PAGE2012 Poster Abstracts

I-01 *Robert Leary* QRPEM, A Quasi-Random Parametric EM Method

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Context: Monte Carlo (MC) parametric EM algorithms such as MCPEM and SAEM are attractive alternatives to traditional FO, FOCE and LAPLACE parametric algorithms. Recently QRPEM (Quasi-Random Parametric EM), a new implementation of an importance sampling based parametric EM algorithm, has been added to the Pharsight Phoenix NLME software. QRPEM differs fundamentally from MCPEM algorithms in that sampling of the posterior distributions is based on "quasi-random" sequences rather than the more usual pseudo-random sequences. Additionally, QRPEM implements the SIR (Sampling-Importance-Resampling) algorithm (Ref. [1, 2]) as an accelerant for cases where mu-modeling is not or cannot be used.

Objectives: Implement the QRPEM algorithm, including the SIR acceleration technique for non-mu-modeled cases, and verify

- a) QRPEM parameter estimates usually closely approximate true maximum likelihood estimates
- b) The theoretical advantages of QR relative to MC sampling are usually achieved in practice
- c) The SIR algorithm is an effective accelerant for the non-mu-modeled case.

Methods: The QRPEM algorithm was implemented with Sobol low discrepancy sequences and a SIR algorithm for accelerating non-mu-modeled cases. Test cases were selected from the literature, including the Monolix test cases from Ref. [3], the PK-PD models from Ref. [4], as well as locally generated. Comparative evaluations were performed among QRPEM with and without SIR acceleration, Adaptive Gaussian Quadrature (AGQ), MCPEM (QRPEM with QR sampling replaced by MC sampling), and ELS FOCE (with interaction). Additionally, individual posterior integrals were extracted from several test cases and evaluated using QR and MC sampling to compare the error decay rates with increasing sample size.

Results:

- a) Evaluation of individual integrals consistently confirmed the theoretically superior $O(N^{-1})$ vs. $O(N^{-1/2})$ asymptotic error decay behaviour of QR sampling.
- b) QRPEM and AGQ typically converged to nearly the same parameter and likelihood values, which were usually closer (and in some cases much closer) to the true ML estimates than MCPEM at the same sample size. .
- c) RMSE of parameter estimates for replicates of simulated data sets typically are smaller with QRPEM than ELS FOCE.

- d) The SIR technique is remarkably effective, generally providing speed-ups of at least 2X and in some cases up to 10X without significant degradation of parameter estimates.

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I-02 *Donghwan Lee* Quantitative Analysis of Reflux Episodes in Gastroesophageal Reflux Disease (GERD)

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Background: The prevalence of gastroesophageal reflux disease (GERD) is about 30% in Western populations and 10% in Asian populations and the number of patients annually increases [1, 2]. Various diagnosis methods was introduced and applied in the past, among which esophageal pH monitoring was the choice of diagnosis. However, it was not useful to diagnose drug (i.e., proton pump inhibitor, PPI) resistant patients with non-acidic refluxes or GERD-like symptoms such as functional heartburn or psychotic reflux. As an alternative approach, combined pH-multichannel intraluminal impedance (pH/MII) monitoring has been introduced not only to quantify the degree of the acidity of refluxes and detect weakly or non-acidic refluxes but also to record bolus passes, which is important to diagnose patients with persistent symptoms despite various medical treatments [3, 4]. Nevertheless, currently there is no gold-standard tool to diagnose PPI non-responders from PPI responders among GERD patients.

Objectives: The purposes of this study was (i) to develop a time-to-event model to characterize the reflux patterns in PPI-resistant and PPI-reactive groups among GERD patients and examine the associated influencing factors, (ii) to assess the feasibility of applying the model-based drug treatment approach in the area of GERD, and (iii) to find diagnosis criteria for PPI-resistant versus PPI-reactive GERD patients.

Methods: A repeated time to events (RTTE) model was developed within the mixed effect model framework using a dataset composed of a series of reflux event times collected through a 24hr combined pH/MII monitoring device from 34 patients who were diagnosed with GERD at Severance hospital, Seoul, Korea and took a PPI once daily in the morning from 2008 to 2010. The PPI was administered with one of the following agents: esomeprazole, rabeprazole, pantoprazole, lansoprazole, esomeprazole, omeprazole, rameprazole.
Exact times of events were assumed and the likelihood at each event time L(t) was formulated as $L(t) = S(s,t)\cdot h(t)$ where S(s,t) and h(t) denote the survival function and the hazard function, respectively, s denotes the previous event time (or start of observation), and t denotes the current event time. Three hazard functions tested were as follows: Constant, $h(t) = \lambda$; Gompertz, $h(t) = \exp(\lambda + \gamma\cdot t)$; Weibull hazard, $h(t) = \lambda + \gamma(\lambda\cdot t)^{\gamma-1}$ [5, 6]. Inter-individual random effect was allowed for each hazard parameter. The drug effects among different PPIs were assumed similar.

The covariate effects were tested with stepwise covariate modeling (SCM) using NM-NM method [7] and the significance levels for selecting or deleting the covariate were $p < 0.05$ for forward selection and $p < 0.001$ for backward elimination, respectively. The following covariates were tested: age, sex, disease duration and characteristics of symptom (typical versus atypical) where typical symptom was defined as the one among regurgitation, heartburn, and chest pain. The baseline (no-covariate) hazard was also allowed to vary between acidic and non-acidic refluxes. This covariate analysis was performed separately for responder and non-responder groups to

formally assess the differences in patient characteristics between the two groups. In addition, in an effort to find a potential marker that could distinguish non-responders from responders, differences between the two groups in the number of acidic refluxes and the ratio of non-acidic to acidic refluxes were further examined.

The goodness of fit of the finally developed model was visually examined by comparing the predictions and the observations for both the population and the individual levels on the basis of the number refluxes per hour over the entire 24-hr period, for acidic and non-acidic refluxes for each of non-responder and responder groups. Finally, visual predictive check (VPC) was performed on the basis of 100 simulations. The plots were delineated using R (http://www.r-project.org).

Results: The median age (range) of the patients (male 12, female 22) was 53 (19-75) years. The median disease duration (range) was 56 (28-400) months. 16 patients had typical symptoms, while 18 had not. The numbers of the PPI responders and Non-responders were 13 and 21, respectively.

The acidic and non-acidic refluxes were best explained by the constant hazard model in both the PPI responder and the non-responder groups. The baseline values of the log hazard in responders were 1.36 and 0.53 for acidic and non-acidic refluxes, respectively, and those in non-responders were 1.03 and 0.65 for acidic and non-acidic refluxes, respectively, indicating the hazard of non-acid refluxes lower than that of acid refluxes in both groups.

The disease duration was found to have a significant effect for the non-responder group, resulting in a decrease in the log hazard by 0.2 per 50 months of disease duration. No other covariate was found significant.
The data showed that in the responder group the number of acidic refluxes and the ratio of acidic to non-acidic refluxes were significantly suppressed compared to the non-responder group as a result of the treatment effect ($p = 0.045$ and 0.027, respectively).

Evaluated by the goodness of fit plot and VPC, in general, the observed trends of the refluxes were well explained by the final model for acidic and non-acidic refluxes for both non-responder and responder groups although over-predictions were found for some data points.

Conclusions: This work represented the feasibility of applying a model-based approach in characterizing reflux patterns in GERD which can be used as a supportive tool for an optimal treatment. This preliminary modeling result showed that the hazard rate is lower in non-acidic refluxes and decreases with the disease duration in non-responders. The model developed has several limitations: no placebo group, a few covariates tested, and a small number of subjects, which will be reinforced in future studies. In addition, model validation will be needed with more subjects in a prospective study.

Nevertheless, it is meaningful that the method developed here analyzed routine clinical data from the perspective of a model-based drug treatment and thus can similarly be applied in various kinds of clinical situations.

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I-03 *Eun-Kyung Lee* Various validation methods to check the estimation methods with stochastic sampling approach

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Objectives: In these days, NONMEM provides new estimation methods to estimate population PK/PD model parameters. These new methods - IMP, SAEM, Bayes, etc - use MCMC techniques to get the final parameter estimates. However MCMC methods use stochastic simulation, it depends on the starting point, burn-in period and stationary properties of chains. Therefore it should be carefully examined before we use the final parameter estimates. In this study, we suggest new method to check the validity of these MCMC method and the final parameters.

Methods: We present various methods to validate estimates of PK/PD model with MCMC techniques. We also propose new method for validation and compare them. Our new method modified the Bayesian model check approach. Also we develop a tool for MCMC validation methods with its own GUI. It is written in R.

Results: Various validation methods are examined. None of them is the outstanding performance for validation. Therefore user needs to use several validation methods at the same time. This developed tool is very helpful to compare several validation methods.

Conclusions: A tool for MCMC validation methods will be very helpful for pharmacometricians to compare various estimation methods, check their models and decide the final model.

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I-04 *Joomi Lee* Population Pharmacokinetics of Sumatriptan in Healthy Korean Male Subjects

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Objectives: Sumatriptan, a selective agonist for vascular serotonin (5-HT1) receptor causing vasoconstriction of cerebral arteries is used for the acute treatment of migraine attack with or without aura. Despite its relatively high inter-individual variability, few reports have addressed the pharmacokinetic (PK) modeling of sumatriptan. The aim of this study was to develop a population PK model of sumatriptan in healthy Korean subjects.

Methods: A randomized, two-period, crossover bioequivalence study was performed in 26 healthy Korean male subjects. All subjects were received either the test or reference formulation as a single 50-mg oral dose of sumatriptan succinate with a 1-week washout period. Blood samples were collected at 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after dosing. Plasma sumatriptan concentrations were analyzed using UPLC/MS/MS. A population PK analysis was performed using plasma concentration data from both formulations through NONMEM (Ver. 7.2).

Results: A one-compartment disposition model described the best fit to a total of 728 concentrations. Because absorption kinetics patterns showed double peak, parallel first-order absorption and numerical transit compartment model were recruited. There were no significant covariates affecting PK parameters. The one-compartment structural model was validated through the visual predictive check (VPC) and bootstrap with no serious model misspecification.

Conclusions: A population PK model was developed and reasonable parameters were obtained from the data of healthy Korean male subjects.

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I-05 *Annabelle Lemenuel-Diot* Identification of a dual mechanism of action (MoA) for Danoprevir (DNV), a protease inhibitor currently in phase 2, using a mechanistic viral kinetic model

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Objectives: DNV is an inhibitor of the HCV NS3/4A protease that has potent activity against HCV, and is currently in Phase 2 development for the treatment of Chronic Hepatitis C. The goal of this analysis was to describe the effect of DNV ± Ritonavir (RTV), which is used to enhance DNV exposures, and ± PEG-IFN/Ribavirin (P/R) on HCV RNA viral loads using a mechanistic viral kinetic (VK) model addressing the host-virus-drug interactions with system and drug effect parameters. The structure of the VK model was previously characterized on a large viral load database of CHC patients treated with P/R [1].

Methods: The effect of DNV has been incorporated in the VK model using available PK and viral load data from treatment-naive, non-cirrhotic patients with HCV genotype 1 infection in phase 1 and 2 clinical studies and was externally validated using another phase 1 study. The system and PEG-IFN effect parameters estimated in the previous model [1] were re-estimated to take advantage of the rich early viral kinetic information from the phase 1 studies. DNV treatment effect was investigated by including an exposure-dependent inhibition and/or induction on various model parameters, estimating parameters using MONOLIX [2].

Results: Re-estimating the free virion clearance, virion production rate, and PEG-IFN effect allowed a better description of the rapid early viral load decline. Free virion clearance was higher compared to previous estimates, in agreement with literature reports [3]. Two MoA were identified: inhibition of virion production and increase of the infected hepatocytes clearance. Good agreement was demonstrated between the observed and predicted time courses of response rate in phase 2 and viral load in phase 1.

Conclusions: A mechanistic VK model was developed to describe the effect of DNV ± RTV, and ± P/R on HCV viral load. Phase 1 data contributed to a better estimation of parameters related to the early viral decline. The additional effect on clearance of infected cells in addition to the inhibition of virion production is in agreement with earlier reports [4,5] suggesting that protease inhibitors have dual MoA; Inhibiting the virion production and restoring the immune response. Enhancement of the infected cells clearance as a second MoA was suggested for another protease inhibitor [6]. Such a VK model was used as a key element of a modeling and simulation framework to further support the development of DNV and potentially other DAA.

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I-06 *Sergei Leonov* Optimal design of population pharmacokinetic/pharmacodynamic studies

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Introduction: Optimal experimental design of population PK/PD studies has received considerable attention in the literature and software development in recent years. Since 2006, the theory of optimal design for nonlinear mixed effects models and its applications in drug development were discussed at the annual PODE workshop (Population Optimum Design of Experiments); see http://www.maths.qmul.ac.uk/~bb/PODE/PODE.html. Discussions included the comparison of different software tools for population optimal design, and results of such comparison were presented at PAGE 2007 and 2011 meetings; see Mentré et al. [1, 2].

Methods and Objectives: The key object in estimation and optimal design for PK/PD models is the Fisher information matrix (FIM) of a particular sampling scheme. For nonlinear mixed models, the FIM does not have a closed-form expression and, therefore, approximate formulae have to be used. As reported in Mentré et al. [2], under the same assumptions all software tools produce identical FIMs. Simple approximations, e.g. linearization of the response, are relatively straightforward to implement and often give quite accurate results. However, there are instances when such simplified approaches lead to a substantial distortion of the variability estimates of model parameters. To improve the quality of the FIM approximation, we propose to calculate the mean response vector and its covariance matrix via Monte Carlo simulations.

Results: The alternative approximation of the FIM is implemented in PkStaMp library which is intended for the construction of *D*-optimal sampling schemes for compartmental PK and combined PK/PD models; see Aliev et al. [3]. We present several examples of the calculation of the FIM via the new approach, and compare the new outputs with those obtained via previously considered options.

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I-07 *Claire Li* Clinical trial simulations of the anticancer agents- abiraterone and nilotinib

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Objectives: Food effects can have a significant impact on the bioavailability of oral anticancer drugs. The objective of this study was to assess inter-individual variability and inter-occasion variability in drug exposure utilizing a proposed oncology clinical trial design for detecting known food effects on clearance for abiraterone, a drug with a large food effect, and nilotinib, a drug with a smaller food effect.

Methods: Clinical trials of abiraterone and nilotinib were simulated based on a proposed oncology clinical trial design. Hypothetical patients, whose pharmacokinetic characteristics mimic those of the actual, cancer patient population, were given simulated doses of 1000 mg abiraterone once daily or 300-400 mg of nilotinib twice daily and virtual blood samples were taken at week 1, week 4, month 2, and month 3. Simulations of clinical trials with sample sizes of 20, 50 and 70 patients were replicated 100 times each using inter-occasion variability levels (exclusive of the food effect) of 10%, 25%, and 40%. Food effects on clearance were incorporated in the pharmacokinetic parameters and nonlinear mixed effect modeling (NONMEM) was used to evaluate the food effect on pharmacokinetic parameters, inter-individual variability, and inter-occasion variability. The model performance was evaluated by goodness-of–fit plots as well as the bias and precision of the parameters and variability.

Results: The percent bias and precision on population clearance in both abiraterone and nilotinib trials ranged within ± 20%. A trend of underestimate the reference values were showed in both treatments. A significant improvement in accuracy as well as variance was found in the individual clearance estimates with only ± 5% deviation. Percent bias and precision of Inter-individual variability were approximately 30% for abiraterone and 10-20% for nilotinib. Both trials showed a noticeable decrease in the inter-occasion variability bias and precision as the number of patients or IOV increased. Overall, besides nilotinib trials with 70 patients and 40% inter-occasion variability , greater than 80% of trials in either abiraterone or nilotinib treatment were able to detect food effect in a statistical significant level (p-value < 0.05, df=1).

Conclusions: The simulated trials suggest that this proposed oncology trial design can be powered to identify inter-occasion variability and inter-individual variability within individuals in the presence of a potential food effect, which impacts the overall drug exposure in cancer patients treated with abiraterone or nilotinib, under different levels of variability.

I-08 *Earvin Liang* Clinical Trial Design Optimization: A Pharmacokinetic Sampling Plan for a Phase 3 Clinical Trial in Mild Alzheimer Disease Patients

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Introduction: One aspect of design optimization concerns finding an efficient pharmacokinetic (PK) sampling schedule to properly characterize PK of a given drug of interest in the target population. ELND005 (Scyllo-inositol) is being investigated as a potentially disease modifying oral treatment for Alzheimer's Disease (AD).

Objective: To identify an optimal PK sampling plan for a Phase 3 clinical trial in Mild AD patients receiving oral ELND005 250 mg or placebo BID over 78 weeks.

Methods: The method underling optimization approach involves the computation of "Fisher information matrix", whose determinant ("criterion") represents the degree of information inherent in the design using WinPOPT (http://www.winpopt.com/) sampling optimization based on a previously developed PK model of ELND005. PK samples are to be collected from 450 patients per arm receiving 250 mg ELND005 or placebo BID. A base PK sample collection study design occurs at baseline visit and weeks 6, 12, 24, 48 and 78, of which 1 sample collected at pre-dose and 2 post-dose collected with at least 1 hour apart from each other during baseline visit, and 2 blood samples drawn at approximately 5 to 9 hours post-dose with at least 1 hour apart from each other during follow-up clinical visits.

Results and Discussion: The base study design is likely to yield a criterion of 86 with %CV for clearance at ~51%. When the PK sampling schedule is modified to 2 post dose samples with one soon after dosing (0.5 hours) and the other at ~2 (Design A), 3 (Design B), or 4 (Design C) hours post-dose during baseline visit, and to 1 post dose sample during the rest of the visits, the criterion and %CV of clearance are likely to improve to 85 and ~34%, 94 and ~20%, and 111 and ~14%, respectively. Either Design is invariant in terms of efficiency to changes in sampling times anywhere between 5-9 hours post morning dose and there is no meaningful gain in efficiency if two samples instead of one are collected during PK visits at weeks 6 to 78. For Designs B and C, if sample size is maintained at 300 and 200 patients while other conditions remain the same, %CV of clearance is likely to increase slightly to ~24% and ~20%, respectively.

Conclusion: Taking into consideration patient compliance, comfort and safety, as well as data richness and consistency, Design B is considered an efficient and practical sampling plan and therefore proposed for the future Phase 3 trials.

I-09 *Floriane Lignet* Computational Model of In Vitro Breast Cancer Cells Spheroid-Formation

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Objectives: The receptor HER2 is over-expressed in 20 to 30% of breast cancers and is associated with invasive phenotypes and poor survival prognosis [1]. Treatments directed against this receptor or the downstream pathways exist but show low efficacy or induce resistance [2]. The objective of this study was to develop a computational model that mimics breast cancer cells spheroid formation in order to better understand and optimize treatment action.

Methods: Our model was developed based on data for wild and HER2+ mammary epithelial cells (MCF10A) grown in 3D Matrigel cultures. It was observed that normal cells form regular duct-like spheroids while HER2 over-expressing cells form irregular, filled structures comparable to ductal carcinoma in-situ, a pre-malignant lesion [3]. Measures of volume, lumen size and compactness of the spheroids were assessed using an image analysis software [4].
We used the Cellular Potts Model [5], a cell-based model, in which virtual cells are sets of points of the computational domain and possess user-defined individual behaviour rules. Simulations were performed in the modelling environment CompuCell3D [6], starting from a single cell that undergoes mitosis. Cells evolve depending on the contact with other cells, extracellular matrix (ECM) and lumen. We determined measures of volume, lumen size and compactness of the simulated spheroid to compare with the data.

Results: Our model includes the following rules: depending on their position in the cluster, cells may proliferate, polarize orthogonally to the lumen or enter apoptosis, and their adhesion properties vary. We performed a sensitivity analysis of the model parameters, estimating the parameter values resulting in normal and mutated structures. We showed that the length of the contact to ECM triggering mitosis is of primary importance in normal spheroids. In addition, passage from a normal phenotype to a tumorigenic phenotype includes a decrease of the apoptosis rate, a higher probability of proliferation, and a loss of polarization.

Conclusions: We developed a computational model that permitted us to highlight the cellular processes involved in the formation of HER2+ structures compared to the wild phenotype of human mammary spheroids. The next step of this project is to integrate the molecular pathways of HER2 signalling and to simulate their blockade by targeted treatments. Comparison with experimental data may give an insight on links between molecular signals and cellular processes [7]

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I-10 *Lars Lindbom* Addressing variability and uncertainty in pooled pre-clinical data improved the quality of compound selection of a gamma secretase modulator in Alzheimer's Disease

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Objectives: Efficient selection of compounds in discovery/early development requires optimal use of data generated to learn about key drug properties (exposure, safety and efficacy) in order to make rational decisions. A complicating factor is the variety of different studies with different study designs, animal strains, sampling routes and frequency and analytical procedures. Also, with many drug properties still being unknown experiments might not be optimally designed eventuating in differences in the quality/informativeness of the data. This results in considerable variability in the data, which needs to be addressed properly to allow bringing all information under one common denominator. Our objective was to analyze exposure and efficacy data from several centrally active gamma secretase modulators (GSMs) using an integrated approach to address all sources of variability and uncertainty and to present the results in a comprehensive manner to improve the quality of decision making. GSMs are developed to inhibit the formation of Aβ42, a fragment of the amyloid precursor protein, which is hypothesized to play a key role in Alzheimer's Disease pathology [1].

Methods: Data from PK and efficacy studies for several GSMs were pooled and analyzed using mixed-effects turn-over models linking the inhibition of Aβ42 to the predicted brain and plasma concentration. The data included studies of (plasma and brain) exposure- and time-response of the effect of GSMs on the change in Aβ42 in brain. Dense PK observations in plasma were available for a small set of animals for each compound. For the majority of the animals a single observation of PK and Aβ42 in plasma and brain was available.

Results: The observed plasma and brain distribution of the GSM compounds, which was found to be non-linear for some compounds, in addition to their delayed effect on the Aβ42 concentration in brain were adequately described. Considerable differences were found in both brain distribution and potency, whereas all compounds showed comparable efficacy.

Conclusions: Using an integrated modeling & simulation approach to show the uncertainty in the concentration-effect relationships from different GSMs allowed to quantitatively compare their potency and efficacy. This allowed considering the differences in the quality/informativeness of the available data in the decision which compound to select for further development in an intuitive and comprehensive manner.

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I-11 *Rocio Lledo* Dose escalation studies for mAb: prior distributions selection and software comparison

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Objectives: During first in human- dose escalations studies, the pharmacokinetic (PK) data may be required to compare the exposure to the toxicological exposure limits or to relate to the pharmacodynamic findings and to adjust the doses to be evaluated accordingly. However, at the time of dose escalation decision, only a truncated PK profile is available - usually less than one half life - making difficult to predict accurately exposure variables such as AUC0-inf. The human PK of monoclonal antibodies (mAb) is in general well predicted from animal data. Therefore, a Bayesian framework with the use of prior information could be useful to support dose escalation studies. The aim of this work was i) to define the prior distributions and ii) to evaluate the performance of the NONMEM prior functionality compared to a full Bayesian method when applied to PK analysis of mAb.

Methods: A two compartment PK model with linear and nonlinear elimination was used as structural PK model.. Prior distributions for the population mean PK parameters and interindividual variabilities were selected based on several sources of information such as scaled PK parameters from monkey and clinical PK data from similar type antibodies, reflecting the knowledge and uncertainty around parameter distributions. The PK model was implemented using the prior functionality in NONMEM and in WinBUGS. Truncated PK data available at the time of each dose escalation were analysed using both approaches and predictions for the next dose level were performed. A comparison in terms of parameter estimates, parameters precision and run time between NONMEM and WINGBUGS results was performed.

Results: The use of prior distributions to inform PK model integrated together with data generated in the study allowed a good estimation of the model parameters. PK parameters estimated in NONMEM using the prior functionality were in close agreement with those produced by the full Bayesian analysis.

Conclusions: A Bayesian framework for dose escalation in FIM studies for mAb has been established, allowing a reliable prediction of the exposure at the next dose level based on limited PK data. The use of the prior functionality in NONMEM yielded similar results and it showed to reduce run times.

I-12 *Rasmus Jansson Löfmark* Enantiospecific reassessment of the pharmacokinetics and pharmacodynamics of oral eflornithine against late-stage T.b. gambiense sleeping sickness

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Objectives: To characterize the stereoselective pharmacokinetics of oral eflornithine in patients with late-stage *T.b.gambiense* sleeping sickness by enantiospecific re-analysis of plasma and cerebrospinal fluid (CSF) samples. A secondary aim was to determine the concentration of L-eflornithine required in plasma or CSF for an efficient eradication of the T. *Brucei* gambiense parasites.

Methods: Plasma and CSF samples from 25 patients were reanalyzed to obtain the L- and D-eflornithine concentrations. A population pharmacokinetic model was fitted to the plasma concentration-time data using NONMEM. The probability of cure was regressed against observed L - and total eflornithine CSF steady-state concentrations, plasma $Css_{,min}$ and AUC_{τ} exposure.

Results: A marked difference in L - and D - eflornithine plasma concentrations was observed. Plasma concentration-time data was modeled with a two-compartment model with linear absorption and oral clearance. Typical oral clearance values of for L - and D - eflornithine were 17.6 (95%CI: 15.7, 19.5) L/h and 8.2 (95%CI: 7.4, 9.0) L/h, respectively. None of the covariates (age, bodyweight, gender, concomitant medication, hemoglobin levels) evaluated were found to significantly influence any model parameter. The distribution of eflornithine enantiomers to the CSF did not appear to be stereoselective. A significant correlation was found between the probability of cure and plasma AUC_{τ}, although not more pronounced for the L - enantiomer than for total eflornithine concentrations.

Conclusions: The findings in this study may explain why an oral treatment of late-stage human African *trypanosomiasis* patients with racemic eflornithine has previously failed; the more potent L - enantiomer is present at much lower concentrations in both plasma and CSF compared with the D - enantiomer. Stereoselective pharmacokinetics needs to be considered should the possibilities for an oral dosage regimen be further explored for eflornithine.

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I-13 *Gaohua Lu* Application of the Simcyp PBPK/PD model to Simulate PK and PD of Nifedipine in Japanese Populations

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Objectives: The recent success in application of systems approach in the area of predicting pharmacokinetics (PK) has led many to believe a similar strategy for the prediction of pharmacodynamic (PD) aspects should be adopted and popularised [1]. Although the fundamentals of mechanism-based PD (MBPD) are not new, integration of these into platforms with a user-friendly interface has not taken place up until now. The aim of this study is to assess the ability of the PD modules within the Simcyp Simulator V.11 to predict PK and PD profiles of nifedipine (NIF) in Japanese populations.

Methods: Prior *in vitro* metabolism and physicochemical parameters of NIF were collated from the literature. These drug-specific data, along with system-specific data, were used in a minimal physiologically-based pharmacokinetic (PBPK) model to predict NIF concentration time profile for a virtual Japanese population. Further, reported parameters in Shimada *et al.* [2] for empirical and operational transduction models of NIF binding to a stimulus response model, as well as the classical Hill function, were used to simulate the decrease in systolic blood pressure. The simulations, using the same PD models, were repeated in the North European Caucasian (NEC) population and the simulation results were compared against clinical data.

Results: PK and PD profiles were successfully simulated in both Japanese and NEC populations, producing results consistent with reported clinical studies [3, 4]. In particular, including an effect compartment in the PD module improved the prediction of PD profiles. Whilst all the models could describe the observed data, the operational transduction model could be considered a more mechanistic account of NIF pharmacological response. The difference between the prediction and observation in the PK/PD in different populations might be due to the differences in the system related parameters and clinical study settings which were not available to be incorporated into simulations.

Conclusions: Implemented PK/PD models within the Simcyp Simulator are able to simulate both the PK and PD profiles of NIF in Japanese and NEC populations. Further applications could be envisaged which are facilitated by the new PBPK/PD link models.

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I-14 *James Lu* Refining the mechanism of CETP mediated lipid transfer in a stochastic model of lipoprotein metabolism and kinetics (LMK model)

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Objectives: The Cholesterol Ester Transfer Protein (CETP) mediates the transfer of cholesteryl esters (CE) and triglycerides (TG) between lipoprotein particles and hence plays a critical role in reverse cholesterol transport. In order to better understand as well as predict the effects of CETP inhibitors and modulators on lipid profiles, a more precise characterization of the lipid transfer mechanism is needed.

Methods: We have implemented a previously published, mechanistic model that describes lipid transfer processes at the level of individual lipoprotein particles [1]. Given a set of values for the kinetic rate parameters, the model can then be simulated stochastically using a variant of the Next Reaction Method, from which the stationary density profiles of the lipoprotein particles and their constituents are obtained by averaging the particle distribution over time. The flexibility of the modelling framework enables a precise formulation of the mechanisms of particle interactions and hence allows one to explore different hypotheses.
In order to simulate pharmacological effects of CETP inhibitors and modulators on the lipid profiles, we first need to differentiate between the existing candidate mechanisms of lipid transfer. To explore the plausibility of various CETP transfer mechanisms, we additionally compared model predictions to literature data on cholesterol fluxes between HDL, VLDL and LDL particles, cholesterol (C) levels in CETP deficiency states and the effects of hypertriglyceridemia on HDL-C levels.

Results: While both the uncoupled exchange and coupled (swapping) mechanisms of CETP mediated transfer can reproduce both the lipid concentrations in HDL and ApoB-containing particles as well as the flux measurement data, the former cannot explain the observed inverse relationship between HDL-C and TG levels in hypertriglyceridemic patients. Analysis of the model with the swapping mechanism suggests that some form of coupling between the CE and TG transfers is needed in the CETP module.

Conclusions: The lipid concentration data from CETP deficient and hypertriglyceridemic patients can discriminate between different mechanisms of CETP mediated lipid transfer within our model of lipoprotein metabolism and kinetics. Once the LMK model is fully calibrated, we plan to translate its detailed, stochastic description to an ODE representation within NONMEM in order to analyse clinical data.

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I-15 *Peiming Ma* Organization of Target-Mediated Disposition (TMD) Models including Michaelis-Menten (MM), rapid-binding (RB), and quasi-steady-state (Qss) models

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Objectives: To illustrate a rigorous way with which simplifications of the general TMD model are derived; to organize TMD models including MM, Qss and RB models; and to identify some confusions in application.

Methods: TMD of a drug refers to the phenomenon that drug interaction with target significantly influences drug disposition. When amount/capacity of accessible target relative to drug is limited, TMD typically manifests nonlinear PK. Many biologics bind to target with high affinity and specificity, and exhibit TMD.
A general TMD model was proposed [1], followed by simplifications of RB and Qss models [2,3]. However, it is not always clear besides fewer equations or parameters why simplifications are indeed so, and not uncommon to see confusions in application.

Results: We present recent work on organizing various TMD models and compare them using known examples. We follow a model scheme in [4] with C, R, and M as drug, target, and drug-target complex concentrations. The association and dissociation processes are governed by a second- and a first-order rate constants k_{on} and k_{off}. The complex may internalize or degrade with a rate constant k_{met}.
A direct simplification of the general TMD model is to assume constant total target R_{tot} [1]. Other simplifications can be made by modifying some differential equations with e.g. RB and Qss assumptions. However, a broad assumption can be the basis for many simplification: $R \cdot C = \kappa M - \alpha R - \beta C + \gamma$. This algebraic equation replaces one of the differential equations, and the resultant equations form a simplification. The Qss assumption $R \cdot C = K_m M$, where $K_m = (k_{off} + k_{met})/k_{on}$, is a special case. Under Qss assumption the MM and Qss models can be directly simplified from the general TMD model. As a second example, if κ, β=0, $\alpha = K_m$, $\gamma = V_{max}/k_{on}$ for a constant V_{max}, the simplification is a model of central, peripheral, and receptor compartments with or MM distribution from the central to receptor compartment and linear elimination from both. This was briefly discussed in [1].
Note that the labeling of K_D and K_m is the only difference between the RB and Qss models, which are indistinguishable for model fitting. Thus, upon fitting either model, we need to ask whether or not the fitted parameter K_D of the RB model is actually K_m, and vice versa.

Conclusions: Our work should provide a more rigorous basis for theoretical and practical research of TMD models, important for investigating PK-PD relationships of many biologics.

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I-16 *Arianna Madrid Aispuro* A Systematic Approach to PKPD Model Development to describe Sleep Effects of Compounds with Different Mechanisms of Action Using Semi-Mechanistic Markov Chain Models

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Objectives: To describe the sleep effects of the non-benzodiazepine hypnotic agent Zopiclone (ZOP), and the selective 5-HT2A antagonist MDL-100,907 (MDL) using a semi-mechanistic pharmacokinetic-pharmacodynamic (PKPD) Markov-chain model previously developed for Zolpidem in healthy rats[1].

Methods: Experimental. Electroencephalogram (EEG) data were obtained in rats. For each 10 second interval, EEG data were converted into awake, REM or NREM stages representing non-ordered categories. The data consisted of a 12 h baseline where EEGs were monitored in the absence of any type of perturbation and a 12 h period during which methylcellulose (MC), ZOP or MDL were administered.Data analysis. The time course of the 9 possible transition probabilities between the 3 sleep stages was described using a non-homogeneous Markov chain model based on piecewise multinomial logistic functions[2], as previously described[1]. Literature PK data was used to generate concentrations of ZOP and MDL over time[3-5]. Analyses were performed using NONMEM VII v2 using the LAPLACIAN estimation method. Model evaluation was based on visual predictive checks (VPCs).

Results: Baseline model. A model selected previously[1] was used to generate VPCs for the baseline data from the new studies. Results indicated that this model was adequate to describe and predict the new data. MC model. The effects of MC administered orally or IP were incorporated using a Bateman function to reflect an increase in the transition probability from NREM to awake as observed in the data. Drug effect model. Exploration of the time course of transition probabilities revealed that both ZOP and MDL elicited a temporal decrease in the transition probability from NREM to awake indicating that sleep was promoted. ZOP exhibited a rebound effect approx. 8-10h after dosing, whereas such rebound phenomena were not observed in the data with MDL. ZOP effects were described using a turnover feedback model.[1, 6] For MDL, the PKPD models that best described the data were the link[7] or indirect response[8] (IDR) models.

Conclusions: The baseline response model used to describe the underlying physiological system (a non-homogeneous Markov chain model based on piecewise multinomial logistic functions) has been shown to be conserved across several studies, thereby supporting its application for future studies. Drug level effects need to be considered separately, contingent on their mechanism of action and the observed responses.

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I-17 *Victor Mangas-Sanjuan* Three Compartment Model To Describe Atipical Permeability Profiles In CACO-2 Cells

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Objectives: Fexofenadine HCl (FEX), a second generation non-sedating histamine H1 receptor antagonist, is an active metabolite of terfenadine. Oral formulations at a dose of 60-120 mg/day are available for FEX. Permeability of FEX was determined in an in vitro cell model at different donor concentrations, and the effect of sodium dodecyl sulfate (SDS) at two concentration levels (10 and 50 µM) on FEX permeability was evaluated.

Methods: The in vitro transport studies were developed in Caco-2 cell in apical-to-basolateral (AB) and basolateral-to-apical (BA) direction. Permeability values were estimated by non-linear regression of cumulative amounts in the receptor chamber, and remaining amounts in donor chamber versus time. The basic kinetic model comprises three compartments, donor, cell and acceptor chamber. The fitting procedures were performed using NONMEM 7.2 software with the first order conditional estimation method (FOCE) for objective function estimation and ADVAN9 subroutine. Several kinetic models were fitted to the data, functional and mechanistic models, selecting the best model with lowest objective function value. The inter-individual and residual variabilities of the kinetic parameters were described with the use of exponential models. Goodness of fit plots and visual predictive check were generated in the aim of confirm the final model.

Results: The analysis of A-B and B-A permeabilities suggested the existence of an efflux mechanism. The best model fit corresponded to a kinetic model with passive mechanism and an efflux carrier located at the apical side of the enterocite. The presence of high concentration of surfactant (50 mM) affects to the passive diffusion of FEX differently for each direction of transport. Permeability as a function of time and Tlag parameters were used to account for the intercept of the cumulative fractions permeated versus time that was different from 0.

Conclusions: Fexofenadine has a low intestinal permeability in vitro in Caco-2 cells and the transport of the drug is concentration-dependent due to the involvement of Pgp. The three compartment modeling based on differential equations improved the basic approach for parameter estimation (fitting permeabilities versus donor concentration) as it allow to characterize apical and basolateral membrane permeabilities, beside having the advantage of its broader applicability i.e with non sink conditions and time dependent permeability.

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I-18 *Mathilde Marchand* How to support a definitive bioequivalence study design using modeling and simulation

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Objectives: The objective was to perform population pharmacokinetic (PK) modeling and clinical trial simulations (CTS) to inform the study design of a future bioequivalence study comparing a reference, marketed, drug product with an innovative supra-bioavailable formulation of the same active moiety, exhibiting non-linear absorption characteristics.

Methods: A pilot clinical bioavailability study comparing three doses of the novel formulation (equivalent to 25%, 51% and 102% of the reference dose) was performed in 16 healthy subjects. A population PK model was developed using NONMEM based on combined drug concentrations resulting from the administration of both formulations (novel and reference). Following successful qualification of the population PK model, CTS were performed using various sources of variability including uncertainty on fixed effect parameters. The design selected to simulate a definitive bioequivalence study was a 2 x 2 Latin square comparing the 2 formulations after single dose, complete washout between periods. To determine the sample size, a target statistical power of 90% was selected. AUC and C_{max} were derived on each simulated profile for each simulated trial. An ANOVA model was used to derive 90% CI for AUC and C_{max} for each simulated trial. 1000 trials were simulated for each sample size.

Results: In the PK model, drug concentrations were analyzed simultaneously with different absorption models and a common disposition model for both formulations. The bioavailability of the novel formulation relative to the reference was adequately described by a power model with a population estimate of -0.339 for the exponent. Three dose levels of the novel formulation (equivalent to 70%, 76% and 82% of the reference, expressed as the active moiety) were selected. Thanks to the supra-bioavailability, a dose containing 76% of the reference dose is likely to demonstrate bioequivalence with the reference. Moreover, 20 subjects would be sufficient to demonstrate bioequivalence on both C_{max} and AUC, with a statistical power in excess of 90%.

Conclusions: The modeling and simulation approach supported the design (i.e. optimal dose and sample size) of a definitive bioequivalence study between a novel formulation and the reference one. The preliminary results of a confirmatory PK study performed with the selected dose showed a close agreement with the CTS-based predictions.

I-19 *John Maringwa* Model-based meta-analysis of summary clinical outcome data in idiopathic pulmonary fibrosis (IPF)

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Objectives: (1) To perform a model-based meta-analysis of comparative effectiveness of various drugs investigated in treating IPF patients, and to assess the effect of trial- and patient disease variables on drug treatment effect. (2) To simulate expected treatment- and trial performance in IPF.

Methods: Publicly available longitudinal summary level data of clinical efficacy outcomes (forced vital capacity, FVC % predicted) from 7 drugs in 11 placebo-controlled IPF trials (2,834 patients) were analyzed using an asymptotic repeated measures regression model to describe the time course of treatment effect (drug, dose) on FVC. A non-parametric placebo model was used to account for heterogeneity in the time course of placebo effect, both between- and within trials.

Results: Significant, time-dependent treatment effects on FVC were identified for pirfenidone and the investigational compound BIBF1120 and for the latter so in a linear dose dependent manner. No statistically significant treatment effect was observed for the other drugs (etanercept, interferon-gamma, sildenafil, bosentan, and azathioprine). Patient disease variables such as baseline FVC values did not appear to impact treatment effect in a significant manner. The maximum estimated treatment effect is 3.29- and 5.14% for pirfenidone and 300mg/day BIBF1120, respectively, while the estimated time to achieve 50% of this maximum effect for both drugs is ~15 weeks. For BIBF1120 doses of 200mg/day and higher, a larger treatment effect on FVC compared to pirfenidone is expected. Trial simulations suggest that a trial with mean baseline FVC of 70%, duration of 52 weeks, and enrolling 40 patients per group will have a power of ~80% to detect a treatment effect of 1.53%.

Conclusions: Pirfenidone and BIBF1120 slow down the decline of lung function (FVC) in IPF patients in a significant manner. At doses of 200mg/day and higher, the effect of BIBF1120 on FVC decline is expected to be larger than for pirfenidone. Model-based simulations allowed exploring several trial design aspects.

I-20 *Eleonora Marostica* Second order Markov modelling of HAMD responses in depression trials

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Objectives: Longitudinal models describing the time course of the clinical endpoint in psychiatric trials are usually empirical. Moreover, conditional on the individual parameters the response model does not structurally account for random fluctuations on the disease. The first attempt to include these aspects, presented in [1] resorting to stochastic difference and differential equations, did not give a completely satisfactory description of inter-individual variability. We propose an extension of the previous work through a more sophisticated continuous-time dynamic model based on second order Markov processes [2]. The proposed model aims to describe appropriately the clinical response and handle flexible dosing schemes.

Methods: A Phase II, double-blind, randomized, placebo-controlled, flexible-dose depression trial was analyzed. We modelled the individual time series of HAMD scores within the framework of population modelling. The typical curve was modelled as an integrated Wiener process [3] whereas a second order Markov model was adopted to describe the individual shifts with respect to the population curve. Two Markov models were analyzed having either (i) two coincident poles or (ii) two distinct poles in the transfer function. Dose changes were accounted for by varying the trend of the response profile. Models statistics were specified through hyperparameters. A unique hyperparameter for the measurement error was considered in order to simultaneously identify the model on the four subpopulations (placebo and drug: non-escalating and escalating subjects). Software R 2.10.0 [4] was adopted according to the empirical Bayes paradigm.

Results: Both models were able to capture the shapes of individual responses. Moreover, good predictive performances in terms of VPCs were obtained. According to the Bayesian Information Criterion, the second order Markov model with two coincident poles in the transfer function should be preferred.

Conclusions: The results demonstrate the feasibility and effectiveness of second order Markov processes as an innovative modelling approach for longitudinal data, when mechanistic knowledge is poor or absent. We showed that the proposed models yield good individual fittings as well as a good estimate of the population response and an appropriate representation of the inter-individual variability. Interestingly, both models are able to easily handle dose changes and account for random perturbations with greater flexibility than previous approaches [1].

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I-21 *Amelie Marsot* Thiopental and esomeprazole in critically ill patients: Drug interaction.

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Objectives: Thiopental is a thiobarbiturate given for induction of anesthesia or in case of brain injuries to reduce intracranial pressure and to manage cerebral ischemia. Esomeprazole is a proton pump inhibitor used to reduce stress ulcers, erosions of the stomach and upper gastrointestinal bleeding that are complications in critically ill patients. Previously a two-compartment model was described in critically ill patients [1] but esomeprazole wasn't yet marketed. A new model is proposed describing the influence of concomitant administration of esomeprazole on the volume of distribution of thiopental.

Methods: 59 critically ill patients (weight: 16.9-114kg) aged 5 to 78 years, admitted in critical care unit for treatment of intracranial hypertension, induced by traumatic (58%), vascular (27%) or other origin (15%) acute brain diseases, were studied. High dose thiopental was administered by continuous infusion. Total mean dose of 295 +/- 181.3 mg/kg was given in 96 +/- 72 hours. Blood thiopental concentrations were determined by a liquid chromatography method. Pharmacokinetic analysis was performed by using a non linear mixed-effect population model (NonMEM software).

Results: A one-compartment open model with first-order elimination including two covariates: body weight on clearance and volume of distribution, and administration of esomeprazole on volume of distribution were used. The population typical mean (percent relative standard error (%RSE)) values for total clearance (CL), central volume of distribution (Vd) in patients with and without administration of esomeprazole were 5.4 L/h (8.5%), 261.0 L (6.6%) and 132.6 L (10.9%), respectively. The interindividual variabilities (%RSE) of CL and Vd were 50.3 % (21.5%) and 24.9% (34.1%), respectively. The residual variability (%RSE) was 7.12 mg (16.7%).

