reduced by 0.1%). The best model, however, was the one based on eCRCL estimates obtained on the first day (dOFV of -13, IIV reduced by 45%, IOV increased by 1.7%) (comparison to base model). In the final model, population CL (median of 3.67 L/h) and V1 (median of 3.89 L) showed a slightly more pronounced inter- than intra-individual variability (38% versus 36% and 68% versus 64%) and a clear reduction (median CL of 2.35 L/h, median V1 of 1.86L) in patients on dialysis.

Conclusions:

When accounting for Cockcroft-Gault creatinine clearance, residual inter- and intra-individual variability were of similar magnitude. Adapting the therapy to changes in serum creatinine concentrations using Cockcroft-Gault or measured creatinine clearance during therapy seems inappropriate.

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III-49: *Parth Upadhyay* Exploring the Relationship Between Midazolam Concentrations And Level Of Sedation In Critically-Ill Mechanically Ventilated Children Using Markov Modelling

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Objectives: While knowledge on the pharmacokinetics (PK) of midazolam in children of various ages and with various disease conditions is increasing, there is only limited information on the pharmacokinetic-pharmacodynamic (PK-PD) relationship of midazolam in critically-ill children. The absence of a method for objectively quantifying sedation has complicated PD analyses. However, analyzing clinically relevant ambiguous endpoints such as sedation and pain continue to remain of interest, often requiring novel PD modelling approaches[1, 2]. In this study, we aimed to investigate the effect of midazolam on sedation in critically-ill mechanically ventilated paediatric-ICU (P-ICU) patients using data from a multi-institutional clinical trial (http://www.trialregister.nl/trialreg/index.asp), no. NTR2030[3]. The trial assessed the efficacy of Daily Sedation Interruption (DSI) by replacing midazolam with blinded infusions of either placebo or midazolam. Sedation was monitored at two hour intervals until patient discomfort supported the re-commencement of midazolam. Markov modelling approaches were investigated to describe the impact of midazolam and other patient specific factors on sedative scores.

Methods: Sedation was categorized into three clinically relevant states using the COMFORT scale (range 6 – 30), where scores lower than 11 or above 22 implied over- and under-sedation, respectively. For scores between 11 – 22, a Nurse Interpreted Sedation Score (NISS, where 1 indicated under-sedation, 2 – adequate sedation and 3 – over-sedation) was prioritized over the COMFORT scores to guide therapeutic decisions.

In total, 4869 COMFORT and NISS scores were available from 83 mechanically ventilated P-ICU patients (median age 3 months, range: 0 to 17 years) [3]. Model development was performed using NONMEM 7.3, with the programming library Perl speaks NONMEM 3.4.2 on the modelling workbench Pirana 2.9.0. Output was assessed on the statistical program R 3.5.1 using the graphical interface R Studio 0.99.887.

Continuous-time and discrete-time structural Markov models (CTMM and DTMM, respectively) were tested on model transitions between sedation states. Inter-individual variability (IIV) was tested log-normally on the CTMM transition rate constants and additively on the logit-transformed parameters in the DTMM model. Individual predicted midazolam plasma concentration (IPRED) at the time of each COMFORT score was calculated using a population-PK model published on the same dataset[4] and tested as a covariate, along with patient age (days) and sex. The presence of organ failure and inflammation, which were both associated with reduced midazolam clearance, were also tested as covariates. Significant covariates were retained on the basis of a difference in objective function (dOFV < -3.84).

Results: Of the 4869 scores, 3137 (64.1%) indicated adequate sedation, and 551 (11.3%) and 1181 (24.3%) indicated under- and over-sedation, respectively. The DTMM had a lower OFV (dOFV -1497.5) and lower

relative standard errors compared to the CTMM. Therefore, further model development was continued using DTMM. The incorporation of IIV was significant on all six transition probabilities (dOFV -66.2). The estimated covariate effect of midazolam, incorporated as an additive continuous covariate to logit-transformed transition probabilities, was 0.209 for the transition between adequate to over-sedation, but insignificant on other transition probabilities. Other covariates failed to improve the model.

Conclusions: In the DTMM model, the sedative effect of midazolam was incorporated as an increased probability of transitioning from adequate to over-sedation. Interestingly, no significant midazolam effect was identified on transitions to and from under-sedation. Further exploration into the use of concomitantly administered sedatives such as clonidine, morphine, fentanyl and ketamine, and alternative methods of determining midazolam exposure may also assist in characterizing midazolam PD in critically-ill children.

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III-50: *David Uster* Predictive performance of population pharmacokinetic models for Bayesian forecasting of coagulation factor VIII in hemophilia A

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Objectives:

Factor VIII is an essential coagulation glycoprotein and commonly substituted in the treatment of hemophilia A, an x-linked inherited bleeding disorder with a deficiency of the aforementioned protein.

Dosing according to instruction inserts only takes into account the body weight of the patient (prophylaxis) and/or the therapeutic indication of factor VIII treatment (i.e. surgery, heavy bleeding). Regarding the prophylactic treatment the time spent below a plasma concentration of 1 IU/dl should be as short as possible as this leads to fewer bleeds and hemarthroses [1].

Due to high interpatient variability in the pharmacokinetics (PK) of factor VIII, the variable response and its high cost, therapeutic drug monitoring (TDM) facilitated by population PK models has gained interest to individually tailor factor VIII dosing. The objective of the present study was to evaluate the predictive performance of population PK models in different settings.

Methods:

For the evaluation, a clinical dataset was available comprising 33 patients with a total of 208 one stage assay observations. Data below the limit of quantification (5.7% of all observations) was not included.

Four published population PK models were recreated and processed using NONMEM® 7.4. The population PK models included in the comparison were all two-compartment models and varied in the covariate inclusion, the handling of endogenous factor VIII levels and the underlying drug product [2–5]. The models accounted for body weight (one in form of lean body weight [3]), while only two accounted for the patients age.

The following scenarios were evaluated to predict plasma concentrations from a densely sampled (5 samples, 0.25 - 48 h after dose) dosing interval: (i) forecasting using dosing information only excluding covariate information (age, body weight), (ii) forecasting using dosing information incl. covariate information, (iii) forecasting using dosing information, covariates and a measured factor VIII trough concentration from the previous dosing interval.

Model-predicted vs observed values in the different scenarios were graphically examined. Furthermore, forecasting metrics were calculated and included relative bias (rBias) and relative root mean square error (rRMSE) describing the accuracy and precision of the prediction. Forecasting performance was stratified including (a) all samples taken between 0 h and 48 h after dose or (b) trough samples (time after dose >40 h) only.

Results:

The inclusion of covariates (scenario i vs ii) led to an improvement of the predictive performance in all models except of age in the model by Björkman et al., 2009 [2] and the rBias was reduced from 43% to 38% on average across models (rRMSE 113% to 105%).

Inclusion of a measured trough concentration of the previous dosing interval additionally to dosing information and covariate information (scenario iii vs ii) improved the predictive performance of all models (except the model of Björkman et al., 2009), and the rBias was reduced from 38% to 29% on average (rRMSE 105% to 95%). The rBias and rRMSE increased significantly in the scenario (iii) when only trough concentrations were used for their calculation (case b) with a mean increase from 29% to 78% and 95% to 161%, respectively.

The best overall predictive performance was displayed using the model by Zhang et al., 2017 [5] in both cases (a) and (b). There was only an exception in scenario (a) (iii) for patients receiving any of the four drugs or the B domain deleted product only (Refacto AF® Pfizer, n = 16). In this case the PK profiles were described more accurately by the model of Hazendonk et al., 2016 [4]. The outcome seems plausible as only the Hazendonk model accounted for discrepancies in plasma concentration measurements of B-domain deleted products by the one-stage assay [6].

Conclusions:

The studied population PK models varied substantially in their predictive performance taking different clinically relevant scenarios (i.e. information provided or subpopulation type) into account. The value of the main covariate body weight was confirmed for Factor VIII plasma concentrations in this external evaluation. The trough level prediction was not optimal and needs to be improved as this is most critical in prophylaxis treatment [1]. Further models will be evaluated and suitable models will be implemented into the TDMx software (www.TDMx.eu, [7]).

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III-51: *Pavan Vaddady* Application of Bayesian Methodology to Inform Imipenem/Relebactam Pediatric Study Design

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Objectives:

A fixed-dose combination of imipenem/cilastatin (IMI) and relebactam (REL), with a 2:1 IMI:REL ratio, is currently developed for pediatric populations to combat severe Gram-negative bacterial infections. The goal of this work is to develop a pediatric population pharmacokinetic (Pop PK) model based on sparse imipenem and REL pediatric pharmacokinetic (PK) data in different age cohorts while leveraging prior adult information to identify dosing regimens that optimize imipenem and REL pharmacokinetic/pharmacodynamic (PK/PD) and safety target attainment for continued investigation.

Methods:

PK data from three different age cohorts (Cohort 1: 12 to < 18 yr, Cohort 2: 6 to < 12 yr and Cohort 3: 2 to < 6 yr) comprising of six patients per cohort was available. For each patient, three PK samples were drawn at predefined time intervals following intravenous administration of single dose of study drug. Leveraging a Bayesian framework, a pediatric Pop PK model comprising of both imipenem and REL components was developed using adult Pop PK parameters and respective covariate relationships as priors. A multivariate normal prior was used for fixed effect parameters and an inverse-Wishart prior was used for both inter-individual variability and residual variability parameters. Allometric scaling was used to describe the differences in clearance and volumes from adult population across pediatric cohorts. Standard allometric exponent of 0.75 was added to body weight (WT) on CL and inter-compartmental clearance (Q), while allometric exponent of 1 was added to WT on central volume (V1) and peripheral volume (V2) respectively.

Virtual pediatric populations were created using 2011 to 2016 National Health and Nutrition Examination Survey (NHANES) data[1], and published serum creatinine distributions[2] comprising of age, gender, weight, height, and serum creatinine measures. Simulations were run using these virtual populations (N=2000 per age cohort) to evaluate the probability of target attainment (PTA) for PK/PD targets (imipenem: %fT>MIC ≥ 30%, REL: AUC0-24h ≥ 38.5 µM.hr) and safety targets (imipenem: AUC0-inf ≤ 216.5 µM.hr, Cmax ≤ 161 µM, REL: AUC0-inf ≤ 190 µM.hr, Cmax ≤ 118 µM). Different dosing regimens, with imipenem dose capped at 500 mg and REL dose capped at 250 mg, were evaluated and a dosing regimen where the predefined targets are jointly achieved that have at least 90% PTA for each age cohort were chosen.

Results:

A two compartment pediatric Pop PK model comprising both imipenem and REL components leveraging priors from adult Pop PK described the observed pediatric data adequately. Priors for key PK parameters CL and V1 were uninformative and priors on Q were informative. Based on the adult Pop PK model, both creatinine clearance (CRCL) and WT on CL, and WT on V1 were chosen as covariates for imipenem; CRCL on CL and WT on V1 were chosen as covariates for REL. Based on the PTA simulations and the aforementioned criteria, a fixed dose of 250 mg REL as an 1 hr infusion was chosen for cohort 1 and a weight-based dose of 7.5 mg/kg REL as 1 hr infusion was chosen for cohorts 2 and 3.

Conclusions:

A comprehensive modeling and simulation based approach was successfully developed to recommend final doses in cohorts 1, 2 and 3 for the upcoming efficacy study. Leveraging Bayesian approach with prior information from the adults aided in the pediatric model development despite sparse PK data in the pediatric study.

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III-52: *Cristina Vaghi* Population modeling of tumor growth curves, the reduced Gompertz model and prediction of the age of a tumor

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Introduction:

Tumor growth curves are classically modeled by ordinary differential equations. In analyzing the Gompertz model several studies have reported a striking correlation between the two parameters of the model [1–6]. Although this observation is still under debate, it might imply a constant maximal tumor size within a given species [3]. We analyzed tumor growth kinetics within the statistical framework of nonlinear mixed-effects (population approach). This allowed for the simultaneous modeling of tumor dynamics and inter-animal variability. Moreover, we computed the population parameters and used these as prior information to predict individual tumor initiation given only three measurements. This question is of fundamental importance in the clinic since the age of a tumor can be used as a proxy for determination of the invisible metastatic burden at diagnosis [14].

Objectives:

- test the descriptive power of different tumor growth models within a population

- study the correlation between the parameters of the Gompertz model within a population and define a novel, simplified model (the reduced Gompertz)

- use the estimated population parameters to perform individual predictions of tumor initiation

Methods:

The experimental data comprised two animal models of breast and lung cancers, with a total of 182 measurements in 86 animals. Nonlinear mixed effects modeling was used to compare different tumor growth equations, namely the Exponential, Logistic and Gompertz models [7]. Moreover, combining the correlation between the two parameters of the Gompertz model with rigorous population parameter estimation, we propose a novel reduced Gompertz model with only one individual parameter. We then considered the problem of predicting the initiation time of a tumor from only three late measurements, comparing the results arising from Bayesian inference and from likelihood maximization. We used the stochastic approximation of the EM algorithm (SAEM) for population analysis [8], implemented in the Monolix software (version 2018R2, Lixoft) and the Hamiltonian Monte Carlo algorithm [9,10] implemented in Stan [11] for Bayesian inference.

Results:

Population analysis: Confirming previous results [12], the Exponential and the Logistic models failed to describe the experimental data whereas the Gompertz model generated very good fits. The correlation

between the Gompertz parameters was confirmed in our analysis. At the population level, the SAEM algorithm estimated a correlation of the random effects equal to 0.981. At the individual level, the two parameters were also highly correlated (R2 > 0.96 in all groups). This suggested a reduction of the number of degrees of freedom of the Gompertz model. The proposed reduced Gompertz model had one parameter with random effects and one parameter with fixed effects within the population. The latter suggested a characteristic constant of tumor growth within a given animal model [4]. We assessed the descriptive power of the reduced Gompertz model and found that performances were similar to the two-parameters Gompertz equation.

Prediction of the age of individual tumors: Thanks to its simplicity, the reduced Gompertz model showed superior predictive power. In addition, drastic improvements were observed when leveraging population priors using Bayesian inference compared to likelihood maximization, both in terms of accuracy (mean error 12.7% versus 88.5% for the breast data and 9.4% versus 67.6% for the lung data) and precision (mean value 15.6 days versus 242 days for the breast data, 7.34 days versus 84.8 days for the lung data). The Gompertz model exhibited a lack of parameter identifiability when likelihood maximization was applied. Using Bayesian inference, the accuracy was significantly better, but precision still inadequate. Overall, the combination of the reduced Gompertz model with Bayesian inference clearly outperformed the other methods for prediction of the age of experimental tumors.

Conclusions:

The method that we proposed here remains to be extended to clinical data, although it will not be possible to have a firm confirmation since the natural history of neoplasms since their inception cannot be observed. Nevertheless, the encouraging results obtained here could allow to give approximate estimates. Personalized estimations of the age of a given patient's tumor would yield important epidemiological insights and could also be informative in routine clinical practice [13].

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III-53: *Stijn van Beek* Population Pharmacokinetics and Model-Informed Precision Dosing of Isoniazid in Tuberculosis Patients

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Objectives: Isoniazid (INH) is a drug used in the first-line treatment of tuberculosis (TB). Interindividual variability (IIV) of INH pharmacokinetics (PK) is known to be high [1], this is mainly because of the polymorphic acetylation into acetyl-INH by N-acetyltransferase 2 [2]. In order to achieve optimal treatment, the use of therapeutic drug monitoring (TDM) is advised [3, 4]. It has been suggested that the area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) as measure of exposure is the most relevant to the efficacy of TB drugs [5-7]. Previously, we have shown the potential of a model-based TDM method for rifampicin in treatment of TB [8]. Although various TDM methods for INH are currently in use, no model-based TDM methods for INH have been described as of yet. Our objective is to develop a population pharmacokinetic model and limited sampling strategy (LSS) for INH to be used in model-based TDM.

Methods: We developed one population PK model with a mixture model for clearance and one model without. Model development in NONMEM v7.4 was based on INH PK data from three studies performed in pulmonary TB patients. These studies included: 1) 14 (127 observations) patients from a Dutch TDM setting [9], 2) 96 (868 observations) patients from South Africa and Tanzania [10], and 3) 59 (591 observations) patients from Tanzania [11]. In total, 169 patients and 1586 observations were included in the analysis. Two LSSs were tested, one with 2, 4 and 6 h sampling and the other with 2 and 4 h sampling. These LSSs were chosen based on practical considerations, available sampling times in the data, and agreement with the LSS developed for rifampicin [8]. The model-predicted AUC_{0-24} of the two LSSs was compared with the prediction on the full dataset for both models. Bias and precision were assessed using the mean error (ME) and root mean square error (RMSE) [12], both expressed as a percentage of the mean model-predicted AUC_{0-24} on the full dataset. We set the target for the ME and RMSE at <20% which we regard as reasonable and is commonly used [13].

Results: The PK of INH was best described by a two-compartmental model in addition to five transit absorption compartments and a well-stirred liver compartment. A priori allometric scaling based on fat free mass was applied on the volume and flow parameters using fixed exponents of 1 and 0.75 respectively. For the model including a mixture on clearance, two subgroups (fast and slow) were implemented to incorporate the polymorphic acetylation of INH. The proportion of fast acetylators in the population was estimated at 38.2% and typical clearance was two-fold higher than for the slow acetylators population. In both models, IIV was included on central volume of distribution (18CV%), clearance (with mixture: 34CV%; without mixture: 49CV%), and absorption rate (62CV%) and was assumed to be log-normally distributed. Values of model parameter estimates were in agreement with those reported in previous works. The relative standard error of the estimates as computed by the covariance step was lower than 15% for all parameters of both models except for the proportion of fast acetylators (23%) in the mixture model and the IIV on the central volume of distribution for both with (20%) and without (18%) mixture model. Goodness-of-fit plots and visual predictive checks showed good performance of both models, while individual plots showed that a few individuals still had a poor fit.
Using the mixture model, the 2, 4 and 6 h LSS (ME: 7.3%; RMSE: 21.5%) performed better than the 2 and 4 h LSS (ME: 0.2%; RMSE: 31.3%). Interestingly, when the mixture model was taken out, the 2, 4 and 6 h LSS

(ME: 10.5%; RMSE: 22.8%) performed slightly worse, and the 2 and 4 h LSS (ME: 8.3%; RMSE: 28.8%) slightly better compared to when a mixture model was included.

Conclusions: The developed population models described the PK of INH well. However, the predictive performance of the models for the purpose of TDM using LSSs does not yet reach the target. The LSS using fewer samples performed better without the presence of a mixture model. This could indicate that the model was unable to identify the mixtures using this LSS. We expect that the addition of acetyl-INH metabolite data might help to improve the identifiability of the mixture model and predictive performance of the model for TDM purpose. In conclusion, we show a promising model-based TDM method for INH which still has potential for improvement.

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III-54: *Arthur Van De Vyver* in vitro PK/PD modeling of immunological synapse-based tumor cell killing and immune activation to predict in vitro efficacy of T-Cell Bispecifics.

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Introduction: T-Cell Bispecifics (TCBs) are antibody constructs with binding specificities to both a tumor antigen and T cell receptor allowing for cross-linking and resulting in the formation of immunological synapses between T- and tumor cells, and subsequent T cell mediated tumor cell lysis. Existing mathematical models link the trimolecular binding of drug with tumor antigen and with CD3-receptor on T cells to tumor cell killing and are aimed at guiding compound optimization [1], providing a new MABEL metric (Minimal Anticipated Biological Effect Level) for dose selection [2], or describing in vivo tumor cell and T cell profiles [3]. Here, we compare model structures that capture relevant processes to predict tumor cell killing with Cibisatamab**,** a novel TCB targeting carcinoembryonic antigen (CEA) in high and low tumor target expressing cells [4]. We therefore fitted various models to an in vitro PKPD study capturing longitudinal data from tumor cell and T-cell dynamics upon Cibisatamab treatment in 2 different cells lines with high and low CEA expression exhibiting distinct efficacy profiles. While full tumor cell killing, T-cell activation and expansion was observed in the high expressing cell line, only partial killing was observed in low expressing cell line with minimal T-cell activation but no T cell expansion.

Objective: The goal of this work was to compare various model variants in their capacity to predict how TCB drives tumor cell killing in function of TCB concentration and target expression levels, observed in vitro with and without consideration of immunological synapse formation and T cell dynamics.

Methods: Three model types with increasing complexity in terms of number of differential equations and parameters were compared. Model 1 is a simple model, directly linking TCB concentration to tumor cell killing [5]. Model 2 & 3 are model variants based on a TCB synapse model from Jiang et al.[1]. These models assume immunological synapse formation to take place due to interaction of TCB with tumor antigen and T cell CD3 as independent binding events. In the first synapse model (model 2), synapse formation will drive tumor cell killing. In the second synapse model (model 3), synapse formation will lead to T cell activation and expansion, which will drive tumor cell killing.

These models were fitted to full time course data from an in vitro study where 2 tumor cell lines with different CEA expression levels, MKN45 (230’000-690’000 CEA/cell) and Cx1 (2’000-11’000 CEA/cell), were co-cultured with hPBMCs (human peripheral blood mononuclear cells) at different Cibisatamab concentrations ranging from 6 to 100’000 pM[4][6]. Tumor cell and T cell counts were measured 24h, 48h, 72h, 96h, and 168h after adding Cibisatamab to the co-culture. Total number of observations was 160, tested in 2 cell lines at 8 dose subgroups monitored at 5 time points. Model fitting was performed in Monolix (2018R1).

The quality of model fitting was assessed by visual inspection and goodness of fit criteria such as observed versus predicted values, visual predictive checks of observations and predictions at each dose, the precision of parameter estimation, and the reduction in objective function values.

Results:

Best model fits were obtained with model 3 (synapse model with T cell dynamics), based on a reduction in objective function values and visual inspection of the fits (observed vs. predicted values, prediction distribution). The simpler model linking drug concentration to tumor killing was not sufficient to accurately describe the tumor kill profiles, and was unable to correctly describe the killing of the low CEA expressing tumor. Both models including synapse formation described tumor killing reasonably well. In addition, the model considering T cell activation (model 3) showed enhanced model performance as indicated by improved objective function values. This is supported by significantly narrowed prediction intervals, especially at higher TCB concentrations.

Conclusion: In the present study, the consideration of synapse formation significantly improved prediction of anti-tumor effects. Considering T cell profiles as part of the mechanistic model further improved performance. Furthermore, it has the potential to allow us to predict tumor cell killing under various T cell conditions in vitro, this can enable us to predict the outcome of varying Effector-to-Target ratios and improve translation to in vivo.

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III-55: *Louvina van der Laan* Pharmacokinetics and drug-drug interactions of lamivudine and abacavir administered with antituberculosis drugs in HIV-infected children with multidrug-resistant tuberculosis

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Objective

An estimated 2.1 million children (<15 years) were living with HIV in 2016(1), the majority in sub-Saharan Africa, where tuberculosis (TB) and HIV epidemics coincide. WHO recommends lamivudine (3TC) and abacavir (ABC) as preferred dual nucleoside reverse transcriptase (NRTI) backbone for first-line antiretroviral treatment (ART) in HIV-infected children (>3 months)(2). As multidrug-resistant (MDR)-TB frequently occurs in young children in settings with high burden of TB and HIV(3), it is important to identify potential interactions between MDR-TB treatment and NRTIs. 3TC is primarily renally eliminated(4), it has low protein binding (generally <36%)(5, 6) and induces p-glycoprotein(7). ABC is extensively metabolised by the liver(8, 9), primarily via urine diphosphate glucuronyltransferase and alcohol dehydrogenase(10), protein binding is 50% and it is a substrate and possible inhibitor of p-glycoprotein(11–13). These are all sites for possible drug-drug interactions (DDIs) with MDR-TB drugs. We describe the pharmacokinetics (PK) of and potential DDIs, between 3TC, ABC and drugs routinely used for MDR-TB treatment in HIV-infected South African children.

Methods

54 HIV-infected children established on a NRTI-containing ART regimen (only 50 on ABC) were included, in two groups: MDR-TB treatment group (n=27) receiving individualised MDR-TB treatment based on the drug susceptibility of the child or known source case (including combinations of high-dose isoniazid, pyrazinamide, ethambutol, ethionamide, terizidone, a fluoroquinolone, and amikacin) and an HIV-infected non TB control group (n=27). 3TC and ABC were dosed as per South African guidelines(14). All children were on combination ART containing either lopinavir/ritonavir or efavirenz. Participants were sampled at 6 time points: 1 hour and immediately before ART dosing, and at 1, 3, 7, and either 5 or 10 hours post ART dosing. Samples were processed with liquid-liquid extraction method using ethyl acetate, followed by LC-MS/MS detection. LLOQ for both drugs were 0.024 mg/L. NONMEM 7.4.3 with FOCE-I was used to develop the population PK model. PsN, Pirana and Xpose were used in the model building process for data exploration, visualization and creation of diagnostics(15). Allometric scaling(16) was used to account for the effect of body size, using either total body weight or fat-free mass(17). Age was tested using a sigmoid Emax maturation model(16, 18). BLQ values were handled by the M6 method(19) and for all imputed values, the additive error was inflated by LLOQ/2.

Results

The median (interquartile range) age and weight were 4.2 (1.6-9.6) years and 13.4 (9.1-21.4) kg for the MDR-TB group and 5.7 (1.6-9.5) years and 15.6 (11.2-23.1) kg for the control group. 3TC [ABC] was given as a suspension (52%) [64%] or tablet (48%) [36%]. Two-compartment models with first-order elimination and

transit compartment absorption described the PK of 3TC and ABC. Allometric scaling with body weight adjusted for the effect of body size, after which maturation could be identified: clearance was predicted to reach half its mature value 2 months after birth for 3TC and 3 months after birth for ABC, with both drugs being fully mature 2 years of age. Since the maturation parameters could not be identified precisely, Bayesian priors(20) based on reports from larger comparable populations(21)(22); 20% uncertainty was used to stabilize the models. The typical clearance in a 15-kg child was estimated at 10.8 L/h for 3TC and 16.3 L/h for ABC. The mean absorption transit time (MTT) for the suspension formulation was significantly faster than tablets (21 vs 39 min 3TC; 5 vs 27 min ABC), with no effect found on bioavailability. No significant difference in bioavailability, clearance, or absorption could be detected between the MDR-TB treatment and control group, as well as the lopinavir/ritonavir and efavirenz containing combination ART.

Conclusions

No significant effect was found on key PK parameters of 3TC and ABC when co-administered with routine drugs used for MDR-TB in HIV-infected children. Both 3TC and ABC suspensions had significantly faster MTT compared to tablets. While these findings need to be considered in the context of the modest sample size, they are reassuring and suggest the absence of major DDIs between 3TC, ABC and the MDR-TB drugs in our study. DDIs require further studies in newer MDR-TB drugs including bedaquiline, delamanid and linezolid, in HIV-infected children.

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III-56: *Jan-Stefan van der Walt* A Population Pharmacokinetic Analysis to Explore the Effect of Hepatic Impairment on Abemaciclib Pharmacokinetics

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Objectives:

Abemaciclib, a potent inhibitor of CDK4&6 for treatment of HR+ HER2- locally advanced or metastatic breast cancer [1,2,3], is primarily metabolised by CYP3A4 to several active metabolites (M2, M18 and M20) [4,5]. The best measure of the active moiety is the potency-adjusted unbound AUC of abemaciclib plus its metabolites. Hepatic impairment (HI) can reduce abemaciclib clearance and affect protein binding. The effects of HI on the active moiety were(1) assessed using a semi-mechanistic population PK model incorporating changes in hepatic blood flow, protein binding and intrinsic clearances, and (2) validated by comparing the Child-Pugh Score (CPS) [6] and NCI criteria [7] to categorize the severity of HI for covariate modeling.

Methods: Body weight, liver volume estimates and PK data (parent and metabolites) after a single dose of 200mg abemaciclib in healthy subjects (HS, n=10), and subjects with mild (n=9), moderate (n=10) and severe (n=6) HI based on CPS (NCT02387814) were analysed. A mechanistic population PK model developed from 12 clinical trials in cancer patients and healthy subjects (8) was used to estimate changes in drug extraction and CYP3A4-mediated metabolism (NONMEM v7.3). For covariate modeling using CPS the relevant parameter-covariate relationships were determined using HI literature and scientific plausibility. Covariate effects were estimated where possible. Alternatively, a range of covariate effect values, selected based on literature, was tested. The best models were selected based on improvement in predictive performance using visual predictive checks (PsN v4.7). For the NCI model, only the covariate relationships included in the final CPS model were tested. A sensitivity analysis was performed to select the final covariate effect values for the NCI model. The abemaciclib, metabolites and active moiety AUC for HI groups were compared to HS by ANOVA. To evaluate potential dose adjustments, steady-state concentrations after once daily (QD) or twice daily (Q12H) doses of 50, 100, 150 and 200mg in subjects with mild, moderate or severe HI were simulated and compared to the clinical efficacy target (200 ng/mL) [9].

Results:

Covariate modeling with CPS criteria resulted in inclusion of three ordinal parameter-covariate relationships: hepatic blood flow decreased 30% (mild), 44% (moderate), and 76% (severe); metabolism of abemaciclib to M2 decreased 15% (mild), 23% (moderate) and 78% (severe); and the fraction of M2 metabolized to M18 decreased 30% (mild), 50% (moderate) and 70% (severe).

These changes resulted in increased abemaciclib and decreased metabolite exposure: the active moiety increased 1.8 (95%CI 1.24-2.42) fold in severe HI, but was not different for mild and moderate HI from HS. At steady-state these changes would result in a significant increase in active moiety exposure in severe HI (2.55 fold, 95%CI 1.25-3.85) but no difference was found for mild and moderate HI. This increase was mainly driven by a 4.47-fold increase in abemaciclib exposure.

When using the NCI criteria, there were 17 HS, 8 mild HI, 7 moderate HI, and only 3 subjects with severe HI. Some individuals changed from moderate CPS category to HS status with NCI. For covariate analyses the HI

severity was reclassified as either HS/mild HI or moderate/severe HI. The hepatic blood flow decreased 80%, the metabolism of abemaciclib to M2 decreased by 75%, and the fraction of M2 metabolized to M18 decreased by 78% in moderate/severe HI compared to HS/mild HI subjects, which was similar the estimates from the CPS model.

Steady-state predictions with the CPS model supported a dose adjustment to 200mg QD for the severe HI group: active moiety exposure was slightly higher (1.28-fold increase) compared to HS. Dose adjustment to 150mg QD resulted in total exposure comparable to HS (0.96 fold). Dose reductions as low as 100mg Q12H maintained trough concentrations above 200 ng/mL in severe HI.

Conclusions: Changes in liver blood-flow and reduced metabolism in severe HI are consistent with increased total active moiety of abemaciclib. Categorizing HI severity using the CPS and NCI criteria provided similar estimates of the effect of severe HI on abemaciclib PK. At steady state, the recommended dose adjustment for severe HI to 200mg QD would result in exposure of the active moiety comparable to HS and maintain the abemaciclib concentrations above the clinical threshold.

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III-57: *Tamara van Donge* Methadone dosing strategies in preterm neonates can be simplified

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Introduction: A dramatic increase in newborn infants with neonatal abstinence syndrome has been observed and these neonates are frequently treated with complex methadone dosing schemes to control their withdrawal symptoms [1]. Despite its abundant use, hardly any data on the pharmacokinetics (PK) of methadone is available in preterm neonates. Therefore we characterized the developmental pharmacokinetics of methadone using population PK modeling and evaluated current dosing strategies and possible simplification in this vulnerable population.

Methods: A single center open-label prospective study was performed to collect PK data in preterm neonates after a single oral dose of 0.1 mg/kg of methadone was administered. A population PK model was built to characterize developmental PK of (R)- and (S)-methadone. Exponential, power and linear model functions were tested to describe covariate effects of continuous variables such as weight and age variables. Model-based simulations were performed to examine the feasibility of a simplified dosing strategy to achieve and maintain target methadone exposure. Methadone target exposure (985 mcg·h/L) was retrieved from an earlier study conducted in term neonates [2].

Results: A total of 121 methadone concentrations were collected from 31 preterm neonates, with overall gestational age range of 26 – 36 weeks with a median of 32 weeks. A one-compartment model with first order absorption and elimination kinetics best described PK data for (R)- and (S)-methadone, including gestational age on clearance by a general power function and on volume of distribution in a linear relationship. The exponents of the effect of gestational age on clearance of methadone were comparable between the two enantiomers (5.29 for (R)-methadone and 5.16 for (S)-methadone). The clearance of methadone increases with increasing gestational age and differs between R- and S-enantiomer, being slightly higher for the former (0.244 versus 0.167 L/h). The population parameter values for apparent volume of distribution for (R)- and (S)-methadone corresponded to 26.9 L and 18 L, respectively. Preterm neonates reached target exposure after 48 hours with currently used dosing schedules. Currently used dosing schedules consist of a weaning period (one week) with starting dose of 0.1 mg/kg and daily dose adjustments of 0.025 or 0.01 mg/kg. Output from simulations revealed that target exposures can be achieved and maintained with a simplified dosing strategy during four days of treatment (starting with 0.1 mg/kg on day 1 and 2, 0.05 mg/kg on day 3 and 0.01 mg/kg on day 4). It is therefore questionable if there is a need for the currently used complex dosing regimen of methadone in neonates.

Conclusion: Clearance of methadone in preterm neonates increases with increasing gestational age and higher clearance values and volumes of distribution can be observed for (R)-methadone as compared to (S)-methadone. Simulations that account for developmental PK changes indicate that a simplified, shorter methadone dosing strategy can maintain target exposure to control withdrawal symptoms in preterm

neonates. Such dosing strategy will not only reduce the risk of measurements errors related to complex dosing schedules, but also lowers the number of interventions in these preterm patients.

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III-58: *Rob van Wijk* Nanoscale pharmacokinetics and pharmacodynamics of isoniazid treatment of tuberculosis in zebrafish larvae

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Objectives: In tuberculosis (TB) research, the zebrafish (1) proves a promising model organism, because the aquatic pathogen *Mycobacterium marinum*, shows similar pathology to *M. tuberculosis* (2). However, to date most studies using zebrafish larvae take drug concentrations in the incubation medium as exposure measure, neglecting the fundamental pharmacological principle that exposure at the site of action drives drug effects and should be used as the basis for between-species translation of pharmacological results(3). Recently, we developed a methodology to measure internal drug exposure in larval homogenates and used mixed-effects modelling approaches to quantify the internal exposure over time(4). Blood concentrations are however essential to quantify distribution volume and absolute clearance values, which is the basis for between-species PK translation. Here, a nanoscale blood sampling method is developed for zebrafish larvae.

To translate pharmacodynamics (PD) between species, differences in disease mechanisms and progression need to be understood and quantified. Here, *in vitro* natural growth curves of *M. marinum* are quantitatively analysed with a multistate tuberculosis pharmacometric (MTP) model that has been previously developed for *M. tuberculosis* and applied to *in vitro*, murine and clinical data(5–7). The effect of the antibiotic isoniazid can then be assessed based on the MTP model for *M. marinum* and internal exposure measures in zebrafish larvae, after which the extrapolation potential to higher vertebrates, including humans, can be assessed.

Methods: Blood sampling on a nanolitre scale was tested from different locations including the aorta and posterior cardinal vein, or by cardiac puncture in larvae of 5 days post fertilization (dpf). LC-MS measurements in pooled samples yielded isoniazid blood concentration. Non-linear mixed effects modelling using NONMEM 7.3(8) through interface Pirana 2.9.6(9) and PsN 4.7.0(10) was used to analyse these concentrations combined with internal amounts from larval homogenates exposed to 5 isoniazid doses to quantify a.o. distribution volume and absolute clearance values.

Natural growth curves of *M. marinum* over 221 days, were obtained from *in vitro* cultures of the E11 and M-USA strain. In the MTP model, which distinguishes fast, slow or non-replicating mycobacteria, Gompertz, logistic, and exponential growth functions were tested for the fast- and slow- multiplying sub-states. Constant, and time- and concentration dependent transfer functions were tested for the fast- to slow-multiplying sub-states, the other transfer rates were fixed to values found for *M. tuberculosis*(5). For the inoculum, different CFUs in the fast- and/or slow multiplying sub-state were estimated. These fits were compared to reported observed and MTP model predicted *in vitro M. tuberculosis* natural growth curves(5).

Results: Blood sampling from the posterior cardinal vein was most reproducible, yielding blood volumes of up to 1.76 nL. To reach quantifiable levels, 19-32 samples were pooled. Isoniazid blood concentrations were 10% of the external concentration and within the range of isoniazid concentrations in patients(11,12). A dose-linear increase in isoniazid internal exposure was observed, with steady states ranging from 30 – 100 pmole/larva. Absolute clearance and distribution volume were estimated at 0.31 uL/h and 2.1 L/kg, respectively.

Model fits with the MTP model showed different natural growths for the two *M. marinum* strains. Gompertz functions for growth with similar growth rates, but a 8-fold lower system capacity for M-USA were found. For M-USA an exponential time-dependent transfer between fast- and slow multiplying sub-states was found and an inoculum with all CFU in the fast multiplying sub-state, while for E-11 a constant transfer between fast- and slow multiplying sub- states and an inoculum with all CFU in the slow multiplying sub- state was found. As a result, M-USA remains in the fast-multiplying state for the majority of the 221 days, while E11 shows a profile more similar to *M. tuberculosis*, shifting to slow- and non-multiplying sub-states after 30-60 days. This suggests that studies using E11 might be more representative for *M. tuberculosis* behaviour.

Conclusion: We quantified for the first time PK and PD of isoniazid treatment of the zebrafish as TB model organism, essential for translation of pharmacological findings to higher vertebrates, including humans.

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III-59: *Filippo Venezia* Preclinical Pharmacokinetic/Pharmacodynamic modeling to evaluate combination efficacy and the modification effect of oncology compounds with anti-angiogenic drugs (Sunitinib, Axitinib)

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Objectives:

Combination therapies may dramatically improve the outcome for cancer patients, and it is expected that such Therapies will eventually become the standard of care for cancer treatment (Morrissey et al., 2016). However, the increasing complexity of combination therapies presents a substantial challenge in the clinical stages of drug development for oncology. Thus, preclinical data evaluation has been emerged as key for the success in cancer combination therapy. Using PK/PD modeling, we were able to support study design in xenografted mice models as well as to evaluate and quantify the combination efficacy and the modification effect of these compounds through a model selection and multi-experimental fit approach.

Methods:

Population PK analysis was performed with a pre-selected PDX model for RCC-derived lung metastasis. A total of 15 mice and 57 concentrations were included in the PK dataset. Different population PK models have been developed to assess inter-individual and between-treatment variability in combination as well as to describe Drug S, Axitinib and Sunitinib pharmacokinetics. A tumor growth model proposed by Simeoni et al. 2004 was used to describe the tumor volumes in untreated mice. Six treatments groups of 8 mice were used to compare drug combination potency. Tumor volume in mm^3 was observed until 69 days and measured twice a week. A multi-experimental fit approach was conducted in order to assess the PK/PD relationship. Model proposed by Li et al. 2016 was used to analyze the combination efficacy. In order to assess the modification effect, we investigated several factors on the different drug effects and used model selection to uncover the compounds which profits or non-profits from combination. Parameter estimation was performed using NONMEM version 7.3 with interaction (FOCE-I) method and data analysis using R version 3.4.0.

Results:

Moderate to high inter-individual and between-treatment variability in PK was observed. In order to support experimental studies on xenografted mice, study design based on population PK analysis was performed to adjust drug exposure between mono- and combination treatment. Interestingly, an exposure discrepancy factor of around 3.5 was identified. Moreover, model-based design results in a more pronounced discrepancy between treatment groups. A linear drug effect was shown to describe the PK/PD relationship on tumor volumes in groups treated with Drug S + Axitinib and Drug S + Sunitinib in PDX mice. Using a multi-experimental approach, we reduced uncertainty to more than 30% compared to a single fit for almost all of our estimates. Our analysis revealed for both combination treatments an antagonistic effect. Interestingly, the potency of both anti-angiogenic compounds was impaired in combination by 80% and 50%, respectively. These counterintuitive findings are in good agreement with our PK analysis, which showed PK modulation in both combination treatments.

Conclusions:

The present study shows the benefit of a preliminary dose adjustment design to support preclinical studies avoiding misinterpretation and reducing resources. This benefit can be only achieved through PK modeling. A PK/PD analysis allowed comparing combination efficacy of the compounds when administered in combination. Moreover, the evaluation of the modification effect in combination confirmed interference of Drug S with anti-angiogenic compounds affecting potency of the anti-angiogenic drugs. We conclude that the evaluation of the modification effect improves the characterization of drug activity in combination. Finally, identifying the modified potency of compounds can guide dose adaptation reducing synergistic toxicity and antagonistic efficacy effects in combination therapy.

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III-60: *Diego Vera* Pharmacokinetic-Pharmacodynamic model for Acute Intermittent Porphyria in porphyric mice treated with a new recombinant PBGD protein

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Objectives: Acute intermittent porphyria (AIP) is a rare autosomal dominant disorder caused by a genetic mutation that reduces the hepatic activity of the porphobilinogen deaminase enzyme (PBGD), the third enzyme in the heme biosynthesis pathway. Precipitating factors lead to acute attacks associated to the accumulation of the neurotoxins 5-Aminolevulinic Acid (ALA) and Porphobilinogen (PBG) [1]. As the current standard-of-care drug, hemin, causes several side effects to chronical patients, new therapies are needed. In a previous work [2] we developed a data-driven disease model capable of describing the time course of excreted amounts of heme precursors in urine of porphyric mice during induced acute attacks. In this project, we aimed to refine the existing disease model to account mechanistically for known autoregulation aspects of the heme pathway, and to develop a more mechanistic pharmacokinetic-pharmacodynamic (PKPD) model using a new recombinant PBGD protein.

Methods: Acute attacks were induced at day 1, 9 and 30 in male AIP mice by intraperitoneal injection of four daily increasing doses of phenobarbital (75, 80, 85 and 90 mg/kg). The PBGD variant was administered at day 2 as a single dose intravenously at two dose levels: 60 and 300 nmol/kg. 24-h urine was collected from mice (n=27) and ALA, PBG and total porphyrins (tPOR) were quantified in control and treated animals. A total of 334 ALA, 338 PBG and 307 tPOR measurements were analyzed. As phenobarbital concentrations were not measured, a PK model was adapted from the literature to simulate phenobarbital concentrations [3]. It was assumed that phenobarbital was completely and instantly absorbed after an intraperitoneal administration. Regarding the PK of the PBGD variant, enzymatic activity data in plasma (n=16, 154 measurements) was used as a surrogate marker of the drug concentrations to build the model. Data was analyzed using the population approach with NONMEM 7.3 software, and Berkeley-Madonna was used to test different feedback mechanisms.

Results: The final disease model assumed that excreted amounts of biomarkers were dependent on the amounts of their respective biomarkers in liver and blood, represented by virtual circulating compartments with arbitrary values of 1 at baseline. Circulating levels of ALA and PBG were considered the precursors of circulating PBG and tPOR, respectively. Phenobarbital concentrations increase circulating ALA synthesis in a linear way. To acknowledge the limited activity of the endogenous PBGD enzyme to transform PBG into porphyrins, the transit between circulating PBG and circulating tPOR was modelled using a Michaelis-Menten process [Vmax equal to 1.21 (arbitrary units/h)]. In addition, a negative feedback of circulating PBG amounts on the transit between circulating ALA and circulating PBG -caused by steric hindrances on the enzyme that catalyzes the reaction from ALA to PBG- was implemented. Regarding the PKPD model, PBGD pharmacokinetics was well described using a two-compartment model with linear elimination. Drug effect was estimated using data for the low PBGD dose of 60 nmol/kg, assuming that recombinant PBGD linearly increases the endogenous enzyme maximum capacity [SLP_PBGD, the parameter governing the linear effect, equal to 9.7e-05 µL x h/pmol uroporphyrins (URO)], in agreement with its known biological action. This model, however, under-predicted the observed PBGD effect for the dose of 300 nmol/kg, indicating

that an additional mechanism was needed. This issue was solved by the incorporation of an additional delayed drug effect (Emax effect, with a C50 equal to 0.20 pmol URO/µL x h) representing the PBGD activity in the liver–PBGD concentrations in liver are known to be significant only for high PBGD doses–. The final disease PKPD model was able to satisfactory describe the median values and dispersion of the data as confirmed from the goodness-of-fit and visual predictive checks.

Conclusions: A more mechanistic pharmacokinetic-pharmacodynamic model for acute intermittent porphyria in porphyric mice has been built. This model successfully describes the time course of urinary data from control mice and treated mice with the new recombinant protein for both dose values tested. This model provides a mechanistic framework to explore the impact of new therapies for acute intermittent porphyria and to extrapolate preclinical results to help taking informed decisions about dosing schemes in phase I clinical trials.

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III-61: *Luka Verrest* Exploring variability in paromomycin pharmacokinetics in East African visceral leishmaniasis patients

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Objectives: There is a high need for new therapies for the neglected tropical parasitic disease visceral leishmaniasis (VL), as effective, safe and affordable treatments are still lacking. Paromomycin sulphate (PM) has been shown to be effective in Indian VL patients[1] and is favourable over other therapies because of its affordability and its reasonable safety profile. However, a similar PM dosing regimen of 15 mg/kg/day for 21 days resulted in a lower efficacy in East Africa[2] and a dose increase or a combination therapy was required to achieve adequate efficacy[3]. In order to obtain a better understanding of the differences between populations, a population PK model of PM in different African patient populations was developed.

Methods: PM PK data was available from a multi-centre randomized controlled trial (RCT) in VL patients from Kenya, Sudan, and Ethiopia[3]. Intramuscular PM monotherapy (20 mg/kg/day for 21 days) was compared to PM plus intravenous sodium stibogluconate (SSG) combination therapy (PM 15 mg/kg/day and SSG 20 mg/kg/day for 17 days). Paromomycin plasma concentrations were obtained using HPLC-UV. In Kenya and Sudan samples were obtained frequently at the first and last day of treatment. In Ethiopian study sites a sparse sampling scheme was used. A population PK model of PM was developed using NONMEM (v 7.3). A total of 388 concentrations from 74 patients were included in the PK analysis. Tested covariates included study site, country, treatment group (monotherapy or combination therapy with SSG), creatinine plasma levels, glomerular filtration rate (GFR), and albumin plasma levels. To evaluate the model fit, a visual predictive check (VPC) was performed.

Results: A one-compartment model with first-order absorption was found to best describe PM in plasma. Typical parameter estimates (CV) were a clearance of 3.86 L/h (8%), central volume of distribution (V_c) of 13.1 L (11%), and an absorption rate constant (k_a) of 1.31 h^{-1}(16%). Body weight was included on clearance and V_c, with fixed powers of 0.75 and 1.00, respectively. Ethiopian patients exhibited deviating concentration-time profiles which were best characterized by a 1.94 (25%) times higher bioavailability (F_{Eth}) and a 3.19 (20%) times slower k_a. Between-subject variability (BSV) was included on clearance (41%) and k_a(52%), and an additional BSV for F_{Eth}(150%) described the overall higher variability in Ethiopian patients. Additionally, for all patients, there was a decrease in clearance over time amounting to -33.2% between start and end of treatment (day 21), which could not be explained by either GFR, creatinin or albumin. $AUC_{0\text{-}tau,SS}$ for 15 mg/kg/day (median [SD]) was significantly higher in Ethiopia (218.2 µg·h/mL [1724.1]) compared to Kenya and Sudan (165.7 µg·h/mL [53.1]). $AUC_{0\text{-}tau,SS}$ for 20 mg/kg/day was not significantly different between Ethiopia (240.6 µg·h/mL [1849.8]) and Kenya and Sudan (258.0 µg·h/mL [193.1]). The high variability in Ethiopia was mainly caused by 6 patients with extremely high $AUC_{0\text{-}tau,SS}$ levels of >2000 µg·h/mL. These patients were all treated at one of the two study sites in Ethiopia. The VPC showed that the model could adequately predict PM in the different countries, as well as the differences in variability.

Conclusions: The developed PK model of PM in East African VL patients showed a slower k_a and higher bioavailability in Ethiopia, compared to Kenya and Sudan, as well as a decrease of clearance over time for

all patients. Accordingly, daily exposure in Ethiopian patients was estimated to be up to 30% increased. In order to explain these differences mechanistically, creatinine, GFR, and albumin were tested on different parameters in the covariate analysis, but no significant covariates could be identified. The difference in exposure between the Ethiopian study sites might suggest a drug related difference, although batch numbers were not different between countries. Other possible causes were considered, e.g. different dose calculation, or administration-related differences such as site of injection. However, these factors could not be verified.
Besides the observed differences in PK between East African countries, differences in clinical efficacy with Indian patients were observed. To further understand this diversity, it is planned to compare the PK of PM in East African populations with the Indian population.

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III-62: *Ludwig Vincent* How to improve the accuracy of Drug-Drug Interaction risk prediction for Mechanism Based Inhibitors

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Objectives: Mechanism-based inhibition (MBI) is a subtype of enzymatic inhibition in which the enzyme is permanently inactivated by an intermediate reactive metabolite that irreversibly binds to the active site. It has been shown that for this type of inhibitors, the recommended methods to predict the risk of drug-drug interactions (DDI) used in early development stages tend to over-estimate the real interaction observed in clinical studies [1][2]. Several factors may impact these predictions and could explain this over-prediction: inhibitor concentration (*[I]*), inhibition parameters (K_I/k_{inact}) or enzyme degradation constants (k_{deg}) used in the calculations. The aim of this work was to evaluate the different DDI risk assessment methods for MBI and the impact of each parameter in order to identify the optimal conditions for a more accurate prediction.

Methods: We first identified 14 MBI drugs and collected the parameters needed to predict DDI (f_u, C_{max}, k_{deg}, $t_{1/2}(CYP)$, K_I, k_{inact}, F_g, $f_m(CYP)$). We then compared the different calculation methods: the basic model, the mechanistic static model and the dynamic PBPK model. We evaluated the impact of each parameter. For PBPK models, we selected drugs for which static models mispredicted the risk, whatever the parameters used (Ritonavir, Saquinavir, Dasatinib and Rofecoxib). The PBPK models were developed and qualified with SimCYP®. As mentioned above, inhibition parameters (K_I, k_{inact}) could have a large impact on DDI risk prediction. Therefore, two experimental methods used for determining these parameters were also compared: i) a conventional method which includes a pre-incubation step with the MBI before the standard substrate co-incubation; ii) an alternative one-step substrate disappearance kinetic method that allows to take the inhibitor depletion and the competitive inhibition into account. The results obtained from the alternative method were computed using the SIVA® software.

Results: The comparison of the DDI risk predictions obtained for 14 MBI drugs with the static method showed that among the 4 possible inhibitor concentration values ??(C_{max}, $C_{max,u}$, C_{in}, $C_{in,u}$) the $C_{max,u}$ gave the largest number of acceptable predictions (respectively 12.2%, 39.3%, 0% and 8.2% of $R_{predicted}/R_{observed}$ ratios contained within the [0.5; 2] interval). The DDI risk assessment performed using PBPK modeling for the 4 selected molecules showed acceptable $R_{predicted}/R_{observed}$ ratios for all the interaction studies simulated and therefore greatly improved the predictions. Using the alternative method, the inhibition parameters K_I and k_{inact} could only be determined for one drug (Ritonavir) and the values were similar to the previously published values.

Conclusions: Our results showed that the basic model more accurately predicts the risk of DDI with MBIs using $C_{max,u}$ as the inhibitor concentration. The alternative method for K_I/k_{inact} determination, that can potentially overcome several hypotheses made by the two-step conventional method, was evaluated but did not show a clear benefit in the case of the Ritonavir. The simultaneous estimation of other parameters (K_{cat}, K_d, $??K_m$) on top of the MBI's parameters (K_I/k_{inact}) may explain the shortcoming of this model. All the more since these parameters are often unknown in early stages of the development. Despite the need of many parameters to be qualified and used as a tool for clinical studies simulations, the use of PBPK modeling showed a real improvement regarding the accuracy of DDI risk prediction for MBIs.

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III-63: *Janet Wade* Population PK analysis with full and reduced covariate models for Sym004, an antibody mixture targeting EGFR

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Introduction: Sym004 is a mixture of two synergistic full-length anti-EGFR antibodies (futuximab & modotuximab) that bind to two separate non-overlapping epitopes on the EGFR and inhibit the sustained growth of cancer cells. A population PK analysis of Sym004 on preliminary data has been performed previously [1].

Objectives:
1. Update the Sym004 population PK model that describes the available PK data from four trials.
2. Build full and reduced covariate models where specific focus will lie on the identification of covariates that could help describe interindividual variability in Sym004 PK. The full covariate model [2] can be considered exploratory in nature. The reduced covariate model will contain only statistically significant and clinically relevant covariates. The implications of different methods used to estimate the standard errors (SEs) of the covariate effects will be explored.

Methods: Sparse and richly sampled Sym004 PK data points (5341) from four completed phase 1 and 2 trials (Sym004-01, Sym004-02, Sym004-05 and Sym004-06) were included in the analysis. The majority of the 330 patients had metastatic colorectal cancer (mCRC) (n=247) and the remaining had various types of advanced solid tumours.
A population PK analysis was performed using NONMEM version 7.3.0. A suitable base structural model that accounted for the observed non-linearity in Sym004 PK was developed comprising of a two-compartment model with both linear and non-linear Michaelis-Menten-(MM) type elimination to describe target mediated drug disposition. An appropriate statistical model that describes the variability in the data was developed.
A full covariate model was developed which contained all pre-defined plausible covariate influences regardless of statistical significance and effect size. The development of the full covariate model required simplification of the statistical model originally defined for the base model due to computational difficulties. The full covariate model was then reduced by backwards deletion, retaining only statistically significant and clinically relevant covariate effects.
The SEs of the model parameters were obtained by MATRIX=RSR, MATRIX=S, bootstrap, and sampling importance resampling (SIR) [3].
The covariates in the analysis included age, weight, sex, race, glomerular filtration rate, albumin, total bilirubin, alanine transaminase, tumour size at baseline, visit-specific tumour size, tumour type, ECOG, time since previous treatment with anti-EGFR, previous treatment with cetuximab, previous treatment with panitumumab, and previous treatment with bevacizumab.

Results: The Sym004 base population PK model included the influence of weight on clearance (CL), maximum capacity of the MM elimination (Vmax), and the volumes of the central and peripheral compartments (V1 and V2, respectively).
The full covariate model contained all predefined plausible covariates regardless of statistical significance; 16, 11, 2 and 1 covariates were included on CL, Vmax, V1 and V2, respectively.
The reduced covariate model included the influences of weight on CL, Vmax, V1 and V2, the influence of sex and albumin on CL, and baseline tumour size of Vmax. Both the full and reduced covariate models

described the data well and as expected, the covariate models reduced the IIVs as compared to the base model.
The estimated standard errors of the covariate effects in the full and reduced covariate models varied with the method used to obtain the SE's. The MATRIX=S method yielded inflated SE estimates compared to other methods.

Conclusions: The full covariate model included all covariates and thus allowed the assessment of which covariates are important for potential dosing modifications, which can be said to have no clinical relevance, and for which covariate effects more information may be needed. In all these three situations the magnitude of the estimated SEs for the covariate effects provides useful information. The reduced covariate model for Sym004 contained well estimated statistically significant influences of weight, albumin, sex and baseline tumour size.

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III-64: *Ulrika Wählby Hamrén* Longitudinal FEV1 and exacerbation risk in COPD: Quantifying the association using joint modelling

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Introduction: Lung function, measured as forced expiratory volume in one second (FEV1), and exacerbations are two important endpoints commonly evaluated in chronic obstructive pulmonary disease (COPD) clinical trials. The correlation between FEV1 and exacerbation risk provides an opportunity to apply joint modelling of the endpoints, to potentially increase statistical power and enable assessment of efficacy in shorter and smaller clinical trials.

Objectives: To evaluate the potential usefulness of joint modelling in respiratory disease by quantifying the association between longitudinal FEV1 and the risk of exacerbation in COPD.