Conclusions: The pharmacokinetic parameters of thiopental in critically ill patients were estimated. These results are comparable to those presented by Russo in patients without administration of esomeprazole. Concomitant administration of thiopental and esomeprazole causes an increase in the volume of distribution of thiopental. A dose adjustment should be made to achieve the target concentrations in patients receiving esomeprazole. Esomeprazole has been reported as an inhibitor of P-glycoprotein which may suggest other potential drug interactions. Further studies on concomitant administration of esomeprazole should be conducted. .

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I-22 *Sílvia Martínez* Population pharmacokinetics of amikacin in newborns

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Objectives: The aim of this study was to establish the population pharmacokinetics (PK) of amikacin in newborns from serum concentration data obtained during the routine therapeutic drug monitoring and to explore the influence of patient covariates on drug disposition.

Methods: Data were retrospectively collected from a study in newborns with postnatal age less than 90 days admitted in the neonatal unit of Vall Hebron (July 2000 to July 2006) who were treated with amikacin, and with at least two serum concentration samples. Amikacin was administered by intravenous (IV) infusion over 30 to 60 min. Blood samples were collected prior to administration, and after 1 hour start of the infusion. Amikacin serum concentrations were quantified using a fluorescence polarization immunoassay (TDx; Abbott Laboratories). Subsequently, the data was analyzed using a nonlinear mixed-effect modeling approach in NONMEM 7. Between subjectpatient variability (BSV) was modeled exponentially, and was evaluated for tested in all the PK parameters. The First order conditional estimation method (FOCE) with interaction (FOCE-I) was used through all the model building process. Parameter precision was evaluated using the bootstrap (n=200).

Results: A total of 451 amikacin serum levels from 148 newborns were included in the analysis. The PK of amikacin after IV administration was best described by a two-compartment linear disposition model. All parameters were estimated with adequate precision (RSE<41%). BSV was estimated for clearance (CL) (34.50 CV%), central compartmental distribution volume (V1) (21.07 CV%) and distributional clearance (Q) (70.21 CV%). Residual variability was modeled using a combined error model. The final model included creatinine clearance (CLCR) and body weight (WGT) on CL, and WGT on V1. All of them reduced the BSV about 39% of the variability on CL and 37% on V1 from the base model. The final covariate relationships identified were: TVCL=(0.094·(CLCR/24.75)^0.649)*((WGT/1470)^0.752) and TVV1=0.640*(WGT/1470)^1.090. The bootstrap indicated that estimates of the fixed and random effects in the final model were estimated with good precision.

Conclusions: The developed population PK model for amikacin in newborns adequately described the observed data. CLCR and WGT were identified as the best predictor for BSV in CL, and WGT was for V1.

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I-23 *Maria Matoses Osborne* Development of a PBPK model for the anticancer drug Vivia009 and its main metabolite administered as a new delivery system in the Rat

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Objectives: Vivia009 is a patented new drug indication that targets B cell population overproliferation in leukemic patients. In order to prevent side effects and to increase drug efficacy in the lymph nodes, a new delivery system (NDS) has been developed and its pharmacokinetic properties are currently being studied. The aim of this study was to develop an integrated PBPK model capable to describe simultaneously the biodistribution of Vivia009 and its main metabolite, after the parent's drug administration as a free solution or as an NDS.

Methods: Fifty-one rats divided in two groups were treated with 0.75 mg/kg of either Vivia009 or Vivia009-NDS given as a bolus. At time points 0.08, 0.16, 0.25, 0.5, 1, 2, 4, 6 and 24 hours, three animals were sacrificed. Samples of plasma, axillary lymph node, brain, spleen and bone marrow were extracted and analysed to quantify Vivia009 and its metabolite. NDS's composition was a mixture of Vivia009, PLGA, polivinil alcohol, poloxamer 188, tween 80 and sucrose, its size varied between 1.2-1.5 µm and the release profile could be characterized from 0-24 h. Analyses were performed with NONMEM version VII using the naïve pool data approach.

Results: A PBPK model was built for Vivia009 and its main metabolite after free drug administration assuming a perfusion limited distribution, and using available data from the literature regarding blood flows, and tissue volumes (1,2). A permeability surface factor was estimated for lymph node, and distinction between vascular and intracellular compartments was required for the case of spleen. Additional model parameters estimated during the fitting were drug and metabolite clearance, apparent fraction of drug metabolised, and tissue to plasma partition coefficients. The latter ones were also calculated using the ratio between AUCtissue/AUCblood (3) resulting similar to the model estimates. Based on the results of the release profile, 30% of the dose of Vivia009-NDS was dissolved before the bolus administration and behaves as a free drug (4). For the formulated fraction of the dose, it was assumed a rapid capture by the macrophages and distribution through the lymphatic system to the tissues.

Conclusions: A PBPK model has been developed to describe simultaneously drug and metabolite distributions obtained from several studies carried out with different drug formulations.

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I-24 *Veronese Mattia* Optimal Experimental Design for receptor drug development with PET studies

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Objectives: To increase the efficiency of pharmacokinetic/pharmacodynamic experiments, optimal experimental design has been used to successfully optimize dose allocation and sampling schedule [1]. In PET receptor occupancy (PET-RO) [2] studies it has been demonstrated that adaptive optimal design (AOD) algorithms improve the assessment of drug kinetic time-courses [3]. However the value of applying adaptive or non-adaptive optimal design methodologies to PET-RO studies depends on several factors including drug affinity to the target as well as feasibility constrains such as sample size, number of scan per subjects and logistical constrains. In this work we presented a simulation study to explore the potentialities of optimal design algorithms when applied to PET-RO, by evaluating the sensitivity of the results to experimental scanning times as well as misspecified drug kinetic assumptions.

Methods: Simulated data were generating according the following PK-BP model (kon=0.088 hrs-1 and koff=0.221 hrs-1, BP0=3, inter-subject variability=30%, proportional error model):
dBP/dt=koff•BP0 - (Cp•kon+koff)•BP
Simulated experimental designs were chosen according to adaptive, non-adaptive optimal designs and non optimized designs by using different levels of parameter misspecifications respect to the true simulated values (range: [-300%;+300%]). For each design, 100 populations each with 12 subjects were considered. Only two time points were assumed per subject, chosen in a time window of 0-36 hours (minimum distance 4 hours). Design optimization was identified using the D-optimality criterion [4]. Three simulated compounds with different brain affinities (low, medium and high) were tested, with Kd(=koff/kon) equal to 15, 2.5 and 0.25 respectively . The dose level was held constant for all the simulations.

Results: For all the drugs and experiments considered, the best performances were achieved using optimal approaches (adaptive and non-adaptive) applied without parameter misspecification. The worst performances were reported by the non-adaptive method when initial parameter assumptions significantly underestimated the true kinetic of the tracer. However, when AOD was applied to the misspecified cases, precision and accuracy of parameters were recovered. Kd was the most robust parameter (bias range [1%;30%]), while kon and koff were much more sensitive to experimental choices (maximum bias 64% and 50% respectively). High-affinity compound were more robust to experimental setting changes than medium or low affinity drugs.

Conclusions: Our results confirmed that an optimal choice of PET scanning times can improve the quality of parameter estimates in PET-RO. In particular if the initial misspecification is limited (

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I-25 *Christophe Meille* Modified model of drug induced thrombocytopenia efficiently projects safe starting dose in human from preclinical data

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Objectives: A semi-mechanistic model quantifying hematotoxicity of anticancer agents has been proposed by Friberg[1] with a chain of 5 compartments reproducing the hematopoietic maturation process. The study aim was, for a new compound RO_A inducing thrombocytopenia in cynomolgus monkey, to 1) adapt this model to describe platelet (PLT) time-course profiles, 2) project the appropriate dosing regimen in humans, and 3) calculate the risk of grade 4 thrombocytopenia at the selected starting dose.

Methods: The analysis included 244 PLT and 144 PK observations from 48 monkeys receiving RO_A oral doses from 10 mg to 500 mg tested in single or repeat dose studies. PK was modeled by a 2-compartment model accounting for an enzyme induction effect. Adaptations of the Friberg model were: zero-order production of progenitors inhibited by drug; effect compartment linking PK to PD; addition of a local feedback mechanism dependent on number of cells in the first compartment and affecting proliferation of cells in subsequent compartments. Population approach was used to estimate PK and PD parameters with MONOLIX 3.2[2]. Model performance was assessed through AIC criterion, goodness of fit and posterior predictive check. Human PK of RO_A was predicted using physiologically based pharmacokinetic (PBPK) modeling in GastroPlus[3]. Human PLT profiles were simulated with doses from 30 to 2000 mg and considering that the drug potency on progenitors is translational across species. The risk of grade 4 thrombocytopenia was assessed by Monte Carlo simulation.

Results: Adding local feedback allowed a good description of a transient increase of PLT in monkeys while thrombocytopenia and subsequent rebound were well described for all the dosing regimens. Simulation of expected PLT profiles in human showed that concentrated daily administration (day 1 to day 5) for 28-day cycles was better tolerated. Risk of grade 4 thrombocytopenia during the first 2 cycles was estimated to be 4%. The overlay of observed and predicted PLT kinetics at the human starting dose was consistent.

Conclusions: A PKPD model of thrombocytopenia was applied on monkey data for human prediction. A new feedback mechanism was needed to describe monkey PLT profiles. With support of modeling, a 100 mg starting dose was selected rather than a 30 mg dose and two escalation steps were saved in the phase I study. Observed PLT profiles at the starting dose are in line with model predictions.

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I-26 *Sven Mensing* Evaluation of the long-term decline of platelets following Navitoclax (ABT-263) administration in Cancer Patients with a semi-physiological pharmacodynamic model

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Objectives: Navitoclax (ABT-263) is a novel small molecule that inhibits Bcl-2 family proteins and promotes apoptosis. Thrombocytopenia is a primary dose limiting toxicity of navitoclax monotherapy, Navitoclax induced accelerated apoptosis of circulating platelets, which differs from typical chemotherapy. Data from Phase 1/2a studies showed a fast drop of platelets after initial administration and a long-term (more than one year) platelets decline in 10-20% patients following continuous administration of navitoclax. The aim of this work was hence to develop a platelet model which is able to describe navitoclax effect on platelet time-course, with an emphasis on the long-term decline.

Methods: The proposed semi-physiological model has 5 compartments, describing the maturation of the platelets in bone marrow and the circulating platelets in blood. Compared with the previously published models that describe drug induced myelosuppression [1,2], the model established in this analysis applied a different feedback mechanism and introduced a new concept of progenitor cell "pool", which describes the levels of bone marrow reserve of platelet progenitor cells at the beginning of navitoclax treatment. The initial size of the "pool" was estimated using the data. The new model better captured the fast drop of the platelets.as well as the long-term decline in platelets following navitoclax administration. Drug effect of navitoclax on circulating platelets was incorporated via an Emax-model. This semi-physiological model was implemented in NONMEM 7.2.0 via ODE's using ADVAN 13.

Results: The proposed semi-physiological model approach was able to describe the long-term decline and the initial drop in platelets seen in our Phase 1/2a studies in cancer patients. The agreement of the model with the data is shown by GoF-Plots as well as VPCs and bootstrap analyses.

Conclusions: We have developed a new semi-physiological platelet model for describing fast drop of platelets after initial navitoclax administration and long-term decline of platelets after continuous administration of navitoclax.

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I-27 *François Mercier* A discussion on two approaches for indirect treatment comparisons based on public-domain metadata: The case of side-effects incidence

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Objectives: In recent years, the adjusted indirect comparisons (ITC) method has been widely used to compare competing treatments in the absence of direct evidence about their relative performance. For instance, if two treatments A and B are compared against a common comparator O via two distinct sets of randomized trials, ITC can be used to derive an indirect estimate of the relative effect of A versus B. Borrowing data from literature, we discuss two ITC methods to estimate the odds-ratio (OR) of side-effects in patients treated for pain.

Methods: Taking the example of a binary response variable, two approaches can be considered to obtain indirect estimates: (1) model in the response 'domain' (e.g. proportion of events) in each treatment group and derive the effect size (OR) between A and B; (2) derive the effect size (A vs. O and B vs. O) from arm-level data and model it to extract the effect size of interest (A vs. B). Pharmacometricians are referring to the first approach as 'model-based meta-analysis' while statisticians and/or epidemiologists use the second simply called 'meta-analysis'. We apply and compare these two approaches in the analysis of AEs frequency (constipation, nausea, dizziness, vomiting, somnolence), as well as frequency of drop-out for AE in 44 randomized controlled trials (representing approximately 14000 patients) evaluating various treatments for pain management.

Results: The two approaches give consistent results. Taking constipation as an example, the comparison of A vs. B gives an OR (95%CI) of 1.53 [1.03, 2.23] using the response 'domain' model and 1.54 [1.04, 2.27] using the effect size 'domain' model. Frequencies of constipation and vomiting frequency appear to be higher with A compared to B. The meta-analysis does not reveal any other significant difference in AE or drop-out for AE frequencies between A and B.

Conclusions: Response or effect-size model-based indirect treatment comparisons lead to similar results. While the response-based models offer more flexibility, effect-size based model are easier to implement and to interpret. Both approaches can be considered as complementary.

I-28 *Enrica Mezzalana* A Target-Mediated Drug Disposition model to quantify the relationship between Anti-CD3 monoclonal antibody and CD3/TCR receptors in Patients with autoimmune diseases.

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Objectives: Otelixizumab is a monoclonal antibody (mAb) directed against human CD3ε, which forms part of the CD3/T-cell receptor (TCR) complex on T lymphocytes. Attempts have been made to model the relationships between Otelixizumab, receptor binding and changes in lymphocytes count [1]. Based on the observed short half-life for Otelixizumab and other anti-CD3 mAbs relative to endogenous Immunoglobulin G it is hypothesised that the antibody is subject to target-mediated drug disposition (TMDD) at clinically relevant doses. TMDD is a phenomenon where a drug binds with high affinity to its pharmacological target, such that this interaction influences the pharmacokinetics of the drug. The aim of the present work was to develop a mechanistic target-mediated drug disposition (TMDD) model for Otelixizumab using published clinical data.

Methods: Published data from 3 clinical trials of Otelixizumab in type 1 diabetes mellitus and psoriasis patients were utilized. Free drug in serum (C) and free (FR), bound (DR) and total (TR) receptors on both CD4+ and CD8+ lymphocytes were measured using immunoassay and flow cytometry, respectively. A general TMDD model [2] and its Quasi Equilibrium (QE) approximation [3] were implemented. The QE TMDD model was also extended as in [4] to account for the two different lymphocytes populations, under the assumption of equal affinity between drug and receptors on CD4+ and CD8+. Berkeley-Madonna, R and NONMEM VII were used to develop the model. Model performances were evaluated through changes in Objective Function, GoF plots and VPCs.

Results: First, attempts were made to fit the general TMDD model to the available data. The sum of measured quantities on CD4+ and CD8+ was used for each of FR, DR and TR. However, the general model was unstable and the QE approximation model was then used. An additional source of model instability was then identified when attempting to estimate the conversion factors between FR, DR and TR and their actually measured quantities (in MESF units) [5]. Sensitivity analyses and simulations were conducted using the QE TMDD model to better characterise the model behaviour.

Conclusions: A general TMDD model and its QE approximation were proposed in the attempt to describe Otelixizumab binding to CD3/TCR on T lymphocytes. A critical factor for model identifiability was found in the relative measurements for free, bound and total receptors. Further strategies for improving model robustness while maintaining the key characteristics of TMDD are discussed.

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I-29 *Jonathan Mochel* Using nonlinear mixed effects modeling to characterize the pharmacokinetics and pharmacodynamics of benazepril in dogs.

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Objectives: In the management of canine heart failure, angiotensin converting enzyme inhibitors (ACEIs) e.g. benazepril are the foremost therapeutic option to offset activation of the Renin-Angiotensin-Aldosterone System (RAAS) [1]. Only limited information on the effect of benazepril on circulating RAAS peptide levels is presently available in veterinary medicine. The objective of this research was to determine the effect of benazepril on the renin-angiotensin cascade using nonlinear mixed effects modeling. Chronobiology of RAAS biomarkers and determinants of their regulation were further investigated.

Methods: Blood specimens were collected from a group of 12 healthy beagle dogs fed a low-sodium diet as an experimental model of RAAS activation. Renin activity (RA) and angiotensin II levels (AII) were determined using immunoassay-based methods. Benazepril and aldosterone concentration (ALD) were quantified in plasma by mass spectrometry. Population PK/PD models were developed using NONMEM version 7.1.2. A covariate search was performed using the stepwise covariate model building tool of PsN. Standard goodness-of-fit diagnostics, normalised prediction distribution errors, as well as posterior predictive checks and bootstraps were performed to assess the adequacy of selected models.

Results: The pharmacokinetic disposition of benazepril was described using a nonlinear binding model, as described by Toutain et al. (2000) [2]. Cosine functions were identified to fit the periodic nature of RA, AII and ALD well, and served as baseline for the further development of PK/PD models to assess the effects of benazepril on the RAAS. Moving down from the “top” of the renin cascade, benazepril evoked a substantial increase in RA, while decreasing AII and ALD. Bodyweight, gender and sodium intake proved the most significant covariates to explain part of the between-subject variability.

Conclusions: Our data show that benazepril markedly influences RAAS dynamics in dogs. Nonlinear mixed effect modeling helped integrating information on benazepril-induced RAAS inhibition over time and identifying the main determinants of between-animal variability. Differences in biomarkers responses reflect the high level of regulation of the renin-angiotensin cascade.

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I-30 *Samer Mouksassi* Equivalence of locally acting drugs based on pharmacodynamic data: development of a novel 1 step method and use of trial simulations to assess sources of variability and power definitive studies

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Objectives: FDA and EMA have proposed using pharmacodynamic (PD) data to assess bioequivalence (BE) of locally-acting product. Dose-scale modelling (DSM) of PD data using a 2-step approach has been proposed, where the reference product is modelled in a first step, and scaling of the test to reference product is performed in a second step. Power calculations of BE studies using DSM are challenging due to the complexity of using of 2-step approach for sample size calculation, and the lack of understanding of sources of variability responsible for the width of 90% confidence intervals (CI). A novel 1-step DSM method was developed to assess BE of locally acting product and trial simulations were performed to power studies with robustness and identify sources of variability.

Methods: PD data from the pulmonary drug albuterol (forced expiratory volume, FEV_1) and gastrointestinal drug orlistat (fecal fat excretion, FFE) were used to perform DSM of test and reference products. A novel 1-step approach was developed by simultaneously modelling the test and reference product using non-linear mixed effect (NLME) modelling techniques and by constructing nonparametric 90% CI. Trial simulations were performed to determine the sample size required to meet BE criterion and identify the most important factors (e.g., steepness of dose-response relationships, precision of E_{max} and ED_{50} parameters) responsible for the width of 90% CI.

Results: The proposed 1-step DSM method resulted in similar or tighter 90% CI as compared to the 2-step DSM method based on the current FEV_1 and FFE data. The 1-step DSM method required around 2000 bootstrap replicates to obtain stable 90% CIs. The 1-step DSM model was used to perform trial simulations to determine the most important drivers of sample size calculation. Within-subject variability in PD data and testing doses close to the real ED_{50} were identified as the most important components responsible for the width of 90% CI.

Conclusion: The novel 1-step DSM method using NLME enabled the use of trial simulations to power definitive studies and increase the likelihood of demonstrating BE. Trial simulations is the tool of choice to power studies of locally acting gastrointestinal drugs (e.g., orlistat, misoprostol, mesalamine) and pulmonary drugs (e.g., albuterol, glycopyrrolate) assuming *a priori* knowledge of the dose-response curve of the reference product is available as well as an estimate of between and within-subject variability.

I-31 *Ricardo Nalda-Molina* Stochastic Simulations Assist to Improve a Poorly Designed Clinical Study for the CSF Pharmacokinetics of Doripenem

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Objectives: To assess the impact of the addition of new subjects, with improved sampling design to the results of a previously performed NONMEM analysis of doripenem in the CSF with sampling design problems, by performing stochastic simulations including uncertainty.

Methods: A previous study (1) investigated the CSF pharmacokinetics of doripenem after IV administration to patients, using NONMEM 7.2. Briefly, the model consists of a standard two compartment model (the parameters of which were taken and fixed from the literature), plus a third distribution compartment corresponding to CSF, parameterized in terms of distribution rate constant (Kcsf) and partition coefficient (PC) which were estimated from CSF data. However, a limited sampling design including mostly one sample per subject and the lack of later samples (after 6 hours) led to a high uncertainty in the parameter estimation. Stochastic simulations of three scenarios were performed, corresponding to the 25th, 50th and 75th percentiles of the uncertainty parameter distribution obtained from the bootstrap analysis of the previous NONMEM results. Simulations and estimation of the dataset (36 patients and 47 CSF samples) with 5, 15, 30 and 60 extra patients, with one sample at 12 hours, for each of the three scenarios, were performed with NONMEM 7.2. Guided by the results of the simulations, two new patients were included in the study, with late sampling times, and a final population pharmacokinetic analysis with the full dataset was performed.

Results: The simulations showed a significant reduction in the standard error of the model parameters estimates, even with only five extra-subjects. Also, it is worth to note that the standard error reduction was more pronounced in the 75th percentile scenario, rather than the 50th percentile as would have expected. Based on the simulations we decided to include new patients in the study. However, the number of new patients we were able to include at the end was only two because of a limited time frame. The final analysis of the full dataset (2) showed a reduction of the estimates standard error (by 75% approximately). Moreover, the new parameter estimates were close to the 75th percentile scenario rather than the 50th, as the results of the simulations suggested.

Conclusions: Stochastic simulations are useful to improve the clinical study design, and inform about the impact of new subjects, and new sampling times, even when the original estimates are biased.

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I-32 *Carmen Navarro* Computer simulations of bioequivalence trials: drugs with sequential metabolism

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Iintroduction: The analyte (parent drug or metabolite) to be evaluated in bioequivalence trials is still today a controversial issue, with different solutions in EMA and FDA guidances [1], [2]. The EMA and FDA guidelines generally recommended measuring the parent drug bioequivalence, but the situations in which are recommended the measurement of metabolite are different. The objective is to evaluate which analyte (parent drug or metabolites) is more sensitive to detect changes in the quality of the problem medicinal product.

Materials and Methods: A semi-physiological model was used, including pre-systemic intestinal and hepatic metabolism and Michaelis-Menten elimination with two metabolites (first and second-generation metabolites of ASA) [3]. Different scenarios depending on the in vivo dissolution rate constant of the problem formulation and dose have been considered, in order to evaluate the loss of sensitivity of parent drug to detect differences between formulations. The studies were simulated using NONMEM VI.

Results: The plasma concentration-time population fit the experimental curves of the literature [4], so the model is considered validated. The analyte sensitive to decline in quality is the ASA in most of cases but not all of them: when there is a large difference between reference and test dissolution rate constant values, in case of 1000 mg of administered dose, SA becomes more sensitive than ASA.

Conclusions: The ASA is more sensitive than its metabolites to detect the decrease in pharmaceutical quality, but not in all cases. The measurement of first generation metabolite could provide any additional information to the parent drug.

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I-33 *Michael Neely* Non-Parametric Bayesian Fitting: A Novel Approach to Population Pharmacokinetic Modeling

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Objectives: Compared with most parametric population modeling methods, our non-parametric (NP) expectation maximization (EM) algorithm calculates exact, rather than approximate likelihoods, and it easily discovers unexpected sub-populations and outliers. However, NPEM cannot calculate credibility intervals around parameter estimates. Therefore, we tested our novel NP Bayesian (NPB) algorithm, derived from [1], that uses stick-breaking to construct a Dirichlet prior (DP) and combines the best of parametric and NP methods.

Methods: We took dosing and weight data from 35 infants enrolled in an IV zidovudine PK study as a template to simulate new observations (obs) after a short IV infusion into one compartment. We set elimination (KE) as a bimodal distribution, with means of 0.5 and 1.0 1/h and weights of 0.3 and 0.7. Volume (V) was unimodal, with a mean of 2.0 L/kg. The SD for each distribution was a CV% of 25%. Noise, ~N(mu=0,sigma=0.01), was added to simulated obs. Using the Pmetrics and rjags packages for R, plus the JAGS software [2], we compared simulated vs. predicted (pred) KE, V, and obs from our NPB and NP Adaptive Grid (NPAG) NPEM algorithms [3].

Results: The simulated (true) means (SD) of KE and V were 0.77 (0.27) and 2.03 (0.28). Obs ranged from <0.01 to 1.64 mg/L, calculated up to 8 hours after dosing, with 5–6 samples per subject. For NPB fitting, we used one MCMC chain, drawing every 10th posterior sample from iteration 10K to 10.5K. The optimal number of stick breaks (support points) for the DP was 17. The NPB weighted mean KE was 0.76 (95% credibility interval 0.73–0.79) with SD of 0.24 (0.20–0.32); weighted mean V was 1.98 (1.92–2.03) and SD was 0.30 (0.25–0.40). The NPAG weighted means (SD) of 23 support points for KE and V were 0.77 (0.27) and 2.03 (0.27). Obs vs. pred plots for both NPB and NPAG were nearly identical, with R^2 for population predictions of 0.81 and 0.81, slope 0.98 and 1.01, and intercept of 0.04 and 0.04, respectively. For posterior predictions, R^2 was 1.00, slope was 1.00, and intercept was 0.00 for both NPB and NPAG, and they each captured the bimodal distribution of KE in marginal plots. NPB parameter estimates were robust to changes in initial values, chain number, and obs noise.

Conclusions: Non-Parametric Bayesian population analysis is a novel and accurate method to estimate PK parameter values, discover subpopulations not specified a priori, and provide robust credibility intervals for all parameter estimates.

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I-34 *Thu Thuy Nguyen* Modelling the impact of fecal ciprofloxacin concentrations on fecal counts of resistant Enterobacteriaceae in piglets treated with ciprofloxacin: towards new means to control the spread of resistance?

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Objectives: The colonic flora is where antibiotic residues select resistant commensal bacteria during treatment [1]. In this prospective randomised study in piglets, we aimed to develop a pharmacokinetic/pharmacodynamic (PK/PD) model to characterize the link between ciprofloxacin (CIP) concentrations and amounts of CIP resistant Enterobacteriaceae (EB) in feces.

Methods: 29 piglets were randomly assigned to oral treatment with placebo (n = 9), CIP 1.5 mg/kg/day (n = 10) or 15 mg/kg/day (n = 10) from day D1 to D5. Fecal samples were recovered at D1, D3, D5, D7, D9, D12, D16 and D27. Fecal concentrations were measured with a microbiological assay. Fecal resistant EB were counted on selective agar with 2 µg/ml of CIP. The fecal PK model of CIP was assimilated to a one compartment model with intravenous infusion and first order elimination. The infusion rate was the daily dose of CIP with a duration of 5 days. The PD model described the fecal amount of resistant EB as the result of a saturable growth and a natural elimination. The drug effect was supposed to inhibit the elimination rate of resistant EB through an Imax model. These models were written with MLXTRAN in MONOLIX 4.1.1 [2]. The joint modeling of data from 20 piglets receiving CIP was performed by nonlinear mixed effect model. Parameters and their variability were estimated using the SAEM algorithm [3] and model evaluation was performed via goodness-of-fit plots.

Results: The proposed PK/PD model adequately described jointly CIP fecal concentrations and resistant EB counts for the 3 treatment groups. Parameters were well estimated with good precision. From the model, predictions with various CIP doses can be provided to investigate the link between doses, concentrations and amounts of resistant EB excreted. Indeed, CIP fecal concentrations increase sharply with doses and resistant EB amounts increase nonlinearly with concentrations.

Conclusion: The proposed model adequately described the data. To our knowledge, this is the first model developed on in vivo data to study the dynamic of resistance in colonic flora. This modeled relationship suggests that removing residual colonic quinolone can help control the spread of resistance [4]. The next step will be to model these data jointly with the susceptible EB counts.

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I-35 *Ronald Niebecker* Modelling of Anti-Drug Antibodies Directed Against a Monoclonal Antibody

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Objectives: Monoclonal antibodies (mAbs) are an important class of biopharmaceuticals. Due to their nature as foreign proteins, they can induce the formation of anti-drug antibodies (ADAs) in patients, which may affect pharmacokinetics (PK), pharmacodynamics and/or safety of the therapeutic mAb. Concerning the PK changes, it is generally assumed that the formation of immune complexes results in a more rapid clearance of the therapeutic mAb [1]. Population PK analyses of mAbs accounting for an immune response are sparse; usually this influential factor was incorporated as a binary variable on clearance in the covariate submodel [2]. Modelling of the immune response could facilitate more complex approaches. Consequently, the objective of the current analysis was to develop and compare different structural models for an immune response surrogate.

Methods: Data from 51 patients with solid tumours enrolled in two phase I/II clinical trials of a mAb were available for analysis. Weekly surface plasmon resonance (SPR)-based measurements (considered as ADA surrogate, given the constraints of immunogenicity analytics [1]) were performed to detect immunogenicity. The assay signal was assumed to comprise background (time-independent) and immune response-dependent signal. For the latter part linear, exponential as well as sigmoidal descriptions of the time course were compared. Modelling was performed using the PRED routine in NONMEM 7.2.

Results: According to SPR measurements, 13 patients developed an immune response. For these patients, the analysis revealed a significantly increased background signal compared to the patients not experiencing an immune response. Based on the observed time of seroconversion (i.e. ADA formation), it was possible to determine a shift factor characterising the start time of the immune response. The resulting signal increase was adequately described by linear or exponential functions. Since the available data did not provide information on the shape of the immune response-dependent signal beyond the phase of linear increase, models featuring additional complexity were not supported.

Conclusions: The development of a model describing the SPR assay signal-time profile as a surrogate of the immune response was possible. Next, the model predictions can be incorporated in population models for the therapeutic mAb to better characterise the alteration of PK caused by formation of ADAs.

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I-36 *Christoph Niederalt* The use of physiologically-based pharmacokinetic modeling in the design of pH-dependent target binding antibodies

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Objectives: Reducing the binding affinity of therapeutic proteins to their target within acidic endosomal space is a strategy to increase the half-life of these drugs [1,2]. The aim of the study was to investigate if physiologically-based pharmacokinetic (PBPK) modeling can be used to design high potency pH-dependent recycling antibodies.

Methods: The PBPK model for proteins implemented in PK-Sim® software was used with additional modifications as necessary. The pharmacokinetic data [2] of pH-dependent binding variants of tocilizumab (TCZ), an antibody against the IL-6 receptor (IL-6R), was predicted in this case study. For experiments with soluble target (hsIL-6R) in wild-type mice the standard PK-Sim® [3] model for proteins was extended by hsIL-6R binding in interstitial space (pH 7.4) and endosomal space of vascular endothelium (assumed pH 6). For experiments with effective membrane bound IL-6R (transgenic mice & cynomolgus) the standard PK-Sim® mouse & monkey models for proteins were extended by membrane-bound and endosomal IL-6R in tissue cells. The processes of biosynthesis, endocytosis & recycling were introduced. The affinity requirements of pH-dependent binding antibodies directed towards soluble and cell-surface targets was explored through simulations using the final model to help guide design of these compounds.

Results: The simulated plasma concentration time profiles of TCZ, its variant PH2 and of hsIL-6R were in good agreement with the experimental data. The plasma concentration time profiles of hsIL-6R with co-administration of TCZ and PH2 were adequately described by assuming that the in vivo affinities were ~4-10-fold different from reported in vitro values. This variance between estimated and reported affinities was true for transgenic mice and cynomolgus data also. Simulations using the final model showed that a complex relationship exists between affinity and potency for pH-dependent binding systems and higher affinity ratios at pH 6 to pH 7.4 were not always better at increasing in vivo potencies.

Conclusions: PBPK modeling can be used to guide design of pH-dependent binding variants for various targets. However, accurate translation of in vitro affinities to in vivo parameters and description of endogenous IL-6 interaction are potential limitations in the process.

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I-37 *Elisabet Nielsen* Target Attainment Analysis to Evaluate Dosing Regimens of an Oral β-Lactam Antibioic

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Objectives: In lack of data supporting mechanism-based PKPD modeling, the selection of dosing regimens within the infectious disease area is commonly based on probability of target attainment (PTA) analysis with the targets relating the drug exposure to the MIC. For β-lactam antibiotics the efficacy has been shown to be related to the percentage of the dosing interval that the free drug concentration exceeds the MIC. The aim of the current study was to (1) evaluate the sensitivity in the PTA for expected PK differences between healthy volunteers and patients (lower CL and/or higher IIV for the latter group) and (2) evaluate a method that acknowledge parameter uncertainty in the PTA analysis.

Methods: A population model was developed in NONMEM 7 based on data from 15 healthy volunteers receiving oral single doses of a β-lactam antibiotic in a randomized cross-over study with intensive PK sampling. Concentration-time profiles following different dosing regimens were simulated and PTA was determined. Simulations were performed with perturbed typical and variability parameters to represent expected parameter distributions in patients. Uncertainty in parameter estimates was acknowledged by performing simulations from a parameter distribution obtained from a non-parametric bootstrap using the sse functionality in PsN.

Results: The PK was well described by a two compartment model with first order elimination with the absorption described by a transit compartment model. Based on the data from healthy volunteers, the IIV was estimated to be between 12-26% for disposition parameters and between 12-46% for absorption parameters. As expected, the β-lactam antibiotic was more effectively dosed 3 times daily than 2 times daily in all simulation settings. When increasing the IIV in the parameters, the PTA curve becomes less steep, with lower target attainment in the high (most interesting) PTA region.

Conclusions: Differences in parameter estimates between healthy volunteers and patients will influence the shape of the PTA curve and thereby also the choice of optimal dosing regimens. Such differences should therefore be taken into consideration in the dose optimization. Simulating from a bootstrap is a simple method to acknowledge and visualize the impact of parameter uncertainty in the PTA analysis.

I-38 *Valerie Nock* Comparison of three PK/PD models for glycated haemoglobin in diabetes type 2 patients treated with lixisenatide

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Objectives: Lixisenatide, a new glucagon-like-peptide receptor agonist, is known to act on the fasting plasma glucose (FPG) and on postprandial glucose concentrations (PPG) [1]. The aim of this work was to investigate different models to mechanistically describe the effect of lixisenatide on glycated haemoglobin (HbA1c) in type 2 diabetes (T2D) patients..

Methods: Information on HbA1c values from 162 patients from 2 randomised, double-blind, placebo-controlled, parallel-group studies in T2D patients inadequately controlled on metformin and treated with doses of 5, 10, 20 or 30 µg once or twice daily was analysed using NONMEM 7.1.. Studies were sponsored by Sanofi-Aventis. Three models were investigated: (i) a turnover model (TO) with a sigmoidal inhibitory drug effect on the glycation rate (KGL), (ii) an FPG dependent lifespan model (LS) [2] and (iii) an extended version (ELS) of this model with an additional, FPG independent glycation rate (KGL2) which was linked to lixisenatide concentrations via a sigmoidal Imax model. Information on PK and PD (model for FPG) parameters from previous analysis [3,4] was used as input following a sequential modelling approach. Model comparison was guided by AIC, GOF plots, acceptable precision of parameter estimates and shrinkage..

Results: Due to stability reasons and based on estimates the lifespan of the erythrocytes was fixed to 101 d (LS, ELS), the rate of erythrocytes entering the circulation to 1.16 g/L/d (LS) and the exponent (γ) linking FPG to KGL was fixed to 0.75 (ELS). The TO model described the data sufficiently well resulting in the lowest AIC. HbA1c values were not sufficiently described when taking only FPG as a predictor into account (LS) whereas the introduction of KGL2 to the model (ELS) improved the fit considerably. The inter-individual variability on IC50 (62.8 ng/L) of KGL2 was estimated to be high (108%) possibly representing the remaining ability of insulin secretion of the patients. Additionally the ELS model enabled the separation and quantification of 2 glycation pathways, an FPG dependent and independent one. The latter, possibly being attributed to PPG, explained about half of the reduction in HbA1c..

Conclusions: For lixisenatide the TO model and the ELS model were superior compared to the LS model which originally was developed for tesaglitazar, a PPAR α/γ agonist with probably no action on PPG. The ELS model was most mechanistically motivated and enabled the quantification of an FPG dependent and FPG independent glycation pathway..

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I-39 *Yook Hwan Noh* Bioequivalence evaluation using population modeling method

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Objectives: In general bioequivalence (BE) study is conducted in healthy volunteers with serial dense blood sampling for pharmacokinetics (PK). However, some drugs are inadequate to administer to healthy volunteers mainly for the toxicity. In this case, population modeling analysis with sparse concentration data in each patient could be an alternative option. The study was designed to explore the possible implementation of modeling method for BE test especially for drugs, the BE study of which can't be conducted in healthy volunteers for ethical reason such as cytotoxic anti-cancer agents with anastrozole as a model drug, BE study in healthy volunteers was done recently.

Methods: We evaluated the bioequivalency with AUC, and C_{max} as metrics using the same concentration data sets. The plasma concentration data was obtained from a BE study conducted in the Clinical Trial Center at the Asan Medical Center (Seoul, Korea). A total of 24 healthy male Korean volunteers were enrolled and evaluated for PK analysis. Participants were randomized to receive 1 mg of the test or reference formulation, and PK parameters were calculated by noncompartmental analysis using Phoenix WinNonlin® 6.1 (Pharsight Corporation, MO, USA). The formulations were considered bioequivalent if the 90% confidence intervals of the geometric mean ratios of test to reference formulations for AUC and C_{max} were within the BE limits of 0.8 to 1.25. Nonlinear mixed-effect modeling for both formulations were also conducted using NONMEM® (ICON development solutions, Dublin, Ireland) and the results were used to characterize and compare the PK. In addition, Individual AUC and C_{max} were calculated using NONMEM®, which were used for the BE test for both formulaltions.

Results: In noncompartmental analysis, the 90% confidence intervals of the geometric mean ratios of test formulation to reference formulation were 0.96-1.08 for C_{max} and 0.93-1.0 for AUC. In modeling analysis both formulations could be best described by a two-compartmental disposition model with lag phase in absorption and the 90% confidence intervals of the geometric mean ratios of test formulation to reference formulation were 0.96-1.04 for C_{max} and 0.92-0.99 for AUC_{last}.

Conclusions: The BE test of both test and reference formulations had similar results for PK parameters such as AUC and C_{max} in both noncompartmental and modeing analysis, which suggest the possible use of modeling analysis in BE test with sparse concentration data.

I-40 *Joakim Nyberg* The robustness of global optimal designs

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Objectives: A drawback with local optimal designs (OD), e.g. D-optimal, is that the parameters of the model are assumed known. This is a strong assumption and therefore robust (global) OD has been a suggested approach, i.e. without assuming that the parameters of the model are known but instead distributions of the parameters are known [1-5].

The objective is to compare different design criteria and to suggest an alternative criterion that overcomes some of the issues with other robust design criteria, such as overweighing certain parameter values.

Methods: Six different criteria were investigated; D-optimal, ED-optimal (ED), API-optimal (API), HCD-optimal (HCD), ED-EFF-optimal (EDEFF) and B-API-optimal (BAPI). ED-EFF-optimal is a criterion that weighs each parameter sample by the corresponding D-optimal design. BAPI (Bias-API), tries to spread the design by forcing each sample to be responsible for a portion of the parameter distribution.

Two models were investigated; A one-parameter fixed effect (4 samples between 0-2 & 100 ind), exp decay model (EXP) and a two-parameter mixed effect (3 doses between 0-6 & 100 ind), Emax model (EMAX) were θ_{ED50} and ω^2_{ED50} (exp IIV of 30%) were the parameters to estimate. A uniform parameter distribution was assumed for EXP, θ_k=[2,22] and for EMAX, θ_{ED50} = [0.1,6.1]. 200 uniformly spread samples from the parameter distribution were used for the robust criteria and a D-optimal design was found for each sample. Multiple simulations and estimations (SSE)were used to check the performance of the designs.

Results: As expected, the D-optimal designs (which use the optimal design in each SSE) is slightly better (bias and precision) than the robust criteria for both models. All the robust designs except ED perform well for the EXP model, while HCD and BAPI perform best for the EMAX model.

Conclusion: ED is not performing well because the method weighs the information from each parameter sample equally (E|FIM|) and hence is too influenced by more informative samples (large |FIM| values), resulting in a less robust design. API and EDEFF perform better by evening out the importance of the parameter samples. HCD performs very well and is much faster than the other robust approaches; however HCD is likely to have problems if the optimal information over the parameter distribution is non-monotonic. The new BAPI criterion also performs well in both models and might better handle non-monotonic information; however it is slower than the HCD criterion.

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I-41 *Kayode Ogungbenro* A semi-mechanistic gastric emptying model for double peaks in pharmacokinetics using LDOPA data

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Objectives: Following PO administration, double-peaked drug concentration-time profiles in plasma can be explained by a number of different mechanisms: delayed gastric emptying; variable absorption; enterohepatic recirculation; drug secretion etc [1, 2]. Such profiles may be inadequately described by classical compartmental models and other empirical modelling approaches can used instead [1, 3, 4]. Levodopa (LDOPA, a key drug in the treatment of Parkinson's disease) demonstrates double peak profiles attributed to its effect on gastric emptying. The main objective of this work was to propose a new semi-mechanistic model for analysing LDOPA PK data taking into account effects on gastric emptying.

Methods: Data from a simultaneous scintigraphy and paracetamol absorption test with and without LDOPA was obtained from the literature [5]. Gastric emptying profiles obtained by scintigraphy in the absence of LDOPA showed constant decline. In the presence of LDOPA, emptying is interrupted for a period associated with double peaks in both the paracetamol and LDOPA PK profiles. A semi-mechanistic emptying model, with compartments for stomach, small intestine, central and peripheral compartments, was developed to describe LDOPA PK and the double peak. A feedback mechanism acting via an effect compartment links the plasma concentration of LDOPA to the rate of gastric emptying, allowing LDOPA PK to vary the rate of gastric emptying and give rise to a multiple peaked plasma PK profile.

Results: The semi-mechanistic model was applied to plasma LDOPA and paracetemol PK data with and without simultaneous analysis of scintigraphy data, in both cases giving a good fit and in the absence of scintigraphy data adequately predicting the stomach profile. The 1st order constant governing gastric emptying was shown to switch between fast and slow values at an effect compartment concentration of ~1mg/L.

Conclusions: The new semi-mechanistic model has been used to describe the double peaks observed in the plasma concentration of LDOPA due to changes in rate of gastric emptying.

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I-42 *Katie Owens* The Pharmacokinetic Profile of Intravenous Paracetamol in Adult Patients Undergoing Major Surgery: A Population Analysis

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Objectives: Intravenous paracetamol is commonly used in the post operative period as part of multimodal analgesia following surgery. [1] Paracetamol is extensively metabolised in the liver by glucuronidation, sulfation and oxidation with less than 5% excreted unchanged in the urine. [2] The aim of the present study was to determine the pharmacokinetic profile of intravenous paracetamol in adult patients undergoing major surgery and determine the time course of metabolic changes during the postoperative period.

Methods:A total of 53 patients were included in the dataset (33 patients from Cork, Ireland, 20 patients from Dunedin, NZ); 28 of the patients were men, the median age (range) was 60 years (33-87) and the median weight (range) was 74 kg (54-129). Patients were given doses of either 1, 1.5 or 2 g of paracetamol by intravenous (IV) infusion. A combination of rich and sparse plasma and urine samples were collected for up to 6 days after surgery. The samples were analysed by high pressure liquid chromatography to determine the amount of paracetamol and its glucuronide and sulfate metabolites. The population pharmacokinetic analysis was performed using Phoenix NLME. Simultaneous modelling of parent paracetamol and its two primary metabolites, paracetamol-glucuronide and paracetamol-sulfate, was conducted to estimate parameters for volumes of distribution, metabolic and urinary clearance.

Results: 53 patients contributed to a total of 4386 observations (2115 plasma concentrations and 2271 urinary excreted amounts) for paracetamol, paracetamol glucuronide and paracetamol sulfate. The pharmacokinetics of parent paracetamol were best described by a 2-compartment model with IV infusion input and linear disposition. The central volume of distribution was found to be 20.4 L/70kg, peripheral volume of distribution of 64.2 L/70kg and a intercompartmental clearance of 61.6 L/h/70kg. A proportional inter-subject error model and proportional residual error model was used. Covariates investigated included age, weight, sex, time after surgery and duration of surgery.

Conclusions: Our preliminary PK findings demonstrated that following major surgery, there were apparent increases in the metabolic conversion to paracetamol-glucuronide and its urinary clearance. Preliminary results support approved dose recommendations of intravenous paracetamol in the postoperative period, as there was no evidence of paracetamol toxicity, or down regulation of metabolic enzymes involved in paracetamol glucuronidation and sulfation.

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I-43 *Sung Min Park* Population pharmacokinetics of S-amlodipine in healthy Korean male subjects

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Objectives: Amlodipine, a third-generation dihydropyridine calcium channel blocker that has been used for hypertension and angina pectoris, is known to have inter-individual pharmacokinetic(PK) variability. The aims of this study were to develop a population PK model of S-amlodipine in healthy Korean subjects and to compare estimated parameters between two amlodipine formulations.

Methods: A randomized, open-label, two-period, crossover bioequivalence study in 30 healthy male adults was performed. All subjects were received either the test or reference formulation as a single 2.5-mg oral dose of S-amlodipine, followed by a 3-week washout period and administration of the alternate formulation. Blood samples were drawn at 0 (pre-dose), 1, 2, 4, 5, 6, 8, 12, 16, 24, 48, 96, 144, and 216 hours after dosing. Plasma S-amlodipine concentrations were analyzed using HPLC/MS/MS. A population PK analysis was conducted using NONMEM (Ver. 7.1).

Results: A 2-compartment model with zero-order absorption provided the best fit to a total of 383 concentrations from healthy subjects. Estimates of the population PK parameter were as follows; k_e, 0.019 h^{-1}; V_c, 1940 L; V_p, 515 L; Q, 102 L/h; $D1$ (Duration of zero-order absorption), 4.99 h. The visual predictive check (VPC) was performed and the result exhibited the acceptable predictive performance of the final model. No significant difference in the PK parameter estimates was observed between the two amlodipine formulations.

Conclusions: A population PK model was successfully developed and reasonable parameters were obtained. Both formulations were identical in the aspect of PK behavior. Further study will be required to find out covariates affecting the difference between the two formulations.

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I-44 *Joanna Parkinson* Translational PKPD modeling of QTc effects in dog and man

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Objectives: The aim of this investigation was to perform a retrospective pharmacokinetic-pharmacodynamic (PKPD) analysis of the heart-rate corrected QT interval (QTc) from conscious dogs and man. QTc prolongation is used as a biomarker for the potentially fatal arrhythmia Torsades de Pointes. In contrast, less is known about safety implications of QT shortening despite a recent increase in the number of drugs with this effect. It is therefore crucial to assess the translation of concentration-dependent QTc response between species, in order to make predictions for the clinical drug safety profile with regards to QTc for drug candidates.

Methods: The heart-rate corrected QT effects of 2 proprietary small molecules (one increasing and one decreasing QTc) and 2 reference drugs known to increase QTc (moxifloxacin and dofetilide) were investigated in conscious dogs and healthy volunteers. For the proprietary compounds, population PK and PD parameters were estimated sequentially - compartmental models were used to describe the PK of drugs and the final PK parameters were then used as an input for the linear PKPD model. The QTc response from dog and man at matching free concentrations were then plotted against each other. The translational relationship was confirmed using published data from reference drugs.

Results: The results showed a clear translational relationship between the QTc response of conscious dog and man. The slope was found to be approximately 1.3 ms and based on this relationship, a QTc change of approximately 7 ms in dog would correspond to approximately a 10 ms change in man. This translational relationship was used to do a prospective and retrospective prediction for clinical QTc response.

Conclusions: A consistent relationship was found between QTc in dog and man based on unbound plasma concentrations. This could be useful in prediction of clinical QTc outcome based on preclinical observations.

I-45 *Zinnia Parra* Tumour Growth Modelling In Immunotherapy

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Objectives:. A vaccine vector that targets the human papillomavirus 16 E7 antigen to dendritic cells, has shown potent immune response against tumour cell lines expressing E7 antigen in a murine model of cervical carcinoma. However a decreased in the response was observed as the time between tumour cell injection and vaccination increased [1]. The aim of the study is to develop a population model in mice able to describe tumour growth dynamics and the effect the vaccine on tumour size to better understand the mechanisms implied.

Methods: 5x105 tumour cells expressing HPV16-E7 proteins were injected into the shaved back of C57BL/6 mice in 200uL of PBS. A single dose of 50ug of vaccine or PBS (control group) was intraperitoneally administered to mice, but on different days after tumour inoculation. Tumour size presented as the average of two perpendicular diameters (mm) was measured at regular intervals. Mice were euthanatized if tumour size reached 20mm.

Results: The model developed presented the following main components: (i) Tumour progression in the animals receiving saline injection was described with an exponential model, (ii) vaccine effects were modelled assuming that vaccines triggers a non-instantaneous immune response inducing cell death. Delayed response was described with a series of transit compartments [2], and (iii) a tolerance effect dependent upon tumour size was also incorporated. A small percentage of treated animals showed, after a period of an apparent complete tumour remission, a relapse. Relapsing was tackled considering a mixture model at the level of the vaccine to trigger the adaptive immune response, and more mechanistically assuming a small but permanent memory immune response.

Conclusions: A population model able to describe the different vaccination protocol outcomes has been successfully developed. Data required of model complexities at both the typical/structural population, and the stochastic level.

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I-46 *Mélanie Pastor* Modeling of the effect of G-CSF in limiting the neutropenic toxicity of carboplatin

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Objectives: While administration of granulocyte-colony stimulating factor (G-CSF) is often used in patients receiving cytotoxic drugs to reduce high grade neutropenia, we need to increase our understanding of the effect of G-CSF in cancer patients. The aim of this work was to develop a semi-physiological model with a population pharmacokinetic-pharmacodynamic (PK-PD) approach in order to reach this goal.

Methods: Absolute neutrophil counts (ANC) were measured in 375 cancer patients receiving carboplatin over 2 cycles. Among them, 47 had G-CSF administration given as a daily or pegylated formulation. A model was built to describe ANC time course in all patients whatever the treatments they received. This model, developed in NONMEM 7.2, was inspired by the "Friberg's model" [1] with two main differences: (i) the carboplatin plasma concentration was assumed to induce cell loss from the stem cell compartment by increasing apoptosis; (ii) the feedback mechanism regulating ANC was a function of the free circulating concentration of G-CSF (endogenous and exogenous when applicable), which was modeled using a previous compartmental model from Krzyzanski et al. [2] with linear (renal) and non-linear elimination (receptor binding to neutrophils and internalization). A modification of their model was made in order to improve data fitting, in line with the observations made by Quartino et al. [3]. As in physiological conditions, free G-CSF could stimulate stem cell proliferation and accelerate maturation time, with two different maximum effects and potency parameters.

Results: Our population PK-PD model well described neutrophil time course after carboplatin administration in all patients as assessed by Visual Predictive Checks and computation of the percentage of patients undergoing high grade neutropenia. High grade neutropenia was much more frequent in patients who did not receive G-CSF. Simulations performed with the model shed light on the differences between G-CSF formulations and dosage regimens (time and frequency of administration) and the consequences on their effects.

Conclusions: The population PK-PD model described here allows a good description of neutrophil time course in 375 patients with various tumors treated with carboplatin, whether or not they received G-CSF. This model appears more physiological than the traditional ones and gives new directions to increase our understanding of the effect of G-CSF in cancer patients.

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I-47 *Pavan Vajjah* Prediction of serum and cerebrospinal fluid concentrations of carbamazepine: An application of parameter estimation and the permeability limited 4-compartment brain model in Simcyp®

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Objective: The objective of the work was to predict the cerebrospinal fluid (CSF) concentration of carbamazepine (CBZ) in humans using the permeability-limited 4-compartment brain model in the Simcyp® Simulator V11 and the default library values for populations related values.

Methods: A total of 108 steady state serum CBZ and carbamazepine-10, 11- epoxide (CBE) and 12 single point pre-dose CSF concentrations from 14 male individuals (age 14 - 44 years, dose range 600-2000mg daily in 2-4 divided doses) were extracted from a literature report [1]. In the first stage of the modelling, the expectation maximisation algorithm within the Simcyp parameter estimation (PE) module was used to optimise the CBZ and CBE parameters using dose normalised concentrations of CBZ and CBE (a Top-Down approach). Subsequently, in the second stage, the retrograde model was used for parent drug to calculate intrinsic clearance values from oral clearance (CLpo) for CBZ metabolism by CYPs 3A4, 3A5 and 2C8, the CLpo for the metabolite was used directly as an *in vivo* input into the Simcyp Simulator (a combination of the Top-Down and Bottom-Up approaches). In the third stage, the model and fitted parameters were used to predict the concentration of CBZ in CSF using the permeability-limited 4-compartment brain model in the Simcyp Simulator assuming passive diffusion of CBZ into brain [2] (a Bottom-Up approach). The simulated CSF concentrations were compared with the observed values.

Results: A full PBPK model with first order absorption provided the best fit to the CBZ serum data. The metabolite data was well described by a minimal PBPK model. A combined error model was the best residual error model both parent and metabolite data. The final model was evaluated using a visual predictive check. The estimated CLpo of carbamazepine was (mean (CV%)) 6.39 (56) L/h. The estimated ka was 0.09 (63) h^{-1}. The estimated CLpo for the metabolite was 22.27 (50) L/h. An initial analysis, in agreement with previously published experimental data [3], shows that active transporters may not influence the transfer of CBZ into CSF. The observed CSF concentrations of CBZ (in literature) fell within the 95 percentile interval of the model predictions, all predicted values were within 2.1-fold of observed values.

Conclusions: The model successfully predicted the concentration of CBZ in CSF using the three stage modelling process that combined the To-Down and Bottom-Up approaches. An application of the permeability-limited 4-compartment brain model within the Simcyp Simulator was demonstrated.

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I-48 *Kirill Peskov* Mechanistic modeling approach relating human gut microbial community to physiologically-relevant biomarkers

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Objectives: The adult human gut houses a microbial community which contains a large number of bacterial species. It is well-known now that the actual composition of this community has a significant influence on human vital functions and may be an important determinant of various pathologies (*e.g.*, obesity, inflammation). However, the mechanisms controlling the assembly of gut microbiota and its relationship with host human tissues remain poorly understood. This paper represents a first attempt in developing an integrated quantitative understanding of factors relating gut microbiota to measures of physiologically-significant blood plasma biomarkers.

Methods: Based on the results of Turnbaugh. *et al.*, 2009, showing that the human gut microbial community is typically formed by two bacterial phyla (Fermicutes and Bacteroides), we developed various sub-models describing generalized metabolic peculiarities of these bacteria, their sensitivity to various nutrients, and processing of endpoint metabolites such as short-chain fatty acids. Individual sub-models were integrated to provide a unified model of microbiota relationships with host tissues. Model predictions were verified against experimental data from the literature, on qualitative and quantitative gut microbial composition, biochemical characterization of particular bacteria, and results of gnotobiotic mice colonization by various microbial cultures.

Results: All individual sub-models provided adequate descriptions of isolated interactions. The integrated model provided good descriptions of literature-reported changes in butyrate, acetate and propionate in response to different bacterial composition (in accordance to the data published by Mahowald *et al.*, 2009). It was shown that different steady-state ratios of short-chain fatty acids produced by one or another microbial composition can be considered as risk factors for obesity.

Conclusions: A mechanistic model of the relationship between human gut microbial community and host tissues was developed. The model can be used to evaluate the potential effect of various compositions of microbial community to the steady state ratios of short-chain fatty acids and *in silico* testing of possible therapies related to interventions and changes in gut microbial composition.

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I-49 *Klas Petersson* Simultaneous modeling of prolactin data following administration of seven D2–receptor antagonists in rats; Model-based in vitro – rat – human scaling

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Objectives: Prolactin elevation is a common side effect of compounds exhibiting antagonism at dopamine D2 –receptors. The time-course of prolactin can be described by a semi-mechanistic model [1] and the estimated potency of the prolactin elevating effect has been shown to correlate with the in vitro values of D2 –receptor affinity in humans on a compound level [2]. The aim of this work was to investigate the same correlation in rats and the potential use of rat data in bridging the in vitro and clinical data

Methods: Risperidone, olanzapine, remoxipride, haloperidol, JNJ-37822681 , JNJ-16157700 , JNJ-39269646 or vehicle were administered for two weeks to groups of 12 Sprague-Dawley rats; six males and six females. Six prolactin samples were taken on day 1 and day 14, and PK samples were collected at the same time points in satellite animals. PK models were developed for all compounds; these were subsequently used to drive a simultaneous fit of an agonist-antagonist interaction model [1] to the prolactin data from all compounds. The estimates of prolactin elevation potency were compared to in vitro values of affinity to rat D2-receptors as well as corresponding potency parameters obtained from human data.

Results: The agonist-antagonist model could adequately describe prolactin data also from rats. Turnover of prolactin in rats was estimated to 8 minutes which is similar to published values [3]. The estimate potency values correlated with in vitro values for rat receptor affinity (R2 =0.58) and to human estimates of the same parameter (R2=0.96).

Conclusions: The AAI model could be applied across species. Estimates of prolactin elevation potency parameters correlated to a higher degree with corresponding potency estimates from human data than in vitro values of rat D2-receptor affinity. The correlation with in vitro values was weaker than found in human; this could be due to more uncertain estimates in rat because of less data. The same compound that was and outlier in the human data was also found to differ in the rat data.

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I-50 *Chiara Piana* Non-adherence to antiretroviral combination therapy in HIV-infected children

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Objectives: Suboptimal adherence to antiretroviral therapy is the most common cause of viral resistance. Despite the magnitude of this problem, precise measures of forgiveness to non-adherence for antiretroviral combination treatments are still lacking. Furthermore, a distinction between the impact of different patterns of non-adherence, such as treatment interruptions or delays in dose intake, has never been performed in a systematic manner. The aim of this analysis is to assess the impact of different patterns of non-adherence on treatment outcome for the antiretroviral combinations currently used as first-line therapy in HIV-infected children.

Methods: Simulation scenarios were evaluated using a hypothetical population of HIV-infected children (n=100) between three months and eleven years. Published pharmacokinetic and pharmacodynamic models were integrated with an established model for viral replication to predict treatment outcome based on different degrees and different patterns of non-adherence to therapy. A logistic regression was used to incorporate the relation between sub-therapeutic drug levels and the probability of developing resistance. The duration of the hypothetical trial was 24 weeks. Viral load at the end of the trial was considered as primary endpoint.

Results: Preliminary results suggest that non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens (efavirenz-lamivudine-abacavir) are susceptible to repeated treatment interruptions of one or two weeks, while allow for delays in drug intake up to 6 hours.

Conclusions: Despite its relevance in therapeutics, the degree of forgiveness of antiretroviral combinations has not been assessed in a quantitative manner. Our results show that simulations can be applied as a tool to explore the impact of different patterns of non-adherence to combination treatment. The use of a model-based approach provides a framework to optimise dosing regimens in paediatric patients and to guide regimen choice taking into account different patterns of adherence.

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I-51 *Sabine Pilari* Mathematical Model of Homeostasis of Endogenous Hormones Following Hormone Replacement Therapy

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Objectives: Hormone replacement therapy (HRT) is widely used to antagonize low levels of endogenous hormones as e.g. in menopause, hypogonadism, and hypothyroidism. In the determination of the pharmacokinetics and bioequivalence of exogenously administered hormones the levels of endogenous hormones has to be taken into account. Current guidelines recommend the analysis of time matched differences between observations under placebo and active treatment in cross-over studies. However, the exogenous introduction of hormones may lead to a shutdown or down-regulation of the endogenous hormone production that may result in constantly declining endogenous hormone concentrations under active treatment. Not taking into account the dynamics of this hormonal interplay and feedback mechanism thus may lead to a bias in AUC and volume of distribution of exogenously administered hormones. Consequently, bioequivalence may falsely be concluded which increases patient risk.

Methods: Exemplary for Testosterone homeostasis, we develop a mechanism-based semi-physiological model to describe the down-regulation of endogenous Testosterone and its metabolite 5alpha-Dihydrotestosterone (DHT) following oral Testosterone replacement therapy. To distinguish exogenously introduced and endogenously produced Testosterone, we particularly make use of extensive measurements of Testosterone and DHT at baseline (prior to HRT), under treatment, and in the washout period. Our model further incorporates the most relevant processes involved in the maintenance of Testosterone homeostasis, i.e., circadian rhythm of endogenous Testosterone production, binding of Testosterone and DHT to sex hormone binding globulin (SHBG) as well as Testosterone feedback on SHBG levels.

Results/Conclusions: We demonstrate that HRT may lead to a shutdown or down-regulation of endogenous hormones. Current guidelines acknowledge the influence of endogenous hormone levels but do not adequately reflect the importance of the temporal dependency. In order to quantify and predict the impact of HRT on endogenous hormone homeostasis, it is indispensable to extensively collect data prior to HRT, under treatment as well as in the washout phase. Alternatively, the use of radio-labeled hormones or additional enrollment of patients without an endogenous production would make it possible to distinguish exogenous and endogenous hormone levels but are likely beyond the capacities of typical phase I units.

I-52 *Venkatesh Pilla Reddy* Translational PKPD modeling in schizophrenia: linking receptor occupancy of antipsychotics to efficacy and safety

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Objectives: To link the brain dopamine D2 receptor occupancy (D2RO) of antipsychotic drugs with clinical endpoints of efficacy and safety to assess the therapeutic window of D2RO.

Methods: Pharmacokinetic-Pharmacodynamic (PK-PD) models were developed to predict the D2 receptor occupancy of antipsychotics. We consider the following currently available atypical antipsychotic drugs: risperidone, olanzapine, ziprasidone, paliperidone, and a recent Phase II test compound (JNJ-37822681). Haloperidol (typical antipsychotic drug) was used as a reference drug to compare the efficacy and safety profiles. Step 1: Patient-specific steady-state concentration was calculated using the post-hoc empirical Bayesian estimate of clearance. Step 2: D2RO was predicted for each patient with empirical and mechanistic-based models using observed D2RO or in vitro (ki values, plasma/brain protein binding) data. Step 3: D2RO was linked to the clinical endpoints of efficacy (Positive and Negative Syndrome Scale, PANSS) and safety (extrapyramidal side effects, EPS). Step 4: Effective D2RO for good clinical efficacy (30% reduction in PANSS score) and minimal EPS events were computed using the model parameters.

Results: Predicted D2RO was in agreement with clinically observed D2RO at relevant antipsychotic doses. The effective D2RO required to achieve 30% reduction in PANSS from baseline score was in the range of 50-70%. Above 80% D2RO, incidence rates of EPS increased sharply.

Conclusions: This modeling framework provides a valuable tool to characterize the relationship between D2RO and clinical effects of antipsychotic drugs and to predict the optimal human dose for new antipsychotic drugs.

I-53 *Elodie Plan* Bayesian Joint Modeling of Bone Mineral Density and Repeated Time-To-Fracture Event for Multiscale Bone Systems Model Extension

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Objectives: A physiologically-based multiscale systems (PBMS) model has been used to describe therapeutic effects in postmenopausal (PM) osteoporosis and other related diseases [1, 2]. This model has been expanded to describe bone-related effects associated with estrogen loss during menopause transition [3]. An extension to include fracture risk would broaden its utility in predicting outcomes affected by disease progression and drug intervention. Fracture risk has previously been associated with bone mineral density (BMD) [4]; however, studies rarely exceed 6 y in observational period length or consider menopause as the onset of the disease.
Our aim was to develop a model simultaneously characterizing BMD and fracture risk based on time since final menstrual period (FMP), in order to extend the PBMS model.

Methods: Publicly available NHANES datasets (demographics, dual energy X-ray absorptiometry, and osteoporosis questionnaire) [5] were accessed to combine data from 1439 PM women, each contributing 1 femoral neck BMD measurement at the time of examination. All non-trauma fractures reported since the age of 50 were included and represented 137 events over a maximum observation range of 35 y. A piecewise linear regression model based on a recent study [6] was applied to predict BMD time-course relative to FMP for each woman. A repeated time-to-event (RTTE) model [7] including time-varying BMD as a predictor was fit to the fractures. The BMD and RTTE analyses were performed simultaneously in WinBUGS 1.4.3 with a Component Pascal ODE specification and a LSODA solver [8].

Results: The estimated population BMD baseline was 0.8 g/cm2, which is consistent with other studies. The profile was satisfactorily described; obtained transmenopausal, PM, and final slopes were -1.8, -1.2, and -0.3%/y, respectively. Covariate effects (BMI, ethnicity, and FMP age) were of similar magnitude than previously reported. The initial posterior median of the fracture hazard was quantified as 0.007 (95% credible interval 0.004-0.011); the associated random effect significantly decreased once the BMD effect was introduced. The RTTE component was integrated into the PBMS model, varying with BMD expressed here as a turnover model linked to osteoblast and osteoclast functions, allowing for age and FMP-related estrogen declines to be associated with changes in fracture rates.

Conclusions: The addition of fracture probability to the PBMS model enables the characterization of a primary endpoint used in osteoporosis clinical trials.

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I-54 *Bart Ploeger* Investigation of a Data Transformation Procedure to Improve Identifiability of Efficacy and Potency: Application to Continuous Elevated Plus-Maze Data in Rats

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Objectives: Many biological variables are not normally distributed, which makes visual data exploration challenging and affects the performance of non-linear mixed effect modeling. Our objective was to develop a data transformation method to facilitate analysis of non-normally distributed data. The effect of the low-trapping, NMDA channel blocker, AZD6765, on the time that prenatally stressed (PNS) animals spent in the open arms of an elevated plus maze (EPM) is used as a case study. The EPM is a plus-shaped maze with 2 open and 2 closed arms. An increase in exploration of the open arms by PNS rats may reflect antidepressant effects.

Methods: Dose ranging, continuous data obtained in the EPM test with male PNS rats receiving a single dose of AZD6765 or saline ip were used with 5-6 repeated measurements up to 9 weeks postdose. The saline treatment group consisted of a non- PNS and a PNS subgroup. An iterative data transformation procedure was followed by calculating: 1) the cumulative sum of time in open arms of the EPM at each time point; 2) the natural logarithm of cumulative sum of time in open arms at each time point. For the analysis of the transformed data, a stepwise modeling approach was followed: 1) the baseline curve (non-PNS) was described; 2) PNS effect on baseline curve was evaluated; 3) the drug effect was assessed.

Results: After the first step in the data transformation, a consistent trend in the data for all treatment groups was obtained: the number of 0 values in the data was reduced and the variability in the data was decreased. Following the second step a close to normal distribution was obtained and a comprehensible PNS effect and dose response was observed. Model development using the transformed data resulted in an adequate description of the dose-response relationship and the observed variability. Potency and efficacy of AZD6765 were quantified.

Conclusion: Data transformation calculations enable data to be converted into a more readily available format that provides a visual representation and allows additional analysis. Data transformation can be applied iteratively and each transformation can produce a different perspective that may provide greater insight and understanding. With the data transformation procedure presented here, potency and efficacy of AZD6765 in the EPM data could be estimated.

I-55 *Arnaud Quelin* How Anti-cancer Targeted Therapies Used in Combination Interact? Analysis with a Semi-mechanistic Model of Minimal Signalling Networks

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Objectives: Targeted agents are specific inhibitors of signalling and metabolic pathways used in oncology to counteract tumour proliferation and angiogenesis. They were developed to offer an efficient and safe alternative or complement to cytotoxic chemotherapies [1]. Nevertheless, their efficacy may be lower than expected due to cross-talks between signalling cascades, resulting in the over-activation of one pathway after the blockage of another. There is a rationale to use agents in combination, targeting several pathways at once. This work aims to theoretically characterize interactions of targeted agents used in combination in minimal signalling networks and the impact on the therapeutic response using a semi-mechanistic pharmacodynamic model.

Methods: Three enzymes X, Y, Z (in either inactive or active state) interacting on either serial or parallel pathway with or without feedback loops were considered. Two drugs D1 and D2, given as continuous infusions could affect the activation of X and Y enzymes.
In each case, the system and the action of both drugs on the system were described by 6 ordinary differential equations. Response surfaces were computed to quantitatively evaluate the magnitude of the combined effect. Sensitivity analyses were performed to identify the most influential parameters. Simulations, graphics and analyses were performed using R software.

Results: 32 different pathway structures were considered (128 with feedback loops). including 16 "coherent" cases where both drugs trigger the same overall effect ;and 16 "non-coherent" cases where drugs trigger opposite overall effect. Non trivial response surfaces were explored at steady state enabling theoretical determination of the best drug combinations and ranges of neutral combinations for which no difference with the baseline activity level exist. When respectively negative or positive feedback loops are added to the network, oscillations or increasing steepness of the response were observed, as previously reported in [2].

Conclusions: Even in a minimal setting (only 3 enzymes), the pathway structure may result in non-trivial response. It is therefore determinant to understand the signalling network and the eventual cross-talks in order to optimise how targeted agents should be combined.

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I-56 *Christian Hove Rasmussen* Pharmacokinetics of concentrated insulin mixtures: a biosimulation approach

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Objectives: Mixtures of soluble and crystalline insulin aspart are currently used in formulated concentrations of 100 U/mL. The purpose of this study is to predict the effect of increasing the concentration of the insulin up to 5 times on the observed pharmacokinetics. An increase in insulin concentration is relevant for obese or insulin resistant subjects since it minimizes the injection volume or the number of injections required for administering a given dose.

Methods: A variety of data from the literature was used to identify the mechanisms governing the absorption process, including images from micro CT scanning, histological cross sections, and measurements of subcutaneous blood flow. The involved mechanisms included dissolution of insulin crystals, self-association of soluble insulin, degradation of both crystalline and soluble insulin in subcutis, and a flow-dependent absorption rate. Most of these processes were characterized using parameters determined from separate experiments and the processes were combined in a biosimulation-type model [1]. To test the performance of the model and identify remaining parameters, individual pharmacokinetic profiles from 19 type 1 diabetic subjects having received soluble human insulin, insulin aspart and biphasic insulin aspart (crossover design) [2] were used to perform a population-based pharmacokinetic analysis in MONOLIX.

Results: The model was able to describe the individual profiles of the subjects using reasonable physiological parameter values. Using these parameters, insulin concentrations of up to 500 U/mL were simulated. The overall absorption process was found to be significantly slower for higher concentrations compared to 100 U/mL. Thus, cmax was lower for both soluble and crystalline insulin and, additionally, a reduction in bioavailability was observed for crystalline mixtures. Both effects were predicted to be most pronounced for human crystalline insulin.

Conclusions: Concentrated insulin mixtures were predicted to be more protracted than 100 U/mL formulations with observed reductions cmax and in some cases reduced bioavailability. Thus, concentrated formulations of insulin are not predicted to be bioequivalent with U100, and subjects using crystalline insulins switching from 100 U/mL to e.g. 500 U/mL would possibly need to adjust their dose. The findings for soluble human insulin correspond with results from two clinical studies for 500 U/mL human insulin [3, 4].

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I-57 *Dinko Rekic* External validation of the bilirubin-atazanavir nomogram for assessment of atazanavir plasma exposure in HIV-1 infected patients

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Objectives: Atazanavir increases bilirubin levels in patients in a concentration dependent manner. Due to less costly and readily available assays, bilirubin has been proposed as a marker of atazanavir exposure. In this work a previously developed nomogram, based on a indirect response bilirubin PK/PD model, for detection of sub-optimal atazanavir exposure is validated against an external patient population [1].

Methods: The bilirubin nomogram was validated against an external dataset of 98 matching bilirubin and atazanavir samples from 76 HIV-1 infected patients. The predictive properties of the nomogram were validated against observed atazanavir plasma concentrations. Additionally the use of the nomogram to detect non-adherence was investigated by simulation.

Results: The bilirubin nomogram predicted underexposure in the external patient population with a sensitivity of 100% (95% CI: 28-100) and a specificity of 91% (95% CI: 84-96). The bilirubin nomogram and monitoring of atazanavir concentrations had similar predictive properties for detecting non-adherence based on simulations. Although both methods performed adequately during the period of non-adherence they had lower predictive power to detect past non-adherence episodes. The nomogram had significantly higher negative predictive value (98% [95% CI: 97-99]) compared to atazanavir measurement (91% [95% CI: 89-92]) in detecting non-adherence in patient secretly taking a dose just before a monitoring event after a period of non-adherence.

Conclusions: Using the bilirubin nomogram for detection of sub-optimal atazanavir exposure in patients is a cost-effective alternative to routine measurements of the actual atazanavir exposure in plasma. Its application may be useful in clinical settings especially so in resource-limited areas.

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Disclosure
Daniel Röshammar is a current employee of AstraZeneca. However, this work is not sponsored by AstraZeneca or any other pharmaceutical company.

I-58 *Sylvie Retout* Prediction of occurrence of thrombocytopenia to select Phase 1b dose and dosing regimen for a selective inhibitor of p53-MDM2 in patients with solid tumors

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Objectives: RG7112 is a selective inhibitor of p53-MDM2 binding that frees p53 from negative control, activating the p53 pathway in cancer cells leading to cell cycle arrest and apoptosis. Data collected in a Phase Ia program reported some occurrence of delayed thrombocytopenia (TCP) for patients receiving doses of RG7112 for 10 days *quo die* every 28 days generating exposures at or near the anticipated expected therapeutic range. The aim of this study was to develop a PK/PD model describing the time course of platelets after RG7112 and to identify doses and dosing regimens that would maintain the exposure into the therapeutic range while limiting the occurrence of TCP in Phase Ib.

Methods: The analysis included 1141 platelets observations from patients receiving RG7112 doses on a 28 day cycle basis, with administrations every day during either 10 days (N=70, 30 mg to 3900 mg) or during 5 days (N=22, 2500 mg). Individual concentration-time profiles were predicted from a previous population PK analysis and a semi-mechanistic model was used to describe the platelet time course. This model was developed pre-clinically to analyze platelet changes in different species receiving RG7112; it involves 5 compartments to link the progenitors in bone marrow to platelets in circulation via a maturation process [1]. The parameters were estimated using NONMEM 7.1 (FOCE INTER). Due to sustained thrombocytopenia observed in some patients, an effect compartment was used to account for a potential accumulation of the drug at the site of action. Model performance was assessed using both goodness of fit plots and posterior predictive check. Then, for different daily doses (1500 mg to 5000 mg) and regimens (28 day cycles with daily doses during 3, 5, or 10 days), we investigated by simulation the tradeoff between the percentage of patients with TCP in the first cycle and the percentage of patients above a given threshold of exposure for anti-tumor activity.

Results: The model well characterizes the platelets time course including the nadir and it shows good predictive performance of occurrence of TCP. The simulations show that, for less than 20% of patients with TCP, 4500 mg daily of RG7112 during 3 days would provide the best benefit/risk ratio.

Conclusions: A robust model of the relationship between the PK of RG7112 and its effect on platelet time course has been developed. It provides a robust quantitative tool to support the dose and dosing regimen selection for future studies.

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I-59 *Benjamin Ribba* A model for low-grade glioma tumor growth and response to chemotherapy and radiotherapy

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Objectives: To develop a tumor growth inhibition model able to describe the evolution of diffuse low-grade gliomas (LGGs) growth dynamics in patients treated with chemotherapy or radiotherapy.

Methods: Model building was performed using longitudinal tumor size (mean tumor diameter) data assessed through imaging techniques in 21 patients treated with first-line PCV chemotherapy. The model was formulated under a population approach as a system of ordinary differential equations incorporating tumor-specific and treatment-related parameters, that reflect the response of proliferative and quiescent tumor tissue to treatment. The model was then applied to the analysis of longitudinal tumor size data in 24 patients treated with first-line temozolomide chemotherapy and in 25 patients treated with first-line radiotherapy. Monolix was used to estimate the population and individual parameters.

Results: The model correctly predicted individual tumor response profiles before, during and after PCV chemotherapy. The same model structure was successfully applied to describe tumor size dynamics in patients treated with temozolomide chemotherapy or radiotherapy. Tumor-specific parameters were consistent across the three treatment modalities.

Conclusions: We developed a tumor growth inhibition model able to describe LGG tumor size evolution in patients treated with chemotherapy or radiotherapy. In the future, this model could constitute a rational tool to conceive more effective chemotherapy schedules.

I-60 *Nikita Rodichenko* Multimodal Physiologically-Based Modelling and Analysis of Kinetics of Drug-Delivery with Modular Nanotransporters (MNT)

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Objectives: The modular nanotransporters (MNT), a recombinant multidomain protein, used for delivery of various cytotoxic agents (radioisotopes, photosensitizers) to solid tumours and metastases [1-3] is currently in pre-clinical evaluation. This study is aimed at assessing delivery kinetics and tumour-specificity of the MNT, and developing a physiologically-based pharmacokinetic model for estimating overall tumour drug exposure, cytotoxicity, and efficiency for various cytotoxic agents and doses. A framework and efficiency criteria are also developed for future population pharmacokinetic analysis.

Methods: Intracellular kinetic multi-compartmental model was constructed and evaluated in MATLAB. Overall tissue distribution model was constructed and evaluated using custom C++ code and NVidia CUDA GPU parallel computing framework. Parameter estimation for intracellular kinetic model was done in MATLAB using Global Optimization Toolbox. Parameter estimation for tissue distribution model was done using custom global optimization routines. Both extracellular and intracellular processes were incorporated into single model and evaluated using CUDA framework.

Results: A method for multimodal estimation of therapeutic efficiency and specificity of tumour-targeting MNT is proposed. Using this method, a model for estimation of therapeutic efficiency and specificity of radioisotope-carrying MNT against dose and radioisotope type was developed. After estimating the model parameters with experimental data, a panel of specificity and efficiency dependence on dose and isotope type was derived. To efficiently carry out computations, a high-performance parallel-computing software for evaluation of tissue distribution of MRT was developed.

Conclusions: Physiologically-based modelling of MNT tissue distribution and intracellular trafficking kinetics allowed preliminary estimation of therapeutic efficiency and tissue-specificity of various MNT-drug conjugates based on limited experimental data. Due to physiologically-based nature of this approach, it allows translation to various organisms, including human, for model-based assessment and evaluation of clinical trials.

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I-61 *Rikke Meldgaard Røge* Integrated model of glucose homeostasis including the effect of exogenous insulin

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Objectives: Insulin therapy for diabetes patients is designed to mimic the endogenous insulin response of non-diabetic subjects and thereby generate normal or near-normal blood glucose levels. In order to regulate the blood glucose in insulin-treated type 2 diabetes mellitus (T2DM) patients, it is important to predict the effect of exogenous insulin on blood glucose. Thus the aim of the study was to develop a model for predicting the 24 hour glucose profiles for T2DM patients and its relation to exogenous insulin administration.

Methods: Data from two trials were included in the analysis. In the first trial two meal tolerance tests (MTT) were performed in 13 T2DM patients. In both MTTs insulin were administered at breakfast and dinner. The insulin was given in the form of biphasic human insulin in one MTT and in the form of biphasic insulin aspart in the other. In the second trial two MTTs were performed in 16 T2DM patients. Biphasic insulin aspart was given immediately before breakfast, lunch, and dinner, but the insulin mixture administered at dinner differed in the two MTTs.
A semi-mechanistic, integrated glucose-insulin (IGI) model has previously been developed to describe MTTs for T2DM patients. The IGI model consists of glucose and endogenous insulin compartments and control mechanisms in the form of effect compartments [1]. The model was extended to allow incorporation of exogenous insulin and its effects on blood glucose. A previously published pharmacokinetic model for insulin aspart [2] was integrated in the IGI model assuming that the effect of insulin aspart was the same as endogenous insulin. The data was analysed using NONMEM7.

Results: The IGI model was extended to include the effect of exogenous insulin. The volume of distribution and clearance of exogenous insulin was initially fixed to the parameters previously obtained for endogenous insulin [1]. However, re-estimating the volume of distribution gave a significant drop in the objective function value. A significant drop in the objective function value was also achieved by including a delayed inhibitory function of glucose concentration on glucose production.

Conclusions: The IGI model was successfully extended with a component for exogenous insulin. The extended IGI model was able to describe the 24 hour glucose profiles of T2DM patients treated with exogenous insulin. This makes the model a useful tool for clinical trial simulation and for predicting effects of different insulin mixtures.

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I-62 *Hyerang Roh* Quantitative assessment of drug response in male patients with severe nocturia receiving a combined medication of solifenacin and tamsulosin

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Background: Nocturia, defined currently by the ICS as the complaint that an individual has to wake at night one or more times to void [1], is a common disorder affecting both elderly(over 70 years) men and elderly women[1-3]. It is known that increased urination frequency, 24-hr urine volume and nocturnal urine volume are the major symptoms of nocturia, and some researchers have reported that a combined medication of alpha 1 blocker and anticholinergic drug provides a better therapy for nocturia patients with benign prostatic hyperplasia than traditional mono-therapies [2,4].

However, so far there has been no method that is able to quantitatively evaluate the drug effect on the improvement of symptoms. A nonlinear mixed effects model, by quantitatively describing the time course of drug response and incorporating random individual differences, can become a solution for this problem and help understand the characteristics of the change in drug effect or disease status over time.

Objectives: With urination frequency data observed from dysuria patients, this study was intended to develop a quantitative method that can provide a time course of predicted drug response for the period not only after a short-term treatment but also after a long-term treatment. In particular, it aimed at estimating the rate of drug effect reaching the maximum drug effect, and up to how much the symptom can be reduced at the maximum effect, in an effort to provide the supportive information in designing an optimal treatment plan.

Methods

1. Data
To quantitatively assess the improvement of combined medication of alpha 1 blocker and anticholinergic drug for male patients with severe nocturia, we selected male patients with more than 3 times of nocturia a day who was treated with tamsulosin (harnal^{R}) as an a1 blocker and solifenacin (vesicare^{R}) q.d. as an anticholinergic drug with the same dose amount q.d. Data were collected for three periods, before the medication, 3 months and 6 months after starting the medication. Obtained data were not from the clinical trial but from the real patients treated in outpatient clinics, which were collected using frequency volume chart (FVC) from the Department of Urology of Chung-Ang university Hospital, collaborated with the department of Urology of Severance Hospital Seoul, Korea.

2. Time varying urination frequency with count model.
To estimate the frequency of urination, a count model with Poisson distribution was used where the urination was considered as an event and the lambda(λ) was described as an expected mean

urination frequency in a certain time interval [5]. Modelling was performed using NONMEM 7.2. Several cosine functions were combined to describe the periodical changes of urination frequency over 24 hours for the data obtained before the drug treatment starts (Placebo model).

To reflect the multiple-dose drug effect on the decline of patients' urination frequency, without loss of generality, the concentration versus time curve of one-compartment pharmacokinetic model for an oral dose was used to describe the periodic nature of the drug effect whose values will be the same every 24 hrs of dosing interval at steady-state.
To consider the decreased change in baseline urination frequency due to cumulative drug effect as the treatment period goes by, concept of "drug progression (K_{dp})" was applied by assuming the exponential decrease of baseline lambda over the treatment time (day) up to BB, where K_{dp} is the rate constant (1/day) accounting for the exponential decrease and BB the maximum decrease expected.

Then, the overall lambda was described as a multiplicative function of placebo model, drug effect model, and drug progression model, multiplied by inter-individual random effect.
Using these concepts, we described the characteristic nature of the time course of urination frequency which is fluctuating over a day but is decreasing overall with treatment time.

Results

1. Data
A total of 20 male patients over the age of 18 were included in this study.

2. Time varying urination frequency with count model.
The model that best described the mean urination frequency patterns before the medication (Placebo model) was the sum of cosine functions with circadian rhythms, composed of 8- and 24-hour periodic functions. The baseline of lambda or mean urination frequency in this model (i.e., period 1) was 1.03.
In terms of drug effect, a similarly decreasing and increasing tendency in mean urination frequency was observed in data obtained in period 2 and 3. An inverse Bateman function adjusted for steady-state well described this tendency in time course of drug effect. The hypothetical elimination rate constant (k10) relevant to drug effect, not the actual elimination rate constant of drug, was 0.000155 (1/time) and hypothetical absorption rate constant (K01), not the actual absorption rate constant, was 0.000591 (1/time).

When it comes to the drug progression effect, K_{dp}, the rate constant accounting for the exponential decrease in baseline lambda, was 0.0319 (1/day), and BB, the coefficient of exponential function that indicates the amount that can be maximally reduced, was 0.229. In this case, $t_{1/2}$ associated with the improvement through the given medication was predicted to be 22 days (= 0.693/0.0319), meaning the baseline urination frequency can be reduced by 11.5% (= 50% of BB = 50% of 0.229) in 22 days. Thus, after about 110 days (= $5t_{1/2}$) of treatment, the reduction in urination frequency is expected be reached the maximum of 22.9%, with no more drug effect or improvement of frequent urination symptom expected beyond that time.

Conclusions: The present results showed that the developed model described the data adequately and provided the useful information that can be used for predicting the time course of treatment effect. It is hoped that the model developed can be used to assess the improvement of symptom of voiding at night and frequent urination systemically. However, this is the preliminary result and further analyses will be needed including covariates analysis that can characterize individual differences in drug effect across patients, so that the model can be used to provide tailored information for each individual patient. Since not only urination frequency but also 24-hr urine

volume and nocturnal urine volume are among the three major symptoms of nocturia [6], further analyses including 24-hr urine volume and nocturnal urine volume should be conducted in the future. If an appropriate model incorporating all three symptom indices were built, it would become a more accurate and useful tool offering a reliable basis for clinicians to make a better decision and set an optimized treatment plan for clinical outcome and ultimately better quality of life for patients.

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I-63 *Rachel Rose* Prediction of the Hypnotic Effects of Zolpidem by Extrapolation of a Mechanism-Based PKPD Model Developed for Triazolam in Healthy Volunteers.

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Objectives: The operational model of agonism [1] is a mechanism-based pharmacodynamic (MBPD) model that incorporates drug specific parameters, available from *in vitro* experiments, and system specific parameters that can be estimated using *in vivo* data. In principle, once a MBPD model has been established for a drug and linked to a mechanistic PBPK model, the PD response for a drug that shares the same mechanism of action can be predicted by changing only the drug specific parameters. The recent success in application of systems approach in predicting pharmacokinetics has led many to believe a similar strategy for prediction of PD aspects should be adopted [2]. This study aimed to establish a MBPD model to describe the hypnotic effects of triazolam, as measured by change in beta-EEG amplitude, and to use this to predict the hypnotic response to zolpidem since the hypnotic effects of both drugs are mediated via α_1 subunit containing $GABA_A$ receptors.

Methods: Simulations of PK and PD were performed using the default triazolam and zolpidem compound files within the Simcyp Simulator (v11.1). *In vitro* K_D values for triazolam and zolpidem and their relative efficacy were identified from review of the literature. The Simcyp Parameter Estimation module was used to estimate the system dependent parameters of the operational model using published concentration-response data from healthy volunteer studies of triazolam [3-6]. The quality of the parameter estimates was tested by the ability of the operational model to predict the PD response following interaction with ketoconazole [5,7] before predicting the response to zolpidem.

Results: The operational model developed using the parameter estimates predicted the PD response to 0.125 and 0.25mg triazolam with and without ketoconazole DDI reasonably well. The maximal response (Rmax) to zolpidem was predicted well by changing only the PBPK model input to the operational model and the *in vitro* K_D. The simulated/observed ratios for Rmax were 0.86-0.91 for 5mg and 10mg zolpidem [3,5,8]. However, the duration of response was overestimated.

Conclusions: The MBPD model developed for triazolam was reasonably successful in predicting the maximal EEG response to zolpidem. Availability of the MBPD models within a user-friendly environment may facilitate wider use of this approach in the prediction of the dose of a drug candidate that produces equivalent clinical efficacy to a well-studied drug with a similar mechanism of action.

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I-64 *Roel Straetemans* Pharmacokinetic/Pharmacodynamic Simulations Of The vWF Targeting Nanobody® ALX-0081 In Pediatric Patients With TTP

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Objectives: Nanobodies® are therapeutic proteins based on the smallest functional fragments of heavy chain antibodies, naturally occurring in *Camelidae*. ALX-0081 is a bivalent Nanobody® drug product, targeting von Willebrand Factor (vWF). The developed pharmacokinetic (PK) /pharmacodynamic (PD) model was used to simulate the drug and biomarker profiles for a virtual paediatric population at steady-state and to compare the derived exposure parameters to those simulated in adults.