Methods: A joint model consisting of two sub-models, a Cox proportional hazards model for time-to-first exacerbation and a linear mixed-effects (LME) model for longitudinal pre-dose FEV1, was developed to evaluate the association between FEV1 and the risk of exacerbation. The sub-models were linked with an association parameter which describes how the estimated individual changes in FEV1 affects the exacerbation hazard. The effects of baseline covariates were tested on the exacerbation hazard. Patient-level data from a 12-month phase 3 clinical study in moderate-to-severe COPD [1], evaluating efficacy of fixed-dose combinations of a long-acting beta agonist (LABA) bronchodilator, formoterol, and an anti-inflammatory inhaled corticosteroid (ICS), budesonide, were used for model development. To evaluate the consistency of the association across studies and mechanisms of action, model parameters were subsequently re-estimated based on two additional phase 3 studies [2,3] and per treatment arm. A comparison to a standard Cox proportional hazards model was also performed. The JM-package [4] in R was used for modelling.

Results: A significant ($p<0.0001$) association between FEV1 and exacerbation risk was estimated, with an approximate 8-9% reduction in exacerbation risk for a 100 mL improvement in FEV1. This estimate was consistent across the three trials and across treatment arms. When considering the limited treatment effects on FEV1 in the COPD studies used in our analysis, on average around 50-90 mL, the average exacerbation risk reduction related to FEV1 improvements is ~4-7%. The instantaneous risk reduction related to the LABA-ICS combination treatment was approximately 30-35% in these studies. Thus, only a minor part of the exacerbation risk is accounted for by longitudinal changes in FEV1.
Breathlessness score and exacerbation history in the previous year were found to be important baseline predictors of exacerbation risk.

Conclusions: The consistent association between longitudinal FEV1 and exacerbation risk across studies supports the usefulness of applying joint modelling in analysis of COPD clinical trials. Due to the relatively modest contribution of FEV1 effects to exacerbation risk reduction, however, multivariate joint models

including additional endpoints/biomarkers (*e.g*. breathlessness score measured longitudinally) should be considered to optimize statistical inference and predictions.

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III-65: *Wenyi Wang* Physiological Response to Endotoxin Infusion in the Piglet: Modelling of changes in hemodynamic outcomes

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Introduction: Sepsis is a life-threatening clinical condition resulting from exaggerated immune activation, often in response to bacterial infection, and it is the leading cause of death among those hospitalized in the intensive care unit (ICU) [1]. The progression of sepsis can be studied in mammals by the administration of endotoxin (ETX), a component in the cell membrane of Gram-negative bacteria, resulting in a systemic inflammatory response [2]. Such an immune activation has large impact on the physiological status of the individual, with clear impact on the respiratory and circulatory system, as the body is under stress [3]. The cardiovascular system plays an important role in the clinical outcome of sepsis and septic shock, with an increase of the mortality rate by 70% to 90% among septic patients with cardiovascular impairments [4]. Previously, non-linear mixed effect modelling has been applied to assess the relation between ETX exposure and immune activation as measured by the cytokine response [5]. The aim with the current project was to investigate the exposure-response relationship between infused ETX and changes to the cardiovascular system, as measured by hemodynamic outcomes.

Methods: Data was acquired from four experimental studies where ETX was administered to anesthetized piglets (n=68) [5-8]. Intravenous infusion of ETX in rates from 0.063 to 16.0 µg/kg/h were used across six-hour studies, with infusion lengths between 1 to 6 hours. Based on the recorded hemodynamic data, sub-models were built for each of the following outcomes: mean pulmonary arterial pressure (MPAP), cardiac output (CO) and heart rate (HR). In order to describe the time-courses for each of the outcomes, baselines with or without inclusion of disease progression (asymptotic) were initially established, before ETX exposure-response models (linear, Emax or sigmoidal Emax) were assessed as either direct or delayed effects.
The non-linear mixed effect model analysis was performed in NONMEM version 7.4.3 (ICON Development Solutions) using FOCE for parameter estimation.

Results: All dose groups showed an approximate doubling of MPAP from the baseline value following infusion with no change in control groups. The increase was described as an indirect effect, where an Emax model was related to the ETX concentration, with an effect compartment incorporated to account for a delay in response, resulting in similar increase across all dose groups, due to a low EC_{50} relative to concentrations (9.54 EU/L) and an E_{max} of 1.01 (a doubling effect of the baseline). The CO only decreased for the groups receiving an ETX infusion. An indirect response model described the decrease in ETX treated groups, with EC_{50} and E_{max} estimated to 5.04 EU/L (again, low compared to ETX exposure) and 0.424 (maximum reduction to 42% of the baseline CO). For HR, the piglets receiving the highest infusion rates showed an approximate doubling over the baseline value mid-way through the six-hour study period, with small increases in controls and at lower infusion rates. An asymptotic model was used to describe the general increase in HR over time, and an Emax model was coupled to the ETX exposure through an effect compartment model describing the ETX effect. All models were evaluated by visual predictive checks (VPC) stratified on the individual design arms, which demonstrated that the models could adequately describe the median of the experimental data.

Conclusions: Models were developed to describe the relationship between ETX exposure and the measured outcomes for the cardiovascular system, including MPAP, CO and HR. The developed models quantifies the changes in the variables over time after exposure to ETX to increase the understanding of the cardiovascular system response. Eventually, the models may be extrapolated to the human to assist treatment of sepsis.

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III-66: *Shijun Wang* Comparison of approaches for estimating covariate effects in full random effects models

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Objectives: The full random effects modeling (FREM) approach [1] has been developed for covariate model building in nonlinear mixed effects (NLME) models. In a FREM model, the covariates are assumed to have mean and between-subjects variability (BSV) and the covariate effect on a parameter is quantified based on the covariance between their BSV as covariate coefficients in the form of matrix. This study aims to compare alternative approaches to estimate the covariate coefficients and their uncertainty based on the BSV matrix.

Methods: With respect to estimate BSV matrix, the FREM approach was successfully implemented on 6 developed PKPD models based on real data. The models were estimated using FOCE and the uncertainty of estimates were obtained with both the sandwich matrix (COV) and through importance sampling estimation method (IMP) with only expectation step. Additionally, a nonparametric bootstrap (n=5000) was implemented to estimate the uncertainty as well as three methods for sampling-importance resampling (SIR) [2]: the SIR implemented in PsN (SIR_P); the built-in SIR method in NONMEM (SIR_T); and NONMEM built-in SIR with post-processing resampling without replacement according to the related importance (SIR_R). Two methods for estimation of the BSV matrix were based on multiple sampling (N=10) from the posterior distributions of individual parameters, using either the normality assumption (IPN) or direct sampling of the individual parameters (IPS). Given the simulated samples, a bootstrap was implemented with sample size being equal to the number of subjects and repeated 2000 times. For each of the bootstrap samples, a covariance matrix could be computed and the mean and variance of covariate coefficients were computed from these.

Results: With respect to the comparison in estimating the covariate coefficients in FREM model, the covariate coefficients matrices estimated by IPN and IPS were compared to the coefficients from FOCE as reference in terms of the Frobenius norm. The relative deviation of IPN and IPS were 0.5% (0.1% to 1%) and 0.5% (0.1% to 1%). In the comparison of uncertainty estimation, at least 2000 samples of BSV matrices were generated by either simulating with a multivariate normal distribution for COV and IMP method or by utilizing the existing samples for the remaining methods. Given the BSV matrices, the corresponding matrices of covariates coefficients could be computed and the variation of covariate coefficients matrix was quantified by the ratio of interquartile range (IQR) to the median of each entry in the matrix. In terms of the 50^{th} percentile of the ratios across all the entries in the matrix, the order of the methods in the mean values of the ratios across all the 6 adopted models are: bootstrap (138%), IMP (133%), COV (124%), and SIR_P (105%); besides, IPN, IPS, SIR_T, and SIR_R obtained similar results from 82% to 87%; and similar order was observed in the 75^{th} percentile of the ratios and the mean values are 441%, 249%, 249%, and 199% for bootstrap, IMP, COV, and SIR_P; 149% to 169% for the remaining method.

Conclusions: The IPN and IPS methods proposed in the project can estimate the BSV matrix in FREM model in a good precision; the order of the methods in estimating uncertainty of covariates coefficient from high to low is bootstrap, IMP, COV, SIR_P; and the estimations of IPN, IPS, SIR_T, and SIR_R are similar and lower than the other four methods.

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III-67: *Zhigang Wang* A Pharmacokinetic-Pharmacodynamic model built on in vitro data predict the antibacterial effect of polymyxin B against Klebsiella Pneumoniae in vivo

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Objectives: Pharmacokinetic-Pharmacodynamic (PKPD) models built on preclinical data can be a useful tool for efficient exploration of antibiotic effects. PKPD models that can characterize bacterial growth, bacterial killing by antibiotics, and selection of resistance, can assist in understanding the interplay between antibiotics and bacteria [1]. Polymyxin B (PMB) is an antibiotic mainly used for the treatment of infections caused by resistant gram-negative bacteria, and is regarded as an antibiotic of last resort. The aim of this work was to explore if an *in silico* semi-mechanistic PKPD model for PMB and *Klebsiella Pneumoniae* built on *in vitro* data from static concentrations [2], can predict *in vivo* data in a thigh infection model by incorporating an *in vivo* PK model.

Methods: Plasma concentrations were sampled 0-8h post-dosing in thigh infected mice models with [CZ1] PMB (1-64 mg/kg) administered subcutaneously. A PK model was developed and applied to predict the unbound PMB concentration-time profiles (fu=0.086) [3] following the dose regimens of 4-32 mg/kg q6h and 8-64 mg/kg q12h. The unbound PK profiles were set to drive the bacterial killing in the PKPD model originally developed for a resistant *K. pneumoniae* strain (MIC 16 mg/L). The CFU counts predicted by the PKPD model at 24h were compared to the observed bacterial counts in the *in vivo* thigh model infected using a susceptible *K. pneumoniae* strain (MIC 0.75 mg/L). The growth rate (K_g) was allowed to be adjusted to *in vivo* conditions, by re-estimation based on bacterial counts observed in un-treated (growth control, GC) animals. In a subsequent step, parameters of the concentration-effect relationship in the PKPD model was allowed to be re-estimated to compensate for differences between the *in vivo* and *in vitro* systems and in the susceptibility (MIC 0.75 vs. 16 mg/L). The modeling and predictions were conducted in NONMEM and evaluated using PsN and R.

Results: Overall 120 PMB concentrations were available, and well described by a PK model comprising a saturable absorption pathway with the maximum absorption rate constant (V_{max}) decreased with higher doses, and parallel linear and capacity-limited elimination. In total, 40 *in vivo* CFU counts were available from the thigh infection model, including 20 CFUs from GC experiments and 20 CFUs following various PMB exposures. The *in vivo* K_g was estimated to be 52% lower than that in the *in vitro* PKPD model[EN1] (dOFV=-2561.96). When Kg was the only parameter refined in the model, the drug effect at doses ≥16 mg/kg q6h and q12h were all under-predicted. When the PMB killing effect (K_{drug}) was allowed to be adjusted, the estimated slope value was 4.9 times higher than what was reported in the *in vitro* model and the model prediction improved along with a decrease in OFV by 6.3 points. Following this refinement, all CFU counts were well described except for the 32 mg/kg q12h dosage, of which the drug effect was still under-predicted, potentially indicating some schedule dependency not well captured by the model developed based on static *in vitro* experiments.

Conclusions: The PKPD model built on *in vitro* data could predict the effect of PMB against *in vivo* *K.pneumoniae* infectious model data reasonably well after re-estimation of K_g and K_{drug}. The predictive

performance of the *in vitro* PKPD model will be further tested in the combined drug effect of PMB with rifampicin and minocycline in *in vivo* models infected by various *K. pneumoniae* strains in the future.

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III-68: *Linda Wanika* Investigating the relationship between Lactate Dehydrogenase and the occurrence of Chronic Lower Respiratory Diseases

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Introduction: Chronic Lower Respiratory Diseases (CLRDs) are a class of diseases that affect the trachea, bronchioles and alveoli, e.g. emphysema, bronchitis and interstitial lung disease (ILD). Patients who suffer from CLRD, often have difficulty breathing and some cancer patients may experience CLRD as an adverse event. An example of this is patients receiving Tyrosine Kinase Inhibitors (TKIs) which have been shown to induce ILD [1]. A plausible method for investigating the occurrence of CLRDs in cancer patients is through analysing biomarkers, routinely taken during a clinical trial. Lactate Dehydrogenase (LDH) is an enzyme found in most cells. LDH levels are usually increased when cellular damage is present and can be used as a biomarker for cell damage and apoptosis [2]. Some studies have concluded that an increase in LDH levels occurs during the occurrence of CLRD [3].

Objectives: This study aims to investigate the relationship between serum LDH levels and the occurrence of CLRD in cancer patients using data analytics and mechanistic modelling. A Cox's Proportional Hazard model is used to investigate the occurrence of CLRD and a mechanistic PK/PD model to simulate the changes to serum LDH levels is used in order to assess whether LDH is a suitable predictive marker for CLRD.

Methods: Clinical trial data were obtained from Project Data Sphere, a clinical trial database platform [4]. Two clinical trials had 712 cancer patients (receiving the drug erlotinib as their treatment) with LDH measurements provided overtime, of which 207 patients experienced a CRLD related event. A Cox's proportional hazard model was performed in Rstudio using *Survival and Survminer* [5-6]. The factors for the model were grouped baseline LDH levels and the %change between the baseline and the onset of a CLRD event. The PK/PD model is composed of a set of nonlinear parameterised ODEs, which simulated the change in LDH in response to erlotinib treatment. This was performed in Rstudio using *RxODE* [7].

Results: Compared to normal *LDH* levels (0-270 U/L), patients with a baseline value between 270-540 U/L were 1.5 times more likely to experience a CLRD (95% CI: 1.1, 2.1, p=0.019). Patients with a baseline *LDH* that was >540 U/L were 2.1 times more likely to experience a CLRD (95% CI: 1.2, 3.5, p=0.008). There was no significant risk associated with an increase in %LDH change. The model was able to predict a CLRD occurrence (10 days from the observed event time) for 15 patients.

Conclusions: This study confirms that high *LDH* levels are correlated against the occurrence of CLRDs and that the analysis of longitudinal *LDH*, (rather than just the baseline value), may be useful in investigating *LDH* as a possible predictor for CLRD. The model will be built upon by incorporating other analyses of *LDH*, such as slope measurements. This would also allow for the prediction of CLRD for patients who have a high baseline *LDH* value. The addition of covariates may also aid in the predictions of CLRD, as well the inclusion of more transit compartments in the PK/PD model to delay the *LDH* increase.

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III-69: *Shayne Watson* Development and Evaluation of a Human Physiologically Based Pharmacokinetic Model to Assess a Mitigation Strategy for Risks Associated with Novel Monoclonal Antibodies

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Introduction:

Creation of molecules that provide more optimal characteristics for consumers continuously evolves in the drug development industry. Monoclonal antibodies (mAb) provide better target specificity and typically a longer systemic exposure resulting in fewer negative effects from the intervention and more prolonged positive effects due to the persistent maintenance of concentration levels. When testing new molecules with these attributes, the inherent risk associated with unknown safety profiles in human also exists. Thus, developing a strategy to preferentially degrade this type of molecule using competition at the FcRn receptor could provide one tool to mitigate this risk. The modelling approach assessed this hypothesis by using exogenous IgG to reduce the time-concentration profile of an extended half-life monoclonal antibody.

Objectives:

- Develop a PBPK model for a human mAb with a designed lower Kd for the FcRn receptor to extend the exposure profile
- Identify the level of exogenous IgG that preferentially degrades a mAb with low Kd in humans

Methods:

A human physiologically-based pharmacokinetic (PBPK) model for mAbs was built based on extrapolation from a previously developed (1) Non-Human Primate (NHP) PBPK model using PK-Sim® as part of the Open Systems Pharmacology Suite (OSPS), version 7.4. (2). PK data was extracted from literature (3,4) using WebPlotDigitizer (5). The PK-Sim® mAb (i.e protein-PK) model extrapolates to different species by considering species-specific measures of in-vitro FcRn binding affinity. It leverages an in-built endosomal degradation model with FcRn-based antibody-recycling considering competition by endogenous IgG. With these underlying assumptions, a test for how exogenous IgG utilized saturation of and competition for FcRn binding to change mAb concentrations. The predictivity of the PBPK software for the IgG competition at FcRn was first validated using experimental data in mice where an unspecific mAb was co-administered with a single iv IgG dose to reduce mAb exposure (6). The human PBPK model on MEDI-524-YTE was then used to evaluate clinical feasibility and applicability of iv IgG competition at FcRn with both a repeated IV bolus and a continuous iv infusion of IgG and to provide insight into the limitations and risks associated with an IgG-based preferential degradation in humans.

Results:

The translated PBPK model for MEDI-524-YTE from NHP to humans slightly under-predicted terminal half-life for higher doses after sc administration. Yet, importantly the model illustrated the difference in half-life for NHP (29 days) to humans (86 days). For validation of the exogenous IgG competition at FcRn, the PBPK software captured the time-concentration profile of the unspecified mAb in mice (data pulled from (6)),

both with and without iv IgG reasonably well with a slight over prediction of the initial distribution phase in both scenarios. Nevertheless, the clearance phase and importantly the decrease in concentration of the unspecific mAb from the IgG bolus was accurately predicted, demonstrating the ability to predict alterations in clearance rate and the resulting concentration profile through the competitive binding at FcRn. Additional simulations in mice revealed that both, repeated bolus doses and continuous IV infusions, can sustainably reduce the concentrations through a constant reduction in half-life. Following this proof of concept, the exogenous IgG infusion was extrapolated for MEDI-524-YTE in humans. Half-life decreased with an increase in dose of IgG (100-1000mg/kg/day) and showed dose-independency across different doses of MEDI-524-YTE (10-1000mg). The half-life reduction plateaued with an IgG infusion nearing 1000 mg/kg/day and took typical half-life from 86 days down to approximately 4-5 days.

Conclusion:

The use of exogenous IgG to reduce concentrations of a mAB provides one opportunity for an interventive approach to decrease the risk of testing new molecules in humans. The risk associated with the intervention should be moderated in the context of the event itself. Importantly, this endeavour suggests this modelling platform provided evidence to mitigate risk when translating into humans.

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III-70: *Sebastian Weber* Qualifying drug dosing regimens in pediatrics using Gaussian Processes

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Objectives

Pediatric drug development is lagged w.r.t. to the respective adult program. Knowledge about a safe and efficacious regimen is available for the adult population prior to initiating pediatric trials. Population pharmacokinetic (popPK) models account for between-subject variation and for population level effects. For the pediatric trials we can utilize the adult models to extrapolate in absence of data to the pediatric population to select the dose regimens. The extrapolation is often performed by applying allometric scaling which adjusts the physiologic parameters of a popPK model by a size measure to account for organ function variation with size like weight. In addition, or as alternative, PBPK modeling can be used to account for the ontogeny of enzymes involved in the drug's PK. It is critical to either confirm the extrapolation assumptions or detect and quantify deviations using the very sparse data of pediatric trials. Commonly parametric modeling of the maturation effect is used, but these parametric forms are not derived from any first principles such that there is a risk of model misspecification. As a solution we propose the use of a data-driven non-parametric approach. We consider that extrapolation is performed using allometric scaling only while a maturation process in the pediatric population could be present which we would like to detect from the pediatric trial data.

Methodology

In practice maturation effects are functions of some age measure and are multiplied onto the individual clearance, for example, as a scaling factor less than unity implying a slower elimination of the drug. We suggest to use the non-parametric Gaussian Processes (GPs) to represent the maturation function [1]. Formally, the GP defines distributions of function values such that any finite combination of points follows a multivariate normal distribution with a covariance function that defines the properties including smoothness of the modelled functions.

We simulate a signal and a no-signal scenario. In both cases an adult model with allometric scaling of the clearance is used to choose weight-based dosing regimens for a simulated pediatric trial. The pediatric trial data is generated with allometric scaling only for the no-signal case and with presence of a maturation function in addition for the signal case. The pediatric trial is chosen to be realistically small with only 20 patients which are assumed to have age 0y – 5y with equally spaced ages and we measure only 10 pre-dose [WS1] measurements per patient. To ease the estimation we constrain the GP to be monotonically increasing and to vanish for large ages which assumes the adult model is correct in the domain of the adult data. The inference is done with Stan 2.18.1 [2].

Results

The results show that the GPs are able to detect maturation effects for the signal case and they do correctly assert the absence of a maturation function in case of the no-signal case. That is, in the signal case the GP correctly resembles the Hill function which was used to simulate the data while in the no-signal case the GP

correctly reduces to 0 for the entire age-range. Furthermore, we evaluate the key design parameters of the pediatric trial sample size and the number of measurements per patient. Here we find that greater gains are made with more measurements per patients rather than increasing the number of patients.

Conclusions

The choice of the dosing regimen for pediatric trials is in most cases based on extrapolation applied to established popPK or PBPK models. We propose the use of constrained non-parametric Gaussian Process (GP) to detect deviations within the original extrapolation model given the new data. In a simulation study we confirmed that this approach can detect an unexpected maturation function of the clearance in a typical sparse data setting of pediatric trials. The advantage of using GPs as compared to parametric approaches is the lower risk of model misspecification and greater uncertainty in age ranges without data, which avoids over-confident conclusions in absence of data. The GP approach can thus serve as basis for detecting deviations from initial extrapolation assumptions and allow for correction of proposed dosing regimens as needed given the available data which warrants adequate treatment of the pediatric population.

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III-71: *Ferdinand Weinelt* A joint pharmacokinetic model of piperacillin/tazobactam including mechanistic renal clearance in critically ill patients

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Objectives: Piperacillin (PIP) is a broad-spectrum β-lactam antibiotic used in combination with the β-lactamase inhibitor tazobactam (TAZ) for the treatment of severe infections in critically ill patients. The alarming spread of antimicrobial resistance motivates further research to optimise antibiotic treatment [1]. The large pharmacokinetic (PK) interindividual variability often observed in critically ill patients, increasing the risk of subtherapeutic plasma concentrations and therapeutic failure [2], further adds to this motivation. The efficacy of PIP is linked to the time the PIP concentration remains above the minimal inhibitory concentration ($T_{>MIC}$) [3] and the efficacy of TAZ is linked to the time the TAZ concentration remains above a bacterial strain specific threshold [4]. Because of the high variability, therapeutic drug monitoring for PIP is advised [5] while TAZ is most often not quantified, assuming similar PK properties to PIP. Given the known drug-drug interaction between PIP and TAZ due to their shared tubular secretion via the organic anion transporters 1 (OAT1) and 3 (OAT3) [6,7] in the kidney, the assumption that the PK of both drugs changes similarly in critically ill patients might be questionable. The objective of the presented work was to quantitatively describe the PK and its variability of PIP and TAZ in a critically ill patient population, mechanistically including the drug-drug interaction in the tubular secretion process of the renal clearance.

Methods: A monocentric prospective observational study was conducted in intensive care units at the University Hospital of Munich in 60 critically ill patients with severe infections. According to clinical guidelines patients were treated with 4 g PIP and 0.5 g TAZ as intravenous 0.5 h infusions twice daily (impaired renal function) or thrice daily (normal renal function). Multiple serum samples were taken over four study days and different patient factors were determined. Both drugs where quantified in the same serum sample by a combined LC-MS/MS assay [8]. Using NONMEM 7.4.3, a nonlinear mixed-effects (NLME) PK model was developed. First-order conditional estimation with interaction was employed and model adequacy was assessed considering plausibility and precision of the parameter estimates and goodness-of-fit plots.

Results: For both, PIP and TAZ a 3-compartment disposition model with a total volume of distribution of 21.6 L for PIP (V_1 4.7 L, V_2 9.1 L, V_3 7.8 L) and a total volume of distribution of 31.7 L for TAZ (V_1 5.15 L, V_2 10.4 L, V_3 16.1 L) was established. The total clearance of both drugs was separated into nonrenal clearance and renal clearance, the later consisting of glomerular filtration and tubular secretion. The linear nonrenal clearance was estimated to be 1.25 L/h for PIP and 1.03 L/h for TAZ, whereas glomerular filtration was set to the glomerular filtration rate assumed to be equal to the creatinine clearance, calculated using 24-hour urine collection method (median of the population 2.8 L/h). Tubular secretion was estimated assuming non-linear Michaelis-Menten kinetics for PIP (VM 1460 mmol/h and KM 500 mM) and linearized Michaelis-Menten kinetics for TAZ (CL_{int} 13.2 L/h) with a competitive inhibition of PIP on TAZ (Ki 22.3 mM).

Interindividual variability for PIP was estimated on KM (224 %CV), V_1 (81.3 %CV), CL (36.0 %CV) and Q_1 (24.6 %CV). For TAZ Interindividual variability was estimated on CL_{int} (82.1 %CV), V_1 (70.7 %CV), CL (34.9 %CV) and Q_1 (54.5 %CV). An additional combined interoccasion variability on the linear CL (38.3 %CV) between a patient's monitored dosing events was implemented.

Conclusions: A joint NLME PK model for PIP and TAZ, mechanistically implementing the drug-drug interaction at the tubular secretion process of the renal clearance, was successfully developed. High interindividual variability in the PK parameters of PIP and TAZ in critically ill patients was identified and quantified. Next, a covariate analysis will be performed to detect patient factors (e.g. demographics, clinical parameters) explaining the large PK variability. Ultimately, the NLME model including covariates will be used to assess whether critically ill patients and/or different subgroups of the study population would benefit from dosing adjustments, further paving the way towards optimal treatment of this fragile population.

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III-72: *Gustaf Wellhagen* Modelling UACR as a clinical endpoint

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Background: Urinary albumin-to-creatinine ratio (UACR) is a common biomarker for drugs in the renal space as an alternative to estimated glomerular filtration rate (eGFR) because it typically has a faster response that allows for shorter studies. However, UACR is highly variable both between individuals and between visits within an individual. Results from a placebo-adjusted change-from-baseline analysis could be biased by variability in the placebo arm. Mixed-effect Model Repeated Measures (MMRM) can be an approach to model such variable data by making fewer/no assumptions regarding the placebo response. Instead, at each visit a new placebo and drug response is estimated independent of other visits. By assuming a dose-response relationship, information can be carried over between dose arms to improve predictions.

Objectives: To investigate the precision and accuracy of placebo-adjusted change from baseline of UACR with different methods: MMRM with or without a dose-response relationship.

Methods: A true dose-response model following an Emax shape with varying ED50 (2, 4, 8, 16, 32, 64, 128 mg) was assumed. Different time-courses of the drug effects were investigated (direct, linear, exponential). For each case, a number (n=1000) of 16-week studies (samples at week -2, -1, 0, 2, 4, 6, 8, 10, 12, 14, 15 and 16) were simulated with placebo and three dose arms (0, 10, 30 and 100 mg). A first-order autoregressive model (AR1) was assumed for the correlation of residuals. The simulated values of UACR were log-transformed changes from baseline. The sample size was titrated to a power of 95% for detecting a 40% reduction in log(UACR) between the highest dose arm and placebo at end-of-study.

In the traditional MMRM analysis, each visit and dose arm had a separate estimate of both the placebo response and the drug effects.

In the MMRM with dose-response analysis, each visit had a separate estimate of the placebo response and Emax, but a shared ED50 parameter, thereby saving two parameters per visit but adding one global.

The precision was assessed through the size of the estimated standard errors of the placebo-adjusted change from baseline, and accuracy through the size of the bias in the same endpoint. Both simulations and estimations were performed in R version 3.2.4 [1]. The nlme() package was used to fit the MMRM with dose-response relationship.

Results: The MMRM with dose-response had lower standard errors for the estimates of placebo-adjusted change from baseline, especially for the lower doses at higher true values of ED50 (mean standard errors at the end of study reduced by 15-60%, 15-25% and 5-10% for the 10, 30 and 100 mg dose arms respectively). The traditional MMRM was unbiased while the MMRM with dose-response had a slight bias at the lower doses, the bias relative to the true effect of the highest dose amounted to up to 2.5% for the two lower doses. The bias increased with higher true ED50.

Conclusion: MMRM with an incorporated dose-response relationship offers an improvement in precision over traditional MMRM analyses. The improvement is mostly seen for lower doses.

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III-73: *Quirin Werthner* Network-based mathematical modelling of HPV transmission and cervical cancer in Germany.

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Introduction: Worldwide, there are an estimated number of 569,800 cervical cancer cases per year due to an infection with human papilloma viruses (HPV) which is associated with about 311,400 deaths every year [1]. Despite recommendations for screening programs and vaccinations by the German Standing Committee on Vaccination (STIKO) as well as reimbursement for these measures, the corresponding German numbers stand at about 4,600 cervical cancer cases and 1,550 deaths per year [2]. Considering Germany's low vaccination rate of 44.6% in female teenagers [3] compared to other western countries like Denmark (81%) or Sweden (78.5%) [4], and the newly arisen recommendation for the vaccination of boys, it is of ever more importance to analyze the current situation including potential barriers to as well as fostering possibilities for the reduction of incidence numbers. Therefore, a network model holds several advantages over compartment models. Namely, the modelling of individuals as separate nodes, together with the added stochasticity, which in combination leads to a more precise modelling of individual interactions and impacts of interventions [5].

Objectives:

- Development of a network-based mathematical model, describing the transmission and natural history of HPV and cervical cancer in Germany.
- Evaluate the potential implications of policy and behavioral changes on the spreading and prevalence of infections and mortality due to cervical cancer.

Methods: The model development was done using R (version 3.4.3) and the package suits *statnet* and *EpiModel* [6,7]. For the model development an approximate Bayesian computation with sequential Monte Carlo (ABC-SMC) was used in an open population modelling approach. The population was set up to consist of 1,000,000 individuals split between men and women from the ages of 12 to 100 to closely reflect the circumstances given by the Saarland region of Germany. Data for this was taken from the Federal Statistical Office of Germany [8].
Each individual was assigned fixed (e.g. gender) and dynamic (e.g. age, infection status) attributes, with infected individuals possessing additional attributes (e.g. diagnosis status, stage). Furthermore, different behavioral attributes were incorporated to fully describe interaction and thus spreading of HPV. Condom use was set to 20% [9] of all sexual intercourses with an assumed 3% rate of faulty condoms. Additionally, different sexual activity levels were taken into account with 21% of men and 15 % of women being categorized as increased sexually active and 8% of men and 6% of women being considered as highly active [10]. The vaccination rate was set to 44.6% [3] for women and in an alternative set up assumed to be 20% for men. Multiple transitions per individual on an annual basis were modeled. The necessary data for the model calibration were obtained from the literature.

Results: The chosen model was an adapted susceptible-infected-recovered (SIR) model with individuals passing from a susceptible to an infected state after being infected via the formation of a relationship with

an infected individual. Furthermore, individuals could pass from the infectious to a recovered as well as to a cancer state through recovery or exacerbation, respectively. Over the course of the next 100 years, the model predicts a substantial reduction of cervical cancer cases. Depending on the actual turn out this might become even more amplified by the upcoming vaccinations for boys in Germany. However, the level of acceptance for HPV vaccination for boys might prove to be a critical point and needs to be assessed. Furthermore, the model predicts an increasing effectivity of HPV vaccination through the usage of nonavalent vaccines and the resulting higher degree of protection against additional high risk HPV types.

Conclusion: A functional model for the description of the natural history and spreading of HPV has been developed. Furthermore, the model allows analyzing of potential impacts of behavioral parameters and policy changes on the prevalence of HPV and cervical cancer in the Saarland region.

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III-74: *Sebastian Wicha* TDMxR: an open-source package for model-based therapeutic drug monitoring in R

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Objectives: Pharmacometric models have gained popularity to support therapeutic drug monitoring (TDM) by model-based techniques such as 'Probabilisting Dosing', i.e. a priori prediction of a likely effective dose considering the covariates of the patient, and 'Bayesian forecasting', i.e. a posteriori prediction of an individual dose using patient covariates and previous TDM measurements [1]. We aimed to develop an R package to facilitate model-based TDM using state-of-the-art pharmacometric techniques.

Methods: TDMxR was developed under R version 3.5.2. The R package 'mrgsolve' [2] was utilized to provide an efficient simulation framework for pharmacometric models. The R package 'data.table' [3] provided an efficient framework to handle large-scale datasets originating from the simulation output. 'doParallel' [4] was utilised for optional parallelization.

Results: TDMxR provides an efficient framework for typical tasks in model-based TDM developed to maximize computing performance. The following options are available:

- Flexible handling of complex dosing regimens
- Performance of stochastic simulations
- Bayesian estimation of individual pharmacokinetic parameters
- Handling of inter-occasion variability incl. weighting functions.
- Simulation from the posterior distribution to visualize uncertainty of the estimated PK or PD profile.
- Probability of target attainment calculation from a priori and a posteriori simulations for user-defined endpoints for PK or PD.
- Deterministic and probabilistic dose optimisation based on user-defined PK or PD targets

The results were successfully cross-validated against NONMEM 7.4.1 and individual parameters estimated by TDMxR were unbiased (absolute mean bias <0.1%) and varied numerically by

Conclusions: TDMxR provides an efficient framework for model-based TDM providing state-of-the-art functionality at optimised computational cost. The R-Shiny-based TDMx software [1] is currently updated to be operated by TDMxR. Further development will include interfaces to other simulation packages and inclusion of an optimal sampling module. A release of the TDMxR package to CRAN is planned.

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III-75: *Mélanie Wilbaux* Projecting MIW815 (ADU-S100) human tumor PK after intra-tumoral injection using a translational modeling approach combining pre-clinical and clinical data

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Introduction:

MIW815 (ADU-S100) is a novel immuno-oncology cyclic dinucleotide compound targeting STING (Stimulator of Interferon Genes). It is currently being evaluated in a Phase I first-in-human single-agent dose-escalation study and in combination with PDR001, a checkpoint inhibitor. MIW815 is administered via intra-tumoral (IT) injection and only plasma concentrations are determined.

Objective:

The objective is to combine pre-clinical tumor concentration data and clinical data through a similar structural model to simulate intra-tumoral PK in human and to enable future support of dose and schedule selection of MIW815.

Methods:

Plasma concentrations (n=740) were available from 47 patients with solid tumors and lymphomas enrolled in the single-agent study. They received IT injection of MIW815 with doses ranging from 50 µg to 6400 µg, weekly administered for 3 weeks followed by one week-off. Full PK profiles up to 4 hours after injected dose were collected at cycle 1 day 1, cycle 1 day 15 and cycle 3 day 1.
Pre-clinical intra-tumoral concentrations (n=32) and plasma concentrations (n=64) up to 5 hours were available in 37 syngeneic mice after a single administration of MIW815 via: (i) IT injection of 20 mg/kg, (ii) sub-cutaneous (SC) administration of 20 mg/kg, or (iii) intra-venous (IV) administration of 1 mg/kg. A multilevel pre-clinical semi-mechanistic PK model was established to describe all these data and to characterize drug distribution between tumor and plasma. Several model structures were probed to describe the intra-tumoral distribution and diffusion to plasma.
The established pre-clinical PK model structure was applied by estimating parameters based on the clinical plasma PK data and used to simulate the intra-tumoral time course of MIW815.
A minimal empirical PK model was also developed in human to describe plasma concentrations and to estimate key PK parameters.
Both pre-clinical and clinical data analyses were developed using non-linear mixed-effects modeling implemented in Monolix 2018R1. Model selection and evaluation were based on statistical criteria, goodness-of-fit plots and simulations-based diagnostics.

Results:

The selected pre-clinical model combined two main components: tumor and systemic circulation. IT injection of MIW815 was described by a transfer from a depot compartment to tumor tissue and a leakage to plasma with estimation of the fraction of drug amount distributed to tissue. Intra-tumoral concentration kinetics were best described by a two-compartment structure, while plasma PK were described by one-

compartment model with linear elimination. An additional tumor-plasma distribution was estimated to describe observed intra-tumoral and plasma concentrations after SC administration. The model was able to describe both plasma and intra-tumoral PK profiles after IT, SC and IV injection.
The same structural model was applied to human plasma PK data. The following assumptions were made: (i) applicability of pre-clinical experimental models (mice) to humans, (ii) similar process describing PK and tumor distribution. Observed human plasma PK data were used to re-estimate all model parameters. This model showed a good prediction of clinical plasma PK. It was also used to perform simulations of human MIW815 PK profiles in the injected tumor for different doses.
Plasma PK in human were also described by an empirical one-compartment model with linear elimination. An alpha-order absorption process was necessary to describe the data, suggesting that a complicated distribution process might be involved between tumor and plasma. Plasma half-life of MIW815 was estimated to be very short.

Conclusions:

A translational modeling approach was applied to develop a semi-mechanistic model and allowed projection of PK profiles in the injected tumor in humans by combining pre-clinical and clinical data. The future plan is to use this model to support human dosing regimen selection by simulating human intra-tumoral PK that matches pre-clinical efficacious concentrations, or that lead to biomarker changes.

III-76: *Justin Wilkins* Population Pharmacokinetics analysis of M5717, a novel antimalarial agent

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Objectives: M5717 is a translation elongation factor 2 (eEF2) inhibitor in development as an antimalarial. It has a long half-life and duration of action and is active against multiple life-cycle stages of *Plasmodium falciparum* and *Plasmodium vivax*. The objective of this study was to describe M5717 pharmacokinetic (PK) concentration versus time data after single ascending oral doses in healthy volunteers, and to assess between-subject PK variability.

Methods: Study MS201618-0013 was a Phase I, first-in-human, randomized, double-blind, placebo-controlled trial of single ascending doses of M5717 to assess the safety, tolerability and pharmacokinetic profile, and to assess the antimalarial activity of M5717 against *P. falciparum* in healthy male and female adult subjects. So far, a total of 36 subjects received oral M5717 in Part A, a single ascending dose (SAD) part designed to investigate the safety, tolerability and PK properties. A total of 22 healthy subjects were enrolled in Part C, a single-centre, open-label part using the *P. falciparum* induced blood stage malaria (IBSM) human challenge model to assess the antimalarial activity of M5717 in subjects infected with malaria under controlled conditions. A total of 1166 PK samples from these 58 subjects, who were administered single doses of M5717 (50 mg, 100 mg, 150 mg, 200 mg, 400 mg, 600 mg, 800 mg, 1000 mg), were available for analysis. NONMEM 7.4.3 was used to develop a population PK model to describe the data. Demographic covariate data were incomplete and therefore not used.

Results: M5717 single-dose PK in healthy subjects appear to be complex. PK were not linear with dose, with multiple secondary peaks observable in the concentration-time curve after a single dose. The most parsimonious model that was able to describe M5717 PK was two-compartmental, with a recirculation component to describe the most significant secondary peak; central volume of distribution (V2/F) and absorption rate constant (ka) were strongly inversely correlated with administered dose. Typical values of model parameters were largely well estimated: apparent oral clearance (CL/F) was estimated to be 21.6 L with interindividual variability (IIV) of 37.7%, apparent central volume of distribution (V2/F) was estimated to be 2480 L with an IIV of 19.5%, apparent peripheral volume of distribution (V3/F) was estimated to be 4010 L, apparent intercompartmental clearance (Q/F) was estimated to be 67.9 L/h, absorption rate constant (ka) was estimated to be 0.927 h^{-1} with an IIV of 66.4%, and relative bioavailability (F1) was fixed to 1 with an IIV of 31.1%. Release of M5717 from the depot compartment for recirculation was estimated to take place 27.2 h after dose administration for a fixed period of 0.5 h. None of the several physiologically-based models describing the relationship between dose and V2 and dose and ka that were tested provided an adequate fit; empirical power models in which dose was treated as a covariate were ultimately used (the coefficients describing the relationships between V2 and dose and between ka and dose were -0.593 and -0.674, respectively). Residual variability was estimated to be 25.7%, applied additively on the logarithmic scale. Diagnostic plots and visual predictive checks were indicative of an acceptable model fit to the data despite the unusual features observed in the PK.

Conclusions: A population PK model was developed to describe the nonlinear dose-exposure relationship for M5717 and its between-subject variability across doses ranging between 50 mg and 1000 mg and was able to describe the observed data acceptably well. Increasing dose was associated with decreasing ka (and therefore slower oral absorption) and decreasing V2/F, suggesting nonlinear distribution.

III-77: *Francis Williams Ojara* Time-to-event analysis framework to evaluate the impact of paclitaxel exposure on peripheral neuropathy in patients with advanced non-small cell lung cancer receiving first-line chemotherapy

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Objectives: Peripheral neuropathy (PN), a dose-limiting paclitaxel-related toxicity, affects >20% of patients on paclitaxel (PTX) therapy and negatively impacts quality of life. The risk of PN was shown to increase with higher PTX dose and exposure (time of plasma concentration above 0.05 µM), by comparing odds of PN for patients at different dose or exposure levels [1,2]. Using parametric time-to-event analysis, accounting for time of occurrence of PN on the risk of PN, we established the relationship between PTX dose and the risk of PN, grades 2 or 3 (PN2+), based on data from the CEPAC-TDM study [3,4]. In this analysis we extend the established time-to-event analysis framework to evaluate the impact of paclitaxel exposure on the risk of PN2+ to support dose adaptation and hence reduce the occurrence of PTX-associated PN.

Methods: Patients (n=365) from the CEPAC-TDM study, who received 3-weekly PTX dosing for ≤ 6 cycles either with standard 200 mg/m^2 PTX or a PK/PD-guided dosing approach were included [4]. Carboplatin or cisplatin were co-administered. PTX PK data was available in the PK/PD-guided dosing arm (n=183). PN symptoms, severity, start and end dates were recorded and classified using the common toxicity criteria (version 4.0) [5]. The risk of 1st-occurrence of PN2+ during treatment was described using a cycle-varying hazard model, including impact of covariates, PTX dose, age, weight, sex, and smoking status [3]. In this analysis, PTX exposure (instead of dose), age, sex, and smoking status were jointly evaluated in a full covariate model (FCM). Since the BSA-guided dosing arm had no PTX PK, PTX exposure metrics ($AUC_{(0\text{-}\infty,cycle)}$, $T_{C>0.01/\ 0.05/\ 0.1\ \mu M}$) was derived using the multiple imputation (MI) approach [6]. 50 sets of PTX exposure metrics were simulated using a PTX PK model [7] and the CEPAC-TDM dataset. For each set, FCM parameters were evaluated. FCM parameters were averaged across imputations [6]. Assessment for the PTX exposure metric that provided the best improvement in model fit (ΔOFV) was first based on FCM evaluation with single imputated PTX PK. The PTX dose-exposure-PN2+ relationship was subsequently explored by simulating incidence of PN2+ for three clinically relevant dosing schedules: 200 mg/m^2 and 175 mg/m^2 (both 3-weekly, 6 cycles, i.e. q3w) and 80 mg/m^2 (weekly for 3 weeks and a week off, 6 cycles i.e. qw). The endpoint of interest was incidence of PN2+ with the different dosing schedules. Randomness of the TTE model and parameter uncertainty were the levels of variability included. Dataset formatting was performed in R (3.4.3) and TTE analysis in NONMEM (7.3.0).

Results: PTX exposure data from MI in the PK/PD-guided dosing arm were closely aligned with estimated PTX exposure based on the PTX concentrations observed in the PK/PD-guided dosing arm: the estimated and typical exposure from single imputation largely fell within the interquartile range of MI PTX exposure, showing reliability of the imputation procedure. Amongst the investigated PTX exposure metrics $AUC_{(0\text{-}\infty,cycle)}$ was the most predictive of PN2+. A 17.1% increase in risk of PN2+ with change in PTX $AUC_{[0\text{-}\infty,\ cycle]}$ from 7.34 ($P_{0.025}$) to 24.6 ($P_{0.975}$) µM·h was predicted. The 80 mg/m^2 (qw) was associated with higher risk of PN2+ compared to 200 mg/m^2 (q3w). A 38% increase in risk of PN2+ with 80 mg/m^2 (qw) over 200 mg/m^2 was predicted: hazard ratio [95% CI] of 1.38 (1.05, 1.78). The risk of PN2+ increased with increase in dose

for the 3-weekly dosing i.e. an 11% increase in risk of PN2+ with 200 mg/m^2 over 175 mg/m^2 was predicted: hazard ratio [95% CI] of 1.11 [1.03, 1.24].

Conclusions: We established a quantitative relationship between PTX exposure and the risk of 1st-occurrence of PN2+, accounting for effects of age, sex and smoking status. Using the multiple imputation approach enabled exposure-PN2+ evaluation for the entire dataset, including patients with no PK data. We found that PTX $AUC_{(0\text{-}\infty,cycle)}$ described better the occurrence of PN2+ compared to $T_{C>0.05\ \mu M}$, reported in literature [2]. Weekly PTX dosing i.e. 80 mg/m^2 (qw) was associated with a significantly higher risk of PN2+ compared to 3-weekly PTX dosing i.e. 200 mg/m^2 (q3w), whereas within the 3-weekly dosing schedule the risk of PN2+ increased with increase in PTX dose. The developed model enables quantification and comparison of the individual risks of PN2+ for commonly used PTX dosing regimens apriori for decision making.

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III-78: *Jan-Georg Wojtyniak* Physiologically-based Pharmaokinetic Modelling of Metoprolol Drug-Drug-Gene Interactions with Paroxetine and CYP2D6

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Introduction: Metoprolol is on the World Health Organization's "List of Essential Medicines" and the most frequently prescribed β1-receptor blocker in Germany[1,2]. However, altered metoprolol exposure can occur due to concomitant use of metoprolol with CYP2D6 inhibitors or inducers (drug-drug interaction (DDI)) or due to CYP2D6 polymorphisms (drug-gene interaction (DGI))[3,4]. Following, this can reduce therapy efficacy or lead to severe adverse drug events (ADE) like hypotension, bradycardia and cardiorespiratory arrest[3]. To overcome this, physiologically-based pharmacokinetic (PBPK) modelling can be applied as a valuable tool for quantifying DDI and DGI effects and following, for the development of dose recommendations under different DDI/DGI scenarios[5].

Objectives:

- Development of PBPK models for metoprolol given as racemate, the enantiomers *R*-metoprolol and *S*-metoprolol, its metabolite α-hydroxymetoprolol and paroxetine as a CYP2D6 inhibitor
- Subsequently, prediction of both, DDI and DGI effects
- Development of metoprolol dose recommendations for various DDI/DGI situations

Methods: PBPK model development was performed with PK-Sim® and MoBi® (version 7.3.0) as part of the Open Systems Pharmacology Suite[6]. Data for model development were extracted from literature, including physicochemical parameters and plasma concentration-time profiles for all compounds and for various CYP2D6 genotypes. Data were separated in internal and external data for model development and evaluation, respectively. After individual development of a metoprolol and a paroxetine model they were coupled to predict the DDI effects of concomitant use. Finally, the models were used for dose optimization. For this purpose, exposure of 200 mg metoprolol q.d. as the area under the plasma concentration-time curve (AUC) at stead-state was simulated as reference value. Afterwards, exposures were simulated for different CYP2D6 metabolizers with and without concomitant administration of 40 mg paroxetine q.d. at steady-state adapting the dose stepwise until matching exposure compared to placebo was reached.

Results: The final model was capable to describe all plasma concentration time profiles satisfactorily with a mean AUC ratio predicted versus observed of 0.87, 0.93, 0.96, 1.0, 1.2 for all *R*-metoprolol, *S*-metoprolol, racemic metoprolol, α -hydroxymetoprolol and paroxetine profiles, respectively. Based on CYP2D6 activity scores CYP2D6 poor- (PM), extensive- (EM) and ultrarapid-metabolizer (UM) profiles could be predicted successfully with mean DGI ratios (predicted AUC ratio PM or UM to EM *versus* observed AUC ratio PM or UM to EM) of 1.18 for PM and 1.22 for UM. Furthermore, an effective coupling enabled the forecast of DDI effects of concomitant use of paroxetine with metoprolol. The DDI mean ratio (predicted AUC ratio metoprolol + paroxetine to metoprolol *versus* observed AUC ratio metoprolol + paroxetine to metoprolol) was 1.42 and hence, within the common acceptance criterion of a twofold deviation. Dose optimization results were in agreement with existing guidelines for metoprolol dose adaption under various DGI

conditions. For example, according to the Dutch Pharmacogenetics Working Group (DPWG) guideline metoprolol dose for UMs should be increased up to 250% whereas the dose for PMs should be reduced by 75%[7]. For the same scenario, model simulations resulted in an increase up to 200% for UMs and a dose reduction of 75% for PMs. Apart from this, model simulations revealed that metoprolol dose should be reduced for all genotypes by 75% if metoprolol is given together with paroxetine.

Conclusion: A functional metoprolol PBPK model to evaluate the pharmacokinetic effects due to CYP2D6 DDIs and DGIs was developed. Overall the model holds the potential for a more personalized medicine by reducing the risk of ADEs or therapy failure.

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III-79: *Dan Wright* Kinetic-pharmacodynamic models in the setting of non-linear drug elimination

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Objectives:

In the absence of pharmacokinetic (PK) data, the time course of drug effects can be modelled using kinetic-pharmacodynamic (KPD) models. A typical KPD model will include an 'effect compartment'-like kinetic model to describe the time course of the drug in the body combined with a full pharmacodynamic (PD) model for drug effects.

It is generally stated that KPD models can only be used in the setting of linear PK when the drug exhibits first-order elimination [1,2]. The prevailing assumption is therefore that the 'kinetic' model requires a rigid structure comprising a standard one-compartment model with intravenous bolus input and *linear* elimination. Generally, other structural forms for the 'kinetic' model are not considered.

Two parameterisations for KPD models have been proposed. Most commonly, the estimated elimination rate of the drug from the 'kinetic' compartment is used to drive the PD effect [3]. This involves substituting the C50 value in a standard Emaxmodel with EDK50, a composite of drug clearance and C50 (EDK50=CL*C50). An alternative parameterisation is to use the amount of drug in the body to drive the PD effect [4]. In this case, the C50 parameter is substituted with A50 representing the amount of drug in the body that gives half the maximal effect.

We propose that a KPD model using the EDK50 parameterisation will result in a poor model fit when the drug exhibits non-linear elimination, while the A50 method will allow a KPD model to be applied in this scenario. Therefore, the aim of this study is to compare the performance of a KPD model with EDK50 and A50 parameterisations in the setting of non-linear elimination.

Methods:

A stochastic simulation and estimation (SSE) study was conducted.

Reference datasets were simulated using a pharmacokinetic-pharmacodynamic model for a hypothetical drug using NONMEM (v.7,3). The PK model was a one-compartment model with an intravenous bolus input and a non-linear elimination. The time course of the biomarker for drug response was described using a turnover model with a zero-order input (Rin) and a first-order output (kout). The drug effects were assumed to result from the inhibition of Rin. Individual model parameters were assumed to be lognormally distributed. The residual error was described using a proportional error model.

The parameter values for generating the reference datasets were; Vmax=0.08mg/h, Km=1mg, V=10L, R_in=7units/h, kout=0.1h-1, Imax=1, C50=0.4mg/L. Between subject variance was set to 0.1 for all parameters and proportional error to 0.01.

500 datasets, each with 90 patients, were simulated with equal number of patients (n=30) receiving a single dose of 4mg, 8mg, or 16mg. For each patient, nine PD biomarker observations were made at 0, 6, 12, 24, 48, 72, 96, 120, and 144 hours.

Four KPD models were fitted to simulated PD biomarker data using NONMEM (v.7.3). All KPD models tested consisted of a one-compartment 'kinetic' model linked to a turnover model via an inhibitory Emax function. The following variations were considered; (1)A50 parameterisation with a linear 'kinetic' model ('Lin-A50'), (2) EDK50 parameterisation with a linear 'kinetic' model ('Lin-EDK50'), (3) A50 parameterisation with a non-linear 'kinetic' model ('NonLin-A50'), (4) EDK50 parameterisation with a non-linear 'kinetic' model ('NonLin-EDK50').

The four KPD models were compared using the Akaike's Information Criterion (AIC), visual predictive checks, goodness of fit plots, the relative bias in parameter estimates, and, the precision of parameter estimates (relative standard error [RSE]).

Results:

The KPD model parameterised using A50 with a non-linear 'kinetic' model (NonLin-A50) provided with best fit to the data as assessed by AIC, VPC and goodness of fit plots. Of the four competing KPD models, only NonLin-A50 was associated with unbiased parameter estimates. The model parameters for Lin-A50 and NonLin-A50 were estimated precisely with %RSE of less than 30% for fixed-effects and %RSE of less than 50% for random-effects parameters.

Conclusions:

In this work, a KPD model with a non-linear 'kinetic' structure and A50 parameterisation, provided unbiased and precise parameter estimates when fitted to data generated under a non-linear drug elimination model. In contrast to the prevailing assumption, our results suggest that KPD models can be used in the setting of non-linear elimination provided the A50 parameterisation is used.

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III-80: *Li Xia* A Physiologically-Based Pharmacokinetic Model of Voriconazole

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Objectives: Voriconazole, a first-line anti-fungal therapy, exhibits nonlinear pharmacokinetics together with large inter-individual variability but has a narrow therapeutic range. We aim to investigate the metabolism of voriconazole to better understand dose- and time-dependent alterations in the pharmacokinetics of the drug and to provide the model basis for safe and effective use according to CYP2C19 genotype.

Methods: *In vitro* assays were conducted to assess mechanism-based inactivation (MBI) of CYP3A4 by voriconazole. These results were combined with 93 published concentration-time curves of voriconazole from clinical trials to develop a whole-body physiologically-based pharmacokinetic (PBPK) model for healthy volunteers. The model was evaluated with the predicted/observed ratio of AUC and C_{max}, geometric mean fold error, as well as the comparison of predicted with observed concentration-time curves from virtual studies over the full range of voriconazole administration dosage regimen (including intravenous and oral, dosing from 1.5 to 6 mg/kg and from 50 to 400 mg). Subsequently, the voriconazole model was coupled with independently developed CYP3A4 substrate models (midazolam and alfentanil) to assess the validity of the model to describe the inhibitory effects of voriconazole on CYP3A4. Sensitivity analysis was conducted for parameters: i) optimized; ii) related to optimized parameters; iii) a strong influence on calculation methods used in the model; iv) significant impact on the model.

Results: The IC_{50} shift assay showed that voriconazole has a MBI on CYP3A4 with a 16-fold difference in the absence and presence of NADPH. The inactivation kinetic assay provided a KI of 9.33 (95% confidence interval: 2.56 to 34.0) µM, supporting the integration of MBI model into the PBPK model. Genetic polymorphisms of CYP2C19 were introduced into the model for rapid metabolizers (RMs, CYP2C19*1/*17 or *1/*17), extensive metabolizers (EMs, *1/*1), intermediate metabolizers (IMs, *1/*2,*1/*3,*2/*17, *2/*2/*17) or poor metabolizers (PMs, *2/*2, *3/*3 or *2/*3) with the CYP2C19 expression values of 0.79, 0.76, 0.40, and 0.01 µmol/L, respectively[1]. PBPK model verification demonstrated good performance of the model, with 82% of predicted/observed AUC ratios and all C_{max} ratios from 28 test datasets being within a 2-fold range. For those studies reporting CYP2C19 genotype, 88% of AUC ratios and 95% of C_{max} ratios were inside the 2-fold range of 41 test profiles. Sensitivity analysis showed that the PBPK model of voriconazole was most sensitive to CYP2C19 kcat, CYP2C19 Km and fraction unbound values (all taken from the literature), with a sensitivity value exceeding a range of -0.5 to 0.5. For the effect of voriconazole on midazolam and alfentanil, the predicted/observed AUC change for these CYP3A4 substrates by voriconazole ranged from 1.01 to 1.36, indicating that CYP3A4 inhibition was appropriately incorporated into the voriconazole model.

Conclusions: Both the *in vitro* assay and model-based simulations confirmed the MBI of CYP3A4 by voriconazole as a pivotal characteristic of the drug's pharmacokinetics. The PBPK model developed here could support individual dose adjustment of voriconazole, also according to genetic polymorphisms of CYP2C19, and DDI risk management.