Methods: The paediatric simulations were performed using NONMEMVII in virtual adolescent populations created for different age groups (12- 18 years) receiving body-weight adjusted repeated SC administrations of ALX-0081. The simulations of PK (ALX-0081 levels) and PD (vWF levels) were done according to the developed PK/PD model[1] with PK adapted to children through allometric scaling. The exposure parameters from the simulated steady-state plasma profiles were calculated and compared to adults.

Results: The predicted steady-state exposure parameters for the different age groups were similar to those in adults, except a slightly lower predicted trough concentration in the 12-year-old group. The biomarker profiles (vWF) were expected to be similar for the 16-18 year age group and in adults. For the 12-14 year age group, higher fluctuations of the free vWF during a dosing interval can lead to a decrease in duration of the inhibition of the clinically relevant biomarker. To reduce the fluctuations of the free vWF levels, a bis in die (bid) dosing of the same total daily dose would be preferred.

Conclusions: Simulations showed that a purely body-weight adjusted dosing regimen would be suitable in adolescents aged 16 to <18 years, where similar exposure compared to adults is expected. In order to achieve free vWF levels comparable to adults, it may be preferred to split the body-weight adjusted dose in two administrations per day in younger adolescents (12 to < 16 years).

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I-65 *Amit Roy* Characterization of the Occurrence, Severity, and Duration of Immune-Related Adverse Events (irAEs) in Advanced Melanoma Patients Treated with Ipilimumab

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Objectives: Ipilimumab is a fully human monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4) that is being developed as a novel immunotherapeutic agent against melanoma, and other solid tumors. The main safety concern with ipilimumab is irAEs that may occur as a consequence of an increase in activated T-cells. The objective of this analysis was to describe the ipilimumab exposure-response (E-R) relationship of the occurrence, severity, and resolution of irAEs, incorporating the modulating effect of steroids that may have been administered to manage severe irAEs.

Methods: The E-R relationship of irAEs was described with data pooled from 498 patients who participated in four phase 2 studies of ipilimumab (CA184004, CA184007, CA184008 and CA184022). A Markov model was employed to describe the probability of transitioning between two of the following three possible irAE states: Grade less than 1 (including no irAE), Grade 2, and Grade 3+ irAE. The transition probabilities were described as a function of ipilimumab serum concentration-time (C-T) profile (predicted by a previously developed population pharmacokinetc [PPK] model) and prior steroid doses. The PPK and E-R models were applied to predict the time-course of irAEs for alternative ipilimumab dosing regimens by clinical trial simulation, assuming no drop-out (to obtain a conservatively high prediction of % irAEs).

Results: Model predicted maximal % of subjects with Grade 2+ irAEs on a given day (mpirAE) were 16.9% and 24.4% for 3 mg/kg and 10 mg/kg respectively, which were in good agreement with observed data (19.0% and 24.3%, respectively). The model predicted time to mpirAE was 78-84 days, which was slightly longer than observed data (43-73 days), indicating that the % of subjects with Grade 2+ irAE may reach a plateau earlier than predicted. The clinical trial simulation results predict that the prevalence of irAEs appears to reach a plateau by the end of 12 weeks, and suggest that continuation of induction doses beyond 12 weeks does not lead to markedly higher rate of irAEs.

Conclusions: The Markov E-R model was predictive of the observed irAE rate. This model suggests that the risk of irAE is near maximal by end of 12 weeks, and that extending the induction dosing regimen (every 3 weeks) beyond 12 weeks does not markedly increase the risk of irAEs. Prospective studies would be required to test this hypothesis and evaluate the benefit/risk of continuous dosing.

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I-66 *Hauke Ruehs* Integrated PK/PD model for oxaliplatin in different human matrices

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Objectives: Oxaliplatin is rapidly transformed after infusion and binds irreversibly to plasma proteins, erythrocytes and DNA, where long half-lives of platinum have been observed.Erythrocytes are loaded with large amounts of platinum. Moreover, DNA adduct levels showed a characteristic time course and may serve as pharmacodynamic (PD) endpoint in clinical trials [1]. The aim of this investigation was to build a model describing the platinum concentration-time profiles in plasma, ultrafiltrated plasma, erythrocytes and leukocyte DNA simultaneously and explain the influence of covariates on the PK/PD of oxaliplatin.

Methods: Platinum concentrations were measured in ultrafiltrate and plasma using a validated flameless atomic absorption spectrometry method. Oxaliplatin-DNA adduct levels were measured using adsorptive stripping voltammetry. Concentration-time profiles were available from 56 cancer patients with different regimes and sampling strategies [1,2]. The model was built using NONMEM® 7.1.2. The forward inclusion, backward deletion procedure was applied to identify covariates.

Results: The unbound platinum, represented by the ultrafiltrated fraction, was best described by a two-compartment model. Protein-bound, intra-erythrocyte platinum and DNA platination were described by one compartment each, linked by first-order kinetics to the central compartment of the unbound fraction. Creatinine clearance was identified as a covariate for the elimination rate from the central unbound compartment.

Conclusions: Our PK/PD model simultaneously describes concentration-time courses of platinum in whole blood, plasma, ultrafiltrate as well as DNA-adduct formation after oxaliplatin administration and can be used for simulations.

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I-67 *Alberto Russu* A new, second-order indirect model of depression time course

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Objectives: The limited understanding of placebo effect and drug action in psychiatric diseases has led to a widespread use of ad-hoc empirical models [1,2] and simple indirect response models [3,4] to describe the time course of clinical scores (e.g. HAMD, PANSS) in psychiatric trials. Open issues include the ability to describe complex response profiles and the handling of different dosing schedules. This motivates the present work, where a new approach inspired by indirect response modelling is proposed.

Methods: A new, second-order indirect model was devised in order to capture the structural properties of the treatment response (initial improvement followed by relapse). We extended the methodology of indirect response modelling to incorporate a feedback mechanism [5]. The model includes a compartment representing the HAMD score, with zero-order response formation (k_in) and first-order dissipation (k_out). Decrease of the HAMD state causes a stimulation of the response rate and therefore a feedback action. Treatment effect was modelled as an inhibitory function on the response rate. The proposed model was applied to two Phase II randomized, double-blind, placebo-controlled trials relative to a GlaxoSmithKline investigational antidepressant. Both studies featured a flexible dosing scheme that allowed non-responding patients to be escalated to a higher dose level. Parameter identification was performed with NONMEM 6.2 [6].

Results: The proposed model was successfully fitted to data of both studies. Individual data were well described. In particular, the new second-order indirect model was able to capture different patterns of response profiles, e.g. patients who improve steadily, non-responders, or patients who relapse into a depressive state after an initial improvement. Additionally, the model was able to describe changes in the response time course due to dose escalations. Visual predictive checks confirmed a proper characterization of the population distribution.

Conclusions: Our results show the feasibility of a new modelling approach for longitudinal psychiatric data. In this work, we extended the well-known methodology of indirect response models to account for the complex patterns of response usually observed in psychiatric trials. This approach represents a step forward with respect to simple empirical models: the greater level of structure of the proposed model allows to describe complex response profiles and to perform simulations with different dosing schedules.

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I-68 *Vargo Ryan* Comparator based dose-response model prediction of clinical irrelevance following near miss bioequivalence results for Cmax

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Objectives: The two intermediate doses of a fixed dose combination in development had low Cmax exposures that did not meet bioequivalence criteria. This work: (1) characterizes the impact of changes in exposure between the test and reference products on efficacy, (2) informs the impact of dosing regimen and formulation on the efficacy of reference products across the class to evaluate the relevance of Cmax and AUC variation.

Methods: Pharmacokinetic exposures were modeled to efficacy in a two stage process because the majority of the reference literature data are dose response. A dose exposure model was developed from the individual exposure data for the reference product. The dose exposure model was simulated to produce dose distributions with the individual exposure data from the test product as input. The dose response model was built across the class of compounds from study level literature data across 245 trials including over 106,000 patients. During development of the dose response model, the impact of dosing regimen and formulation on efficacy was evaluated. The dose distributions generated from the dose exposure model were used as input in the dose response model simulations to evaluate the impact on efficacy.

Results: The dose exposure model of the reference drug had a nonlinear slope for Cmax (1.31, 95% CI (1.24, 1.37)) and for AUC (1.07, 95% CI (1.01, 1.13)). Twice a day dosing and extended release formulations have blunted peak exposure when compared to the similar total daily dose of immediate release formulation. The dose response model concluded that twice daily dosing and extended release formulations had better efficacy when compared to the similar total daily dose of immediate release formulation. This result is consistent with the literature data that Cmax is not clinically relevant for efficacy suggesting that concentration need to be maintained above a certain threshold for most of the day, which is more closely related to AUC. Using the dose distributions generated from simulation of the dose exposure model with the test product AUC and Cmax exposures, the absolute difference in efficacy change from baseline versus the references ranged from 0.24-0.65% and 0.42-1.12%, respectively.

Conclusion: The results predict that even with the most conservative assumption that Cmax is the driver for efficacy, the efficacy difference between the products is not clinically relevant.

I-69 *Yu-Yuan Chiu* Dose-Response Model of Lurasidone Treatment in Schizophrenia

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Objectives: Characterization of dose-response relationships for psychotropic agents may be difficult to determine based on results of individual clinical trials, due to various confounds such as variability in attrition and placebo-response rates. As a consequence, post-marketing changes in recommended therapeutic dosing ranges for antipsychotic drugs are not uncommon. The goal of this exposure-response analysis was to more precisely clarify dose-response effects for lurasidone.

Methods: TeData were pooled from five 6-week, randomized, double-blind, placebo-controlled, once-daily, fixed-dose studies of lurasidone in the dosing range of 40-160 mg for the treatment of an acute exacerbation of schizophrenia. The PANSS and exposure data were fitted using the nonlinear mixed effects modeling methodology implemented in the NONMEM software (Version VI).xt regarding methods.

Results: In the final exposure-response model, LS mean change-from-baseline in PANSS exhibited a linear trend relative to dose of lurasidone. The 160 mg dose provided the greatest clinical benefit in terms of PANSS reduction relative to lower doses. In addition, the 120 mg dose produced improvement in PANSS that was intermediate between 80 mg and 160 mg. LS mean change in PANSS exhibited a linear trend relative to dose on treatment days 14, 28, 35, and 42. A time effect rate analysis indicated that 50% of the reduction in PANSS total score observed during acute treatment for each dose group occurred in the first 9 days after starting treatment. Between-study variability in clinical response was evident in the placebo group, but not in the lurasidone group, and was contributed to by demographic covariates (age, weight and race). A log-linear hazard model indicated that patients were more likely to drop out when baseline PANSS scores were higher, and during the initial hospitalization period. However, dropout rate was not correlated with dose of lurasidone.

Conclusions: In this pooled analysis, the effect of lurasidone was described using a linear dose-response model for drug effect, with increased treatment response observed at higher doses of lurasidone. Attrition was not correlated with lurasidone dose.

II-01 *Teijo Saari* Significant changes in pharmacokinetics of sufentanil during target controlled infusion of sufentanil for cardiac anaesthesia.

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Objectives: Target controlled infusion (TCI) with sufentanil is usually performed with Gepts model [1], which was derived from patients undergoing general surgery. We studied the performance of TCI during coronary artery bypass surgery with cardiopulmonary bypass (CPB) with a special emphasis on the effect of CPB on the protein binding.

Methods: After IRB approval, written informed consent was obtained from 13 male patients undergoing coronary artery bypass surgery. Anaesthesia was managed with propofol and TCI of sufentanil, using the Gepts model. Six timed arterial samples were drawn from each patient. The accuracy of the TCI model was assessed by the prediction error (PE) and a pharmacokinetic model was determined by population analysis (NONMEM 7.2) using linear multicompartment models. The influence of demographic and clinical characteristics on the elimination clearance and volumes of distribution were examined.

Results: The median prediction error of the TCI with Gepts model before, during and after CPB was 59.6%, 3.9 % and -10.4 %, respectively. The unbound sufentanil concentrations increased significantly during CPB. Pharmacokinetics were adequately described by a two-compartment model (median PE=-2.2%, median absolute PE=21.2%). The elimination clearance CL1 was significantly higher during and after CPB when compared to the pre-bypass phase. Volumes of distribution increased slightly during and after CPB. CL1 could be modelled as a function of hepatic blood flow and free fraction ("well-stirred" model). V1 and V2 could be modelled as a function of free fraction.

Conclusion: Dosing based on Gepts model led to an overshoot of total sufentanil concentrations at the beginning of cardiac anaesthesia. Also, the observed higher unbound sufentanil concentrations during CPB may have an impact in postoperative pain therapy. Significant changes of sufentanil pharmacokinetics during CPB could be attributed to changes in protein binding and hepatic blood flow. However, because of a sparse sampling in the present trial, further studies are warranted to confirm the present results.

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II-02 *Muhammad Waqas Sadiq* Oxymorphone PKPD relationship and blood-brain barrier transport studied with microdialysis

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Objectives: This study aimed to characterize the BBB transport and pharmacokinetic and pharmacodynamic (PKPD) relationship of oxymorphone in rats using population modeling and to quantify its contribution to the analgesia as a metabolite of oxycodone.

Methods: Transport of oxymorphone across the BBB was studied with microdialysis (MD) in male Sprague-Dawley rats. Samples from microdialysis blood and brain probes were analyzed with LC-MS/MS. The analgesic effect of oxymorphone was studied in rats by measuring the tail flick latency. The study consisted of a PKPD experiment with combined microdialysis and antinociceptive effect measurements (Group 1, n = 8) as well as a separate antinociceptive effect experiment (Group 2, n = 9). In Group 2, the dose of oxymorphone administered was 10 times lower than in Group 1. Non-linear mixed effects modeling was used to analyze the PK data from plasma, MD brain and blood samples and the PD data of tail flick latency, using NONMEM, and Pirana as the modeling environment. Censored observations in the PD data from Group 1 were treated with the 'M3 method' [1] adapted to handle data above the upper limit of quantification (15 seconds) in the PKPD model in order to fully utilize the PD information. Model selection and evaluation was performed using likelihood ratio tests and visual predictive checks.

Results: Oxymorphone had higher unbound concentration in brain than in blood with a ratio of unbound drug in brain interstitial fluid to unbound in blood ($K_{p,uu}$) of 1.87 (10%), indicating the presence of active uptake transport of oxymorphone [2]. The uptake clearance (CLin) into the brain for oxymorphone was 72.4 µl/min/g-brain and the efflux clearance (Clout) was 38.7 µl/min/g-brain. The integrated PK model with an Emax effect model best described the oxymorphone BBB transport and PKPD relationship. All parameters could be estimated with high precision (RSE<15%), except for EC50 and Emax. The EC50 (unbound brain concentrations) of oxymorphone was estimated 62.6 (82%) ng/ml, corresponding to an unbound plasma EC50 of 33.5 ng/ml.

Conclusions: Oxymorphone has active uptake transport at the BBB, thus low distribution to the CNS is not the explanation for its probable lack of contribution to the effects of oxycodone. However the amount of oxymorphone produced by metabolism is not enough to contribute significantly in producing analgesia after oxycodone administration.

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II-03 *Mark Sale* Identification of optimal NONMEM models using a multi-objective genetic algorithm.

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Objectives: Investigate multi-objective genetic algorithm (MOGA) to identify optimal NONMEM models**.**

Methods: MOGA is a global search algorithm that is useful when there is a tradeoff between multiple objectives, and therefore a single, strictly numerical solution isn't appropriate. Specifically for NONMEM, there is a well-known tradeoff between parsimony (number of estimated parameters) and goodness of fit, (-2ll). MOGA identifies non-dominated solutions based on several objectives. Non-dominated solutions, NONMEM models in this case, meet two criteria: 1) no models in the solution space can be superior on all objectives; and 2) the model must be superior to any other model in the solution space on at least one objective. Initially, a random "population" of NONMEM models is created. Using MOGA, models from this population can be selected based on non-domination without weighting or preference for any of the objectives. These selected "parent" models will, in general, be among the better models in the initial population of models. The parent models will then be "bred", using standard genetic algorithm methods to cross over and mutate them in a search for still better models. This is repeated until the optimal set is stable. The specific algorithm used in this example is NSGA-II (Non-dominated, Sorted Genetic Algorithm, 1). The set of non-dominated models can then be presented to the user for additional evaluation (based on biological plausibility, plots, etc.).

A model solution search space was defined for this analysis. The solution search space included: number of compartments, presence|absence of a mixture model, various covariate relationships, various between subject and residual variance structures. The objectives used for the present search were:

- Goodness of fit (-2ll)
- Number of estimated parameters
- "Quality" of solution scored as 0-3, based on convergence, covariance step and correlation test.
- Global adjusted p-value from NPDE (2)

Results: MOGA was able to identify a set of optimal models. Plots of the results demonstrate a clear inverse relationship between the different objectives. In addition, a decrease (worsening) of NPDE but a continued decline (improvement) in -2ll is seen with models having more than 15 parameters, suggesting that models exceeding that number of parameters, for the data set from this study, may be overparameterized.

Conclusions: A multi-objective genetic algorithm is capable of identifying a set of optimal NONMEM models.

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II-04 *Nikolaos Tsamandouras* Mapping in vitro and in vivo derived CYP3A ontogeny function: A critical comparison between various ontogeny models

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Objectives: The aims of this study are to:
1) Deconvolute components of clearance based on known ontogenies and explore any age-dependence of fraction metabolised (fm) using iv clearance (CL) data
2) Compare performance of three existing CYP3A ontogeny models in prediction of observed MDZ CL
3) Produce a novel ontogeny function for CYP3A based on MDZ CL_{int} using deconvoluted CL_{iv}

Methods: MDZ CL_{iv} values were collected from the literature. Unbound intrinsic clearance (CLu_{int}) was calculated by a retrograde approach. Three CYP3A ontogeny models proposed by Bjorkman[1], Edington[2] and Johnson[3] were used within Simcyp v11 to simulate paediatric populations to predict MDZ CL in neonates, infants, children and adolescents. The ratio of CL_{int} in paediatric to CL_{int} adults was used from deconvolution stage to derive a new ontogeny function for CYP3A. CL predictions from these models were compared with those of Anderson (allometrically scaled to 70 kg by 0.75 exponent)[4]. Two assumptions for MPPGL ontogeny (fixed MPPGL value in all ages vs the Barter[5] model) were studied.

Results: At birth, MDZ fm by CYP3A4, CYP3A7 and UGT1A4 was calculated to be 82%, 8% and 10%. Edington ontogeny model overpredicted MDZ CL up to 100 weeks post menstrual age. Comparison between simulated and observed CL showed that Johnson model, with average 5% difference with observed CL_{iv}, was the best CYP3A ontogeny model and was also the best predictor of CL in neonates and infants. Using a fixed age-independent MPPGL value of 40 mg/g improved the CL predictions even further. A new model for ontogeny of CL_{int} was successfully derived by deconvolution of CL_{iv} using well stirred liver model assumptions.

Conclusions: Although the existing models performed well, the new model combines existing knowledge from clinical observations and could be used with more confidence to predict age dependent CL of other drugs where CYP3A has substantial role. Application of this model and deriving similar ontogeny models for other enzymes warrant further studies.

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II-05 *Maria Luisa Sardu* Biomarker-driven Models of Tumour Growth Inhibition in preclinical animal studies

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Objectives: A biomarker - in the context of mechanism-based PK-PD modelling - is a measurement that defines quantitatively a process on the causal path between drug administration and clinical outcome [1]. The aim of this work is to investigate mathematical models that link biomarker modulation (due to the action of anticancer compounds) to tumour growth inhibition in preclinical experimental models. A major goal is the derivation of tumour growth inhibition models that are biomarker-driven rather than directly linked to drug pharmacokinetics. Being dependent on measurements which are likely to be more directly related to tumour response, this model formulation should provide more accurate predictions of the antitumor treatment effects.

Methods: To describe mathematically tumour growth we propose a biomarker-driven version of the TGI Simeoni model [2,3], herein named B-Simeoni, where the input is not represented by the drug concentration but depends on the drug-induced biomarker modulation. Different alternative formulations of the B-Simeoni model were considered. Constraints on the potency parameter were derived to ensure consistency of the outcomes of Simeoni and B-Simeoni models. This was done by equating the steady-state tumour volumes predicted following constant drug concentrations. The specific biomarker inhibition needed to maintain a certain constant tumour volume was mathematically determined. NONMEM (vers. VI) was used to analyze and simulate data sets.

Results: To assess the applicability of the modeling approach in a population context, simulated data were analyzed. Parameter estimates were fully satisfactory both on the side of data fitting and CV values. Moreover, the B-Simeoni model was tested on tumor growth inhibition data taken from the literature [4]. Also in this case, identification was successful in terms of both data fitting and CV values.

Conclusions: Building on the Simeoni TGI model, different mathematical models linking tumor growth inhibition and biomarker modulation have been proposed. The steady-state relationship that links tumor volume to drug concentration and biomarker inhibition was devised. This made it possible to express the potency parameter of the newly proposed B-Simeoni model as a function of the potency parameter of the standard Simeoni model, thus reducing unnecessary redundancy. Both experimental individual data and simulated population ones confirmed model suitability.

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II-06 *Andre Schäftlein* Microdialysate-corrected mid-interval model versus microdialysate-based integral model - Population pharmacokinetics of levofloxacin in peripheral tissues

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Objectives: Microdialysis (µD) has become the method of choice to determine unbound interstitial fluid (ISF) concentration of antiinfectives in peripheral tissues (PT) [1]. This interval sampling method requires the correction of the measured microdialysate concentrations (CµD) by the recovery rate (RR). The aim of this analysis was to compare two population PK modelling approaches with respect to descriptive and predictive performance for CµD of levofloxacin (LEV). A second objective was to investigate covariates (demographics, clinical chemistry, disease severity) on the PK of LEV into the ISF of PT.

Methods: Plasma and µD concentrations in adipose and muscle ISF of 39 patients from 5 clinical trials [2-4] receiving 500 mg LEV once daily were analysed using NONMEM 7.2. by two approaches: (i) the microdialysate-corrected mid-interval (MCM) model, correcting CµD by RR prior to the data analysis and assigning the corrected CµD to the middle of the sampling interval; (ii) the microdialysate-based integral (MBI) model [5] which simultaneously analyses RR and CµD data and assigns CµD to the end of the sampling interval. Comparison was guided by plausibility and precision of parameter estimates, GOF plots and VPCs. Covariate selection was based on OFV, relevant influence on the PK and the ability to explain interindividual variability (IIV) on PK parameters.

Results: PK parameter estimates of the MBI model better agreed with published ones [6], also revealing higher precision than of the MCM model. In contrast to the MBI model the MCM model did not adequately describe the concentration-time profiles in both ISF of PT and its predictive performance was worse. Albumin being a marker for the colloid osmotic pressure significantly influenced intercompartmental CL (plasma to adipose ISF) explaining ~20% of IIV. Additionally renal function and disease severity showed an impact on CL of LEV.

Conclusions: CµD in the ISF of PT was best described and predicted by the MBI model. This approach enabled the differentiation between µD-specific processes and physiologically-based distribution of LEV. Based on this, more mechanistically-motivated models will be developed to explain the distribution of antiinfectives in ISF of PT.

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II-07 *Emilie Schindler* PKPD-Modeling of Standard Uptake Value (SUV) in Gastro-Intestinal Stromal Tumors (GIST) patients treated with sunitinib

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Objectives: A change in tumor glucose utilization, as determined by the maximal standardized uptake value (SUV), may be a significantly better predictor of early tumor response and clinical outcome compared with conventional tumor size measurements (RECIST) in patients treated with the multi-targeted tyrosine kinase inhibitor sunitinib [1]. The aim of this analysis was to characterize the time-course of SUV and investigate potential longitudinal relationships between sunitinib dose, AUC, biomarkers (VEGF, sVEGFR-2 and sKIT), and SUV in patients with gastro-intestinal stromal tumors (GIST).

Methods: SUV measurements ([^{18}F]-fluorodeoxyglucose uptake determined by PET corrected for body weight, n=158) were available from 47 patients followed for a median time of 14 weeks of treatment with three different oral doses of sunitinib under three different treatment schedules. Dose, daily AUC and relative change in the three biomarkers from baseline over time, predicted by earlier developed models [2], were evaluated as drivers for the change in SUV in a longitudinal tumor growth inhibition model previously applied for tumor size (SLD, sum of longest diameters) [3].

Results: The longitudinal SUV data were well characterized by the tumor growth inhibition model with a fast initial decline in SUV, followed by a more static phase. Daily AUC was found to be the best predictor for SUV response and the model showed no additional improvement when also including model predicted sKIT, VEGF or sVEGFR-2 time courses as predictors.

Conclusions: The present results indicate that the daily AUC can potentially be used to predict early metabolic tumor response, as determined by SUV. In a previous analysis [3], sKIT was shown to be the best predictor of tumor size [4]. However, because of the rapid SUV response, it is not surprising that sKIT, with a turnover time of 14 weeks, didn't characterize the SUV data. It remains to be shown if SUV response is a better predictor of survival than response in SLD or angiogenic biomarkers.

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II-08 *Alessandro Schipani* Simultaneous population pharmacokinetic modelling of atazanavir and ritonavir in HIV-infected adults and assessment of different dose reduction strategies

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Objectives: Atazanavir (ATV) is a protease inhibitor (PI) used as part of combination HIV therapy. ATV is metabolised by CYP3A4/3A5. A target minimum effective concentration (MEC) of 0.15 mg/L at trough has been recommended for optimal viral suppression. ATV is co-administered with ritonavir (RTV) and licensed at a dose of ATV/RTV 300/100 mg once daily. The concentration of RTV maximal inhibition of CYP3A4 may occur with a lower RTV dose than 100 mg. There are clear advantages to lower doses of RTV (better tolerated, cheaper to manufacture, easier to co-formulate), but current there are also obstacles. The objective of this study was to develop a simultaneous population PK model to describe ATV/RTV PK (300/100 mg) and to assess the effect of RTV dose reduction on ATV PK. Simulations of ATV concentration-time profiles were performed at doses of ATV/RTV 300/50 mg, 200/50 mg and 200/100 mg once daily.

Methods: A total of 288 ATV and 312 RTV plasma concentrations from 30 patients were included to build a population pharmacokinetic model using the stochastic approximation expectation maximization algorithm implemented in MONOLIX 3.2 software.

Results: A maximum-effect model in which RTV inhibited the elimination of ATV was used to describe the relationship between RTV concentrations and ATV clearance (CL/*F*). A RTV concentration of 0.22 mg/liter was associated with 50% maximum inhibition of ATV CL/*F*. The population prediction of ATV CL/*F* in the absence of RTV was 16.6 liters/h (relative standard error, 7.0%)**,** and the apparent volume of distribution and absorption rate constant were 106 liters (relative standard error, 8%) and 0.87 h^{-1} (fixed), respectively. Simulated average ATV trough concentrations at ATV/RTV 300/50 mg, 200/50 mg and 200/100 mg once daily were 45%, 63% and 33% lower, respectively, than that of the standard dose.

Conclusions: A population model to simultaneously describe the pharmacokinetics of ATV and RTV was developed and validated in HIV-infected individuals. The simulated median ATV trough concentrations following dose reductions were reduced compared to the licensed dose but were still above the ATV MEC (2.9, 1.9 and 3.6 fold for ATV/RTV 300/50 mg, 200/50 mg and 200/100 mg, respectively). Simulated data for the 300/50 mg regimen are consistent with the clinical data. This modelling approach aids our understanding of the interaction between ATV and RTV and informs the design of dose reduction strategies, particularly in relation to RTV.

II-09 *Rik Schoemaker* Modelling and simulation of spontaneously reported adverse events after administration of lacosamide

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Objectives: To develop a PK/PD model of spontaneously reported adverse events (AE) with the antiepileptic drug lacosamide and to apply it to predicting the changes in time profile and incidence of adverse events following switch from a conventional immediate release (IR) tablet to a modified release (MR) formulation.

Methods: PK and AE data were obtained from a double blind placebo-controlled steady-state parallel group Thorough QT study involving 193 healthy volunteers. PK data from a pilot bioavailability study with single dose MR formulations were also included. Plasma concentrations were fitted to a pharmacokinetic model using non-linear mixed-effects modelling implemented in NONMEM V7.2.0. AE data consisted of the five most frequent spontaneously reported AEs: nausea, vomiting, dizziness, oral hypoaesthesia and headache. Each AE was modelled using non-linear mixed-effects modelling (Laplacian method) with a proportional odds model for ordered categorical data with a Markov element[1] accounting for the correlation between successive scores, a linear concentration effect relationship, and a component describing AE incidence reduction over time.

Results: A one-compartment model with first-order absorption, diurnal effect on clearance and combined (multiplicative + additive) error was shown to adequately describe lacosamide pharmacokinetics. The final PK model allowed simulation of the once-daily multiple administration of the MR formulation in comparison with twice-daily administration of the IR form. Simulations suggest that these two administration modes cover a similar concentration range with lower peaks for the MR formulation and predict a modest reduction in incidence of adverse events for the MR formulation compared with the IR formulation at the same total daily dose.

Conclusions: Modelling and simulation of lacosamide pharmacokinetics and of the spontaneously reported AEs suggest that slowing down the absorption rate can possibly result in improved tolerability.

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II-10 *Bernard Sebastien* Impact of delayed effect in Concentration-QT analyses.

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Objectives: In connection with the development of specific statistical methods for the analysis of thorough QT studies, growing attention has been recently paid on the PKPD models to consider for Concentration-QT analyses. For this purpose, PKPD models considered, generally assume direct concentration-QT increase relationships: assumption mostly assessed using graphical diagnostic methods. The purpose of this work is to quantitatively assess, using both simulations and tools of asymptotic statistics, the impact of lagged effect on the estimates obtained with the standard PKPD models routinely used for assessment of concentration - QT relationships.

Methods: The true model assumes a linear relationship between time-matched QT change and the lagged PK concentration, whereas the working analysis concentration - QT model is the standard mixed linear model using time-matched QT change as dependant variable, the observed PK concentration plus a time effect (considered as a factor) as independent variable. Methods of asymptotic statistics are used to derive the limit value of the slope and time effects parameters in the mis-specified model. These results are illustrated with simulations exploring behaviour of the estimates in a non-asymptotic setting.

Results: Both asymptotic calculations and simulations confirm systematic under-estimation of slope parameter when the true model involves a lagged effect but not the working analysis model: the bias, which depends on the covariance structure of the PK profile, grows as the lag time increases. Also the lag time impacts the time effect parameter in the working analysis model: the magnitude of this time effect could be then used as quantitative diagnostics for the presence of lagged effect.

Conclusions: Ignoring a lag-time effect induces systematic underestimation of the concentration effect through biased estimation of slope parameter in direct analysis model. Also, as complementary sensitivity analyses, approximate lag-time corrected slope estimates can be computed in considering lag time as tuning parameter instead of a parameter to be estimated. These corrected estimates can have some usefulness as exploratory results, but cannot probably fully replace comprehensive PKPD modelling of both PK and PD parameters when hysteresis is suspected.

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II-11 *Eric Sherer* Three case studies of pharmacokinetic model building using a multi-objective genetic algorithm

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Objectives: The scope of most manual PK model building searches is constrained by the time and effort associated with model evaluation. In an effort to more thoroughly search the global solution space, we developed a single-objective, hybrid genetic algorithm (SOHGA) approach to PK modeling building to search the global solution space for candidate models with the lowest fitness function(1). However, a limitation to SOHGA is the ad hoc nature of the fitness function used for model comparisons. A potential solution is the use of a multi-objective genetic algorithm (MOGA) which compares candidate models along multiple dimensions. The objective of this work is to compare the fits of PK models identified using manual, SOHGA, and MOGA methods.

Methods: PK models were developed independently using manual, SOHGA, and MOGA methods for each of three compounds: intravenous citalopram(2), oral perphenazine(3), and oral ziprasidone(4). All search methods were given identical options which included ADVAN/TRANS structure, inclusion of inter-occasion variability and block structure, covariate inclusion and associated function form, and form of the residual variability. For the MOGA search, we used the non-dominated, sorted genetic algorithm(5) evaluated along four dimensions: NONMEM objective function value (OFV); number of estimated parameters; convergence, covariance step, and correlation test; and global adjusted p-value from NPDE(6). The final manual and SOHGA models were compared with the MOGA candidate with the same number of parameters that converged with the lowest OFV. Models within 10 points were considered equivalent.

Results: The MOGA models were significantly better than the manual models for citalopram and ziprasidone. For ziprasidone, the difference is likely because the absorption rate constant was fixed in the manual models due to difficulties with model convergence giving MOGA model an extra degree of freedom. For citalopram, only 1 of 5 covariate effects was shared between the models so the MOGA covariate search identified a model with a lower OFV. There were no significant differences between the OFV values of the final SOHGA candidate model and the MOGA model.

Conclusions: For three test cases, a MOGA model building identified models with equal or lower OFV versus the manual approach. The MOGA approach identified models with equal OFV versus the SOHGA approach but with the intrinsic advantage of a broader view of the candidate solution space.

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II-12 *Kwang-Hee Shin* Population Pharmacokinetics and Pharmacodynamics of Escitalopram in Healthy Volunteers

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Objectives: Pharmacokinetic-pharmacodynamic (PK-PD) modeling has been suggested for the prediction of brain receptor occupancy by antipsychotics. Escitalopram, a selective serotonin reuptake inhibitor, is used for depression or obsessive-compulsive disorder (OCD). This study aimed to assess escitalopram PK and PD profile using positron emission tomography (PET) data in healthy volunteers to explore the relationship between plasma drug concentration and transporter occupancy.

Methods: The population PK and PD analysis was performed using nonlinear mixed effect model (NONMEM® VII) based on plasma concentrations and transporter occupancies from PET imaging in healthy volunteers receiving escitalopram 5-20 mg dose range. Sequential PK-PD model was developed and the first-order conditional estimation in NONMEM was employed for model run. A one-compartment model with first order absorption and first-order elimination described the PK. The influence of demographic characteristics on PK parameters was examined. The serotonin transporter occupancy was calculated from binding potential of PET imaging. A sigmoid E_{max} model was employed to describe transporter occupancy by escitalopram in the caudate nucleus.

Results: Twelve subjects contributed to 144 escitalopram concentrations and 139 binding potential data for caudate. Oral clearance was 34.7 L/h (CV 35.1%), oral volume of distribution was 1280 L (CV 10.4%) and the absorption rate constant was 3.22 hr^{-1} (CV 68.7%). Of the covariates including age, weight, height evaluated, none of the covariate showed an influence on escitalopram PK parameters. The transporter occupancy in the caudate was correlated with escitalopram concentration. Sigmoid E_{max} model was well fitted for transporter occupancy in the caudate nucleus. EC50 was 1.67 ng/mL (CV 0.01%) and Hill coefficient was 0.681 (CV 25.9%).

Conclusions: PK-PD model for escitalopram was developed for healthy volunteers. Therapeutically effective serotonin transporter occupancy for OCD is unclear although that for depression was reported about 80% [1]. Further PK-PD modeling using occupancy for escitalopram may be useful tool to predict clinically relevant plasma concentration and drug effect in OCD patients.

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II-13 *Satoshi Shoji* Population Pharmacokinetics/Pharmacodynamics of Ampicillin/Sulbactam in Patients with Moderate or Severe Community-Acquired Pneumonia

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Introduction and Objectives: Unasyn® (injectable combination of sulbactam sodium and ampicillin sodium, dose ratio 1:2) has been marketed over 60 countries in the world, and prescribed for the treatment of various types of infections. It is currently used in doses up to 12g/day however in Japan approved doses are up to 6 g/day. The aim of this analysis was to study the pharmacokinetics (PK) of ampicillin and sulbactam after doses of 12g/day divided in 4 doses (i.e. 3 g QID) in Japanese patients with moderate or severe community-acquired pneumonia. The PK model was then used to explore the efficacy of the drug through the calculation of the expected time above the minimum inhibitory concentration (MIC) for the different pathogens identified in the patients.

Methods: The population PK analysis was performed using NONMEM 6.2 based on log-transformed plasma concentration samples. Simultaneous fit of the concentration data of both drugs was evaluated by the use of the L2 item in NONMEM. The MIC concentration for ampicillin/sulbactam was reported as ampicillin concentration. The time above MIC (TAM) during the treatment duration period for all the patients for which the MIC value was available was integrated using the following equation:

$$dA/dt = CPD^{GAM}/(CPD^{GAM}+MIC^{GAM})$$

Where *CPD* is ampicillin concentration at each time point, *MIC* is the MIC value for each patient, *GAM* is a factor fixed to 99, in order to create a function which gives an all or nothing response. When divided by the duration of the treatment (hrs), the fraction time above MIC was obtained.

Results: In total, 222 plasma concentration observations for both sulbactam and ampicillin coming from 47 patients were available for the analysis. A two-compartment model described both the ampicillin and the sulbactam PK, where inter-patient variability was estimated for clearance and for peripheral volume. Creatinine clearance and body weight were included in the final model. Final PK parameters were similar between the two compounds and similar to previously reported values [1 - 3]. The percentage of time above the MIC value established for each identified pathogen ranged from 55 to 100%. Simulations showed how the QID schedule provided concentrations over the MIC [for all the range seen in the study (0.06-16)] for at least 50% of the time.

Conclusion: A PK model that described both ampicillin and sulbactam plasma concentration data was established. This model was used to make inferences on the efficacy of the drug through the calculation of TAM for different pathogens and different dosing schedules.

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II-14 *Hanna Silber* Population pharmacokinetics of cyclosporine A in cats

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Objectives: To evaluate the pharmacokinetics of cyclosporine A (CsA) in healthy cats following single dose administration and to explore the effect of food on the resulting blood concentration time profile.

Methods: The dataset was based on a four-way cross over study in 12 healthy cats. Each cat was given 1 intravenous (i.v.) dose and 3 oral doses. The i.v. dose was 2 mg/kg and the oral dose was 7 mg/kg. The i.v. dose was given to fasted cats and the oral dose was given to fasted or fed cats, or mixed with food. Blood concentrations were measured up to 72 hours following each dose. A 2-week wash out period separated each dose from the previous. A population pharmacokinetic model was developed using non-linear mixed effects modeling in NONMEM VI [1]. Different structural models for disposition and absorption were evaluated to obtain the best description of the data. The effect of food on rate and extent of absorption was investigated. Goodness-of-fit was assessed using the objective function value for comparison of competing models in combination with graphical assessment. Standard errors of the model parameters were derived using a bootstrap (n=100). The predictive properties were assessed by a VPC (n=1000).

Results: A linear 3-compartment model was found to describe the blood concentrations of CsA following single dose administration. The absorption was described using a transit compartment model [2]. The absorption rate was about 4 fold lower when CsA was mixed in food and more than 10-fold lower when administered to fed compared to fasted cats. Bioavailability was reduced from 26% to 20% when CsA was given to fed cats compared to when CsA was given to fasted cats or mixed with food. These results were in line with previous results from the non compartment analysis. Precision of parameter estimates was obtained using a bootstrap and most parameters were found to be estimated with high certainty (RSE<30%). Some of the absorption parameters as well as the inter-individual parameter estimates had a higher standard error estimate (RSE ~ 50%). The VPC showed that the simulation properties of the model were satisfactory.

Conclusions: A 3-compartment linear disposition model was found to satisfactorily describe the data following single dose administration of CsA and the effect of food on rate and extent of absorption could be quantified.

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II-15 *Monica Simeoni* Estimation of Remifentanil Metabolic Ratio Using a Mixture Model

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Objectives: Remifentanil is a selective mu-opioid receptor agonist indicated as an analgesic. Plasma concentrations of its active metabolite, remifentanil acid, during short duration treatments were characterised by a single-compartment model in some patients and by a two-compartment model in others. The exposure to both remifentanil and this metabolite during prolonged treatment remained to be established. This work aimed to quantify steady-state metabolite-to-drug ratio (metabolic ratio) for this drug by a population model, using non-steady-state data collected during highly variable adaptive dosing.

Methods: Concentrations of remifentanil and remifentanil acid were available from a three-day study with frequent sampling and a 10-day study with sparse sampling. A mixture population pharmacokinetic model was developed using the data from the three-day study. The model was assessed in terms of observed concentrations and the derived endpoint of interest (the metabolic ratio) by an individual-based evaluation method, to accommodate the high variation in dosing regimen, both among patients and over time. The data from the 10-day study were then added to the dataset; and the most probable model for patients in this study was determined using individual objective function values.

Results: The mixture model adequately described the concentrations of both remifentanil and its metabolite from both trials. The individual-based evaluation allowed informative assessment of the model despite of the highly variable dosing regimen. Generally, the kinetics of the metabolite was better described by two compartments in patients with normal or mildly impaired renal function, and by one compartment in patients with more severely impaired renal function. Preliminary results from the dense dataset suggested that the geometric mean of the metabolic ratio was 16 in the former group and 78 in the latter group.

Conclusions: The joint parent-metabolite mixture population model enabled the integration of all relevant data, to maximise analytical power and to preserve the correlation among parameters. The model can be used to simulate the distribution of the concentration profiles of both compounds in any proposed dosing regimen.

II-16 *Nicolas Simon* A joint PK/PD-PD model of levodopa in patients with Parkinson's disease: Motor effect and Movement disorder

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Objectives: After several years of treatment with levodopa, patients with Parkinson's disease often present movement disorders such as dyskinesia. This side effect is extremely limiting for these patients and efforts should be done to find how to avoid their occurrence. A first concern is to establish whether it's possible to adapt treatment to obtain a satisfactory effect without dyskinesia. This approach requires not only a PK/PD model but a joint model of both effects. This study aimed to develop a PK/PD-PD joint model of motor effect and dyskinesia following administration of levodopa

Methods: Parkinsonian patients with dyskinesia were enrolled: after a wash-out period of 12 hours, they received a single 150% dose of their usual daily dosing of levodopa. Eight blood samples were taken before administration and at 0.5, 1, 1.5, 2, 3 and 5 hours following levodopa administration. Pharmacodynamic assessments used the Unified Parkinson Disease Rating Score (UPDRS) and the Goetz's dyskinesia scale. A PK/PD model for each effect was first established and then several joint models were investigated.

Results: Thirty patients were included in the study. A first compartment model described the PK data, the Ka was 1.86 1/h, the volume of distribution was 36.2L and the oral clearance 31.6L/h. The motor effect and the dyskinesia were best described by effect-compartment models. From different joint models tested, the best consisted of a single KE0, 1.54 1/h, with separate EC50, 1890µg/L and 6990µg/L for UPDRS and dyskinesia. A large interpatient variability was found to affect levodopa EC50 for UPDRS (CV 54%) as well as EC50 for dyskinesia (CV 80%).

Conclusions: The study describes the simultaneous occurrence of motor effect and dyskinesia with separate values of EC50. However, the wide inter-individual variability limits the ability to dissociate these effects even with individualizing the levodopa regimen.

II-17 *Jean Smeets* Development of a mechanistic based model for neonatal Fc receptor recycling to design human serum albumin mutants with extended half-lives

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Objectives: Similar to immunoglobulins, increasing the pH dependent affinity of binding to neonatal Fc receptor (FcRn) is a possible strategy for engineering human serum albumin (HSA) mutants with longer half-life than natural HSA [1]. The purpose of this study was to develop a mechanism-based model to help in the identification of HSA mutants with appropriate in vivo half-life and to evaluate the possible translation of half-life between animal models and human for HSA mutants.

Methods: The final model contained distribution of HSA, degradation of free HSA in the endosome and recycling of HSA bound to the FcRn receptors. The model further included competition between endogenous and exogenous albumin and explicitly accounted for their different affinities to FcRn. The mechanism-based model was originally validated against literature albumin profiles of wild-type albumin from mouse, monkey and human. Plasma concentration profiles from HSA wild-type and three mutants following intravenous administration to huFcRn transgenic mice were compared to model predictions. Due to the model complexity compared to the simplicity of the observed PK profiles, it was neither possible nor desirable to fit all model parameters to data. For mouse and human all but two model parameters could be obtained from literature, and the unknown parameters were derived from steady state conditions. Monkey parameters were scaled from human.