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III-81: *Rujia Xie* Pharmacokinetic-Pharmacodynamic Analysis of Anidulafungin in Pediatric and Adult Patients with Invasive Fungal Infections

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Objectives: Anidulafungin (ANID) is an intravenous (IV) echinocandin synthesized from a fermentation product of *Aspergillus nidulans*. ANID is approved for treatment of invasive candidiasis including candidemia (ICC) in adult patients worldwide. The approved adult dosing regimen is a 200 mg loading dose (LD) followed by 100 mg maintenance dose (MD) once daily (QD). Previously, the pharmacokinetics (PK) of ANID have been evaluated in healthy adult subjects, subjects with renal or hepatic impairment, subjects with fungal infections, and pediatric subjects aged 2 to 17 years. ANID exhibits linear and predictable PK. The objectives of our analyses were to describe the PK of ANID in pediatric and adult subjects with ICC, to explore the relationships of exposure-efficacy and safety, and to confirm the proposed pediatric dosing regimen is appropriate.

Methods: Four studies (2 adult and one pediatric ICC clinical studies, and one Investigator-Initiated Research (IIR) pediatric PK study conducted by Duke University in neonates and infants) were included in the PK analysis. Adults received a 200 mg LD followed by 100 mg MD QD, and pediatric subjects received a 3 mg/kg (maximum 200 mg) LD followed by 1.5 mg/kg (maximum 100 mg) MD QD.

The 3 clinical studies were included in exposure-efficacy and exposure-safety graphical and logistic regression analyses. ANID exposures ($AUC_{0\text{-}24,ss}$ and $C_{min,ss}$) were examined graphically as potential predictors for efficacy endpoints (global response of success/failure and all-cause mortality) and incidence of all-cause treatment-emergent hepatic and/or gastrointestinal (GI) adverse events (AE) for subjects with PK data. Probability of efficacy outcomes and incidence of AEs were graphically evaluated for 5 $AUC_{0\text{-}24,ss}$ quantile groups (quantile <=20%, >20%-40%, >40%-60%, >60%-80%, >80%).

A nonlinear mixed effects modeling approach (NONMEM) was used for the analyses. The estimation methods were first-order conditional estimation method with interaction (FOCEI) for PK and LAPLACE for binary safety data.

Results: One hundred and sixty three subjects (95 males and 68 females) from the 4 studies were included in the PK analysis, in which 14 from the Duke IIR, 66 from the pediatric study, and 83 from the adult studies provided 797 ANID concentrations (391 from pediatric subjects). ANID PK was best characterized by a 2-compartment model with 1st order elimination. Body weight was a covariate on clearance (CL), central volume of distribution (Vc), and peripheral volume of distribution (Vp). No other covariates (eg. age or sex) were identified as statistically significant. A typical subject weighing 70 kg had estimated CL, Vc, Vp, and inter-compartmental clearance (Q) of 1.16 L/h, 26.7 L, 22.4 L, and 2.37 L/h, respectively. The inter-individual variability for CL, Vc, Vp and Q were 37.9%, 46.5%, 53.8% and 52.2%, respectively. Predicted mean $AUC_{0\text{-}24,ss}$ (for MD doses) were 80.8, 82.9, 82.8, 86.8, and 91.1 µg*h/mL for neonates, children aged 1 month < 2 years, 2-0-24,ss and $C_{min,ss}$) across the five age groups were comparable. Visual predictive check (VPC) and prediction corrected VPC (pcVPC) plots indicate that in general the final model predicts the data

well across the studies, with good match between the median, 5th and 95th percentiles for the observed and simulated data across the age groups.

Probability of treatment failure or death does not appear to be related to low exposures. There appeared to be a trend in relationship between exposure and incidence of all-cause hepatic AEs but not GI AEs. None of the exposure parameters were identified as a statistically significant predictor for the incidence of hepatic or GI AEs.

Conclusions: The proposed IV dosing regimen, a 3.0 mg/kg (maximum 200 mg) LD followed by 1.5 mg/kg (maximum 100 mg) MD QD, is considered appropriate for pediatric patients 1 month to

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III-82: *Estelle Yau* A global sensitivity analysis of the Rodgers and Rowland equations predicting drug distribution in PBPK models

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Objectives: Physiologically-based pharmacokinetic (PBPK) models allow prediction of a drug's pharmacokinetics (PK) by separating drug and system's properties allowing their use for the investigation of "what if" type of questions. The multidimensional nature of PBPK models in terms of parameters and outputs generally hinders estimation of uncertain or unknown model parameters, where heterogeneous and subjective approaches for parameter estimation using PBPK models exist in the literature [1]. One possible approach to aid parameter estimation with PBPK models can be the use of Bayesian methods [2].However, before initiating parameter estimation procedures the application of parameter sensitivity analysis (SA) is generally recommended. Herein, a comprehensive sensitivity analysis was conducted to identify key parameters explaining variability/uncertainty in models for predicting drug distribution [3,4] and potentially reduce the dimensionality by excluding uninfluential parameters/tissue.

Methods: A global SA (GSA) was performed on Rodgers et al. mechanistic equations for tissue-to-plasma unbound partition coefficient (Kpu) predictions [3,4]. Sets of hypothetical strong basic, weak basic, acidic and neutral drugs (n=1000 for each drug class) were generated using realistic value ranges of physicochemical drug properties (lipophilicity [logP], plasma protein binding [fup], blood:plasma partition [BP] and acid/basic nature [pKa]). Partial rank correlation coefficients (PRCC) [5,6] were used to identify the most influential drug parameters within explored ranges on Kpu predictions. The significance of a non-zero PRCC value was tested using a two-sided Student's t-test. Given the relationship between lipophilicity and plasma protein binding, several degrees of correlation between logP and fup were considered [7]. In addition, the sensitivity to physiological parameters was explored by incorporating 30% variability/uncertainty on different biological parameters (fractional tissue lipid volumes, fractional tissue water volumes, and acid phospholipid and proteins levels) [8].

Results: All tissues showed comparable drug parameter sensitivities to Kpu predictions for neutral and acidic compounds, while for weak and strong bases, some tissues showed distinct sensitivities that could be clustered into 4 representative tissues (adipose, heart, muscle and lung). Given the explored parameter space of hypothetical drugs, logP and fraction of drug unbound (fup) were generally the most influential parameters (and $p<0.001$) on Kpu predictions for different drug classes. For strong bases, BP was the most influential parameter on several tissue Kpu predictions. pKa for weak bases and pKa and fup for strong bases were the least influential parameters. For acids, fup, logP and pKa had similar sensitivity ranking to Kpu predictions. The PRCC analysis from different degrees of correlation between logP and fup showed similar results with logP remaining the most influential parameters for neutrals and weak bases, while for acids and weak bases logP was generally not the most sensitive parameter. Based on the assessment of prototypical single drugs per drug class, variability/uncertainty in tissue composition data (30% CV of input) had a limited impact on Kpu predictions (<30% CV on output) for all classes except for strong bases with low fup which could reach a CV of 45% in tissue Kpu predictions. Variability/uncertainty in acid phospholipid and in proteins levels were identified as having the most impact on Kpu predictions. This impact on Kpu predictions also propagated into volume at steady (Vss) predictions (>30% CV on Vss output).

Conclusions: Based on the GSA and within certain value ranges, if a dimensionality reduction is needed less influential parameters for Kpu predictions in each drug class might be assigned fixed values in the context of Bayesian parameter estimation. Variability in tissue composition, particularly related to acid phospholipid and protein concentrations can be influential when predicting Kpu for strong bases with low fup. This study represents the first step towards the development of a systematic Bayesian framework for PBPK parameter estimation in this project.

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III-83: *Anyue Yin* Population pharmacokinetics and pharmacogenetics analysis of mitotane in adrenocortical carcinoma patients towards individualized dosing

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Introduction: Mitotane, a highly lipophilic compound with an extremely long half-life, is the only agent approved for treatment of adrenocortical carcinoma (ACC)[1]. To ensure treatment efficacy and avoid toxicity, mitotane plasma concentration is advised to be maintained between the therapeutic range of 14-20 mg/L[1], which requires therapeutic drug monitoring (TDM). However, the lack of ability to predict mitotane plasma concentrations may result in a suboptimal time period to reach the therapeutic window or unexpected toxicity[2].

Objectives: We aim to develop a population pharmacokinetics (PK) model to characterize and predict the drug concentration of mitotane in ACC patients. Subsequently, we aim to identify covariates that affect mitotane clearance and thereby facilitate mitotane dose optimization and individualization for ACC patients.

Methods: Routine mitotane TDM trough concentration data, as well as a limited amount of intensive sampling data, was collected retrospectively from patients diagnosed with ACC from the Dutch Adrenal Network.

Population PK modelling analysis was performed with NONMEM (version 7.4.1). Data below LLOQ (<4%) was omitted. Inter-occasion variability (IOV) of apparent systematic clearance (CL/F) was included and every 200 days period was defined as an occasion. Absorption rate constant was first estimated based on the data of patients who contributed drug absorption information and then fixed to analyses the full dataset.

The effects of potential covariates on parameters were evaluated. Lean body weight (LBW) of a patient was calculated with James function and the fat amount (FAT) was estimated as body weight minus LBW. DNA samples were analyzed using DMET^{TM} plus array[3] (Affymetrix UK Ltd), and SNPs with call rate ≥ 97% and minor allele frequency ≥ 0.1 were included. Association between genotypes and ETA of CL/F was first

assessed with R software (version 3.4.1), with ANOVA test or t-test which depended on the number of genotype groups. Subsequently, the effect of SNPs that were identified to be potentially related to mitotane clearance ($p < 0.05$) and other potential covariates on CL/F and apparent distribution volume (V/F) were explored. Stepwise covariate modelling (SCM) function implemented with Perl-Speaks-NONMEM was applied[4]. Both a forward inclusion ($p < 0.05$, degree of freedom=1) and a backward elimination process ($p < 0.01$, degree of freedom=1) were performed. After evaluating the model, simulations were performed to identify optimal treatment regimens for different patients.

Results: A 2-compartment model with first-order absorption and elimination best described the 881 concentration data points collected from 48 patients. Of the investigated SNPs, 12 SNPs, located in the genes CYP2B6, CYP2C18, CYP2C19, SLCO1B1, SLCO1B3, and VKORC1, were found to be potentially related to mitotane clearance. After SCM, LBW, genotypes of SLCO1B1 (rs4149057), CYP2C19*2, and SLCO1B3 (A1125 / I233M) were identified to influence CL/F of mitotane significantly, which decreased the CV% of CL/F from 67.0% to 43.4%. FAT was identified to influence the central V/F significantly. The predictability and stability of the model were confirmed to be acceptable by VPC and Bootstrap. The starting dose of an individual patient was identified by making the simulated mitotane concentration (PRED) at the 98^{th} day reach 14 mg/L. Starting by increasing the dose by 0.5g every 21 days until the target was reached or increasing by 1.5g after 126 days for patients still not reaching the target by then was demonstrated to shorten the period required to reach the target while limiting the risk of toxicity. Assuming TDM will be performed every 14 days and dose will be adjusted 7 days after blood collection, simulation results showed that increasing mitotane dose by 1.5g if the concentration < 14 mg/L, keeping dose same if the concentration is within 14-18mg/L, decreasing dose by 1g if the concentration reached 18-20 mg/L, and decreasing dose by 3g if the concentration > 20mg/L was a good protocol to maintain mitotane concentration within 14-20mg/L.

Conclusions: A 2-compartment model was demonstrated to well characterize mitotane concentrations from ACC patients. LBW, genotypes of SLCO1B1 (rs4149057), CYP2C19*2, and SLCO1B3 (A1125 / I233M) were identified to affect mitotane CL/F and FAT was identified to affect the central V/F. An optimal treatment schedule was developed by simulation with the final model.

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III-84: *Jinqiu Yin* Pharmacokinetic-pharmacodynamic modeling of colistin against Pseudomonas aeruginosa-associated biofilm infections

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Objectives:

Chronic lung infections can be challenging to treat with conventional antibiotic dose regimens due to formation of microbial biofilms [1]. The reduced antibiotic susceptibility of biofilms is mediated by several mechanisms including decreased antibiotic exposure within the biofilm and altered drug susceptibility phenotypes. *Pseudomonas aeruginosa* is one important pathogen associated with chronic lung infections, which can readily transition into a biofilm phenotype. Currently, pharmacokinetic targets to derive antibiotic dose regimens are based on assays that use planktonic cultures. However, when studying optimization of biofilm-associated infections it is important to assay antibiotic activity specifically for biofilms. Several assays to quantify antibiotic activity in biofilms are available, including the alginate bead assay [2]. The alginate bead assays are based on the generation of small alginate beads, mimicking the biofilm aggregates observed in chronic biofilm-associated infections. Pharmacokinetic pharmacodynamic (PK-PD) models quantifying dynamic relationships between drug exposure and bacterial growth or kill kinetics are increasingly used to optimize treatment strategies with antibiotics. However, these modeling approaches have primarily focused on analysis of static or dynamic time kill assays of planktonic cultures exposed to antibiotics. In the current contribution we develop a PK-PD model to characterize kill kinetics in the alginate bead biofilm assay for *P. aeruginosa* PAO1 biofilms treated with colistin.

Methods:

Data: Planktonic bacteria (*P. aeruginosa* PAO1) were immobilized in spherical alginate beads (50-100 µm), as previously described [2]. The beads were exposed for 24 hours to different concentrations of colistin ranging from 1-265 mg/L, and at different time points viable bacteria were quantified in triplicate using plating.

Model development: We tested different model structures formulated as sets of ordinary differential equations (ODEs) to describe the observed kill kinetics. A nonlinear mixed effect modeling approach was used to analyze the data. Prior to analysis bacterial counts were log10-transformed. In a first step, a natural growth model was developed. For antibiotic concentration-effect relationships we consider both linear and Hill equations.

Results:

The natural growth kinetics could be described using capacity-limited growth function, with B_{max} quantifying the maximum number of bacteria, estimated at 9.45 log10 CFU/mL (relative standard error, RSE 1%). The model for the full dataset including colistin exposures included two sub-populations of bacteria: drug sensitive (S) and resistant (R), where resistant indicated a reduce antibiotic susceptibility. A first-order transfer rate (K_{sr}) from the S to R was estimated at 0.0003 h^{-1} (RSE 38%) and included if drug is present. We estimated bacterial baseline concentrations (B_0) at the start of the experiment at 5.86 log10

CFU/mL (RSE 2%). B_0 was assumed to only consist of bacterial sub-population S. A single common growth rate (Kg) was identified for both S and R, estimated at 0.767 h^{-1} (RSE 4%). A common death rate was fixed to a previously reported value. We included two separate slope models to describe the drug dependent kill for S and R sub-populations, with slope terms for S and R estimated at 0.427 (RSE 16%) and 0.002 mg/L (RSE 7%), respectively.

Conclusions:

We successfully developed a full dynamical model to quantify the bacterial growth kinetics of *P. aeruginosa* PAO1 against colistin. The model will be used to investigate the efficacy of clinical colistin dose regimens [3].

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III-85: *Sirin Yonucu* Explaining inter-species differences to anti-PDL1 cancer immunotherapy using a translational quantitative systems pharmacology approach

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Objectives:

Tumor cells can exploit host immune checkpoints to allow them to evade eradication by the immune system. For several immune checkpoint targets, therapeutic agents have been successfully developed, and for various additional targets, drugs are being actively developed. In this context, the checkpoint receptor PD-1 is an important drug target that inhibits T cell function after activation by its ligand. Five immune checkpoint inhibitors have currently been approved for blockade of PD-1 and its ligand PD-L1 [1]. The anti-tumor activity of these drugs is seen in a subset within a broad range of cancers, and the response is durable when it is achieved [2]. However, there are pressing questions about who will benefit from this treatment, what is the best dosing schedule and how should we combine them with other drugs to maximize the anti-tumor response. Research on these questions would also reveal the ways to convert non-responding patients to responders of immunotherapy. Preclinical models are crucial to evaluate novel drugs and drug targets. However, there are currently important discrepancies between preclinical and clinical results for immune checkpoint inhibitors, and several drug candidates have recently failed in clinical studies. An important reason for this could be the complexity of the underlying immune-pharmacological mechanisms that mediate the ultimately observed response.

Quantitative systems pharmacology (QSP) approaches can facilitate understanding of inter-species differences in response to immune checkpoint inhibitor therapy and may guide the design of optimal dose regimens for evaluation in clinical trials. In the current analysis, we aimed to develop a QSP model for tumor-immune system interactions for treatment with the anti-PD-L1 inhibitor pembrolizumab, based on a previously developed mathematical model in mice [3].

Methods:

The previously-developed mathematical model by Kosinsky et al. [3] consists of a system of ODEs for the immune system such as inactivated and activated T cells, PD-L1, dendritic cell maturation (DCm), systematic antigen presentation level (Agsys), immune suppressive cells accumulation (ISC) and immune activation rate (IAR) as systems variables to describe the tumor growth dynamics. We first considered the human pharmacokinetic (PK) of the drug using the study of Ahamadi et al. [4] and applied them to the model equations. Subsequently, we identified human parameters from clinical datasets in combination with principles of allometric scaling. For undetermined parameters, we used parameter sensitivity analysis to identify parameter sets that can reproduce clinical response as described in Chatterjee et al. [5].

Results:

The scaled human QSP model was able to describe similar treatment response distributions for different dosing regimens previously reported [5]. Sensitivity analysis of the model showed that the most sensitive parameters are tumor growth rate, T cell kill rate and sensitivity of dendritic cell maturation to tumor cell death rate. Variation in the distribution of drug response among patients could be reproduced by adding inter-patient variability to tumor growth rate. The initial tumor size in human simulations was much larger

than the largest mouse tumors given in Kosinsky et al. [3]. Lumped parameters that determine ISC and IAR were re-evaluated since the magnitudes of these quantities depend on the tumor size. Reproduction of PD-L1 levels of patients at the start of the therapy is achieved by the addition of inter-patient variability to the parameter that stands for the sensitivity of PD-L1 expression up-regulation to activated T cell count. This parameter was fixed based on the fact that nearly half of the population had more than 50% of tumor cells with membranous PD-L1 staining [5].

Conclusions:

Simulation results showed the critical parameters that determine the tumor response to the drug in humans were tumor growth rate, T cell kill rate and sensitivity of dendritic cell maturation to tumor cell death rate. To achieve a similar inter-individual variation with the clinical outcomes, we needed to add inter-individual variability in tumor growth parameters in our model framework.

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III-86: *Jurij Zdovc* Population pharmacokinetic modeling of cisplatin in patients with small cell lung cancer using informative priors

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Objectives: The small cell lung cancer (SCLC) is the most aggressive type of lung cancer and is diagnosed in around 15% of all lung cancer cases. Cisplatin in combination with etoposide is recommended as a standard, first line of treatment for the extensive stage SCLC. Cisplatin is associated with dose-limiting side effects such as nephrotoxicity, nausea, vomiting and ototoxicity [1, 2]. A two-compartment model was previously reported to describe the pharmacokinetics of cisplatin when administered in a form of intravenous infusion. The dosing is conventionally adjusted with respect to the body surface area (BSA), however, BSA alone cannot explain all inter-individual variability. Moreover, estimated pharmacokinetic parameters reported from several population pharmacokinetic studies vary substantially, leading to a high variability in the estimated exposure [3–7]. Thus we aim to assess the exposure of SCLC patients to cisplatin with population pharmacokinetic approach, comparing several clinical studies.

Methods: This was a prospective clinical study in 17 patients with SCLC, treated with cisplatin-etoposide at the University Clinic of Respiratory and Allergic Diseases Golnik. Cisplatin dose was based on BSA (55 – 85 mg/m^2; calculated with the Mosteller equation [8]) and was administered as a 1-hour infusion on the second day of each treatment cycle. Treatment cycle was repeated every three weeks. Plasma samples (n = 100) from total of 58 treatment cycles were collected between 7 minutes and 7 hours after the start of the infusion. Population pharmacokinetic analysis was performed using the nonlinear mixed-effects modelling software NONMEM® 7.3. Based on the previous studies we analyzed a one- and two-compartment model with and without the informative priors from published population pharmacokinetic studies [3–5]. Priors were included in the model as a $PRIOR block in the form of NWPRI file. From the estimated individual cisplatin clearance (CL) and the dose administered we calculated the AUC for every cycle for every patient (AUC = Dose/CL_i). The study was approved by the Slovenian Ethics Committee for Research in Medicine (approval ref. no. 0120-220/2018/3) and was carried out according to the Helsinki declaration.

Results: There were 6 females and 12 males in the study group. Median age was 63 years and median creatinine clearance was 85.1 mL/min, which indicated a normal renal function. The medians of body weight and BSA of our patients were 84 kg and 2.0 m^2, respectively, which was higher than in the groups of reported clinical studies. Without the use of priors, we were able to fit a one-compartment model to our data. However, considering our small sample size and low power of our study it was possible our data was uninformative. Therefore, the use of a one-compartment model could be biased, since the pharmacokinetics of cisplatin is usually described by a two-compartment model. Using the informative prior distribution of pharmacokinetic parameters from three clinical studies, the structural model was a two-compartment model. Estimate of CL depended on the study from which the prior was used. However in all cases the final estimate of CL was higher than initial prior estimate, with final estimates ranging between 28.9 L/h and 45.1 L/h. This could imply our patients had a higher CL than patients from other studies. Moreover, goodness-of-fit indicated all models with priors overestimated the plasma cisplatin concentrations. Besides, CL estimated with a base one-compartment model without priors was 65 L/h. This is in accordance with the hypothesis that our patients had a higher CL. The underlying reason for deviations

is currently unknown, however, we hypothesize higher BSA of our patients could be involved. The disease could be a factor as well, since this is a first study of cisplatin in patients with SCLC. From this perspective, the results indicate our patients were underexposed to cisplatin. The estimated individual exposure of our patients to cisplatin across all models ranged between 1.55 mg*h/L and 4.81 mg*h/L.

Conclusions: Despite cisplatin has been used for several years, the variability in pharmacokinetics and patients' exposure is still high. Further studies are necessary to identify additional factors influencing exposure of patients with SCLC.

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III-87: *Yang Zhang* Ways to improve the efficiency of pharmacometric model implemented in R using deSovle – an example with a PK model for ADC

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Introduction:

Implementation of a pharmacometric model in R is a prerequisite for accomplishing different tasks – from a demonstration plot to a full scale simulation; from parameter estimation to evaluating a trial design.

Numerous attempts to reduce the burden of implementing pharmacometric models in R have been made which resulted in new packages on CRAN as well as github. Yet when drilling down to the implementation of pharmacometric models by numerically solving the ordinary differential equations, LSODA still remains the dominating algorithm and is available in one of the most widely used packages for solving ODEs, deSolve.

This work is intended to implement a relatively complex compartmental pharmacometric model in R ultilizing the default method (LSODA) of deSolve and compare the performance in terms of time of execution among different implementations.

Objectives:

To check different implementations of a PMX model in R and compare the time needed to execute

Methods:

A PK model for an antibody drug conjugate (ADC) was chosen as an exemplary model due to its complexity as well as a target binding component which is used more and more often. The model consists of 7 compartments with 2 compartments for the ADC, 3 for the toxophore and 2 for the active agent metabolized from the toxophore.

The model was first implemented purely in R. Then the computation of the derivatives for each compartment (i.e., the right hand sides of the ODEs) was conducted using compiled code written in C++ (via the Rcpp package[1]), C or Fortran (using the interfaces provided by R)[2]. Explicitly computing the Jacobian matrix was added using the same way as the calculation of the r.h.s of the ODEs – R, C++ via Rcpp, C or Fortran. In total, eight implementations were compared in terms of total execution time for 100 repetitions.

The execution environment was a server with CPU base frequency of 2.5GHz running Red Hat Enterprise Linux Server release 6.9 (Santiago). R (3.2.5) with deSolve (version 1.13) and Rcpp (0.12.4) was deployed and the compiler used was GCC version 4.4.7.

Results:

For the implementation without explicit computing the Jacobian matrix, the pure R version took more than 1000 seconds to complete 100 executions while using Rcpp could reduce the time to about 3 minutes

(183.015 sec). Using C and Fortran further reduced the time to less than 1.5 seconds (1.379 second for C implementation and 1.402 sec for Fortran implementation). On the other hand, adding a function to compute the Jacobian matrix increased the efficiency of the ODE solver for all except the C version. For the pure R implementation, adding specific codes for the Jacobian shortened the execution time to 28.511 sec. For C++ version, there was an almost 30 times increase in speed (6.232 sec for the version with explicit Jacobian computation compared to 183.15 sec without). Unexpectively, the C implementation with explicit function for Jacobian actually prolonged the execution to 9.810 sec.In contrast the Fortran implementation with separate subroutine for Jacobian was the fastest one among those tested which needed just 0.271 sec to provide the results.

Conclusions:

When implementing a pharmacometric model in R several approaches are available to improve the performance. As shown in this example the efficiency gain can be quite large. Depending the experience of the user, explicit calculation of Jacobian matrix and / or conducting parts of the computation using compiled codes (C++, C or Fortran) may be considered to accelerate the process.

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III-88: *Chenyan Zhao* Colistin to overcome resistance to ciprofloxacin - Quantifying combined effects of colistin and ciprofloxacin against four E. coli strains with different ciprofloxacin susceptibility in an in silico PKPD model

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Introduction/Objectives: Resistance to ciprofloxacin (CIP) is common for *E. coli* worldwide and colistin (CST) may overcome and/or prevent emergence of resistance when co-administered. This study aimed to quantify any CIP and CST interaction by an *in silico* PKPD model to explore if the combination results in an improved anti-bacterial effect compared to either drug alone.

Materials/methods: *In vitro* static time-kill experiments were performed with four *E. coli* strains: MG1655 WT (MIC_{CIP}=0.023 mg/L, MIC_{CST}=0.5 mg/L), two isogenic mutant strains (MIC_{CIP}=0.38 and 1.0 mg/L, MIC_{CST}=0.5 mg/L) and one clinical strain (MIC_{CIP}=0.047 mg/L, MIC_{CST}=0.75 mg/L). Bacteria were exposed to each of the antibiotics in the concentration range 0.0625–16xMIC for up to 32 hours. CST concentrations were measured and an *in silico* model was built to describe the change in bacteria-free CST concentrations in the tubes[1]. To characterize the bacterial counts under CST monodrug exposure, a previously developed model for *P. aeruginosa* exposed to CST[2] was adopted and refined. The CIP effect on all 4 strains have been characterized earlier[3]. Optimal design (OD) based on the combination of monodrug models facilitated the selection of concentrations and sampling times for the drug combination experiments. Interaction models, quantifying the combined antibiotic effect on the bacteria, were investigated. The drug effect under various clinically achievable doses of CIP and CST were compared using predictions from the final PKPD model.

Results: Overall 300 time-kill curves were available for analysis (99 curves for CST as monodrug, 129 for CIP monodrug and 72 for CST and CIP in combination). During PKPD modelling, CST starting (0 hour) concentrations were set to the measured with inter-experimental variability (fixed to 10% CV). Time-varying CST concentrations were satisfactorily characterized by a model with two compartments representing bound and unbound CST. The CST monodrug model described the data well, with the four strains sharing the same model structure and the three isogenic strains sharing parameter values. CST resistance was modelled by adaptive resistance[2] with the resistance onset rate being drug concentration-independent. Through OD, the chosen concentration range for combination experiments was CIP of 0.125-2xMIC and CST of 0.125-0.375xMIC. The general pharmacodynamic drug interaction (GPDI) model[4] collapsed to a concentration-independent interaction function, which could fit the interaction data better than a power interaction model[5] (dOFV=604, *df*=2). The interaction parameters were assumed to impact the drug potency (EC50). The parameter estimates indicated that when co-administered, CST increased CIP EC50 by 21.5% and 47.6% for clinical and three isogenic strains, respectively. The impact of CIP on CST was negligible except for the clinical strain where CST EC50decreased by 36.6%. Model predictions indicated that CST+CIP has a positive combination effect for the clinical strain with a higher and longer lasting bacterial killing than for either drug alone. For the isogenic strains, the superiority of the combination over monodrug exposure was dependent on the relative exposure of the two drugs, but not worse than CST alone when the CIP monodrug effect appeared to be higher than the combination.

Conclusions: A PKPD model was successfully developed to characterize observed *in vitro E. coli* bacterial counts over time when exposed to CIP and CST alone and in combination. A positive combination effect of CIP and CST were seen in most cases, but the interaction was both strain- and concentration-dependent. The clinical benefit of the combination needs to be further explored.

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III-89: *Xuan Zhou* Model-Based Estimation of Probability of Pharmacological Success for CNS Compounds

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Introduction
At the early stage of drug development, it's important to raise a question: what proportion of patients can be expected to achieve adequate pharmacological response without unacceptable toxicity? The answer helps us quantify a compound's pharmacology strength for supporting a progression decision, for assessing the rigor of clinical trials to test the compound and the target, and for differentiating candidate assets. We define the probability of pharmacological success (PoPS) as the probability that a desirable proportion of patients achieve the required level of pharmacological response. This probability is based on our understanding of the target and the compound, such as target dynamics, drug level at site of action and duration of action. We present a GSK funded case of using simulations to evaluate the PoPS of a therapy for treating a brain disease, where target X is present both inside and outside the brain, and two compounds A and B have different brain penetration. The therapeutic approach aims to reduce the target's activity in the brain, while preserving some of its peripheral activity for safety.

Objectives
To understand 1) what proportion of patients can achieve the required pharmacological response, which is to normalize brain target activity and maintain 10% peripheral activity; 2) what PK or PD parameters have the most significant impact on this proportion; 3) what the trial success rate will be based on certain predefined criteria; 4) what the optimal dose will be for each compound; 5) what the adequate sample size will be in a study to observe the required pharmacological response; and 6) how do the two compounds compare in the above aspects.

Methods
Human pharmacokinetics for both compounds were predicted from non-clinical data. Assuming concentration fluctuation is low, we modelled the steady-state average free concentration as a simple Emax function for both central and peripheral effects without delay. The IC50 value derived in vitro from human cell lines were used, and the maximal inhibition was assumed to be 100%. A moderate 30% between-subject variability was assigned to the pharmacokinetic and pharmacodynamic parameters. Where there was parameter uncertainty, a Bayesian prior of uniform distribution over a credible range was applied. Subject-level data (N=1000) for 1000 trials were simulated taking into account parameter uncertainty (elevation folds of target activity Fe in patients and unbound brain/plasma concentration ratio kp,uu). Success criteria for a clinical trial were set as ≥80% subjects with required activities in the brain and in the periphery, while <5% subjects with undesirable peripheral inhibition. The percentage of the 1000 simulations which met the criteria was calculated as the success rate, or PoPS. The optimal doses for the two compounds were selected from the peak level of the success rate. We also tested the required sample size of a potential trial that can reflect the success rate for the overall population. All simulations were performed by using the Simulx function of the R package mlxR (Lixoft, Orsay, France).

Results
With the assumed parameter uncertainty, typically 83.7% patients given compound A can have sufficient brain response (target activity normalized to the level as healthy subjects') without undesirable peripheral

response (maintain at least 10% as in healthy subjects'), while the percentage for compound B is 78.4%. The most impactful parameter for this proportion and the subsequent overall PoPS is Kp,uu, and Fe has a major effect on the dose selection. The predicted population optimal dose for compound A was 32 mg/day with 72.4% maximal success rate, while the optimal dose for compound B is 10 mg/day but with only 35% maximum success rate. A sample size of at least 35 patients is required to reliably reflect the probably of success for the population. Conceivably, the trial success rate could be enhanced by individualized dose titration using a peripheral pharmacology biomarker.

Conclusion

This work helped us understand the strength of the compounds' intrinsic pharmacological profiles and the pharmacological underpinning of the trial, as well as the impact of dose, patient population and sample size. It highlights the importance of the "PoPS" concept and illustrates the application of a simulation-based approach for its estimation.

III-90: *Tom Zwart* Population pharmacokinetics and limited sampling of iohexol as a renal function marker in renal transplant donors

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Objectives: Iohexol plasma clearance (IPC)-based glomerular filtration rate (GFR) estimation is a promising strategy for renal function evaluation. This method, which encompasses a single intravenous injection of iohexol, is particularly viable for populations without chronic kidney disease in which estimated GFR is not accurate enough or in which 24 h creatinine clearance is not feasible [1]. Current IPC-based GFR estimation methods typically rely on extrapolation of the iohexol area under the concentration-time curve (AUC) of only the linear terminal elimination phase, mostly using linear regression and the Bröchner-Mortensen correction to estimate the full AUC [2, 3]. The iohexol AUC divided by the dose then yields its plasma clearance, which reflects the patients' GFR. The need to obtain up to seven blood samples during the linear elimination phase is an important disadvantage and has hampered the implementation of this method in routine clinical care. Here, a population pharmacokinetic (popPK) model and limited sampling strategy (LSS) were developed to provide a clinically feasible method for IPC-based GFR estimation.

Methods: Blood samples (n=328) drawn at 5 min up to 4 h after iohexol injection were available from 49 potential renal transplant donors screened at Leiden University Medical Center. Nonlinear mixed-effects modelling was applied to develop a popPK model using NONMEM, and the PsN Toolkit[4] and Piraña[5] as modelling environment. Graphics and LSS statistics were performed in R. The first-order conditional estimation method with interaction (FOCE-I) was applied throughout the model development. Model selection was based on a statistically significant change in the objective function value (?OFV) between a modified model and its precursor, with ?OFV>6.63 ($p<0.01$, df=1, χ^2 distribution) resulting in selection of the modified model. Model evaluation was performed using standard diagnostic plots and visual predictive checks (VPC). Internal validation of the final model was performed using a bootstrap analysis (n=1000). The final model was used to develop a LSS based on the individual predicted GFR. The individual predicted GFR as calculated with the final model and the full dataset (GFR_{full}) was compared to the GFR as calculated with one, two, three or four sample(s) drawn during the first 3 h (GFR_{lss}). LSS predictive performance was assessed using the Pearson correlation coefficient (r^2), mean percentage prediction error (MPE), root mean squared percentage prediction error (RMSE) and the percentage of GFR_{lss} exceeding the 5% margins around the GFR_{full}.

Results: Iohexol pharmacokinetics were best described by a two-compartmental first order elimination model with proportional residual error and a full variance-covariance matrix of random effects. Total body clearance (CL), intercompartmental clearance (Q) and the volumes of distribution of the central (V_c) and peripheral (V_p) compartments were 4.89 L h^{-1} (6% RSE), 7.26 L h^{-1} (25%), 9.20 L (6%) and 5.48 L (14%), respectively. Interindividual variability for CL, Q, V_c and V_p was 34.4% (14% RSE; 0% shrinkage), 86.2% (18%; 11%), 35.2% (12%; 6%) and 41.7% (44%; 9%), respectively. Random residual variability was 5.4% (42%; 25%). The VPC of the final model showed a complete overlap between predicted and observed intervals. The bootstrap analysis showed adequate parameter reliability. The best GFR_{lss} for one, two, three and four sample-based strategies were iohexol C_{2h} (r^2: 0.968; MPE: 3.04%; RMSE: 9.35%; <5% discordance: 73.47%) ,

$C_{30min,3h}$ (0.997; 0.97%; 2.03%; 95.92%), $C_{5min,30min,3h}$ (0.999; 0.67%; 2.04%; 95.92%) and $C_{30min,1h,2.5h,3h}$ (0.996; 0.62%; 1.93%; 97.96%), respectively. Two LSS were of particular clinical interest; $C_{5min,2h,3h}$ and $C_{5min,1h,2h,3h}$, as these could provide options for blood draw alignment with sampling for abbreviated AUC-based therapeutic drug monitoring of tacrolimus ($C_{trough,2h,3h}$)[6] and mycophenolic acid ($C_{trough,1h,2h,3h}$)[7, 8] in transplant recipients. Both $C_{5min,2h,3h}$ (0.993; 0.16%; 3.07%; 95.92%) and $C_{5min,1h,2h,3h}$ (0.997; 0.36%; 2.22%; 95.92%) showed good predictive performance.

Conclusions: The iohexol popPK model and LSS provide some clinically feasible and accurate options for IPC-based GFR estimation and pave the way for implementation of this method in routine clinical care. This approach fills a clear gap for clinical situations in which current GFR estimation methods are not satisfactory or not clinically feasible.

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IV-01: *Christiane Dings* Mathematical modeling of the oral glucose tolerance test in pre-diabetic patients: An IMI DIRECT study

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Objectives: The oral glucose tolerance test (OGTT) is well-established and commonly used for the diagnosis and study of type 2 diabetes mellitus (T2DM). However, the individual response to the standardized load of 75 g glucose shows very high inter-individual variability. Anthropometric parameters like high BMI and waist-hip-ratio are well-known risk factors for developing type 2 diabetes and influence OGTT results. Therefore, to distinguish between variability in glucose tolerance caused by these anthropometric factors and individual disease progression, we aimed to develop a mathematical model that simultaneously describes glucose, insulin and c-peptide levels during OGTT which included anthropometric factors as covariates.

Methods: The model was developed using data from the Diabetes Research on Patient Stratification (DIRECT) study [1], in which 2282 pre-diabetic participants were included which had with frequently sampled glucose, insulin, and c-peptide measurements during OGTT [2]. The model was developed using non-linear mixed-effects modeling techniques implemented in the software NONMEM (version 7.3.0). Covariate modeling was performed stepwise. First, covariates were preselected in R (version 3.2.5) using generalized additive modeling with the NONMEM output of the empirical Bayes estimates and Akaike information criterion as the selection criterion. Then, the preselected covariates were included in the model in NONMEM followed by backward elimination.

Results: The developed model simultaneously describes glucose, insulin, and c-peptide using a one-compartment turn-over model for each biomarker. The data was characterized best when oral glucose absorption was described by a transit model with a first-order absorption rate and one transit compartment. Glucose utilization followed a second-order process dependent on glucose and insulin concentrations. Endogenous glucose release was decreased exponentially by the change in insulin levels. A Hill function dependent on the glucose concentration was used to describe the release of c-peptide and was multiplied by a bioavailability factor to depict the release of insulin, accounting for its pre-systemic hepatic clearance. The effect of incretin hormones was implemented in the Hill function on the effect of glucose in an additive way. C-peptide elimination followed a first-order, insulin degradation followed a saturable process. The effects of continuous covariates were implemented using a power model normalized to the population medians: BMI (median 27.5 kg/m²) was found to positively influence fasting insulin and c-peptide concentrations. A 10% higher BMI resulted in an 11.5% rise in insulin AUC. Waist circumference (median 99 cm) had a positive effect on the maximum c-peptide release rate and the fasting glucose concentration and a negative effect on the glucose utilization rate. A 10% higher waist circumference resulted in a rise in glucose AUC of 11.3%. Glucose utilization was further dependent on body height (median 175 cm) and a change to 185 cm height resulted in a 7.5% lower glucose AUC. Female sex was found to have an influence on the apparent volume of distribution of glucose (94.1% higher), the glucose absorption rate constant (65.4% higher), fasting glucose concentration (5.8% lower) and glucose sensitivity (10.2% lower). The glucose AUC was 6.9% lower in females than in males. However, there are significant

differences in these model parameters between the four study centers in which the study was conducted at and for which the proportion of included females was different (0-72.1% females). The precision of all parameter estimates was excellent (relative standard error <12%). The inter-individual variability (IIV) was between 10.0 and 95.7%CV. The covariates explained up to 9.1%CV of the IIV.

Conclusions: A mathematical model describing the OGTT in pre-diabetic participants was developed successfully. Higher waist circumference and BMI were influencing several model parameters linked to lower glucose tolerance. The effects of sex could not be explained by what is known so far and seem to be driven by the difference between the study centers. The model is a step towards characterizing T2DM disease status while taking the physical condition of the subject into consideration.

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IV-02: *Anne-Gaelle Dosne* Exposure-response analysis of erdafitinib and pharmacodynamic-guided dose individualization in patients with locally advanced or metastatic urothelial carcinoma

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Erdafitinib is an oral, pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor, in development for the treatment of locally advanced or metastatic urothelial carcinoma (mUC) and other cancers with certain FGFR genetic alterations. Consistent with the erdafitinib mechanism of action, serum phosphate (PO4) is a pharmacodynamic (PD) marker of FGFR engagement, and proposed to be a biomarker for efficacy and safety. To maximize efficacy and limit toxicity, erdafitinib dosing in the pivotal, Phase 2, multicenter, open-label BLC2001 study (NCT02365597) was adapted for each individual based on their PO4 concentrations after 2-4 weeks of erdafitinib treatment.

Objectives:

To characterize the exposure-response (ER) relationship between PO4 and selected efficacy and safety endpoints based on data from study BLC2001, to confirm PO4 as a biomarker for erdafitinib dose individualization.

Methods:

The ER analysis was performed using data from patients randomized to one of two dosing regimens: 6 mg group (6 mg erdafitinib daily with PD-guided up-titration to 8 mg daily, based on PO4 at Day 28); and the 8 mg group (8 mg erdafitinib with PD-guided up-titration to 9 mg based on PO4 at Day 14). The relationship between erdafitinib exposure and PO4 concentrations was described earlier using a population PK-PD model[1], which was used to conduct simulations to support the proposed PD-guided dosing regimen[1]. Individual average PO4 values were derived based on posthoc PK and PK-PD parameter estimates, which were used as the exposure metric for ER analysis. Efficacy endpoints included objective response rate based on best response (ORR), progression-free survival (PFS), and disease control rate (DCR). Safety was assessed by incidence of selected clinical safety endpoints: eye disorders, central serous retinopathy (CSR), nail disorders, palmar-plantar erythrodysaesthesia (PPES) and skin disorders. The ER relationship between average PO4 and ORR, PFS, or adverse events (AE) was evaluated using either logistic regression or Cox models. Baseline prognostic factors were also evaluated in these models. The analysis was carried out using the R Project for Statistical Computing, version 3.4.1 or higher for Windows[2].

Results:

For the efficacy ER analysis, data from 156 chemotherapy-relapsed/refractory patients in the 6 mg group (n=68) and the 8 mg group (n=88) were available. The safety ER analysis included data from 177 patients (n=78 in the 6 mg group and n=99 in the 8 mg group). Higher average daily PO4 from the start of erdafitinib up to the first response assessment (planned at 6 weeks) was associated with significantly higher ORR, with the type of FGFR alterations included as a significant covariate (Odds Ratio (OR): 1.38; 95%, CI: 1.02-1.86 for 1 mg/dL increase in PO4; p=0.04), longer PFS (Hazard Ratio (HR): 0.80; 95%CI: 0.67-0.94 for 1 mg/dL

increase in PO4; p=0.01), and greater DCR (by PO4 terciles, p<0.001). Results showed that achieving PO4 concentrations above 5.5 mg/dL following PD-guided individualized up-titration and recommended dose modification was expected to be associated with clinically relevant improvement in ORR and PFS in the target population. Further, the PK-PD model revealed an attenuation of the erdafitinib effect on PO4 over time, contributing to decreasing PO4 levels. Including PO4 as a time-dependent covariate in the Cox model for PFS led to a similar HR estimate compared to average PO4 up to 6 weeks, and showed that decreasing PO4 levels over time are likely not relevant for PFS. The incidence of key AEs of any grade, including eye, nail or skin disorders, as well as CSR and PPES, had a positive and statistically significant relationship with average daily PO4 up to the day of event (OR range 1.61-2.84 for 1 mg/dL increase in PO4). The magnitude of the association was strongest (OR>2 for 1 mg/dL increase PO4) for nail and eye disorders.

Conclusions:

The relationship between PO4 and efficacy/safety as characterized in the ER analysis justified the erdafitinib dose individualization to maximize the benefit/risk ratio of erdafitinib treatment.

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IV-03: *Erwin Dreesen* A population pharmacokinetic and exposure-response model to support therapeutic drug monitoring during vedolizumab induction therapy

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Objectives: Vedolizumab (VDZ) is a monoclonal antibody used to treat patients with ulcerative colitis (UC) and Crohn's disease (CD). Patients receive fixed 300 mg IV doses of VDZ at week (w)0, w2 and w6 (induction therapy) and q8w thereafter (maintenance therapy). Despite a significantly higher response rate to VDZ than to placebo, only a minority of patients achieved disease remission upon VDZ induction therapy [1-3]. VDZ exposure differs widely between patients and exposure-response (E-R) relationships have been established [4]. We previously demonstrated that VDZ dose optimisation to a w2 trough concentration (TC)>28.9 mg/L predicted 75% of patients with UC to achieve endoscopic remission (ER; decrease in Mayo endoscopic subscore [MES] from 3 [severe disease] or 2 [moderate disease] at baseline to 1 [mild disease] or 0 [inactive disease] at w14 of therapy). We aimed to develop a population pharmacokinetic (popPK) model and an E-R model to support individualised VDZ dose optimisation to a predefined TC target and the associated therapeutic outcome.

Methods: A total of 939 consecutive trough samples (from w2 to w30) of 178 patients (66 UC, 112 CD; excl. 1/179 patients with antibodies to VDZ) was used to develop a popPK model [4]. We analysed these data under a known 2cmt model with parallel linear and nonlinear clearance by using prior distributions from the GEMINI popPK model [5] to support estimation of PK parameters that were poorly supported by the current data (NONMEM 7.4 with $PRIOR). Classical stepwise covariate selection procedure was employed (forward α=0.01, backward α=0.001). An E-R Markov model was implemented to explore the relationship between individual model-predicted VDZ TC at w2 and the probability of achieving ER at w14 in patients with UC (incl. 54/66 patients who had $MES_{baseline}$>1). The predicted VDZ TC were modelled to affect the transition probabilities between MES states from baseline to w14 [6]. Simulations were performed using Berkeley-Madonna 8.3.18.

Results: Our model with fully data-driven estimation of the linear clearance (CL_L; 0.207 L/day [3%], typical value [relative standard error]) and volume of distribution in the central compartment (V_c; 4.62 L [9%]) showed good predictive ability. Linear terminal elimination half-life of VDZ was 23.2 days. Lower albumin, mean platelet volume and haemoglobin, and higher C-reactive protein and fat-free mass [7] were associated with higher CL_L, thus predicting lower VDZ exposure. Only 11% and 4% of the interindividual variability (IIV) of $CL_L$and V_c was explained by these covariates, leaving 28% and 42% of the IIV unexplained.

Given the large unpredictable IIV and the absence of a safety exposure limit, it is reasonable to provide an optimised, fixed starting dose to all patients [8]. Optimising this starting dose from 300 mg to 600 mg predicted the probability of attaining the 28.9 mg/L w2 target to increase from 44% to 96% (N=2000 simulated patients). Model-based dose individualisation may be implemented from w2 onwards to target all patients to the w6 exposure target and reduce drug expenditures due to unnecessary overexposure.

ER was achieved in 32/54 patients with UC. The objective function value (OFV) dropped with 18.2 points from the null model, where transition probabilities between MES were driven by chance alone, to the E-R model informed by the individual predicted VDZ TC at w2. A VDZ TC at w2 of 7.0 mg/L [31%] was estimated

to yield a 50% probability of going from $MES_{baseline}$3 to MES_{w14}2. A VDZ TC at w2 of 14.1 mg/L [28%] was estimated to yield a 50% probability of going from $MES_{baseline}$ 2 to MES_{w14} 1 or 0. Targeting all patients in our cohort (63% and 37% at $MES_{baseline}$ 3 and 2, resp.) to the previously established 28.9 mg/L VDZ TC at w2 predicted a 59% probability of achieving ER:

0.63x[(28.9/7.0)/(1+(28.9 /7.0))x(28.9 /14.1)/(1+(28.9/14.1))]+0.37x[(28.9/14.1)/(1+(28.9/14.1))]
=0.63x0.54+0.37x0.67
=0.59

Conclusions: Patients with UC may benefit from a double VDZ starting dose. Our models may be implemented in a therapeutic drug monitoring (TDM) software tool to support dose optimisation for precise attainment of exposure targets after w2 [4] and the associated outcome probabilities. TDM can aid the go/no-go decision for continuing to VDZ maintenance therapy. When a patient does not achieve ER despite 'sufficient' VDZ exposure, pharmacodynamic failure is implicit and the patient may be switched to therapy with another mechanism of action.

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IV-04: *Ronan Duchesne* Identifiability in nonlinear mixed effect models: the example of in vitro erythropoiesis

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Introduction:

Mounting evidence demonstrates the importance of heterogeneity in biological processes. This increasing awareness has accompanied the development of Nonlinear Mixed Effect Models (NLME) in the last decades, to describe data involving an important amount of variability.

NLME consist in models in which parameters are defined by distributions of random variables instead of constant values. Different samples from these random variables model the repeated measurement of the same process on different individuals belonging to the same population.

Yet, the choice of the parameter distributions to be used in NLME might not be straightforward from raw data. More generally, it might be difficult to recover precise parameter estimates from small datasets. This difficulty at estimating precise parameter values is known as identifiability issues.

When confronted with a unidentifiable model (i.e. data are not sufficient to estimate all parameters), one essentially has two options: trying to generate novel, more informative, data in order to characterize all parameters; or trying to reduce the model in order to have fewer parameters to estimate, and ultimately facilitate their estimation.

The first one can usually be completed by using a step of experimental design, for which several algorithms already exist (1). However, it remains unclear how to proceed when reducing a NLME to make it identifiable. More importantly, the question of how to assess, or even define, the identifiability of NLME is mostly an open problem (2). Most of the current methods quantify the uncertainty on the parameter estimates using the Fisher Information Matrix (FIM), which is proven to render biased results (3).

Objectives:

This work aims at two objectives. Most importantly, we want to devise a procedure to reduce a NLME in order to make it identifiable. Thus, we also look for an empirical way of assessing the identifiability of a NLME without using the FIM.

Methods:

We address these issues through the example of a NLME for the dynamics of the in vitro erythropoiesis. Erythropoiesis is the process by which mature red blood cells are produced by the differentiation of immature progenitors in the bone marrow. These progenitors can either keep self-renewing, or engage into differentiation. A variety of mathematical models have focused on describing the dynamics of erythropoiesis in vivo, and we recently described a model focusing on the kinetics of cell populations differentiating in vitro (4), which we proved to be identifiable. Our NLME is based upon this previously described dynamical model.

We use experimental cell counts of different cell populations, at regularly spaced time points during the course of erythroid differentiation, to estimate model parameters. These parameters are the proliferation and differentiation rates of the cells in the culture. The population of individuals to be fitted by the model is made of repeated samples of this experiment, each repetition giving qualitatively similar though quantitatively different results due to inter-individual (*i.e.* inter-experiments) heterogeneity. We implemented the model in Monolix (5).

Results:

We illustrate the difficulty of fitting whole parameter distributions from such experimental datasets (meaning that our model is unidentifiable). First, we use an approximation of identifiability based on the random sampling of the initial guesses of the parameters estimates, and the comparison of the resulting estimated parameter values (2). We say that a parameter is unidentifiable when different initial guesses lead to different parameter values which render the same likelihood value (3). We then elaborate a simplified version of the model, with less parameters to be estimated, that is identifiable. Using the correlations between population parameters estimates, we reduce the number of fixed effects parameters to estimate. Then, we compare the population and individual parameters distributions, by the empirical shrinkage of the individual random effects, to simplify the random effects structure. The improvement of the parameter identifiability can be measured by the decrease in the standard deviation of the parameter estimates. In our final model, depending on the parameters, this ranges from 10% to 50% of the standard deviation in the initial model.

Conclusions:

We developed an empirical stand-in of identifiability for NLME, and we demonstrate how to use it for model reduction. In the end, we improve the estimation of parameters in our NLME, which we will use for predictive purposes in the future.

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IV-05: *Vincent Duval* A continuous-time Markov model (CTMM) for investigator's global assessment (IGA) score in moderate-to-severe atopic dermatitis treated with subcutaneous nemolizumab.

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Objectives: To characterize the time-course and exposure-response relationship of the investigator's global assessment (IGA) score in subjects with moderate-to-severe atopic dermatitis (AD) treated with subcutaneous nemolizumab, a humanized antibody against interleukin-31 receptor A.

Methods: A total of 3,818 IGA scores collected from 486 AD patients were available from two randomized placebo-controlled clinical studies: a phase 2a safety and efficacy study (CIM003JG: N = 261, dose range: 0.1-2 mg/kg Q4W) [1] and a phase 2b dose-range finding study (RD.03.SPR.114322: N = 225, dose groups: 20 mg loading dose (LD) + 10 mg , 60 mg LD + 30 mg or 90 mg Q4W) [2]. The 6-point IGA scale from CIM003JG (ranging 0-5) was adapted into the 5-point IGA scale from RD.03.SPR.114322 (ranging 0-4) by lumping scores of 4 and 5 into one "severe" category. In addition, the proportion of observed scores of 0 was small (1.8%) and therefore lumped together with scores of 1 in the analysis. Longitudinal nemolizumab serum concentrations were described by a one-compartment distribution population pharmacokinetic (popPK) model with linear elimination, firstorder absorption with lag time and dose effect on bioavailability. Inter-individual variability (IIV) was included in clearance (CL), volume of distribution (V) and the absorption rate constant. CL and V were correlated at an individual level. Concentrations were log-transformed for analysis. Hence, the residual error was additive in the log domain. Covariate effects of serum albumin on CL and body weight on CL and V were identified. A previously developed continuoustime Markov model (CTMM) [3] was extended to describe longitudinal IGA scores. The CTMM assimilated the probability of each IGA score to a compartment amount and modelled the ascending (toward worse scores) and descending (toward better scores) transitions between compartments. Linear and non-linear drug effects driven by model-predicted daily concentrations and placebo effects were evaluated on the rate constants of ascending transitions (λasc) and descending transitions (λdesc). The effect of covariates (age, body weight, sex, and baseline IGA) on model parameters was assessed. A minimal CTMM approach was also evaluated [4]. All models were implemented in NONMEM 7.3 [5].

Results: Longitudinal IGA data were best described by a 4-compartment CTMM with a stimulating drug effect common to all λdesc. A simplified IIV structure using one term common to all λasc and one term common to all λdesc improved numerical stability without significantly worsening model fit. A statistically significant linear effect of time (i.e., placebo effect) on λasc was identified in study RD.03.SPR.114322, but not in study CIM003JG. Baseline IGA score of 4 or 5 was found to be a significant covariate for all λasc. All model parameters, except for the drug concentration producing half of maximal effect (64% RSE), were estimated with acceptable precision (≤31% RSE and ≤23% RSE for fixed and random effects, respectively). Visual predictive checks showed an adequate predictive performance of the model for all scores and dose levels up to 24 weeks of treatment. The alternative minimal CTMM could well describe the time-courses of most IGA scores but failed to describe the placebo data. It was therefore not retained.

Conclusions: The developed CTMM provides a good description of the IGA data in AD patients treated with a wide range of nemolizumab doses. The IGA model, combined with models for two other pharmacodynamic endpoints – the eczema area and severity index (EASI) and weekly average peak pruritus numeric rating scale (PP-NRS), both described in a separate abstract – will further be used to support the development program of nemolizumab.

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IV-06: *Dimitra Eleftheriadou* Aluminium biokinetics: Elucidating the speciation kinetics of the aluminium-citrate system in vitro.

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Objectives: As an element, aluminium (Al) does not undergo metabolism in biological systems, but rather distributes into a plethora of distinct chemical states. This process is known as speciation. Among the variety of organic ligands present in biological systems, citrate (Cit) is the most relevant ligand for aluminium [1]. Detailed representation of the speciation of aluminium with citrate on the molecular level is lacking in existing aluminium biokinetic models [2]. However, this information is essential for understanding the involvement of aluminium in biological processes. For example, it is known that aluminium ions (Al^{3+}) adsorb onto calcium hydroxyapatite crystals [3]. Accordingly, knowledge of the speciation kinetics of Al^{3+} is crucial for the prediction of its bone accumulation in children under conditions of life-long exposure. Due to the lack of detailed *in vivo* data on the speciation of aluminium, this knowledge needs to be translated from *in vitro* experimental data. The objective is to identify the physiologically relevant species and the underlying chemical reactions in the aquatic Al-Cit system. A further objective is to estimate the rate constants of these chemical reactions and thereby enabling the prediction of the kinetics of the Al-Cit system.