Results: For human and monkey the model predictions were in good agreement with literature-reported data, and the parameters were found to be mutually scalable. Distribution parameters were fitted to the HSA profile of huFcRn transgenic mouse PK profile, in order to obtain a good prediction of the mouse PK. The model was applied to predict the half-life of HSA mutants as a function of FcRn affinity. Half-life changes caused by improved affinity were found to be similar for monkey and human but up to 2 orders of magnitude smaller for mouse. Simulations were performed which showed that increased affinity has a small effect on the terminal half-life for HSA in the huFcRn transgenic mouse due to a high affinity of endogenous MSA for the huFcRn receptor.

Conclusions: The mechanism-based model provides a convenient tool to help identify HSA mutants with optimal in vivo PK. Furthermore, the model suggests that in huFcRn transgenic mice a large change in FcRn affinity results in a relatively small change in HSA half-life compared to monkey and human.

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II-18 *Nelleke Snelder* Quantification of Antidepressant and Sedative Effect of Two NMDA Channel Blockers, AZD6765 and Ketamine, in an Animal Model of Depression Using Count Data

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Objectives: Prenatally stressed (PNS) rats show robust and long-lasting reduction in open-arm exploration on the elevated plus maze (EPM). The EPM is a plus-shaped maze with 2 open and 2 closed arms. An increase in exploration of the open arms by PNS rats indicates antidepressant effects. General activity is assessed by the number of entries into closed arms. The aim of the current study was to develop a count model to characterize the antidepressant and sedative effects of the two NMDA channel blockers, ketamine and AZD6765, on the number of open and closed entries in PNS rats.

Methods: Rats were dosed ip with saline, AZD6765 (0.3-10 mg/kg), or ketamine (1-10 mg/kg) and tested on the EPM at 1 h and 14 days postdosing. The vehicle group consisted of non-PNS and PNS rats. The rats were placed in the middle of the EPM and the number of open and closed entries was recorded for a 5 min period. Different Poisson models were investigated using NONMEM to describe the observed number of entries: normal and overdispersed Poisson with or without zero-inflation (to account for a higher probability of zero entries). Firstly, a model was developed to describe the sedative effect on the number of closed entries. Secondly, the sedative effect was included in the model to describe the number of open entries. Different dose-effect relationships were examined for the number of open and closed entries as well as the probability of zero entries. Final models were selected based on the objective function value and/or diagnostic plots (VPC and observed vs simulated distribution of the number of entries).

Results: An overdispersed Poisson model with zero-inflation adequately described the number of open and closed entries. A sigmoidal E_{max} dose-effect relationship was used to describe the sedative effect of ketamine. The antidepressant effect of both compounds could be described with an E_{max} model. The efficacy of AZD6765 was higher and the duration of the effect longer than for ketamine, even though the potency of ketamine was higher.

Conclusions: The NMDA channel blockers, ketamine and AZD6765, both showed antidepressant effects in the PNS-EPM model through prolonged increased explorative behavior compared with vehicle treatment. Using a count data modeling approach, a clear sedative effect of ketamine was quantified.

II-19 *Alexander Solms* Using Population PBPK Modelling to interpret Population PK results exemplified for Levofloxacin in Plasma and Interstitial Fluid

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Objectives: A key aim of covariate modelling is to represent the influence of covariates on PK parameters. Structural parameters, e.g. the volume of distribution (Vss), are lumped parameters with apparent rather than physiological meaning. Therefore it is often difficult to attribute the covariate relation to changes in specific anatomical or physiological characteristics. Based on a novel population (POP) physiological-based PK (PBPK) approach [1] and on densely obtained Levofloxacin (LEV) plasma (PL) & unbound interstitial fluid (ISF) concentrations in adipose (ADI) and muscle (MUS), the objective was to study the impact of variations in anatomy and variations in tissue characteristics on the overall observed variability in Vss.

Material and Methods: We used a generic 13-cmt PBPK model for LEV with tissue-to-unbound-PL partition coefficients according to [2]. The physiological and physiochemical parameters were taken from [2,3,4,5]. In the POP PBPK model the inter-individual variability (IIV) in anatomical parameters, e.g. blood flows and organ weights, was modeled via a LBW-scaling approach [1]. PL and ISF data for LEV and clinical chemistry measurements were collected in [6,7,8]. Fraction unbound, blood-to-PL ratio and clearance values were estimated based on measurements of hematocrit, serum albumin and creatinine- and PL LEV concentrations. A detailed POP PK analysis in NONMEMTM of those data and the related results were provided in [9]. Simulations were performed with R 2.14.1.

Results: POP PK and PBPK predictions could adaequatly describe the measured concentrations and resulted in comparable estimates of the overall Vss. Based on the POP PBPK model the coefficient of variation (CV) on the physiological ADI & MUS volume were predicted to be 33% and 10%. Thereon based predictions of Vss resulted in a likewise 3-fold larger IIV for ADI than MUS (31% vs. 10%). In comparison, the POP PK resulted in an almost identical IIV in Vss ADI & MUS (CV ~74%). Underestimation of IIV in the POP PBPK model might partially be attributable to IIV in tissue composition. This would be consistent with experimental observations [10].

Conclusions: As expected, anatomical IIV can only explain part of the IIV in Vss. Our approach quantified the contribution of the anatomical IIV. Such information is expected to help understanding to what extent a covariate-relationship involving body size descriptors reflects differences in anatomy and to what extent it might reflect an yet unidentified interaction.

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II-20 *Hankil Son* Development of a longitudinal model to describe the QT-time course in healthy volunteers given placebo and moxifloxacin

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Background: ICH Guidance E14 on the evaluation of QT/QTc Interval prolongation for non-antiarrhythmic drugs was endorsed in 2005. Standard statistical analysis of QT measurements from these studies usually compares time-matched baseline corrected QTc of placebo and active treatments. In thorough-QT (TQT) studies, moxifloxacin is often used as a positive control to assess the relative risk of a test drug [1,2]. Recent work has examined the time course of moxifloxacin and placebo effects [3-7]. Characterising the moxifloxacin effect over time, the influence of any covariates on this effect is important to interpret future TQT studies. With this background, this work analyzed QT interval data observed in placebo and moxifloxacin treatments obtained from a meta-analysis of subject-level data from 12 QT studies drawn from different drug programmes and comprising 750 subjects of diverse demographic characteristics.

Objectives: The purpose of this work was to develop a longitudinal model to describe the time course of QT interval in healthy volunteers given placebo and moxifloxacin treatments and to examine the source of variability affecting on QT interval with a focus on the variability in demographic factors and inter-study differences.

Methods: Electrocardiograph (ECG) data from placebo and 400mg moxifloxacin treatments were analyzed using NONMEM software. The longitudinal QT interval model incorporating the variability in demographic factors and the inter-study difference was developed within a mixed effect model framework according to the following steps: individual correction, baseline correction, drug effect, inter-study difference, covariate effect, and model evaluation. The data from 12 studies were modeled together using a meta-analysis approach.
- Individual correction: The exponent on RR in the QT correction facor was estimated for each individual rather than assuming fixed values as used in the Bazett and Fridericia corrections.
- Baseline correction: Following an appropriate individual correction of the QT interval for heart rate, a mixed effect model was fit to the data obtained from the placebo treatment to explore the circadian effect on the baseline QT interval using cosine functions with up to three periods (24, 12, 6 or 8 hours). Interindividual variability was included in acrophase and amplitude for each period.
- Drug effect: The data obtained from the moxifloxacin treatment were then analyzed by fixing the baseline structural model to the one obtained from the placebo treatment in the previous step. The drug effect on QT interval was described as a direct function of time and QT measurements was modeled and tested using diverse equations.
- Inter-study difference: The variability among different studies was modeled using a fixed study-effect method on the assumption that the model parameters of the individuals follow the same distributions across studies [7]. The method assumes that there are different unrelated model parameter values between different studies, and the study effect is introduced as a covariate for the model parameter.
- Covariate effect: The covariate effect is analyzed by a stepwise covariate model building process.

Categorical covariates such as sex, race and smoking and continuous covariates such as age, height, weight, BMI, or average amount of alcohol drinking were tested.
- Model evaluation: Visual Predictive Checks were used to examine the model fit to the observed data.

Results: The corrected QT interval estimated yielded the heart-rate correction slope of alpha being 0.35 with 16% (CV) of intersubject variation. A two-oscillator model with 24- and 12-hour period best described the circadian variation of baseline QT measurements. For moxifloxacin effect on QT interval, a Bateman function was selected to represent the elongating aspect of QT interval for the early phase followed by shortening for the later part of the observation. The difference among the 12 studies was best modeled using separate baseline mesor parameters for each study, ranging between 378 and 410. In the covariate effect, the baseline corrected QT interval and the magnitude of drug effect were found significantly higher in women than in men. The acrophase for 24-hour period circadian rhythm was estimated lower in Asian than in other ethnic groups. Age was also found to be an important covariate, showing the baseline value increased with age. When the final model was evaluated using VPC, the model was found to adequately described the observed data.

Conclusions: The present analysis was carried out as a meta-analysis using observed data across a number of QT trials. The developed longitudinal mixed-effect model well described the time course of the QT interval when the source of variability on the QT interval was appropriately included. The model provided the useful information on potential covariates such as sex, age, and race influencing the QT interval. The final model may influence future trial design and will assist in contextualizing information from future TQT studies.

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II-21 *Alexandre Sostelly* Dose and dose schedule optimization of anticancer drugs

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Objectives: Anticancer drug dose and dose schedule are known to affect the tumor response. Tumor growth inhibition (TGI) models establish the relationship between tumor growth dynamics and drug effects and can help to identify optimal dose schedules. Moreover, numerous factors, such as tumor resistance and dose-effect relationship, can affect drug effect and have to be accounted for to maximize the tumor response. We aim at optimizing anticancer dose and dose schedule using population optimal design methodology by taking into account both tumor resistance and the dose-effect relationship.

Methods: We used the TGI model from Claret *et al.*[1] applied to a theoretical phase II capecitabine study as a basis for this work. Optimization of dose and dose schedule was performed in PopED v.2.11 [2]. Optimizations maximized the change in tumor size from baseline after 2 treatment cycles (6 weeks) within clinical constraints using a penalty function. The criterion is affected by variability and the mean criterion was computed using 500 LHS samples taken from the parameter distributions. To obtain a clinically relevant dose schedule, we constrained the dose interval to 1 day and doses to be the same for each week of the cycle. The total dose was fixed to that used in clinical practice and daily doses were not allowed to exceed $5 g.m^{-2}$.
Impact of tumor resistance has been evaluated by changing the resistance development rate value in the TGI model and impact of the dose-effect relationship (linear and Emax type) has been investigated by modifying the drug exposure parameter. To compare the optimized dose schedules, the mean dose time (MDT) was computed to reflect the dose density within the cycle.

Results and Discussion: In case of linear exposure-response, the optimal schedule frontloads doses in the 1^{st} week of the cycle ($MDT=4 g.m^{-2}.d^{-1}$) for any degree of tumor resistance development rate. In the case of Emax type exposure, the optimal dose schedule depends on the magnitude of resistance development rate. At maximal effect, the optimal schedule equally distributes doses in the cycle for low and medium degree of resistance ($MDT=10.3 g.m^{-2}.d^{-1}$) whereas it frontloads doses for high degree of resistance ($MDT=4.7 g.m^{-2}.d^{-1}$). At minimal effect, the optimal schedule frontloads doses in the 1^{st} week for any resistance degree ($MDT=4 g.m^{-2}.d^{-1}$). Between maximal and minimal effect, MDT decreases when resistance degree increases. Our approach allows optimizing anticancer dose and dose schedule based on clinically relevant criterion and within clinical constraints.

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II-22 *Alexander Staab* A Model-based Meta-analysis Comparison of the Effects of Linagliptin and Sitagliptin on HbA1c Levels in Patients with Type 2 Diabetes Mellitus

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Objectives: Linagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor developed for treatment of Type 2 diabetes mellitus. Sitagliptin is another available DPP-4 inhibitor and serves as a relevant comparator. Our objective was to estimate the magnitude of the HbA1c lowering effects of linagliptin and sitagliptin, based on a comprehensive analysis of available clinical trial data. Specifically, we sought to provide the comparison by means of a longitudinal dose-response meta-analysis based on indirect comparisons. Given appropriate covariate adjustment to account for differences in study designs and patient population, one may infer the efficacies of linagliptin and sitagliptin relative to placebo when administered to comparable patients under comparable conditions.

Methods: An analysis data set was assembled based on a systematic review of available clinical trials for sitagliptin and summary statistics computed from Boehringer Ingelheim internal data sources for linagliptin. A Bayesian hierarchical model was developed to describe HbA1c levels as a function of dose, time, and selected covariates. Covariates related to demographics and study design were evaluated and incorporated in the model where appropriate. Standard model diagnostics were applied to ensure adequate model convergence and model fit. Population simulations based on the selected model were used to evaluate the average effects of linagliptin and sitagliptin in a reference population over 24 weeks of treatment.

Results: The final model described HbA1c levels for placebo treated individuals as a nonlinear function of time. Drug effects were incorporated as multiplicative adjustments to the placebo time course, and additional multiplicative covariate adjustments were made for baseline HbA1c, washout duration and race. Population simulations assuming a study design with no washout and a mean baseline HbA1c of 8% resulted in expected HbA1c differences from placebo at 24 weeks of -0.810 percentage points for linagliptin 5 mg (90% credible interval from -0.881 to -0.740) and -0.807 percentage points for sitagliptin 100 mg (90% credible interval from -0.878 to -0.737).

Conclusion: Consistent with the common mechanism of action, this model-based meta-analysis showed that the new DPP-4 inhibitor linagliptin (5 mg qd) results in a comparable efficacy as seen with the DPP-4 inhibitor sitagliptin (100 mg qd).

II-23 *David Stepensky* Inter-patient variability of local vs. systemic effects of TNF-α-neutralizing antibodies in rheumatoid arthritis

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Objectives: To estimate the inter-patient variability in the rheumatoid arthritis (RA) disease state and in the pharmacokinetics and pharmacodynamics of TNF-α-neutralizing antibodies. To estimate the resulting variability in the time course of local (intraarticular) vs. systemic concentrations of TNF-α and in the efficacy of RA treatment.

Methods: The available data from the scientific literature on the inter-patient variability of the RA disease state and the pharmacokinetics of TNF-α-neutralizing antibodies were analyzed using a target-mediated drug disposition (TMDD) model with three sites of antibody-TNF-α interaction (the synovial fluid of the affected joints, the central and peripheral compartments).

Results: The variability in the RA disease state and in subcutaneous absorption, distribution and elimination of the TNF-α-neutralizing antibodies was estimated. The time course of the TNF-α levels was affected to the highest extent by the disease state (i.e., baseline TNF-α secretion rates in the individual compartments) and the rate of antibody elimination. Variability of all the analyzed parameters had limited effect on the balance of systemic vs. local TNF-α-neutralizing effects of the studied antibodies due to their high permeability from the diseased joints to the central circulation in the RA patients.

Conclusions: Despite the extensive clinical use of TNF-α-neutralizing antibodies, the parameters that govern their efficiency in individual RA patients have not been identified. The effects of treatment on the local TNF-α levels in the affected joints and their correlation with the clinical markers of RA are largely unknown. Efficient RA treatment using TNF-α-neutralizing antibodies should take into account the inter-patient variability of local vs. systemic factors related to the disease state and the antibody pharmacokinetics. Similar analysis of inter-patient variability in local and systemic interactions between drugs and the target should be taken into account for other drugs acting on soluble targets (growth factors, interferons, interleukins, immunoglobulins, etc.).

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II-24 *Jasper Stevens* Nonlinear mixed effects evaluation of Hamilton Depression Rating Score following combination treatment of presynaptic- and postsynaptic glutamate receptor inhibitors in bipolar depression patients

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Objectives: Presynaptic- and postsynaptic glutamatergic modulation is associated with anti-depressant activity that takes several weeks to reach a maximal full effect [1]. Limiting mood elevation after single drug administration may be the result of compensatory synaptic processes [2, 3]. Therefore, using augmentation treatment with agents having presynaptic- and postsynaptic effects on the glutamatergic system (lamotrigine and memantine, respectively), this study aims to evaluate the effect of augmentation therapy on the rate of change in mood elevation in patients with bipolar depression.

Methods: In a recent pilot study [4], 29 bipolar depression outpatients on a stable lamotrigine dose regimen received placebo or memantine pills daily (titrated up by 5 mg per week to 20 mg) in a randomized, double blind, parallel group, 8-week study. Patients were evaluated weekly using the 17-item Hamilton Depression Rating Score (HDRS) and all data were analyzed simultaneously. In this study, linear-, exponential-, maximal effect-, Gompertz- and inverse Bateman functions were evaluated using a Bayesian approach population pharmacodynamic model framework. In these models, differences in parameters were examined across the memantine and placebo augmentation groups.

Results: A Gompertz function with a treatment switch on the parameter describing the speed of HDSR decline best described the data. Between subject variability was identified on baseline HDRS and amplitude of score improvement.

Conclusions: This pharmacodynamic approach identified an increased speed of response after memantine augmentation, compared to placebo augmentation in bipolar depression patients.

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II-25 *Elisabet Størset* Population pharmacokinetics of tacrolimus to aid individualized dosing in kidney transplant recipients

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Objectives: Tacrolimus is a potent immunosuppressive agent, frequently used after kidney transplantation. High variability between subjects and dosing occasions in addition to apparently time varying pharmacokinetics makes target concentration intervention (TCI) challenging. Initial doses are typically based only on total body weight. Tacrolimus is highly distributed into and bound to erythrocytes [1], but hematocrit is not used for TCI. Several population pharmacokinetic models have been developed [2-5], but few are reported to be in use for initial dosing or Bayesian forecasting, even though there is wide agreement of its potential clinical value. The aims of this study were (1) to identify predictable differences between kidney transplant recipients for initial dosing of tacrolimus, (2) to develop a population model suitable for Bayesian forecasting and (3) to evaluate the use of hematocrit for tacrolimus TCI [6].

Methods: A total of 1546 blood samples were collected from four independent studies. Twenty-nine patients contributed full pharmacokinetic profiles from 44 occasions, and 44 patients contributed trough concentrations from the first 10 weeks after transplantation. A two compartment model with first order absorption and lag time, using study specific absorption rate constants and residual error models was used to describe the data. Between occasion variability was tested on all parameters. The following covariates were examined: *CYP3A5* genotype, hematocrit, age, weight, height, sex, albumin, serum creatinine, C-reactive protein, liver function tests, steroid dose, concomitant use of interactive drugs, acute rejection episodes and time after transplantation. Modeling was done with NONMEM 7.2, using the first order conditional method with interaction.

Results: Relative bioavailability was decreased by 53 % in CYP3A5 expressers, by 27 % in females, by up to 21 % with higher prednisolone doses and was 104 % higher immediately after transplantation. The two latter effects were best described by sigmoid E_{max} models ($Pred_{50}$ 16 mg/day, Day_{50} 1.4 days). Allometric scaling to fat free mass revealed a relationship between PK and body size in kidney transplanted adults. Studies using total body weight have not found a relationship with size [2-5]. A linear hematocrit associated change in blood concentration explained the time related changes in pharmacokinetics after day 2 post-transplant. Assuming F=0.2 [7], the blood clearance of tacrolimus (2.7 L/h/60kg fat free mass) means it has a low extraction ratio. Pharmacologically active unbound drug clearance should not be affected by changes in hematocrit. Hematocrit based standardization of measured and target concentrations may lead to more consistent clinical effects.

Conclusions: Initial dosing may be improved if determined by *CYP3A5* *1/*3 genotype, sex, prednisolone dose and allometric scaling to fat free mass. The model should be suitable for Bayesian forecasting during the first 10 weeks after transplantation. Measured blood concentrations should be adjusted using hematocrit to achieve a hematocrit standardized target concentration.

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II-26 *Fran Stringer* A Novel Pharmacodynamic Modeling Approach to Determine Long Term Disease Progression Rates in Japanese Type 2 Diabetes Patients: Pioglitazone vs. Conventional Therapy

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Objectives: Type 2 diabetes mellitus (T2DM) is a slowly progressing disease, making changes in disease trajectory difficult to assess in short term trials. However, the prediction of long term drug effects is often relevant early in clinical development. Disease system analysis can describe and explain changes in disease status as a function of time and drug therapy, separating symptomatic from protective effects on the disease[1]. This approach has been utilised in Caucasian T2DM patients to discriminate between standard of care (SoC) and new therapy[2]. Long term analysis in the UKPDS demonstrated symptomatic effects for both lifestyle and classical anti-diabetic agents[3]. Short term benefits were demonstrated but no effect on disease modification was found with all agents failing to alter the long-term rate of disease progression. Up until now, no disease progression analysis in Japanese subjects has been undertaken on mid to long-term data.

Methods: A study in Japanese T2DM patients (n=587) was conducted over 4 years comparing pioglitazone to SoC treatment[4]. Patients received pioglitazone with other oral glucose-lowering drugs (excluding another TZD) or oral glucose-lowering drugs excluding TZD. The aims were firstly to determine disease progression rates in Japanese subjects and secondly to evaluate the relative drug effect of pioglitazone vs. SoC on HbA1c levels and underlying disease progression. The disease progression model was implemented to distinguish symptomatic drug effects on disease status from effects on disease progress.

Results: The disease process was modeled using an indirect response model for HbA1c, with a proportional time-dependent increase in the HbA1c level relative to the baseline at study start. Pioglitazone showed a superior decrease in HbA1c resulting from stronger symptomatic inhibition of HbA1c, in addition to modification of the disease rate relative to SoC treated patients. The disease progression rates estimated in the Japanese population were found to be comparable to those in the Caucasian population.

Conclusion: The work presented here describes the first comprehensive disease progression model in Japanese patients comparing pioglitazone with SoC to enhance the understanding of drug action on disease status and long-term disease progression. This disease systems analysis result can be utilized to create a framework to enable more accurate long term prediction of drug effects when only short term trial data is available.

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II-28 *Herbert Struemper* Target-mediated clearance of ofatumumab: a tale of different disease states

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Objectives: Ofatumumab is a CD20-targeted monoclonal antibody indicated for the treatment of patients with refractory chronic lymphocytic leukemia (CLL) and under investigation in other hematological malignancies and autoimmune conditions. The objective of this analysis was to revise a previous population pharmacokinetic (popPK) model for ofatumumab [1] based on additional data in refractory CLL (Study Hx-CD20-406) and to analyze the differential impact of the disease state on target-mediated clearance (TMC).

Methods: PopPK analysis was performed on data from 4 Phase I and II studies (rheumatoid arthritis (RA), 2 doses, 300-1000 mg, N=187; follicular lymphoma (FL), 4 doses, 300-1000 mg, N=38; relapsed CLL, 4 doses, 100-2000 mg, N=33; refractory CLL, 12 doses, 300+11x2000 mg, N=219) using NONMEM. The starting point of this analysis was a linear two-compartment model representing nonspecific clearance (NSC) of ofatumumab, augmented by a TMC component representing the specific clearance of ofatumumab by CD20 expressed on B cells and the interconnected kinetics of drug and target levels. Various parameterizations of the TMC component were explored to obtain a concise and flexible representation of B-cell kinetics in the different populations. *Post hoc* parameters and predicted drug and target profiles were used to examine the relative contributions of NSC and TMC and their changes over time.

Results: The nonspecific linear model component had a systemic clearance of 0.31 L/d (7.5 mL/h), inter-compartmental clearance of 0.93 L/d, central volume of 3.3 L and peripheral volume of 2.1 L. The terminal half-life of 21.8 days for the linear model component is consistent with other IgG antibodies. The predicted target kinetics reproduced the features of B-cell depletion observed in refractory CLL (initial rapid decline and eventual rebound of B-cell counts). Accordingly, TMC was initially large compared to NSC but was reduced (absolutely and relative to NSC) when target levels decreased. The magnitude of TMC relative to NSC was largest for refractory CLL (initial dominance of TMC over NSC) followed by relapsed CLL, FL, and RA (TMC was initially small, negligible after second dose).

Conclusions: This analysis demonstrates that the relative and temporal impact of TMC can vary considerably between disease states. The resulting model allows the simulation of ofatumumab PK in untested disease populations if data or hypotheses for disease-specific B-cell turnover are available.

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II-29 *Elin Svensson* Linear approximation methods for fast evaluation of random effects models

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Objectives: To develop and assess a fast method for evaluation of IIV, IOV and residual variability (RV) model components.

Methods: The linear approximation used was based on a previously described first-order conditional estimates linearization [1]. Three real data analyses described elsewhere [2, 3, 4] were used to compare the results from nonlinear models with the corresponding linear version. Derivatives from a basic nonlinear model were used in the extended linear models.
The results were assessed based on the difference in objective function value (ΔOFV) between a basic model and extended models for the nonlinear and linear estimation methods respectively. The RV models evaluated were extensions to an additive, a proportional or a combined additive and proportional error model and included IIV on the RV, autocorrelation, a power model and time dependence. IIV and IOV variances and covariances, not estimated in the basic model, were added in the extended models. The analysis was carried out in NONMEM 7.2 [5] aided by PsN [6].

Results: The nonlinear and linear approaches gave the same results for models with additive RV. For models with proportional RV the ETA estimates sometimes got caught in local minimas which caused deviating results. Modelling the data on logarithmic scale and hence transforming the RV to additive solved the problem. For models with a combined RV a strategy including a dynamic scedasticity and transform-both-sides model [7] proved successful.
The ΔOFV from the linear and the conventional nonlinear models agreed well for all the evaluated RV models. For IIV and IOV evaluation the ΔOFV agreed well in the lower range but for large ΔOFV and when inclusion of variability resulted in a large change of typical values of the parameters some discrepancies were seen. The agreement was good also for IIV and IOV correlations. The linear analysis identified the same extended models as the conventional nonlinear analysis. The total runtime for estimating the four alternative RV models for one of the example data sets was 2.4 h and 3.7 min for the nonlinear and linear models respectively.

Conclusions: The linear approximation substantially decreases runtimes and has successfully been used for evaluation of a broad range of random effects models. The method can be implemented in PsN to further automate and speed up the model development process.

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II-30 *Stina Syvänen* P-glycoprotein alterations at the blood-brain barrier influences [11C]flumazenil brain concentrations but does not interfere with estimation of GABAA receptor density in a rodent model of epilepsy

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Objectives: [^{11}C]flumazenil positron emission tomography (PET) is used to assess $GABA_A$ receptor function in people with epilepsy and to localize epileptic foci prior to resective surgery. The binding kinetics of [^{11}C]flumazenil is dependent on $GABA_A$ receptor density (B_{max}) and affinity (K_D). Recently, flumazenil was reported to be effluxed from the brain by P-glycoprotein (P-gp) [1]. It is believed that P-gp function is upregulated in epilepsy, and further that an upregulation in P-gp could alter transport of [^{11}C]flumazenil into the brain and thereby confound interpretation of [^{11}C]flumazenil PET. Thus, the objective of this study was to investigate if flumazenil blood-brain barrier transport and binding to $GABA_A$ receptors is altered in epileptic rats compared to controls, and whether changes in P-gp function may confound interpretation [^{11}C]flumazenil PET.

Methods: 15 epileptic and 14 control rats underwent 2 consecutive PET scans. [^{11}C]flumazenil was mixed with different amounts of unlabelled flumazenil to cover a wide range of receptor occupancies during the scan. Prior to the second scan, the rats were pre-treated with P-gp inhibitor tariquidar. A full pharmacokinetic model for [^{11}C]flumazenil pharmacokinetics in plasma and brain was developed in NONMEM VI. Systematic covariate analysis was performed to identify covariates significant for changes in [^{11}C]flumazenil transport across the blood-brain barrier as well as in B_{max} and K_D.

Results: $GABA_A$ receptor density, B_{max}, was estimated as 44 ± 2 ng×mL^{-1} in the hippocampus in naïve control rats and was decreased by 12% in epileptic rats compared to controls. The receptor affinity, K_D, was similar in both rat groups and was estimated as 5.9 ± 0.9 ng×mL^{-1}. There was no difference in flumazenil transport across the blood-brain barrier between control and epileptic rats and the effect of tariquidar treatment was similar in both rat groups. Tariquidar treatment decreased flumazenil transport out of the brain by 73%, confirming earlier reports of P-gp interaction, but did not influence B_{max} or K_D compared to the baseline scan.

Conclusions: B_{max} was decreased in epileptic rats compared with controls, but no alteration in blood-brain barrier transport of flumazenil was observed. P-gp inhibition by tariquidar treatment increased brain concentrations of flumazenil in both groups, but B_{max} and K_D estimates were not influenced suggesting that [^{11}C]flumazenil scanning is not confounded by alterations in P-gp function.

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II-31 *Takeshi Tajima* Mechanism-based assessment on the pharmacodynamics of neuromuscular relaxants and general consideration for receptor blockers

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Objectives: Neuromuscular relaxants exert the pharmacological effect blocking nicotinic receptors at neuromuscular junction. For the pharmacodynamics, 1) in vitro affinity for receptor and in vivo potency are neither in concord nor in a proportional relationship; Even for a drug with high affinity, a substantial concentration is needed to evoke the blockade effect, 2) the slop of dose-effect curve or concentration-effect curve is different among drugs, suggesting a drug with higher affinity has a steeper slop. In this study, the underlying mechanisms were investigated using a dynamic model based on physiological and pharmacological mechanisms.

Methods: A dynamic model was developed taking into account: i) released transmitter acetylcholine (ACh) binds to receptor and evokes muscle contraction, ii) tension of muscle contraction depends on receptor occupancy by ACh, iii) a relaxant binds to receptor competitively inhibiting receptor binding of ACh and depresses muscle tension. Concentration-effect curves were simulated for drugs with various dissociation constants of drug-receptor complex (Kc). Relationship of Kc with EC50 and apparent slop (γ) of concentration-effect curves was investigated.

Results: Drugs with Kc of 0.001, 0.01, 0.1 and 1.0 μM show EC50 of 0.146, 0.285, 1.70 and 15.8 μM, and γ of 11.8, 6.84, 5.19 and 5.00, respectively. Comparing drugs with low affinity (Kc=1.0) and moderate affinity (Kc=0.1), the difference of Kc is almost proportionally reflected in EC50 and has little impact on γ. However, with increasing affinity (decreasing Kc), Kc is under-proportionally reflected in EC50 and γ increases. Receptor density (about 0.2 μM) is a responsible factor. Drugs need to occlude receptors to exert the effect. So, even a drug with high affinity needs concentrations close to receptor density, and EC50 does not become so small. Further, for a drug with high affinity, the amount of drug binding to receptors is non-negligible relative to the total amount of drug in the action site. Free concentration dose not approximate total concentration, which causes the change of slope.

Conclusions: A mechanism-based dynamic model provided convincing explanations. Regarding not only muscle relaxants but also other therapeutic drugs blocking relevant receptors, the pharmacodynamics might be affected by affinity for receptor and receptor density when receptors densely locate in the action sites.

II-32 *Daniel Tatosian* Strategic comparator modeling and simulation to optimize dose selection for a dose-range finding study

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Objectives: Drug X is under development using a rapid straight-to-IIB development paradigm. To support dose selection for this dose-range-finding study, Pharmacokinetic/Pharmacodynamic (PK/PD) models were developed for drug X and a reference drug Y to conduct clinical trial simulations.

Methods: PK/PD models describing the PK and PD of an intermediate biomarker for Drug X and an internal reference Drug Y were developed. Additional PD-PD models relating the observed trough and individual-predicted average levels of intermediate biomarker A to the primary efficacy endpoint were developed. Using the linkage through the intermediate biomarker, the combined PK/PD models were used to conduct clinical trial simulations to evaluate the probabilities that given a selected set of Phase IIB doses, a dose-response relationship could be accurately determined.

Results: The plasma pharmacokinetic and intermediate biomarker data for Drug X could be described by nonlinear distribution of the drug to target biomarker present in both the central (sampling) and peripheral compartments. A linear 2 compartment model described the PK of Drug Y. The relationship of drug concentration to the intermediate biomarker was well characterized by an empirical Emax model. The relationship between the trough levels of the intermediate biomarker and primary endpoint was captured by sigmoidal Emax models. As a sensitivity analysis around the assumption of trough relation to efficacy, a second model relating the individual-predicted weighted average intermediate biomarker levels to primary endpoint was also developed. Trial simulations from both models were conducted for various IIB study sizes and dose selections, with parameter distributions obtained from bootstrapping the datasets. From the clinical trial simulations, probabilities to accurately capture the predicted dose-response model were calculated by refitting each simulated trial to a dose-response model and comparing the accuracy to the predicted true dose-response model.

Conclusions: PK/PD models were developed for a new drug under development and a reference drug, with a shared intermediate biomarker. By using the shared intermediate biomarker to bridge, trial simulations were conducted to enhance the decision-making and guide the development team to optimize the doses selected for the dose-range finding study.

II-33 *David Ternant* A model predicting expected infliximab serum concentrations using only dose and time since last infusion

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Objectives: Infliximab, an anti-TNF-α antibody, has profoundly modified the treatment of several inflammatory diseases but its pharmacokinetics (PK) is highly variable between patients. This variability influences the clinical response. The objective of this study was to describe infliximab pharmacokinetics using routine therapeutic drug monitoring (TDM) data and to develop a model allowing the prediction of infliximab concentrations using only dose and time since last perfusion.

Methods: Between 2005 and 2010, infliximab concentrations were monitored in 655 patients treated with infliximab in Tours university hospital. Infliximab concentrations associated with positive antibodies toward infliximab were removed from the analysis. To describe infliximab pharmacokinetics, a one-compartment PK model was used. A simplified model for TDM (TDM model) was built to devise the expected infliximab concentrations us ing only dose and time since last infusion. This model described, for each visit, a monoexponential decrease of infliximab concentrations since the last infusion. 2/3 and 1/3 patients were randomly assigned to estimation and validation groups, respectively. In the validation group, infliximab concentrations were predicted using typical PK and TDM model parameter estimates. To validate both PK and TDM models, their respective concentration predictions were compared.

Results: A total of 354 patients were eligible. They were treated for rheumatoid arthritis (RA, n=49), ankylosing spondylitis (AS, n=132), inflammatory bowel disease (IBD, n=112), both AS and IBD (AS-IBD, n=7), Psoriatic rheumatism (PR, n=44) and other diseases (OTH, n=10). Both PK and TDM models described the data satisfactorily and provided estimations of volume of distribution (Vd) and clearance (CL). Using PK analysis, median Vd, CL and half-life (T½) were 6.7 L, 0.3 2 L/day and 14 days, respectively. Using TDM model, apparent volume (Vd*) and clearance (CL*) were 5.7 L and 0.27 L/day, respectively. The two types of PK parameters were similarly influenced by covariates: Vd and Vd* were influenced by disease whereas CL and CL* were influenced by disease, weight and sex. The validation step showed that the two models provided similar concentration predictions.

Conclusions: Infliximab PK is different between SPA, AS and IBD patients. The developed TDM model is precise and accurate and may be used for TDM of infliximab.

II-34 *Nadia Terranova* Modelling of protozoa dynamics and drug effects in a murine model of malaria infection

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Objectives: In humans, severe malaria is responsible of over a million of deaths every year. The development of new antimalarial compounds and vaccines is a critical for malaria eradication. Of particular interest is the development of compounds that are effective against Plasmodium falciparum. A new murine model has been developed to assess the therapeutic efficacy of antimalarial drugs using human erythrocytes, which better reflects disease processes (i.e., protozoa clearance) in humans [1]. The objective of this investigation was to develop a PKPD model describing protozoa dynamics and drug effects following chronic administration of atovaquone.

Methods: To measure the efficacy of atovaquone against infection by Plasmodium falciparum, female humanized mice were engrafted with human erythrocytes as performed in [1] and then infected with a specific strain of this parasite. The experiment included control and active treatment groups. Blood concentrations of atovaquone were collected in treated animals .Protozoa load and fraction or infected human erythrocytes were used as pharmacodynamic endpoints. The parasite dynamics, pharmacokinetics and pharmacokinetic-pharmacodynamic relationships of atovaquone were characterised using nonlinear mixed effects modelling (NONMEM v.7.1).

Results: The pharmacokinetics of atovaquone was described by one compartment model with first order absorption. Parasite dynamics were evaluated using a user-defined compartmental model, in which infected and non-infected erythrocyte pools are defined. Drug effect was successfully parameterised in terms of an Imax model. Preliminary results indicate that the model is able to describe experimental data, in spite of considerable variability in parasite load.

Conclusions: Model-based approaches have been applied successfully to describe drug effects in experimental models of viral infection and translate preclinical findings into therapeutic recommendations. Our exercise suggests that comparable advantages exist for the evaluation of treatment effect and recrudescence in parasitic infections. Further validation of the proposed PKPD model is still ongoing, which will demonstrate the potential generalisability of the approach.

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II-35 *Hoai Thu Thai* Residual-based bootstrap methods for estimating uncertainty of parameters in nonlinear mixed-effects models with heteroscedastic error

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Objectives: Bootstrap methods are used for estimating uncertainty of parameters in multi-level or linear mixed-effects models with homoscedastic error [1-2]. Residual-based bootstrap methods which resample both random effects and residuals are an alternative approach to case bootstrap, which resamples the individuals. Residual bootstrap may be a good way to approach the data generating process [3]. However, most PKPD applications use the case bootstrap, for which software is available [4-5]. We propose to investigate the residual bootstrap for nonlinear mixed-effect models (NLMEM) with heteroscedastic error.

Methods: We implemented nonparametric and parametric versions of residual bootstrap, as well as the case bootstrap in R 2.14. In the nonparametric method, the standardized residuals and random effects were corrected for shrinkage [6-7]. In the parametric method, they were sampled from the estimated distributions. The performance of the three bootstraps was assessed by a simulation study based on clinical trials of aflibercept, an anti-VEGF drug, in cancer patients. We assumed that the PK of aflibercept follows a two-compartment infusion model with 1st order elimination. A frequent sampling design (30 subjects and 9 samples per subject) and a sparse sampling design (68 subjects and 4 samples per subject) were investigated using 100 replicates and 1000 bootstrap samples per replicate for each bootstrap method. Each bootstrap dataset was fit with Monolix 4.1. The bootstrap approaches were compared in term of bias of parameters, standard errors (SE) and coverage rate of the 95% confidence interval of all parameter estimates. The bootstrap estimates were also compared to the asymptotic estimates.

Results: Monolix provided good estimates for parameters except for the correlation between clearance (CL) and intercompartment clearance (Q) in both simulated designs and Q in the sparse design. Compared to the asymptotic approach, the three bootstraps provided SE closer to the empirical SE for some parameters but farther for others, while all methods provided similar coverage rates close to 95% for all parameters in both designs.

Conclusion: The residual bootstrap works as well as the case bootstrap for both designs in NLMEM with heteroscedasticity. However, none of the bootstraps evaluated provide a better description of uncertainty compared to the asymptotic approach in these simulation settings. Models with higher nonlinearity should be investigated in the future.

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II-36 *Kirstin Thelen* Dynamically simulating the effect of food on gastric emptying using a detailed physiological model for gastrointestinal transit and absorption

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Objectives: It is well-known that food can influence drug absorption through different physicochemical and physiological mechanisms.[1] One important factor represents the rate of gastric emptying (GE), which controls the delivery of drugs to the absorption sites in the intestine. In order to predict the impact of meal ingestion on drug absorption, the relationship between the characteristics of a meal and the GE rate was analyzed, characterized and integrated into a novel model for gastrointestinal transit and absorption.[2,3]

Methods: In a comprehensive literature search, information about the impact of various meals on GE function was collected. The data was analyzed for the influence of the characteristics of the meal including its volume, energy content and composition on the GE rate. Seven mathematical functions were tested for the ability to describe the experimental GE profiles. The most suitable function retrieved was subsequently implemented into the detailed absorption model that is part of the physiologically-based pharmacokinetic (PBPK) software tool PK-Sim®. With the help of this function, the impact of co-administration of a meal on the pharmacokinetics (PK) of an orally administered drug was predicted for a population of 500 male individuals using the example of paracetamol.

Results: More than 100 datasets for GE profiles following ingestion of various meals were obtained. In agreement with literature information, the meal energy content was found to be the principal factor determining the GE rate. A mathematical function of the Weibull type was identified to be the most appropriate empirical function to describe the relevant phases of the experimental GE profiles irrespective of the composition of the meal. Based on the PBPK model for paracetamol administered in the fasted state and using the optimized function, the impact of food ingestion on paracetamol PK could be predicted well.

Conclusions: The influence of meal ingestion on GE rate in humans was analyzed on the basis of extensive literature information. The comprehensive set of data was successfully transferred into an empirical GE function that can be used to physiologically simulate the food-related effect of GE on the PK of orally administered drugs. Further physiological changes associated with the ingestion of meals and that are considered to influence the PK of drugs such as luminal pH, gastrointestinal liquid volumes and splanchnic blood flow will be studied soon.

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II-37 *Mirjam Trame* Evaluating the Influence of Different Covariates on Enoxaparin Pharmacokinetics in Neonates, Infants and Children

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Objectives: Enoxaparin, a low-molecular-weight-heparin, is used off-label in children for prevention of symptomatic thromboembolism. However, little is known regarding its pharmacokinetics (PK) in children. The aim of this investigation was to further evaluate the PK by using additional data and covariate analysis combined with previous study data. [1]

Methods: Data from 126 patients (median age: 5.9 years; median weight (WT): 24 kg) receiving enoxaparin either as a once or twice daily dose regimen, were analysed. All studied patients received enoxaparin during secondary prophylaxis therapy. Using NONMEM, steady-state plasma concentration-time data were analysed. The following patient characteristics were assessed as covariates on PK parameters using conventional and linearised stepwise covariate model (SCM) building: age, WT, body surface area (BSA), serum creatinine, estimated Glomerular Filtration Rate (eGFR), Body Mass Index, and Antithrombin. Missing covariates were handled using: a Slope-Intercept model for WT imputation from postmenstrual age (PMA); the Boyd equation, using the imputed WT as an independent variable, to calculate missing BSA values [2]; the Mosteller formula to calculate missing heights from the imputed BSA and WT; and either the Lund-Malmö equation or the updated Schwartz equation for eGFR imputation, depending on age or height availability, respectively. [3,4]

Results:A two-compartment model with interindividual variability (IIV) on clearance (CL) and central volume of distribution (V2) best described the data. Allometrically scaled WT was included in the base model on CL and V terms with exponents ¾ and 1, respectively. As enoxaparin is mainly cleared renally it was hypothesised that CL might be parameterised as a sum of an eGFR-dependent renal and a WT- or BSA-dependent non-renal component. However, the SCM did not find any parameter-covariate relations statistical significant for inclusion. For a 24 kg subject the final parameter estimates (IIV %) were: CL 0.44 L/h (59%), V2 4.12 L (21%), intercompartimental clearance (Q) 5.02 L/h, peripheral volume of distribution (V3) 0.0022 L and absorption rate constant (ka) 0.39 h-1.

Conclusions: This population PK analysis confirms our previous findings [1] that no dose adjustments based on a covariate other than WT are needed for renally healthy patients. The model describes enoxaparin disposition in all age groups in our study population from neonates to adolescents.

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II-38 *Kellie Turner* Adapting a Target-mediated Drug Disposition (TMDD) Model to Account for Delayed tmax Following IV Infusion of a Monoclonal Antibody

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Objectives: The aim of the analysis was to build a semi-mechanistic model to describe the PK of a monoclonal antibody administered by IV infusion.

Methods: A population pharmacokinetic (PK) analysis was conducted using NONMEM version 7.2 to describe the IV-infusion data. Estimation methods included first order conditional estimation with interaction (FOCEI), Monte Carlo importance sampling expectation maximization (IMP), and IMP assisted by mode a posteriori estimation (IMPMAP). The final model was selected based upon change in objective function value (OFV), precision estimates, diagnostic plots, and visual predictive checks (VPCs).