Methods: Based on existing literature, we constructed a chemical reaction network that captures the physiologically relevant speciation processes in the aquatic Al-Cit system. In order to describe the kinetics of the reaction network, we used data where species fractions were measured at various pH values and time points [4,5]. We linearly interpolated the original, pH-dependent data to obtain time-dependent data of species fractions. The reactions in the reaction network were modelled as ordinary differential equations (ODE). The corresponding kinetic parameters were estimated via the maximisation of the likelihood function by using the Nelder Mead optimisation algorithm.

Results: The resulting reaction network describes the formation of a number of different Al-Cit species, including the following: Al^{3+}, $AlHCit^{+}$, AlCit, $Al(H_{-1}Cit)^{-}$ and $Al_3OH(H_{-1}Cit)_3^{4-}$. The hydroxo-species $Al(OH)^{4-}$ and the polynuclear species $Al_3(OH)_4(H_{-1}Cit)_3^{7-}$ were excluded from the reaction network, since they predominate in non-physiological pH ranges (higher than 9). Review of relevant literature revealed that the species identified in Al-Cit speciation studies are highly dependent on the experimental conditions (temperature, initial pH, initial Al:Cit molar concentration ratios). The reaction network was based on measurements, where the initial conditions correspond to an equimolar Al:Cit concentration ratio or citrate excess. Equimolar Al:Cit ratios are expected in the plasma after acute Al intoxication, while pronounced citrate excess is assumed to resemble typical chronic exposure scenarios [5,6].

Conclusions: Overall, our analysis shows that a system of non-linear ODEs is well-suited to describe the speciation kinetics of the Al-Cit system. The proposed chemical reaction network and corresponding ODEs pave the way for enhancing existing aluminium biokinetic models with a new level of detail on the molecular scale. Ultimately, this will lead to a deeper understanding of aluminium toxicodynamics, since it will allow to explicitly account for the impairment of biological processes by individual aluminium species.

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IV-07: *Douglas J. Eleveld* Aging and maturation as a reliability problem: The Weibull distribution and age- and maturation-adjustment functions

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Objectives: In covariate analysis, age is often examined for its relationship with model parameters. An individual's age is informative for characteristics of physiological mechanisms which we attempt to duplicate in PK and PD models. These can be gradual changes associated with aging as well as more abrupt changes in young children associated with maturation. There is no "theory of aging" to guide model development and current approaches are empirical. There is considerable diversity in age-adjustment functions[1] in current literature, and researchers are not often challenged as to their choices. The purpose of this investigation is to apply techniques from reliability engineering[2] to age-adjustment functions. The premise is the number of functional physiological units (and thus biological function) over time after ontogenesis is analogous to the number of remaining functional products over time after manufacture. Physiological units/ products may fail (or gain function) over time according to a hazard function. The Weibull cumulative distribution function (CDF) *f(age)=1-exp(-(age/λ)**k)* is used in reliability engineering to gain insight into product failure mechanisms. The value of *k* may indicate early-failure (*k*<1, "infant-mortality" or decreasing hazard) or aging (*k*>1, "wear-out" or increasing hazard) effects.

Methods: Two PK models and datasets were chosen with a wide age-range, for Propofol[3] and Vancomycin[4]. The age- and maturation-correction functions in each model (3 for Propofol and 2 for Vancomycin) were plug-in replaced by Weibull CDF and the model re-estimated. Parameters λ and *k* were estimated, with *k* being fixed to 1 if supported.

Results: All 5 age- and maturation-adjustment function in the considered models could be approximated by the Weibull CDF with only moderate change in objective function (12.7 for Propofol and -7.78 for Vancomycin). Early maturation of clearance showed increasing hazard over time (*k*>1), suggesting positive feedback mechanisms drive maturation. Advanced age showed "wear-out" for vancomycin clearance (*k*>1), whereas the hazard for loss of propofol clearance appears independent of time (*k*=1).

Conclusion: Age- and maturation-correction functions showing diverse behaviors can be modelled in a unified framework with Weibull CDF functions with only moderate impact on the final model fit. The estimated *k* parameter determines whether the hazard increases, decreases or remains constant over time and this may be insightful for understanding physiological mechanisms. Use of the Weibull CDF for age-correction may reduce empiricism and help refine theoretical approaches for age- and maturation-correction functions in covariate analysis.

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IV-08: *Esther Encinas* Use of modeling and simulation methods to support the generic application of a vaginal delivery system

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Introduction: A pharmaceutical company developed a generic contraceptive vaginal delivery system containing etonogestrel (ENG, 0.120 mg/day) and ethinyl estradiol (EE, 0.015 mg/day), equivalent according to *in vitro* criteria and bioequivalent *in vivo* to the Reference (R) NuvaRing®. A 2x2 crossover bioequivalence study was conducted in 48 females under the recommended 21-day use [1], but health authorities were concerned about its appropriateness to support the extended 28-day use for the test (T) ring, a deviation already allowed for NuvaRing [1].

Objectives: To develop an *in vitro-in vivo* correlation (IVIVC) model, based on *in vivo* 21-day PK data and 28-day *in vitro* release profiles of ENG and EE from both T and R vaginal rings, aimed to support that enough serum levels of EE/ENG are achieved during the additional 4th week of use. The ultimate purpose was to evaluate the representativeness of *in vitro* release rate to *in vivo* behaviour for two bioequivalent products but prolonged in time, once in equilibrium.

Methods: A direct (one step) differential equation-based IVIVC model (an alternative method to classical two-step level A IVIVC approach [2]) was developed and was able to predict, within a traditional compartmental model framework [3], the entire *in vivo* plasma PK profile based on *in vitro* release rates (N=12 replicates in discriminative medium), separately for ENG and EE components. The approach requires first model parameterization of the *in vitro* dissolution rates that can then be integrated into an input driving a compartmental PK structure for the *in vivo* behaviour.
In vivo concentrations were modeled via inclusion of both the (separately developed) *in vitro* dissolution rate model structure, transformed by scaling into the *in vivo* release rate, and the *in vivo* PK simultaneously. NuvaRing data were used in model development; the *in vitro* parameters introduced in the global *in vitro*/*in vivo* structure were fixed to those estimated in *in vitro* modeling and appropriate time-scales were estimated as fixed effects together with systemic PK. The bioavailability was modeled with a time-dependent function, consistent with reports for both ENG [4] and EE [5]. An impulse function represented 21- or 28-day removal of the ring.
When predicting *in vivo* profiles from the generic ring, the previously estimated *in vivo* parameters were then fixed, while the *in vitro* parameter set was switched with that of T to drive the simulation. Once externally qualified through prediction errors (PE) and visual predictive check (VPC) against PK observations for T, the direct IVIVC model was used in extrapolating in time by prolonging exposure to the input rate from 21 to 28 days. Predictability was confirmed by comparison with literature 28-day PK data for NuvaRing. All modeling was conducted in NONMEM v7.3 (FOCE method) and graphics were performed using S-PLUS v8.

Results: A novel bi-exponential decay function best described *in vitro* dissolution rates for both ENG and EE. The direct IVIVC for vaginal ring compounds comprised a two-compartment disposition model with a total of 13 parameters, including an impulse function to represent removal of the ring at either 21 or 28 days and a time scale to transform *in vitro* to *in vivo*. Proportional error was assumed for the random effects. All the direct IVIVC population parameters for EE and ENG were well estimated using R data (SEE<30%),

whereas external validation was confirmed by adequate prediction of *in vivo* 21-day PK for T (PE<5% for exposure and plasma concentration at Day 21, AUC_{0-21} and C_{21}, for both analytes). When extrapolating to Day 28, PE against literature observations for NuvaRing [6] was <10% for AUC_{0-28} and C_{28}, thus proving that *in vitro* release rate adequately represents *in vivo* behaviour of vaginal delivery systems and that the model is suitable for prediction of extended use. Plasma levels of ENG and EE predicted at Day 28 were similar for T and R, and well above the efficacy thresholds (e.g., 90 pg/ml for ENG [7,8]). T/R ratios predicted for both AUC_{0-28} and C_{28} of ENG were 0.95, while they were 0.92 and 0.94, respectively, for EE.

Conclusions: Direct IVIVC modeling & simulation supported the appropriateness of the generic vaginal delivery system for 28-day lengthened use by showing that sufficient serum levels of ENG and EE are maintained for an additional 4th week, thus evidencing a negligible risk of bioinequivalence at 28 days.

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IV-09: *Aline Engbers* Postnatal age, gestational age and small for gestational age drive the pharmacokinetics of ibuprofen enantiomers in very preterm neonates with patent ductus arteriosus

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Objectives: Racemic ibuprofen is widely used in neonatal intensive care units for the treatment of preterm neonates with patent ductus arteriosus (PDA). While postnatal age has been identified as driving factor of the pharmacokinetics of ibuprofen, a bodyweight-based dosing regimen of 10-5-5 mg/kg administered on three consecutive days is still widely used.[1] Only a limited number of studies considered the pharmacokinetics of the separate enantiomers of ibuprofen, while only the S-ibuprofen enantiomer is pharmacologically active.[2,3] This study therefore develops a population pharmacokinetic model of both enantiomers of ibuprofen in preterm neonates, needed to develop optimized dosing guidelines.

Methods: Data from the DINO study (Drug dosage Improvement NeOnates, NCT 02421068) were available for analysis. This study included preterm infants requiring one of nine frequently used off-label drugs in this population. Pharmacokinetic and pharmacodynamic data were collected opportunistically. A total of 210 samples were available from 67 preterm infants in which S-ibuprofen could be quantified above the limit of quantification (LOQ) of 1 µg/mL. In 65 of the 210 samples R-ibuprofen concentrations were above the LOQ. Covariates that were available for analysis were postnatal age (median at treatment initiation 3 (range 1-12) days), gestational age (26 (24-30) weeks), postmenstrual age (27.0 (24.6-31.6) weeks), birthweight (0.87 (0.47-1.5) kg), current weight (0.82 (0.45-1.6) kg), small for gestational age (defined as birth weight < 10^{th} percentile for their gestational age, n=7) and gender. Neonates were treated according to the standard of care in different hospitals, resulting in a varied dosing regimen. The regimen started with a median loading dose of 10.2 (range 5.0-22.4) mg/kg, followed by a maintenance dose of 7.0 (4.4-28.4) mg/kg for two days. This cycle was repeated until closure of the ductus was achieved.

A population pharmacokinetic model was developed in NONMEM (V.7.3).[4] The total dose of ibuprofen was assumed to consist of 50% S- and 50% R-ibuprofen, and was therefore divided by two and directed to two compartments. First a pharmacokinetic model of S-ibuprofen was developed, because of the limited number of available R-ibuprofen concentrations. For this model covariates were evaluated using stepwise covariate modelling, using significance levels of $p \leq 0.01$ for forward inclusion and $p \leq 0.005$ for backwards elimination. R-ibuprofen concentrations were then added to the model to describe the pharmacokinetics of both enantiomers in parallel. The M3-method was used to describe the data below the limit of

quantification.[5] In the enantiomer model potential conversion of R-ibuprofen to S-ibuprofen was examined, as well as the effect of postnatal age on the elimination of R-ibuprofen, based on the results of Gregoire *et al*.[3]

Results: For a typical preterm neonate (born after 26 weeks, appropriate for gestational age and 3 days old) clearance of S-ibuprofen (CL_S) and volume of distribution (V_S) were 3.9 mL/h (RSE 12%) and 236 mL (RSE 7%), with inter-individual variability of 44.9% (RSE 16%) and 22.7% (RSE 33%) respectively. Maturation of CL_S was substantially affected by postnatal age with an estimated exponent of 2.33 (RSE 16%), resulting in a 127% increase in CL_S in one week for an infant starting treatment at a postnatal age of 1 day. Additionally, CL_S was found to increase with gestational age (exponent of 5.47, RSE 19%) and CL_S was estimated to be 3.9 times higher compared to small for gestational age infants (RSE 34%). Estimated clearance of R-ibuprofen (CL_R) was 153 mL/h (RSE 18%) which increased linearly with postnatal age with a slope of 19.4 mL/h/day (RSE 49%). Volume of distribution of R-ibuprofen (V_R) was estimated at 344 mL (RSE 13%). Both V_S and V_R increased with current body weight, One exponent of 0.456 (RSE 36%) was able to describe this change for both parameters and performed similarly to when two parameters were estimated. Conversion from R- to S-ibuprofen could not be identified.

Conclusions: The findings of this study suggest that the current practice of bodyweight-based dosing of ibuprofen in preterm neonates may be suboptimal and that dosing based on PNA may lead to a more uniform area under the concentration-time curve. When target exposure has been defined, model-based simulations can form the basis for the development of individualized dosing regimen.

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IV-10: *Muhammad Faisal* Simultaneous semi-mechanistic population pharmacokinetic analysis of enalapril and enalaprilat in serum and urine following the administration of child appropriate oro-dispersible mini-tablets.

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Objectives: Since many years, children with chronic heart failure are lacking approved drug and child appropriate dosage formulation in Europe and in the USA [1]. A European drug and dosage form development program for off-patent drug enalapril using an oro-dispersible mini-tablet (ODMT) aims at to evaluate the pharmacokinetics (PK) of administered inactive pro-drug enalapril and its active metabolite enalaprilat by developing a combined population PK model. As a first step, enalapril was administered as 10 mg ODMTs versus a marketed 10 mg Renitec® formulation to 24 healthy adults during a phase I clinical trial [2]. The detailed model informed PK analysis was used to evaluate the impact of dosage formulation on the PK of enalapril and enalaprilat by evaluating the difference in PK of the administered drug and metabolite in serum and urine.

Methods: A simultaneous semi-mechanistic population PK model was developed to predict full profile serum and urine concentrations of enalapril and enalaprilat using NONMEM software version 7.4.0. First-order conditional estimation with interaction was used to estimate parameters including mean transit time (MTT), rate constants of absorption and elimination, the volume of distribution (VD), bioavailability, inter-compartmental distribution and rate constant of metabolite formation. Relationship of model parameters with biometric covariates was evaluated. Model performance was evaluated using the goodness of fit plots. Visual predictive check, bootstrap confidence interval, and sampling importance-resampling procedures were used for model validation. Parameter estimates of enalapril and enalaprilat of both formulations were correlated using paired t-test with p

Results: One and two-compartment model adequately predicted serum enalapril and enalaprilat concentrations, respectively. Delay phase of enalarpil absorption and enalaprilat formation was predicted using transit compartments. Normalized body weight was identified as covariate related to VD of enalapril. Only a significant difference (p=0.03) in MTT of enalapril absorption by 5 minutes from ODMT was found compared to reference tablets. No other difference in the PK of enalapril and enalaprilat was observed in serum and urine.

Conclusions: The Inactive prodrug Enalapril administered using child-appropriate ODMTs appeared 5 minutes earlier in serum compared to the reference formulation. However, no difference in the formation and disposition of active metabolite enalaprilat was observed in serum and urine. The use of enalapril ODMTs is expected to have similar pharmacodynamics response as compared to conventional formulations.

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IV-11: *Undine Falkenhagen* Structural model selection: Is the chi-square distribution appropriate for likelihood ratio tests?

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Objectives: Many software packages used in pharmacokinetic modelling use log-likelihood associated objective functions to fit and select models. This model selection framework corresponds to a likelihood ratio test comparing models of different complexity. A model with more parameters is chosen only if it reduces the objective function value by more than a specific threshold in comparison to a simpler model [1]. This threshold is commonly chosen as a quantile of a chi-square distribution, which originated from Wilks' theorem on the distribution of the likelihood ratio test statistic (LRTS) [2]. The theorem states that under certain conditions and if the simpler model is the true model, the LRTS is asymptotically chi-square distributed with degree of freedom equal to the number of added parameters in the more complex model. This would ensure that the type I error equals alpha if we use the (1-alpha)-quantile of the chi-square distribution as threshold. However, the premises of Wilks' theorem, including the identifiability of the parameters, are not always fulfilled. In these cases the distribution of the LRTS does not necessarily behave like a chi-square distribution and can deviate substantially [3, 4]. One example where this occurs is the comparison of one- and two-compartmental models [5]. The objective was to illustrate and quantify the resulting differences between the chi-square distribution and the correct distribution including the implications on type I error and power in a simulation study.

Methods: We considered the scenario of the comparison of classical one- and two-compartment models. Here the difference of parameters is two and therefore one would commonly use the quantile of a chi-square distribution with two degrees of freedom. To quantify the deviation of the correct test statistic distribution from the chi-square distribution, we simulated 10,000 concentration time profiles of a classical one-compartment model and calculated the LRTS for each. We assumed a multiplicative log-normally distributed residual error and used different volumes of distributions, clearances, magnitudes of residual error and sampling time points for the one-compartment model. The resulting distributions of the simulated test statistics were compared to the chi-square distribution with two degrees of freedom. In particular the 95%-quantiles were compared.

Results: While the chi-square distribution is independent of design and model parameters, the correct distribution of the likelihood ratio test statistic does depend on the parameter values of the one-compartment model and also on the sampling time points. None of the simulated distributions coincided with the chi-square distribution with two degrees of freedom, some coincided with a chi-square distribution with one degree of freedom. In all considered cases, the quantiles of the chi-square distribution were larger than the quantiles of the simulated distribution. This implies that the use of the chi-square quantiles is more restrictive than intended, i.e. aiming for an alpha level of 5% resulted in an actual alpha level of approximately 1-2%. As a consequence, the power of the test can be reduced leading to a higher likelihood of accepting a one-compartment model where a two-compartment model would be correct. The 95%-quantiles of the simulated test statistics deviate up to two-fold from the 95%-quantile of the chi-square distribution.

Conclusion: The commonly used chi-square quantiles, only dependent on the number of parameters but not on the specific model and design, are not very accurate as thresholds for model selection decisions. The deviations can have a substantial influence on type I error and power. Therefore, simulating the quantiles rather than using the chi-square quantiles should be considered.

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IV-12: *Alan Faraj* Drug effect of clofazimine on persisting mycobacteria explain an unexpected increase in bacterial load from patients

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Introduction

Clofazimine (CFZ) and pyrazinamide (PZA) are important components of recommended standard multi-drug treatments of TB. Paradoxically, in a Phase IIa clinical trial aiming to define the early bactericidal activity (EBA) of CFZ and PZA monotherapy over the first 14 days of treatment, no significant drug effect could be demonstrated for the two drugs using traditional statistical analysis [1]. An unexpected numerical increase in colony forming units (CFU) over time, was observed with CFZ monotherapy.

Objectives

This work aimed to establish exposure-response relationships of both drugs in monotherapy and to explain the numerical increase in CFU after CFZ monotherapy, using a model-based approach.

Methods

Pharmacokinetic (PK) and CFU data from 14 and 15 patients after CFZ or PZA in monotherapy [1], respectively was analysed using nonlinear mixed effect modelling. A population PK model was developed for CFZ. For PZA, a previously developed PK model was applied [2]. Adequate model-predicted individual PK profiles were linked to the Multistate Tuberculosis Pharmacometric (MTP) model [3,4] to explore exposure-response relationships on the killing of the multiplying, semi-dormant, persistent and/or inhibition of multiplying bacteria alone and in combination. In order to challenge the consistency of the results, a sensitivity analysis was performed where the relative ratio of the bacterial subpopulations was varied. The exposure-response relationships were subsequently re-estimated.

Results

A two-compartment model with first order absorption and elimination together with an absorption lag-time was supported by the clofazimine PK data. Inter-individual variability (IIV) was supported for apparent oral clearance (CL/F), apparent volume of distribution (V/F) and the first-order absorption (ka) parameter. Inter-occasional variability (IOV) was supported for bioavailability. No statistically significant covariate relationship was found using body weight, age and sex on CL/F or V/F. Using the MTP model [3,4], statistically significant exposure-response relationships were characterized for both drugs, with a linear concentration-dependent killing effect for CFZ on persistent tubercular bacilli and a linear concentration dependent effect for PZA on semi-dormant mycobacteria. The final model could explain the original findings of paradoxical increase in CFU with CFZ treatment as well as no effect with PZA when the analysis did not include variables for different metabolic states of mycobacteria.

Conclusions

A novel semi-mechanistic model-based analysis of individual PK and sputum CFU counts revealed significant activity of CFZ and PZA on persistent and semi-dormant mycobacteria, respectively, which remained undetected with traditional methods of quantification, of anti-tuberculosis drug effect. Further, the drug effect on persistent tubercular bacilli explained the unexpected increase in CFU after CFZ monotherapy. We propose that this quantitative approach that provides a rational framework for analysing drug effects in Phase IIa EBA studies, can accelerate anti-TB drug development.

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IV-13: *Anam Fayyaz* Development and Performance Verification of a semi-PBPK Model for Topical Ocular Delivery of Pilocarpine and Timolol to Rabbit Eyes

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Introduction:

Eye drops/topical drops are among the most convenient ocular drug administration route, as they are non-invasive, self-administered and show high patient compliance (1, 2). Poor corneal permeability and drainage through the tear outflow cause poor bioavailability and potentially increase adverse effects when drugs are delivered through this route (3, 4). A mechanistic model integrating eye anatomical and physiological parameters with drug properties and formulation characteristics can help getting better insight into drug bioavailability and disposition in the interior eye which is currently lacking (4). *In vitro in vivo* extrapolation approaches linked with physiologically based pharmacokinetic modeling provides a powerful tool to serve this purpose. Such models can reduce, refine and replace animal studies and inform and speed up ocular drug development (5)

Objectives:

To build a general semi-physiologically based pharmacokinetic model for topical ocular drug delivery of small molecule drugs to rabbit eye. Further, to verify the model predictive performance for topically administered pilocarpine and timolol to rabbit eye.

Material and Methods:

Anatomical and physiological data from rabbit eye were collated and analysed from the literature. A physiologically based model for modelling administration of topical ocular drugs to rabbit eye was developed considering 4 compartments, namely the tear fluid, cornea, aqueous humor and a reservoir compartment. The model was built in Matlab and simulations were run to predict the concentration profiles of drug in different ocular tissues.

Pilocarpine and timolol (in solution) were selected as two model drugs mainly due to availability from the literature of the concentration time profiles for different rabbit ocular tissues. The model requires drug related parameters: 1) permeability from tear fluid to cornea (corneal epithelial rabbit study timolol, *ex-vivo* study pilocarpine), 2) clearance from tear fluid to conjunctiva (*in vivo* precorneal clearance study for both), 3) clearance from cornea to aqueous humor (simulation model timolol, apparent rate constant converted to clearance values pilocarpine), 4) clearance from aqueous humor (determined from intracameral injection study for both drugs), 5) volume of distribution in aqueous humor (determined from intracameral injection study for both drugs), 6) volume and flows in and out of the reservoir (determined from intracameral injection study for both drugs).

Results:

The model performance for pilocarpine and timolol models were compared against the reported observed values. The observed C_{max} and AUC in aqueous humor for pilocarpine were 1.11 µg/ml and 63.2 µg.min/ml. While the predicted values are 1.20 µg/ml and 76.08 µg.min/ml respectively. The observed C_{max} and AUC in aqueous humor for timolol were 3.0 µg/ml and 322.1 µg.min/ml. While the predicted values are 3.67 µg/ml and 420.343 µg.min/ml respectively. These results show that the predictions were acceptable with less than 2-fold difference then the observations.

Conclusion:

A semi-PBPK model for topical ocular drug delivery of small molecules to rabbit eyes was developed for pilocarpine and timolol. The model is able to simulate the distribution of drugs in different tissues of the eye after instillation of a drug solution in the eye (with acceptable predictability). We will assess the model performance for a wider range of drugs and expand it to other anterior eye tissue compartments.

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IV-14: *Anam Fayyaz* Development and Performance Verification of a semi-PBPK Model for Topical Ocular Delivery of Pilocarpine and Timolol to Rabbit Eyes

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Introduction:

Eye drops and topical drug dosage forms are among the most convenient ocular drug administration routes, as they are non-invasive, self-administered and show high patient compliance (1, 2). However, poor corneal permeability and drainage through the tear outflow can cause poor bioavailability (3). A predictive mechanistic model integrating eye anatomical and physiological parameters with the active pharmaceutical ingredient properties and formulation characteristics can assist with getting better insight into drug bioavailability and disposition in the interior eye which is currently lacking (4,5). In vitro in vivo extrapolation approaches linked with physiologically based pharmacokinetic (PBPK) modeling provides a powerful tool to serve this purpose. Such models can reduce, refine and replace animal studies and inform and speed up ocular drug development (5).

Objectives:

To build a general semi-physiologically based pharmacokinetic model for topical ocular drug delivery of small molecule drugs to rabbit eyes. Further, to assess the model predictive performance for topically administered pilocarpine and timolol to the rabbit eyes.

Material and Methods:

The rabbit eye anatomical and physiological data were collated from literature and analysed. A semi physiologically based model for simulating topical ocular drug administration to rabbit eyes was developed considering four compartments, namely the tear fluid, cornea, aqueous humor and a reservoir compartment. Currently, the eye is represented using a compartmental structure with three compartments (tear fluid, cornea, and aqueous humor) representing sites where drug concentration can be measured and a reservoir compartment used to model peripheral distribution. The movement of the drug between the compartments is described by a series of ODEs. Although this is a simplified representation of the processes occurring in the eye, - it can provide an appropriate balance of model complexity and computational time for the purposes of this modelling exercise. The model was built in Matlab and used to predict the concentration profiles in different ocular compartments.

Pilocarpine and timolol (both in solution) were selected as two model drugs - due to availability of observed concentration time profiles in different rabbit eye tissues.

The model parameters and their sources are presented in Table 1.

Parameter	Timolol	Pilocarpine
Permeability from tear fluid to cornea	Estimated from corneal epithelial rabbit study	Fitted
Clearance from tear fluid to conjunctiva	Estimated from *in-vivo* precorneal clearance study	Estimated from *in-vitro* precorneal clearance study

Clearance from cornea to aqueous humor	Fitted	Fitted
Clearance from aqueous humor	Estimated from intracameral injection study	Estimated from intracameral injection study
Volume and flows in and out of the reservoir	Estimated from intracameral injection study	Estimated from intracameral injection study

Results:
The model performance for pilocarpine and timolol were compared against the observed values. The observed Cmax and AUC in aqueous humor for pilocarpine were 1.1 µg/mL and 63.2 µg.min/mL. While the predicted values are 1.20 µg/mL and 76.0 µg.min/mL respectively. The observed Cmax and AUC in aqueous humor for timolol were 3.0 µg/mL and 322.1 µg.min/mL. While the predicted values are 3.6 µg/mL and 420.3 µg.min/mL respectively. These results show that the simulations results were within 2-fold of the observations.

Conclusion:
A semi-PBPK model for topical ocular drug delivery of small molecules in rabbit eyes was developed. The model is able to simulate the distribution of drugs in different tissues of the eye after instillation of a drug solution in the eye (with acceptable performance). We aim to develop predictive models/algorithms to determine the rest of the model parameters and assess its performance for a wider range of drugs.

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IV-15: *Rebekka Fendt* Evaluating the benefit of individual patient data for physiologically based pharmacokinetic (PBPK) simulations

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Objectives:

In this work, individualized physiologically-based pharmacokinetic (PBPK) models were built based on information from a clinical study in healthy volunteers. The mechanistic nature of PBPK models allows incorporating knowledge about the studied healthy volunteers such as biometrics (height, weight, age, sex) or physiological data (hematocrit, glomerular filtration rate, liver blood flow). The goal of the study was to evaluate whether incorporation of this individual information improves the agreement of the volunteer-specific PK simulations with corresponding PK measurements.

Methods:

PK data were obtained recently in a drug cocktail trial [1]. In this study, six drugs (caffeine, codeine, midazolam, pravastatin, talinolol and torsemide) were given simultaneously to healthy individuals (n=106). In addition to the plasma PK data, the data set included information on biometrics, physiology, pharmacogenetics and lifestyle of the study volunteers. A previously established midazolam PBPK model was employed to simulate individual PBPK profiles. All simulations were performed with PK-Sim® as part of the Open Systems Pharmacology Suite [2] and MATLAB.

Results:

PK data of midazolam, a probe drug for CYP3A4 activity, were analysed in this study. As a starting point, the midazolam PBPK model was fitted to the mean concentration of all volunteers. The model was simulated with the biometrics of the PK-Sim® reference individual (caucasian, male, 30 years, 73 kg, 1.76 m).

The PBPK model of midazolam was able to describe the time course of the mean data very well, including the maximum concentration (Cmax) and the time of the maximum concentration (tmax). All observed data were within the 2-fold range of predicted concentrations and the concordance correlation coefficient was 0.99. The maximum predicted versus observed ratio was 1.3.

To systematically assess the benefit mediated by the additional consideration of volunteer-specific information, the original PBPK model of the reference individual was individualized with respect to height, weight, age and sex.

In step 1, PK data of each volunteer were compared to the base PBPK simulation described above. The concordance correlation coefficient was 0.75 and 80.1% of the observed data were within the 2-fold range of predicted concentrations.

In step 2, the biometrics (height, weight, age, sex) of the virtual volunteers were set to the reported biometrics of the study volunteers and compared to the respective PK data. The results of the individualized PBPK models were similar to the simulations with the reference individual in step 1. The concordance correlation coefficient was 0.74 and 76.1% of the observed data were within the 2-fold range of predicted concentrations.

In step 3, CYP3A4 expression was fitted individually to PK data of each volunteer using the reference individual. The concordance correlation coefficient was 0.88 and 97.0% of the observed data were within the 2-fold range of predicted concentrations.

In step 4, CYP3A4 expression was fitted to the volunteer-specific PK profiles using the biometrics of the respective individual. These results were again similar to the results that were obtained for PBPK simulations with a reference individual. The concordance correlation coefficient was 0.87 and 97.2% of the observed data were within the 2-fold range of predicted concentrations.

Conclusions:

Inclusion of biometric information (height, weight, age, sex) of study individuals did not improve the predictive performance of midazolam PBPK model simulations. The individual PK data are already well described by a simulation with a reference individual (80% of the data being in the 2-fold range). Similar results were obtained by applying the same approach to a caffeine PBPK model. As a next step, physiological information about the glomerular filtration rate, albumin concentration, hematocrit and liver blood flow rates will be fed into the model. The presented approach contributes to a profound understanding of PK variability which is crucial for optimization of efficacy and safety in clinical science.

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IV-16: *Valentina Fermanelli* Correlation structure of Apolipoprotein A4, C3, E kinetics parameters

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Objectives: Apolipoproteins are a family of proteins attached to the surface of lipoproteins, the particles that facilitate the transportation of the lipids in the blood. The apolipoproteins are distributed among lipoprotein subtypes and are involved in the regulation of the lipoprotein kinetics. Apo-E is needed for the lipoprotein to be removed by the liver. ApoC-III inhibits the lipoprotein lipase. ApoA4 has an unknown function, but it has been supposed that it can be involved in regulating the food intake.

The plasma kinetics of lipoproteins are well studied. However, secretion and clearance of the apolipoproteins is less studied.

Biological aim: We aimed at investigating the relations between the production rate, elimination rate and concentrations of these three apolipoproteins. We aimed also at finding a correlation structure with additional biological parameters.

Modeling aim:We developed non-linear mixed effects models for each apolipoprotein as well as a combined model including all tree proteins. We wanted to check whether there would be substantial differences in the estimation of the parameters and whether the biological conclusion would be affected by the modeling approach.

Methods: Labelled leucine was subministered as bolus injection in 20 non-diabetic individuals. Peptide based proteomics was used to extract time series data of tracer enrichment in each apolipoprotein and GC/MS was used to measuring the tracer enrichment of free leucine in the blood. A linear ODE kinetic model was used to describe the process of formation of the apolipoproteins. Parameters was calculated separately for each apolipoprotein and in a combined model. The multicompartmental model for each apolipoprotein consists of 10 compartments: four compartments constitute the leucine kinetics, 5 compartments form a delay representing synthesis and secretion of the apolipoprotein, where the leucine is used as a building block of the apolipoprotein, and a last compartment, representing the apolipoprotein kinetics in the blood. The calculations of the kinetics parameters using a population approach were performed in Monolix. The correlation structure among the parameters has been analyzed using R.

Results: Biological results: The pool sizes and apoE, apoC-III and apoA4 correlated stronger with their secretion than with their clearance. Both apoE and apoC-III, which are known to be important for triglyceride rich lipoproteins metabolism, were closely linked to measures of plasma TG metabolism. ApoA4, on the other hand, were linked to HDL metabolism.

Comparison of the models: No biologically relevant difference could be detected for the parameters estimated with the two different models (combined estimation of the three apolipoproteins versus the separate estimation for each apolipoproteins). The correlation structure is also preserved.

Conclusions: Two models have been used to analyze longitudinal data of ApoE, ApoC3 and ApoA4. Both have yielded a similar correlation structure among the biologically relevant parameters. The correlation structure is biologically reasonable.

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IV-17: *Chiara Fornari* Importance of stability analysis when using non-linear semi-mechanistic models to describe drug-induced haematotoxicity

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Introduction/ Objectives: Stability analysis, which is often overlooked in the fields of pharmacometrics and quantitative systems pharmacology [1], is an essential tool to explore and understand systems' behaviour [2]. The semi-mechanistic model developed by Friberg *et al*. [3] to describe drug-induced haematotoxicity is regularly used to explore the relationship between known physiological behaviors and parameter values, but a formal stability analysis would be essential for the full comprehension of the application of this model to describe haematopoiesis during homeostasis and subjected to perturbations.

To our knowledge, the stability properties of this model [3] have not been assessed before, and here we use stability analysis techniques to gain new insights into the relationship between parameters and system behaviours. Lastly, we discuss these results in the context of non-linear mixed effects modelling, highlighting the consequences in prediction performance, and providing recommendations for future analysis.

Methods: The stability analysis of the semi-mechanistic model developed by Friberg *et al*. [3] was performed linearizing the system of non-linear differential equations around the steady state of interest (namely the homeostatic values, X^*), and then characterizing the long-term behaviour of the linearized system in the neighbourhood of this steady state (X^*), [2]. The Routh-Hurwitz criteria [2] were used to investigate the nature of the steady state X^*, and Routh-Hurwitz conditions were solved in Mathematica (Wolfram Research, Inc, ver 11.0).

Results: We showed that solutions converging to homeostasis represent drug-induced cytopenia, stable oscillatory solutions may represent cyclic cytopenia [4], or periodic leukemias [5], while unstable solutions do not describe physiological hematopoiesis. In details, we demonstrated that the feedback power parameter (γ) is a critical parameter for this model, which becomes unstable for values of γ greater than the bifurcation threshold ($\gamma^*=0.5685\ldots$). γ^* is called a Hopf bifurcation point [2], and the equilibrium X^* loses its stability over time when γ crosses the critical point γ^*, exhibiting growing oscillations. This stability condition ($\gamma < \gamma^*$) derives from the model structure itself, and it is independent of the other parameter values, such as the size of compartments or the maturation time, and of the type of toxicity or perturbation.

Conclusion: In this analysis, we highlighted the importance of assessing the dynamics of the semi-mechanistic model developed by Friberg *et al*. [3], and appropriately defining parameter settings when using this model. More precisely, we showed how to properly configure parameter estimation algorithms to guarantee mathematical stability and, hence, avoid a non-physiological behaviour of the system.

Therefore, given the broad usage of this framework in the pharmacometrics and systems pharmacology fields [6], we believe that this analysis could be beneficial for modellers working in this community, and we

highly recommend incorporating these results when applying Friberg model [3] to describe drug-induce haematotoxicity data.

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IV-18: *Jose Francis* A semi-mechanistic model to characterise the influence of nevirapine- and lopinavir/ritonavir-based therapy on artemether and dihydroartemisinin exposure

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Objectives: Artemether-lumefantrine is the most widely recommended first-line treatment for uncomplicated falciparum malaria globally. Considering the substantial geographic overlap of HIV and malaria, it is important to understand any potential drug-drug interactions. Artemether is rapidly converted to active metabolite dihydroartemisinin (DHA) by CYP3A4 isoenzymes, of which it is also an inducer, and it undergoes significant first-pass hepatic metabolism. DHA is further metabolised by UGT isoenzymes. Nevirapine (NVP) is an inducer whereas ritonavir is a potent inhibitor of CYP3A4, which can lead to potential drug-drug interactions. The aim of the present analysis was to explore the impact of nevirapine- and lopinavir/ritonavir (LPV/r) -based antiretroviral therapy (ART) on artemether and DHA exposure with a semi- mechanistic parent to metabolite population pharmacokinetic model.

Methods: Malaria-negative but HIV positive adults were recruited in three different arms; (a) Artemether-Lumefantrine (AL) alone, (b) AL+ NVP-based ART and (3) AL + LPV/r-based ART. All patients received the standard recommended dose of the fixed AL combination, i.e. 80 mg artemether plus 480 mg lumefantrine twice daily for three days. Intensive sampling after the first and the last dose was performed for the drug concentration measurements. The pharmacokinetic data was analysed using NONMEM 7.4 with FOCE-I. The parent drug and the metabolite were initially analysed separately and then a semi-mechanistic parent-to-metabolite model was developed aiming to quantify drug-drug interactions.

Results: : Data were available from a total of 55 patients with 1217 concentration observations for both artemether and DHA. The median weight and age overall were 59 kg (45.5-88) and 32.3 years (19.6-60.9) respectively. A semi-mechanistic model was developed accounting for artemether conversion to DHA both in the GI tract and the liver. A transit compartment absorption model characterised the delayed appearance of the artemether into the GI tract compartment, where a (logit transformed) GI-extraction parameter was applied to capture the metabolism of artemether into DHA. Both artemether and DHA are then absorbed into the bloodstream, but first undergo hepatic-first pass, which was described with a well-stirred model as explained in Gordi *et al*. The effect of concomitant ART was tested on the pre-hepatic bioavailability and hepatic drug clearance parameters. The pre-hepatic bioavailability of artemether was estimated to be 6.41% for the first dose in the control arm but was reduced to 1.39% for the consecutive doses due to auto-induction of CYP3A4. The estimates for this pre-hepatic bioavailability were lowered to 0.79% and 0.47% with respect to the first dose and the consecutive doses in the NVP-based ART arm compared to the first dose in the control arm and this was due to the induction effect of NVP on CYP3A4 for the first dose and additional auto-induction effect for the consecutive doses. There was no significant influence of LPV/r-based ART on artemether exposure except for the similar decrease as in the control arm from the second dose which corresponds to the auto-induction effect. LPV/r-based ART was found to increase DHA exposure, which was instead not affected by NVP-based ART.

Conclusions: Our model reveals that, after oral administration, a significant proportion of CYP3A4-mediated metabolism of artemether into DHA happens pre-hepatically, at the GI tract level. The exposure of

artemether was reduced significantly after the first dose due to the auto-induction on CYP3A4 isoenzymes. NVP-based ART reduced the systemic exposure of artemether significantly but had no influence on DHA exposure. The concomitant administration of LPV/r-based ART increased the systemic exposure of DHA. This could be due to ritonavir's inhibitory effect on UGT isoenzymes, or because of the inhibition of an alternative metabolic pathway clearing artemether without the formation of DHA. An individual patient data meta-analysis on these drug-drug interactions and subsequent dose modifications is recommended to inform better treatment of malaria-HIV co-infected patients.

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IV-19: *Yu Fu* Hemodynamic systems model to characterize cardiovascular drug effects

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Objectives:

The cardiovascular hemodynamic system is complex and highly regulated. Drugs can affect hemodynamic function through different modes of action. Early prediction and quantification of cardiovascular drug effects during preclinical drug development is crucially important to support dose selection and decision making during drug development. Previously a minimal mathematical systems model to quantify drug effects on key hemodynamic variables was developed using rat experimental data for eight compounds by Snelder *et al* ("Snelder model") [1,2]. The model characterizes drug effects on the interrelationship between five hemodynamic biomarkers including heart rate, stroke volume, total peripheral resistance, cardiac output and mean arterial pressure. The current study aims to evaluate the structural and practical identifiability of the Snelder model in order to evaluate the performance of this model to identify and quantify drug effects from preclinical hemodynamic experiments.

Methods:

We performed a structural identifiability analysis using the Matlab toolbox GenSSI 2.0 with different combinations of observations, including heart rate, cardiac output and mean atrial pressure [3]. Practical identifiability was evaluated using stochastic simulation and estimation (SSE) using Perl-speaks-NONMEM to determine if the model can be used to identify and quantify drug mode of action. We used 250 samples to perform each SSE analysis. Datasets consisted of 5 animals with densely sampled hemodynamic biomarkers, reflecting a typical experimental design. We simulated and re-estimated several study designs evaluating drug effects with different magnitudes for EC_{50} in association with three potential sites of action (heart rate, stroke volume and total peripheral pressure). The simulated study designs utilized informatively sampled observations. Using the SSE analysis we quantified the number of models that correctly identified drug mode of action, and we evaluated bias and precision of drug effect parameters.

Results:

The cardiovascular-hemodynamic model proposed by Snelder is structurally globally identifiable based on observations of heart rate, cardiac output and mean arterial pressure. The models is also structurally and globally identifiable based on observations for heart rate and mean arterial pressure. The SSE analyses indicated that a true drug effect could be identified for EC_{50} values within a factor 0.1-10 of peak drug concentrations based on successful minimization and statistical significance of $p<0.05$. The power to identify a significant drug effect was 100% for all values of EC_{50}. Although our structural identifiability analysis indicated that the model is structurally identifiable based on heart rate and mean arterial pressure, we found that models including observations for heart rate, cardiac output and mean atrial pressure showed an increased percentages of successful minimization compared to models that only include heart rate and mean atrial pressure.

Conclusions:

Our analysis supports the use of the Snelder model to identify and quantify drug mode of action in preclinical cardiovascular experiments and may be of relevance to guide design optimization of experimental studies.

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IV-20: *Aline Fuchs* Assessment of translation of PKPD relationship from animal to human for malaria compounds

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Introduction:

Activity of antimalarial candidate compounds is first tested in severe combined immunodeficient (SCID) mice engrafted with human erythrocytes and infected with *Plasmodium falciparum* parasites, one of the five malaria parasites infecting humans but not mice. A range of doses are tested and the compound concentrations and parasitemia are measured in each mouse. A PKPD model is build and used, in combination with a prediction of human PK, to make an initial estimation of the efficacious dose in humans. This estimated dose is used to prioritize the compounds to be tested in humans. Before going into patients, the compound is administered at subtherapeutic doses to volunteers inoculated with *P. falciparum* infected red blood cells. From a PKPD analysis based on human data, the initially estimated dose is revised with the human PK model. Five compounds have now been tested in both mice and Volunteers Infected Studies (VIS) and a retrospective analysis to compare the PKPD models in mice and in humans has been initiated.

Objectives:

To assess if the PKPD relationship translates from SCID mice to humans

Methods:

For each compound and each study, in SCID mice and in volunteers, a population PKPD model was developed with a two-stage approach: first a population PK model was built; secondly, the individual PK parameters were used as regression parameters and the PD parameters were estimated. The PD model consisted of the balance between a parasite net growth rate and a drug killing rate. Systematically, four models linking the drug killing rate to the drug concentration were tested: a sigmoidal Emax model, an effect compartment model, a turnover model and a direct effect model model in which an additional clearance term accounts for the removal of dead parasites from the body (clearance model). This was introduced since it was believed that the mechanisms for clearing dead parasites were different between mice and humans. For this model, Emax was either fixed to the invitro value or estimated with SCID mice and VIS data. Of all models, the best model was selected based on model convergence, goodness-of-fit plots, reliability of parameters estimates and BIC.

The Emax values obtained in SCID and VIS were compared. Also, simulations of parasitemia profiles for a range of doses were undertaken with the VIS PKPD model on one hand; and with the VIS PK model combined with the SCID PD model where the net parasite growth rate and baseline parasitemia were replaced with the VIS values. The minimum dose needed to clear 6 log parasites, the criterion for selecting a discovery compound for clinical development, are compared for these two scenarios.

To test if the clearance model, aimed at accounting for possible differences in dead parasites clearing mechanisms between SCID and VIS, could improve the dose predicted, additional simulations were made where the Emax, EC50 and Hill values estimated in the SCID model were used in an Emax model combined with the VIS PK model – making the assumption that humans will clear the parasites very quickly. The minimum dose needed to clear 6 log parasites was estimated and compared with the dose from the VIS PKPD model.

Results:

The best PKPD model was never the same in SCID and in VIS. The Emax model was never the best model in SCID but was in VIS for 3 compounds out of 5. These differences in the structural model between SCID and VIS are believed to be due to the different nature of data collected in SCID mice experiments and VIS since the parasites targeted by the compounds in SCID and VIS are the same. Only the clearance of the dead parasites may be different across species.

The Emax parameters were within a 3-fold margin between SCID and human and within a 2-fold margin for 4 out of the 5 compounds. Doses predicted based on 6 log parasite clearance were within a 2-fold margin between SCID and human.

The clearance model did not improve the agreement between doses predicted to clear 6 log parasites.

Conclusions:

This ongoing analysis represents a unique opportunity to better understand and assess the translation from the preclinical model to human for antimalarial compounds. Human dose prediction assuming the PKPD relationship is the same in SCID and in humans shows reasonable predictions for all 5 compounds Further analysis is planned to investigate possible improvement

This work will help MMV to refine its methodology in predicting human dose to select the most promising compounds.

IV-21: *Laura Fuhr* Physiologically based pharmacokinetic modeling of the dabigatran antidote idarucizumab

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Introduction: The direct oral anticoagulant dabigatran is an important alternative to warfarin, as it has predictable pharmacokinetics (PK), anticoagulant effects and can be applied in a fixed-dose regimen [1]. Since 2015, the antibody fragment idarucizumab is approved as specific dabigatran antidote, which enables quick and effective elimination of dabigatran and its anticoagulant action in case of heavy bleeding or emergency surgery [2]. Physiologically based pharmacokinetic (PBPK) modeling is a mathematical tool to investigate and predict the absorption, distribution, metabolism and excretion of small and large molecules throughout the body. In this study, PBPK modeling was applied to establish a PBPK model of idarucizumab and to investigate the influence of age, renal disease and ethnicity on the pharmacokinetics of idarucizumab.

Objectives:

- To develop a whole-body PBPK model of idarucizumab in healthy Caucasian adults
- To extend this model to other populations to accurately describe the impact of age, renal impairment and Japanese ethnicity on the PK of idarucizumab

Methods: The PBPK model was developed with PK-Sim® and MoBi® (Version 7.2.1) [3]. Drug-dependent parameters as well as plasma and urine concentration-time profiles of clinical studies were obtained from literature. First, a model of idarucizumab in healthy Caucasian adults was developed using 13 clinical studies (dose range 20 mg - 8000 mg, intravenous administration [4]). In a second step, changes in anatomy and physiology caused by aging, renal disease or a different ethnical background, such as body height, body weight or glomerular filtration rate (GFR), were implemented. For this model extension, 7 clinical studies of elderly or renally impaired individuals and 4 studies of Japanese subjects were used (dose range 1000 mg - 5000 mg, intravenous administration [5,6]). Finally, the model performance was evaluated by comparison of predicted to observed plasma concentration-time profiles, areas under the plasma concentration-time curve (AUC) and peak plasma concentrations (C_{max}) of the external dataset.

Results: The final whole-body PBPK model of idarucizumab applies endosomal degradation of idarucizumab in the vascular endothelium, as well as glomerular filtration with reabsorption and subsequent degradation of idarucizumab in the cells of the proximal tubule. To enable the mechanistic modeling of these renal processes, the standard PK-Sim/MoBi® kidney structure was extended by a tubule compartment, according to a previously described approach by Balazki et al. [7]. The degradation of idarucizumab in the tubule cells was described using Michaelis-Menten kinetics. New insights into the metabolic processes in the tubule were gained, as a correlation between renal function and the degradation rate of idarucizumab in the proximal tubule could be shown. All predicted AUC and C_{max} values are within two-fold of the observed values, demonstrating the good model performance. The geometric mean fold errors (GMFEs) between predicted and calculated AUC and C_{max} values are 1.11 and 1.12, respectively. Comparison of predicted to observed plasma concentration-time points shows that 96% of all simulated concentrations lie within the boundaries of the two-fold acceptance limits.

Conclusion: The presented PBPK model of idarucizumab precisely describes and predicts the observed plasma concentration-time profiles and fraction excreted to urine over the full reported dosing range. The model can be applied to predict the PK of idarucizumab in healthy, elderly and renally impaired Caucasian individuals as well as in healthy Japanese subjects. As a future application, the established model will be coupled to a PBPK/PD model of dabigatran, to predict the effect of idarucizumab on the PK and clinical outcome of dabigatran administration and to support the treatment of patients with idarucizumab.

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IV-22: *Masato Fukae* Population pharmacokinetic modeling of esaxerenone: a novel nonsteroidal mineralocorticoid receptor blocker

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Objectives: Esaxerenone is a novel nonsteroidal mineralocorticoid receptor blocker that was approved as an antihypertensive agent in Japan in 2019. In the present study, a population pharmacokinetic (PopPK) modeling was performed to 1) characterize typical PK of esaxerenone, 2) identify influential covariates, and 3) aid dose-adjustment recommendations.

Methods: Analysis included a total of 8263 esaxerenone plasma concentrations collected from 1623 Japanese subjects across 15 studies (7 Phase I studies, including one intravenous administration arm, 5 Phase II studies and 3 Phase III studies). Esaxerenone doses administered were ranged from 0.625 up to 200 mg. Development of the base model was guided by data exploration, biological/pharmacological plausibility, objective function value, precision of parameter estimates, and goodness-of-fit (GOF) plots. Since drug-drug interaction (DDI) studies reported that itraconazole and rifampicin affected the exposure to esaxerenone, and a single ascending dose study suggested lower absolute bioavailability (F) at high doses (equal to or more than 50 mg), these effects were incorporated into the base model. Afterwards a full covariate modeling was performed. The following covariates were tested on both clearance (CL) and central volume of distribution (Vc): hypertension, diabetic nephropathy, sex, age and body weight at baseline. Additional covariates were tested on CL, including alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), gamma-glutamyl transferase (GGT), estimated glomerular filtration rate based on serum creatinine (eGFR), smoking status, concomitant use of strong inhibitors/inducers of CYP3A taken systemically in the Phase II/III studies, and moderate renal impairment. The performance of the final model was evaluated by the standard GOF procedures and a prediction-corrected visual predictive check. Based on the final model, simulations were performed to visualize the influence of identified covariates on the exposure at steady state to esaxerenone. The analysis was performed in NONMEM 7.2 via PsN 4.6.0, where first order conditional estimation with a log-transform both sides approach was employed. Post-processing and model evaluations were performed in R version 3.3.1.

Results: Observed plasma esaxerenone concentrations were described adequately by a three-compartment model with sequential zero- and first-order absorption and first-order elimination. The parameter estimates (inter-individual variability, expressed as % coefficient of variation) of F, CL and Vc were 0.853 (not estimated), 3.28 L/h (18.2%) and 43.4 L (16.9%), respectively. The final PopPK model included the following covariates: concomitant use of itraconazole or rifampicin and high doses on F; age, body weight, smoking status, AST, eGFR and concomitant use of itraconazole or rifampicin on CL; and age and body weight on Vc. None of the other covariates tested (hypertension, diabetic nephropathy, sex, ALP, ALT, TBIL, GGT, moderate renal impairment, strong inhibitor and inducer of CYP3A in Phase II/III studies) had substantial effects on esaxerenone exposure. Simulation from the final model showed 63.8% increase and 68.4% decrease in average concentration at steady-state (CavSS) by itraconazole and rifampicin use, respectively. Compared to patients with typical body weight (68 kg), patients with extremely light (40 kg) and heavy (120 kg) body weight showed a 35.7% increase and a 28.3% decrease, respectively, in CavSS. The effects of the other covariates were within the traditional bioequivalence range of 80% to 125%, suggesting that they are unlikely to be clinically meaningful.

Conclusions: The present analysis revealed the small variability in esaxerenone PK, detected influential covariates and quantified the effects of these covariates. These results indicated that no dose adjustment is necessary on the basis of these covariates from a viewpoint of PK.

IV-23: *Fanny Gallais* Population pharmacokinetics of ibrutinib and its dihydrodiol metabolite in patients with lymphoid malignancies

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Introduction: Ibrutinib (Imbruvica®) is a targeted therapy used for the treatment of chronic lymphocytic leukaemia (CLL) and other B-cell malignancies. The Bruton Tyrosine kinase (BTK) plays an essential role in the B cell antigen receptor (BCR) pathway, which is involved in these diseases. Ibrutinib binds covalently to BTK, leading to its irreversible inhibition, and therefore alters the BCR pathway (1). Ibrutinib pharmacokinetics (PK) are highly variable between patients. Its oral bioavailability is poor (F=3%) due to high first pass hepatic metabolism. One of its metabolites, dihydrodiol-ibrutinib (DHD-ibrutinib), is 15 times less active than ibrutinib but its concentrations are up to twice those of ibrutinb (2).

Objectives:

- Develop a population PK (popPK) model for ibrutinib and its dihydrodiol metabolite
- Quantify and explain PK interindividual variability (IIV) in this population

Methods: The "PKE3I" study was initiated in 2016 at IUCT-oncopole (Toulouse, France). A total of 93 patients treated by ibrutinib were included in the study and followed for two years. A rich PK sampling (6 samples: before drug intake, 0.5, 1, 2, 4 and 6h after drug intake) was scheduled one month after treatment initiation. In addition, single blood samples were taken at months 2, 3 and 6 to obtain trough concentrations. Concentrations of ibrutinib and its dihydrodiol metabolite were quantified by ultra-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) using a previously developed technique. The lower limit of quantification (LLOQ) was 0.98 ng/mL. A popPK approach was used to develop a compartmental model for ibrutinib and DHD-ibrutinib. The model was developed in Nonmem 7.4, graphical analysis were assessed in R 3.4.2.

Results: A total of 89 patients performed PK blood sampling. Overall, 1501 drug concentrations were included in the popPK analysis. Concentrations below the LLOQ (4% of total concentrations) were set to LLOQ/2=0.49ng/mL. The base model consists in one dosing compartment, 2 compartments for ibrutinib and 2 compartments for DHD-ibrutinib. Absorption was described by a sequential zero-first order process (D1=0.93h, KAI=1.48/h) and a lag time (ALAG1=0.23h). Ibrutinib can be either excreted (CLIBRU/F=208L/h, IIV_CLIBRU=67.6%) or metabolized (KMET/F=182L/h, IIV_KMET=81.6%) into DHD-ibrutinib which is then excreted (CLDHD=188L/h, IIV_CLDHD=52.7%). A link between dosing compartment and DHD-ibrutinib central compartment was added to assess for high first-pass hepatic metabolism (KA_DHD=1.18/h, IIV_KADHD=63.2%) (3). Non-zero covariance terms in the omega matrix were found to improve the model. Inter-occasion variability (IOV) was evaluated on all PK parameters and found to be statistically significant for CLIBRU (IOV_CLIBRU=48.2%), CLDHD (IOV_CLDHD=22.3%) and central volume of distribution V2 (IOV_V2=40.9%). Proportional residual variability is 35% for ibrutinib and 25% for DHD-ibrutinib. The impact of available morphological, biological and clinical covariates will be assessed using a stepwise approach.

Conclusions: Marostica et al. proposed a first popPK model for ibrutinib (4). Our study improved this model by adding the DHD-ibrutinib metabolite and simultaneously taking into account ibrutinib and DHD-ibrutinb concentrations. The final model fits the data well. Interindividual variability was quantified. Covariates remain to be tested to explain this variability. This PK model will further be used for PKPD modelling. The objective will be to describe lymphocyte dynamics under ibrutinib treatment.

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IV-24: *Fiona G. Gao* Prediction of human pharmacokinetics of subcutaneously administered insulin formulations

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Introduction: In 2035, one out of ten people in the global population is supposed to suffer diabetes [1]. Patients with type 1 diabetes and patients with late stage of type 2 diabetes need to inject insulin to help manage their blood sugar levels. Subcutaneous injection is the most popular administration route for insulin due to effectiveness, compliance and safety issues. Including rapid-acting insulin, regular human insulin and long-acting insulin, all these commercial insulin products were brought to the market to ensure that the patients could have a complete near-normal 24-hour a day glycemic control. The different insulin formulations follow different pharmacokinetics after subcutaneous administration. The formulation of Apidra ensures the rapid dissociation and absorption after subcutaneous injection. Insulin glulisine appears earlier in the blood than human insulin of Actrapid. Protaphane provides a basal concentration of insulin to control fasting hyperglycemia and blood glucose concentrations before meals throughout the day.

Objectives:

- Discriminate the absorption rates of insulin with different formulations
- Integrate in vitro parameters, i.e. diffusion rate into a MBPK model to predict the *in vivo* pharmacokinetics of different insulin formulation
- Verify the MBPK model and confirm the sensitivity of the model to different input parameters

Methods: An agarose gel based *in vitro* diffusion assay was designed to determine the diffusion rate of monomeric insulin – Apidra and hexameric insulin – Actrapid as well as the hexameric insulin in the depot formulation – Protaphane that was either pretreated with heparin to dissociate the insulin molecules from protamine or not. To simulate the PK profiles of different insulin formulations, a mechanism-based pharmacokinetic (MBPK) model was built in the software Stella Architect. A multi-compartment model including lymphatic system was selected according to the model evaluation criteria. The PK simulations were performed based on *in vitro* determined absorption rate, estimated *in vivo* parameters and physiological parameters from literature. Further, granisetron, as a hydrophilic small molecule drug, was chosen to confirm the discriminative power of the *in vitro* diffusion assay as well as the wide utilizability of different MBPK model variants. The model was verified by analyzing the prediction results and comparing the predictions with clinical observations. In addition, local sensitivity analysis and global sensitivity analysis were conducted to evaluate the impact of different input parameters on the simulation outputs.

Results: The diffusion rate of monomeric insulin was higher than hexameric insulin, while the hexameric insulin in the depot formulation, once released after pretreatment with heparin, diffused at the same rate as regular human insulin in the formulation of Actrapid. Moreover, this diffusion assay was also suitable for testing hydrophilic small molecule drugs. As an example, granisetron, whose molecular weight is about 20 times lower than monomeric insulin, diffused about 5 times faster than Apidra. The diffusion rates obtained from *in vitro* test were integrated in a MBPK model variant. For all the case, C_{max} can be very precisely predicted, the highest prediction error was 4.5%. For Apidra, the T_{max} is higher predicted, while, for Actrapid, it was lower predicted. Especially for larger dose of Actrapid, the prediction error was quite high.

According to the AUC_{last} values, it was found that there was an overestimation for Apidra. For Actrapid, the prediction of AUC was quite good. It was suggested that the model used in WinNonlin is quite suitable for the relative stable hexamer. An extra elimination or degradation compartment is supposed to be necessary for the parameter estimation in WinNonlin because of the instability and fragility of monomeric insulin. Furthermore, according to local sensitivity analysis, 10% change of the diffusion rate affected significantly the prediction of C_{max} and T_{max}, but logically not AUC_{last}.

Conclusions: The diffusion assay is a promising *in vitro* method to emulate the *in vivo* absorption and thus, discriminate the absorption rates among different insulin formulations. The feasibility of MBPK model to predict *in vivo* pharmacokinetics was supported and improved by reliable *in vitro* assay. To investigate the pharmacokinetics of Protaphane, the release mechanism of insulin from the crystalline complex should be clarified.

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IV-25: *Kamunkhwala Gausi* Pharmacokinetics of isoniazid preventative therapy among HIV-infected pregnant women in high tuberculosis incidence settings

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Objectives:

Tuberculosis (TB) predominantly affects women of reproductive age and pregnant women are at elevated risk of progression from latent to active TB (2). TB during pregnancy or early postpartum can result in adverse maternal outcomes, infant TB, or death (3). World Health Organization guidelines recommend $\geq$6 months of isoniazid preventive therapy (IPT) for all people living with HIV from low- and middle-income countries (LMIC) where TB is endemic receive, including pregnant women (4). Since no information is available on the pharmacokinetics of isoniazid given as IPT in pregnancy concomitantly with ART, we evaluated these factors in a study.

Methods:

HIV-infected pregnant women at 14 to 34 weeks of gestation either established on or starting ART were recruited from 8 LMIC into a phase IV randomized, double-blind placebo-controlled multicenter international trial (IMPAACT P1078). The study had two arms: Arm A (immediately started on isoniazid 300 mg daily for 28 weeks, then placebo) and Arm B (started on placebo, then switched to isoniazid 300 mg daily at 12 weeks postpartum). A subset of women underwent intensive PK sampling (pre-dose, 1, 2, 4, 6, 8, and 12 hours after isoniazid dosing), while the remaining women underwent sparse PK sampling, with one single sample drawn around 2 hours after a self-reported dose. Sampling occurred once during pregnancy at ≥2 weeks after recruitment and again at 12-21 weeks after delivery. Genetic samples were collected to identify the genotype of NAT2, which was then used to categorize patients into extensive, intermediate or slow acetylators (5). The intensive data was used to develop the base model since the women were monitored closely (the dosing time for intensively sampled patients was monitored while the sparse sampled was safe-reported) and had more sampling time points. Then the sparse data was fitted on the model developed using the intensive data and using this model outliers in the sparse data where identified and removed from modeling. Records of concentration below the limit of quantification were imputed with half of the lower limit of quantification (LLOQ) value (0.105 ug/ml), and the lower limit of the additive error was fixed to 20% of the respective LLOQ.

Results:

847 women were samples of which 32 were intensively sampled, providing 1315 observations of which 88 outlier observations were removed. 748 (88%) were on efavirenz-based ART, 80 (9%) where on nevirapine and 17 (3%) were on lopinavir and 2 (0%) where on atazanavir. 21% of the patient's had missing genotype for NAT2. The pharmacokinetics of isoniazid was well described using a two-compartment disposition model with first-order absorption through a chain of transit compartments, and first-order elimination implemented with a well-stirred liver model, able to describe both hepatic clearance and first-pass extraction with the parameter of hepatic intrinsic clearance (CL_{int}). This model required the following assumptions: isoniazid protein binding of 5% and a fixed plasma liver flow of 50 L/h for a typical individual weighing 70 kg (6). Allometric scaling based on fat-free mass was applied on clearance and hepatic plasma flow, and total body weight was applied on volume parameters. The effect of NAT2 genotype on oral clearance was significant as expected and was included in the model. Patients with missing genotype were allocated to either of the three phenotypes using a mixture model with three subpopulations (7). The model predicted a typical patient with fat-free mass of 38 kg to have isoniazid oral clearance values of 13.8, 36.6, and 68.7 L/h if slow, intermediate, or extensive acetylator, respectively. After adjusting for body size and NAT2 genotype, pregnancy was found to increase isoniazid clearance by 26% (Delta OFV=49.6).

Conclusions:

The exposure of isoniazid was decreased during pregnancy, due to increased clearance, with respect to a few weeks after delivery. However, the values of isoniazid clearance in all the three *NAT2* acetylator groups in the post-pregnancy phase were higher compared to historical nonpregnant ranges. It is then possible that even in this post-delivery phase the clearance of isoniazid may be larger than in non-pregnant state, but this needs further investigation. The clinical implications of the reduction in exposure of isoniazid on the effectiveness of TB treatment, especially preventive treatment, need further investigation.

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IV-26: *Sergey Gavrilov* Longitudinal assessment of tumor size and neutrophil count in multivariate joint models are more predictive of survival than their baseline values in patients with non-small cell lung cancer

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Introduction: Tumor size, quantified by the Sum of Longest Diameters of target lesions (SLD), has been established as a prognostic marker for NSCLC survival of patients with non-small cell lung cancer (NSCLC), while neutrophil count (NEU) and other hemogram measurements have recently been investigated. Joint models of survival and longitudinal biomarkers, e.g. SLD [1] are a useful framework for survival prediction. Gain in prognostic accuracy of SLD and NEU when measured longitudinally has not been established.

Objectives: The aim of this work was to quantify the association of selected clinical biomarkers ECOG, SLD and NEU with overall survival (OS) in NSCLC data, and systematically test joint model prediction performance when using baseline vs. longitudinal biomarkers SLD and NEU.

Methods: We used two datasets: one set (studies NCT02087423 [2] and NCT01693562 [3]) included 679 NSCLC patients (53% with PDL1 expression >=25%, 41% - <25%, 6% - unknown) from clinical studies of durvalumab, an anti PD-L1 inhibitor (10 mg/kg intravenously every two weeks). Another set (study NCT00322452 [4]) included 354 NSCLC patients (27% mutant EGFR, 17% - wild-type, 56% - unknown) from a clinical study of gefitinib, an EGFR inhibitor (250 mg oral daily). We used the first set to develop three models of OS, all with ECOG as a baseline covariate: a Cox proportional hazards model with SLD and NEU as baseline covariates (COX); a joint model of OS and longitudinal SLD and baseline NEU (JM SLD); and a joint model of OS and longitudinal SLD and NEU (JM SLD&NEU).

In order to estimate and compare the predictive accuracy of these models, we evaluated model performance using area under the receiver-operating characteristic curves (ROC AUC) and Brier scores (BS). Time-dependent ROC AUCs and BSs were calculated for patients from the first, training durvalumab set and the second, prediction set for gefitinib using longitudinal data with different cut-offs in time. Marginal survival was calculated by simulating times of death or event-free survival using the joint models qualified using the data from durvalumab dataset. For each simulation, baseline and longitudinal data were picked from 300 resampled patients from gefitinib dataset. There were 500 simulated datasets. We calculated the median and range over the simulated survival distributions and compared them with the observed Kaplan-Meier (KM) curve.

Results: Patients in the durvalumab and the gefitinib datasets were similar in demographic and disease characteristics and baseline SLD; however, SLD declined at a faster rate in EGFR mutant than EGFR wild-type on gefitinib or patients on durvalumab; NEU were uniformly lower on gefitinib than durvalumab; and OS was better on gefitinib than durvalumab.

Starting from a 2-month cut-off of using longitudinal data, JM SLD and JM SLD&NEU outperformed the COX model on both the training durvalumab and the gefitinib datasets. Moreover, multivariate JM SLD&NEU showed better performance in comparison to JM SLD.

For instance, the following results were obtained, using a 4-month cut-off of longitudinal data and for up to 12-month individual patient survival discrimination after start of treatment: the COX model had a ROC AUC = 0.66, BS = 0.22 based on the training durvalumab dataset, and ROC AUC = 0.61, BS = 0.18 for the gefitinib dataset. JM SLD scored ROC AUC = 0.74, BS = 0.19 for the durvalumab dataset, and ROC AUC = 0.77, BS = 0.14 for the gefitinib dataset. JM SLD&NEU scored ROC AUC = 0.81, BS = 0.17 for the durvalumab, and ROC AUC = 0.82, BS = 0.13 for the gefitinib dataset. Noninformative models would have ROC AUC 0.5 and BS 0.25.

OS predictions agreed with the observed KM estimate better using JM SLD and JM SLD&NEU than COX, for both durvalumab and gefitinib datasets.

Conclusions: Using longitudinal data for SLD and NEU in joint models increased individual discrimination performance and marginal survival predictions vs. baseline data in COX models. Different marginal survival in durvalumab and gefitinib treated patients was explained by differences of SLD and NEU kinetics in these different disease entities and a common modeled relationship between SLD and NEU and survival in the models.

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IV-27: *Peter Gennemark* Determination of antisense oligonucleotide tissue half-life

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Objectives: To estimate the tissue half-life of an antisense oligonucleotide (ASO) accurately and precisely, by properly designing and analysing a cynomolgus monkey study. The half-life determines tissue accumulation upon chronic dosing and is pivotal in the human dose-response prediction.

Methods: ASO pharmacokinetics (PK) is largely sequence-independent and characterized by rapid (hours) distribution to tissue and slow (weeks) terminal half-life dependent on re-distribution from tissue to blood [1]. Therefore, one expects accumulation of drug in tissue for standard (such as once weekly or monthly) dosing intervals. Determination of tissue half-life is of general interest to interpret safety aspects, and to predict efficacy if target is situated in tissue. Here, the liver PK of an ASO was to be measured in 28 cynomolgus monkeys using four monthly subcutaneous (SC) injections (2, 8 or 32 mg/kg) plus one extra loading dose after one week. To investigate toxicology aspects of the ASO, 6 monkeys per dose group (18 in total) were to be terminated two days after the last dose. We sought a suitable termination schedule for the remaining 10 monkeys to estimate tissue half-life. To this end, we used Yu et al.'s cynomolgus monkey population model describing plasma and liver PK of an ASO [2]. The model contains three compartments, representing plasma, liver and all other tissues. We considered a space of 20 experimentally plausible designs, plus one rich design with >100 monkeys to serve as baseline. The search space is hence not exhaustive but represent designs that could realistically be achieved in practice. For each design we simulated 1000 studies. A one-compartment model with dose-dependent volume of distribution was simultaneously fitted to data from all dose groups in each simulated study. The non-linearity represents saturated liver uptake at high doses, and a similar non-linearity was used by Yu et al. The absorption rate was fixed to 1 1/day. The secondary parameter thalf and its precision and its bias with respect to the estimate of the rich design was calculated for each design.

Results: The two best proposed designs (bias 4-11%; 90% confidence of thalf within 14-17% of point estimate) included one satellite group (either 2 or 8 mg/kg) that was observed during washout 3 months after the last dose (N=4) and the remaining 6 animals assigned to the other two dose groups, three to each. The two following best proposed designs (bias 10-29%; 90% confidence of thalf within 17-24% of point estimate) included a satellite single dose group (2 or 8 mg/kg) that was observed in time-series during days 3 to 57 (N=6), and another satellite group (32 mg/kg) was observed during washout 3 months after the last dose (N=4). Repeating the analysis with a linear PK model gave qualitatively similar results. For robustness, it was decided to go for the latter designs to ensure that the half-life could be determined without a modelling approach in case the tested ASO would exhibit significantly different PK from the ASO considered in Yu et al. The design with a dose of 8 mg/kg, and not 2 mg/kg, of the first satellite group was run in vivo to reduce the risk of obtaining data below the limit of quantification. The liver exposure half-life was estimated to 17.6 (15, 21; 5th and 95th percentiles) days based on mathematical modelling taking all liver exposure data simultaneously into account. General learnings from this analysis include: (1) ASO toxicology studies can inform the human dose-response prediction, (2) the best designs sample the majority of animals at steady state, and a few animals in time-series, (3) robustness of the thalf estimate may increase by sampling a larger fraction of the animals in time-series, to avoid non-conclusive data in case accumulation turns out to be negligible, (4) the lowest dose is often of greatest interest from an efficacy point of view but carefully consider the risk of obtaining data below the limit of quantification, and (5) if

longitudinal target engagement biomarker data are available, consider dose-response-time modelling to infer the tissue half-life [3]. Concerning (5), naturally, robustness increases if several approaches are combined.

Conclusion: Modelling and reasoning were used to design a cynomolgus monkey study to determine the tissue half-life of an ASO with predicted bias <20% and good precision. From the resulting data, the tissue half-life could be inferred as 17.6 (15, 21; 5th and 95th percentiles) days.

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IV-28: *Eva Germovsek* A time-to-event model relating integrated craving to hazard of starting smoking across different nicotine replacement therapy formulations

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Objectives: Tobacco use is a major public and individual health problem, with recent estimations showing it causes over 7 million avoidable deaths yearly [1]. This is mainly due to the fact that smoking increases the risk of developing cancer, but it also causes chronic obstructive pulmonary disease, accelerates cardiovascular disease development, increases the risk of infectious diseases and insulin resistance, etc. To reduce tobacco use, nicotine replacement therapy (NRT) formulations are commonly used since they reduce individual's craving for nicotine and thus increase the probability of stopping smoking [2, 3]. The aim of this work was to quantitatively investigate how a pharmacodynamic marker of long-term withdrawal symptom response (i.e. 'integrated' craving, meaning craving over a period of time) is linked to smoking cessation.

Methods: Retrospective data that were available for analysis were collected in 19 separate studies, and included three NRT formulations, specifically: inhaler, mouth spray, or patch, and also data from the combination use of inhaler and patch. Smokers, who were instructed not to smoke, were included in either the active (where they received NRT) or the placebo treatment arm. If a subject was not present on a visit, this was (per definition in the studies) conservatively defined as non-abstinence. Integrated craving was assessed with three craving scales: a 4-category scale, a 5-category scale, and a 100 mm visual analogue scale (VAS). Abstinence status was a binary response, and was modelled using a time-to-event (TTE) model, where the event was non-abstinence. Since events were only assessed at study visits, the exact time of an event was unknown, and interval-censoring was used. Several hazard functions were explored, where hazard was time-constant, time-varying (i.e. Gompertz, Weibull distributions were used), or a combination of both. Integrated craving at previous and current (i.e. when an event was recorded) visit was investigated as a predictor on the hazard. NONMEM 7.4 (ICON Development Solutions, Ellicott City, Maryland) with the Laplace approximation was used to obtain the likelihood.

Results: The data included 9,323 adult subjects with median (range) 2 (0-99) previous attempts to quit smoking, and median (range) age 42 (17-81) years and body mass index 25 (13-64) kg/m^2. The largest proportion of subjects (30%) smoked their first cigarette 6-30 minutes after waking up, and the smallest proportion of subjects (6%) >60 minutes after waking up. In total, 9% of subjects remained smoking abstinent until the end of the studies, with study lengths ranging from 3 weeks to 2 years. A combination of time-constant and the Gompertz hazard proved best to describe the data, with hazard decreasing over time. Current integrated craving provided a better fit than previous craving. Integrated craving was positively related with the hazard of having an event, and was included in the model using a sigmoidal E_{max} function as it showed a better fit to the data (dOFV=-2015), compared to a linear relationship between craving and hazard. The integrated craving giving 50% of maximal hazard due to craving ($Crav_{50}$) was 0.81 (relative standard error (RSE) 5%) for the 4-category scale, and 24.5 (3% RSE) for the VAS. For craving measured with the 5-category scale $Crav_{50}$ was 0.98 (1% RSE) and 1.24 (7% RSE) for single NRT formulations and for combination of inhaler and patch, respectively. Hill exponent was estimated as 12 (17% RSE). Hazard at 1 year was 0.13/month for maximal craving from different scales, and 0.014/month for craving of zero (i.e. lowest craving).

Conclusions: A time-to-event model was developed, where integrated craving was related to hazard in a sigmoidal E_{max} fashion, and showed that higher craving is related to lower probability of remaining abstinent. Future work will involve developing a model to connect all craving scales (similarly as done in [4]) and investigating other predictors, such as markers of smoking addiction.

Disclosures: EG, MCK and MOK declare no conflicts of interest; AH, ÅW, PS and AV are (former) employees of subsidiary companies of Johnson & Johnson.

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IV-29: *Bill Gillespie* Torsten: Stan functions for pharmacometric applications. New functionality including within chain parallel computation.

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Introduction/Objectives: Stan is a widely used, open-source, probabilistic programming language and Bayesian inference engine [1, 2]. It provides a general model specification language and uses HMC simulation for fully Bayesian data analysis. Torsten is a library of Stan functions that simplifies implementation of pharmacometric (PMX) models and extends the range of models that may be implemented [3]. The objective of the work presented here is to improve and extend Torsten. This includes the addition of new functions and enhancements to existing ones.

Methods: Torsten is open source software. Its functions are written in C++ and they comply with Stan development requirements. They may be accessed by all Stan interfaces such as RStan and CmdStan. Torsten now includes versions of Stan's ordinary differential equation (ODE) solvers that have been revised to improve performance and provide MPI-based parallel computing, Existing Torsten PMX functions now use those functions instead of those in Stan. Also added to both Stan and Torsten is a new ODE solver using the Adams-Mouton method from the CVODES package [4]. Previous Torsten PMX functions calculated model states for one individual at a time. We have implemented new population functions that calculate the model states for a group of individuals in a single function call. Those functions also employ MPI to distribute those calculations over multiple processors, thus providing efficient within chain parallel computation. We have developed a Stan interface to user-provided numerical partial differential equation (PDE) solvers. So far the interface has been tested on three external solvers: OpenSees, libMesh and MFEM. More can be added with similar fashion.

Results: Here we show the parallel speedup using Torsten's BDF integrator for stiff ODEs with a neutropenia model described by a system of 8 ODEs. In this model we solve a group of ODE systems. Each ODE system in the group is the same but with different parameters. We fix the group size to 1000 and solve it with Torsten's MPI solver using different numbers of processors.

MPI performance of the neutropenia model solved by Torsten's BDF integrator

n_processor	Walltime(ms)	Speedup	efficiency
1	9774	1.000	1.000
2	4943	1.977	0.989
4	2453	3.985	0.996
8	1350	7.240	0.905
16	1140	8.574	0.536
32	788	12.404	0.388
64	710	13.766	0.215
128	534	18.303	0.143
256	446	21.915	0.086
512	451	21.672	0.042

Similar speedup is seen with the Adams-Moulton integrator. Based on the above ODE integrators, Torsten's new population PMX functions take NONMEM-compatible event inputs so they can be directly applied in a Stan inference model. Below we show the MPI performance results for a two compartment model solved by Torsten's PMX function using the BDF integrator. The inference model contains a population of 8, with the parameters being each individual's CL, Q, V1, V2, and ka. In each MCMC run the number of warmup and post-warmup samples is 200 each.

MPI performance of the two-cpt inference model by Torsten's PMX solver (BDF integrator)

n_processor	Walltime(ms)	Speedup	efficiency
1	7850	1.000	1.000
2	4067	1.930	0.965
4	2186	3.591	0.898
8	1255	6.255	0.782

Conclusions: Recent developments in Stan and Torsten significantly improve computational efficiency and extend the range of models that may be implemented. The addition of within chain parallel computation to Stan/Torsten makes fully Bayesian analysis with Stan an increasingly practical option for PMX applications.

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IV-30: *Anais Glatard* Amisulpride: Real-World Evidence of Dose Adaptation and Effect on Prolactin levels using PK/PD modeling

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Objectives: Amisulpride is administered orally at a wide range of doses (100-800 mg daily) for treating schizophrenia. Therapeutic drug monitoring of amisulpride is strongly recommended with a therapeutic reference range of 100-320 ng/mL for plasma trough concentrations [1]. The advantage of amisulpride is its low propensity for body weight gain, the major adverse effect of second-generation antipsychotic. However, hyperprolactinemia is reported in more than 90% of patients [2]. While hyperprolactinemia is asymptomatic in some cases, it frequently results in gonadal dysfunctions. The objectives of this work were first to characterize the pharmacokinetic (PK) profile of amisulpride and to detect sources of variability in order to suggest optimal dosage regimens for reference range achievement. Secondly, we aimed to develop a PK/PD model describing the relationship between amisulpride concentrations and prolactin data in an adult and elderly psychiatric population.

Methods: PK and clinical data were obtained from patients from the Department of Psychiatry of the Lausanne University Hospital. With the use of a one-compartment model with first order absorption (Ka) and a bioavailability of 48%, the influence of demographic, clinical (body weight (BW), lean body weight (LBW) [3], body mass index (BMI), smoking status, creatinine clearance estimated by the Cockcroft-Gault formula (CLCRCG) if BMI< 25 kg/m^2 and the Cockcroft-Gault formula integrating the LBW if BMI≥ 25 kg/m^2 [4]) and genetic characteristics as well as comedications (inhibitor of P-gp or lithium) on amisulpride clearance (CL) and volume of distribution (V) was quantified. Trough concentrations at steady-state ($Cmin_{SS}$) after administration of several dosage regimens were simulated with the final PK model in 500 virtual patients according to various influential covariates. The final PK model was combined with a direct Emax model to describe the prolactin data. As prolactin levels were markedly different in males and females, the gender effect on Emax (the typical maximum prolactin elevation) was directly included in the structural model development. Influence of age, menopause, BW, LBW, season and concomitant antipsychotics that might have increased prolactin levels were quantified on Emax. Finally, prolactin levels were predicted by using the final PK/PD model at time of trough amisulpride concentrations.

Results: A total of 513 amisulpride plasma concentrations from 242 patients (18-91 years, median BMI = 25 kg/m^2) and 101 prolactin measurements from a subset of 68 patients were available for analyses. In the final PK/PD model, population parameters for CL, V, Ka, baseline prolactin levels, Emax in females and EC50 were 43.9 L/h, 926 L, 0.9 h^{-1} (fixed as previously published [5]), 16 ng/mL, 141 ng/mL and 42 ng/mL, respectively. Inter-individual variabilities on CL, V and Emax were 34%, 58% and 50%. Age ($p \leq 0.001$) and LBW ($p=0.007$) had a significant effect on CL which was decreased by 0.5 in a 80-year compared to a 40-year individual (LBW = 50 kg) and increased by 1.5 in a 40-year individual with LBW = 100 kg *vs.* LBW = 50 kg. Emax parameter was decreased by 53% in males. $Cmin_{SS}$ were higher than the recommended range in

72% of the 60-year individuals receiving 400 mg b.i.d. and were lower than the recommended range in 79% of the 20-year individuals receiving 300 mg q.d. The maximum recommended dose in elderly patients, *i.e.* 200 mg b.i.d. [6] resulted in $Cmin_{SS}$ higher than the recommended range in 72% of those having a LBW of 40 kg. In our sample analysis when amisulpride trough concentrations are in the therapeutic reference range, model-predicted prolactin levels were over the normal values (model-predicted median = 71 ng/mL, range = 41-135 ng/mL and 138 ng/mL, 75-309 ng/mL, normal values: ≤ 20 ng/mL and ≤ 25 ng/mL in males and females respectively).

Conclusions: In the present study, LBW had a more significant effect on CL than BW supposedly because LBW better estimates body size in overweight or obese patients, representing half of our study population. This work suggests that amisulpride dose adaptation with age and LBW is essential in order to reach the recommended range in patients. When amisulpride $Cmin_{SS}$ are in the recommended range, model-predicted prolactin levels were above the normal values in all patients indicating that amisulpride dose reduction is not appropriate when aiming to reduce prolactin levels.

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IV-31: *Ferran Gonzalez* Pharmacokinetic model development for total and free vancomycin in critically ill children

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Objectives: Vancomycin is an antibiotic agent used against Gram-positive bacterial infections. In order to achieve optimal target concentrations, it is essential to develop pharmacokinetic (PK) models. Specifically, determining the PK properties in paediatric populations is of clinical importance, since these are at high risk of inadequate concentrations. A number of vancomycin PK studies have already been performed in children, in which PK models were fitted to total vancomycin plasma concentration. However, to improve vancomycin dosages, unbound concentration needs to be considered, since this matrix is driving antimicrobial efficacy [1]. Therefore, the aim of this study was to develop a PK model of vancomycin considering total and unbound plasma concentration.

Methods: Data from a multicentric clinical trial were used, in which intermittent and continuous intravenous doses were administered to a cohort of 76 subjects aged between 0 and 14 years. A total of 395 samples were collected, measuring plasma concentrations of total and unbound vancomycin, albumin, creatinine and C-reactive Protein. Population PK models were developed using NONMEM VII. Initially, one and two-compartment models with first-order elimination rates were fitted to the total plasma concentration of vancomycin. A priori allometric weight scaling on clearance ($wt^{0.75}$) and volume (wt) was added, and a sigmoid maturation function driven by postmenstrual age was included for clearance. Finally, a two-compartment model using the same scaling, covariates and elimination rate was accounted for plasma protein binding to fit total and unbound vancomycin simultaneously, assuming linear protein binding.

Results: A two-compartment model with first-order elimination rate and maturation function described the PK of total vancomycin significantly better than the one-compartment model (Δobj = 275.6). The final parameter estimates, standardised to a 70kg mature individual, were 6.7 L/h for clearance (CL), 12.3 L for the central volume of distribution, 11.6 L/h for the inter-compartmental CL , 15.8 L for the peripheral volume of distribution, 60.5 weeks for PMA50 and 1.9 for the Hill coefficient.

The two-compartment model fitted to the unbound and total vancomycin together resulted in the following estimated parameters for free vancomycin: 9.3 L/h CL, 15.6 L for the central volume of distribution, 11.7 L/h for the inter-compartmental CL and 21.1 L for the peripheral volume of distribution. Fraction unbound was estimated to be 0.7 and the estimated maturation parameters resulted in 59.3 weeks for PMA_{50} and a Hill coefficient of 2.0.

Conclusions: In conclusion, PK models to estimate population parameters of vancomycin when using unbound and total plasma concentrations were developed. The estimated pharmacokinetic parameters were consistent with previous studies [2, 3]. Finally, the two-compartment model fitted to the unbound

and total concentration together exhibited a good distribution of the residuals. Future work will include a more exhaustive covariate analysis, and secondary structural and covariate model building by means of a genetic algorithm.

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IV-32: *Ignacio González* Pharmacokinetic/Pharmacodynamic Modelling of in vivo IL-13 Modulation by a monoclonal antibody (MEDI7836)

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Objectives: A joint pharmacokinetic (PK) and pharmacodynamic (PD) model was built in NONMEM, version 7.3 from a first-in-human trial of a novel biologic, MEDI7836. MEDI7836 is a human immunoglobulin G1 lambda (IgG1λ-YTE) monoclonal antibody (mAb), with an Fc modification to reduce clearance. MEDI7836 specifically binds to and functionally neutralizes interleukin-13 (IL-13) by preventing interactions with both IL-13 receptors (IL-13Rα1 and IL-13Rα2).

Methods: Thirty-two healthy male adults were enrolled into this single dose-escalation clinical trial. Four different active doses were tested (30 mg, 105 mg, 300 mg, and 600 mg) with 6 patients each and 8 patients received placebo. Following single subcutaneous administration, individual time courses of MEDI7836 concentrations, and the resulting IL-13 modulation *in vivo* (PD) were quantified. PK and PD samples were taken from day 1 to day 281. The average number of samples taken per subject was 14 PK and 15 PD samples, respectively. Baseline body weight, baseline age, race and immunogenicity status were recorded and tested as covariates. The performance of the final PK-PD model was evaluated by conducting a visual predictive check (VPC) and bootstrap. All post-processing graphical and statistical analyses were completed with R version 3.5.1.

Results: A first-order absorption and 2-compartment disposition with linear elimination model adequately described the PK data. Residual variability was modelled using a combined (additive + proportional) error model. Mean (%CV) of CL, V1, V2 and Q were estimated at 0.437 L/d (52%), 3.96 L (67%), 7.46 L (46%), and 1.06 L/d. Covariate analysis revealed an impact of anti-drug antibody (ADA) on CL, with treatment emergent ADA positive subjects showing a 74% CL increase (0.76 L/d [ADA +] *vs* 0.437 L/d [ADA -])). A binding PK-PD indirect response model was built to characterize the exposure-driven modulation of the target (IL-13) over time. Validation data indicated the bioanalytical assay quantified the level of target that was not in-complex with drug (i.e. a free IL-13 assay). However, reported data suggested dose-dependent increase in IL-13 plasma-concentration over time, indicative of a total IL-13 assay. The target time course was thus modelled as a linear combination of free target and a percentage (to be estimated from data) of the drug-target complex. Complex formation/dissociation parameters were assumed constant based on *in vitro* experiments and sequential PKPD modelling was utilized. A relatively fast turnover and low baseline levels of IL-13 were estimated, and the fraction of complex detected by the assay was predicted to be around 10%. No relationship was found between any of the covariates and PD parameters. Expectation-maximization (SAEM with interaction and IMP) estimation methods were selected to achieve a successful minimization avoiding convergence problems. VPC (n = 1,000) plots showed that the final model could describe both MEDI7836 kinetics and IL-13 modulation with reasonable accuracy across the dose range tested. All final model estimates were close to the median values of the bootstrap estimates (1,000 resampled datasets) and were within the 95% confidence interval.

Conclusions:

A population PKPD binding model linking exposure of MEDI7836 with IL-13 modulation in the serum adequately characterized the exposure-response observed in a first-in-human trial and helped rationalize unexpected results from a bioanalytical free PD assay kit.

IV-33: *Mario Gonzalez Sales* Assembling pharmacometric datasets in R: the puzzle package

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Introduction: The pharmacometrics workflow has routine steps: 1) assemble the dataset, 2) explore, 3) model the data, 4) evaluate, 5) validate the model, and 6) communicate the findings. The automation of these steps saves time and money, reduces the risk of errors, and increases reproducibility. Currently, there are a number of excellent tools available to enhance steps 2-6).[1-11] However, to the best of our knowledge, there is no open-source tool to support step 1). Because of the core or 'heart' of each pharmacometric analysis is a dataset, and the time required to construct a pharmacometrics dataset can sometimes be higher than the effort required for the modeling *per se*, Syneos Health's pharmacometrics team has created puzzle, an open-source R package that is freely available on Github (https://github.com/syneoshealth/puzzle).

Objective: The objectives of this work have been:

- To develop an R package to simplify the time consuming and error prone task of assembling pharmacometrics datasets in order to speed up the pharmacometrics workflow.
- To increase the reproducibility of pharmacometric analysis by decreasing the probability of errors during the data assembling step and facilitating the quality control task.

Methods: Puzzle consists of a series of functions written in R. These functions create, from tabulated files, datasets that are compatible with the formatting requirements of the NONMEM® software.[12] In order to facilitate its use and to decrease the slope of the learning curve, users are only required to learn the behavior and syntax of one function, puzzle(). Nevertheless, the puzzle package involves additional functions intentionally working "under the hood" to enhance the user experience. Furthermore, a web interface is also available and was developed as a shiny application that can be used for those users with little or no experience using R, or for those pharmacometricians not feeling comfortable with the R syntax.

Results: With only one function, puzzle(), complex pharmacometrics databases can easily be assembled. Users are able to select from different absorption processes such as zero- and first-order, or a combination of both. Furthermore, datasets containing data from one or more analytes, and/or one or more responses, and/or time in- and/or dependent covariates, and/or urine data can be simultaneously assembled. The output of puzzle() is always a ".csv" file that can be read by NONMEM® because it is fully compatible with its formatting rules. The puzzle package can be easily installed using the following R syntax: devtools::install_github("syneoshealth/puzzle").

Conclusions: The puzzle package is a powerful and efficient tool that helps modelers, programmers and pharmacometricians through the difficult and complex process of assembling pharmacometrics datasets. In particular, it is the first open-source tool supporting pharmacometricians during the challenging, error prone, and time consuming process of data assembling.

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IV-34: *Katharina Martha Götz* Predictive Systems Medicine Modelling of Myelosuppression and Recovery of Hematopoietic Cells among Adult Patients with Hematopoietic Cell Transplantation

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Introduction: Allogeneic Hematopoietic Cell Transplantation (HCT) can cure or improve the outcome in a variety of hematological diseases. Currently, predictive scores of severe complications such as viral infections, graft-versus-host disease (GVHD) and relapse after HCT are insufficient. Consequently, early lifesaving interventions cannot always be applied on time. The collaborative project XplOit [1] started in 2016 with the aim to improve the outcome of adult patients after HCT by the application of systems medicine modelling, in order to reveal underlying processes of HCT complications. Furthermore, patients' individual course of disease should be predicted.

Objectives: The objective was to describe, characterize and predict myelosuppression after conditioning chemotherapy and recovery of blood cells after HCT via mathematical models of leukopoiesis and thrombopoiesis.

Methods: Retrospectively collected daily measured cell counts of patients with HCT due to different diagnoses at University Hospital Essen, Germany, were analyzed. Model development and validation were performed independently for each of the two submodels, both consisting of a structural and stochastic model. Each structural model was developed stepwise by examining turnover models and further literature models. Given the developed models of leukopoiesis and thrombopoiesis and their estimated parameters, we informed the models based on a smaller dataset until day three after HCT and predicted individual profiles from day three to six weeks after HCT (Bayesian approach). Parameter estimation and simulations were performed using non-linear-mixed-effects methods implemented in the software NONMEM (version 7.4.3) and the graphical interface Pirana (version 2.9.9). Statistical evaluation and graphics were created within the software R (version 3.4.3) and its graphical interface RStudio (version 1.1.423).

Results: 58,731 individual leukocyte and 58,776 thrombocyte measurements of 1245 HCT patients were used for leukopoiesis and thrombopoiesis model development. The final structural models were adapted from Friberg et al. [2], originally developed to describe suppression and recovery of neutrophils in patients after administration of myelosuppressive chemotherapeutics. Due to missing information on the exact conditioning regimen, we assumed the drug effects of the conditioning regimen prior to HCT. The following population parameters were estimated: a leukocyte baseline of 5.67 cells/nL and a thrombocyte baseline of 89.50 cells/nL. To cover the feedback mechanisms of circulating on proliferating cells, the estimated parameter γ is 1.9 higher in the thrombopoiesis model compared to the leukopoiesis model (0.11 and 0.06, respectively), whereas the drug effect on proliferating stem cells is comparable in both models (0.72 and 0.66, respectively). Thrombocytes showed an increased mean transit time of 6.00 days compared to leukocytes (4.42 days). In the validation cohort (457 patients) the observed individual, hematologic recovery data matched very well with the model's predictions.

Conclusions: We developed models of hematopoietic recovery among adult patients with HCT that show a good descriptive performance. The estimated leukocyte baseline presents a normal value. Similarly, the estimated thrombocyte baseline presents with mild thrombocytopenia according to the common toxicity

criteria for adverse events (CTCAE) [3]. In conclusion, with *a priori* information the models adequately predict nadir and recovery of leukocytes and thrombocytes in a smaller dataset from day three to six weeks after HCT.

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IV-35: *Iztok Grabnar* Oxcarbazepine and its active metabolite 10-monohydroxycarbamazepine clearance maturation in paediatric patients with epilepsy

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Introduction: Oxcarbazepine (OXC) is a second generation antiepileptic drug approved for treatment of partial seizures in adults and children as monotherapy or adjunctive therapy. After oral administration OXC is rapidly absorbed and metabolized to its 10-monohydroxy derivative (MHD) which is mostly responsible for the pharmacological effects. MHD is further metabolised with glucuronidation, is eliminated renally and to minor extent by metabolism to dihidroxy derivative [1]. There is a high variability in reported therapeutic ranges of MHD suggesting high variability in pharmacokinetics and a potential benefit of therapeutic drug monitoring (reference range of MHD trough concentrations 3-35 mg/L). Oxcarbazepine use in paediatric patients is particularly challenging due to lack of pharmacokinetic studies to support dosing regimen [2-9].

Objectives: The objective of this study was to develop OXC-MHD parent-metabolite population pharmacokinetic model in paediatric patients (0.5-3 years) to assess the OXC and MHD clearance maturation and to evaluate the recommended dosing regimen in children. To our knowledge this is the only OXC-MHD model in this age group.

Methods: In this prospective study we included 18 patients with epilepsy on stable mono- or combination therapy with OXC for at least one month. Steady-state blood samples were collected immediately before dosing (0) and after 1, 2, 4, 6, and 8 h post dose for determination of OXC and MHD plasma concentration. Pharmacokinetic analysis was performed in NONMEM (ver. 7.3), Perl-speaks-NONMEM and Xpose were used for model development and evaluations. FOCE-I was used for parameter estimation. Initially, only OXC concentration measurements were analysed to develop the structural model of the parent drug. The structural models tested were one- and two-compartment models with first-order absorption and elimination (ADVAN2 and ADVAN4 subroutines). This preliminary analysis confirmed that pharmacokinetics of OXC are more adequately described by a two-compartment model. Subsequently, we built a parent-metabolite model with user-defined differential equations (ADVAN 9). Based on previous analyses [10] we assumed complete OXC absorption. Absorption was modelled as a first-order process. Additionally, we assumed that 10% of OXC is presystemically metabolized to MHD (first-pass metabolism) and that OXC is completely transformed to MHD [10]. Patient weight (WT) and age were introduced into the model using a theoretical allometric relationship and a sigmoidal maturation function (MF) of post menstrual age (PMA in weeks) [11].

Results: The structural model comprised of a two-compartment model for the disposition of OXC and a one-compartment model for the disposition of MHD. The estimated parameters were absorption rate constant (K_a), volume of the central and peripheral compartment of the parent drug ($V_{1,OXC}$ and $V_{2,OXC}$, respectively), elimination and distribution clearance of the parent drug (CL_{OXC} and Q_{OXC}, respectively), and clearance and distribution volume of the metabolite (CL_{MHD} and $V_{1,MHD}$, respectively). Available data allowed estimation of interindividual variability (IIV) of of K_a, $V_{1,OXC}$, CL_{OXC}, and CL_{MHD}. Allometric scaling of all clearance and volume parameters with theoretic exponents of 0.75 and 1, respectively; improved the model fit and decreased OFV by 37.2 units. After adjustment for size the significance of clearance

maturation was investigated. Inclusion of the maturation function on CL_{OXC} decreased OFV by 10.6. Further inclusion of the maturation function on CL_{MHD} provided additional decrease of OFV by 5.43. The final model was:

K_a = 0.863 h^{-1}; IIV = 75.0%
$CL_{OXC} = 127\times(WT/70)^{0.75}\times(PMA^{4.57}/(58.2^{4.57}+PMA^{4.57}))$ L/h; IIV = 7.40%
$V_{1,OXC} = 141\times(WT/70)^{1}$ L; IIV = 206%
$V_{2,OXC} = 2260\times(WT/70)^{1}$ L
$Q_{OXC} = 103\times(WT/70)^{0.75}$ L/h
$CL_{MHD} = 0.489\times(WT/70)^{0.75}\times(PMA^{6.15}/(55.1^{6.15}+PMA^{6.15}))$ L/h; IIV = 12.7%
$V_{1,MHD} = 19.7\times(WT/70)^{1}$ L

The standard diagnostic plots and VPC indicated no significant bias.

Conclusion: A population OXC-MHD parent-metabolite pharmacokinetic model was developed which confirms important changes in pharmacokinetics in infants. The model can be used to evaluate the recommended dosage regimen with Monte Carlo simulations.

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IV-36: *Silvia Grandoni* Development and evaluation of a PBPK model to study the pharmacokinetics of inhaled drugs in rats

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Objectives: development and evaluation of a PBPK model to study the pharmacokinetics of inhaled drugs in rats, using test compounds with different solubility and permeability characteristics.

Methods: a physiologically-based pulmonary model was integrated in a previously developed in house WB-PBPK model [1], with the aim of simulating intratracheal (IT) administrations in rats. The pulmonary model structure reflects the division of the respiratory system in a central and peripheral region, as previously proposed in [2] and [3] and each region is characterized by a different volume, surface and perfusion (the first region is connected with the systemic circulation, the second one with the pulmonary circulation). In each region the drug deposits, following a certain deposition pattern, in its undissolved form, then it can dissolve in the lung fluid and be absorbed through the tissue. The mucociliary clearance process is added as acting on the undissolved drug in the central region. Lung tissue is modelled as a permeability limited tissue as proposed in [4], a bidirectional transport is considered, so that there is a drug exchange between lung tissue and fluids (i.e., the epithelial lining fluid and blood) via passive transport. An additional monodirectional transport is also included in the model to take into account the possible action of the efflux transporters such as the P-glyco proteins. The quantification of the lung tissue permeability was done through a simple modelling of the in vitro Calu3 permeability test data. This model is composed by three compartments: the apical media, the cells and the basolateral media. It is assumed that the main fluxes in the system are due to the passive bidirectional transport between lung cells and the two fluids and to the monodirectional efflux from the tissue to the epithelial lining fluid; furthermore, the drug binding to the Calu3 cells is included. The model was tested using in-house plasma and lung concentration data obtained after IT administration in rats. We started from compounds with high pulmonary solubility, for which the permeation through the lung tissue is the absorption rate limiting step with the aim of testing the permeability model, after that, the model was tested considering compounds with low solubility to test the whole model.

Results: the model was evaluated by using experimental data obtained after IT administration of 9 different compounds, through a visual comparison between the simulated profiles and the experimental data and a quantitative comparison between the Area Under the Curve (AUC), the maximum concentration (Cmax) and the Mean Residence Time (MRT) computed on the simulated plasma and lung concentration profiles and on the collected data. The first comparison, focused on the highly soluble compounds, showed that the model is able to correctly predict the time course of the plasma and lung concentration, both in terms of profile shape and of PK parameters. Average fold errors related to plasma and lung were computed and are close to 1. Similar results were found for poorly soluble compounds.

Conclusions: the results obtained suggest that the model is able to describe the plasma and lung concentration-time profiles in the preclinical species rat and can be considered as a base for translational purposes.

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IV-37: *Ana-Marija Grisic* Semimechanistic clearance models of oncology monoclonal antibodies and impact of study design: cetuximab as a case study

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Objectives:

Monoclonal antibodies (mAbs) undergo nonspecific linear and target-mediated nonlinear disposition, as well as recently described time-dependent elimination [1-4]. However, the data analyzed can heavily impact the resulting final model, leading to disagreement in identified pharmacokinetic (PK) models for the same mAb, as in case of cetuximab, an anti-epidermal growth factor receptor mAb widely used in oncology [5-7].

This study aimed to (1) characterize cetuximab population PK (PPK) and compare various (semimechanistic) clearance (CL) models and (2) investigate the impact of CL model misspecification on derived exposure metrics under different study designs.

Methods:

In total, 3,821 PK samples from 2 multicenter clinical trials in patients (N=226) with metastatic colorectal cancer were used to develop the PPK model of cetuximab using the nonlinear mixed-effects modeling approach. In trial A (phase I, N=62), patients were initially treated for 6 weeks with cetuximab (doses ranged from 250 mg/m^2 q1w to 700 mg/m^2 q2w) and afterward received FOLFIRI co-therapy. In trial B (phase I/II, N=164), patients were initially treated for 3 weeks with cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 q1w) and irinotecan. Afterward, a subset of patients underwent cetuximab dose escalation (to the maximum dose of 500 mg/m^2 q1w). The sampling comprised longitudinal C_{min} samples plus a C_{max} sample at the end of the first infusion and dense sampling over 1 dosing interval. Six CL models were investigated: (1) linear (LCL) [7], (2) linear with exponential change over time (TVARCL) [8], (3) Michaelis-Menten (MMCL) [5], (4) linear and Michaelis-Menten (LCL+MMCL), (5) linear with exponential change over time and Michaelis-Menten (TVARCL+MMCL), and (6) linear and 0th-order (LCL+0.EL) [6].

To address the impact of CL model misspecification on accuracy (root mean square error) and bias [9] in derived exposure metrics (area under the curve [AUC] and C_{min} after second dose and at assumed steady state), the stochastic simulation and estimation approach (SSE procedure in PsN) was employed to compare the reference and 5 alternative models under 6 study designs that differed in dose range (multiple dose levels vs single dose level) and sampling density (rich, semisparse, and sparse).

Results:

The PPK model that best described the data was a 2-compartment model with parallel Michaelis-Menten and linear elimination that changed exponentially over time. The baseline linear CL of 17.4 mL/h was

estimated to decrease over time with a mean maximal decrease of ≈23% (38% CV), and the time to half-maximal decrease reached ≈5 months after the first dose. To address potential mechanisms [2,4], the time-varying CL in responders and nonresponders (as per Response Evaluation Criteria in Solid Tumors criteria) was compared: the CL decrease was of higher magnitude in responders than in nonresponders. These results underline the bidirectional PK-PD relationship anticipated for mAbs and its influence on unidirectional assumption of exposure-response causality. Thus, in case of time-varying CL the concept of purely drug exposure–based therapeutic drug monitoring needs to be expanded.

The second part of our analysis addressed the impact of CL model misspecification on derived exposure metrics under different study designs. Overall, for all 4 investigated exposure metrics and across all study designs, the TVARCL model resulted in the lowest inaccuracy and MMCL model resulted in highest inaccuracy and bias relative to the reference (TVARCL+MMCL) model; C_{min} is least impacted by model-misspecification both in terms of accuracy and bias.

Conclusions:

This study is the first to report a combination of nonlinear and time-varying linear CL for a mAb elimination and to propose a consolidated model for cetuximab. The change of CL over time correlated with the patients' response status. The effect of CL model misspecification on derived exposure metrics was influenced by the underlying study design. Steady-state C_{min} was the most robust PK metric. The alternative model that was most likely to be identified was TVARCL. This analysis contributes to understanding of exposure-response dynamics and informing design of future clinical trials of oncology mAbs.

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IV-38: *Jinju Guk* Modelling the dose-effect relationship between DAV132, an activated charcoal based product, and fecal concentration of moxifloxacin in healthy volunteers

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Objectives: The administration of antibiotics leads to disruption of the intestinal microbiota, which plays an important role in various host processes, including resistance to colonization and infection by potentially pathogenic bacteria in the intestines [1,2]. We previously modeled the co-evolution of plasma and fecal concentration of free moxifloxacin, a fluoroquinolone antibiotic, and of microbiota disruption in humans [3]. DAV132 is an oral product which delivers a powerful charcoal-based adsorbent to the late intestine, which reduces free fecal moxifloxacin concentrations in a dose-dependent manner [4,5]. We wished to develop a model of DAV132 effect on free fecal Moxifloxacin concentration using data of a randomized clinical trial where healthy volunteers received orally moxifloxacin alone or with 10 different doses of DAV132.

Methods: A total of 131 healthy volunteers (HVs) were recruited in the randomized clinical trial (Sponsored by Da Volterra) and received oral moxifloxacin (400 mg OAD) for 5 days alone or associated with various DAV132 doses for 7 days: 0 (no DAV132) 2g/d, 3g/d, 6g/d, 10g/d, 15g/d and 22.5g/d (2g/d was given BID, 22.5g/d TID, the other doses BID and TID). Plasma moxifloxacin concentrations were measured at Day 1 and Day 5 and fecal samples were taken daily from Day 1 to Day 9, at Day 12, Day 16 and Day 37 to measure free moxifloxacin concentrations by LC/MS/MS. The previously developed model of plasma and fecal moxifloxacin pharmacokinetics was used to characterize the pharmacokinetic properties of moxifloxacin and its fecal excretion [3]. Several models accounting for DAV132 kinetics in the gastrointestinal tract were studied. The effect of the amount of charcoal in the distal ileum of the large intestine (called the fecal compartment) in reducing the free fecal moxifloxacin was modeled. The analyses were performed using nonlinear mixed effect models and the Stochastic Approximation Expectation-Maximization in Monolix 2018R2 (Lixoft, France).

Results: Plasma concentrations of moxifloxacin were well described by a two-compartment model with two-transit compartment and free fecal moxifloxacin concentrations were successfully explained by a connection to plasma concentrations through two-transit compartments. The elimination of moxifloxacin in feces was modeled as in [3], but adding a diffusion of moxifloxacin between the last transit elimination compartment and the fecal compartment. DAV132 was modeled with a transit compartment model and charcoal is assumed to be delivered in the fecal compartment. A specific model of the adsorption of charcoal and moxifloxacin in the fecal compartment was derived. This model allowed to describe the huge reduction of free fecal moxifloxacin concentrations when given 7.5 g of DAV132 TID and the low effect of small doses of DAV132.

Conclusions: The developed model was able to capture the delayed effect of moxifloxacin adsorption by charcoal following DAV132 administration and the relationship between DAV132 dose and the reduction in free fecal moxifloxacin concentrations.

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IV-39: *Tingjie Guo* Exploring practical limitations of model-based Bayesian dose optimization in intensive care patients

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Introduction

Model-based dose adaptation (MBDA) based on empirical Bayes estimates (EBE) plays an important role in optimizing drug treatment in intensive care (ICU) patients. MBDA requires dosing histories and patient-specific covariates, which can be subject to human error. For instance, delays between electronic health records and actual dosing times are inevitable during routine patient care. A strength of MBDA is the possibility to include historical pharmacokinetic (PK) data, which may improve parameters estimation. This strength may turn into a weakness due to high PK variability in ICU patients. The aim of this study was to investigate the impact of: 1) delays in recorded versus actual dosing, and 2) inclusion of historical PK data from ICU patients, on the EBEs and associated dosing recommendations.

Methods

Vancomycin PK model

We used a published one-compartmental population PK model of vancomycin in ICU patients [1]. The model was validated in external datasets [2].

Dosing time error

Dosing time delay (DTD) was defined as the delay between recorded and actual time of dosing. We evaluated the impact of DTDs on EBEs and derived metrics to quantify its impact on treatment efficacy. A dataset was simulated (1000 patients) by sampling covariates (weight, CLcr) from a historical dataset [2]. A dose regimen of 1000 mg B.I.D was assumed. The simulated PK data was used to calculate EBEs for different DTDs (0, 0.25, 0.5, 1, 2 hours or sampled from a truncated normal distribution). We considered two scenarios: S1: sampling after the 1st dose; S2: sampling before the 4th dose. Sampling times for these scenarios were obtained according to the following designs: D1: trough; D2: mid-interval; D3: peak & trough; D4: peak & mid-interval; D5: peak, mid-interval & trough. For these simulation scenarios we generated recommendations of both loading dose (LD) and maintenance dose (MD) required to reach the efficacy target of $AUC_{24h,ss}$≥400 mg*h/L. For these recommendations we computed the probability of target attainment (PTA), and a probability of contradicted dose decision (PCD), reflecting a contradicted direction of the dose recommendation (e.g. predicted dose reduction instead of dose increase).

Inclusion of historical data

To assess the value of historical data in predicting vancomycin concentrations in ICU patients, we calculated EBEs in a real dataset of 490 patients [2], which included PK data for multiple occasions. We generated splits in the dataset for each patient, predicting "future" left-out concentrations based on previously observed data. In a simulation study, we investigated the impact of including historical PK data assuming random inter-occasion variability or time-varying changes in PK parameters.

Results

Dosing time error

When including more than one sample, the EBEs for volume of distribution (V) showed clear bias (mean error (ME) <0.417) but for clearance (CL) were subtle (ME>-0.096) when DTD increased. When no DTD occurred, EBEs for CL and V were unbiased but imprecise (RMSE of both >0.2). When drawing samples before the 4^{th} dose instead of after the 1^{st} dose, the PCD of MD decreased while the PCD of LD increased. The average PCD was >10% for the MD in all scenarios. An increase in DTD of >0.5h can lead to the decrease of PTA (<15%) compared to when no DTD occurred. Nonetheless, the PTA was <60% in all evaluated scenarios suggesting the undertreatment for ICU patients despite adapted dose.

Inclusion of historical data

When including historical PK data for >3 days (and < 14 days) in the past, vancomycin concentrations were underpredicted (<20%). When only historical samples from the previous day were included, no bias was observed. A time-varying trend for CL was observed indicating deterioration in vancomycin CL not captured by the included covariate for renal function. Our simulation study confirmed that a time-varying decreases in CL can explain the observed behavior and quantified the impact in dose adjustment errors. In contrast, introducing random inter-occasion variability (20%) into the simulated data did not reproduce the bias of predicted concentration when including historical data. This finding underlines the importance of considering time-varying trends in PK parameters in ICU patients.

Conclusions

Errors in recorded versus actual dosing times lead to bias in EBEs and may impact treatment efficacy. Inclusion of historical PK data to support MBDA may negatively impact model-based dose recommendations.

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IV-40: *Stefanie Hamacher* Population pharmacokinetics of cannabidiol in healthy subjects

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Objectives: Cannabidiol (CBD) is a lipophilic and non-psychoactive compound from hemp plant Cannabis sativa [1]. It inhibits cellular uptake and hydrolysis of endocannabinoids in the central nervous system [2]. Endocannabinoids play a role in patients with psychiatric disorders and therefore there is a promising therapeutic potential for CBD as possible medication [3,4]. Because information on the pharmacokinetic (PK) characteristics of CBD applied orally as a pure substance is limited, the objective of this project was to describe the PK of a single CBD dose using a population PK model.

Methods: Twenty-four healthy subjects (14 (58.3%) male, mean ± SD age 29.1 ± 8.2 years, height 174.9 ± 9.2 cm, body weight 72.1 ± 14.3 kg, BMI 23.4 ± 3.0 kg/m^2) received a single oral dose of 200 mg immediate release CBD formulated as CBD powder in a rapidly dissolving capsule. The volunteers fasted from 10 hours prior to dosing until 4.333 hours thereafter when a standardized meal was provided. PK blood samples were taken at baseline and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 24 hours after CBD administration. 238 plasma concentrations were included in development of a population pharmacokinetic model and the investigation of possible demographic covariates using NONMEM 7.4.1. The bootstrap resampling method was used to assess bias and precision of parameter estimates. Since the bioavailability (F) of CBD for oral administration is not known, it was fixed to 1.