Results: PK data were available from 23 individuals. Samples for determination of total antibody concentrations were taken prior to infusion, mid-infusion, end of infusion, and at 2, 4, 24, 72-120, 144-192, and 336 hours after the end of the infusion. Clearance decreased with increasing dose from the first to the third of six escalating dose levels before levelling, consistent with TMDD. The model-building process began with a TMDD model using FOCEI. A two-compartment TMDD model using quasi-equilibrium approximation (1) was tested, but was not adequate because the antibody plasma concentrations continued to rise for 2-4 hours after the end of the IV infusion in a majority of individuals. Therefore, a transit model was added to the TMDD model and tested with FOCEI. Due to problems with model minimization, covariance step failure, and protracted run times with FOCEI, the IMP method was tested, but the OFV increased with successive iterations. Therefore, the IMPMAP method was implemented to test a series of 1 to 5 transit compartments. Compared to FOCEI, run times were shorter with IMPMAP, and the model successfully minimized with covariance step completion. Finally, a model with infusion into a depot compartment and 4 transit compartments followed by a 2-compartment TMDD was selected that best fit the data.

Conclusions: The population PK model for this monoclonal antibody adequately described the data, and can be used for clinical trial dosing scenario simulations. This model, or sub-sections of the model, may also apply to other compounds administered by IV infusion that show a delayed tmax. Furthermore, the IMPMAP estimation method offers a useful alternative to FOCEI for complex PK/PD models such as this TMDD model with depot and transit compartments.

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II-39 *Wanchana Ungphakorn* Development of Sparse Sampling Study of Oral Ciprofloxacin for Severely Malnourished Children

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Objectives: The population approach is a powerful tool to estimate pharmacokinetic (PK) parameters and to identify inter- and intra-individual variability from sparse sampling data but requires careful consideration of design issues to maximise the information that can be extracted from the data. The aims of this study were to (1) use optimal design methods to develop study designs and sampling windows for population PK studies of oral ciprofloxacin in malnourished children and (2) to investigate the influence of prior information on the results of optimal design methods.

Methods: The optimal design was developed using the population Fisher information matrix which is implemented in the PopDes program [1]. A modified Fedorov exchange algorithm with a grid size of 0.25 was used for the optimisation. The structural model, PK parameters and variability obtained from different patient populations were used as input information [2-4]. The maximum number of elementary designs was fixed at 3. Different proportions of subjects and different numbers of samples were examined and both the sample size and sampling windows were determined. The sampling time was limited to between 0 and 12 hours after the dose for most designs but the effect of sampling after a second dose was also investigated.

Results: For 3- and 4-sample designs, the optimal number of groups was 3 and 2, respectively. When using 2 groups, the number of subjects in each group could be varied. If up to 5 samples were allowed to be taken from each patient, one group of subjects would be adequate. The first sampling time point was dependent on the input variable which was related to the lag time specified in the model; however, the last sampling time was always 12 hours. Samples taken only after the first dose gave sufficient information. The expected CV of all parameters was less than 10% with sample sizes of 25 and 40 for 5- and 4-sample designs, respectively. For 3 samples, the CV for Ka remained above 20% despite increasing the sample size to 100. Thus, a higher cut-off point of 20% was used for Ka. It was found that a total of 40 subjects would be enough for a 3-sample study design.

Conclusion: Optimal study designs and sampling windows have been developed for future PK studies in malnourished children. Since the optimal designs were dependent on the prior information, prior knowledge of drug concentration-time profiles should be used with optimal design methods when designing population PK studies.

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II-40 *Pyry Välitalo* Optimal design for a population pharmacokinetic study of oxycodone in preterm neonates, neonates and infants

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Objectives: While the pharmacokinetics of oxycodone in children older than 6 months of age has been characterized, only one study is available for children aged 0-6 months[1]. Therefore we designed a new study about pharmacokinetics of oxycodone in children aged 0-24 months, which would include a larger number of patients than the previous study.

Methods: Data from two previous studies[1,2] was gathered and pooled (527 samples from 63 patients). The data were fitted into a two-compartment model, scaling clearance by weight with an exponent of 0.75, and estimating a sigmoidal age-dependent maturation function for clearance. The sampling times and number of children in different age groups were optimized using PopED[3]. Prior Fisher Information Matrix was incorporated into the optimization, because data from the new study will be combined with existing data from previous studies to fully characterize the developmental pharmacokinetics of oxycodone. The optimization results were verified by stochastic simulation and estimation (SSE).

Results: The clearance was well predicted by the maturation function (ωcl=43 %). The model predicted a weight-scaled clearance commensurate to 50% of adult value at time of birth, followed by a fast maturation. The other pharmacokinetic parameters were similar to those observed for older children. The optimized study design mostly contained children younger than 3 months of age. The data on optimal number of children of different ages, and optimal sampling times are presented as figures in the poster. The SSE procedure predicted relative standard errors below 20 % for all parameters.

Conclusions: Based on predicted standard errors, the upcoming study should be able to characterize the developmental pharmacokinetics of oxycodone with fairly good precision. Since the empirical maturation model predictions of oxycodone clearance are different from the maturation curves of the relevant CYP enzyme maturation curves[4], additional emphasis on the metabolic routes of oxycodone in children was considered important for the study. For that reason, collection of urinary samples was added to the study protocol.

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II-41 *Marta Valle* Population pharmacokinetics of rupatadine in children 2-11 years of age with allergic rhinitis

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Background: Rupatadine is a second generation antihistamine H1 and antagonist of PAF approved in Europe for the treatment of allergic rhinitis and skin conditions for which a pediatric solution is under development.

Objectives: (i) To evaluate the population pharmacokinetics (POPPK) of rupatadine oral solution in children 2-5 and 6-11 years of age with rhinitis allergy and (ii) to determine if the currently proposed regimen dose as a function of weight is enough to achieve similar plasma concentrations to those observed in adults older than 12 years.

Methods: A POPPK model was developed. Data from two studies performed in children with rhinitis allergy were analyzed: Study 1, included 11 children, 6-11 years old, a full PK profile in each children was obtained after a single oral dose of rupatadine. Study 2, 4 blood samples were obtained in 44 children, 2-5 years old after 14 and 28 days of treatment. Doses were 5 mg if weight > 25kg, or 2.5 mg if weight 10-25kg. Models were developed using NONMEM (version VI) with FOCE. Compartmental models were used assuming linear processes. The effect of different covariates (age, sex, height, weight and BMI) on the parameters was also evaluated. The final model was validated and further used to simulate plasma concentrations of rupatadine using different dose regimens for children with different weights.

Results: A two-compartment model with first-order absorption and elimination best described the PK of rupatadine in children (2-11 years-old). Weight influenced the clearance of rupatadine according to a linear function. Estimated parameters (RSE %) were : Lag=0.15h (6), ka=0.49h-1 (12), Vc=118L (37), Vp=3730L (29), Cld=210L/h (19), CL(20kg)=219L. Interindividual variability was estimated for Vc (139%) and CL (39%). Internal validation of the model showed a good predictive interval. Simulations showed that the proposed doses showed similar plasma concentrations previously described in adults ≥ 12 years old.

Conclusions: The population PK analysis of rupatadine in children 2-11 years old follows a bicompartmental disposition with first-order absorption. Rupatadine clearance increases with age. The used range of doses provided similar plasma concentrations to those associated with efficacy and safety in adults ≥ 12 years old.

II-42 *Sven van Dijkman* Characterisation of response and disease progression in paediatric epilepsy

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Objectives: Differences in response rate and efficacy occur across patients and across epilepsy types. Such differences may be explained by intrinsic (e.g., insensitivity to mechanism of action (MoA)) and extrinsic factors (e.g., endpoints, measurement method). The possibility of predicting treatment response taking into account pharmacological effects, placebo response and disease progression is critical for drug development, as the effect of add-on therapy can be confounded by the underlying disease progression. Despite the high incidence of epilepsy in the paediatric population, no systematic efforts have been made to describe its course and progression.

Methods: Given the chronic and paroxysmal nature of seizures, epilepsy can be described by Markovian processes. Markov models consist of series of states and transition rates which reflect the course of the disease, transitions between states can be used to describe placebo (PE) and treatment effects (TE). Here we propose the use of a hidden markov model (HMM) to relate frequency of seizures to underlying activity. PK [1] and PD profiles for valproate (VPA)-treated paediatric epilepsy patients were simulated using literature data. A HMM was fitted to these data describing short-term (ictal vs. interIctal) and long term (remission, resistance and death) states, including parameterisation of TE (Emax model) on the transition rates. The feasibility of this approach to discriminate between drug and disease-specific parameters and the stability of the model were evaluated using a bootstrap procedure.

Results: Five states and their respective transitions were implemented in the HMM. The probabilities of the transitions of individuals between states were modeled as the sum of the natural course (NC), the PE and TE. Parameters estimated using the Laplacian method were NC, PE, onset of PE and KE0. The model described the gradual decrease in seizure frequency including a more profound drop between the 5th and 10th day, representing an effect delay due to MoA and loading phase of the drug. Diagnostics showed adequate goodness-of-fit, with clear distinction between TE, PE and NC of disease.

Conclusions: Preliminary results suggest that a HMM can be used to accurately fit longitudinal data from chronically treated patients. Although demographic covariate effects have not been implemented yet, transition rates were shown to be sensitive to drug effects and may provide the basis for predicting long term response in the presence of disease progression.

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II-43 *Coen van Hasselt* Model-based evaluation and optimization of cardiac monitoring protocols for adjuvant treatment of breast cancer with trastuzumab

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IntroductionTrastuzumab treatment is associated with occurrence of cardiac toxicity, for which monitoring of the left ventricular ejection fraction (LVEF) is indicated. The performance of the currently used monitoring protocol as defined in the summary of product characteristics (SPC) is however unknown.

ObjectivesThe objectives of this analysis were to: i) quantitatively evaluate the currently used cardiac monitoring strategy, as defined in the SPC; ii) suggest further improvements in cardiac monitoring strategies by inclusion of adaptive properties to the current monitoring protocol; iii) demonstrate how a model-based framework can be applied to evaluate repeated measurement (cardiac) monitoring protocols.

MethodsA model-based framework was developed comprising a PK-PD-model for trastuzumab associated changes in LVEF, and a protocol-execution model, describing treatment interventions based on the observed response. Three monitoring protocol scenarios were considered: S1) the SPC-based protocol which represents the currently used monitoring protocol, S2) an adaptive protocol is based on S1, but which includes exclusion of low-risk patients, and S3) a protocol considers a scoring-based algorithm for determining if an intervention is necessary. Evaluation metrics were defined allowing evaluation of diagnostic and therapeutic properties of monitoring strategies. These included the observed area above the LVEF

ResultsFor scenario S3 it was found that patients not experiencing cardiac toxicity receive a marginally higher dose intensity then patients in S1/S2. The success of a protocol-defined dose reduction was improved from 40.2% for the SPC-based protocol, to 75.8% for a scoring-based protocol, thereby decreasing the observed severity of cardiotoxicity. The mean number of LVEF measurements was reduced by 17%, when the monitoring protocol for low-risk patients is adjusted.

ConclusionThis model-based evaluation approach enabled successful evaluation and optimization of cardiac monitoring protocols. The proposed framework and associated evaluation metrics could be applied for evaluation of drugs requiring longitudinal monitoring of (cardiac) toxicity.

II-44 *Charlotte van Kesteren* Predictive performance of a busulfan pharmacokinetic-model in children and young adults from five international transplant centers: a study of varying doses, underlying diseases, ethnicities, body weights, ages and body mass indices

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Objectives: Recently a paediatric pharmacokinetic (PK) model was developed for busulfan in order to explain the wide variability in PK of busulfan in children, as this variability is known to influence the outcome of hematopoietic stem cell transplantation (HSCT) in terms of toxicity and event free survival. The current study assesses the predictive performance of this busulfan PK-model in a new, more diverse pediatric population, including data from patients with different underlying diseases, ethnicities, body weights, ages and body mass indices, from five international paediatric transplant centers.

Methods: The previously published (original) busulfan PK-model was developed from data of 245 patients (0.1-26 years of age). To externally validate this model, data were collected from another 158 patients (0.1-35 years) who underwent HSCT in five international transplant centers. Observed *versus* predicted plots, normalized prediction distribution error analysis, refit of the model on the external (n=158) and combined datasets (n=403), and subpopulation analyses were evaluated.

Results: The original busulfan PK-model was found to be stable and parameter estimates precise. Concentrations predicted by this model were in good agreement with the observed concentrations from the five external datasets. Plasma concentrations in patients with different underlying diseases, ethnicities, body weights, ages and body mass indices were adequately predicted.

Conclusions: Our pediatric busulfan PK-model has been externally validated. This model predicts busulfan concentrations in pediatric and young adult patients ranging between 3 and 86 kg without bias and with good precision, regardless of transplant center, underlying disease, ethnicity, body weight, age or body mass index. This busulfan PK-model forms the basis for individualized busulfan dosing.

II-45 *Eline van Maanen* A step-wise analysis of multiple biomarkers drives the development of a Semi-Mechanistic Comprehensive Model. Application to modulation of Amyloid-β.

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Objectives: Integrating different biomarkers, to model a biological cascade of responses, results in technical challenges in NONMEM. An example of such is discussed for the multi-step production of amyloid protein (Aβ) and clearance from brain. Altered Aβ processing is hypothesized to lead to development of Alzheimer's disease (AD). The objective was to develop an approach to build a comprehensive model describing biomarker inter-relationships and their responses to inhibitors acting on different sequence in the Aβ processing pathway and clearance to CSF as an aid to drug development targeting AD.

Methods: Data on 4 biomarkers (sAPPβ, Aβ40, Aβ42, sAPPα) measured in CSF in cisterna-magna-ported rhesus monkeys receiving BACE (1 study) or GS (2 studies) inhibitors were available. BACE acts earlier in the cascade, affecting all 4 biomarkers; GS affects Aβ40 and Aβ42. A step-wise modeling approach was followed: I) Each biomarker-inhibitor combination was evaluated. II) For BACE a comprehensive biomarker model was developed by sequentially adding each biomarker, using one drug effect term to account for response of all 4 biomarkers. III) Aβ40 and Aβ42 response to GS was integrated into the model.

Results: I) For each biomarker-inhibitor combination comparable model structures and IC50 estimates were obtained. II) An indirect response model described sAPPβ response to BACE. The sAPPβ pool was then used as moderator to describe the baseline and behavior of Aβ40 and Aβ42 in presence of BACE. Next, sAPPα (informing an alternate pathway) was incorporated in the model. A precursor pool, shared by sAPPα and sAPPβ, was introduced to describe all 4 biomarkers with one common drug effect. The effect of BACE was built-in the model as inhibition of loss of this precursor pool. Different transit rates for transit compartments from site-of-action (brain) to measurement-site (CSF) allowed the rate of onset of response to differ for each biomarker. III) The response of Aβ40 and Aβ42 to GS was built-in the model, as inhibition of the exit-rate constant of the sAPPβ pool.

Conclusions: A step-wise modeling approach was developed to facilitate the build of a comprehensive model for describing 4 biomarkers measured in response to 2 inhibitors. The model characterized the response and inter-relationships of the biomarkers and gives insight into the mechanism and rate-limiting processes of the system. It is expected that the model will aid further development of drugs targeting AD.

II-46 *Nieves Velez de Mendizabal* Discrete distribution models for relapsing-remitting dynamics observed in Multiple Sclerosis

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Objectives: Multiple sclerosis (MS) is a prototypic autoimmune disease which affects to the central nervous system (CNS) with a relapsing-remitting symptomatology (RRMS) [1]. The focal inflammatory events of the CNS are evident on MRI as contrast enhancing lesions (CELs). The natural history of a CEL is highly unpredictable. For the appropriate design of future longitudinal studies and clinical trials, it would be relevant to know the distribution of new CELs. Here we analyzed the best statistical model fitting the distribution of CELs developed by nine RRMS patients whom underwent monthly MRI for 48 months.

Methods: Subjects. Data for this study were obtained from the NINDS-NIH [2]. Nine patients, not receiving immunomodulatory treatment with RRMS who underwent monthly MRI assessments with gadolinium, were studied for 48 months. The number of CELs was recorded for each consecutive month. Data analysis. Fifteen models based on seven different probability distributions were explored: Poisson model [PS], Poisson model with Markov elements, PMAK2, nested PMAK2, nested nested PMAK2 , Poisson model with mixture distribution [PMIX], Zero-Inflated Poisson model [ZIP], Generalized Poisson model [GP, GP PMAK2, GP nested PMAK2], Negative Binomial model [NB, NB PMAK2 , NB nested PMAK2 , NB nested nested PMAK2] and Zero-Inflated Negative Binomial model [ZINB]. Analyses were performed using NONMEM VII v2 (LAPLACIAN). Model evaluation was based on the comparison of several dynamic descriptors calculated for both raw and simulated data.

Results: Based mainly on the -2xLog(Likelihood), and the goodness of a developed Visual Numerical Predictive Check, the selected model was the negative binomial with lambda affected each time t by the observations of the 2 previous time points, t-1 and t-2.

Conclusions: In this study we analyzed the best statistical model fitting the distribution of CELs. Significant improvements were observed in the probability distribution models when the information about what happened in the two previous months was incorporated, although the importance of these previous observations seems to be diluted along the disease course. In the future, mechanistic elements, such as the balance between effector and regulatory T cell, will be incorporated [3] in order to identify latent variables that explain variations in the parameter lambda.

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II-47 *Anders Viberg* Using modeling and simulation to evaluate placebo run-in for pain studies

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Objectives: In clinical trials investigating the treatment effect on neuropatic pain, the treatment effect is often compared at end of treatment as the difference in response between the active and the placebo group. A problem with these designs is that a pronounced and variable placebo response often is seen. The studies therefore need to be very large to provide the information needed. The objectives of this study was to see if a placebo run-in could increase the information acquired in a phase IIb study by reducing the variability in placebo response.

Methods: In neuropathic pain studies, pain is measured using an 11 graded numerical rating scale (NRS) where 0 is no pain and 10 is the worst imaginable pain. This is recorded by the patient daily before treatment until end of study. Placebo data from previous studies was used to develop a placebo model. The model predicts that the placebo response mainly occurs during the first 10 days, and thereafter the effect is stable. A design including placebo treatment for all patients during the first 10 days was suggested. Studies of the new and the previous design were simulated in NONMEM assuming a drug effect which follows a linear exposure response with delta NRS of 1.2 at a dose of 150 mg. The results from the two different designs were thereafter compared both in terms of statistical significance levels to detect an exposure response but also in precision of the estimated dose to achieve delta NRS of 1.2.

Results: With the new design the number of individuals could be reduced to 20% compared with the previous design and still achieve sufficient statistical significance to detect an exposure response. Even more important, much fewer individuals were required to be able to correctly determine a dose for phase III.

Conclusions: By using a study design where all patients in a pain study were treated with placebo initially and thereafter randomized to treatment it could be shown, using modeling and simulation, that the dose required for effective treatment in phase III could be better predicted. This will increase the probability of a successful phase III study or alternatively reduce cost and time for the phase IIb study

II-48 *Marie Vigan* Evaluation of estimation methods for repeated time to event models: application to analysis of bone events during treatment of Gaucher Disease.

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Objectives: The analysis of repeated time to event (RTTE) data requires frailty models [1] and specific estimation algorithms. Karlsson et al. [2] compared SAEM and Laplace estimation in NONMEM but neither SAEM in MONOLIX nor Adaptative Gaussian Quadrature (AGQ) in SAS. The first aim of this simulation study is to assess the performance of the SAEM [3] algorithm in MONOLIX and the AGQ procedure in PROC NLMIXED of SAS. Gaucher Disease (GD) [4] is a rare autosomal–recessive disorder, due to the deficiency of a lysosomal enzyme, glucocerebrosidase. The second aim of this study is to evaluate the frequency of occurrence of bones events (BE) in GD patients treated by imiglucerase.

Methods: This simulation study mimicked GD data. We simulated occurrence of BE by an exponential model with random effects additive on log lambda. We simulated 100 datasets with 200 subjects. We defined the fixed effects lambda=0.002 $month^{-1}$, its variance $omega^2$=1 and a maximum follow-up of 144 months. We simulated 3 types of censorship: max follow-up, low or high censure. Number of subjects, lambda and omega were varied to evaluate the estimation capacities of the algorithms. They were evaluated through the relative bias and the relative root mean square error (RMSE). For the application, we analyzed occurrence of BE in the 185 patients of the French GD registry treated by imiglucerase. Data were censored until the closing date or treatment discontinuation. Estimations were performed with SAS v.9.3 [5] (with 5 quadrature points) and MONOLIX v.4.0 [6] (with 3 Markov chains).

Results: The two algorithms showed equal performances. Biases on lambda are low (-2% to 2%), and biases on omega are slightly negative (-9% to -2%). RMSE are reasonable and decrease as the number of subject increases (

Conclusions: Despite the small number of repeated events, both algorithms provide a good estimate of the parameters. We need to extend this simulation study to other conditions, and study the covariate impact. To our knowledge, it was the first study of RTTE simulation analyzed with MONOLIX.

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II-49 *Nageshwar Budha* Population Analysis of wet-AMD Disease Progression and The Therapeutic Effect of Ranibizumab

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Objectives: The aim of this study was to develop a population based model to describe the disease progression of the wet form of age related macular degeneration (wet-AMD) and the therapeutic effect of ranibizumab.

Methods: Visual acuity (VA) data from two randomized Phase 3 studies were utilized in model development. First, the natural progression of wet-AMD was modeled as a dynamic process [1] using the data from sham arms. The disease progression model assumed that VA will approach a steady-state untreated value which was estimated as the percent of decrease in VA (Pdelta) from baseline. The effect of ranibizumab was then modeled using data from treatment arms by assuming the same disease progression (mean value of Pdelta) and allowing the drug concentration in the vitreous to alter the steady-state of VA via an Emax model. All parameters in the model were assumed to follow a log-normal distribution, and an additive residual error model was adopted. Model development was conducted using the MLEM population module in APADT 5.

Results: The VA profiles were well described by the disease progression model for patients in the sham arms, and by the drug effect model for patients treated with ranibizumab. The mean value of Pdelta was 52.8%, indicating that the VA in untreated patients will decrease by half on average. Estimated baseline VA for both models was around 57 letters with similar CV (26%). The population mean value of EC50 for VA was 0.01 mg/ml, and was below the average trough concentration of ranibizumab in the vitreous following the FDA approved 0.5 mg per eye monthly regimen. The inter-individual variability of EC50 was large (264%), and was attributed to the following a) large difference in the sensitivity to ranibizumab among patients; b) the use of population mean value [3] to simulate the concentration-time profile of ranibizumab in the vitrous for all treated patients; c) the use of population mean disease progression parameter (Pdelta) in the modeling of treatment effect (information regarding the pre-treatment disease progression were not available).

Conclusions: A population based semi-mechanistic model was developed to describe the disease progression of wet-AMD and the therapeutic effect of ranibizumab. Key model parameters were estimated and evaluated for their physiological and clinical relevance. This model could be used to access the effects of varied dosing scenarios and PK/PD properties on the disease progression of VA.

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II-50 *Sandra Visser* MModel-based meta analysis of γ-secretase inhibitor data; has Aβ production inhibition been adequately tested as therapeutic approach in mild AD?

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Objectives: A growing body of pathological, biomarker, genetic and mechanistic data strongly suggests that Ab amyloidosis plays a key role in Alzheimer's disease (AD) pathogenesis. The Ab peptide is generated from amyloid precursor protein, APP, via the sequential cleavages by b-and g-secretase. g-secretase inhibitors (GSI) are being developed as putative AD therapeutics and have reached late stage clinical testing. Unfortunately, to date none of them have resulted in significant improvement for patients, which led to questions regarding the validity of the ‘amyloid hypothesis'. The aim of the current work was to perform a model based meta analysis on Ab biomarkers from published clinical trials with GSI. Literature and in house data were used to evaluate if the amyloid hypothesis has been tested and explore if this could have been predicted from preclinical data.

Methods: Clinical data on Ab levels and drug exposure over time for 5 GSI were digitized from literature references. Preclinical and in vitro data from various species were collected both in house and extracted from the literature. A descriptive model based analysis was undertaken using summary level time-concentration-effect data. A combination of a composite Emax and a turnover model was used to describe the biphasic effects. From the parameter estimates, the exposure giving 50% inhibition from baseline was derived and compared between species.

Results: All GSI demonstrate biphasic effects on Ab levels in plasma. For all GSI, the average plasma Ab effect over 24 h at therapeutic doses was an increase rather than the intended decrease. The limited information on inhibition on CNS Ab production did not exclude presence of biphasic responses in the central compartment, nor indicate a significant reduction in Ab levels at intended therapeutic doses. Preclinical species and in vitro tests did demonstrate similar behavior in plasma Ab levels and the inhibitory potencies were in similar range as for human.

Conclusions: The inhibition on CNS Ab production in recent clinical trials has been very limited both in size and duration, suggesting that more efficacious Ab production inhibitingdrugs need to be tested that lower Ab substantially over the dosing interval period prior to drawing any conclusions regarding the validity of the ‘amyloid hypothesis'. Properly designed PKPD experiments in preclinical species can assist in clinical study design and dose selection.

II-51 *Georgios Vlasakakis* Landscape on technical and conceptual requirements in Drug/Disease Modelling & Simulation

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Objectives: A survey was performed between Nov 2011 and Jan 2012 among the Drug/Disease Modelling and Simulation (DD M&S) community to better understand the technical and theoretical requirements for DD M&S.

Methods: The target audience of the survey was: members of the IMI DDMoRe (Drug Disease Model Resources) project consortium, members of their institutions and companies, colleagues in the DD M&S community, regulators. A mailing list was created based on the input from all WP9 members. The survey was designed as an online questionnaire using the SurveyMonkey system and defined four target groups, namely those who (i) develop models/perform DD M&S activities ('modellers'), (ii) apply/interpret results from DD M&S or produce data without hands-on involvement ('appliers'), (iii) review DD M&S results ('reviewers'), (iv) are involved with all the above ('all'). Questions in all four groups (n=22-29) included free text, multiple choice questions, and scaling questions with weights assigned to the answers. Descriptive statistics and graphs were used to tabulate the answers.

Results: After database cleaning, 137 responses were available from academia (54%), pharmaceutical industry (43%) and SME (3%). When asked to define their primary DD M&S activity, almost 2/3 identified themselves as 'modellers', 1/4 as 'all' and the remaining as 'reviewers' or 'appliers'. Regarding the level of experience 64% of the responders work at senior positions and 36 % at training positions (PhD, post-docs).

The survey included 4 sections: perceived impact and communication of DD M&S within organisations, current DD M&S concepts, methodologies and tools used, perceived gaps in the environment and personal challenges. The impact of DD M&S is perceived as large throughout the drug development pipeline, being used from basic understanding of drug features to decision making both for drug approval and therapeutic use. Lack of training, time and resources was often cited as a difficulty for applying DD M&S approaches, and a large majority (70%) of responders, although often already trained in several aspects of the DD M&S, would participate in further training courses if given the chance.

Conclusions: The survey provided a landscape of impact, weaknesses and requirements in DD M&S. It will be used to develop a competence framework for future training and education

curricula, which will go beyond technical and statistical competences; understanding of the clinical implications of modelling assumptions as well as communication skills are urgently needed.

II-52 *Max von Kleist* PK-PD Modelling of the Reverse Transcriptase Inhibitor Tenofovir and Quantification of its Prophylactic Efficacy against HIV-1 Infection

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Objectives: Almost thirty years after the discovery of HIV-1, the AIDS epidemic is still not controlled. While the search for a vaccine continues, the use of antiretroviral drugs to prevent HIV-1 infection has been suggested. One key strategy is antiviral pre-exposure prophylaxis (PrEP), which, when taken by healthy individuals at risk, aims to protect them from acquiring infection. The pro-drug tenofovir-disoproxil-fumarate (TDF) is a key component in all currently tested regimens. The aim of this study is to predict the efficacy of different prophylactic strategies with TDF and to assess the sensitivity towards the number of transmitted viruses, timing of TDF administration and adherence.

Methods: We developed a pharmacokinetic model for TDF and its active anabolite tenofovir-diphosphate (TFV-DP) and validated it with data from 4 different trials, including 4 distinct dosing regimes. The pharmacokinetics of TFV-DP was coupled to a model of HIV dynamics. Subsequently, viral decay following TDF mono-therapy was predicted, consistent with available data [1]. A stochastic approach was then used to estimate the probability of HIV-1 infection for (i) daily TDF-based PrEP, (ii) one week TDF started either shortly before, or -after viral exposure and (iii) a single dose oral TDF taken before viral challenge (sd-PrEP).

Results: The predicted relative prophylactic efficacy of TDF was negatively correlated with the number of transmitted viruses for all evaluated regimens. Once daily TDF-based PrEP with 300mg could prevent approx. 80% infections, in agreement with clinical data (TDF-only sub-study of Partners PrEP) and was relatively unaffected by poor adherence. Sd-PrEP efficacy with 300mg or 600mg was limited by a slow accumulation of active compound and could prevent approx. 50% infections, when given at least 24h before virus exposure. The efficacy dropped to about 10%, when given 1h before. Efficacy was marginally increased with increasing dosage or prolonged (one week) administration. Post-exposure prophylaxis was likewise limited by a slow accumulation of active compound.

Conclusions: The prophylactic efficacy of TDF depends on the number of transmitted viruses, which may be exploited by combining prophylactic strategies with strategies that lower the number of transmitted viruses, such as ‘treatment for prevention'/ ‘test-and-treat' strategies [2].

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II-53 *Carin Wallsten* Quantification of the Drug Effect and Exploration of Mechanism of Action of Two NMDA Channel Blockers, AZD6765 and Ketamine, using Mouse EEG Data

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Objectives: AZD6765 and ketamine are NMDA channel blockers, which differ in how they interact with the NMDA channel. Ketamine has shown effects in major depressive disorder (MDD) [1] and AZD6765 is under clinical development for MDD. A therapeutic hypothesis is that NMDA channel blockers normalize aberrant electrical activity in key depression-associated brain networks. Change in the EEG amplitude within the gamma frequency band is a potential pharmacodynamic biomarker of NMDA antagonist-mediated cortical disinhibition. Our first objective was to estimate the potency and efficacy of AZD6765 and ketamine, using the change in gamma EEG, and secondly to explore if the degree of trapping in the NMDA ion channel (AZD6765 is a low and ketamine a high trapping compound) affects the underlying mechanism of action on the gamma EEG.

Methods: The EEG was recorded in mice for 5 single doses of each of the compounds (30 min baseline and 90 min postdose recording in 2 min bins) and the data analyzed using a population approach. The PK of the compounds was obtained from satellite animals and estimated population PK parameters were used as input for the analysis of the time-course of the drug effects in the EEG studies.

Results: Both AZD6765 and ketamine increased the gamma EEG with increasing plasma concentration. For AZD6765, the delay between the change in plasma concentration and gamma EEG was best described with a turnover model with inhibition of the turnover rate, using a sigmoidal E_{max} model. In addition, a negative moderator feedback mechanism was identified. The ketamine data could not be described assuming an inhibition of the turnover rate, but were best described using a direct and delayed effect, using a turnover model with stimulation of the production of the EEG signal.

Conclusions: In this study, ketamine caused a greater increase in gamma EEG than did AZD6765. PK-PD modeling of the gamma EEG showed some differences between the compounds, which may be related to a difference in mechanism of action and different degree of trapping in the NMDA channel. This hypothesis warrants further investigation.

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II-54 *Bing Wang* Population pharmacokinetics and pharmacodynamics of mavrilimumab in rheumatoid arthritis patients

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Objectives: Mavrilimumab, a fully-human monoclonal antibody targeting the granulocyte-macrophase colony stimulating factor (GM-CSF) receptor α, demonstrated promising efficacy results in a Phase 2a study in patients with rheumatoid arthritis (RA). The objective of this investigation was to characterize the exposure-response relationship of mavrilimumab using the population modeling approach.

Methods: Adult subjects with active RA received seven subcutaneous administrations of placebo or mavrilimumab (10, 30, 50 or 100 mg) once every other week. Mavrilimumab pharmacokinetics (PK) and efficacy data (DAS28-CRP, ACR20 and ACR50) were analyzed using NONMEM 7. A direct pharmacodynamic model with placebo effect was developed to describe DAS28 response. The dichotomous ACR response was modeled using logistic regression.

Results: Mavrilimumab PK was adequately described by a 2-compartment model with first-order absorption from the subcutaneous dosing site and parallel elimination pathways by the reticuloendothelium system and GM-CSF receptor α. In adult RA patients the maximum placebo effect (Pmax) on DAS28 was estimated to be a 1.29 unit reduction, while the additional drug effect (Emax) was a 0.66 unit reduction. There was a strong correlation between DAS28 and a multi-biomarker disease activity (MBDA) score at baseline. The model predicted probabilities of ACR20 response at Week 12 were 0.40 for placebo and 0.42 to 0.64 for RA patients receiving bi-weekly mavrilimumab administrations. The predicted probability of ACR50 response ranged from 0.12 (placebo) to 0.32 (100 mg). The estimated drug potency (EC50) for ACR20 and ACR50 responses were higher than for DAS28.

Conclusions: Mavrilimumab administrations resulted in significant improvement in RA disease activities, which were directly related to the PK exposure. The MBDA score based on 12 biomarkers was a relevant predictor of DAS28 at baseline. Stochastic clinical trial simulations facilitated the optimal design of late-stage trials of mavrilimumab.

II-55 *Chenguang Wang* Scaling morphine across the human life-span using a bodyweight-dependent allometric exponent model

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Objectives: Morphine clearance has been successfully scaled from preterm neonates to 3-year-old children on the basis of a bodyweight-based exponential function [1]. Due to the high value for the exponent of this function, this model cannot be extrapolated to an older age-range. To scale clearance across the entire human life-span, recently, a bodyweight-dependent allometric exponent (BDE) model was developed on the basis of an allometric equation in which the exponent sigmoidally decreased with bodyweight [2]. The aim of current study is to extend the paediatric morphine model to a wider age-range using a BDE model.

Methods: Morphine and morphine-3-glucuronide (M3G) data from 356 (pre)term neonates, infants, children [3] and adults [4], and morphine data from 146 adolescents [unpublished study] were analyzed with NONMEM 7.2. Two scaling models were developed: I. in adults and children less than 3 years old taking into account morphine and M3G data; II. in all patients taking into account morphine data only. In model I, a previously published model [3] was used for morphine and M3G in which the BDE model [2] was tested as a covariate model for the formation and elimination clearance of M3G. In model II, a two-compartment model was used for morphine in which the BDE model [2] was tested as covariate model for total morphine clearance.

Results: In model I, the formation and elimination clearance of M3G was most adequately described by a BDE model in which the exponent was found to decrease from 1.44 to 0.83 for M3G formation and from 1 to 0.5 for M3G elimination. Half the decrease in exponents was reached at 4.2 and 5.4 kg, respectively. The stratified observed *versus* population predicted plots of M3G concentrations were unbiased for every age-group. In model II, similar descriptive and predictive performances were found as in model I. The exponent of the BDE model was found to decrease from 1.44 to 0.98 and half the decrease was reached at 4.2 kg.

Conclusions: The BDE model was able to scale both total morphine clearance and glucuronidation clearance through the M3G pathway across all age-ranges between (pre)term neonates and adults. The unbiased descriptive and predictive performance of the BDE models allow for further investigations in the ontogeny of UGT2B7-mediated drug glucuronidation.

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II-56 *Sebastian Weber* Mixed effect modeling of neuronal cell differentiation kinetics from longitudinal phase-contrast imaging data

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Objectives: Neuronal cell fate decisions are an active field of research and the detection of the cell phenotype differentiation, i.e. the outgrowth of neurites, is essential. We have developed the first classification approach capable of detecting the differentiated phenotype by using phase contrast imaging of live cell populations only [1]. In contrast to standard techniques, this represents a non-destructive and interference free sampling, which enables longitudinal studies of a cell population. Hence, this allows for the first time a mixed effect analysis in this context. The main motivation is to gain a more detailed understanding of cell differentiation kinetics and to start implementing mechanistic modeling.

Methods: As a model system we use PC12 cells [2], which undergo cell differentiation under treatment with nerve growth factor (NGF). We monitored control (CTL) cells without treatment and cells treated with NGF on dedicated wells. We recorded 300 images each day per well in a line-wise spatial recording pattern. As this pattern remains constant over the observation time, we approximately monitor the same cell population each day in each image. Image feature extraction is performed in MATLAB and further statistical analysis is done in R, which we use for fitting mixed effect models by glmer from lme4 [3].

Results: The key step was to identify the image features, which detect the differentiated phenotype and are suitable for further modeling. First, cells or cell clumps are detected in each image in a segmentation step. Then for each cell segment the ratio of the convex hull covering area and the cell area itself is calculated. A cell segment is counted as being differentiated if the ratio is much larger than 1, since a non-differentiated cell is round and has a ratio of 1. Hence, we obtain binomial count data and model the number of cell segments and the number of differentiated cell segments. We set up a logistic regression which contains terms up to quadratic order in time and includes a random effect for the intercept and linear term. Main results are that (i) the treatment is statistically highly significant when comparing the reduced to the full model, (ii) the maximal treatment effect is on day 2 and (iii) the treatment effect diminishes thereafter.

Conclusions: We have successfully applied mixed effect modeling for the analysis of neuronal cell differentiation kinetics by means of an empirical model. Possible extensions include a full mechanistic modeling, modeling of different treatment concentrations and mixture modeling to detect non-responders.

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II-57 *Thomas Wendl* A whole-body physiologically-based pharmacokinetic Model for ketoconazole in different species ready to be used to predict dynamic drug-drug-interactions

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Objectives: Ketoconazole (KTZ) is a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) enzyme system. As coadministration of KTZ with drugs mainly metabolized by CYP3A4 may lead to increased plasma levels of these drugs, a dynamic whole-body physiologically-based pharmacokinetic (WB-PBPK) model of KTZ is essential to accurately predict drug pharmacokinetics (PK) under KTZ coadministration. In this study, a ready to use WB-PBPK Model for KTZ in different species is developed.

Methods: A WB-PBPK model of KTZ for rats, dogs and humans was established in PK-Sim® and MoBi® [1] using biometrical data, physico-chemical and mass balance information about KTZ. The established model was adjusted to plasma concentration-time profiles available in literature [2-4] and validated using independent data.

Results: The established models describe the plasma concentration-time profiles of KTZ with good accuracy. The performance of predicting drug-KTZ-interactions is demonstrated by linking the KTZ model to a previously established midazolam WB-PBPK model. Midazolam plasma concentration-time profiles under KTZ coadministration are adequately predicted by the model.

Conclusions: The established KTZ WB-PBPK model can be used to predict the PK of drugs undergoing CYP3A4 metabolization under KTZ coadministration.

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II-58 *Shelby Wilson* The Enhancement of Tumor Vaccine Efficacy by Immunotherapy

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Objectives: We highlight how immunotherapy might be used to overcome the effects of two immuno-regulatory agents exploited by cancer: regulatory T cells and the Transforming Growth Factor (TGF)-beta protein. Using experimental data, we develop a mathematical model to gain insight into the cooperative interaction between anti-TGF-beta and vaccine treatments.

Methods: We develop a model consisting of ordinary differential equations that follows the dynamics of the tumor size, TGF-beta concentration, activated cytotoxic effector cells, and regulatory T cells. Nonlinear least squares is used to fit model parameters to experimental data. Using numerical simulations and stability analysis, we study the following scenarios: a control case of no treatment, anti-TGF-beta treatment, vaccine treatment, and combined anti-TGF-beta vaccine treatments.

Results: Consistent with experimental data, we show that monotherapy alone cannot successfully eradicate a tumor and conclude that tumor eradication requires the combination of these therapeutic approaches.

Conclusions: We demonstrate that our model captures the observed experimental results, and hence can be potentially used in designing future experiments involving this approach to immunotherapy.

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II-59 *Gudrun Wuerthwein* Population Pharmacokinetics of caspofungin in a phase II dose escalation study

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Objectives: Caspofungin (CAS) is used for management of proven or probable invasive fungal infections. In a multicenter phase II dose escalation study, dose-dependent pharmacokinetics of CAS was studied.

Methods: CAS was administered as 2h infusion at doses from 70 to 200 mg QD. CAS pharmacokinetic sampling (n=468 samples) was performed on day 1 and at peak and trough time points at days 4, 7, 14, and 28 (70 mg: 9 (96), 100 mg: 8 (80), 50 mg: 9 (94), 200 mg: 20 (198) patients (plasma samples)). Trough levels were analysed descriptively. Population pharmacokinetic analysis was performed using NONMEM and Pirana. For model evaluation, Bootstrap analysis, prediction corrected (pcVPC) as well as standardized (SVPC) visual predictive check were performed.

Results: There was no difference in log-transformed dose-normalized trough levels of CAS (ANOVA). CAS concentration data fitted best to a two-compartment model with proportional error model, interindividual variability (IIV) on clearance (CL), central (V1) and peripheral (V2) volume of distribution, covariance on CL and V1 and interoccasion variability (IOV) on CL. (CL 0.403 L/h ± 31 %, IOV on CL: 16 %, V1: 5.73 L ± 32 %, Q: 0.843 L/h, V2: 6.53 L ± 67 %). None of the covariates tested (weight, age, dose level, sex, serum bilirubin) further improved the model. Bootstrap results show robustness of the final PopPK model, pcVPC and SVPC confirm its predictability. Based on the final model, simulated peak plasma concentrations at steady state ranged from 14.1 to 40.2 mg/L (34 %), trough concentrations from 4.3 to 12.3 mg/L (52 %), and area under the concentration-time curve from 174 to 496 mg/L*h (36 %) for the dosage range of 70 to 200 mg QD (geometric mean, geometric coefficient of variation).

Conclusion: CAS showed linear pharmacokinetics across the investigated dosage range of 70 to 200 mg QD. Following administration of 100 mg QD, drug exposure in the study patients were slightly higher (15 %) relative to results found in healthy volunteers.

II-60 *Wenyuan Xiong* Pharmacokinetic interspecies extrapolation of a fully human mAb from animal to human

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Objectives: Identify the nonlinear animal PK of anti-LX, a fully human mAb directed against ligand X and predict the human exposure from the animal profiles, to support the dosing regimen selection in first-in-man (FIM) study.

Methods: PK and TK data from 48 mice and 21 monkeys were pooled and analyzed with population approach. In the model, PK parameters were scaled between species to human by allometric relationship to simulate human exposure and its variability. EC95 derived from mouse target occupany data was defined as the efficacy threshold. Dosing regimen of achieving at least 95% target occupancy in 70% of population was recommended as reference for the dose escalation in first in human trial.

Results: anti-LX demonstrated pronounced non-linear PK characteristics in mouse and monkey, which is speculated to be target-mediated clearance relevant. Nevertheless, limited PK samples impeded the development of a full mechanistic target-mediated drug disposition (TMDD) model. Two-compartment model with mixed linear and Michaelis-Menten elimination pathways, a simplification of TMDD model, characterized the PK profiles of anti-LX with good precision. Systematic inter-species variability of target affinity (Km) between mouse and monkey, random inter-individual variability of linear clearance, target density (Vm) and target affinity in monkey were identified. By assuming the same target affinity between human and monkey, human exposure was simulated with PK parameters of apparent volume of distribution, linear clearance and target density scaled up allometrically by the body weight with power factors of 1, 0.75 and 0.75, respectively. Time above target effective concentration in the predicted human profile is considered to be the key criteria to select the dose level for the human study. Simulation resutl suggested, a dose of 10mg/kg(90min infusion) administrated every other week could achieve a trough concentration above the efficacy threshold. Sensitivity analysis showed, deviating from the assumption of equivalent target affinity between monkeys and human has minor impact to the conclusion.

Conclusions: Two-compartment model with mixed elimination, a simplification of TMDD model, well described the PK profile of anti-LX both in mouse and monkey. Allometric scaled human simulation suggested that for maintaining a trough concentration of 50 µg/mL, a dose of 10 mg/kg (90min infusion) can be administered every other week. This supports the selection of the dose range and frequency to be tested in the FIM study, to maintain a minimum trough serum level for a PD response.

II-61 *Stefano Zamuner* PK-PD modelling of aOSM in RA patient study including exploration of carrier protein effect.