Results: Individual concentration vs. time-profiles showed a high variability, observed maximal concentrations have a variation coefficient of 234%. Additionally, there were double peaks with varying height ratios in most of the subjects. Second peaks appeared about 3 hours after the first peak and 4.5 hours after dosing, i.e. when lunch was served. One zero-order absorption process each, starting (with a lag time) just after dosing for one (estimated) fraction of the dose and being delayed until lunch for the remaining fraction of the dose, together with a two-compartment model, linear elimination and a proportional error model was most suitable to describe the data. Demographic covariates sex, age, weight and BMI had no significant influence on clearance (CL) and central volume of distribution (Vc) and were not included in the model. PK parameters were estimated as follows: % dose splitting ratio (1st fraction : 2nd fraction)= 81.7 [78.9 - 90.0] : 18.3 [10.0 - 21.1] (median [95% CI] from bootstrap), CL/F = 4125 [2867 - 5570] l/h, Vc/F = 60007 [40990 - 73558] l, peripheral volume of distribution (Vp)/F = 142178 [125477 - 193536] l, inter-compartmental clearance (Q)/F = 8530 [6707 - 11087] l/h, 1st absorption lag time (ALAG1) = 0.48 [0.36 - 0.61] h, 2nd absorption lag time (ALAG2) = 4.333 h (fixed), duration of 1st zero-order absorption (D1) = 1.20 [0.86 - 1.71] h and duration of 2nd zero-order absorption (D2) = 0.112 [UF1] [sh2] [0.107 - 0.117] h. High inter-individual variability was associated with F (157%), dose splitting ratio (561%), CL (83%), Vc (67%), ALAG1 (50%) and D1 (90%).

Conclusions: A population PK model was developed successfully to describe the highly variable concentration vs. time profiles of oral CBD taken in the fasted state. Systemic exposure was low, suggesting

a bioavailability which is considerably lower than the value of 6% reported for CBD in a different setting [5]. Moreover, the model is compatible with an effect of food intake on CBD absorption.

Acknowledgment: The Stanley Medical Research Institute (non-profit organization) provided financial support for the clinical trial.

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IV-41: *Felix Hammann* Population pharmacokinetics and generation of dosing nomograms of daptomycin at a Swiss university hospital

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Introduction

The lipopeptide antibiotic daptomycin is primarily used in the treatment of systemic infections with gram-positive bacteria, usually administered as a 30 minute infusion. It exhibits dose-linear pharmacokinetics, and is primarily eliminated unchanged via the kidneys. Efficacy correlates with the ratio of area under the curve (AUC) over minimum inhibitory concentration (MIC), and thus varies with the targeted organism's sensitivity to the drug. An AUC:MIC > 800 is considered bacteriocidal, and a ratio of > 400 and < 800 bacteriostatic [1]. Because of this relationship, daptomycin is often subject to therapeutic drug monitoring (TDM). At the University Hospital Basel (UHBS), this is currently done by sampling 2 and 24h post-dose to calculate AUC 0-24h, Cmax, and Cmin after steady-state has been reached, a modification of Begg's method [2].

Objectives

- -create a pharmacokinetic model for *a priori*and *a posteriori*dose optimization
- -generate dosing nomograms from simulation to guide clinicians without prompt access to a pharmacometric model

Methods

Patients

Samples were collected retrospectively from measurements made during routine daptomycin TDM from January 2014 until December 2017 at the UHBS. Available covariates included demographic data, chemistry and hematology labs, infection specific data (type, site, organism, MIC where available), and clinical outcome at time of discharge from the hospital.

Data Analysis

Population pharmacokinetic analysis was carried out using NONMEM (Version 7.4.3; Icon Development Solutions, http://www.iconplc.com, Ellicott City, MD, USA). The first order conditional estimation with eta-epsilon interaction (FOCE-I)was used throughout all runs. We selected models based on goodness-of-fit statistics, graphical analysis with visual predictive checks, and model plausibility.

Results

A total of 32 patients were enrolled, totaling 111 samples from 1-7 different occasions. None were below the limit of quantification and all samples were used in modeling. The final model was a one-compartment

model with linear elimination (volume of distribution (Vd) 13.9 L (intra-individual variability (IIV): 31%) and clearance (CL) 0.48 L/h (IIV: 36%)) and a proportional residual error (0.24). These results are in agreement with previously reported daptomycin PKs (e.g. [3]). Estimated glomerular filtration rate (eGFR, Cockroft-Gault) was positively and serum albumin negatively correlated with CL. Patients on ICU had an additional 0.31 L/h in CL. We found no covariate effects on Vd.

We generated dosing nomograms by simulating concentration profiles at steady state for a broad range of doses (2-14 mg/kg) and computing AUC 0-24h for typical patients (weight 70 kg, albumin 19.8 g/L) on the wards and on ICU. Although the dose-toxicity relationship for rhabdomyolysis, a dreaded though rare adverse effect of daptomycin, remains controversial, some practitioners prefer to keep the concentration at 24h below 24 mg/L [4]. In the nomograms we indicated with a dashed line where these concentrations arose in our simulations.

Conclusions

This retrospective analysis of routine TDM at a large university hospital gave similar results for what is already known about the PK of daptomycin. Given that daptomycin is administered mostly in severe or even life-threatening situations where there may not be enough time to wait for a well-founded dose recommendation, we believe that nomograms can help make more informed decisions. They are interpretable by non-pharmacometricians, familiar to clinicians, and cheaply available. Most importantly, they can convey the practically relevant aspects of the often multidimensional relationships captured by pharmacometric models more intuitively than a set of differential equations can.

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IV-42: *Lutz Harnisch* Dose Selection Process for Younger Children Participating in a Phase 3 Study to Evaluate the Efficacy and Safety of Rivipansel (GMI-1070) in the Treatment of Vaso-occlusive Crisis in Hospitalized Patients With Sickle Cell Disease

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Introduction: Rivipansel is a pan-selectin inhibitor in development for the treatment of sickle cell disease (SCD) vaso-occlusive crisis (VOC). A single phase 3 study was planned to evaluate the efficacy and safety of rivipansel (GMI-1070) in the treatment of VOC in hospitalized patients with SCD. Selection of the dose to be used in this phase 3 study was based on the efficacy, safety, and pharmacokinetic (PK) results from the rivipansel phase 2 study. Modeling and Simulation (M&S) was used to determine the dosing for adults and children aged >6 years with SCD. To ensure that the predicted drug exposure is actually achieved in patients aged 6–11 years (cohort 2), we conducted a blinded review of the PK data obtained from several subjects enrolled in cohort 2. The methodology for this evaluation is presented here.

Methods: Pharmacokinetic data for 109 subjects receiving doses of 2 to 40 mg/kg in 4 previous studies (3 Phase 1 and 1 Phase 2) were integrated to build a 3-compartment model, which was used to perform simulations to aid dose selection. As rivipansel is almost entirely renally excreted, the simulations of clearance considered renal function as well as hyperfiltration, as this type of altered renal filtration is common in SCD patients. This model allowed for scaling of the PK exposure from the model developed in adults and older children (aged 12–17 years) (1) into the model for younger children (aged 6–11 years).

To confirm the predicted exposure in cohort 2, in particular their average concentration at steady-state ($C_{avg,ss}$), age- and weight-dependent cumulative distribution functions (CDFs) of parameters in the population PK model (eg, CL V_{ss}) were derived for the first 6 actively treated children. During this blinded review, concentration time profiles for these children were generated and empirical Bayesian estimates (EBEs) for their corresponding $C_{avg,ss}$ were derived. The percentiles in which the EBEs fell within the simulated CDFs from the model were used to guide decisions for a potential dose adjustment.

Results: The PK data from the Phase 2 study supported fixed flat dosing for patient aged 12 years and older. Pharmacokinetic M&S predicted that a loading dose of 1680 mg followed by a maintenance dose of 840 mg every 12 hours would result in exposures similar to those observed with the lower dose used in the Phase 2 study, such that a minimum plasma concentration >10 µg/mL would be maintained throughout the dosing interval. For patients in cohort 2, weight-based dosing was considered, as it is the most conservative approach, given that children in this age range have not been studied previously. For each dosing regimen tested, the simulated demographic target distribution in pediatric SCD patients was used to derive concentration-time profiles. The simulations showed that for children aged 6–11 years, a 40-mg/kg loading dose (maximum 1680 mg) followed by 20 mg/kg every 12 hours (maximum 840 mg) would likely result in concentrations similar to those observed with the 20/10 mg/kg dosing used in adults in the Phase 2 study. To confirm the validity of the exposure predictions, PK assessments were performed in the Phase 3 study and a blinded interim analysis of pediatric exposures was conducted.

Conclusions: A population PK model for rivipansel has been developed, applicable to the whole target SCD population of adults and children older than 12 years. Its applicability in children aged 6–11 years is under investigation as part of the ongoing Phase 3 study, and interim assessments of the PK exposure have been

done in small cohorts of 6 patients. The corresponding decision framework has been implemented, exercised successfully, with the results of potential dose adaptations to be published once the Phase 3 study has been concluded.

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IV-43: *Paul Healy* PKPD bridging and extrapolation of efficacy for the use of gabapentin and tramadol in paediatric chronic pain.

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Objectives: Neuropathic and chronic pain in children has been considered rare although in recent years the diagnosis and prevalence of this syndrome seems to be increasing. Often, the drugs used for treating pain in adults are used off-label in children[1]. The GAPP consortium was set up to establish the dose rationale and assess the efficacy of gabapentin in paediatric patients aged between 3 months and ≤18 years, who have been diagnosed with chronic pain, as compared to tramadol. Given the challenges to generate efficacy data in this group of patients, particularly in younger patients, in whom pain assessment relies upon non-verbal measurements, pharmacokinetic (PK) bridging is used to optimise exposure to gabapentin and tramadol, scaling drug disposition characteristics from adults to children. The primary objective of our investigation was to establish the dose rationale for gabapentin and tramadol in paediatric patients with chronic pain to be enrolled in a prospective non-inferiority study including 94 paediatric patients. A secondary objective was to optimise the titration phase and sampling schemes for the evaluation of pharmacokinetics and pharmacodynamics (i.e. pain response) of gabapentin and tramadol, considering effects of clinical and demographic covariates on PK.

Methods: Nonlinear mixed effects modelling was used to scale the PK of gabapentin and tramadol assuming comparable exposure-response relationships between adults and children. A one-compartment model for gabapentin[1] and a two-compartment model for tramadol[2] was integrated into a clinical trial simulation framework for evaluating paediatric exposure to a range of dosing regimens based on body weight as the main covariate factor affecting the disposition of both drugs. Analysis included extrapolation of drug disposition parameters from adults to children using allometric scaling principles and PK data from published literature[3]. Clinical trial simulations were performed to optimise study protocol procedures, focussing on suitable titration and maintenance phases. In addition, attention was given to the optimisation of blood sampling for PK evaluation, to ensure minimum invasiveness and patient burden.

Results: Simulations showed that efficacious mean steady-state exposure (area under the concentration vs. time curve, AUC_{0-8}) of 32.8 µg*h/mL and mean steady-state concentrations of 200-300 ng/mL can be achieved during maintenance phase of treatment with gabapentin and tramadol, respectively. These levels are preceded by titration steps, with doses ranging from 7-63 mg/kg in patients between 5-15 kg and 5-45 mg/kg in patients >15kg. For tramadol, the target exposure was associated with a maximum daily intake of 8 mg/kg preceded by the similar titration steps, with doses ranging of 1-8 mg/kg t.i.d. An evaluation of the feasibility of sparse blood sampling for the analysis of pharmacokinetics revealed that a minimum of four samples per patient was required to allow estimation of the parameters of interest.

Conclusions: In contrast to evidence generation based on empirical protocols, the GABA-1 study illustrates how quantitative clinical pharmacology principles can be used during the design phase of a study to ensure a robust dose rationale. Moreover, use of clinical trial simulations has provided an opportunity to identify suitable titration steps for subsequent characterisation of underlying pharmacokinetic-pharmacodynamic relationships for gabapentin and tramadol in the target paediatric population.

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IV-44: *Guenter Heimann* An Industry Perspective on Extrapolation in Pediatric Drug Development: A Quantitative Approach to Assess Similarity of Adult and Pediatric Efficacy.

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Objectives:

Recruitment of patients into pediatric studies is difficult and slow, and traditional fully powered pivotal trials are prohibitive.

For indications and drugs where the disease progression in children is similar to that in adults, and where the pharmacology of the drug is similar to that in adults, one may fully extrapolate efficacy from adults to children. Often, however, there is not yet enough evidence to apply full extrapolation. In these cases one may want to apply a partial extrapolation approach, and one needs to collect some efficacy data in children to demonstrate that the adult and the children efficacy are similar.

In this talk, we use three real (but anonymized) examples were extrapolation was or is applied, to explain the principles behind our approach. In two of these examples, some aspects of the extrapolation were done in an ad-hoc manner. We propose a better approach, which we applied for the third example. One of the objectives of this better approach is that its operating characteristics improves with increasing sample size in the pediatric study.

Methods:

In principle, our extrapolation approach consists of three steps: (1) the adult data are used to develop a model which links exposure and baseline risk factors to clinical outcome or surrogate markers, (2) the model is then used to predict the clinical outcome of the pediatric study conditional on observed exposure and covariates, and (3) the predicted outcome is then compared to the observed outcome to validate the model. Successful validation serves as supportive evidence to justify partial or full extrapolation.

In order to validate the prediction, our proposal is to simulate (from the adult model) a predictive distribution for the outcome each of the n pediatric patient separately (conditional on the exposure and risk factors), and to calculate the percent of this distribution below the actual observation. If the adult model is adequately predicting the pediatric data, one obtains n approximately uniformly distributed “observations”. We use these n percentages and a Cramer von Mises test statistic to provide a confidence interval for the deviation from uniformity (see [1], [2], and [3]).

Note that the approach proposed here are closely related and applicable to VPCs and the normalized prediction distribution errors (NPDE) as discussed in [7] and earlier by [4] and [6]. In our case, each pediatric subject only contributes one observation and hence the issue of decorrelation does not apply.

Results:

The first example is from a transplantation program. A model to predict organ rejection in an individual as a function of exposure over time was developed [4] for the original adult submission. This model is a proportional hazards model with time dependent covariates. The corresponding pediatric study consisted of 21 children, some of which were censored. A popPK model was used to estimate the exposure over time. The adult model was used to simulated 1000 pediatric studies with 21 children, conditional on the estimated exposure over time, and the observed censoring times. For each of these simulated studies, the overall number of organ rejections was counted, to obtain a predictive distribution for the number of organ rejections in 21 children. The validation was done by comparing the overall number of observed organ rejections with this predictive distribution.

In the second example, the same principle was applied to a survival endpoint. Here a predictive distribution for the Kaplan Meier estimator was provided. And compared to the observed Kaplan Meier estimator.

We show that the validation approaches applied in these examples do not improve with increasing sample size of the pediatric study. The revised approach, however, does have a better operating characteristic with increasing sample size.

Conclusions:

Full or partial extrapolation is based on scientific and empirical evidence that the adult label can be applied to children as well. Our approach mimics this objective better than using adult data as historical information and/or to generate informative priors for a separate analysis of the pediatric data.

The adult model can be a simple or complex statistical model, Bayesian or frequentist, or a population pharmacodynamic model. It should contain all relevant baseline risk factors. This is important to be able to address differences in the baseline distribution between adults and children with regard to these risk factors.

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IV-45: *Farina Hellmann* Population pharmacokinetic modelling in Ewing sarcoma patients focussing on etoposide as an example

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Introduction: Ewing sarcoma is a very aggressive bone tumour, which often occurs in adolescents or young adulthood [1]. The incidence of treatment-associated toxicity varies significantly between children, adolescents and adults [2]. These toxicities are often worse in young children and reduce with advancing age. Furthermore, the survival rates differ between age groups with younger patients having a better outcome as compared to older patients [3]. The standard induction therapy of Ewing sarcoma patients contains the drugs vincristine, ifosfamide, doxorubicin, etoposide and cyclophosphamide. Population pharmacokinetic modelling of these drugs can help to further elucidate the age-dependent differences in toxicity and survival of Ewing sarcoma patients and therefore, improve the therapy.

Objectives:

- Investigation of a possible age-dependency in the clearance of vincristine, ifosfamide, doxorubicin, etoposide and cyclophosphamide in Ewing sarcoma patients
- Analysis of possible predictors of treatment-associated toxicity in Ewing sarcoma patients such as age and gender
- Development of improved strategies regarding toxicity and survival for the treatment of Ewing sarcoma patients

Methods: The Northern Institute for Cancer Research (NICR) at Newcastle University is running an ongoing clinical pharmacology study to investigate differences in drug disposition between Ewing sarcoma patients of different ages and the early prediction of vincristine, ifosfamide, doxorubicin and etoposide (VIDE) toxicity in this patient population (short title: PK 2013 01; EUDRACT Number: 2013-000052-17). In total, 120 adolescent Ewing sarcoma patients treated with standard dose induction chemotherapy VIDE or vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide (VDC/IE), will be recruited to the PK 2013 01 study. Blood samples are collected from patients at defined time points for the quantification of all drugs mentioned above on a single course of VIDE or VDC/IE treatment. The plasma concentrations are used to develop population pharmacokinetic models with NONMEM® for the drugs.

Results: For etoposide, a two compartment model with a combined error model was developed based on the 247 plasma concentrations of 58 patients. All pharmacokinetic parameters are scaled to the body surface area of the patients. The model estimates for clearance and central volume of distribution are 1.97 L/h/1.55 m² and 5.59 L/1.55 m², respectively. The peripheral clearance amounts to 0.947 L/h/1.55 m² and the peripheral volume of distribution is determined as 3.76 L/1.55 m². All pharmacokinetic parameters have a residual standard error (RSE) below 30 % indicating an adequate precision. In the current etoposide model, no other covariates investigated, including age or gender, exhibited a significant effect on one or more pharmacokinetic parameters. Following completion of patient recruitment the dataset for the entire patient population will be used to revise the model. However, these preliminary data suggest that no age-dependent differences in etoposide pharmacokinetics can be detected in this patient population.

Conclusion: No differences in the pharmacokinetics of etoposide with age or gender were identified following analysis of preliminary data. Additional analyses are ongoing for the drugs vincristine, ifosfamide, doxorubicin and cyclophosphamide

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IV-46: *Emilie Hénin* Therapeutic drug monitoring strategies for Envarsus in de novo renal transplant patients using population modelling and simulations

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Objectives:

Tacrolimus is a pivotal immunosuppressant agent used in solid-organ transplantation necessitating therapeutic drug monitoring (TDM), due to its narrow therapeutic window. Its original formulation, Prograf®, is an immediate-release capsule to be administered twice daily. Envarsus® has been developed recently to be administered once daily: the Meltdose® drug delivery technology enables a broader absorption throughout the gastro-intestinal tract and a sustained consistent tacrolimus concentration.

The objectives of this study was to develop a population PK model for tacrolimus concentrations after Envarsus administration, in *de novo* renal transplant recipients, and to explore by simulation the performance of TDM strategies.

Methods:

Thirty-three *de novo* renal transplant recipients, receiving Envarsus once daily, were monitored for 28 days. A total of 1951 tacrolimus concentration measurements were collected over 0-24 hour period, on day 1, 3 7 and 14, and at trough on day 2, 3, 4, 5, 6, 7, 8, 14, 15, 21 and 28. Envarsus treatment was initiated on transplantation day, at 0.17 mg/kg; dose was then adjusted based the basis of tacrolimus trough level (TTL) in order to target 5-15 ng/mL from day 4 to 8 and 5-10 ng/mL from day 15 to 22.

Population PK model development was guided by parsimony principles, quality of estimations, model diagnostics and predictive performance.

Several TDM strategies, evaluating both *a priori* adaptation to covariates and *a posteriori* schedule for TDM based on TTL, were simulated and compared in terms of Envarsus dose and number of patients reaching the TTL target.

Model development, parameter estimation and simulations were performed using NONMEM 7.3.

Results:

Envarsus pharmacokinetics were adequately described by a 1-compartment disposition model with first-order elimination; absorption was characterised by three parallel chains composed respectively of 3, 6 and 9 compartments, allowing a 3-phase absorption profile. 13.3% of the dose had a fast absorption (mean transit time, MTT of 1.06h), 61.2% had a medium absorption (MTT of 4.81h) and 25.5% had slow absorption (MTT of 26.1h). Inter-individual variability was accounted on clearance, volume, repartition among transit chains and fast and medium MTTs. Eta-shrinkage was lower than 11% on all parameters. Inter-occasion variability was accounted on relative bioavailability, no trend was found between occasions. Residual error was additive on the log scale, with a separate magnitude for 24-hour profiles (26.9%) and TTL (34.9%).

Parameter-covariate relationships were identified for Envarsus PK: bodyweight at inclusion had an allometric impact on clearance (+0.75 FIX) and on volume (+1 FIX); and CYP3A5 polymorphism resulted in a 67% increase in *1/*3 compared to *3/*3 patients.

Simulations of the TDM strategy implemented in the original study (0.170 mg/kg up to day 3, dose adaptation based on TTL on days 4, 7, 15 and 22) were in accordance with the observed TTL profiles. The median TTL profile was in accordance with the specified target ranges. The proportion of patients reaching the specified target was below 40% on day 3, and rose above 70% from day 7.

An alternative TDM strategy allowed maintaining concentrations within the specified target. On day 1, the dose was *a priori* adapted to covariates, in median 0.160 mg/kg and 0.272 mg/kg for *3/*3 and *1/*3 patients respectively. Subsequently, doses were adapted based on TTL: on day 2, median doses were 0.061 mg/kg and 0.094 mg/kg for *3/*3 and *1/*3 patients respectively; on day 3, median doses were 0.085 mg/kg and 0.137 mg/kg; on day 4 and onwards, median doses were 0.0759 mg/kg and 0.147 mg/kg. The proportion of patients reaching the specified target was maintained over 70% from day 2 and onwards.

This model-based approach allowed a better exploration of dose adaptation strategies to maintain tacrolimus concentrations within specified range after Envarsus administration in de novo renal transplant patients.

IV-47: *Charlotte Kloft* Review of NMLE articles published in clinical journals with a higher impact factor

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Objectives: Pharmacometrics aims to understand the drug-patient interaction, describe the quantitative aspects of disease and pharmacology, connecting various fields such as physiology, pharmacology, pharmacotherapy, clinical pharmacy, mathematical modelling, statistics, systems biology, pharmacokinetics/-dynamics in a coherent framework to understand and improve human health. As such we need to communicate within multidisciplinary teams and convey our results to clinicians, editors and statisticians in a translational manner.
The aim of this review was to identify publications that have applied the nonlinear mixed effects (NLME) modelling approach since its first appearance in 1979, and have been published in high impact clinical journals.

Methods: The search terms "nonlinear mixed effect modeling" OR "nonlinear mixed effect modelling" OR nonmem OR monolix OR pharmacometric* were used to search three databases (Pubmed, Web of Science and Embase) for articles published in English between 1979 and 2018. Journal impact factor (IF) were identified via Web of Science or the journal's webpage. Articles published in journals with an IF > 6.7 were read in full to examine the presentation of the NMLE methods. This cut-off was selected based on: i) CPT was the journal with the highest IF in the top 20 journals that NLME article are published in, ii) the IF of Clinical Pharmacology and Therapeutics (CPT) currently is 6.655, and iii) CPT holds position 7 when all journals were ranked based on the frequency of publishing NLME articles.

Results: Of the over 12,000 identified articles, 4910 articles remained after duplication were removed and titles and abstracts were scanned. An increasing number of articles per year were published since 1979 in 655 unique journals. A majority (51%) of these articles are published in only 13 journals. Journal's impact factors (IF) ranged from 0.1 to 26.3 (Journal of Clinical Oncology). The journal (CPT: Pharmacometrics & Systems Pharmacology) most commonly publishing NLME articles has currently no IF. The median impact factor was 3.08. In total, 10.6% of articles are published in journals with no IF.
One-hundred (2.0%) articles are published in journals with IF> 6.7. Over 64.9% of these articles had a first/corresponding author from academia, 27.7% from a hospital and 7.4% from industry. The most common author teams were academics and clinicians (38.1%) followed by academics and authors from industry (14.9%). When published in high IF journals, presentation of the methods used and the description of the results was seldom according to standards, only 14% of article can be considered acceptable. [1, 2] Nineteen (19%) of the articles in higher IF journals have had a higher average number of citations per year compared to the journal's IF, which is less compared to other fields. [3]

Conclusions: Communication of results and their impact arising from NLME studies could improve and ultimately patients' outcome and health. Increased quality peer-review within the area and further engagement with statistician and clinicians may increase the opportunity of pharmacometrics to increase its impact.

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IV-48: *Thomas Henthorn* A population pharmacokinetic model of dense delta-9-tetrahydrocannabinol (THC), 11-OH-THC, and THCCOOH data and its use to estimate daily exposure in an observational cannabis study with sparse data

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Introduction: Population pharmacokinetic (popPK) modeling of delta-9-tetrahydrocannabinol (THC), but not including those of the major metabolites, has been performed in a clinical research setting with dense plasma sampling following a closely monitored administration by smoking and vaping.[1-3] To interpret sparse, observational plasma THC and metabolite concentrations, we aimed to develop a comprehensive popPK model of THC and its metabolites as a Bayesian prior for further modeling of sparse, observational data.

Objectives:

- Develop a population PK model of THC, 11-OH-THC and THCCOOH from a Phase 1 clinical trial conducted at the National Institute of Drug Abuse (NIDA)
- Estimate daily consumption of THC from sparse data (plasma THC, 11-OH-THC, and THCCOOH concentrations) in a cohort of regular cannabis users in Boulder, Colorado.

Methods: Previously at NIDA, six sequestered subjects smoked in a rigorously-paced manner two different concentrations of marijuana cigarettes (1.75% and 3.55% THC) over 10 min one week apart in a within subject, randomized, crossover, placebo-controlled study. Frequent blood samples were obtained during and immediately after each smoking event and then less frequently for one week for the measurement of THC, 11-OH-THC and THCCOOH by GC-MS.[4] A multicompartment popPK model was developed using Phoenix NMLE 8.1. In Colorado, blood samples were obtained from 16 regular users of cannabis at four time points: recruitment, in a mobile lab immediately before smoking in their home, upon returning to the mobile lab and then again one hour later for analysis of THC and metabolites by LC-MS/MS[5]. These data were analyzed with the Bayesian prior from the dense popPK analysis, including estimates of (1) daily THC consumption prior to recruitment, (2) daily THC consumption in the interval between recruitment and home-smoking and (3) the dose consumed during the home-smoking event.

Results: For the NIDA data, a 3-compartment PK model of THC was superior to 1- or 2-compartment models, assuming a fraction absorbed of 0.25[1], (typical values: V1=28.5L , V2=45.6L, V3=3372L, Q2=1.35L/min, Q3=1.31L/min and Cle=0.72 L/min) with extension to metabolite kinetics (typical values: Clethc->11-oh-thc=0.43L/min, Cle11-oh-thc-> thccooh=1.62L/min, Clethccooh=0.12 L/min). In the Colorado cohort, baseline daily THC consumption was estimated to be 2.56$\pm$3.27 (mean$\pm$SD) NIDA cannabis cigarette equivalents (5.6% THC). Consumption dropped to 0.87$\pm$0.97 cigarettes in the interval prior to home-smoking and 0.45$\pm$0.26 while in their home that was estimated to have begun 14 minutes prior to returning to the mobile lab. Correlations between these model-derived estimates and survey estimates of daily THC consumption and amount smoked in the home were significant ($p<0.01$).

Conclusion: Our 3-compartment THC model is very similar to those previously described.[1-3] We have successfully extended population THC modeling to include two of its commonly measured metabolites. This modeling development is important because THC metabolites are often the only measurable constituents in blood and urine in observational cannabis studies because of low THC concentrations soon after consumption due its extensive tissue distribution. THCCOOH and THC-COOH-glucuronide concentrations are more persistent as their production clearances exceed their elimination clearances. A population model of THC and its metabolites provides a valid supplement to generally non-quantitative cannabis consumption questionaires. Without a population PK approach, often randomly obtained, sparse THC/metabolite blood concentration data from observational studies were difficult for investigators to interpret. We show that a popPK model of THC and its metabolites results in quantitative estimates of THC exposure even in observational studies with sparse data. Extending the current population PK modeling to include THCCOOH-glucuronide would be highly useful since this metabolite persists in blood and urine even longer than THCCOOH.

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IV-49: *Lukas Kovar* Physiologically-based pharmacokinetic (PBPK) modelling of nicotine and its main metabolite cotinine in healthy volunteers and smokers

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Introduction: Since nicotine is the pharmacologically active substance in tobacco responsible for addiction it also plays a distinctive role in causing smoking-induced diseases such as chronic obstructive pulmonary disease (COPD) and lung cancer [1]. Hence, a better understanding of the pharmacokinetics of nicotine could help to derive new strategies of smoking cessation and to get a better understanding of the involvement of nicotine in pathophysiological processes.

Objectives:

- Development and evaluation of a whole-body physiologically-based pharmacokinetic (PBPK) model of nicotine including its main metabolite cotinine after intravenous (i.v.) administration in healthy volunteers
- Model adjustment for a smoking population to predict the pharmacokinetics in smokers

Methods: A parent-metabolite PBPK model of nicotine and cotinine was built in PK-Sim® (Version 7.4.0) as part of the Open Systems Pharmacology Suite [2]. Firstly, a cotinine model was established with data from i.v. administration in healthy volunteers. Subsequently, the model was complemented by the parent compound nicotine using i.v. plasma concentration-time profiles. Physicochemical parameters as well as plasma profiles of nicotine after i.v. single dose (SD) and multiple dose administration (range 15 µg/kg to 288 µg/kg) and mean profiles of cotinine after i.v. SD administration (range 5 mg to 20 mg) were obtained from published literature. Moreover, nicotine and cotinine fractions excreted to urine were available for several dosing regimens. For PBPK model building, 14 plasma profiles out of 5 clinical studies (46 study participants, all nonsmokers) were split into an internal (6 plasma profiles, 4 fractions excreted to urine) and an external (8 plasma profiles) dataset. When necessary, parameters were estimated based on the internal dataset. Model evaluation was performed with the external dataset by comparing observed and predicted plasma profiles. Conclusively, the model was adjusted for smokers and used to predict 10 different plasma profiles of nicotine and cotinine in smokers.

Results: About 75% of administered nicotine is metabolized to cotinine in the liver, mainly via CYP2A6 metabolism, representing the major route of elimination of nicotine [3]. Therefore, the model includes this important CYP2A6 metabolism of nicotine. The corresponding Michaelis-Menten constant K_M was fitted within the range of literature values to 34 µM, the catalytic rate constant k_{cat} was fitted to 14.69 min^{-1}. Additionally, nicotine is cleared by an unspecific hepatic clearance (0.51 min^{-1}, first order kinetics) and glomerular filtration (GFR fraction of 1.00). The elimination routes are consistent with published literature [3]. For cotinine itself, the model contains an unspecific hepatic metabolism (0.03 min^{-1}, first order kinetics) and a glomerular filtration (GFR fraction of 0.07). The final model was capable to precisely describe and predict all profiles of the internal and external dataset with a mean area under the plasma concentration-time curve (AUC) ratio (AUC predicted / AUC observed) of 1.0, 0.61 and 1.10 for all nicotine, cotinine metabolite and administered cotinine profiles, respectively. Moreover, the individual AUC ratios of all plasma profiles were within twofold range. Fraction excreted to urine of nicotine and cotinine were

accurately described (mean ratio (predicted vs. observed): 1.30 and 1.00 for nicotine and cotinine). According to published data, nicotine clearance in smokers appears to be about 15% lower compared to nonsmokers [4] resulting in higher AUC values. After adjusting the model to physiological characteristics of smokers like an increased haematocrit and lower nicotine metabolic capacity, the PBPK model was also able to predict this increase in AUC (AUC ratio: 1.02 and 0.73 for nicotine and cotinine).

Conclusions: The successfully developed whole-body PBPK model of nicotine and its main metabolite cotinine including CYP2A6 metabolism was able to predict nicotine and cotinine plasma profiles of different dosing regimens for both smokers and nonsmokers in an excellent way. The i.v. administration has been implemented successfully in the model which will be augmented by inhalative and transdermal administration processes. This may help finding more successful strategies of smoking cessation in order to decrease tobacco addiction and improving the understanding of nicotine involvement in pathophysiological processes.

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IV-50: *Anneke Himstedt* Prediction of pulmonary exposure based on plasma pharmacokinetics: A comparison of different model-based approaches.

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Introduction: Different model-based approaches were applied to characterize the pharmacokinetics (PK) of orally inhaled drugs, differing prominently in the structural representation of pulmonary absorption processes. While it has been theorized that these empirical models can be used to infer on the pulmonary PK based on plasma data after both intravenous and inhalational administration [1], the predictions and conclusions drawn from these approaches have never been systematically compared.

Objective: To compare five published empirical pulmonary absorption models of varying complexity with regard to the suitability of these models to correctly infer on lung exposure considering different pulmonary PK characteristics. These compartmental models comprised (i) three, (ii) two, (iii) one single (parallel) first-order absorption process(es), (iv) one single absorption process with simultaneous non-absorptive pulmonary loss, and (v) a transit absorption model.

Methods: The five models were built and parameterized based on the respective publications [2-6]. The models were used for a simulation/re-estimation analysis performed with R (Version 3.2.2) [7], employing the deSolve package (Version 1.20) [8]. Since the focus of this work lay on the comparison of pulmonary absorption models, only PK profiles after oral inhalation were considered and the systemic parameters were fixed to the published values during the estimation process. Furthermore, the oral absorption compartments were removed from the models.

The models were deemed exchangeable with regard to the characterization of systemic exposure if the newly predicted plasma concentration-time profiles deviated from the originally simulated data used for fitting by less than five percent. When plasma equivalence was given, the model simulations were compared with regard to lung exposure (measured as area under the lung concentration-time curve, $AUC_{0\text{-}inf,Lung}$) and drug concentration in the lungs after 24 hours ($C_{24h,Lung}$).

Results: All pulmonary absorption models, except for the one including three parallel absorption processes, were exchangeable regarding the plasma concentration-time profiles. The resulting predictions of lung exposure and lung concentration after 24 hours differed greatly and were not interchangeable even though the plasma profiles indicated so (values for $AUC_{0\text{-}inf,Lung}$ and $C_{24h,Lung}$ deviated over 6 and 8 orders of magnitude, respectively).

Conclusions: This simulation/re-estimation study showed that information on plasma PK alone is not sufficient to draw conclusions about the extent and duration of lung exposure using typically applied empirical models. However, it has to be noted that the physiological assumptions implied in the investigated models differ, so that prior knowledge about the pulmonary processes affecting the respective drug after oral inhalation might still allow for correct interpretation of model predictions.

In conclusion, additional quantitative information on the underlying physiological processes is crucial to carefully select an adequate model-based approach to infer on pulmonary PK from systemic exposure.

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IV-51: *Richard Höglund* Multidrug-resistant genotypes are associated with therapeutic failure of antimalarial therapy in Cambodia; a pharmacometric approach

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Objectives: Artemisinin-based combination therapy is the recommended first-line treatment for malaria. However, recent data report emerging multi-drug resistant *falciparum* malaria in western Cambodia and South-East Asia [1]. This threaten our ability to treat and control malaria in the region and it would have severe consequences if spread globally. The fixed-dose oral combination therapy of dihydroartemisinin-piperaquine administered once daily for three days has previously shown good efficacy, but decreased efficacy of this combination has been reported over the last couple of years [2]. The aim of the study was to evaluate the pharmacokinetic and pharmacodynamic properties of the standard treatment of dihydroartemisinin-piperaquine in Cambodia and evaluate the impact of different molecular markers on the risk of therapeutic failure (i.e. recrudescence malaria).

Methods: Capillary plasma samples were collected at three different sites in Cambodia over two seasons after a standard treatment dose of dihydroartemisinin-piperaquine. Piperaquine drug concentrations were measured in these samples and malaria reinfections during the 63 days of follow-up were characterised as new infections or therapeutic failures (recrudescent malaria) using PCR genotyping. Genotyping was also performed to identify mutations associated with resistance. Piperaquine drug measurements and time to recrudescent malaria were evaluated with nonlinear mixed-effects modelling (NONMEM 7.3). Due to the sparse nature of the collected pharmacokinetic samples, a prior approach were utilized to describe the pharmacokinetic properties of piperaquine. The prior model was a previously published pooled analysis, including 728 patients and a conversion factor between venous and capillary concentrations [3]. The pharmacodynamic data were evaluated with an interval-censored time-to-event model.

Results: The pharmacokinetic properties of piperaquine were described successfully with a prior approach, which consisted of a three-compartment disposition model with a transit compartment model describing the absorption. The outcome time-to-event data was successfully characterised by a Gompez hazard model, linking piperaquine plasma concentration to the baseline hazard with a sigmoidal effect model. Plasmepsin copy number amplification and K13-gene mutation were found to have a significant and substantial impact on the risk of therapeutic failure. Simulations were carried out to determine the clinical impact of different levels of resistance.

Conclusions: Unacceptably high failure rates of 38.5% and 16.9% were seen in sites in western and northern Cambodia, respectively, compared to 3.03% in eastern Cambodia. This was successfully described by a pharmacokinetic-pharmacodynamic nonlinear mixed-effects model for piperaquine, identifying that both the molecular marker for artemisinin resistance (mutation of the K13-propeller) and for piperaquine resistance (increase in plasmepsin copy number) had a substantial impact on therapeutic outcome. Simulations demonstrated that even a quite moderate frequency of K13-mutation and increased plasmepsin copy number resulted in unacceptable therapeutic efficacy (<90%).

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IV-52: *Nick Holford* Rational dosing of caffeine using target concentration intervention to improve treatment of apnea of prematurity

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Objective: Apnea of prematurity (AOP) is defined as an attack of apnea for at least 20 seconds, with bradycardia and cyanosis. It is a common phenomenon in the neonatal intensive care unit. Caffeine is used to suppress or to prevent AOP attacks. The objective of this study is to develop a rational method to predict the dose of caffeine by using the effects to determine the target concentration and provide support for clinicians to determine the dose required to reach the target concentration.

Methods: Caffeine concentrations were measured prospectively in a study of its pharmacokinetics (PK) in premature neonates with AOP. The PK was described with a mixed effect one compartment first order elimination model. The baseline hazard was described by a Gompertz distribution. The pharmacodynamics (PD) caffeine were modelled using a sigmoid Emax model directly on the hazard of an AOP attack. PD covariates included adenosine receptor genotype and various methods of spontaneous breathing ventilation support (LFNC, HFNC, CPAP, BIPAP, BNCPAP) or mechanical ventilation (CMV, HOV). The hazard was set to 0 during mechanical ventilation. The pharmacodynamic (PD) and hazard model was developed using NONMEM 7.41. Visual predictive checks (VPC) was performed for model evaluation.

Results: Caffeine concentrations (1004 measurements) with fixed protocol dosing in 222 premature neonates had a wide distribution (median 8.7 mg/L, 90% within 2.9 and18.1 mg/L after 2 days of treatment). Both fixed (size and post-menstrual age) and random effects on between subject variability in clearance were important. Between occasion variability in clearance was small. The bootstrap hazard and PD parameter estimates are shown in Table 1.

Table 1 Parameters of AOP hazard and pharmacodynamics of caffeine

Parameter	Description	Units	Bootstrap average
L_LZ	Baseline hazard	1/h	0.00496
B_GOM	Gompertz hazard	.	-0.00167
CAF_EMAX	Emax for caffeine effect on hazard	1/h	0.492
CAF_C50	C50 for caffeine effect on hazard	mg/L	1.80
CAF_HILL	Hill exponent for conjugate effect on hazard	.	2.64

The PD parameters were used to simulate the link between caffeine concentration and reduction of AOP hazard. The C50 suggests that a target concentration of 5 mg/L would achieve close to maximum achievable benefit and this was chosen as the target concentration. A Bayesian dose forecasting procedure was developed using NextDose (www.nextdose.org) which clinicians can use to calculate initial doses and

then use measured caffeine concentrations to further individualize treatment to achieve the target concentration.

Conclusion: Caffeine approaches its maximum effect and suppresses AOP attacks by about 50% at a concentration of 5 mg/L. The small between occasion variability and wide variation in concentrations with fixed dosing mean that target concentration intervention can be expected to improve outcomes. NextDose provides an easily available tool for clinicians to apply clinical pharmacology to improve patient care.

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IV-53: *Chih-hsuan Hsin* Impact of intestinal and renal membrane transporter ABCB1 gene polymorphisms on the pharmacokinetics of digoxin in healthy Caucasian subjects

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Introduction/Objectives:

Membrane transporters play an essential role in drug development due to potential transporter-based interactions. When the activity of membrane transporters is altered by inhibition, induction or in presence of certain genetic polymorphisms, the pharmacokinetics and -dynamics of substrate drugs might change relevantly.[1] P-glycoprotein (P-gp, gene code ABCB1), the first well characterized membrane transporter, has been shown to affect the pharmacokinetics of numerous clinically relevant drugs[2] , including digoxin. Therefore, the FDA recommends to evaluate potential drug-drug interactions based on P-gp using digoxin as a phenotyping drug, since the rate of digoxin transport is limited by P-gp in the intestine and kidney.[3,4,5] However, results of phenotyping might be confounded by ABCB1 polymorphisms. Particularly, the single nucleotide polymorphisms (SNPs) c.1236C>T (rs1128503), c.2677 G>T/A (rs2032582) and c.3435 C>T (rs1045642) have been associated with changes in P-gp transporter kinetics.[6] Studies on the effects of c.1236C>T, c.2677 G>T/A and c.3435 C>T on digoxin pharmacokinetics currently are inconclusive,[7] which might be a consequence of considering only one of the 3 SNPs to define genotypes. Since SNPs are in linkage disequilibrium and form common haplotypes,[8] considering the entire haplotype structure might be necessary to properly assess the role of common polymorphisms in digoxin pharmacokinetics. [8]

To quantify differences in digoxin pharmacokinetics between subjects with common haplotypes using a population pharmacokinetic modeling approach.

Methods:

Data from 40 healthy Caucasian subjects participating in two clinical trials (mean age 40.4±16, mean body mass index 24.0 ±3.18kg/m^2) who received single oral doses of 0.5 mg digoxin was evaluated. Blood and urine samples were collected by a dense sampling scheme and a validated high-pressure liquid chromatography–tandem mass spectrometry method was used to quantify digoxin concentrations. Genotyping of ABCB1 was carried out using the DMET™ Plus Array[9] (Affymetrix, Santa Clara, California, United States). The following ABCB1 haplotypes were defined: *1/*1 (CC/GG/CC), *1/*2 (CC/GG/CT), *1/*13 (CT/GT/CT) and *13/*13 (TT/TT/TT) (base pairs of SNPs c.1236/2677/3435) with 12, 4, 15 and 9 subjects, respectively.[8] A population pharmacokinetic model was developed using NONMEM 7.4.1[10] by starting with a one-compartment model and increasing the model complexity step-wise. After identification of a proper base model, the effect of haplotypes on pharmacokinetic parameters related to absorption and elimination of digoxin was evaluated via a step-wise procedure. For all modelling steps, changes in objective function value OFV, goodness of fit (GOF) and visual predictive checks (VPC) were considered.

Results:

A three compartmental model with zero order absorption and linear elimination appropriately described the observed pharmacokinetic data. The estimated median clearance CL/F was 15.8 L/h (19.7%), of which 53.8% (55.6%) were attributed to renal clearance (CV%). The median central (V1/F) and peripheral (V2/F, V3/F) volumes of distribution were 135 L (18.4%), 140 L (100.8%) and 452 L (35.4%), respectively. The estimated median duration of zero order absorption was 0.461 h (8.5%) with a lag-time of 0.086 h (58.8%). Homozygote carriers of ABCB1*13/*13 showed a lower CL/F (63.6% compared to other volunteers) while the renal clearance showed no difference between genotypes. Consequently, total exposure in terms of AUC was higher in ABCB1*13/*13 (compared to *ABCB1*1/*1).

The identified difference in ABCB1*13/*13 is in line with a previous study by Xu et al., who reported a higher AUC in subjects with this haplotype.[11] Other main pharmacokinetic parameters were also comparable to published data.[12, 13] A previous study by Frankfort *et al.* did not show a significant correlation between CL/F and ABCB1*13 or ABCB1*1 haplotypes.[14] However, their study was performed in medicated geriatric patients under steady state conditions, which prevents from a direct comparison to our results.

Conclusions:

The developed joint model described digoxin plasma concentrations and urinary excretion in two clinical trials well. ABCB1*13/*13 influenced only non-renal pharmacokinetic processes. The genotype effect supports the use of digoxin as a probe to assess intestinal P-gp activity. Considering haplotypes might be important when using digoxin as a P-gp phenotyping drug.

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IV-54: *Ka Ho, Matthew Hui* Evaluation of Parameter Estimation when Fitting a Mixture Model with Covariate Effects using NONMEM

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Objectives: It has been in doubt whether parameter estimates are reliable when fitting a mixture model to pharmacokinetic data using NONMEM. In the case that a pharmacokinetic (PK) parameter is being modeled with a combination of the mixture model and covariate model, it is arguable that it may be mathematically challenging to distinguish the discrete random effects from the covariate effects, particularly when the two types of effects act in the opposite directions. The current study aims at evaluating the estimation of parameter estimates, especially the covariate effect and the individual probabilities, using a simulation approach, by which true values are available for evaluation. Three objectives were set:

- Simulate PK datasets assuming the mixture model and the covariate effect, followed by parameter estimations;
- Identify factors associated with the biases in the estimations of covariate coefficient (CC), individual probabilities (IP) and other parameters; and
- Quantify any significant association identified.

Methods: The one-compartment model with first-order absorption, a single covariate effect on clearance (CL) and a mixture model of two subgroups with different typical values of clearance was applied. The following parameters were block-sampled and varied between simulated datasets: typical values of PK parameters, i.e., CL of the subgroups, volume of distribution (Vd) and absorption rate constant (ka), inter-individual variances of CL (CVCL), mixing proportion of the subgroups, residual variability, number of subjects, covariate effect and covariate skewness. Each virtual subject received a single dose and was sampled at 12 occasions. Parameters were estimated using FOCE+I in NONMEM with the same model. For each of CC, IP, and other parameters, the estimation errors were plotted against other parameters to identify the presence of probabilistic and/or systematic biases under different circumstances. In the case of significant findings, the results would be further quantified.

Results: 59,049 PK datasets were simulated and then subjected to parameter estimations. The median errors in the estimation of CC were mostly within ±1% and did not show apparent trend against various parameters investigated. The sizes of errors in the estimates of CC were found to be associated with (1) the change in objective function value after removing the mixture model per observation (dOFV/obs) (95% ranges of relative errors were estimated to be 28% and 13% for dOFV/obs of 0.01 and 0.1, respectively), (2) the estimated CVCL (13% and 33% for CV of 10% and 50%, respectively), and (3) the number of subjects in the dataset (47% and 11% for 20 and 300 subject, respectively). As to estimated IP, previous findings that (1) the IP of each subject classified to his estimated subgroup is overestimated, and that (2) IP is more reliable when dOFV/obs is large could be replicated.[1] In the current study, it could also be observed that IP tends to be more overestimated when estimated CC is larger than the estimated ratio of typical values of clearance between the two subgroups (fast/slow), RCL. When estimated CC is half of RCL, overestimation of IP could reach 9%; but when estimated CC is 1.5-fold of RCL, overestimation of IP could reach as high as 27%.

Conclusions: The current study revealed that the change in objective function value after removing the mixture model is highly associated with the estimation error of covariate effects. In fact, together with

previous findings, the current study again demonstrated how indicative the change in objective function value is against the reliability of model parameter estimates. [1,2] The current results quantified the biases in the estimation of parameter estimates when fitting a mixture model with covariate effects in NONMEM and could be of value for reference in future attempts to develop similar models.

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IV-55: *Ziad Hussein* Population Pharmacokinetics of Lemborexant, a Dual Orexin Receptor Antagonist, in Healthy Adult and Elderly Subjects and Subjects with Primary Insomnia

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Objectives: To describe lemborexant PK and quantify the effects of intrinsic and extrinsic factors in healthy adults, elderly, and in subjects with insomnia disorder, based on six extensively sampled Phase 1, one Phase 2 and two Phase 3 sparsely sampled studies.

Methods: The 12230-observation dataset included 1892 subjects who were 18 to 88 years old weighing 37 to 168 kg and predominantly female (66%). The dataset included lemborexant doses up to 100 mg, administered QD in the morning or at bedtime. Inclusion of known absorption-related predictors based on Phase 1 data, preceded forward addition ($p<0.01$) and backward elimination ($p<0.001$) of covariates to constitute the final lemborexant population model. The pre-defined factors included were body weight, age, sex, BMI, race, food, formulation, creatinine clearance, laboratory parameters, concomitant medications (e.g. gastric pH modifiers) and disease characteristics (primary/secondary insomnia). NONMEM and R were used to illustrate clinical relevance covariates under several simulation scenarios and derive PK measures. Visual predictive checks (VPC) and nonparametric bootstrap were used for model qualification and validation. NONMEM SAEM/IMP estimation under MPI parallelization enabled the analysis of this large pooled PK dataset, not readily feasible using the conventional estimation approach (FOCEI).

Results: Informed by extensively sampled Phase 1-2 data, initial lemborexant population pharmacokinetics were described using a linear 3-compartment model with mixed zero (D1) and first order (Ka), lag-time absorption process. The model included a combined (additive/proportional) residual error with distinct parameters for periods before and after 3 hrs post-dosing. This base model also incorporated absorption-related covariate effects: bedtime dosing on D1, the effect of food on Ka and relative bioavailability (F1), and the effect of formulation on D1 and Ka. Due to the absence of PK sampling in the first 9 hours following bedtime dosing for the Phase 2 and two Phase 3 sparsely sampled studies, the inclusion of covariates in the final model was constrained to the clearance parameter (CL). High eta (η) shrinkage (>60%) was noted for all between-subject variability parameters except CL. Final model lemborexant parameters were oral clearance (CL/F) of 22.7 L/hr, steady-state volume of distribution (Vss/F) of 1070 L and inter-compartmental clearances (Q3 and Q4) of 32.1 and 31.0 L/hr, respectively. For the tablet, D1 was 0.118 hrs with bedtime dosing increasing D1 by 2.33-fold; Ka was estimated to be 0.595 (1/hr). The effect of food decreased Ka by 30% while increasing F1 by 21%. Lemborexant CL/F decreased with increasing BMI (exponent = - 0.428), increasing ALP levels (exponent = - 0.118) and was 26% lower in the elderly (≥ 65 years).

Conclusions: Simulations assuming an elderly, high BMI/ALP cohort were predicted not to exceed the observed range of exposures across studies, supporting no specific lemborexant dose adjustment.

IV-56: *Eman Ibrahim* Obesity and NAFLD activity score increase rate of fibrosis progression in a continuous-time Markov modelling of fibrosis progression in a long-term follow-up biopsy NAFLD cohort.

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Objectives:

Nonalcoholic fatty liver disease (NAFLD) is now one of the most common causes of liver-related morbidity and mortality. The best predictor of outcome is liver fibrosis stage (1). NAFLD is defined as the presence of hepatic steatosis in at least 5% of hepatocytes on liver biopsy examination in individuals who consume little or no alcohol, after exclusion of other causes of liver disease. NAFLD is classified into 2 subtypes: nonalcoholic fatty liver (NAFL), which is generally benign with very low risk of progression and nonalcoholic steatohepatitis (NASH), which is characterized by hepatocellular injury, inflammation with a risk of progression to advanced fibrosis (2). Currently there are no approved drug therapies for NASH and lifestyle advice to achieve weight loss is considered the most important part of standard of care. Furthermore, the disease progression has not been fully understood. The aim of this work was to perform a model-based analysis of fibrosis progression from stage 0 to 4 in NAFLD patients including the investigation of body mass index (BMI) impact and other potential covariates on disease progression.

Methods:

A continuous-time Markov model with first order markovian features was used to describe the forward and backward transition probability rates between different fibrosis stages and assess effects of different measured covariates on these transitions. The transition probabilities were fitted against clinical data collected from biopsy-proven NAFLD patients who were followed with repeat biopsy over two decades (3). The analyzed dataset included disease stage observations which were not equally spaced in time. Therefore, the continuous-time Markov modeling approach was chosen as it can also effectively handle the dependency between successive observations of ordered fibrosis stages. The choice of the included covariates was based on their statistical and clinical significance. Missing covariate values were imputed using mean substitution. The software used were NONMEM 7.3.0 and R-studio 3.2.4.

Results:

In total 70 patients underwent biopsy at baseline and at first follow-up after on average 14 (range: 10 - 17) years. 34 of them also underwent a third biopsy after another 10 (range: 8 - 12) years. The developed Markov model allowed the estimation of the transition probability rates between different fibrosis stages. Addition of covariates on specific forward rates for BMI group (obese defined by BMI > 30, and non-obese), age group (cut-off 55 years (4)) and NAFLD activity score (NAS) caused a significant reduction on the objective function value (OFV), while gender and type-2 diabetes did not. The average half-life of the transition probability that correspond to one fibrosis stage of progression from stage 0 to 2 was 8.1 years in non-obese patients and 3.6 years in obese patients both with age below 55 and NAS 3. The transition

probability rates increased exponentially with the increase in NAS from fibrosis stage 0 to 3. The average half-life of the backwards transition probability that correspond to one stage of fibrosis regression was 7.9 years. The average half-life of the transition probability that correspond to one fibrosis stage of progression was in line with previous results of a meta-analysis, where the overall fibrosis progression half-life in patients with NAFLD was 5.7 years (95% CI, 4.3-9.9) (5). Moreover, Visual predictive checks using 1000 simulated data sets were made to evaluate the predictive ability of the model.

Conclusions:

The Markov model provided a good description of proportions of patients in the respective fibrosis stages over time. The initial results show that the rate of fibrosis progression is higher in obese patients than in non-obese patients in the early stages of the disease. Finally, the effect of obesity and NAS on fibrosis progression could be successfully quantified.

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IV-57: *Hiroyuki Iida* Modelling the biomarker-driven tumour growth inhibition by a novel pan-Trk inhibitor ONO-7579 in xenografted mice

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Objectives: Oncogenic rearrangements of neurotrophic tyrosine receptor kinase (NTRK) encode chimeric proteins with constitutive kinase activity, which promote tumour cell growth and survival. Patients with NTRK fusion-positive cancers well responded to treatment with tropomyosin receptor kinase (Trk) inhibitors in clinical studies [1]. ONO-7579 is a highly potent and selective oral pan-Trk inhibitor which selectively inhibits Trk autophosphorylation, associated with the down-stream signalling [2]. The objective of this work is to define relationship between phosphorylated TrkA (pTrKA) and antitumour effect in KM12 xenografted model mice with PK/PD modelling approach in order to contribute to determination of recommended dose with biomarker in early clinical development.

Methods: KM12 cells were transplanted subcutaneously into female BALBnu/CrlCrlj mice. A single dose of ONO-7579 was orally administered at doses of 0.06 and 0.6 mg/kg to evaluate the time-course of ONO-7579 concentration and pTrkA level in tumour. On the other hand, repeated doses of ONO-7579 were orally administered once daily for 12 days at 0.06, 0.2, and 0.6 mg/kg to evaluate the time-course of tumour volume. Plasma and tumour concentrations of ONO-7579 and pTrkA level in tumour were obtained from both studies. The resulting data were integrated and empirical model analyses were performed with NONMEM 7.1.2. Plasma PK model, tumour PK model, tumour PK/pTrkA model and pTrkA/tumour volume model were developed in a sequential manner. The relationship between tumour growth rate and pTrkA inhibition in the tumour was predicted by using the developed model.

Results: Plasma concentration of ONO-7579 was well described with oral 1-compartment model. Tumour concentration of ONO-7579 was higher than plasma concentration, and tumour compartment was added on the plasma compartment. Though delay in distribution from plasma to tumour was observed, tumour concentration of ONO-7579 and pTrkA level in tumour were well described with direct Emax model. Time-course of tumour volume were well described with first-order growth/death model, with the pTrkA inhibition effect included as a sigmoid Emax model on tumour growth rate. Though ONO-7579 hardly exerts antitumour effect at pTrkA inhibition rate ≤ 60%, ONO-7579 starts to sharply increase the tumour growth inhibition at pTrkA inhibition rate > 60%. It turned out that pTrkA inhibition rate ≥ 91.5% was required in order to reduce tumour volume. The result indicates that there is a threshold of pTrkA inhibition rate where antitumour effect is exerted. Also, dosage and administration where, for example, pTrkA continues to be fully inhibited at trough concentration can be proposed so that ONO-7579 will be effective in clinical studies.

Conclusions: PK/PD/Efficacy model has identified “switch-like” relationship between pTrkA inhibition rate and antitumour effect in KM12 xenografted model mice, and demonstrated that pTrkA in tumour can be an effective biomarker to consider dosing regimen of ONO-7579 in clinical studies.

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IV-58: *Luis Ilia* Quantitative comparison of in vitro and in vivo variability of microdialysis experiments using nonlinear mixed-effects modelling on the example of linezolid

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Objectives: Developing and finding the optimal dosing regimen of antiinfectives with the goal of optimising therapeutic outcome and preventing the emergence and spread of resistance remain main challenges in our healthcare system. Knowledge of concentrations at target sites such as interstitial space fluid (ISF) is gaining high attention to predict probability of pharmacokinetic/pharmacodynamics (PK/PD) attainment. This knowledge can be gathered using the minimally invasive microdialysis (µD) sampling technique [1] which is based on passive diffusion of molecules across a semipermeable membrane at the tip of a µD catheter. The catheter is continuously perfused with a drug-free solution (perfusate) that closely resembles the composition of the surrounding tissue fluid at a low flow rate. Unbound drug in the extracellular tissue fluid can be determined by measuring the drug concentration in the collected dialysate. Catheter calibration as retrodialysis needs to be performed to account for relative recovery values less than 100%. However, variability after using *in vivo* retrodialysis as calibration method remains high, which prompts *in vitro* investigation to identify and quantify its sources. In this work, the antibiotic linezolid (LIN) was studied *in vitro* with a focus on the variability in relative recovery and its impact on microdialysate concentrations, compared to *in vivo* µD.

Methods: An *in vivo* ISF LIN concentration-time profile (C(t) profile) obtained from the typical patient profile of a clinical µD study [2], [3] was mimicked in a µD system. Samples were taken from the flask which represents the ISF and collected from three different µD catheters (CMA 60, 20 kDa cut-off) simultaneously over eight hours. As calibration method retrodialysis was consecutively performed twice and thrice respectively. This was repeated on four different occasions using the same catheters. Nonlinear mixed-effects (NLME) modelling was performed using NONMEM® (7.4.3) to characterise the LIN C(t) profile in the µD system and to quantify the different levels of variability. An integrated ISF and micro-/retrodialysis modelling approach was chosen to evaluate data from all three available sources (ISF, micro- and retrodialysis) simultaneously [4]. Afterwards, variabilities associated with relative recovery were compared to variability from *in vivo* clinical data.

Results: The clinical LIN C(t) profile of a typical patient was successfully mimicked by the µD system by optimising pump flow rates and infusion concentrations. The LIN C(t) profile in the *in vitro* system was successfully described using a one compartmental model with linear clearance for the flask and three µD measurement compartments. The predictive performance of the PK model was adequate and typical parameter estimates (95% CI) were in line with the experimental settings. Estimated ISF-compartment volume and clearance were 91.1 mL (85.1 – 97.0 mL) and 155 µL/min (133 – 167 µL/min), compared to a flask volume of 100 mL and pump rate of 145 µL/min. The typical relative recovery of 91.9% from µD was comparable to the values derived from the retrodialysis experiments (85.1–96.2%). Recovery variability was split up in intracatheter and intercatheter variability which were 2.60%CV (1.97 - 3.23%CV) and 2.80%CV (2.34 – 3.26%CV) respectively, compared to 27.2%CV (21.8 – 32.0%CV) and 26.1%CV (16.7 – 33.8%CV) *in vivo*.

Conclusion: The established µD system and model-based analysis provide quantitative and qualitative insights into the µD sampling technique, specifically its variabilities, for the case compound LIN. *In vitro* derived variability was up to ten times lower than *in vivo*. This suggest that the current *in vivo* assessment of sources of µD variability might be confounded by other factors such as variability in the conducted retrodialysis experiments or in the sampled target site. An integrated approach considering additional *in vitro* and *in vivo* data might identify these confounding factors and thus aid in further elucidating the high variability in clinical µD studies.

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IV-59: *Khalid Iqbal* Modelling tissue pharmacokinetics: A comparison of empiric and mechanistic PBPK modelling approaches of different complexity exemplified with moxifloxacin

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Objectives: Suboptimal tissue site exposure is a critical factor for therapeutic failure, potentially stimulating antibiotic resistance and is hence crucial to investigate using a pharmacometric approach. Thereby, a pharmacometric model shall provide good predictive performance and provide mechanistic insight into the tissue pharmacokinetics (PK). The aim of this study was to (i) develop an empirical, a whole-body physiologically-based (WBPBPK) and minimal-PBPK model for moxifloxacin in septic patients integrating microdialysis data from the target sites subcutaneous and muscle tissue and (ii) to compare their predictive performance and mechanistic inferences.

Methods: Plasma (total and unbound), subcutaneous and muscle tissue samples from 10 septic patients were collected at day 1, 3 and 5 after intravenous once daily dosing of 400 mg moxifloxacin. Microdialysis was used to collect samples from subcutaneous and muscle tissue.

In the first step, an integrated empiric microdialysis pharmacometric model [1] was developed on the data where all compartment parameters were empirically estimated.

In the second step, a WBPBPK model consisting of fifteen physiologically-motivated compartments including plasma, skin and muscle compartments was built. Blood flows and tissue volumes were calculated from the ICRP report [2], scaled by sex and body weight. Tissue partition coefficients (KP) were calculated based upon their physicochemical properties [3] and used as informative priors (uncertainty: 25%) during estimation from the available clinical data.

In the third step, a minimal-PBPK model [4] was built by lumping various tissue compartments into central and peripheral compartment while retaining the clinically important muscle and subcutaneous tissues unlumped. KP values were calculated as for the WPBPK model.

All models included estimation of recovery measurements from the microdialysis data [1]. Visual predictive checks (VPC's) were used to compare the predictive performance of all the models. NONMEM® 7.4 was used for all estimation and simulation tasks.

Results: For the empiric approach, a four compartment model with total body weight as a covariate on clearance (CL) and central volume of distribution (V1) best described the plasma and tissue PK of moxifloxacin. For a 75 kg patient, CL was 12.6 L/h (interindividual variability, IIV: 21.5 %CV), V1 was 15.5 L (IIV: 44.8 %) and peripheral volume of distribution (V2) was 98. 7 L (IIV: 93.8 %). The distribution volumes of

the tissues were only imprecisely estimated and differed substantially from the volume of the interstitial space fluid (ca. 12 L).

The WBPBPK model predicted the typical concentration time profiles of plasma and target tissues adequately and the compartments were physiologically meaningful. Yet, variability was overpredicted if inter-individual variability on KP values was estimated and the model was unstable and exhibited very long run times.

The minimal PBPK model combined the good predictive performance, high model stability and short run times of the empirical model with the physiologically plausible description of the tissue PK. Additionally, the PBPK models indicated blood-flow mediated distribution to muscle and permeation-restricted distribution to subcutaneous tissue –a mechanistic insight that was not provided by the empiric approach.

Conclusions: Moxifloxacin displayed good tissue penetration to muscle and skin tissue. The minimal PBPK modelling approach provided an attractive framework for modelling of the tissue PK of moxifloxacin in a mechanistically plausible and efficient way and combined the favourable properties of the empiric and WBPBPK approach. Application of the presented approach to further tissue PK studies is warranted.

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IV-60: *Itziar Irurzun-Arana* ACESO (A Cancer Evolution Simulation Optimizer)

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Objectives: The identification of drug administration schedules to avoid the emergence of resistance is a major challenge in cancer research. Here we propose a computational strategy to explore the effects of pharmacokinetics and drug interactions in evolutionary models of cancer progression and emergence of resistance, with the ultimate goal of identifying optimum dosing strategies.

Methods: Our approach combines stochastic evolutionary models of heterogeneous tumor cell populations with pharmacokinetics and drug-drug interaction models. This approach is made up of a cell-level description of the changes in sensitive and resistant cells over time and in response to treatment in the form of a stochastic model known as "multi-type branching process" [1]. A branching process is a stochastic model of cell division, mutations events and cell death used to describe the growth and composition of tumor cell populations. In this model, sensitive cells accumulate mutations at a given rate per cell division, generating new clones harboring specific drug-resistance mechanisms. The birth and death rates of each cell type are affected by the varying drug concentrations; therefore accounting for pharmacokinetic processes is also crucial. In order to simulate pharmacokinetic models we included the *mrgsolve* R package and we provide the codes of the most commonly used pharmacokinetic models to ease the degree of competency needed to perform simulations of these models. To assess drug interaction effects on the different rates of the model, we used non-parametric methods. This forms a multiscale description of drug metabolism and cancer evolution [2].

Results: In this work we present an R package called ACESO (A Cancer Evolution Simulation Optimizer) which incorporates a model that consist on a multi-scale description of how a heterogeneous cell population evolve over time depending on the drug administration schedule. This tool can then be used to search through different possible drug administration strategies to identify the one that is predicted to be best, for instance because it minimizes the risk of resistance or the expected number of cancer cells over time. Using ACESO, the different strategies can also be tested for robustness due to variability in pharmacokinetic parameters among patients, variable growth and death rates of sensitive and resistant cells as well as different compositions of the tumor at the start of therapy. We demonstrate the use of this tool using publicly available data from the Harvard Medical School Library of Integrated Network-based Cellular Signatures (LINCS) Database [3].

Conclusions: We present an accessible tool called ACESO to explore the dynamic evolution of heterogeneous tumor cell populations while taking pharmacokinetic and drug interaction effects into account to rationally identify optimum treatment administration strategies. This work represents a crucial step towards making clinically relevant predictions since it incorporates the most important aspects governing treatment response and cancer evolution.

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IV-61: *Kris Oliver Jalusic* Pharmacokinetics of vancomycin in the cerebrospinal fluid in critically ill patients

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Introduction: Although the penetration into the central nervous system is believed to be poor, vancomycin is the recommended therapy in patients suffering from ventriculitis [1][2]. To determine the distribution of vancomycin into the cerebrospinal fluid (CSF), the pharmacokinetics of vancomycin in patients with ventriculitis were evaluated and covaraiate relationships explored.

Objectives:

- Investigating dosage adjustments for vancomycin in critically ill patients with regard to adequate drug concentrations in the CSF
- Screening of covariates that influence the pharmacokinetics of vancomycin in critically ill patients

Methods: For the population pharmacokinetic model, 29 patients were recruited in an intermediate care unit at the university hospital of Münster in the period between January 2014 and June 2015. A total of 184 Blood and 133 CSF samples were collected. All patients had a clinical evidence of EVD (External ventricular drainage) -associated ventriculitis [3]. Vancomycin was either applied as bolus 6h (n=23) or continous infusion (n=6) with daily plasma and CSF trough concentrations measured. In the interval dosing scheme, the doses were adjusted to reach serum trough levels of 15-20 mg/L. For continuous dosing, adjustments targeted serum concentrations of 20-25 mg/L. This dosing regimen was designed to achieve vancomycin CSF trough concentrations above 1 mg/L [4]. For all patients demographic covariates, as well as leucocytes count, creatine, creatine clearance, C-reactive protein, urea in serum and total protein, glucose, lactate, granulocytes, cell count, erythrocytes in the CSF

The enzyme-multiplied immunoassay technique was used to analyse plasma concentrations [5]. The therapy with vancomycin was continued for 7 to 14 days, unless the antibiotic therapy was deescalated or adverse events led to a discontinuation. The population pharmacokinetic analysis was conducted by using nonlinear mixed effects modelling (NONMEM®).

Results: The median and range for the concentration in plasma were as follows 17.7(2.4-49.1) [mg/L] and the median concentration in the CSF 2.9 (1.1-11.0) [mg/L], respectively. For the final population pharmacokinetic model a three-compartment model with linear elimination was developed. Two compartments describe vancomycin pharmacokinetics in plasma with a third discribing the disribution into the CSF. Creatinine clearance (Cl_{Cr}) and lactate were detected as significant covariates. The model shows that the total vancomycin plasma clearance (Cl) depends on Cl_{Cr}. Furthermore, the clearance (Cl_{dif}) between the central and CSF compartment correlates with blood lactate concentration. Based on the final model, the following values were estimated by NONMEM®: Cl = 5.15 L/h, Q = 3.31 L/h, Cl_{dif} = 0.0031 L/h, $V_{central}$ = 42.1 L, V_{CSF} = 0.32 L and the value of $V_{peripheral}$ was fixed to 86.2 L. Monte-Carlo simulations for diffent dosing regiments indicate that a dose of 4 g per day, administered every 8 hours, adequately results in the CSF target concentrations of 1 mg/L.

Conclusion: In the daily clinical routine, the final PK model can be useful in dosing of vancomycin in critically ill patients. The lactate concentration is a determinant of CSF vancomycin concentrations.

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IV-62: *Petra Jauslin* Modeling bounded scales for evaluation of treatment response to subcutaneous nemolizumab in moderate to severe atopic dermatitis

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Objectives: To characterize, in patients with moderate-to-severe atopic dermatitis (AD), the pharmacokinetic-pharmacodynamic relationship between serum concentrations of nemolizumab (a humanized antibody against interleukin-31 receptor A) and the following clinical outcome variables: eczema area and severity index (EASI, score range 0-72) and weekly average of peak pruritus numeric rating scale (PP-NRS, score range 0-10).

Methods: A total of 3'620 EASI scores from 525 patients and 4'578 weekly PP-NRS scores from 225 patients were analyzed. EASI scores were available from three randomized placebo-controlled clinical studies: a phase 1 SAD study (CIM001PJ: N=36, dose range: 0.3-3 mg/kg) [1], a phase 2a safety and efficacy study (CIM003JG: N=264, dose range: 0.1-2 mg/kg Q4W or 2QW) [2] and a phase 2b dose-range finding study (RD.03.SPR.114322: N=225, dose groups: 20 mg loading dose (LD) + 10 mg, 60 mg LD + 30 mg and 90 mg Q4W) [3]. PP-NRS scores were only available from the phase 2b study RD.03.SPR.114322. Both endpoints were modelled as continuous bounded scales. Logistic functions were used to transform the amount in the indirect response model compartment from [0, +∞] to the bounded scales of EASI ([0, 72]) or PP-NRS ([0, 10]). Longitudinal nemolizumab serum concentrations were described by a one-compartment population pharmacokinetic (popPK) model with linear elimination, first-order absorption with lag time and dose effect on bioavailability. Inter-individual variability (IIV) was included in clearance (CL), volume of distribution (V) and the absorption rate constant. CL and V were correlated at an individual level. Concentrations were log-transformed for analysis. Hence, the residual error was additive in the log domain. Covariate effects of serum albumin on CL and body weight on CL and V were identified. Empirical Bayes post hoc estimates generated from the popPK model were then used to drive turnover models for the respective pharmacodynamic (PD) endpoints. The structure of a model for pruritus visual analogue scale by Saito et al [4] was used as a starting point for both the EASI and the PP-NRS models. The drug effect was described with an inhibiting effect on the zero-order rate constant for production of response (R_{in}) in both cases. Linear and non-linear link functions and placebo effects were evaluated. For the description of EASI scores, a baseline model was implemented, in which the observed baseline response was included as a covariate acknowledging the residual variability [5]. The effect of covariates (age, body weight, and sex) on model parameters was assessed. All models were developed in NONMEM 7.3 [6].

Results: In both PD models, an inhibiting Imax model was chosen as most appropriate link function. For EASI, IC_{50} was difficult to estimate with sufficient precision. To stabilize the model, IC_{50} was therefore replaced by the parameter S_0, computed as $Imax/IC_{50}$, as suggested by Schoemaker et al [7]. A constant placebo effect was introduced as additive to the drug effect in both models. For EASI, this placebo effect was considerably larger in the Phase 2b study than in the earlier trials. It was therefore modeled as a study-specific parameter. IIV was included in S_0, the first-order rate constant for loss of response (k_{out}) and the placebo effect (P_1). For PP-NRS, IIV was included on estimated baseline PP-NRS, Imax, P_1, and k_{out}. Owing to eta correlations, an omega block for these random effects was included in the covariate matrix. The residual error was combined additive and proportional for both models, and no covariates were identified in either case. All model parameters were estimated with acceptable precision (<30% RSE for fixed effects

and ≤35% RSE for random effects). Visual predictive checks showed adequate predictive performance of the models (overall, as well as stratified by study [for EASI] and dose [for both models]).

Conclusions: The developed turnover models provide a good description of the EASI and PP-NRS data in AD patients treated with a wide range of nemolizumab doses. These models, together with a continuous-time Markov model for an additional PD endpoint (investigator's global assessment [IGA] score, described in a separate abstract) allowed for the characterization of nemolizumab effect in patients with moderate-to-severe AD and will further support the development program of nemolizumab.

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IV-64: *Jin Jin* Model-informed artificial intelligence (AI) solution enabling real-time predictions: towards next generation modeling

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Introduction/Objectives: The introduction of nonlinear mixed-effects modeling has led to a revolution in the analysis of pharmacokinetic (PK) and pharmacodynamic (PD) data. However, the specialized modeling expertise and the analysis time do not allow for an easy adoption of modeling tools by experimental scientists and clinicians at the bench-/bed-side to generate impactful insights in real-time. With the increasing amount and complexity of data being generated and the acceleration of drug development, such challenge is growing.

Methods: We propose a deep-learning framework whereby neural networks are trained by PK/PD and Quantitative System Pharmacology (QSP) models to enable the automated identification of specific patterns in data. The identified patterns can be used to classify the type of drug effect, as well as quantify the relevant parameters. This approach relies on modelers providing the appropriate training data (simulated from existing models) and utilize pertinent methodologies to develop and train the neural networks, which subsequently can be deployed as AI solutions to process and generate insights (e.g., via parametric characterization) from newly observed data. We demonstrate a prototype of the proposed approach utilizing Mathematica (version 11.3) [1] as the deep-learning framework.

Results: We show how a number of different neural network architectures [2] can be utilized to perform various modeling tasks. Within the context of analyzing PK and PK/PD data, neural networks can give rise to: (1) improved accuracy in the estimation of PK parameters (e.g., AUC) as compared to the traditional NCA calculation based on sparse observed data; (2) the ability to identify population PK and PK/PD parameters without conducting traditional modeling. In the context of safety, neural network can be used to infer hematological toxicity mechanisms and parameters from an in-vitro multilineage assay, which have previously required solution via global optimization techniques based on a QSP model [3]. The network dimensions chosen depend on the sizes of the inputs and outputs as well as the task, with representative examples shown in Table 1. To increase the reliability of neural network predictions, we show that adding L2 regularization with an appropriate choice of regularization parameters and drop-out layers can improve their tolerance to data noise while retaining the accuracy of predictions. These deep-learning problems can be solved effectively using the adaptive moment estimation (Adam) method [2]. In all these applications, while the training of the neural network may require some significant computational modeling effort upfront, at deployment the networks can make inferences (e.g., parameter estimates) at a fraction of a second.

Conclusions: With an appropriate choice of network architecture and regularization, we demonstrate that deep-learning has the potential to perform a number of routine PK/PD and QSP modeling tasks accurately, reliably and efficiently. These early explorations suggest that the proposed deep-learning framework could have broad applications in generating insights from data. We envision a future of human-machine partnership whereby repetitive modeling tasks are done by machines so as to free human modelers to carry out more scientific innovations and real-time decision impacts [4].

Table 1

Examples	Training Data	Neural Network		
		Input Layer	Intermediary Layers	Output Layer
PK: Estimate AUC from 5 time points	Simulated time-concentration in 300,000 virtual subjects from compartmental PK models	2x5 matrix (time - concentration)	2 convolutional, 12 rectified linear units (ReLU), 10 fully connected [2]	AUC estimate
Safety: Estimate 28 QSP parameters from in-vitro multilineage assay [3]	Simulated concentration-response in 100,000 virtual experiments from QSP model [3]	14x6 matrix (concentration - response)	2 convolutional, 4 ReLU, 3 fully connected layers [2]	28 parameters

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IV-65: *Mats Jirstrand* A challenge model of TNFα turnover with LPS provocations and drug intervention

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Objectives: Tumor necrosis factor alpha (TNF_α) is a pro-inflammatory cytokine associated with the pathogenesis of several immune-mediated diseases. Free TNF_α is almost undetectable in blood of healthy organisms. Experimentally, the effect of inflammatory mediators is studied *in-vivo* after intravenous administration of lipopolysaccharides (LPS), where the challenger causes a rapid but transient release of TNF_α. Hence, the base line of the biomarker under study is vanishing and only a transient effect is available for quantifying the effect of drug intervention. This poses a challenging situation for assessing the pharmacodynamic effect by exploratory data analysis and modeling of experimental data [1]. The objectives of this work were to

- Demonstrate how to assess a pharmacodynamic effect represented by a biomarker with a baseline below the limit of detection.
- Demonstrate how exploratory data analysis may provide guidance in formulating a model, which enables a better understanding of target biology.

Methods: Three different LPS challenges (Study 1: increasing intravenous dose 0, 3, 30 and 300 $\mu g \cdot kg^{-1}$ LPS) and three inhibitory test-compound doses (Study 2: increasing oral doses of test-compound 0, 0.3, 3 and 30 $mg \cdot kg^{-1}$ followed after two hours by an intravenous dose 30 $\mu g \cdot kg^{-1}$ LPS) were investigated using TNF_α-response as a biomarker of target behavior. The test-compound is a selective inhibitor of phosphodiesterase (PDE) type 4 isoforms. Data was pooled from two preclinical studies in rats. A mechanism-based biomarker model of TNF_α-response was developed, which includes both external provocations of LPS challenge and test-compound intervention. The model contained system properties, challenge characteristics, and test-compound related parameters. Test-compound exposure was modeled by means of first-order input and Michaelis-Menten type of nonlinear elimination. Lack of LPS exposure time course data was solved by using a biophase model. A transduction type of model with non-linear stimulation of TNF_α release was finally selected. TNF_α-response was represented by a turnover model with a periphery compartment to account for observed transient effects in the elimination phase. Both stimulation through LPS and inhibition by the test-compound act on TNF_α release. Typical features of a challenge experiment were shown by means of model simulations. Experimental shortcomings of present and published designs are identified and discussed. Parameter estimation was performed in three stages using Monolix [2]. In the first two stages test-compound parameters and TNF_α turnover parameters after LPS challenge without test-compound intervention were fitted. In the last stage, TNF_α time courses with combined LPS challenge and drug intervention were fitted.

Results: Experimental data show a 30 min time lag in onset coupled to a peak-shift in TNF_α-response at increasing LPS doses, which suggests a nonlinear stimulation of TNF_α release. The elimination rate constant of LPS from the biophase compartment, the transit compartment rate constant, and the fractional turnover rate of TNF_α-response were all of the same order of magnitude (with half-lives of 7, 18 and 10 min, respectively). Test-compound potency was estimated to 20 nM with a 70% partial reduction in TNF_α-response at the highest dose of 30 $mg \cdot kg^{-1}$. Model simulations were done with a fixed test-compound dose

(3 mg·kg-1) and increasing LPS challenges in order to clarify the behavior of the model. Predictions show suppression of TNF_α peak response proportional to LPS challenge, as well as a peak-shift in TNF_α-response with increasing LPS doses. A more extensive presentation of the model-based analysis surveyed on this poster can be found in [3].

Conclusions:

- Future selection of drug candidates may focus the estimation on potency and efficacy by applying the selected structure consisting of a TNF_α system and LPS challenge characteristics
- Repeated LPS-challenges may reveal how the rate and extent of replenishment of TNF_α pools occur
- Tackling a biomarker with a baseline below the limit of detection requires elaborate models

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IV-66: *Curtis Johnston* M-EASE-2: A Modelling and simulation study conducted to further characterize the efficacy of low-dose Empagliflozin as Adjunctive to inSulin thErapy (M-EASE) in Type 1 Diabetes Mellitus (T1DM)

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Objectives: The objective of this modelling and simulation study was to further characterize the empagliflozin (EMPA) 2.5 mg qd dose independent of data from EASE-3 [1], a phase 3 study investigating this dose. Specifically, this exposure-response modelling study (M-EASE-2) was performed to simulate the placebo-corrected change from baseline in the study population of a second phase 3 trial (EASE-2) which did not investigate this dose [1]. Moreover, covariate effects for the exposure-response relation were assessed during model building.

Methods: M-EASE-2 model development was informed by data from EASE-2 (52 weeks, EMPA 10 and 25 mg qd) and EASE-1 (4-week phase 2 study [2], EMPA 2.5, 10, 25 mg qd). Furthermore, prior information for AUC_{50} from an analysis in patients with T2DM [3], was used during parameter estimation. Predictions of EMPA exposure, based on individual parameter estimates from a previous population PK analysis, were used as input for this exposure-response analysis. The analysis was conducted in NONMEM Version 7.4, applying Markov chain Monte Carlo Bayesian estimation. The effect of EMPA exposure on HbA1c was modelled as a direct E_{max} model including a placebo effect. Investigation of the covariate effects was undertaken using a full covariate modelling approach. The primary covariates of interest were pre-defined based on findings in previously conducted analyses including patient sex and baseline weight, eGFR and HbA1c. Indication-specific factors were also evaluated including daily insulin dose at baseline and insulin dose type (INSDT): multiple daily injections vs. continuous subcutaneous insulin infusion. For internal and external model evaluation via visual posterior predictive checks, 500 Monte Carlo simulation replicates each using 500 samples from the posterior distribution of model parameters were generated. External model qualification focused on an out of sample prediction using data from EASE-3. For trial simulations investigating the effect of EMPA 2.5 mg in the study population of EASE-2, 500 Monte Carlo simulation trial replicates with 239 patients were created. Each simulation utilized a random sample from the posterior distribution of model parameters and variability terms (inter-subject and intra-subject variability). The impact of prior information on HbA1c lowering was investigated via sensitivity analysis (varied informativeness and point estimate).

Results: A direct response model best described the effect of EMPA exposure on changes in HbA1c. Drug effect was characterized by a E_{max} model driven by $AUC_{\tau,ss}$, with a time-dependent linear placebo effect. Typical population PD parameters (95% credible interval) were: Baseline HbA1c: 8.14% (8.07%, 8.22%); AUC_{50}: 498 (296, 819) nmol·h/L; E_{max}: 0.579% (0.491%, 0.678%); Placebo Effect: 2.61×10^{-5} (1.96×10^{-5}, 3.29×10^{-5}) %/h. Inter-individual variance (CV %) for baseline HbA1c and E_{max} were 7.2% and 38%, respectively. The proportional and additive residual variability estimates (CV% and SD) were 4.6% and 0.11, respectively. Sensitivity analyses for the AUC_{50} estimate demonstrated that the informative prior on AUC_{50} resulted in conservative estimates of the HbA1c lowering for EMPA 2.5 mg. The simulations performed for external qualification were consistent with EASE-3 results. The simulated median (95% CI) placebo-corrected HbA1c change for EMPA 2.5 mg was -0.29% (-0.39%, -0.19%) at Week 26 and -0.29% (-0.40%, -0.19%) at Week 52. Moderate effects influencing the placebo-corrected change of HbA1c at Week 26 relative to baseline were

observed for INSDT, baseline HbA1c and baseline eGFR. Simulations to illustrate the impact of baseline HbA1c on change in HbA1c were performed. For a 2.5 mg dose, a median placebo adjusted change in HbA1c at 26 weeks relative to baseline of -0.28% versus -0.32% was predicted for a baseline HbA1c of 8.0% and 9.0%, respectively.

Conclusions: The exposure-response model successfully predicted the time-course and dose-related changes of HbA1c in EASE-3, a study not included in the model development. This external model qualification demonstrated the utility of the developed model to predict hypothetical outcomes in populations similar to the EASE-2 population reliably. M-EASE-2, a descriptive modelling and simulation approach, illustrated how pharmacometric analyses can be utilized to create further evidence of efficacy and substantiate clinical findings.

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IV-67: *Daniel Jonker* The impact of septic shock on the pharmacokinetics and pharmacodynamics of selepressin

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Introduction:

In critically ill patients, marked changes in pharmacokinetics and pharmacodynamics occur due to, for example, increased distribution volume and decreased renal clearance [1]. Further, in septic shock marked vasodilation is accompanied by increases in vasoactive mediators including vasopressin and catecholamines, which may affect the PD effects of vasopressors but not much data are available. Selepressin is a selective V1a receptor agonist that is effective in maintaining blood pressure in septic shock [2]. The PK and blood pressure effects of selepressin have been studied in a first-in-man trial in healthy subjects as well as in two phase 2 trials in patients with sepsis requiring vasopressor treatment [3], offering the opportunity to assess the impact of septic shock on the PK and PD of selepressin.

Objectives:

To compare the PK and PD of selepressin in healthy subjects and in subjects with sepsis requiring vasopressor treatment and to identify covariates that affect selepressin exposure.

Methods:

In the first-in-man trial (A), healthy subjects were administered an IV infusion of selepressin (n = 30, 4 groups) or placebo (n = 12) for 6 hours. The two patient trials (B and C) included subjects with sepsis requiring vasopressor support, who received selepressin (or placebo) add-on to norepinephrine until shock resolution for up to 7 days. In trial B, patients received IV selepressin at a fixed infusion rate (n = 31, 3 groups), or placebo (n = 21). Trial C was an open-label feasibility trial in 30 patients in which selepressin infusion rate could be increased from the initial rate.

A population PK model was developed using the data from the three trials. The covariates of interest were pre-defined and included baseline values of body weight and creatinine clearance (CrCL), and age, sex, fluid balance, renal replacement therapy (yes/no) and acute kidney injury class. Fluid balance was assessed in 24 h collection periods by subtracting the volume of fluids administered from the volume excreted. For the trial in healthy subjects, an exposure-response model was developed relating selepressin concentrations to changes in mean arterial pressure (MAP). In patients, such a model could not be developed as infusion rates of norepinephrine were adjusted to maintain MAP at the intended target of 65-80 mmHg. Instead, the selepressin exposure-response relationship for norepinephrine infusion rate was explored.

Results:

A two compartment PK model described selepressin plasma concentrations adequately in all trials. In the patient trials, the median duration of selepressin infusion ranged from 33 to 76 hours across groups in trial B and from 21 to 53 hours in trial C. During the first 24 hours of treatment, on average 7.5 L of fluids were administered in trial B, and a similar volume in trial C. The peripheral and central volumes of distribution were estimated to be respectively 2.8 [90% CI: 1.5 - 5.2] and 1.7 [90% CI: 1.4-2.0] times higher in patients

than in healthy subjects. Selepressin clearance was 1.4 times lower in patients than in healthy subjects. The main covariate identified for selepressin clearance was body weight, with selepressin exposure estimated to be 1.3 [90% CI: 1.2 – 1.4] times higher in a subject weighing 45 kg compared to a subject weighing 77 kg. The effects of age and CrCL on clearance were of similar magnitude but could not be estimated independently from each other due to CrCL decreasing with age.

In healthy subjects, an increase in the placebo-corrected change from baseline in MAP was described using a linear exposure-response model without effect delay. The increase in MAP amounted to 9 mmHg at a plasma concentration of 0.8 ng/mL. In patients, selepressin could substitute for norepinephrine to maintain MAP at 65-80 mmHg, in the presence of an exposure-dependent reduction in norepinephrine infusion rate without sign of an effect delay. At a plasma concentration of 0.8 ng/mL selepressin, the norepinephrine requirement was decreased by 0.1 µg/kg/min. In comparison, a MAP increase by 10 mmHg requires an increase in norepinephrine infusion rate of 0.1-0.2 µg/kg/min [4-6].

Conclusion:

The PK of selepressin differ between healthy subjects and patients with septic shock, the main difference being a marked increase in distribution volume. Judging from the decrease in norepinephrine requirement, the blood pressure response to selepressin is qualitatively similar in patients and healthy subjects.

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IV-68: *Felix Jost* Application of a feedback optimal control algorithm to a population pharmacokinetic-pharmacodynamic model of cytarabine-derived and lenograstim-reduced myelosuppression in acute myeloid leukemia

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Objectives:

The aim of this work was the development of a population pharmacokinetic-pharmacodynamic (PK/PD) model describing the dynamics of white blood cells (WBC) of acute myeloid leukemia (AML) patients treated with cytotoxic cytarabine (Ara-C) and support of lenograstim (G-CSF, granulocyte-colony stimulating factor) during consolidation therapy. Further, we investigated a computational approach which proposes individually optimized treatment schedules of Ara-C and lenograstim together with optimal WBC measurement time points from optimal experimental designs. The efficacy of the optimized treatment schedules is quantified by the consideration of leukemic cells within the model.

Methods:

The second priority consolidation arm of the AMLSG 12-09 study [1] was provided by the Department of Internal Medicine III, University Hospital Ulm, Ulm, Germany and used for model development, validation and calibration. The dataset includes WBC count measurements (6-16 per cycle) from 86 consolidation Ara-C cycles (CCs), partitioned in one, two, and three consecutive CCs from 20, 6, and 18 AML patients (median 65 years, 19 (43%) male) from 2010 and 2012 which were treated with high- or intermediate-dosage of Ara-C at days 1,2 and 3. The treatment schedule intended daily 263µg lenograstim administrations starting 9 days after the start of Ara-C treatment until hematological recovery, i.e. neutrophil count >0.5G/L, was achieved. We linked and extended the myelosuppression model considering endogenous G-CSF [2] with a PK model for Ara-C [3] and lenograstim [4]. As no endogenous G-CSF measurements were observed, the modeling process, especially the linkage of endogenous and exogenous G-CSF, was guided by the observed G-CSF concentrations shown in Figures 1 and 2 from [4,5]. The PK/PD model was fitted to the WBC count measurements using nonlinear mixed-effects modeling implemented in NONMEM 7.4. To obtain a clinical impact from mathematically optimized treatment schedules, cytokine-dependent leukemic cells were incorporated to the PK/PD model via a two compartment model presented by Stiehl *et al.* [5]. The interaction between WBCs and leukemic cells occurs through competition for G-CSF. Then, the feedback optimal control algorithm from [6] was applied to the novel PK/PD model as follows: For one exemplary patient the first two CCs were used for model personalization. Then, the treatment plan and the measurement time points of the third CC were optimized and compared to the actual CC. For this we minimized the amount of leukemic cells with respect to a lower bound of 1G/L on the WBC count dynamics and a total administered amount of high-dosage Ara-C, currently being the standard treatment in one CC for patients aged 60 years and younger [7]. As initial condition of the leukemic cell dynamics we assumed a relative amount of 5% compared to the healthy cells.

Results:

The WBC concentration-time data were best described by the extended myelosuppression model considering a parametrized secondary PD effect of Ara-C on the proliferation speed. The lenograstim administration was modelled by an additional depot compartment. The absorption rate constant was fixed to a value such that the simulated G-CSF concentrations qualitatively coincided with published concentration-time profiles. The linkage between the central compartment of the PK model and the endogenous G-CSF compartment of the PD model was modelled by a first-order process using the absorption rate constant of the depot compartment. We used the same constant as no observed G-CSF concentrations were available to identify a parametrized version of the model. Regarding the obtained optimal treatment plan from the feedback algorithm, the optimization suggests two consecutive CCs leading to nadir values close to 1G/L compared to the actual third CC with a measured nadir value of 0.5G/L.

Conclusions:

We present a PK/PD model for predicting leukopenia during consolidation therapy of AML patients treated with Ara-C and lenograstim. In a case study we demonstrate a computational approach minimizing the number of leukemic cells through optimized treatment schedules and thereby satisfying clinically important constraints such as a WBC count threshold of 1G/L.

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IV-69: *Fabian Jung* Simulation of the environmental exposure to fenofibrate nanomaterials based on in vitro- and in silico methods

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Introduction: A rising number of active pharmaceutical ingredients (API) possess physicochemical properties unfavorable for oral absorption [1]. While traditional approaches tried to overcome this issue by applying increased doses, a growing number of enhanced formulations such as nanoparticle have been entered the market recently [1,2]. On the other side, the growing number of nanoformulations in the pharmaceutical market has raised concerns about contamination of the aquatic ecosystems [3].

Objectives: Aim of the current work was the evaluation of possible benefits and risks of API nanosizing for patients and environment with regard to pharmacokinetic, ecotoxicology and particle size specific properties.

Methods: The different aspects in the risk assessment were studied on the model compound fenofibrate in the commercial available formulations Lipidil® 200 Lipidil 145 One® as well as a new developed semi-liquid formulation (Ecocaps). A PBPK model was developed to predict the human pharmacokinetic as well as the emitted amount and particle size of fenofibrate and its metabolite, fenofibric acid, to the environment. The current approach combined therefore *in vitro* studies of release properties, ecotoxicology in zebra fish embryos and particle transformation during a simulated gastrointestinal (GI) transit. For the dissolution experiments, an absorption-related biorelevant medium was developed which enable a final dissolution plateau similar to the fraction absorbed found *in vivo*. The different formulations were then tested in these medium until the dissolution process was completed and the resulting release profiles were fitted and converted to differential equations. The toxicity of fenofibrate and fenofibric acid was investigated in a fish embryo toxicity test (FET) and lethal concentration (LC_{50}) values were calculated. Finally the transformation of nanoparticle during the transit through the GI tract was measured with nanoparticle tracking analysis (NTA) using biorelevant media for stomach (FaSSGF), intestine (FaSSIF-V2) and colon (FaSSCOF).

Results: Particle measurements revealed a broad and asymmetric size distribution in the micrometer range for the product Lipidl® 200. The Lipidil 145 One® tablet, on the other side, exhibited a Gaussian size distribution in the nanometer range while the new Ecocaps formulation was ranked in between. Dissolution experiments under biosimilar conditions revealed superior release properties for the nanoformulation as well as the Ecocaps compared to the microproduct Lipidil® 200. These results were successfully transformed to pharmacokinetic simulations of the different formulations, demonstrated by absolute average fold errors (AAFE) of 1.5 (Lipidil® 200) and 1.4 (Lipidil 146 One®). Furthermore, the ratios of c_{max} and AUC of the commercial products were found to be within the range of 0.8 and 1.25, which is applied by regulatory authorities to assess bioequivalence [3]. The FET assay showed an increased toxicity for fenofibrate (LC_{50} 29.58) compared to fenofibric acid (LC_{50} 53.32). The particle tracking analysis of the nanoparticle displayed stability in the gastric and intestinal compartment, but a remarkably aggregation in the colonic compartment resulting in a 57.0% lower particle concentration.

Conclusions: In conclusion, the combination of biorelevant release testing with PBPK modelling enabled a detailed environmental exposure analysis of fenofibrate. Within the limits of this simulation, the fractions of fenofibrate and fenofibric acid but also the content of nanoparticles after digestion was predicted. It could be shown that nanosizing enabled a higher bioavailability of fenofibrate without a significant risk of environmental emission of nanoparticles and additionally, a lower ecotoxicological exposure due to the higher detoxification of the API in humans.

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IV-70: *Wannee kantasiripitak* A population pharmacokinetic and exposure-response model of golimumab for targeting endoscopic remission in patients with ulcerative colitis

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Objectives: Golimumab (GLM, Simponi®) is a fully human anti-tumour necrosis factor-alpha monoclonal antibody for the treatment of moderately to severely active ulcerative colitis (UC). Endoscopic remission (ER; a decrease in Mayo endoscopic subscore [MES] from 3 [severe disease] or 2 [moderate disease] at baseline to 1 [mild disease] or 0 [inactive disease] at week 14) has been focused as a therapeutic target in patients with UC as it is associated with improved long-term clinical outcomes. [1] Higher serum trough concentrations (TC) of GLM six weeks after start of therapy were associated with a greater proportion of patients achieving ER.[2]

Our aims are to develop a population pharmacokinetic (popPK) model and an exposure-response model that links GLM exposure metrics (TC and area under the concentration-time curve [AUC]), derived from the popPK model, to probabilities of transitioning between MES states from baseline to week 14.

Methods: GLM concentration-time data of 56 patients with UC (414 peripheral venepuncture [VP] samples and 296 dried blood spot [DBS] samples) were obtained from 2 study centres (University Hospitals Leuven, Belgium and Ljubljana University Medical Centre, Slovenia).[3–5] Serum and DBS concentrations were fitted simultaneously by estimation of a population conversion factor that related individually predicted serum and DBS concentrations.[6] A popPK model was developed in NONMEM (version 7.4). A first-order conditional estimation method with interaction was employed to obtain PK parameter estimates. Residual error models were tested for serum and DBS concentrations separately. The stepwise covariate modelling approach was employed to obtain the final covariate model (forward $\alpha = 0.010$, backward $\alpha = 0.001$). The developed PK model was used to derive GLM exposure metrics (i.e., TC and AUC).

A logistic regression exposure-response model was implemented to describe the relationship between these GLM exposure metrics and the response.[7] We assumed that only ordered transitions can occur (i.e., patients going from states 3 to combined 1 and 0 transitioned through state 2 and vice versa) and that the transition probabilities between states can be inversed (e.g. $P_{3\grave{a}2}=1-P_{2\grave{a}3}$). Sampling importance resampling (SIR) was adopted for parameter uncertainty estimation.[8]

Results: Data were described by a two-compartment model with linear absorption and elimination. The estimated PK parameters (typical value [relative standard error]) were absorption rate constant (k_a: 0.495 1/day [15%]), apparent total body clearance (CL/F: 0.417 L/day [9%]), apparent volume of distribution in the central compartment (V_c/F: 8.82 L [8%]), apparent volume of distribution in the peripheral compartment (V_p/F: 3.85 L [43%]), apparent intercompartmental clearance (Q/F: 0.469 L/day [20%], and conversion factor (4.14 [3%])). The residual error was best described using combined additive and proportional error models for VP and DBS samples separately. Median values of the estimated parameters

from the SIR were in good agreement with the NONMEM point estimates, and the 95% confidence intervals were narrow, indicating acceptable precision. The CL/F was 31% higher in patients when antibodies to GLM were present. Patients who had previously received biologicals had a 4-fold higher V_p/F. The unexplained interindividual variability remained large after the introduction of the two covariates (57% and 221% for CL/F and V_p/F, respectively). A total of 14/40 patients (35%, 16/56 had no endoscopy data available) achieved ER. A GLM TC at week 14 was the best predictor of ER (lowest objective function value). A GLM TC at week 14 of 0.5 mg/L [48%] corresponded to a 50% probability of going from MES 3 to 2. A GLM TC at week 14 of 4.1 mg/L [36%] corresponded to a 50% probability of going from MES 2 to 1 or 0. Targeting the patients in our cohort (55% and 45% at MES 3 and 2 at baseline, respectively) to the TC of 3.2 mg/L at week 14 predicted a 41% probability of achieving ER:

0.55x[(3.2/0.5)/(1+(3.2/0.5))x(3.2 /4.1)/(1+(3.2 /4.1))] + 0.45x[(3.2/4.1)/(1+(3.2/4.1))]

= 0.55x0.38 + 0.45x0.44 = 0.41.

Patients with MES at baseline of 3 and 2 had a 38% and 44% chance for achieving ER at w14, respectively.

Conclusion: Our popPK and exposure-response models allow dose selection for targeting a certain GLM exposure and the associated probability of ER.

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IV-71: *Evangelos Karakitsios* A methodology to estimate population pharmacokinetic parameters from aggregate concentration-time data and its application to gevokizumab.

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Objectives: The aim of the present study was to develop and assess the performance of a methodology to estimate the population pharmacokinetic (PK) parameters along with the Inter-Individual Variabilities (IIVs) from reported aggregate concentration-time data, in particular mean plasma concentrations and their standard deviations (SDs) versus time, such as those often found in published graphs. This method was applied to published data of gevokizumab, a novel monoclonal anti-interleukin-1β antibody in order to estimate population pharmacokinetic (PopPK) parameters of a minimal physiological pharmacokinetic model (mPBPK).

Methods: A function was constructed in R based on an mPBPK model [1] that predicts (output) the mean concentrations and their standard deviations (SD) from a Monte Carlo (MC) simulation of a number of patients generated from the distributions of the mPBPK model parameters including IIV for some of them (input). The model was parametrized in terms of the vascular reflection coefficients σ1 and σ2 for tight and leaky tissues, respectively, drug plasma clearance CL, and the IIV terms ω_{CL} and ω_V, for the SD of the lognormal distributions of plasma clearance and volume of human body respectively. This function was fitted to data of mean concentration and SD in order to estimate the model parameters and their corresponding IIV using Maximum likelihood method with a quasi-Newton optimiser. Latin Hypercube sampling was used for the MC step to improve speed. Also, two separate exponential residual error terms were assumed, one for the means and one for the SDs. To evaluate the performance of the method simulations and estimations were carried out calculating the bias and precision of the estimates, from 1000 simulated datasets. Furthermore representative VPCs from the simulated datasets were plotted. Ultimately, scanned data from literature of gevokizumab [2] were used to estimate the population parameters of an mPBPK model of the drug and the goodness of fit was assessed using diagnostic plots. The entire analysis was performed using R software (Rstudio).

Results: The per cent relative bias in the population parameters σ1, σ2, CL, ω_{CL} and ω_V was -0.11, 0.15, -0.14, -6.6 and 5.8 respectively. The respective per cent relative root mean squared error was 1.3, 1.8, 0.6, 8.1 and 9.0. The results show that the method is capable of estimating all the parameters with satisfactory bias and precision. Also, internal validation of VPC resulted that the model is robust and describes well the data including the observed variability. The estimates of the pharmacokinetic parameters of gevokizumab took the following values (SE in parentheses) in the final model: σ1=0.973 (3.37%), σ2=0.750 (3.10%), CLp=0.00652 L/hr (0.0168%), ω_{CL}=0.0974 (1.36%), ω_V=0.102 (1.08%) and residual error parameters were sigma1=0.112 and sigma2=0.461.

Conclusions: We present a methodology to estimate population pharmacokinetic parameters using only patients' mean plasma concentrations and their SDs vs time. The methodology describes adequately simulated data, indicating that the loss of information from averaging can be recovered. This method could be applied to any PK model in order to estimate PopPK parameters when only a published graph with aggregate PK profile and SDs is available.

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IV-72: *Vangelis Karalis* An In Vitro – In Vivo Simulation Methodology for Predicting the Outcome of Bioequivalence Studies

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Introduction: The role of modeling and simulation methodologies in drug development is emerging.

Objectives: To develop an in vitro - in vivo simulation (IVIVS) approach aiming at predicting the in vivo pharmacokinetic (PK) performance and the probability of success of a bioequivalence (BE) study. Relying only on in vitro dissolution data, the final aim of this methodology is to assist the R&D department selecting the appropriate test product lot (if many), clinical design, and sample size (N). This IVIVS approach was applied twice to two different irbesartan/hydrochlorothiazide BE studies.

Methods: The IVIVS methodology can conceptually be split into three steps: in vitro, in vivo, and IVIVS (1). A) In vitro: Mathematical models (e.g., Weibull, first-order) are used to describe the individual dissolution profiles at the three pH values. In a subsequent step, these models are used to simulate a single dissolution profile. Several scenarios are used to imitate drug transit through the gastrointestinal tract in terms of residence time at each pH condition (i.e., stomach, small intestine). B) In vivo: Using literature or actual in vivo concentration-time data for the drug under study, a PK model is developed using non-liner mixed effects (NLME) modeling approaches. C) IVIVS: This step applies a joint in vitro – in vivo model incorporating the models developed in 'A' and 'B'. Using the mean and variability estimates for each PK parameter, Monte Carlo simulations are performed and virtual subjects are generated assuming several levels of between- and within-subject variabilities and PK scenarios. The typical BE measures (Cmax, AUCt, and AUCinf) are calculated for each simulated individual using non-compartmental approaches. In turn, the estimated BE measures are set into a certain clinical design (e.g., 2x2, 3x3, 2x4). For each BE study, the typical statistical assessment is applied as imposed by the regulatory authorities (2,3). Each virtual BE study is repeated for thousands/millions of times and the statistical power is estimated. The same procedure can be followed several times taking into consideration the sample size, clinical design, sampling scheme, and anticipated difference in the PK parameters between the two formulations. Thus, an overall table with the statistical power of each scenario is constructed where the most probable case can be selected. In order to validate the reliability of the proposed methodology, the whole procedure is applied twice, firstly using literature PK parameters and secondly using estimated PK parameters from in vivo data through NLME approaches. The two BE studies utilized in this analysis refer to 2x2, single dose irbesartan/hydrochlorothiazide trials [study 1: 300 mg /25 mg, N=32 (2011), study 2: 150 mg / 12.5 mg, N=46 (2008)]. The computational work is performed in MATLAB® which is finally implemented in the form of a graphical user interface (GUI), while Monolix® 2018R2 was used for the in vivo fittings of step 'B'.

Results: In study 1, the actual in vitro data were utilized, while the PK information for irbesartan/hydrochlorothiazide came from the literature. Based on the IVIVS methodology, the overall predicted statistical power for the several scenarios tested was 81%. The actual BE study, as illustrated in the relevant report, resulted in a power of 86%. For study 2, the new dissolution data were utilized, while the PK estimates came from NLME fitting to the C-t data of study 1. For irbesartan, a two-compartment model was derived assuming first order absorption and elimination from the central compartment and combined residual error model (ka=0.665 h^{-1}, Cl/F= $1.34*10^4$l/h, V1/F= $3.64*10^4$l, Q/F= $8.92*10^3$l/h, V2/F= $6.61*10^4$l/h). In case of hydrochlorothiazide, a similar PK model was found with the following population estimates: Tlag=0.404 h, ka=0.773 h^{-1}, V1/F=$1.37*10^5$ml, V2/F=$1.46*10^5$ml, Q/F=$2.54*10^4$(ml/h), and

CL/F=3.45*10^4l/h. Using the same scenarios, as in case of the first IVIVS for study 1, the overall predicted probability of success for 46 subjects was 91%, whereas the actual power of the study reported in the protocol was 89%.

Conclusions: A new in vitro – in vivo simulation methodology is presented aiming at predicting the in vivo outcome (drug plasma concentration and probability of success of a BE study) based on in vitro dissolution studies. The proposed methodology was applied successfully to two irbesartan/hydrochlorothiazide BE studies.

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IV-73: *Eleni Karatza* Investigation of the impact of population parameters describing gastric emptying on bioequivalence metrics

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Introduction: Gastric emptying was shown to significantly affect the disposition of losartan (LOS), which is a BCS class I compound and its active metabolite (EXP-3174) [1]. This phenomenon was also noted to affect the bioequivalence outcome of BCS class I and III compounds [2].

Objectives: In the first place this study aimed to the validate the two models developed in order to describe gastric emptying using delay differential equations (DDE) or a sinusoidal equation. In the second place through this work, we intended to investigate which among their parameters may significantly affect bioequivalence (BE) metrics, namely Cmax and AUC.

Methods: LOS and EXP-3174 plasma concentration profiles were obtained from a single dose, 2x2 bioequivalence study in 31 men and women, receiving 100mg (2x50mg) losartan potassium in the form of immediate release tablets. Following a population pharmacokinetic analysis using Monolix ® 2018R1 the disposition of LOS and metabolite EXP-3174 were described by a joint two compartment-one compartment model with delayed first order metabolite formation. Plasma oscillations noted in certain losartan C-t profiles were attributed to gastric emptying that was best modeled either by first order gastric emptying followed by delayed first order absorption constant (**Delay-model**) or by a sinusoidal equation describing gastric emptying followed by first order absorption (**Sinus-model**) [3]. Matlab® DDE solver (dde23) was used to solve the equations obtained using parameters estimated by population modeling. The C-t profiles obtained were compared to the empirical C-t profiles using Wilcoxon paired rank test. Principal component analysis (PCA) was performed with the individual parameter estimates obtained from each model separately and the respective bioequivalence metrics (Cmax, AUC and Tmax) of each volunteer using R.

Results: Predicted concentrations obtained were similar to the empirical concentrations in both cases examined. Indeed, there was no statistically significant difference of the mean empirical C-t profile and solution of the Delay-model ($p=0.2744$) or solution of the Sinus-model ($p=0.5966$) using the population estimates. This finding was also evident through the superposition of the three C-t profiles obtained. Using PCA in both cases five principal components (PC) were identified explaining 82% of cumulative variability using individual parameter estimates of the Delay-model and 80% of cumulative variability using individual parameter estimates of the Sinus-model. Results from PCA using individual model parameters derived from the Delay-model and bioequivalence metrics showed through loadings of PC1 that constant lag time (0.4543) was significantly correlated with Cmax (-0.8959) and AUC (-0.8151).Additionally, through loadings of PC3 gastric emptying rate constant (0.7961) and delayed first order absorption constant (0.8235) were significantly correlated with Tmax (-0.8213). Results from PCA using individual model parameters derived from the Sinus-model and bioequivalence metrics showed through loadings of PC1 that amplitude of gastric emptying (-0.3630) and 2π/period of gastric emptying (-0.4286) were significantly correlated with AUC (-0.9018) and Cmax(-0.8279). In addition, through loadings of PC3 amplitude of gastric emptying (-0.8365), 2π/period of gastric emptying (-0.3004) and first order absorption rate constant (0.8507) were significantly correlated with Cmax (0.3999) and Tmax(-0.6963).

Conclusions: These findings indicate that gastric emptying may be modeled efficiently using both approaches proposed herein. A significant effect of parameters describing gastric emptying on

bioequivalence metrics was noted suggesting that this phenomenon may affect the outcome of a bioequivalence study using BCS class I compounds

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IV-74: *Tatiana Karelina* Amyloid β in vitro prion properties and in vivo pathology exacerbation mechanisms studied by translation quantitative systems pharmacology model for prediction of anti-protofibril immunotherapy effects

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Objectives: Clinical trials for Alzheimer's disease (AD) are focused at present time mostly at clearing different forms of accumulated amyloid (Ab). Complicated relationship between different markers of Ab pathology (soluble vs insoluble forms) requires mechanistic understanding of their formation and accumulation. Translational quantitative systems pharmacology (QSP) model of Ab distribution and aggregation has been developed and published earlier [1]. However, it has some limitations: it did not consider HWM oligomers (protofibrils) as intermediate step in aggregation; disease progression in mouse and humans was described mostly through empirical time-dependent functions independently and simultaneously influencing multiple processes (Ab degradation, production, nucleation). While some external age-dependent mechanisms driving Ab pathology may exist in human, in transgenic mouse Ab mutation and overexpression are the only cause of appearance of Ab plaques and thus it should be described without additional drivers. The objective of the study was to describe the behavior of the diverse amyloid species, by analysis of in vitro information on aggregation and antibody (mAb) effect; to capture the accumulation of Ab during pathology in AD subjects and preclinical models (Tg2576 mice) in the model using similar mechanisms; to study the biomarker efficacy of different types of therapies: beta-secretase inhibitors (BACEi) and immunotherapy in preclinical and clinical models.

Methods: The model describes Ab production, clearance and distribution in brain, CSF, plasma and other tissues, as well as different ways of Ab aggregation in the brain [1]. Reactions describing amyloid precursor (APP) processing were added. Different intermediates in the amyloid polymerization process are considered in the model (dimers, protofibrils) to capture available information about amyloid aggregation. The novel approach for hetero-polymerization description was elaborated to describe information about properties of Ab40 and Ab42 during aggregation and mutual influence on formation of specific toxic species. Secondary nucleation process is taken into account, assuming that new fibril formation is favored in presence preexisting fibrillary oligomers. Multiple feedback regulations from amyloid species on the amyloid related processes (production, degradation) were considered for description of pathology in Ab overexpressing mice (Tg2576). Analogous mechanisms were tested in the model for human. Immunotherapy was assumed to influence both aggregation process and degradation of amyloid by glial cells. Mouse, transgenic mouse, healthy and AD human data on Ab species concentration in different compartments as well as available PD data have been used for verification and validation.