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Objectives: A humanised IgG1 monoclonal antibody (mAb) against human Oncostatin M (OSM) has been recently developed for the treatment of rheumatoid arthritis (RA) [1]. The anti-OSM antibody blocks the interaction of OSM with its cell surface signaling receptor component, gp130. Oncostatin M is a member of the interleukin (IL)-6 family of secreted cytokines and is present in the inflamed synovium and blood of patients with RA. Recent negative results in RA indication suggested that the anti-OSM antibody was not sufficiently potent for a cytokine target. In this hypothesis, OSM-antibody complex can act as a carrier protein [2], which prolongs the half life of the cytokine, resulting in accumulation of the complex especially in the joints where it is not efficiently cleared.

Methods: A non-linear mixed effect longitudinal PK-PD analysis on primary efficacy endpoint (DAS28) in RA patient was conducted using a set-point model [3]. Inclusion of covariate effects (i.e. drug exposure and baseline DAS28 on the structure model parameters) has been carried out using SCM procedure in PsN 3.4.2 [4]. In addition, a few target meditated drug disposition (TMDD) models were explored to describe relationship between drug level, free and total serum OSM including investigation of potential carrier protein / agonist effect. Simulations of different scenarios were conducted using Berkeley Madonna software version 8.3.18.

Results: A set point model was successfully estimated and class of exposures was found as a significant covariate. Subjects in the low exposures tertiles showed better response compared with intermediate and high exposures (U-shape curve). Based on these results it has been hypothesised that at high doses, required to fully neutralise the target, there was an increased risk of a protein carrier/ agonist effect in patient. Consequently, TMDD models were developed to account for potential carrier protein effect in the synovial tissue.

Conclusions: Antibodies acting as carrier proteins is not unprecedented and have been documented both preclinically and clinically with mAbs against other soluble cytokines such as IL-2, IL-3, IL-4, IL-6 and IL-7 [5]. This phenomenon is complex to predict and it is related to several factors as target turnover, different antibody and target location (i.e. plasma vs. tissue compartment) and antibody affinity. Quantitative approaches may be of help to identify and describe these potential risks.

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II-62 *Stefan Zeiser* Population PK Modeling of Dapivirine Released from Vaginal Rings

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Objectives: Dapivirine is a non-nucleoside reverse transcriptase inhibitor with potent antiviral activity against HIV-1. International Partnership for Microbicides has developed a vaginal ring containing dapivirine (25 mg) to protect women against HIV infection through sexual intercourse. These rings are placed in the upper third of the vagina where they slowly release the active drug. A population PK model was built to describe the time course of vaginal fluid levels of dapivirine at the introitus and cervix. The goal was to predict dapivirine concentrations after various intervals of ring removal, and to predict vaginal fluid concentrations when the rings are inserted successively every four weeks.

Methods: Non-linear mixed effects PK modeling using NONMEM was performed based on vaginal fluid dapivirine concentrations at the area of the introitus and cervix. The model consists of one compartment with a first order drug elimination process. Release and distribution of dapivirine to the introitus and cervix are described by a first and zero order process. The model characterizes the fraction of dapivirine that is distributed to the introitus and cervix, and the fraction that is released by zero and first order processes.

Results: Besides a small bias at the early release phase and during the washout phase, the model described all data well. Fixed effects parameters could be estimated with high precision (CV

Conclusions: Despite the high variability in the data, the PK of dapivirine in vaginal fluids could be described adequately by the presented model. The high precision in parameter estimates allows the use of this model as a potential tool for predicting exposure in several ring application scenarios.

II-63 *Jianping Zhang* Population Analysis of Tumor Growth Inhibition and Progression-Free Survival Following Lapatinib Treatment in Patients with Advanced/Metastatic Breast Cancer

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Objectives: Lapatinib (Tykerb™) is a potent and selective inhibitor of the EGFR and HER2 tyrosine kinases. It is approved for the treatment of patients with advanced or metastatic breast cancer overexpressing HER2. The aim of this work was to characterize the effect of lapatinib on tumor growth dynamics and to predict progression free survival (PFS) based on tumor size measurements.

Methods: Data from 3 Phase II studies including 314 patients contributing 975 tumor size measurements for up to 92 weeks were utilized. Dosing regimens were 1250 or 1500 mg once daily (QD) or 500 mg twice daily (BID). Tumor size was measured as the sum of the longest diameter of selected lesions. The tumor growth inhibition model was based on Claret et al. (2009) with a slight variation. Progression-free survival (PFS) analysis was conducted based on data from 1 of the Phase II studies. PFS results were recorded from a total of 124 patients ranging from 7 to 93 weeks. A survival model with log-normal distribution was constructed to characterize the PFS as a function of various covariates. The population analysis was performed using the nonlinear mixed effects modelling approach. Visual predictive check was implemented for final model evaluation.

Results: Treatment with lapatinib resulted in an average 39% (KD) suppression of tumor growth rate (KL). Lapatinib was more effective in patients with FISH ratio ≥ 2 resulting in an average 96% suppression of KL. Asian and Hispanic patients were more responsive to lapatinib with an average 81% suppression of KL. Patients with twice daily dosing regimen were 32% less likely to develop drug resistance. Percentage tumor reduction from baseline at Week 8 was found to be the best predictor of PFS.

Conclusions: The population models developed in this analysis adequately characterized tumor growth inhibition by Lapatinib and its impact on progression-free survival in patients with advanced/metastatic breast cancer. Our findings confirm some aspects of clinical practice and may guide future investigation to improve therapy.

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II-64 *Chao Zhang* Model-based evaluation of the pharmacokinetic differences between adults and children administered lopinavir and ritonavir in combination with rifampicin

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Objectives: Doubling the dose of lopinavir/ritonavir has been shown to compensate for the induction effect of rifampicin in adults, but fails to result in adequate concentrations in most young children [1]. The objective of this study was to develop a population pharmacokinetic model to investigate the pharmacokinetic differences between children and adults in the drug-drug interactions between lopinavir, ritonavir and rifampicin.

Methods: The data from three previously published pharmacokinetic studies were combined. Lopinavir and ritonavir concentrations were included from: 21 HIV-infected adults established on standard twice daily doses of lopinavir/ritonavir which were escalated up to 2-fold after the introduction of rifampicin; 35 HIV-infected children with tuberculosis were given adjusted lopinavir/ritonavir dose co-administration with rifampicin; and 39 HIV-infected children without tuberculosis given standard lopinavir/ritonavir doses. An integrated population pharmacokinetic model describing lopinavir and ritonavir pharmacokinetics in adults and children with and without concomitant rifampicin was developed using NONMEM 7.

Results: Rifampicin reduced the bioavailability of lopinavir by 72.8%in children (an effect that was moderated by the dose of ritonavir) and 20.6% in adults.The bioavailability of ritonavir was decreased by 72.2% and 48.2% in the presence of rifampicin, in children and adults respectively. Hence, compared to adults, the relative bioavailability of lopinavir and ritonavir in children was 89% and 11.8% respectively for a 1.8 mg/kgritonavir dose. Conversely, rifampicin increased the oral clearance of both lopinavir and ritonavir to a lesser extentin children than in adults. In children, the absorption rate of lopinavir was reduced, and the mean transit time of ritonavir was lengthened, compared to those in adults.

Conclusions: The model described substantially different effects of rifampicin on the bioavailability and oral clearance of lopinavir and ritonavir between adults and children. Hence, such drug-drug interactions should be evaluated in children as adult studies cannot be relied on to predict the magnitude of paediatric drug-drug interactions.

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II-65 *Wei Zhao* Population pharmacokinetics and dosing optimization of vancomycin continuous infusion in neonates

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Objective: Pharmacokinetic data are limited for vancomycin continuous infusion in neonates. Different dosing regimens were currently used in routine. The aim of this work is to evaluate the likelihood of achieving the targeted concentration with currently used dosing regimens and to optimize vancomycin therapy in neonates

Methods: Vancomycin concentrations during routine TDM were collected prospectively from neonates receiving vancomycin continuous infusion in 3 hospitals. Vancomycin concentrations were compared among the different dosage regimens and the relationship with age, weight and renal function was evaluated. The population was developed based on TDM results using NONMEM software. The dosing regimen was then optimized using developed model.

Results: Two hundred and seven concentrations were obtained from 116 neonates. Preterm neonates presented larger variability than term neonates. TDM results demonstrated that the risk of underdosing (<15 mg/L) and overdosing (>25 mg/L) were 26% and 27%, respectively. The loading dose strategy presented fewer neonates with subtherapeutic levels. The uniform weight-normalized dosage regimen (mg/kg) was not suitable for the whole neonatal period. A one-compartment model was then developed. The covariate analysis identified birth weight, current weight, postnatal age and serum creatinine as significant predictors of vancomycin dosing. The model evaluation supported the predictive performance of developed model. The model-based dosing regimen achieved the target concentrations in typical neonates (preterm, median and term) and simulated clinical trials.

Conclusions: The loading dose strategy with consideration of the baby's birth weight, current weight, postnatal age and serum creatinine could be used in routine to individualize vancomycin continuous infusion therapy in neonates.

II-66 *Kirill Zhudenkov* SBPOP – An Integrative Computational Platform for Model-Based Drug Development

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Objectives: An important key to the discovery and development of new medicines is an understanding of the disease mechanisms. Within Pharma industry the application of methods from systems biology [1] is still relatively limited. In this work we present the SBPOP (Systems Biology and Population) platform, a framework for modeling, simulation, and analysis of biological and pharmacological models that originally has its roots in the area of systems biology but is extended to also address the specific needs within the Pharma industry, such as the simulation of clinical trials and interfaces to nonlinear mixed effect (NLME) modeling packages.

Methods: The SBPOP platform has been developed as a Matlab toolbox. It uses multiple features available in Matlab® (The MathWorks, Natick, USA), such as the handling of multiple data arrays, mathematical statistics, differential equation integration methods, parameter estimations techniques, model-based data simulation, and interfaces with external software packages.

Results: The SBPOP platform consists of 3 linked packages. The first one, SBTOOLBOX2, is responsible for model development, experiment and measurement representation working via command line or a graphical user interface. Second one, SBPD, is used for project-level representations and parameter estimation. These 2 modules are available (http://www.sbtoolbox2.org). Third package of SBPOP allows for general clinical and trial simulations, dosing schedules and interfaces to NLME modeling tools. Currently, this feature is not generally available.

Conclusions: The SBPOP platform provides the user with flexibility, to work in PK/PD projects. SBPOP provides a range of well documented modeling techniques, which may be used within Pharma projects. In Early Discovery, it allows for the gathering of CSV or XLS formatted data, into working project, with the ability to set all initial values as relevant for each experiment, and to fit model parameters. Going into further stages of research and/or clinical development, where larger amount of data may be available, SBPOP allows for the generation and use of Monolix and NONMEM population modeling projects, based on previously assessed models. Effectively, the SBPOP is a universal, integrative platform for the development, testing and simulation of PK/PD modeling projects, at all stages of Pharma discovery and development.

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II-67 *Bela Patel* Probability-Based Risk Assessment of QT Prolongation in Early Phase Drug Development

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Objectives: Drugs A and B are structurally similar molecules in Phase I development for the treatment of conditions associated with delayed gastric emptying. As part of early safety assessment, probabilistic modeling was used to provide quantification of risk for QTc prolongation in healthy volunteers within and above the range of predicted therapeutic doses.

Methods: Data were collected from first time in human studies of drug A (N=48, 1-150mg) and B (N=17, 10-125mg). A nonlinear mixed-effect analysis of the concentration-QT relationship was performed in NONMEM 6.0 (ICON Development Solutions) with time-matched PK and ECG parameters over 48 hours [1, 2]. Simulations were conducted for predicted therapeutic doses of both molecules in ModelRisk 4.0 (Vose Software) to calculate the risk profile, i.e. percentage of subjects with upper 90%CI of ddQTci (QT corrected individually by RR, baseline and placebo)>10msec. Random simulations (N=1000) was conducted in 100 subjects to generate QTci based on the final PK/QT model and correlation of RR at baseline and Tmax for active doses and placebo and at Cmax values randomly sampled from observed distribution. These results were then used to calculate ddQTci used for risk assessment and compared to the predicted QT prologation directly calculated from 90%CI of NONMEM slope estimate at observed Cmax for both molecules.

Results: The probabilistic approach suggested that the likelihood of having upper 90%CI of ddQTci above 10msec is minimal at all doses tested for drug A with a median upper 90%CI of 1.3msec at the top dose studied. The likelihood for drug B is minimal at 10mg (0.3%, median upper 90%CI of 3.3msec) but increased to 40% at 80mg (median upper 90%CI of 9.2msec). The calculation for QTc based on 90%CI of slope and observed mean Cmax suggested an upper 90%CI of 2.5msec at the top dose for drug A, 1.8msec for drug B at 10mg and 20msec at 80mg. Overall, probabilistic simulations are in agreement with conclusions derived from the slope-Cmax calculations.

Conclusions: The probabilistic approach was used to characterize the risk of QT prolongation for two Phase I molecules from the same class. It provided a more thorough evaluation of QTc prolongation and allowed the clinical team to evaluate and compare the safety profiles, contributing to candidate progression decisions.

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II-68 *Parviz Ghahramani* Population Pharmacokinetic Model for Cariprazine and its Major Metabolites in Patients with Acute Exacerbation of Schizophrenia

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Introduction: Cariprazine is a D3-preferring dopamine D3/D2 receptor partial agonist antipsychotic in development for the treatment of schizophrenia and bipolar mania.

Objectives: To develop a population pharmacokinetic model of cariprazine (CAR) and its two main metabolites, desmethyl-cariprazine (dCAR) and didesmethyl-cariprazine (ddCAR), and to characterize their pharmacokinetic profile in schizophrenic patients following once daily dosing with CAR.

Methods: Data from one Phase I and three Phase II studies in patients with acute exacerbation of schizophrenia or schizoaffective disorder were used in the population pharmacokinetic analysis. All four studies were multiple-dose, ranging from 0.5-12.5 mg/day for up to 48 weeks of dosing. During the studies, sparse plasma samples were collected from patients in the Phase II studies. Serial plasma samples on days 1 and 22 of dosing were obtained from patients in the Phase I study. GAM was used for the initial selection of potentially significant covariates. These covariates were used as a starting point in covariate search within NONMEM (Version 7.1).

Results: The final models are based on the 10323 plasma concentrations collected from 678 patients (approximately 21 samples per patient in the Phase I study and a median of 4 samples per patient in other studies). Results of NONMEM modeling showed that the best model describing the data for CAR, dCAR and ddCAR were the sequentially fitted two-compartment distribution with first order absorption and saturable rate of transfer from central to peripheral compartment. On average, at doses ranging from 1.5 to 4.5 mg/day, it takes 4-6 days for CAR and dCAR to achieve steady-state (functional half-life 2-3 days), and 19-23 days for ddCAR to reach steady-state (functional half-life 8-10 days). No significant covariates were identified to influence the pharmacokinetics of any of the moieties.

Conclusions: The population pharmacokinetic models adequately described the pharmacokinetic profiles of cariprazine and its two major metabolites in schizophrenic patients and could be utilized in the assessment and selection of optimal therapeutic doses.

	Mean Estimate		
	CAR	**dCAR**	**ddCAR**
Ka (h^{-1})	0.88	-	-
CL (L/h)	22.7	80.9	10.4
Vc (L)	717 (fixed)	130	1902.32
Vmax (mmol/h)	9.32 (fixed)	0.338 (fixed)	0.274 (fixed)
Km (mmol)	0.253 (fixed)	0.472 (fixed)	1.13 (fixed)
Intercompartment transfer rate const.	2.75	0.0597	0.0477

Absorption lag time (h)	0.939	-	-
Proportional shift in Km due to morning dosing	1.76	-	-
Residual st.dev.	0.59	0.51	0.45

III-01 *Khaled Abduljalil* Predicting the Developmental PK/PD of Cyclosporine (CsA) in Paediatrics

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Background: Physiologically Based Pharmacokinetic models, to the best of our knowledge, have not been applied in modelling of developmental changes in concentration-response relationship across the paediatric age range. One study has shown that the development of the immune system was an important determinant of variation in CsA therapy in the paediatric population[1].
The pharmacodynamics (PD) changes coupled with the age related changes in PK, due to developmental physiology and CYP3A4 ontogeny will result in both altered exposure and response in children.

Objectives: To simulate the developmental immunosuppressive effect of CsA in a virtual healthy paediatric population stratified for their ages using the Simcyp paediatric simulator.

Methods: Prior *in vitro* and *in vivo* information on the metabolism and kinetics of CsA and developmental knowledge on physiology of paediatric population were incorporated into the Simcyp Simulator. Simulations of cyclosporine PK and the decrease in Peripheral Blood Monocyte effects were performed in infant (0-1 y), pre-adolescent (4-12 y) and adult (>12 y) populations using Paediatric Simcyp. The proliferation of PBM *in vitro* was used as a PD marker of the immunosuppressive effect of CsA. The PKPD relationship was taken from Marshall et al., 1999[1] and the simulated PK/PD profiles were compared to original observations[1&2].

Results: Simulated/observed ratios for C_{0h}, C_{2hr}, and $AUC_{0\text{-}8hr}$, are 1.17, 0.75, and 1.06 - fold, respectively for the pre-adolescent group. Simulated $AUC_{0\text{-}24,ss}$ for blood concentrations showed no significant difference between this group and adults, but was about 2-fold lower than that of infants. By accounting for the difference in the sensitivity of PD in infant compared with older children and adult, the AUCR increased by about 26% in infant, but was only 6% lower in adults compared with pre-adolescent group.

Conclusions: Simulation results for reduction of PBM following CsA in neonates compared with the pre-adolescence and adult population showed consistency with clinical observations in terms of different effects of age and on drug exposure and effect. The higher sensitivity in neonates to CsA may necessitate reduction of the drug dose in this population. Clinical trial simulations similar to the one shown in this study can be used to investigate the design of POPPK-PD studies in different ages and their power.

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III-02 *Mona Alameddine* Pragmatic Approach for Interpreting Antiretroviral Drug Concentrations Based on a Systematic Review of Population Pharmacokinetic Studies

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Objectives: The study objective was to derive reference pharmacokinetic curves of antiretroviral drugs (ART) based on available population pharmacokinetic (Pop-PK) studies that can be used to optimize therapeutic drug monitoring guided dosage adjustment.

Methods: A systematic search of Pop-PK studies of 8 ART in adults was performed in PubMed. To simulate reference PK curves, a summary of the PK parameters was obtained for each drug based on meta-analysis approach**.** Most models used one-compartment model, thus chosen as reference model. Models using bi-exponential disposition were simplified to one-compartment, since the first distribution phase was rapid and not determinant for the description of the terminal elimination phase, mostly relevant for this project. Different absorption were standardized for first-order absorption processes.
Apparent clearance (CL), apparent volume of distribution of the terminal phase (V_z) and absorption rate constant (ka) and inter-individual variability were pooled into summary mean value, weighted by number of plasma levels; intra-individual variability was weighted by number of individuals in each study.
Simulations based on summary PK parameters served to construct concentration PK percentiles (NONMEM®).
Concordance between individual and summary parameters was assessed graphically using Forest-plots. To test robustness, difference in simulated curves based on published and summary parameters was calculated using efavirenz as probe drug.

Results: CL was readily accessible from all studies. For studies with one-compartment, V_z was central volume of distribution; for two-compartment, V_z was CL/λ_z. ka was directly used or derived based on the mean absorption time (MAT) for more complicated absorption models, assuming MAT=1/ka.
The value of CL for each drug was in excellent agreement throughout all Pop-PK models, suggesting that minimal concentration derived from summary models was adequately characterized. The comparison of the concentration vs. time profile for efavirenz between published and summary PK parameters revealed not more than 20% difference. Although our approach appears adequate for estimation of elimination phase, the simplification of absorption phase might lead to small bias shortly after drug intake.

Conclusions: Simulated reference percentile curves based on such an approach represent a useful tool for interpretating drug concentrations. This Pop-PK meta-analysis approach should be further validated and could be extended to elaborate more sophisticated computerized tool for the Bayesian TDM of ART.

III-03 *Azucena Aldaz* Capecitabine: a pharmacokinetic model derived from its clinical use

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Objectives: Capecitabine, a fluorouracil (5FU) prodrug, has proven efficacy in those tumors in which fluoruracil is effective. To be active, it requires an intracellular activation by phosphorylation. Two enzymes are important in its disposition: cytidin deaminase and dihydropyrimidin dehydrogenase. Capecitabine is increasingly used due to the oral administration even if it is more expensive than 5FU.The main problems with its use are toxicity and treatment adherence. It is therefore necessary to optimise its administration, and the same exposition goals as with 5FU can be applied. Therefore a population pharmacokinetic model must be developed and incorporated to a bayesian prediction programme in order to select the best dosing schedule to achieve the pharmacological goal.With this aim, the following objective was established: To characterise the population pharmacokinetics of capecitabine.

Methods: Capecitabine was administered orally to 7 patients at standard doses. Plasma samples were collected at 10 different sampling times. Capecitabine, 5DFUR, 5 FU and FUH_2 were quantified by HPLC(1). A population pharmacokinetic model was performed using NONMEM version VI. Model discrimination was based on the minimum value of the objective function and visual inspection of goodness of fit plots. Due to the small number of patients, and the different profiles of Capecitabine and its metabolites, volume of the latter was fixed to one for estimation issues

Results: Capecitabine plasma concentration profile and its metabolites were properly described using a five-compartment model, with first order absorption and Alag time. This model allows a good fit for both concentrations of capecitabine and its metabolites in the 7 patients with the exception of the fifth patient FUH_2.The model estimated high variability in Ka, Alag time, Volume and Clearance of Capecitabine.

Conclusions: The resulting model is a good proposal for estimating the optimal strategy of sampling in a larger number of patients to allow at a later stage to obtain a more robust model for clinical use. The oncologists increasingly demand tools that optimize chemotherapeutic treatments

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III-04 *Oskar Alskär* Using allometric scaling on an integrated glucose insulin model for humans to investigate anti-diabetics drug effects in rats.

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Objectives: The aim of this project was to allometrically down-scale an integrated glucose insulin model (IGI), developed on clinical drug development data [1], to characterize the relationship between glucose and insulin in male Han Wistar rats after an intravenous glucose tolerance test (IVGTT) and to assess the effect of the incretin mimetic Exendin-4 (EX-4).

Methods: Data of blood glucose and plasma insulin from an IVGTT was used in this population analysis. The previously published study [2] was conducted in 28 conscious, healthy male Han Wistar rats, of which 7 were injected with EX-4. Three different glucose doses (0.2, 0.5, 1.0 g glucose/kg LBM) and two different doses of EX-4 (2.4, 3.2 µg/kg LBM) were investigated. As no concentration data of EX-4 was available, PK was predicted using a previously published target mediated pharmacokinetic model [3] of EX-4 in rats. The disposition parameters and feed-back rate constants in the IGI model were allometrically scaled from healthy humans, using an exponent of 1 for volume, 0.75 for clearance and -0.25 for rate constants. The control mechanisms between glucose and insulin and also the effect of EX-4 were estimated using NONMEM 7. Model development was guided by goodness of fit, objective function value and VPCs.

Results: Using allometric scaling of the pharmacokinetic parameters described the data well. A better fit was however attained when re-estimating the peripheral volume of distribution. The model was able to identify the effect site of EX-4 on insulin secretion. An Emax model for EX-4 effect gave the best fit of the different concentration-effect relationships investigated.

Conclusion: These results indicate that the IGI-model has potential to be used in the design and analysis of preclinical studies for new anti-diabetic medication.

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III-05 *Claire Ambery* Application of population dose-response and dose frequency in respiratory

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Objectives: Drug discovery is expensive. Early clinical studies need to deliver more by answering key development questions, in particular, the dose response relationship and optimal dosing regimen. Here we present a case study for the determination of a dose response relationship after once daily dosing and subsequent assessment of pharmacodynamic similarity for two dosing regimens for a topically active novel drug undergoing clinical investigation. Data were obtained from a parallel design, placebo-controlled study with 3 different doses given once and twice daily. Trough measurements for clinical response (forced expiratory volume in 1 second - FEV_1) were obtained during the course of study. Approximately 50 subjects received each treatment.

Methods: A population Emax model was used to describe the change from baseline dose-response relationship for Drug X following once daily (reference) and twice daily (test) administration.

$$Response_i = Emax * Dose_i * F^x / (ED50 + Dose_i * F^x) + \eta$$

The parameters are Emax (maximum response), ED50 (dose that achieves 50% of maximum drug effect) and F (relative bioavailability, where X = 0 or 1 indicates once daily or twice daily dosing). Dose is the total daily dose. The model assumed that test and reference had the same Emax and differed only in their ED50 values. Drug X dose levels investigated were QD1, QD2 and QD3 (once daily); and BD1, BD2 and BD3 (twice daily). Diagnostic methods and posterior predictive checks were used to assess the appropriateness of the population model. To evaluate pharmacodynamic similarity for the two dosing regimens a 90% confidence interval for the model parameter F was constructed using bootstrap [3]. A total of 2000 runs were conducted. The software's NONMEM, PsN and R were used.

Results: Preliminary findings show responses at baseline were similar for each treatment. Diagnostic methods and posterior predictive checks showed the goodness of fit of the dose-response model to the data. The bootstrap median and 90% confidence interval for the model parameter F was 1.13 (0.53, 2.99), this was a reasonable quantification of the variability of the data.

Conclusions: The dose response relationship for Drug X was defined. Although the study was not designed to assess the bioequivalence between once and twice daily dosing regimens the dose scale method nevertheless provided a quantitative assessment of the similarity of the two dosing regimens.

III-06 *Orna Amir* Mechanistic NSCLC vascular tumor model: insights to prognosis towards personalized medicine

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Objectives: Predicting a cancer patient's likelihood to respond to treatment a priori is one of the greatest challenges both in drug development and in personalized medicine. The aim of this study was to create a prognostic tool for NSCLC using a mechanistic angiogenesis based vascular tumor (VT) model and to assess the quality of data necessary to calibrate the model and identify predictive covariates.

Methods: A mechanistic VT model for NSCLC was created based on literature data: biological data for untreated patients, PK models for cisplatin and pemetrexed and maximal PD effects were estimated from in-vitro data. PD EC50 and critical VT model parameters were fitted to population response data. Furthermore, a Baysian analysis was conducted with a synthetic data set in which a fictitious covariate to parameter relationship was used to generate population parameters yielding a synthetic data set. This set was then sparsely sampled and used to fit individual parameters given the prior population data.

Results: Model estimated response rates for cisplatin were 10.8% overall response rate (ORR), 55.2% stable disease (SD), and 34.0% progressive disease (PD) as compared to 12.8%(ORR), 49.1%(SD), and 38.1% (PD) [1]. Estimated response rates for pemetrexed were 9.8% (ORR), 48.7% (SD), and 41.5% (PD) as compared to 9.1%(ORR), 45.8%(SD), and 45.1% (PD) [2]. As observed clinically, patients with higher blood volume had a higher chance of being responders. The model was validated on the observed median time to progression (TTP), not used in the calibration phase. The predictions for placebo, cisplatin and pemetrexed were 1.7, 3.8, and 2.8 months, respectively, as compared to the observed 1.8[3], 3.7, and 3.4 months. Additionally, the Bayesian analysis was able to identify the fictitious covariate relationship given 4 tumor measurements taken once every other cycle.

Conclusions: The NSCLC VT model has been shown to be a robust model with the potential of being a prognostic tool. Bayesian analysis shows that the model can be calibrated on a limited and clinically feasible data set. As such we believe the model has a high potential as a clinically predictive tool both for identifying subpopulations that would not otherwise be obvious and eventually for use as a tool for treatment personalization.

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III-07 *Jacqueline Anderson* PKPD modelling of human chlorpyrifos poisoning

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Objectives: : Death from chlorpyrifos (CPF) poisoning, a common organophosphorus (OP) pesticide is an increasingly worrying problem in Sri Lanka. However, inaccurate information regarding dose amount and time are common in the data collected and make appreciation of lethal dose difficult. It would be useful to characterise the PKPD relationships involved to better understand the time course of poisoning and potential hazards. The aim of this project is to extend upon a previous PK model to incorporate PD aspects of organophosphate acute poisoning.

Methods: A PK model for CPF and its metabolites was developed using NONMEM 7.2. The model was derived from sparse acute poisoning data from patients (n = 75; 7 Female, age 15-65, 2-8 samples per subject). The reported volumes ingested ranged from 10 to 350 ml. CPF, chlorpyrifos oxon (CPO), RBC-AChE, BChE, and urinary metabolites were measured at each time point.

Results:A 2-compartment model for the parent compound with first order absorption kinetics and a one compartment disposition for the metabolite chlorpyrifos oxon best described the data. Dose uncertainty was accounted for by allowing each individual's dose to deviate from the median dose volume of 50mls using the reported volume intake as a covariate on the bioavailability parameter. For the parent Ka was estimated and fixed to 1.64 (Hr), Cl was 0.9 (L/Hr) SE 0.109, and Vd was7.39 (L) SE 1.3, with a residual error of 37%. The estimated dose range was on average 30mls less than reported. The CPO data collected was too highly variable for validation however Cl and Vd are both large and correlated with CPF. A turnover model was developed to describe the CPF - AChE and BChE(enzymes, biomarkers of toxicity) relationship, with an proportional Emax model on the elimination of the enzyme.

Conclusion: The developed PK model could well characterise the observed concentrations of 0.1 – 18.32 nM. CPO data was too variable for validation completion. Survival PD data is currently being incorporated into the model including cholinesterase inhibition, an important biomarker. We hope this extended model will help us to better understand acute chlorpyrifos poisoning toxicology and the relationship between dose and PD outcomes.

III-08 *Eduardo Asín* Population pharmacokinetics of piperacillin in critically ill patients undergoing continuous renal replacement therapies

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Objective: The aim of this study was to develop a population pharmacokinetic (PPK) model of piperacillin (PIP) administered to patients of the Intensive Care Unit (ICU) undergoing continuous venovenous hemofiltration.

Methods: Plasma concentration-time data were obtained from 16 patients who received piperacillin/tazobactam (4 g/0.5 g) every 4, 6 or 8 hours. Blood and ultrafiltrate samples were drawn at 0, 0.3, 0.5, 0.75, 1, 3, 4, 6 and 8 hours after dosing and were analyzed using HPLC-UV. Piperacillin plasma concentrations were modelled using NONMEM VI. Disposition of the total drug plasma concentration was modelled using compartmental models. Once a base model was selected, patient characteristics including demographic, clinical, and laboratory were explored for influence on PK parameters. Age, body weight, ultrafiltrate flow, creatinine clearance, the unbound drug fraction in plasma, proteinemia, albuminemia and serum bilirubin, were continuous covariates evaluated for significance. Sex, SOFA score (Sepsis-related Organ Failure Assessment), APACHE II score and diagnosis of sepsis were the categorical covariates studied. The sieving coefficient, defined as the fraction of the drug eliminated across the membrane during CRRT, was calculated as the ratio of area under the ultrafiltrate concentration curve to area under the serum concentration curve.

Results: Sixteen critically ill patients with a median age of 57 (range 18-77) were enrolled in the study. Piperacillin plasma concentrations were best described by a two-compartment model. The data supported the inclusion of IIV in total plasma clearance and the apparent volume of distribution. Total body clearance included a non-renal, a renal and an extracorporeal component.

Conclusions: A two-compartment pharmacokinetic model for piperacillin in patients undergoing continuous renal replacement therapies was developed. Considering that the main objective of antimicrobial treatment is to maintain free-drug plasma concentration above the MIC of the infecting pathogen, this model could be used to determine the probability of PKPD target attainment and to estimate appropriate piperacillin/tazobactam dosage guidelines in these patients.

III-09 *Bengt Hamren* Log likelihood profile intervals for ED50

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Objectives: Wald type of confidence intervals are easily computed but relies on approximately normal distribution of estimators. Log likelihood profile intervals require more computation but, in contrast to Wald type of confidence intervals, they are invariant to any monotonic transformation of the parameter under investigation and are valid under less strict assumptions. This abstract presents a comparison of confidence intervals for the ED50 parameter of the 3-parameter Emax model.

Methods: Wald confidence intervals was computed for ED50 with and without using a log-transformation and was compared to log likelihood profile intervals. Data was simulated with a fixed set of doses but for a wide range of true values for ED50. Confidence intervals were computed and the coverage probability was estimated based on 10000 replicated data sets. All evaluations was performed in R. The nls function was used to compute Wald confidence intervals whereas a linear search based on the lm and logLik function was used to compute profile intervals.

Results: Maximum likelihood estimation of the Emax model requires iterative estimation techniques, but conditional on ED50 the 3-parameter Emax model is linear in the remaining 2 parameters and hence profiling can be done within the framework of linear regression models. With respect to total coverage probability Wald intervals without log transformation performed as good, or better, than those computed with a log transformation. However a much larger difference in favor of intervals with a transformation was seen on coverage probability of the lower and upper bound respectively. Lower bounds without the log transformation were consistently too optimistic whereas the upper was consistently too conservative. The reverse bias was seen for Wald intervals with a log transformation but only at lower or upper end of the studied values for ED50. The log likelihood profile upper and lower bounds overall hade coverage probability closest to the nominal level and hence further improved on the Wald intervals.

Conclusions: Although log likelihood profile intervals for the ED50 parameter of the 3-parameter Emax model are slightly more computational intensive a numerical stable algorithm is easily implemented in high level languages such as R. Compared to Wald type of confidence intervals log likelihood profile intervals have overall coverage probabilities closest to the nominal level.

III-10 *Daren Austin* A closed-form solution set-point model of treatment response in multiple diseases

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Objectives: Many clinical trials demonstrate a profound placebo response once patients enter the trial, which may invalidate interpretation of trial outcome. The intent of this work is to develop a simple, semi-mechanistic, disease progression model that has validity in multiple diseases, in order to provide an alternative tool for model-based inference..

Methods: Disease status is characterized using a simple linear turnover model and patients assumed to enter the trial at equilibrium. The action of entering the trial resets the equilibrium to a new set-point, which reflects the action of placebo and drug intervention. Subsequent disease trajectories are assumed to follow deterministic dynamics to the new equilibrium. The model is applied to two instances: Rituximab for Idiotypic Membranous Glomerular Nephropathy (IMGN) where placebo response is inferred[1], and aOSM for Rheumatoid Arthritis (RA), where the Proof of Concept study is analyzed to make inference of drug activity[2].

Results: Assuming that disease status, D(t), is described by the simple linear ordinary differential equation dD(t)/dt = Kin – Kout D(t), at trial entry patients are assumed to be at equilibrium D0 = Kin/Kout. Once the trial has begun, the parameters are assumed to change and the equilibrium point is modified such that Kout' = Kout (1+Pi), where Pi is a random effect defining the magnitude of the treatment interaction (including placebo). Solution of this model is straightforward; D(t) = D0(1-1/(1+Pi))exp(-(1+Pi) Kout t)+D0/(1+Pi). Since the effect of the intervention, Pi, is a random variable, the simple model has the advantage over traditional mixture models, in that individual patients can deteriorate whilst the population improves. The population dynamics (including weighted mean response) is captured in a closed-form. The model was used to adequately describe two clinical trial scenarios, and was fitted to data using SAS and NONMEM. The model is extended to cases where disease progression parameters may be time-dependent and infer both relapse and progression.

Conclusions: A simple set-point model can be used to describe disease progression in Proof of Concept trials. The observation that entering a trial changes the disease equilibrium has been validated in two clinical settings. A closed-form solution makes model implementation simple and allows for inference of treatment effects when considering trial design and simulation.

References:
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[2] Zamuner et al. (2012) PAGE abstract.

III-11 *Nicolas Azzopardi* Modelization of bevacizumab effect on number of episodes of epistaxis in Hereditary Haemorrhagic Telangiectasia (HHT)

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Context: Hereditary Haemorrhagic Telangiectasia (HHT) is a genetic disorder of the blood vessels, which affects approximately 1 in 5,000 people. Patients with HHT suffer from unpredictable, recurrent, severe nasal bleeding which requires emergency care, nasal packing, blood transfusions, and invasive procedures. Anti-vascular endothelial growth factor (VEGF) drugs, such as bevacizumab, were previously shown to be effective in HHT.

Objectives: To describe the relationship between bevacizumab pharmacokinetics, VEGF concentrations and the reduction of the number of epistaxis episodes in HHT.

Methods: This study was a single-center, phase II trial. Seventeen HHT patients were administered 6 infusions of bevacizumab 5 mg/kg every 14 days. The total duration of the treatment was 2.5 months. Patients were followed up for 6 months after the beginning of bevacizumab treatment. Concentrations of bevacizumab and total VEGF were measured over time. Bevacizumab concentrations were described using a two-compartment model with first-order elimination. Concentrations of free and bound VEGF were described using a semi-mechanistic model. Free VEGF production and elimination are described by zero-order (k_{in}) and first-order (k_{out}) constants, respectively. Bevacizumab binds to free VEGF with a second-order constant (k_{on}). Bevacizumab-VEGF complex is assumed to be totally eliminated with a first order constant (k_{deg}). In addition, the probability of daily epistaxis episodes was described using a Poisson model, which parameter (lambda) was influenced by bevacizumab pharmacokinetics. An effect compartment was used. A population approach was applied using MONOLIX 4.1.2.

Results: A total of 230 and 140 blood samples were available for analysis of bevacizumab and total VEGF concentrations, respectively. Population values for PK-PD parameters (interindividual CV%) were: central volume of distribution (V_1) = 3.0 L (11%), elimination clearance (CL) = 0.17 L/day (24%), peripheral volume of distribution (V_2) = 2.0 L (50%), distribution clearance (Q) = 0.44 L/day (25%), k_{in} = 0.0026 µM/day (47%), k_{out} = 0.29 1/day (78%), k_{on} = 0.12 1/µM/day (61%) and k_{deg} = 0.17 1/day (26%), k_{e0} = 0.00048 1/day (194%), $lambda_0$ = 0.46 (114%), IC_{50} = 3.7 mg/L (170%).

Conclusions: In this preliminary study of patients with HHT, short treatment of bevacizumab was associated with a long-lasting reduced number of episodes of epistaxis.

Trial registration: clinicaltrials.gov Identifier: NCT00843440.

III-12 *Gaurav Bajaj* Model-based analysis of disease progression in pancreatic cancer based on registry data collected from the Surveillance, Epidemiology, and End Result (SEER) database

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Objectives: Pancreatic cancer is the fourth leading cause of cancer related deaths in United States. With most patients diagnosed with pancreatic adenocarcinoma (AC) in advanced stages and few months to survive, the disease is considered largely incurable due to minimal effects of treatment. Sample size in pancreatic cancer trials is usually small and poses a significant challenge for comparing treatment effects across trials. Our objective is to develop a parametric survival model using data from Surveillance, Epidemiology, and End Result (SEER) registry [1], identify relevant covariates to stratify patients in future trials and predict disease outcome.

Methods: Data from 82,251 patients was extracted using site (pancreas) and histology codes (duct, mucinous and monopormphic AC) in the SEER database and refined based on the specific cause of death. Predictors effecting disease outcome were chosen from previous studies and in consultation with clinical expertise. Categorical predictors influencing survival were tested using non-parametric analysis. Both semi-parametric and parametric approaches were used for testing continuous predictors, and multivariate modeling was done with variable reduction based on a manual backward elimination using significance level of α=0.05. Model evaluation was done using Cox-Snell, Martingale, and Score residuals [2]. Analyses were performed using SAS 9.2.

Results: Median overall survival in pancreatic cancer patients was 4 months which is similar to previous studies. Predictors that influence survival were tumor characteristics, therapy, and LN status. Treatments that improved survival outcome were LN removal, surgery of the tumor, chemotherapy and radiotherapy with hazard ratios (HR) 0.63, 0.46, 0.52, and 0.90 respectively. HR for tumor size and LN status were 1.01 and 1.05. SEER data was best fitted by the log-logistic parametric distribution and model selection was based on -2 Log likelihood, Akaike information criterion and residual analysis.

Conclusions: While the SEER dataset lacks granularity in terms of time dependent information, it provides valuable information on tumor size, LN status, and treatment. Parametric analysis shows that the pancreatic cancer data from SEER follows log-logistic regression model. Future efforts include model validation against a dataset from prospective clinical trial and the development of a trial simulation model informed by this and previously published trials.

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III-13 *Francesco Bellanti* Deferiprone sampling optimisation in a pharmacokinetic bridging study including children with β-thalassaemia

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Objectives: Practical and ethical constraints impose special requirements for clinical trials in children. The application of population PK analysis to sparse data allows reducing the burden in such a vulnerable population [1]; yet it is important to optimise the quality of the information gathered. The aim of this analysis is to optimise sampling times for the evaluation of deferiprone PK in children in a prospective clinical investigation in order to subsequently optimise the dosing regimen in the same population.

Methods: A one-compartment PK model with first order oral absorption has been developed on adults' data using a non-linear mixed effects approach, as implemented in NONMEM VII. Two covariate models have been used to optimise sampling times in children, namely M1 (body weight with a linear correlation on CL/F and Vd/F), and M2 (fixed allometric scaling on the same parameters). Uncertainty (20%) in CL/F and Vd/F estimates has been accounted for in the optimisation procedures. The study consisted of a parallel design with three dose levels randomised across 18 children (aged between 2 and 10 years). The final sampling scheme (maximum of 5 samples per subject) has been selected based on the outcome of four scenarios in PopED 2.12. The accuracy and precision of parameters estimates were estimated for primary and secondary (i.e., AUC and Cmax) PK parameters. Predicted AUC and Cmax estimates were compared with simulated data using frequent sampling (n=12) according to the trapezoidal rule.

Results: Given practical constraints, the selected sampling scheme was the result of a compromise between full optimisation and feasibility in a real clinical trial. The accuracy of primary PK parameters estimates was below 10% except for KA (-11%); whereas precision, as expected, was slightly lower given the small sample size (> 30% for Vd/F and KA). AUC values (mean and standard deviation) were found to be 33.37 (19.24) and 35.61 (20.22) mcg/ml.h and Cmax values 10.17 (6.05) and 10.94 (6.68) μg/ml in sparse and frequent sampling respectively.

Conclusions: The results of our analysis illustrate that despite feasibility issues, study characteristics can be optimised using ED-optimality concepts. Predefined sampling schemes and sample sizes do not warrant accurate model structure and parameter identifiability. Of particular importance is the accurate estimation of the magnitude of the covariate effects, as they may determine the final dose recommendation for the population of interest.

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III-14 *Brendan Bender* A multicompartmental population PK model elucidating the complex disposition of trastuzumab emtansine (T-DM1): an antibody-drug conjugate for the treatment of HER2-positive cancer

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Objectives: T-DM1 is an antibody-drug conjugate (ADC) in clinical development for treatment of HER2-positive cancers. T-DM1 drug product is a mix of drug:antibody ratio (DAR) moieties in which trastuzumab is conjugated with 1–8 molecules of the microtubule inhibitor DM1. T-DM1 targets the HER2 receptor to deliver DM1 intracellularly to kill tumor cells. A population pharmacokinetic (PK) model was developed from preclinical data to conceptualize this system, and to quantify PK and rates of DM1 deconjugation.

Methods: Model development was done using NONMEM 7 software. Preclinical data included T-DM1 PK studies in rats (N=34) and cynomolgus monkeys (N=18) at doses from 0.3–30 mg/kg, and in vitro plasma stability. Two different lots of nonclinical T-DM1 dose solution were used, one with an average DAR=3.1 (3.1 DM1/trastuzumab) and one with an average DAR=1.5. Concentrations of the DAR moieties (free trastuzumab (DAR0) and DAR1–DAR8) were obtained using affinity capture liquid chromatography-mass spectrophotometry [1] and ELISA. The model was fit simultaneously to total trastuzumab and DAR concentrations from in vivo and in vitro data. Total trastuzumab clearance (CLtrastuzumab) was modeled as composed of plasma degradation and in vivo antibody clearance processes. T-DM1 CL was modeled as composed of CLtrastuzumab and first order deconjugation of DM1 from DAR moieties. The data allowed for a robust analysis and is an extension upon previous modeling work based on monkey data(n=4)[2].