Results: Model correctly reproduces the specific properties of Ab40 and Ab42 observed in vitro: difference in rate of ThT fluorescence increase at different portions of Ab40 and Ab42 with minimal fluorescence (no mature fibrils) at the equal Ab40 and Ab42 amounts. Several hypothetic feedback mechanisms were tested to explain the exacerbation of pathology in Tg2576 mouse after 5 months, and only combination of the degradation inhibition and amyloid production increase have allowed for correct description of soluble and insoluble species accumulation. The Tg2576 mouse model was validated across BACEi (verubecestat) data [2], and it correctly describes the difference between vehicle and chronic treatment: about 60% decrease for soluble Ab in the brain and 20% difference for total Ab after 12 weeks of treatment. Model satisfactorily describes the accumulation of insoluble and soluble Ab species during AD and results of published clinical trials: gamma- and beta-secretase inhibitors. Based on vitro data, mechanistic description of

immunotherapy by mAb158 was elaborated. It was introduced into the integrated model and verified on the SUVR data from BAN2401 study [3] and was shown to describe concentration dependent effect of mAb on SUVR (decline by up to 0.3) for early AD population. Simulations for such a therapy predict a significant decline of protofibrils in the brain (by 50%). For the moderate AD population, no effect on SUVR is predicted, but the decrease of protofibrils is still close to 50%.

Conclusions: The QSP model allows for prediction of the dynamics of the different Ab species during pathology progression and treatment. It can serve as a tool for better understanding of the specific immunotherapy mechanism of action, based on in vitro data, and for prediction of clinical trial results.

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IV-75: *Adrien Tessier* Use of mixture models in pharmacometric model-based analysis of confirmatory trials: part I - simulation study evaluating type I error and power of proof-of-concept trials

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Objectives: Proof-of-concept studies (POC) are designed to eliminate inefficient drugs. Statistics underlying such decision are critical. Pharmacometric approaches based on nonlinear mixed effect models achieves higher power to detect a drug effect compare to traditional statistical hypothesis tests [1] but drawbacks come from model building process, where multiple tests or model misspecifications result in an inflated type I error. This error is of major concern as it can result in the pursuit of inefficient drugs development. To use pharmacometric models as primary analysis in confirmatory trials such as POC, it is required to develop approaches that could better control type I error. To compare, using simulations, a standard modelling approach to the use of a mixture model with respect to type I error control and power of detecting a drug effect in a typical POC design. A treatment-response model was used as motivating example.

Methods: One POC design was simulated where patients received a placebo or active treatment (30 patients per arm, 1:1 randomisation). Response was observed as a continuous variable at pre-dose (0) and at times 1, 2 and 3 after administration. Two datasets were simulated: (i) base, using a baseline parameter and a placebo effect model (including an asymptotic progression with an exponential model); (ii) full, adding a treatment effect model to the base model. Random effects were simulated for baseline and treatment effect through exponential models, and for maximal placebo effect through a multiplicative model allowing negative values of the placebo effect. A covariance was simulated between random effects of baseline and maximal placebo effect. The residual error was additive. 500 replicates of each dataset were generated and fitted using the same model as used for simulation (True model) or including different misspecifications (False models): (i) direct placebo effect, (ii) time-proportional placebo effect, (iii) omission of the covariance between random effects of baseline and maximal placebo effect, (iv) time-proportional treatment effect, and (v) an additional covariance between random effects of baseline and treatment effect. Each model were divided in two nested models. The standard modelling approach contrasted models without (base) or with (full) the treatment effect. The other approach utilized a mixture model where each patients' data were described by either the base (placebo) or the full (placebo + treatment) model. The two contrasted models were: (i) a model with equal probability for the two mixtures (as per randomisation), and (ii) a model where the probability for each mixture was an estimated function with allocation arm as a covariate. A likelihood ratio test (LRT) was then performed to compare the nested models, using nominal cut-off from the chi-squared distribution, or after calibration through randomization test [2]. The fraction of the 500 base and full dataset where LRT was significant predicted the type I error and power respectively. NONMEM 7.4.3 and PsN 4.8.8 were used to address simulation, estimation with FOCE method and randomization test.

Results: Overall, type I error for the nominal cut-off was better controlled at the nominal 5% with the mixture model approach. Type I errors for the True and False models 1-5 were 2.03%, 2.35%, 57%, 1.24%, 1.49%, 2.58% (standard) and 4.87%, 5.24%, 4.95%, 7.11%, 5.56%, 7.2% (mixture model). The power of detecting a true drug effect was higher for the mixture model in 5 out of the 6 scenarios when the using the nominal, chi-square, cut-off value and higher for the standard approach in 5 out of 6 scenarios when a randomization calibrated cut-off was used.

Conclusions: The sometimes very low type I errors for the standard approach, are likely linked to the random effect variance does not constitute a full degree of freedom as shown previously [3]. The inflated type 1 error for the standard approach for false model 2 is likely linked to the placebo model not appropriately being able to capture the time-course of change from baseline. The use of mixture models to evaluate the treatment effect in POC achieved a better control of the type I error compared to a standard modelling approach. After calibration it resulted in lower power than the standard approach, likely related to one extra parameter being estimated. The results here are in agreement with similar evaluations on real data [4].

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IV-76: *Hidefumi Kasai* Tumor Response Index (TRI): model-based prediction of tumor response and survival in metastatic colorectal cancer patients treated by mFOLFOX6 with bevacizumab

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Objectives: Tumor growth models have been developed for several chemotherapeutic and molecular targeted drugs and the predicted tumor growth index has been shown to be a promising biomarker for survival. FOLFOX is a combination regimen of oxaliplatin (L-OHP) and 5-fluorouracil (5-FU), and although mFOLFOX with bevacizumab is a standard regimen for colorectal cancer, there have been no reports on modeling and simulation regarding this regimen. Therefore, we aimed to develop a tumor shrinkage model that contains the exposure of chemotherapeutic agents following mFOLFOX regimen and to explore any indices to discriminate the patient response and survival.

Methods: All data used in this analysis were obtained from a post-marketing Phase II multicenter clinical study of first-line mFOLFOX6 with bevacizumab therapy [1]. L-OHP (85 mg/m^2) and 5-FU (400 mg/m^2 intravenous injection followed by 2400 mg/m^2 infusion) were administered with bevacizumab and levofolinate calcium to patients (n=65) of metastatic colorectal cancer. The regimen was repeated every 2 weeks. Tumor growth model was assumed to be composed of two types of tumor cells: sensitive and resistant cells. Both cells were postulated to grow and die with same rate constants Kgrow and Kkill, respectively, but the drugs were assumed to be effective only to the sensitive cells killing. Sensitive cells were converted to resistant cells with a first order rate constant, Kts, which was affected by the drug exposure. Drug concentrations of L-OHP and 5-FU were estimated using the PPK models with their respective covariate effects [2, 3]. The average concentrations over a dosing interval were calculated and then standardized to their standard doses. The sum of the standardized average concentrations of L-OHP and 5-FU was postulated to increase Kkill. Parametric progression-free and overall survival models were constructed using the estimated entire tumor size profiles. All the analyses were performed using the Phoenix NLME software Version 8.1 (Certara, LP, Princeton, NJ).

Results: The sensitive and resistant cells model fitted the tumor size data well. The standardized average concentration of L-OHP and 5-FU had significant effect on increasing Kkill. The fs, ratio of sensitive cells, was estimated to 0.464 at the baseline, and the sensitive cells were decreased through the treatment according to the cumulative AUCs of the drugs. Tumor Response Index (TRI), defined as Kkill/Kgrow, clearly discriminated between the responder (CR and PR, n=34) and non-responder (SD and PD, n=31) ($P<0.001$). Developed survival models using Weibull hazard described well both PFS and OS, with significant covariates of baseline tumor size and the TRI.

Conclusions: We have developed a tumor shrinkage model for colorectal cancer, with identifying a potential predictive index (Tumor Response Index) to discriminate responder or non-responder for tumor shrinkage. PFS and OS were also reasonably described by the constructed model. Although both the constructed models need to be validated in a future trial for their predictability, they will be useful to evaluate clinical efficacy of the other regimens containing L-OHP and/or 5-FU.

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IV-77: *Takayuki Katsube* Evaluation of Variance-based Global Sensitivity Analysis for Covariate Effects

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Objectives: Understanding a contribution of each covariate effect to an interested index (e.g., maximum concentration [C_{max}], area under the concentration-time curve) is important to assess an impact of each covariate effect, e.g., for dose adjustment based on the covariates. A variance of inter-individual variability (IIV) for the index is considered to be variances from individual covariates and from individual random variables which are defined as ETA in NONMEM [1]. Variance ratios using global sensitivity analysis approach [2, 3] can be useful to efficiently assess the contribution of each covariate effect and each random effect on the index. In this study, the contribution of covariate effect and random effect on the index was evaluated based on the variance ratios using global sensitivity analysis approach.

Methods: Monte-Carlo simulations were conducted to simulate covariates and ETAs, calculate outputs for an index based on the simulated covariates and ETAs, and calculate ratios of the variance explained by each covariate or of the variance explained by each random variable of ETAs over the overall variance of the index using soboljansen in R library ”sensitivity” [4]. As a simple example model, an oral 1-compartment pharmacokinetic (PK) model with mono-exponential covariate model on each parameter and no IIV for any PK parameters was used to assess the variance ratios of each covariate or ETA to C_{max} or time above a specified concentration ($T_{>C}$) at steady state. As an assessment based on real data, the variance ratio of each covariate or ETA to peak platelet count was assessed using the pharmacokinetic/pharmacodynamic (PK/PD) covariate model (oral 3-compartment PK and 4-compartment pharmacodynamic [PD] linked model) of lusutrombopag, a thrombopoietin receptor agonist to induce thrombopoiesis [5]. The PK/PD model included the effects of body weight on apparent total clearance (CL/F) and apparent volume of distribution (V/F) with power models. Body weight (covariate) was resampled from the original dataset, and ETAs for PK/PD parameters were simulated according to the parameter estimates.

Results: The variance ratios using the oral 1-compartment model demonstrated the variability for C_{max} was highly dependent on the covariate on V/F, and the variability for $T_{>C}$ was highly dependent on the covariate on CL/F. These results were consistent with visual inspections based on the simulated concentration profiles. The assessments based on the PK/PD model of lusutrombopag suggested that the variability for peak platelet count was mainly dependent on ETA of 50% effective concentration (EC_{50}) and ETA of baseline platelet count, accounting for 35% with ETA of EC_{50} and 55% with ETA of baseline platelet count. Body weight did not affect the variability for peak platelet counts, suggesting no clinically relevant effect of body weight on the platelet counts, although body weight was an influential factor for the exposure of lusutrombopag.

Conclusions: The contribution of covariate effects to the index was quantified based on the variance ratios. The variance-based global sensitivity analysis would be proposed as an efficient approach to assess the impact of covariate effect.

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IV-78: *Aida Kawuma* Dolutegravir pharmacokinetics in co-administration with rifampicin.

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Objectives:

Dolutegravir (DTG) is being introduced as first-line antiretroviral therapy across most of Africa. The antitubercular agent rifampicin (RIF) is the mainstay of tuberculosis treatment. Rifampicin is also a potent inducer of both UGT1A1 and CYP3A4, which are involved in dolutegravir metabolism, and of both P-glycoprotein and Breast Cancer Resistance Protein, which are efflux drug transporters of dolutegravir. The interaction between dolutegravir and rifampicin is of particular interest because tuberculosis is the most common opportunistic infection associated with HIV infection in resource-limited settings, killing over 25% of people with HIV-TB coinfection (Tshikuka Mulumba et al. 2012). It has been shown that rifampicin decreases overall dolutegravir exposure and the dolutegravir label now recommends twice-daily dosing of 50 mg for persons co-infected with tuberculosis and on rifampicin-based regimes. However, twice daily dosing presents a number of challenges especially in resource-limited settings including adherence and availability of the single 50mg dolutegravir pill as opposed to the fixed-dose combination pill of dolutegravir-tenofovir-lamivudine. Therefore, assessing the use of alternative dolutegravir dosing regimens when co-administering with rifampicin is important.

The main objective of the analysis was to develop a population pharmacokinetic model in healthy volunteers to characterize dolutegravir pharmacokinetics and its interaction with rifampicin.

Methods:

Pharmacokinetic data were available from a healthy volunteer study in which 16 participants were sequentially given 50 mg of DTG for 7 days, 100 mg of DTG for 7 days, 600 mg of RIF for 14 days, 50 mg of DTG with RIF for 7 days and 100 mg of DTG with RIF for 7days. Intensive pharmacokinetic samples for dolutegravir were obtained on the 7^{th} day of each of the weeks at pre-dose and 2, 4, 8, 12, and 24 hours' post-dose. Compartmental analysis of the data in NONMEM was employed to develop a pharmacokinetic model to describe dolutegravir drug disposition and to evaluate the extent to which rifampicin co-administration influenced the pharmacokinetics of dolutegravir.

Results:

16 participants were screened and enrolled into the study and 14 (9 males and 5 females) completed all sampling days. The median (range) weight and age was 79.1 (55-105.6) kg and 32 (22-55) years respectively. 11 of the participants were of white ethnicity while one was of Asian ethnicity and two of Afro-Caribbean ethnicity.

The pharmacokinetics of dolutegravir was well described by a linear one-compartment model with first-order absorption. The typical subject was estimated to have a clearance of 1.07 L/h and a volume of distribution of 19.3 L. Rifampicin administration increased dolutegravir clearance significantly by more than 50%, thus lowering overall dolutegravir exposure.

Conclusions:

We propose a pharmacokinetic model of dolutegravir, whose parameter estimates are in keeping with previous reports (Zhang et al. 2015). As previously reported (Dooley et al. 2013), our model captured the induction effect of rifampicin on the efflux drug transporters and enzymes metabolizing dolutegravir, hence significantly increasing its clearance. This model offers a platform to explore different dosing regimens to inform dolutegravir dosing in patients who are co-infected with tuberculosis and on rifampicin-based therapy.

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IV-79: *Ron Keizer* Continuous learning in model-informed precision dosing: a case study

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Background: Model-informed precision dosing (MIPD) has the potential to optimize drug dosing for many narrow-therapeutic window and biomarker-guided drugs.[1-3] However, choosing the optimal model from literature for a new target population is often difficult, especially if no retrospective data is available to evaluate existing models. Naively applying existing models into a new population often introduces significant bias and/or imprecision.[4,5] Developing new models for each new patient population requires the collection of a sufficiently-sized dataset, collected either retrospectively or prospectively, as well as considerable time and effort to develop the model, delaying potential optimal treatment of patients using MIPD by months to years. An alternative approach we have proposed previously is to implement a "continuous learning" (CL) strategy[4,6]. Specifically, this approach entails:

1. Implementing an initial model in the point-of-care (POC) MIPD tool.
2. Using data collected in the tool to update the underlying model parameters, and then implementing the updated model in the POC tool on a (semi-)continuous basis.

The initial model can be taken either from literature or pre-specified and trained on a small initial test dataset representative of the target population.

Objectives: Evaluate the potential improvement in predictive performance of CL applied to MIPD vancomycin dosing

Methods: De-identified patient data (dosing history, time-varying covariate data, TDM sampling for vancomycin in adults) from two large US hospitals (site A and B) collected on the InsightRX platform during routine care were used. Three parametric population PK (popPK) models were selected that previously showed good performance and were built on data from a general adult population[7], a hemato-oncological population[8] and an obese population[9]. Additionally, a new popPK model was defined with a pre-specified model structure based on prior knowledge of vancomycin PK (2 compartment iv linear PK model, eGFR estimated using Cockcroft-Gault affecting clearance using a power function, and allometric scaling of clearance and volume parameters). This pre-specified CL model was then trained on test datasets with varying sizes (n = 50, 100, 250, 500 patients) for each site. The predictive performance of the literature and CL models was evaluated in a holdout dataset of n=346 and n=120 patients for site A and B respectively. Predictive precision was defined as the ability of the tool to predict the next vancomycin trough level for the patient given all data available prior to the collected level. This metric, quantified as the root mean squared error (RMSE), was calculated iteratively over the individual patient data for the second level and onward. Computation was automated using NONMEM FOCEI and the PsN proseval tool.

Results: In site A, CL improved predictive precision by 16–39% compared to the literature models: RMSE for the CL models was 4.4–4.7 mg/L while RMSE for literature models was 5.6–7.2 mg/L. In site B, except for the CL model trained at n=50 patients, CL improved predictive precision by 19–40% (RMSE = 4.2–4.3 mg/L vs 5.4–7.0 mg/L). In site B, the CL model trained on the lowest number of patients (n=50) showed much poorer predictive performance (RMSE 13.0 mg/L) than the literature and other CL models.

Conclusion: Continuous learning can allow for a considerable improvement in the predictive capacity compared to existing models from literature. While application of CL models trained on small datasets may lead to increased error, the sample size necessary to build new models that surpass existing models is attainable in clinical practice. The benefit of training the model on increasingly larger datasets appears limited in this case study, but might be useful to allow further optimization of model structure, identification of additional covariates, or conditioning of the model on smaller, more specific subpopulations. Further studies are ongoing to investigate the feasibility and performance of this approach in other drugs and populations.

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IV-80: *Zackary Kenz* Inflammation and Fibrosis in Nonalcoloholic Steatohepatitis (NASH) Characterized by a Mathematical Model

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Introduction:

Non-alcoholic fatty liver disease (NAFLD) is of growing concern within developed countries, with recent estimates suggesting up to 30% of the US population may be affected [1]. NAFLD represents a spectrum of pathophysiology, ranging from hepatic steatosis, through non-alcoholic steatohepatitis (NASH) and hepatic fibrosis, and may result in cirrhosis and liver failure. Inflammation in NASH can be driven by the release of extracellular vesicles from steatotic hepatocytes, intensifying and modulating disease progression. Hepatic fibrosis in NASH is caused by excessive accumulation of extracellular matrix (ECM) proteins. Fibrosis progresses over time due to an increased number of activated hepatic stellate cells (HSCs) and subsequently increased production of hepatic ECM proteins. The relay race of steatosis, inflammation, and subsequent zonal ECM accumulation has not been captured in mathematical models of NASH fibrosis prior to this work.

Objectives:

Build a mechanistic model for NAFLD/NASH inflammation and fibrosis where patient variability can be overlaid. Utilize the model going forward to guide development of therapeutics aimed at treating NASH.

Methods:

Mathematical models of inflammation and fibrosis were developed as sub-models within the NAFLDsym quantitative systems pharmacology (QSP) model to represent dynamics of disease enhancement, collagen turnover, as well as zonal accumulation of collagen during the development of fibrosis in NASH. The model consists of a system of ordinary differential equations (ODEs) which describe the following processes in three discrete acinar zones of the liver: inflammatory cell responses and regulation due to steatosis; regulation of inflammatory response; activated hepatic stellate cell-driven collagen I and III synthesis; MMP/TIMP modulation of collagen degradation; and collagen crosslinking by lysyl oxidase.

Inflammatory macrophage and neutrophil populations as described in clinical data [2] were represented as a function of cellular activation due to extracellular vesicle release from lipid-laden hepatocytes [3] and cellular recruitment rates. Related changes in pro- and anti-inflammatory mediators as well as pro-fibrotic mediators consistent with disease progression were calibrated using clinical studies, for example [4,5]. Collagen I and III synthesis rates and amounts were estimated across the stages of fibrosis using a combination of clinical studies measuring turnover of $^{2}H_2O$-labeled collagen [6] as well as collagen content from Elastica van Gieson-stained liver biopsy tissues in NASH patients [6,7]. The amount of collagen present across the stages of fibrosis was optimized by balancing the enzymatic activity of MMP/TIMP and lysyl oxidase. The spatio-temporal pattern of zonal collagen accumulation observed in histological scoring of fibrosis patients was captured by varying the K_m of TGF-β driven activation of HSCs, with the K_m increasing from the centrilobular (CL) to periportal (PP) to midlobular (ML) zones of the hepatic acinus.

Variability in the inflammation response, collagen synthesis rates, and hepatic collagen content across stages of fibrosis was accounted for by the creation of a simulated population (SimPops®) which incorporated variability in parameters related to stellate cell activation and collagen synthesis/degradation, as well as other mechanisms related to the pathophysiology of NAFLD/NASH.

Results:

NAFLDsym simulations accurately recapitulate a large range of inflammatory responses to steatotic hepatocytes as well as zonal accumulation of collagen during the progression of fibrosis. These simulation results are consistent with clinical study data [2-7] in key disease-related aspects of steatosis (e.g., liver fat), inflammation (e.g., pro- and anti-inflammatory and fibrotic mediators), and fibrosis (e.g., collagen synthesis and deposition).

Conclusions:

The integration of inflammation and fibrosis sub-models into the NAFLDsym QSP model accurately captures disease progression and zonal patterns of collagen accumulation in NASH-driven hepatic fibrosis and shows simulation results consistent with non-linear increases in hepatic collagen observed across fibrosis stages in NASH patients. This mechanistic mathematical model is serving as a useful tool to guide development of therapeutics aimed at treating NASH.

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IV-81: *Yun Kim* A population pharmacokinetic/pharmacodynamic analysis of rosuvastatin according to OATP1B1 and BCRP polymorphisms in young and elderly subjects

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Introduction: Rosuvastatin is one of the most hydrophilic statins (3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitors) used for the treatment of hyperlipidemia. Rosuvastatin is taken up into the liver predominantly via the organic anion-transporting polypeptide 1B1 (OATP1B1, gene SLCO1B1), and also is a substrate of the breast cancer resistance protein (BCRP, gene ABCG2), which is an efflux transporter expressed in various normal tissues. Genetic polymorphisms of OATP1B1 and BCRP are known to be associated with inter-individual variability in the pharmacokinetics (PKs)/pharmacodynamics (PDs) of rosuvastatin. However, there is currently limited information regarding how genetic polymorphisms of OATP1B1 and BCRP quantitatively affect the PK/PD of rosuvastatin using a population approach in young and especially in elderly subjects.

Objectives: This study was conducted to determine how genetic polymorphisms of OATP1B1 and BCRP quantitatively influence the PK/PD after multiple administrations of rosuvastatin, and to investigate clinical covariates in healthy young and elderly subjects.

Methods: We obtained the PK/PD data from two separate clinical trials, one of which involved 20 elderly subjects (age 65-85 years), and the other of which involved 34 young subjects (age 20-50 years). Both studies were designed as open-label, one-sequence, and multiple oral administration of 20 mg of rosuvastatin for 21 days. A population PK/PD model was developed using 468 rosuvastatin concentrations at steady state, and 220 low-density lipoprotein cholesterol (LDL-c) concentrations in 52 subjects. The First-Order Conditional Estimation with Interaction estimation method was used with NONMEM (version 7.3). A physiological indirect response model was incorporated to explain the change of LDL-c levels. PD modeling was performed after fixing all the PK parameters. The effects of demographics including class (young or elderly), baseline serum creatinine (BScr), and the phenotypes of OATP1B1 and BCRP on the PK/PD of rosuvastatin were evaluated. Transporter phenotypes were converted by genotypes at rs2231142 for ABCG2 [C/C, normal function (NF); C/A, intermediate function (IF); A/A, low function (LF)] and at rs4149056 for SLCO1B1 (T/T, NF; T/C, IF; C/C, LF).

Results: A two-compartment model with a simultaneous zero- and first-order absorption model along with lag times adequately described the time-concentration profiles of rosuvastatin. The typical values of the clearance (CL) and inter-compartmental clearance (Q) were found to 39.7 and 50.9 L/h, respectively. The absorption process of rosuvastatin was explained by first-order absorption rate constant (k_a, 0.264 /h) with lag time (1.48 h), and duration of zero-order absorption (D_2, 0.709 h) with lag time (0.675 h). The PK model showed that 83.7% of the administered dose of rosuvastatin was absorbed by the first-order process and the remaining 16.3% was absorbed by the zero-order process. Reduced function of BCRP, BScr, and effect of elderly were found to be significant covariates for the CL of rosuvastatin. The CL estimates in BCRP IF and LF decreased 24.2% and 50.2% compared to that in NF. We also observed the CL and Q in elderly were approximately 20% and 16% lower than young subjects, respectively. The profile of the LDL-c lowering effect of rosuvastatin was appropriately described by the physiological indirect response model. Multiple

administration of rosuvastatin inhibited the LDL-c synthesis rate constant (Kin, 1.29 mg/dL/hr) along with maximum inhibitory effect (Imax, 0.966) model and concentration resulting in 50% of Imax (IC50) was shown as 0.0672 μg/L. Baseline of LDL-c was identified with significant covariates (BMI, body mass index; BScr) as the following regression equation: Baseline (mg/dL) = 113 x $(BMI/23.8)^{0.803}$ x $(BScr/0.96)^{0.494}$.

Conclusions: The PK/PD parameters of rosuvastatin were quantitatively described by the developed population model. This PK/PD model in the contribution of BCRP, elderly effect, and demographic data to the variability of rosuvastatin can be served as a tool to predict the PK/PD of rosuvastatin, thus providing a rationale for individualized optimal dosing to improve clinical outcome.

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IV-82: *NaYoung Kim* Development of predictive model for acute kidney injury after minimally invasive partial nephrectomy

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Objectives:

The incidence of renal cell carcinoma is increasing in worldwide and surgical excision via partial nephrectomy or radical nephrectomy is considered as the first-line treatment for localized renal cell carcinoma. Minimally invasive laparoscopic or robotic nephrectomy has shown similar oncologic outcomes with lower complication compared to open nephrectomy even for a locally advanced renal cell carcinoma, thus minimally invasive nephrectomy is now considered as a valuable alternative to open nephrectomy. However, postoperative acute kidney injury was reported in 20–24% of patients undergone minimally invasive partial nephrectomy, although the minimally invasive nephrectomy is known to reduce acute kidney injury incidence compared with open nephrectomy. The data for incidence of acute kidney injury after minimally invasive radical nephrectomy is limited, but it may be higher compared to minimally invasive partial nephrectomy. Postoperative acute kidney injury is a major factor for chronic kidney disease and both acute kidney injury and chronic kidney disease are significantly associated with adverse postoperative outcome and death after nephrectomy. Thus, acute kidney injury is still a matter of concern even with the development of the minimally invasive technique, and identification of patients at risk before surgery is important.

Therefore, the objectives of this study were: (1) to develop a predictive model of postoperative acute kidney injury and identify its risk factors; and (2) to develop a scoring system for postoperative acute kidney injury that facilitates the use of the predictive model.

Methods:

A total of 1,025 patients who underwent laparoscopic or robot-assisted laparoscopic partial nephrectomy were identified from the electronic medical records of a single institution. The dataset was randomly split into training and test sets in a ratio of 8:2. A stepwise logistic regression was performed on the training dataset to select the most significant covariates. This process was repeated 100 times with different random seeds, whereupon the frequency of each covariate inclusion was calculated. Using only those covariates that were selected in more than 95% of the resampled datasets, a multivariate logistic regression model predicting the incidence of acute kidney injury within 48 postoperative hours was built. A scoring system was developed based on the final model using RShiny.

Results:

Parenchymal mass removed, warm ischemia time, female gender, history of hypertension, intraoperative bleeding, neutrophil-lymphocyte ratio at postoperative day 1, and platelet count at immediately after operation were identified as significant risk factors. The prediction value in validation was area under the curve (AUC) = 82.26%. A scoring system was developed with a weighted score in each parameter.

Conclusions:

A scoring system would help clinicians to identify the patients at risk before surgery and guide clinicians to reduce modifiable risk factors. Prophylactic management to reduce intraoperative bleeding and inflammation should be considered to reduce acute kidney injury after minimally invasive partial nephrectomy.

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IV-83: *Seoyoung Kim* Population Pharmacokinetic-Pharmacodynamic Modeling of Escitalopram in Patients with Obsessive-Compulsive Disorder Using Yale-Brown Obsessive Compulsive Scale

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Objectives: The aim of this study was to develop pharmacokinetic-pharmacodynamic (PKPD) model of escitalopram concentration and its therapeutic effect on obsessive-compulsive symptom.

Methods: The steady-state plasma escitalopram concentrations and Yale-Brown Obsessive Compulsive Scale (YBOCS) scores from 91 patients who were enrolled in the prior escitalopram clinical trial were used in this analysis. Subjects were randomly assigned to two groups with different maintenance dose of escitalopram, 20 or 40mg. The serial plasma escitalopram concentrations from 12 healthy volunteers were used for the development of escitalopram PK model [1]. The changes in YBOCS score per escitalopram treatment were described sequentially by a PD model using the patient PK model predicted concentration. All the PKPD models were developed using NONMEM®.

Results: The escitalopram PK data from the patients and healthy volunteers were modeled using two-compartment model with a sequential zero-order drug input (D1) and first-order absorption (Ka). The clearance of escitalopram for patients was estimated to be 43% lower than healthy subjects. When developing patient PK model, a few parameters including absorption parameters were fixed at estimated values from healthy volunteer data because of very sparse PK sampling for patients, mostly only 2 samples from up to 136 days of treatment. The relationship between exposure from escitalopram maintenance dose and YBOCS score was described by an inhibitory model employing sigmoid Emax function of effect compartment concentration. The baseline YBOCS score (E0) was estimated to be 26.9, maximum decrease (Imax) and sigmoidicity, 52.8% and 1.53, respectively.

Conclusions: The developed PKPD model adequately describes the exposure response relationship of escitalopram and the improvement in YBOCS score.

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IV-84: *Dohyun Kim* Optimization of dosing strategy for Colistin using population pharmacokinetic model based on the Bayesian inference

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Objectives : With increasing incidence of infections caused by multi drug resistance (MDR) Gram negative pathogen and paucity of new agents to confront to these infection, the old drug colistin is reemerged as a last line treatment. It is administrated intravenously in the form of prodrug, colistin methanesulfonate (CMS), which is less toxic and hydrolyzed to colistin within the body. However accurate pharmacokinetic (PK) and pharmacodynamics (PD) properties of colistin are still poorly understood. The aim of this study is to develop a Population PK (PopPK) model and improve the optimal dosing strategy based on model derived simulated concentration data.

Methods : Previous 3 literatures(1, 2, 3) were considered to obtain PopPK models and parameters. Based on these models, we generated virtual concentration data. The structural model consists of 2-compartment model for CMS and 1-compartment model for colistin. Model parameters were estimated using Bayesian inference. Stan version 2.18 (Stan Development Team) with the R package Rstan (Stan Development Team) was used. To estimate parameters of two-compartment PK models of CMS and 1-compartment PK model of colistin, we utilized popular priors. we used Gaussian priors for creatinine clearance, (CL) and central compartment volume (Vc) of CMS of individual, set inverse gamma priors for random effects and error. And choose uniform priors for first-order transfer rate constants k_{12}, k_{21} of CMS. We obtain 5,000 posterior samples from the Markov chain Monte Carlo (MCMC) posterior simulation after a burn-in period of 5,000 samples. The MCMC algorithm was simulated with the RStan. And the predictability of developed model was tested with real concentration data of colistin.

Result : In the current study, the PK parameters for the population model were estimated and then individual drug concentrations were predicted by the developed PopPK model of colistin. The model provided reasonable estimates for population PK parameters and its individual drug concentration prediction performance was also comparable with the other alternative colistin PopPK models.

Conclusion : This study developed PopPK model of colistin based on RStan, which can be comparable predictability to the previous PopPK models and this model is the first model that considers characteristics of Korean population demographic characters. We expect that this result will contribute to elucidate pharmacokinetic properties of colistin and to build therapeutic drug monitoring support tool for the colistin in Korean population.

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IV-85: *Lena Klopp-Schulze* Exposure-response analyses of the bifunctional fusion protein bintrafusp alfa (M7824) in early drug development

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Objectives: Bintrafusp alfa* (M7824) is an innovative first-in-class bifunctional fusion protein composed of the two extracellular domains of transforming growth factor-beta (TGF-β) receptor II to function as a TGF-β "trap" fused to a human IgG1 monoclonal antibody against programmed death-ligand 1 (PD-L1). Currently in phase 1, two trials (NCT02517398 and NCT02699515) are ongoing in cancer patients with advanced solid tumors to investigate the clinical potential of bintrafusp alfa as a new immuno-oncology therapeutic agent. The objective of the presented study is to assess benefit-risks of bintrafusp alfa and to support an adequate dose selection for phase II performing exposure-response (E-R) analyses for efficacy and safety.

Methods: For both E-R analyses, individual clearance (CL) parameter estimates and exposure metrices (area under the curve after a single dose [$AUC_{0\text{-}336h}$] and steady-state [AUC_{ss}]) were obtained from the population PK model of bintrafusp alfa with time-invariant CL [2]. CL, $AUC_{0\text{-}336h}$ and AUC_{ss} were investigated separately as predictors of response. For the exposure-safety analyses, derived exposure metrics and adverse event (AE) data from 673 patients with 17 different tumor types treated with 0.3-30 mg/kg, 500 or 1200 mg every two weeks (Q2W) from two phase 1 trials were assessed by applying logistic regression modeling to various AEs: Immune-related AEs (irAE), infusion-related reactions (IRR), treatment-emergent AEs (TEAE), skin AEs related to PD-L1 (sPDAE) and related to TGF-β (sTGAE). For the exposure-efficacy analyses, derived exposure metrics and efficacy data from 80 second-line non-small cell lung cancer patients treated with either 500 mg Q2W or 1200 mg Q2W were evaluated using logistic regression models for best overall response (BOR) and Kaplan-Meier and Cox regression analyses for progression-free survival (PFS). To explore influential or confounding covariates, multivariate logistic and Cox regression analyses were performed using the full-model approach [1] separately for each exposure metric. Reduced logistic models were derived by removing the least informative covariates in a stepwise manner until no further reduction in the Akaike information criterion could be achieved. There was no adjustment for multiplicity for the reported CI corresponding to the different efficacy endpoints, exposure metrics or covariates. The E-R analyses were performed using R (v. 3.2.2).

Results: Both exposure-response analyses for BOR and PFS showed a shallow trend towards a relationship between exposure and efficacy variables. Univariate and multivariate Cox regression analyses detected an association between exposure and PFS ($AUC_{0\text{-}336h}$-PFS multivariate model: HR 0.820 [95%CI 0.692-0.972] per $AUC_{0\text{-}336h}$ increase of 10,000 mg·h/L). In multivariate Cox models, metastasis at baseline was identified as influential covariate on PFS (HR 3.307 [95%CI 1.360-8.039]). A definitive relationship between exposure-BOR could not be confirmed, although a weak trend was apparent ($AUC_{0\text{-}336h}$-BOR: OR 1.301 [95% CI: 0.899-1.970] per $AUC_{0\text{-}336h}$ increase of 10,000 mg·h/L). Metastasis, smoking status and maximal change of neutrophil/lymphocyte ratio from baseline (not a baseline variable) were detected as potentially influential covariates besides exposure on BOR (these remained in the reduced models). The multivariate exposure-safety analyses found irAE, sPDAE and sTGAE incidences to be positively correlated with exposure (OR of ≤1.354 per AUC increase of 10,000 mg·h/L). Additionally, the number of cycles and concomitant corticosteroids and biologics were positively correlated with AE incidences.

Conclusions: A weak association between exposure and efficacy was indicated by both exposure-efficacy analyses of BOR and PFS. Interestingly, a strong association was observed between time-invariant CL and efficacy (univariate model: OR 0.341 [95% CI: 0.133-0.750] per CL increase of 0.005 L/h), which is likely a manifestation of the disease state on PK [2] and therefore confounding the true relationship between exposure-efficacy. The power to detect influential covariates was limited with most effects being highly uncertain. AE incidences were generally weakly or not correlated with exposure of bintrafusp alfa. Overall, the emerging PK, efficacy and safety data of bintrafusp alfa from preclinical and phase 1 clinical studies [4-5] jointly support the recommended dose selection of 1200 Q2W for future clinical trials.

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IV-86: *Franziska Isabelle Kluwe* Model-based characterisation of nonlinear voriconazole pharmacokinetics following two different routes of administration

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Objectives: Voriconazole (VRC) is an antifungal drug used for prophylaxis and therapy of various fungal infections. The main route of elimination from the systemic circulation is CYP-mediated hepatic metabolism to various (inactive) metabolites [1]. High variability and nonlinearity in VRC pharmacokinetics were described previously [2]. Nonlinearity in the elimination of VRC is mainly attributed to suspected saturation and autoinhibition of metabolising CYP enzymes. Understanding the pharmacokinetics of VRC and identify factors contributing to the high variability is crucial for ensuring safe and effective concentrations. Therefore, the current work aimed at investigating the pharmacokinetics of VRC in healthy volunteers after approved sequence dosing with a special focus on a (semi-)mechanistic implementation of nonlinear elimination. A covariate analysis was performed to identify factors (e.g. *CYP2C19* genotype) or other aspects (time- and/or concentration- and/or formulation-dependency) explaining the high pharmacokinetic variability.

Methods: An exhaustive literature research using PubMed [3] was performed to identify structural models used to describe the pharmacokinetics of VRC and covariates potentially explaining the pharmacokinetic variability. The clinical data used for model development arose from a prospective, open-labelled, uncontrolled study conducted in collaboration with the Medical University of Vienna (Eudra-CT: 2008-008524-32) [2]. Ten healthy male individuals (age: 21–46 years, weight: 65–83 kg) received the approved sequence dosing regimen for VRC of initially short-term i.v. infusions and subsequently p.o. administrations every 12 hours (2x6 mg/kg i.v., 2x4 mg/kg i.v., 3x200 mg p.o.). Intensive plasma sampling was carried out over 4 days and VRC plasma concentrations were determined after ultrafiltration by high-performance liquid chromatography [4]. Among several other continuous and categorical other covariates, *CYP2C9* and *CYP2C19* genotyping data was available for the study participants. All data was analysed using R, RStudio and NONMEM together with PsN, Pirana and Xpose4 [5-8]. To assess the model performance, precision of parameter estimates and graphical model evaluation techniques, such as goodness-of-fit plots and visual-predictive checks, were utilised.

Results: Different structural models describing the pharmacokinetics of VRC and factors (covariates) potentially explaining the pharmacokinetic variability were identified. Among the published models for VRC, clearance was implemented aslinear clearance, (time-dependent) nonlinear (Michaelis-Menten) clearance or parallel linear and (time-dependent) nonlinear (Michaelis-Menten) clearance [9]. In addition, in this work, to more mechanistically describe the pharmacokinetics and study the time course of VRC autoinhibition, usage of an additional inhibition compartment [10] and an enzyme turn-over model was investigated [11]. VRC plasma concentrations were best described by a two-compartment distribution model (191 and 469 L) with an absorption rate constant of 0.91 h^{-1}, bioavailability of 85% and intercompartmental clearance of 79.6 L/h. In the final model, clearance (10.7 L/h) was inhibited over time to approximately a third of its original value, dependent on the concentrations in an additional inhibition

compartment. Interindividual variability for clearance, volumes of distribution, absorption rate constant and bioavailability using an exponential model was highest for clearance (65.4 CV%). Implementation of *CYP2C19* genotyping information (presence or absence of *CYP2C19*2*), explained around half of the interindividual variability in clearance.

Conclusions: The developed model adequately characterised the pharmacokinetics of VRC in plasma using a semi-mechanistic approach integrating knowledge about the metabolism of VRC. Substantial interindividual variabilitywas identified especially in clearance of healthy volunteers despite standard dosing, mainly due to differences in *CYP2C19* genotype. As a next step, using prior information from *in vitro* or bottom-up (PBPK) models and metabolite data (plasma/urine) to inform the model and different pathways, can further contribute to elucidate and understand VRC pharmacokinetics, to explain the high variability by covariates and to draw consequences for optimal dosing.

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IV-87: *Lisa Alina Kneller* Impact of Cytochrome P450 2D6, -3A4 and P-glycoprotein on Risperidone's and 9-Hydroxyrisperidone's plasma concentrations using a whole-body PBPK approach

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Objectives: The genetic polymorphism of Cytochrome P450 (CYP) 2D6 plays an influential role on the appearance of positive and adverse drug reactions to antipsychotics, such as risperidone (RIS) [1]. Consequently, pharmacokinetics of RIS and its active metabolite 9-Hydroxyrisperidone (9-OH-RIS) can be substantially altered showing large inter-individual variability in its plasma concentrations between the different phenotypes [2,3].
The objective of the study is to develop a physiologically-based pharmacokinetic (PBPK) model considering the CYP2D6 genetic polymorphism for RIS and 9-OH-RIS taking CYP3A4 and P-glycoprotein transporter into account [4].

Methods: Based on available literature knowledge about RIS, 9-OH-RIS, and relevant physiological changes according to different CYP2D6 phenotypes, several PBPK models were developed using the software PK-Sim® as part of the Open Systems Pharmacology Suite [5,6].
The initial model was further evaluated based on RIS's and 9-OH-RIS's measured plasma concentrations from a single dose study including 71 genotyped healthy volunteers treated with 1 mg oral RIS. According to CYP2D6 genotype, all subjects were classified as [7]: extensive metabolizer (EM, n=33), intermediate metabolizer (IM, n=26), poor metabolizer (PM, n=6) and ultra-rapid metabolizer (UM, n=6).
In addition, all single dose simulations were transmitted to steady-state condition (3 mg RIS twice a day) due to linear pharmacokinetics of the active moiety (RIS plus 9-OH-RIS).

Results: PBPK models were able to accurately describe RIS exposure after 1 mg single dose administration especially in the concentration range ≥ 1 µg/L, illustrated by a minimal bias and a good precision. About 90.3% of all weighted residuals vs. observed plasma concentrations ≥ 1 µg/L were in the ± 30% range. Regarding whole PBPK simulation over 96 h, mean prediction error (MPE) and mean absolute prediction error (MAPE) of RIS were 52.2 % and 54.2 % for EM's, 37.4 % and 43.6 % for IM's, 28.0 % and 49.4 % for PM's and 45.4 % and 62.6 % for UM's. MPE and MAPE of 9-OH-RIS amount -22.2 % and 22.7 % for EM's, -10.6 % and 18.7 % for IM's, -7.80 % and 15.4 % for PM's and -28.3 % and 28.3 % for UM's. In this connection a clear association between the number of active CYP2D6 alleles and the pharmacokinetic parameters for RIS and 9-OH-RIS was observed.
During steady-state, RIS/9-OH-RIS ratio increased progressively according to reduced CYP2D6 activity, resulting in a mean ratio of 4.96 for PM whereas EM show a mean ratio of 0.27.

Conclusions: PBPK modelling can provide a valuable tool to predict RIS's and 9-OH-RIS's pharmacokinetics in healthy volunteers, according to the different CYP2D6 phenotypes taking CYP3A4 and P-glycoprotein transporter into account. All newly developed single dose PBPK models accurately describe RIS's and 9-OH-RIS's plasma concentrations of healthy volunteers.
Our simulation show that the calculation of RIS/9-OH-RIS ratio can be used to phenotype patients using

clinical data from therapeutic drug monitoring. To ensure the best therapy for each subject, dose optimization according to different CYP2D6 phenotypes can be subsequently applied.

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IV-88: *Stephan Koehne-Voss* A comparison of relative exposure estimates from single trough, multiple trough, and full population PK sampling designs

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Objectives: In clinical studies it is often of interest to estimate how drug exposure changes with patient characteristics. Pharmacokinetic (PK) exposure information can be obtained using single trough, multiple trough, or full population PK sampling designs [1]. The last design is considered the most informative one but requires patients to stay at the site for the duration of the sampling. Collecting trough samples only is often preferred in practice. It is therefore of interest to study if estimates of relative exposure derived from single trough, multiple trough, and full population PK sampling designs are comparable.

Methods: The three different sampling designs require different exposure metrics and data analysis models. In trough sampling designs the ratio of steady state trough samples (C_{min}) is used to describe the exposure of a patient with certain covariate characteristics relative to a reference patient. For full population PK sampling designs the most commonly used exposure metric is the ratio of the Areas Under the Curve (AUCs). Data from single trough designs are typically analysed with a linear model while linear and nonlinear mixed effect models are employed for the repeated trough and full population PK design, respectively.

We performed a simulation study to compare estimates of relative exposure from the different sampling designs. The PK model was assumed to be a one compartment model with CL=0.58 L/h, V=10 L, ka=0.2 1/h, Dose=100, tau=12 h. Note that the half-life of the drug ($t_{1/2}$=12 h) matches the dosing interval (tau). We used exponential between subject and residual error models with standard deviations of $w_{CL} = w_V = 0.3$, $std_{Res} = 0.2$.

We looked at two different covariate models. Covariate Model 1 was an allometric scaling model in which weight affects apparent clearance and volume of distribution according to $CL_i = CL \cdot (WGT_i/70)^{0.75}$ and $Vi = V \cdot (WGT_i/70)^1$. Weight was normally distributed WGT~N(70,15^2). We want to estimate the exposure of a 120 kg subject relative to 70 kg. Covariate Model 2 described an effect of Globular Filtration Rate (GFR) on apparent clearance, $CL_i = CL \cdot (GFR_i/90)^{0.5}$, where GFR was uniformly distributed U(30, 120). We want to estimate the exposure of a subject with GFR=45 mL/min/SA (moderate renal impairment) relative to a subject with GFR=90 mL/min/SA (normal renal function).

We simulated 500 studies with 100 subjects each. For the single and multiple trough designs we generated 1 and 3 steady state samples. For the full population PK design we simulated 3 samples at steady state pre-dose, 2.5 h, and 6.5 h. This sampling scheme was defined by fixing one sample at pre-dose and optimizing the times for the other two samples with PopED 0.3.2 [2], not taking into account covariates. For each simulated study we estimated the relative exposure using a linear model for the single trough design ($logC_{min,i} = a+b \cdot logWGT_i+e_i$), a linear mixed model with a random effect u_i at subject level for the multiple trough design ($logC_{min,ij} = a+b \cdot logWGT_i+u_i+e_{ij}$), and a nonlinear mixed effect model implemented in Monolix 2018R1 [3].

Results: In Covariate Model 1, the relative exposure of a subject with 120 kg relative to a 70 kg subject was estimated. The mean estimates over the n=500 simulated studies were 0.68, 0.68, and 0.67 for the single

trough, multiple trough, and full population PK sampling design. Relative standard errors were 7.5%, 6.8%, and 6.4%.

In Covariate Model 2, the exposure of a subject with GFR=45 mL/min/SA (moderate renal impairment) relative to a subject with GFR=90 mL/min/SA (normal renal function) was estimated. The mean estimates over the n=500 simulated studies were 1.44, 1.45, and 1.45 for the single trough, multiple trough, and full population PK sampling design. Relative standard errors were 5.9%, 5.7%, and 7.0%.

Conclusions: : In the scenarios studied in our simulations the estimates of relative exposure generated from the different sampling designs were comparable. Single trough designs are not encouraged by FDA [1]. If the objective of a PK study is to estimate relative exposure then our results indicate that multiple trough designs can be a valid alternative to full population PK designs. However, our findings may not generalize to situations where the dosing interval of a drug is substantially longer than its half-life or more complex (e.g. nonlinear) models are required to describe the kinetics of the drug.

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IV-89: *Galina Kolesova* Application of different approaches to generate virtual patient populations for QSP model of Physiologically based pharmacokinetic model of anti-PD-1 therapeutic antibodies

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Introduction: Conventional approach of QSP modelling includes the procedure of fitting of a model output to series of mean data values. As a result parameters of the model represent fixed numbers enabling to describe mean data. However, the results of clinical trials include description of variability in patient response to a drug which is typically expressed in terms of conventional statistics such as standard deviations from mean values. To allow a QSP model to reproduce the variability in response to a drug technique of generation of virtual patient population is usually applied. In framework of the technique some selected parameters of the QSP model are represented as random variable with some distribution. The empiric distribution is determined on the basis of mean data and statistics measured clinically via generation and selection of virtual patient populations described by a series of parameters randomly chosen from distribution of the selected parameters. Several techniques can be applied to generate virtual patient populations.

Objectives: In the study we propose and compare two different techniques to generate virtual patient populations basing on experimentally measured mean data and statistics. We apply these techniques to determine distribution of selected parameters of two different models: the one of Physiologically based pharmacokinetic model of anti-PD-1 therapeutic antibodies [1] and the model imitating skin inflammation. We use the distributions to reproduce variability of initial experimental data, i.e. to compare predictive power of these techniques.

Methods: We used following models:

- a minimal physiologically based pharmacokinetic (PBPK) model of drug disposition focusing on a group of immune checkpoint inhibitors blocking the PD-1 receptor;
- the model describing interaction between keratinocytes and T-cells.

Experimental data are given in the form of mean (*m*) and standard deviation (*sd*). The source of variability in QSP model is selected variabe parameters. Distributions of the selected variable parameters are chosen in such a way to provide coincidence between experimentally observed and simulated statistics (*m* and *sd*). The following techniques were applied to generate virtual patient populations:

Approach 1 (based on Bayesian approach [2])

- Assume that prior distributions of the parameters , to which the model is most sensitive, are described by particular distribution (e.g. truncated normal) with some parameters
- Means of parameters' values are fixed (results of the fitting of the model)
- To obtain the desired distribution of the control function we use Monte-Carlo Markov Chain (MCMC)

Approach 2 (Monte-Carlo based approach)

- Generate a series of control function values from appropriate distribution characterized by m and sd.
- Fit the model parameters to every control function value.
- As a result of fitting one obtains a series of vectors of parameters' values. This series represents sample from required parameters' distribution.

To accelerate both procedures one can use some approximation of the model results with respect to chosen variable parameters. This approximation may be used instead of exact model output during MCMC algorithm or for parameters fitting.

Results: We provide the proof of concepts by the example of the model of skin inflammation. To test the approaches instead of real control function we used a function constructed as linear combination of the model variables. Both approaches were used to generate virtual patients populations. The approaches were compared in terms of distribution characteristics approximation quality and operation time needed.

- Approach 1

	Data	Results with model approximation	Results with exact model
m	$3.5 \cdot 10^6$	$3.5 \cdot 10^6$	$3.5 \cdot 10^6$
sd	$2.8 \cdot 10^5$	$2.9 \cdot 10^5$	$2.9 \cdot 10^5$

- Approach 2

Control function means:

Time, hour	168	336	672	1008	1344
Data	-12.01	-24.57	-37.95	-41.77	-42.87
Results with model approximation	-13.11	-27.27	-36.90	-37.22	-37.06
Results with exact model	-22.30	-33.49	-42.05	-43.45	-44.37

Control function standard deviations:

Time, hour	168	336	672	1008	1344
Data	24.49	32.66	38.78	40.82	40.82
Results with model approximation	29.16	29.82	31.95	33.55	34.84
Results with exact model	36.17	33.04	32.57	33.79	34.59

Conclusion: Both approaches proposed are capable for reproducing the control function distribution characteristics. The choice of a specific technique is determined by characteristics of the particular problem. Namely, in case of distribution with relatively small sd both methods work similarly. However, to reproduce distributions with relatively large sd second methodology is preferable.

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S-01: *Niklas Hartung* A flexible and transparent MATLAB framework for empirical and mechanistic pharmacometric modelling

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Objectives: There exist a number of established software tools for well-defined modelling purposes, like NONMEM or Monolix [1-2] for the population analysis of clinical data based on classical compartment models; or GastroPlus, PK-Sim and SimCYP [3-5] to study absorption, special subpopulations or drug-drug interactions. Many questions, however, require the development of new models that go beyond a given, hard-coded model, often starting with a simple model that is subsequently refined to account for the most relevant processes of the question at hand. None of the established software tools fully supports this modelling process in terms of the desirable transparency, flexibility and support for handling large data bases of drug and species-specific data. The objective was to develop a MATLAB-based modelling toolbox to fill this gap.

Methods: Building on a MATLAB toolbox that has been used over the years in teaching physiologically-based pharmacokinetic modelling during the A2-module of the PharMetrX PhD program [6] and on previous work on lumping [7] and pharmacokinetics of monoclonal antibodies [8-10], we developed a novel modelling environment written in the MATLAB language. Core values guiding the toolbox development were flexibility and transparency. The central infrastructure was implemented using an object-oriented approach. The toolbox offers support to handle physiological and drug databases, checks unit compatibility during any computation, and allows to document and track assumptions underlying experimental data, thereon based derived parameter values or modelling assumptions. All databases are customizable and there are no restrictions on the models that can be implemented.

Results: The modelling framework was developed with MATLAB (R2018b). To support computation with units during a complete modelling workflow, we extended the contributed MATLAB Physical Units toolbox (version 4.1.0.0) [11]. Any quantity computed during modelling exercise comes with an associated unit, and unit consistency of operations is enforced. A physiological database and a compound database are provided, as well as several scaling methods for the creation of virtual populations and prediction of mixed drug-species parameters like tissue partition coefficients. All databases, scaling and prediction methods are annotated with metadata (e.g., species origin or scalability of a parameter) that are propagated through model development, making the implications of these assumptions during modelling transparent. A variety of models, ranging from empirical and lumped mechanistic to mechanistic PBPK models for small molecules and monoclonal antibodies, are implemented. A modular specification of model components allows high-level modelling at the scripting level, as illustrated by prepared demo projects. To allow most wide-spread use, the developed MATLAB modelling toolbox is contributed as open-source to the community.

Conclusions: The developed MATLAB toolbox provides a flexible and transparent pharmacometric modelling environment with unit and assumption tracking capacities. It can be used for projects requiring capabilities to develop new models or customize physiological and drug-related parameters and prediction/extrapolation methods.

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[4] https://www.open-systems-pharmacology.org/
[5] https://www.certara.com/software/pbpk-modeling-and-simulation/
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S-02: *Rikard Nordgren* Perl speaks NONMEM (PsN)

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PsN [1][2][3] is an open source toolbox for population PK/PD model building using NONMEM. It has broad functionality ranging from results extraction to advanced computer-intensive statistical methods. PsN simplifies the organization of NONMEM output files, helps with starting jobs on different types of clusters (i.e. slurm, torque, sge and lsf) and can perform a cornucopia of different statistical, computational and other methods, including: **benchmark** – combinatoric benchmarking of different NONMEM control stream settings, **bootstrap** – assessing uncertainty of parameter estimates, **cdd** – case deletion diagnostic to look for influential individuals, **crossval** – model cross validation, **frem** – full random effects modelling, **llp** – log likelihood profiling, **nmoutput2so** – converting NONMEM results into the standard output file format, **parallel_retries** – estimate the same model multiple times with different initial parameter estimates, **qa** – fast and automatic assumption assessment and quality assurance of models, **resmod** – residual modelling for quickly assessing appropriateness of structural and residual error models, **scm** – stepwise covariate model, **simeval** – simulation evaluation diagnostics of outliers, **sir** – sampling importance resampling for parameter uncertainty assessment, **sse** – stochastic simulation and estimation, **transform** – do changes to a model programmatically and **vpc** – visual predictive check.

Updates to PsN since PAGE 2018 include improvement of the **qa** tool. Extensive testing of many different input models has been performed and improvements to tools used by qa has been made to support a wider range of ways of coding models. Efforts has also been put in to make the output of qa easier to understand and interpret. The R code included in PsN for the automatic plotting via the -rplots functionality has been moved in parts to a new R package called “PsNR”. This makes it easier to install other R package dependencies. The installation of PsNR can be done at PsN install time or at any time before or later using the R devtools package. Minor uppdates include the addition of the new clean-level 5, the common option debug_rmd to retain the tex file adter rendering rmarkdown with -rplots and a stratification option for cross validation.

PsN can automatically generate plots for most of the different tools by adding the -rplots option. This automatically generates documents with, for example, visual predictive checks as part of the PsN output, without the need to manually run any R script. Many of these plots use functionality in the Xpose4 R package [4]. It is possible to customize the plots or replace them entirely by using custom R templates. These templates can either be plain R or R Markdown.

PsN is freely available at https://uupharmacometrics.github.io/PsN, the userguides for the different tools can be found at https://uupharmacometrics.github.io/PsN/docs.html and the new R package needed for R plots can be found at https://github.com/UUPharmacometrics/PsNR.

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