Results: A three compartment PK model, with a catenary chain of 8 subcompartments within the central compartment, described all DAR concentration–time data well. In rats and monkeys, values for CLtrastuzumab were 2.32 and 16.0 mL/day, respectively. Terminal half-lives for total trastuzumab and T-DM1 were 10.5 and 8.33 days in rats, and 15.3 and 11.6 days in monkeys, respectively. Higher conjugated DAR moieties (DAR3–DAR8) deconjugated faster than lower conjugated DAR moieties (DAR1, DAR2). There was no difference between species with regard to plasma stability.

Conclusions: The disposition of all individual DAR moieties for T-DM1 was well described by a multicompartmental PK model. This model can be used to predict concentrations of DAR moieties, free trastuzumab, total trastuzumab, T-DM1, as well as the average DAR versus time. This modeling and simulation analysis provides a framework for study designs towards PK and PKPD modeling of T-DM1 and other similar ADCs.

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III-15 *Margherita Bennetts* Delta Method Application: Landmark Prediction and Confidence Interval for a Non-Linear Longitudinal Model

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Objectives: Longitudinal model based meta-analysis (MBMA) is performed, using all the relevant in-house and published data, to better understand efficacy and safety characteristics of competitor drugs alongside compounds in development. However, in the Drug Development process new compounds often need to show differentiation from standard of care for a Landmark endpoint to meet strategy decisions.
To compare four different methods for producing a landmark prediction and confidence interval from a longitudinal model

Methods: A non-linear longitudinal model was fitted to NIH CPSI (National Institute of Health Chronic Prostatitis Symptom Index) Total Score data for the three As of accepted care (A1 Adreno-receptor antagonist, Anti-Inflammatory & NSAID) and placebo. The final model was a 3 parameter Emax model over time and was performed using NONMEM.
Differentiation from standard of care would be required at 6 hours post dose for a drug in development.
Four methods were employed and compared to calculate the landmark prediction for standard of care:

1. Simulation in NONMEM, altering the model file to incorporate parameter uncertainty.
2. Calculating the Delta Method formulae for the model and implementing using matrix multiplication in R.
3. A simple simulation in R using parameter uncertainty.
4. Utilising the delta method function in the R msm package.

Results: All four methods produced similar results.

	Difference	StdErr	95% Lower	95% Upper
Delta Matrix Multiplication	-3.733389	1.297707	-6.276896	-1.189883
Delta Function	-3.733389	1.297707	-6.276896	-1.189883
NONMEM Simulation	-3.736108	1.281891	-6.23505	-1.15085
Simple Simulation	-3.72785	1.303936	-6.283564	-1.172136

Conclusion: The Delta Method is a quick method to produce prediction standard errors. Although a black box the Delta Method function in R gives the same result and removes the need for differentiation and computer intensive simulation.

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III-16 *Aliénor Bergès* Development of a mechanistic PK/PD model to guide dose selection of a combined treatment for systemic amyloidosis

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Introduction/Objectives: Amyloidosis is a rare fatal disease caused by progressive extracellular deposition of amyloid fibrils which damage tissue structure and function[1]. There are no treatments which directly target and clear amyloid from the tissues. A novel treatment approach is under development and targets serum amyloid P component (SAP), an endogeneous protein decorating amyloid fibrils in all forms of amyloidosis. The high (mg/mL) circulating concentrations of SAP, combined with a fast turnover, make administration of anti-SAP antibody alone a challenging prospect as binding to circulating SAP may limit antibody distribution to target tissues. Therefore, a two stage approach combining a small and large molecule is proposed. A small palindromic molecule called **C**arboxy **P**yrrolidine **H**exanoyl **P**yrrolidine **C**arboxylate (CPHPC) will be administered first in order to deplete SAP in plasma. The anti-SAP antibody will then be administered (while CPHPC is continued) and is expected to partition rapidly to amyloid deposits within tissues and induce a macrophage giant cell reaction resulting in clearance of the amyloid in situ.
We propose a mechanistic PK/PD model aimed to simultaneously predict the time profile of CPHPC, anti-SAP antibody and SAP in plasma and in tissues. The integrated use of all these data will allow investigation of the optimal dosing regimen of the antibody in combination with CPHPC.

Methods: A compartmental model including target mediated disposition was used to represent the different sites of interest (plasma, non amyloid tissues and amyloid tissues). The information related to SAP came from literature [2,3] and internal clinical data. The drug effect of CPHPC alone on SAP in plasma was evaluated in-house and was quantitatively described by a PKPD model using a non-linear mixed effect approach in NONMEM VII [4]. The anti-SAP antibody has not yet been administered to man and therefore data were limited to in-vitro binding assays and pre-clinical PK studies in plasma. A series of hypothetical plasma and tissue profiles of antibody was simulated using Berkley Madonna 8.3.18.

Results/Discussion: Given the limited current information on the antibody, we tested the antibody effect in the PKPD model using different scenarios, primarily related to antibody elimination (in the presence and absence of target mediated processes), and to the rate and extent of antibody distribution in the tissues.
Further imaging, liver biopsy and clinical data may be used to update the PKPD model in terms of antibody distribution across targeted organs affected by amyloid (e.g. liver, heart, kidney) and in terms of antibody-SAP complex in-situ degradation.

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III-17 *Tarjinder Sahota* A mechanistic PK/PD model to predict the pharmacological depletion of serum amyloid P component in healthy volunteers

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Introduction/Objectives: Amyloidosis is a rare fatal disease caused by progressive extracellular deposition of amyloid fibrils which damage tissue structure and function[1]. There are no treatments which directly target and clear amyloid from the tissues. A novel treatment approach is under development and targets serum amyloid P component (SAP), an endogeneous protein decorating amyloid fibrils in all forms of amyloidosis. Part of this approach involves the administration of a small palindromic molecule called Carboxy Pyrrolidine Hexanoyl Pyrrolidine Carboxylate (CPHPC) to deplete SAP to low concentrations in plasma. Free CPHPC has been found in preclinical studies to be cleared at almost glomerular filtration rate with a volume of distribution consistent with plasma and interstitial space distribution.
We propose the development of a mechanistic PK/PD model to allow for the prediction of CPHPC and SAP concentration-time profiles in plasma and in tissue. The model is being used to inform CPHPC dose selection in patients and will be subsequently extended to predict the effect of an additional antibody therapy[2].

Methods: Data came from an open label, adaptive study where CPHPC was administered to healthy volunteers and plasma CPHPC and SAP sampling were conducted from baseline (day 1) to follow up (day 28). All measurements were total concentrations (including free and bound fractions from the CPHPC-SAP complex).These data together with literature values of SAP turnover[3,4] were used to develop a mechanistic PKPD model using a non-linear mixed effect approach in NONMEM VII.

Results/Discussion: CPHPC disposition was best described by a two compartment model with rapid first order elimination (major elimination pathway) and target mediated clearance. Target mediated clearance was consistent with the assumption that the CPHPC-SAP complex was rapidly eliminated and the dissociation rate was negligible in comparison. SAP kinetics were best described by an indirect effect model with target mediated clearance, and a saturable peripheral compartment indicative of an extravascular binding to fixed non-amyloid ligands with negligible turnover and internalisation rates.
The model performed well in diagnostics and provided predictions of extravascular SAP concentration and plasma SAP concentration as a function of CPHPC exposure.
A potential limitation of the current approach is the availability of data in plasma only. Therefore, any difference in extravascular SAP concentrations between healthy volunteers and patients can only be inferred by the model.

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III-18 *Kirsten Bergmann* Comparing a mechanistic with an empirical approach to assess resistance development of antibacterials in vitro.

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Objectives: Already early in the preclinical phase, resistance development of bacteria against antibacterials can be observed. The use of dynamic models, already in an early stage, for rapid screening and/or more mechanistic insight in the resistance development is therefore important. The aim of the current study was to compare a series of models to describe resistance development and consequently describe the time course of the bacterial count.

Methods: The pharmacodynamic properties of 3 antibacterial compounds (two Novel siderophore conjugated Beta-Lactams and one LpxC inhibitor) were investigated in *in vitro* static concentration time kill experiments against Klebsiella pneumoniae (KP-1487) and Pseudomonas aeroginosa (PA-UC12120). The resulting bacterial count-time profiles were analysed with NONMEM using two approaches. The first approach used an empirical one-population adaptation model. The bacteria kill was described by a (sigmoidal) E_{max} relationship and the EC_{50} value was allowed to change with time and/or compound concentration to describe the resistance development of the bacteria. The second approach was a mechanistic two-population mutation model. This model takes into consideration that the susceptible bacteria can mutate to become resistant to the antibiotic. For this matter a new model is proposed, taking into account the probability of a mutation occurring. For both approaches the M3-method was applied to take into account the samples below the limit of quantification (LOQ).

Results: Both the empirical adaptation model and the mechanistic mutation model adequately captured the development of resistance during drug exposure to the 3 compounds. Moreover the models described the time course of the bacterial count well. In addition, for the mechanistic model, implementing the new estimation method was necessary to obtain more realistic mutation rates. Both approaches resulted in similar human dose predictions to obtain -1 and -2 log kill after 24h.

Conclusions: A tool box, including an empirical model with an adaptive EC_{50} (including various adaptation functions, depending on concentration and/or time) and a mechanistic mutation model was developed to analyze *in vitro* bacterial count-time profiles. Depending on the aim of the analysis and on the available data, the empirical model (e.g. for rapid screening) or the mechanistic mutation model (e.g. for more mechanistic insight) might be preferred.

III-19 *Julie Bertrand* Population Pharmacokinetic-Pharmacogenetic study of Efavirenz in combination with Rifampicin in HIV-Infected Cambodian Patients

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Objectives: To monitor efavirenz plasma concentrations in Cambodian patients of the CAMELIA-ANRS1295-CIPRA KH001 trial and to explore genetic variations as factors of variability, especially due to concomitant use of rifampicin.

Methods: Analyses included 307 HIV-1 infected patients. All received efavirenz and nucleoside analogs once daily and efavirenz trough plasma concentrations were measured 12h after drug intake at weeks 2 and 6 after the onset of HAART and at weeks 22 and 50 after the tuberculosis treatment onset along with intensive pharmacokinetic profiles (6 samples) in 10 patients.
A one compartment model with delayed zero-order absorption and first-order elimination was used accounting for between and within subject variability on Cl/F and a scale bioavailability parameter F fixed to 1.
Efavirenz is mainly eliminated through CYP2B6 with CYP3A5 and CYP2A6 as alternative pathways and rifampicin is a known inhibitor of the OATP-C transporter as well as an inducer of the PXR transporter which influences CYP3A4 and P-glycoprotein expression levels. Therefore in the present study patients were genotyped for *CYP2B6G516T*, *CYP2B6C1459T*, *CYP3A4*1B*, *CYP3A5A6986G*, *CYP2A6*9*, *ABCB1C3435T* and *OATP-CT521C* polymorphisms. Due to the duration of study and the related improvement in patient's condition, weight was entered as covariate on Cl/F with an allometric scaling.

Results: Allele frequencies of *CYP2B6 516T*, *OATP-C 521C*, *ABCB1 3435T* and *CYP3A5 6986G* (loss-of-function variant) were 0.30, 0.14, 0.36 and 0.36, respectively.
Efavirenz Cl/F was found to be significantly related to the *CYP2B6G516T* polymorphism and the transaminase levels. The latter covariate was not kept in the final model as the magnitude of its effect and the decrease in inter-individual variance after addition in the model were not clinically relevant. Cl/F average value in the population was 11 L/h for *CYP2B6 516GG*, 7.41 L/h for *CYP2B6 516GT* and 3.81 L/h for *CYP2B6 516TT* patients. Its addition in the model decreased the estimate of Cl/F coefficient of inter-individual variation from 32 to 20%.

Conclusions: Because the first samples were collected following at least 2 weeks of efavirenz on top of 4 weeks of rifampicin, we did not use the auto-induction and concurrent enzyme induction model proposed by Zhu et al. [1]. No other genetic marker than *CYP2B6G516T* was found associated to efavirenz Cl/F in the present study, yet there were very few carriers of the OATPC-C allele.

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III-20 *Roberto Bizzotto* Glucose Homeostasis Modeling: Improvement of the Insulin Action Component

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Objectives: Glucose homeostasis models are important for predicting the effects of antidiabetic drugs. Some relevant models already exist [1]; however, the complexity of the system requires refinements of the model components to achieve better accuracy. In current models, glucose clearance is typically dependent on insulin but not on glucose concentration. This is not correct [2], but a quantitative analysis of the phenomenon is lacking, and the aim of this study was address this issue.

Methods: Data were obtained from a combined hyperglycemic/hyperinsulinemic clamp [3] in 8 healthy subjects, with glucose (5-18 mmol/L) and insulin (20-10000 pmol/L) spanning wide ranges. A glucose tracer was used to calculate glucose clearance. A model (A) was developed based on a circulatory model of glucose kinetics [4] and a model for insulin action that includes a simplified description of interstitial diffusion and insulin-controlled glucose transport across the cell membrane. Model parameters were estimated in each subject individually using Matlab/Simulink. A prototypal glucose homeostasis model (B) was then set up by adding a b-cell [5] and glucose appearance [6] submodel. Model B was used to simulate an oral glucose test (OGTT), including or excluding the glucose effect on clearance of model A.

Results: Estimation of model A parameters provided a good fit of the tracer data. The model was able to reproduce a characteristic feature of these data, i.e., the lack of glucose clearance increase in presence of hyperinsulinemia accompanied by hyperglycemia. The prediction of the dependence of glucose clearance on glucose concentration was qualitatively in agreement with what is known from the literature. In a representative subject, glucose clearance at an insulin concentration of 500 pmol/L was reduced from 81 to 42 ml min-1m-2 when glucose was raised from 5 to 10 mmol/L. The OGTT simulation with model B showed that the impact of the glucose effect on clearance was remarkable: including vs. excluding the effect produced an increase in 2-h glucose post OGTT from 6.7 to 7.6 mmol/L.

Conclusions: The new glucose clearance model can describe experimental characteristics that cannot be reproduced by more classical models; accounting for the dependence of glucose clearance on glucose concentration has a remarkable impact on glucose homeostasis. Thus, this model is expected to improve the representation of glucose homeostasis, with benefit for the prediction of drug effects.

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III-21 *Marcus Björnsson* A population PK/PD model for bispectral index of the fast acting anesthetic AZD3043 in healthy volunteers

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Objectives: The objective of the analysis was to describe the population pharmacokinetics (PK) of the sedative and anesthetic compound AZD3043 and its pharmacological effect assessed by the bispectral index (BIS) in healthy volunteers.

Methods: In two clinical studies, in a total of 125 healthy volunteers, AZD3043 was given either as a 1-min infusion (1 to 6 mg/kg/min), as a 30-min infusion (1 to 81 mg/kg/h) or as a 1-min infusion (0.8 to 4 mg/kg/min) immediately followed by a 30-min infusion (10 to 40 mg/kg/h). Arterial plasma concentrations of AZD3043 were measured up to 150 minutes after the start of infusion, and BIS were recorded until the subject was regarded as awake after sedation or anesthesia. A population pharmacokinetic/pharmacodynamic analysis was performed using NONMEM 7 (ICON, Hanover, MD, USA) [1] and PsN [2]. Goodness of fit was assessed using objective function values, standard errors, graphics and visual predictive checks.

Results: A 3-compartment model, with a lag-time for the drug to appear at the site of sampling, described the PK of AZD3043. The clearance (CL) and volume of distribution (V) parameters were allometrically scaled with body weight. CL was high, 2.1 L/min, suggesting elimination occured not only in the liver as the CL was higher than liver blood flow. Plasma esterase activity did not, however, influence CL. Peripheral V's were low, but increased with increasing dose. V_{ss} (sum of all V's) ranged from 12 L in the lowest dose group to 35 L in the highest dose group. A sigmoid E_{max} model was used to describe the relationship between arterial concentrations and BIS. EC_{50} was estimated to 54 µmol/L. Between-subject variability in EC_{50} was 35%, suggesting that individual titration to the desired effect may be needed. An effect compartment model, with a half-life of k_{e0} estimated to 1 min, was used to describe the delay in effects in relation to the concentrations. A two-compartment effect-site model [3] did not improve the fit, suggesting rapid and/or limited distribution within the brain.

Conclusions: AZD3043 was rapidly metabolized and distributed. The extent of distribution was low but dose dependent. The short half-life and rapid equilibration with the effect site was reflected in a fast onset and offset of effects on BIS.

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III-22 *Michael Block* Physiological modeling of inter-individual variability: Combining PBPK modeling and Markov-Chain-Monte-Carlo approaches

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Objectives: The assessment of inter-individual variability is a key aspect in physiology-based pharmacokinetic (PBPK) modeling. Physiological differences like age or blood protein content have to be considered since these factors contribute to the pharmacokinetic (PK) variation. Only if the population wide variation of parameters is known in detail, reliable extrapolations to other populations can be performed. Markov-Chain-Monte-Carlo (MCMC) approaches provide a state of the art method to determine such variations for better predictions of individualized PK [1, 2]. We here present a combined approach of PBPK modeling and MCMC for the identification of the distribution of both individual as well as substance-specific parameters in a pravastatin data set [3]. Our aim is to determine the main sources of variability of PK and identify whether homogeneous subpopulations exist.

Methods: PBPK models enable a comprehensive simulation of drug PK at the whole-body scale based on drug distribution models and extensive collections of physiological parameters. By integration of specific experimental data, models are used to analyze and investigate the expected PK in groups of healthy volunteers or patients by processing population simulations. Identifying parameter distributions requires a Bayesian formulation of the population PBPK approach. In order to analyze these models it is necessary to sample from the so-called “posterior” parameter distribution, i.e. how likely is a parameter value given the information contained in the measured data. Since these distributions are high-dimensional, Markov-Chain-Monte-Carlo (MCMC) algorithms are used. This approach is applied to a pravastatin example [3]. The resulting marginal posterior distributions are analyzed for multi-modality which is then compared to clinical data to identify homogeneous subpopulations.

Results: Analysis of the marginal posterior distributions identified clearance and metabolization processes as main sources of variation. Moreover, homogeneous subpopulations could be identified from the results which can be assigned to a polymorphism in gene SLCO1B1 encoding the hepatic organ anion transporter OATP1B1 [3].

Conclusions: The presented approach of combined PBPK-MCMC is a systematic approach to characterize inter-individual variability of physiological parameters. It allows the identification of main sources of PK-variability and the identification of clinically relevant homogeneous subpopulations.

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III-23 *Michael Bolger* GastroPlus PBPK/PD Model Applied to Estimating Dose for an Elderly Population in an Alzheimer's Disease Clinical Trial

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Objectives: Certain neurosteroid metabolites of progesterone are known to be positive allosteric modulators of the GABAa receptor and have application as anticonvulsant, anxiolytic, and sedative hypnotic agents [1]. More recently 3alpha-hydroxy-5alpha-pregnan-20-one (AP-alpha) has been shown to promote neurogenesis in mice in vitro and in vivo [2-3]. In addition, AP-alpha has be shown to restore hippocampal-dependent learning and memory and neural progenitor cell survival in aging 3xTgAD and nonTg mice [4].
Our objective was to explore the application of mechanistic absorption PBPK/PD modeling and simulation to the translation of basic science discoveries and preclinical data in support of developmental human clinical trials.

Methods: ADMET Predictor(TM) (Simulations Plus, Inc.) was used to estimate the biopharmaceutical properties of AP-alpha [5]. Data from the literature on the pharmacokinetics and pharmacodynamics of AP-alpha in mice and humans were compared to PBPK/PD models built using GastroPlus 8.0(TM) (Simulations Plus, Inc.) to establish a prediction for a dosing regimen and expected human exposure in support of a developmental clinical trial in Alzheimer's patients. An indirect-link effect compartment PD model [6] was parameterized using data from iv administration of AP-alpha to healthy women, and measurements of the % change in saccadic eye movement [7].

Results: The mouse PBPK model was able to explain the observed plasma concentrations at three doses (1, 10, and 20 mg/Kg) and the observed cortex level following the 1 mg/Kg dose. Human clinical trial data for intravenous doses of AP-alpha linked to a pharmacodynamic model of saccadic eye movement were successfully modeled. Finally, an intravenous dosing regimen for an elderly population was proposed to achieve similar brain concentrations as observed in the mouse preclinical studies but to avoid the sedation inducing concentrations observed in the previous human clinical trials.

Conclusions: The validated PBPK/PD model for allopregnanolone supplied prospective plasma and brain concentrations for iv dosing in an elderly population. Final results from the developmental clinical trial will be compared to this prediction when the studies are complete. GastroPlus can be used for translational research and facilitates multidisciplinary collaborations.

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III-24 *Irina Bondareva* Population Pharmacokinetics of Phenytoin Estimated from Repeated Therapeutic Drug Monitoring (TDM) Data of Epileptic Patients

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Objectives: Phenytoin (PHN) is widely used in the treatment of epilepsy for a long time. The pharmacokinetic (PK) characteristics of PHN increase the risk for toxicity: saturable concentration-dependent metabolism, relatively narrow therapeutic index, wide interindividual PK variability, clinically significant drug-drug interactions. The objective of the study is to develop a nonlinear model of PHN pharmacokinetics and to estimate its parameters from TDM data of adult epileptic patients on chronic PHN – monotherapy.

Methods: PHN monitoring data were routinely collected in the Laboratory of Pharmacokinetics of Moscow Medical University. PHN concentrations were measured by high performance liquid chromatography. The assay error pattern was used as: SD=0.1+0.011C+0.003C*C (where SD is standard deviation of the assay at measured PHN concentration C). The population PK analysis was performed using the NPEM program (USC*PACK software) based on a one-compartment model with the first-order absorption and Michaelis-Menten elimination kinetics. This study included 42 patients (28.7±10.7 years) for whom at least two pairs of measured serum levels (peak – trough strategy) related to different PHN dosages were available (182 PHN serum levels totally, PHN dose 274.4±141.7 mg/d).

Results: Assuming 100% bioavailability of orally-administered PHN, estimated median population PK parameter values for the rate constant of absorption (Kabs = 1.72 1/h, CV = 65.8%), the apparent volume of distribution (Vd = 0.6 L/kg, CV = 54.2%), the maximum rate of metabolism (Vmax = 0.35 mg/kg/h, CV = 36.8%) and the Michaelis-Menten constant (Km = 7.5 mg/L, CV = 40.2%) are in good agreement with those reported in the literature.

Conclusions: The study demonstrated wide interindividual variability in PHN pharmacokinetics and the need for TDM and individualizing of PHN dosage regimens. All feedback methods improve the predictability of steady-state (SS) PHN serum concentration (Css) in comparison with predictions based on the population parameter values. However, a reliable Css value for PHN often can be obtained only after about 2 - 3 weeks on an unchanged dosage regimen. Therefore, Bayesian approach for PHN concentration prediction based on minimum sampling SS or non-SS TDM measurements appear to be preferable. Bayesian feedback adaptive control and the proposed population model can improve PHN dosage adjustment and can identify how close a patient is to the more saturated part of the PK curve.

III-25 *Emma Bostrom* Modeling and Simulation of Pharmacokinetics and H3 Receptor Occupancy for Dose Setting in a Phase IIa Study

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Objectives: AZD5213 is a histamine 3 (H3) autoreceptor antagonist currently under development for symptomatic treatment of Alzheimer's disease. Sleep disturbances is a well-known class-effect for H3 antagonists [(1)] and is associated with high H3 receptor occupancy (RO) at night. Therefore the preferred time course of RO during a dosing interval would be high RO during day (for cognitive improvement) and low RO during night. The objective of the modeling and simulation was to investigate if it was possible to obtain large diurnal fluctuations in RO for AZD5213 as well as to suggest doses that provide a wide spread in predicted diurnal RO vs. time-profiles for a Phase IIa study.

Methods: Data from a multiple ascending dose study in healthy volunteers was used to build a population pharmacokinetic model in NONMEM. The final population model was implemented in Berkeley Madonna. The model predicted plasma concentrations (Cp) were used together with the reported Ki-value for H3 RO from a human PET-study in order to calculate the anticipated RO vs. time profile using the formula RO(%) = 100*Cp/(Cp+Ki). For each investigated dose, 1000 stochastic simulations of RO vs. time at steady state were carried out and the results were transferred to R for calculation of medians and 90% prediction intervals and plotting.

Results: The pharmacokinetics was well described using a two-compartment model with 1st order absorption. Diagnostic plots and visual predictive checks proved the model fitted the data well. Using simulations, the predicted plasma concentration and RO vs. time profiles for a number of doses were explored and doses with a wide range of fluctuations in RO over the dosing interval could be identified. Following this analysis, it was decided to proceed to Phase II with three doses; 0.5 mg, 2 mg and 6 mg.

Conclusions: Using population modeling and stochastic simulations of pharmacokinetic data and the Ki-value from a PET study, it was possible to explore the predicted RO vs. time profiles for a range of different AZD5213 doses. This activity was essential for suggesting what doses to use in a Phase IIa study.

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III-26 *Salim Bouchene* Whole Body Physiologically-Based Pharmacokinetic Model of Colistin and Colistimethate sodium in Critically Ill Patients

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Objectives: Colistin is used as a salvage therapy for MDR GNB infections and administered as a prodrug, colistimethate sodium (CMS). Characterizing tissue distribution of colistin is a major issue to optimize bacteria kill and avoid toxicity. Whole Body Physiologically Based Pharmacokinetic (WBPBPK) models are increasingly used to predict pharmacokinetic behavior of drugs. The aim of the study is to develop a WPBPK model to describe human PK of CMS and colistin in critically ill patients that could eventually be used to predict bacteria kill in different tissues.

Methods: Thirty-one patients [1,2] with MDR-GNB infections treated with colistin were included in the analysis (10 females; mean age, 62 years; mean creatinine CL, 80ml/min). CMS was intravenously administered at doses of 80, 160, 240 or 480mg every 8 hours through a 15-min infusion. Venous blood was collected after the first and fourth infusions. CMS is cleared renally and via hydrolysis to colistin (assumed to occur in all tissues) whereas colistin is mainly eliminated non-renally [3].

A WBPBPK was developed assuming each tissue as a single, perfusion limited and well-stirred compartment. All clearances and K_p values of CMS and colistin were estimated using the prior functionality in NONMEM 7. Prior information was collected from literature, *in-silico* prediction equations [4] and *in vitro* experiments. Predictions of concentration-time profiles of CMS and colistin in tissues were also obtained.

Results: The WBPBPK model described well both CMS and colistin plasma concentrations over time. CMS renal clearance was estimated to be 6.2 L/h whereas non-renal clearance was 1.2 L/h. Colistin total clearance was 32 L/h. Steady-state volumes of distribution of CMS and colistin were 56 L and 137 L, respectively.

Extensive distribution of colistin in tissues was predicted which could be due to pathophysiological changes of tissue composition in critically ill patients [5], non-specific binding properties of colistin as well as an intracellular distribution.

Conclusions: The WBPBPK model described both plasma concentration-time profiles of CMS and colistin. It also predicted an extensive tissue distribution of colistin which should be further explored to determine the optimized, efficient and non-toxic concentration.

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III-27 *Marion Bouillon-Pichault* Modeling of pain scores from a flexible titration study using longitudinal and ordered categorical approaches

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Objectives: In clinical pain studies, the primary endpoint is frequently reported using an 11-point Numeric Rating Scale, ranging from 0, no pain, to 10, worst pain imagined. These data are thus ordinal, categorical and bounded at both sides. Data from a double blind, placebo controlled, and flexible titration study on Drug A were modelled. To account for characteristics of the distribution of the pain scores and the design of the study two different approaches were investigated: a longitudinal and an ordered categorical approach.

Methods: In the longitudinal approach, the pain score was calculated as mean change from baseline over a week in order to be able to treat the dependent variable as normally distributed. A time dependent Emax model was fitted with the baseline as a covariate on the Emax parameter. Dose could not successfully be included in the model. This was probably due to the flexible titration design of the study leading to confounding between subject sensitivity, time and dose received. Thus, the population was divided into sub-populations according to highest received dose or to drug sensitivity level. The Emax model was separately applied to each of these sub-populations in order to estimate the maximal pain reduction per highest dose or per drug sensitivity level.

In the ordered categorical approach, the individual twice daily pain scores were fitted using a model including dose, baseline, period of the day of pain assessment (morning or evening) and time (day) as covariates. This approach allows direct modelling of the cumulative probabilities to reach a pain score.

Results: Both approaches adequately described the data. With the longitudinal approach, the maximal effects of Drug A per highest dose seemed to reach a plateau at the higher doses whereas the maximal effects of Drug A per drug sensitivity level seemed to be stable among the dose range. The ordered categorical approach showed increased cumulative probabilities of lower pain scores when the dose increases.

Conclusions: The longitudinal approach did not succeed in establishing a relationship between dose and efficacy while the ordered categorical approach succeeded in integrating both time and dose in the modelling of pain scores observed in a flexible titration design. However, this approach requires extensive computation time and is less straightforward to apply and to understand than the longitudinal approach.

III-28 *Frances Brightman* Predicting in vivo drug response and synergistic combinations from three-dimensional tumour cell cultures

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Physiomics plc

Objectives: Synergistic combinations of standard-of-care drugs or new chemical or biological entities show much promise in the treatment of cancer, and there is a great deal of interest in this strategy. However, the increasing number of possible combinations makes the task of selecting the best regimens particularly difficult. Although xenografts represent a convenient and relatively inexpensive approach to assessing the likely efficacy of proposed dosing regimens in vivo, the number of permutations that can be tested is still limited by practical considerations. We have therefore explored the use of three-dimensional tumor cell cultures (microtissues) as a more cost-effective alternative to xenografts for validating Virtual Tumor™ predictions.

Methods: We have developed a computerized PK-PD model of a growing tumor, called the Virtual Tumor™. We previously demonstrated that this platform can successfully simulate the outcome of various drug combination schedules in xenografts, as well as predict optimal drug schedules and combinations. In particular, we predicted that the efficacy of a gemcitabine-docetaxel combination could vary greatly depending on the scheduling of the drug administration, and verified these findings in vivo in the MX-1 xenograft mouse model. We have now conducted a comparable study using MX-1 microtissues, in which the cultures were treated with these same two drugs in isolation or in combination, according to various regimens.

Results: Here we show how the microtissue Virtual Tumor™ model can be employed to simulate microtissue growth and response to drug treatment, and the capability of this model to predict drug synergy.

Conclusions: We discuss the potential for microtissues to be used as a surrogate for xenografts, in conjunction with the Virtual Tumor™, for designing new drug regimens, testing possible schedules for combinations of different drugs and prioritizing the most effective drug combinations.

III-29 *Margreke Brill* Population pharmacokinetic model for cefazolin in serum and subcutaneous adipose tissue in morbidly obese and normal weight patients

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Objectives: Morbidly obese patients are prone to surgical site infections. To reduce the risk of infection a prophylactic antibiotic agent is administered before initial surgical incision to attain adequate levels of antibiotic in the bloodstream and subcutaneous tissues. For gastric surgery, cefazolin is the prophylactic antibiotic agent of choice. Currently it is unknown how morbid obesity affects cefazolin pharmacokinetics, particularly in view of tissue penetration. In this study, we aimed to investigate the pharmacokinetics of unbound serum and subcutaneous tissue cefazolin concentrations in morbidly obese patients.

Methods: Eight morbidly obese patients with a median BMI of 45.4 (41-57) kg/m2 and 6 normal weight patient with a median BMI of 28.7 (24-31) kg/m2 participated in the study. At induction of anesthesia, patients received cefazolin 2 gram i.v.. Unbound serum concentrations were measured at T=0, 5, 10, 30, 60, 120 and 240 min. Using microdialysis, samples to measure unbound cefazolin concentrations in subcutaneous adipose tissue of the abdomen were collected every 20 minutes until 240 minutes after dosing. In the analysis, unbound cefazolin serum concentration profiles of 19 morbidly obese patients were considered [1]. The influence of body weight and other covariates on cefazolin pharmacokinetics in serum and subcutaneous tissue were evaluated using population pharmacokinetic modeling with NONMEM VI.

Results: The AUCtissue/AUCserum ratio was 0.87 ± 0.4 in morbidly obese and 1.11 ± 0.3 in normal weight patients (p=0.16), however time above minimal inhibitory concentration of 90% of Staphylococcus Aureus species in Europe, 1 mg/L, was 100% until 4 hours after dose for all patients. A one compartment model for cefazolin in serum with a one compartment model of cefazolin in subcutaneous tissue best described the data. Body weight was a significant covariate for central volume of distribution (decrease in -2LL of 11 points) and for clearance (decrease in -2LL of 5 points) and was able to explain 23% and 3% of the inter individual variability, respectively. No other covariates were found.

Conclusions: We found that body weight is of strong influence on cefazolin central volume of distribution and of slight influence on clearance. This implicates lower unbound cefazolin serum and subcutaneous adipose tissue concentrations with increasing body weight.

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III-30 *Thierry Buclin* Monitoring Blood Prostate-Specific Antigen (PSA) after Radical Prostatectomy

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Objectives: PSA monitoring is used to detect cancer relapse after prostatectomy. PSA doubling time (PSADT) is a useful concept to interpret PSA results; however several modes of calculation compete. This retrospective observational study aimed to describe PSA trajectories and progression free survival after prostatectomy and to assess various PSADT calculations for their predictive performance regarding relapse.

Methods: 102 patients were drawn from a lab database over 10 years, having PSA concentration regularly monitored after prostatectomy (904 values). Their medical records were scanned for pTNM grade, Gleason score, capsular invasion, relapse-free survival, subsequent investigations and treatments. Relapse was defined by evidence of recurrence or metastases or by the initiation of secondary anticancer treatment. We modeled PSA trajectories according to Stein [1] using NONMEM 7, allowing prognostic factors to influence PSA regrowth rate. PSADT calculations used 1) the 2-point method, 2) the Log-slope method or 3) post-hoc individual predictions derived from population-based Bayesian estimates of PSA regrowth rate, from measurements limited to 1, 2, 3 and 5 years of follow up. We compared calculations including either all or only >0.1ng/mL PSA values, as sometimes recommended. The prognostic value of PSADT estimates (inversed) was assessed by survival analysis and Cox proportional hazard models.

Results: Cancer recurred in 52 patients (1-19 y follow up, median 5). Log-transformed PSA trajectories were fairly linear within patients, but markedly divergent between patients. T and N grades strongly predicted relapse (HR: 5.2 for T³3, 3.8 for N=1, $p<0.001$) and significantly influenced PSA regrowth rate (´5.14, resp. ´11.3). PSADT still improved outcome prediction, already at 1 year follow up, with Log-slope estimates predicting relapse (HR: 1.3 per y^{-1} of $PSADT^{-1}$, p=0.04) better than Bayesian post-hoc regrowth rates (HR: 1.3, p=0.16) and 2-point estimates (HR: 1.0, p=0.97). Considering all PSA values was more efficient than selecting those >0.1ng/mL.

Conclusions: Known prognostic markers mainly account for highly variable PSA trajectories after prostatectomy for cancer. Yet the regular follow-up of PSA and calculation of PSADT remains warranted for relapse prediction and detection. A sophisticated population-based Bayesian approach does not improve the performance of the simple Log-slope method for PSADT calculation, while the 2-point method is worse.

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III-31 *Núria Buil Bruna* Modeling evaluation of different in vitro experimental designs to characterise antitumor drug effect

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Objectives: Several pharmacodynamic models describing *in vivo* tumor growth have been reported in literature. However, relatively few models exist for *in vitro* cell growth [1-3]. This is partly due to current experimental protocols being generally designed for empirical analyses which offer poor prospects for *in vivo* prediction. Here we evaluate three alternative *in vitro* study designs for developing (semi)mechanistic cell growth models to predict the antitumor effect of Oxaliplatin (L-OHP).

Methods: Three different study designs were performed on SW480 cells, a human colon carcinoma cell line. The first study (S1) represented a typical *in vitro* study characterised by continuous drug exposure up to 72 hours, usually performed to obtain empirical statistics (i.e. EC_{50}). In the second (S2) and third (S3) studies cells were exposed to L-OHP for periods of time between 4 and 24 hours. After each exposure time, L-OHP was removed and cells were supplemented with drug-free growth medium. S3 also included a second exposure of L-OHP. The Alamar Blue technique used allowed for multiple measurements of cell count over a period of 168 hours. Data from the three studies were analysed independently with NONMEM VII. To assess the predictive performance of each model, an external validation simulation exercise was performed for each study using the models developed for the remaining two studies. Results were summarised based on the prediction errors computed as the mean absolute performance error (MAE).

Results: The Gompertz model was used to describe the proliferation growth of SW480 cells. The effect of L-OHP was incorporated as an activation of delayed drug induced signal, which was described using four signal transduction (transit) compartments. This process reflected the inhibition of cell proliferation followed by an apoptotic death. All models successfully described their own study data. The lowest MAE resulted when models developed for S2 and S3 were used to evaluate model predictive performance while the worst results were those found after S1 model based simulations. A model integrating data from the three studies is currently under development.

Conclusions: The models obtained with S2 and S3 showed the best predictive performance. Therefore, we recommend *in vitro* cell growth studies be performed, if possible, according to the proposed design to facilitate the estimation of predictive (semi)mechanistic tumor cell growth models.

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III-32 *Theresa Cain* A systems approach to predicting differences in pharmacological response to a CYP1A2 substrate, resulting from pharmacokinetic differences in non-smokers, passive smokers and heavy smokers

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Objectives: Induction of CYP1A2 by cigarette smoke is well established. A recent report suggests the possibility of predicting consequential pharmacokinetic (PK) differences using *in vitro-in vivo* extrapolation (IVIVE) combined with physiologically-based PK (PBPK) [1]. Although reports on PK differences between non-smokers and smokers are abundant, studies on the associated pharmacodynamic (PD) responses are infrequent. This study aimed to predict differences in pharmacological response resulting from PK differences in passive smokers and heavy smokers, using theophylline as an example of a CYP1A2 substrate, with forced expiratory volume (FEV_1) as a marker of response.

Methods: The Simcyp Simulator (V11.1) was used to simulate the PK/PD profiles of ten trials with ten subjects using the study design and PD parameters (Emax model with an effect compartment) from a PK/PD study of Caucasian non-smokers with moderate respiratory dysfunction [2]. A population of heavy smokers (> 20 cigarettes/day) was modelled with an increased CYP1A2 abundance of 94 pmol P450/mg protein (CV 43%) [1].Similarly, a population of passive smokers was modelled using data on the effects of passive smoking on theophylline clearance [3]. The PK of theophylline in heavy and passive smokers were simulated and compared with clinical data [3, 4]. Based on the PD model in non-smokers and PK differences in the three groups, PD responses in individuals exposed to cigarette smoke were simulated. Models did not consider the direct effect of cigarette smoke on FEV_1.

Results: Both the PK/PD models in non-smokers and the simulated PK profiles in heavy smokers and passive smokers predicted the clinical data adequately. Clearance in heavy smokers and passive smokers was on average 1.72 and 1.44 fold higher than in non-smokers, respectively. The area under the concentration-response curve corrected for baseline (AUCRcorr) in both heavy smokers and passive smokers was lower than in non-smokers (by on average 20% and 12%, respectively).

Conclusions: The Simcyp PBPK/PD model was able to differentiate the responses due to PK differences in smokers and non-smokers. A shortcoming of this PD model is the lack of baseline data to account for direct effects of cigarette smoke on FEV_1. However, similar models using alternate PD markers can be developed and used to predict dosage adjustments in candidate drug molecules that are metabolised predominantly by CYP1A2, with a known PD profile in non-smokers.

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III-33 *Sophie Callies* Sensitivity analysis to help the assessment of variance: application to Target Mediated Drug Disposition (TMDD) PK/PD model describing the effect of a monoclonal antibody (mAb) on a circadian biomarker.

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Objectives: To assess the variance parameters of the PKPD model using a sensitivity analysis. To describe, using the model, the change of the biomarker input rate following administration of the mAb.

Methods: Approximately 10 PK and 9 PD data per individual were available over a time frame of 2 weeks (or more). Multi-compartments PK models with non-linear TMDD clearance were fit to the mAb serum concentration versus time data (Gibiansky et al, 2008, 2009). An indirect response model, with a sigmoid Emax function describing the effect of the mAb on the input rate of the biomarker, was fit to the pharmacodynamic data. In addition, to account for the biomarker circadian rhythmic change, this model also included a cosine function to describe the input rate of the biomarker. NONMEM version VII.2 was used to model the data with the First Order Conditional Estimation with Interaction (FOCEI) method implemented. Visual predictive checks, standard error on the estimates, objective function values and diagnostic plots were used to drive the model development.

Results: A three-compartment PK model with non-linear target mediated drug disposition clearance adequately fit the mAb PK data. This model was found to be better than a two compartment model. The indirect response PKPD model, mentioned in the method section, adequately describe the mean profiles of the biomarker. All fixed effects - mean parameters (e.g clearances, volumes, EC50, Emax) were reliably estimated with standard error on the estimates (SEE) less than 25 % (except for EC50, SEE 34%). The random effects - variance parameters could only be estimated on a few of the fixed effects parameters and were less precisely estimated than the fixed effects. This issue in the estimation of variances led to inflated distributions in the visual predictive check plots. Therefore a sensitivity analysis was carried out to determine the best estimates for the random variance parameters.

Conclusions: Reliable estimation of variance parameters can be challenging when the structural model is complex (such as the model presented in this abstract with non-linear TMDD model and circadian change of the biomarker). The sensitivity analysis helps better estimate the variance parameters in order to get more reliable predictions of the variability in the biomarker response. This model will be used to help predict biomarker response through simulation and will be applied to make dosing decisions.

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III-34 *Yu-Jung Cha* Population Pharmacokinetics of Etanercept in Healthy Korean Male Volunteers

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Objectives: Etanercept is a soluble recombinant human tumor necrosis factor receptor (TNFR) fusion protein which is used for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriasis and other inflammatory diseases. A model characterizing the population pharmacokinetics (PK) of etanercept was explored. The aim of this study was to evaluate the relationships between PK parameters and explanatory covariates of etanercept in healthy Koreans.

Methods: Plasma concentration data from 35 individuals receiving single dose of etanercept (Enbrel®) 25 mg by subcutaneous injection into the abdomen were used. A total of 476 concentration data obtained before dosing and 3, 6, 12, 24, 36, 48, 60, 72, 96, 144, 216, 312 and 480 hour after drug injection. The population PK analysis was conducted using nonlinear mixed effect modeling approach NONMEM® (version 6.2) based on the plasma concentrations. The first order conditional estimation (FOCE) with interaction method was employed to fit the model run. The demographic characteristics including age, weight, and height were examined as covariates.

Results: A two compartment disposition model with first-order absorption and elimination was best characterized the PKs of etanercept. The parameter estimates of central volume of distribution (V/F), oral clearance (CL/F), inter-compartment clearance (Q), and peripheral volume of distribution (V2) were, 8.65 L, 0.0837 L/h, 0.431 L/h, and 3.34 L, respectively. The influence of covariates on PK parameters was insignificant.

Conclusions: PK model for etanercept was developed in healthy Korean population. The PKs of etanercept was adequately fitted by a two-compartment model with first-order absorption and elimination. This PK model can be used for PK-PD modeling studies to predict etanercept exposure and time course of clinical improvement in Korean patients.

III-35 *Quentin Chalret du Rieu* Semi-mechanistic thrombocytopenia model of a new histone deacetylase inhibitor (HDACi) in development, with a drug-induced apoptosis of megakaryocytes.

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Objectives: To develop a semi mechanistic thrombocytopenia model of a new HDAC inhibitor in development, taking into account the pharmacological knowledge of the molecule. Therefore, the aim is to assess by modelling and simulation the compound effect on both progenitor cells and megakaryocytes. A second objective is the evaluation of structural and experimental identifiability of the final enriched model.

Methods: The study included 35 patients suffering from solid tumors who received drug S over 4-week cycles. Three dosing regimens were tested. Overall 181 platelet samples from the first treatment cycle were analyzed simultaneously with NONMEM 7.2, FOCE-I. Sequential Pharmacokinetic/Pharmacodynamic (PK/PD) modelling was performed, where individual Bayesian estimates of PK parameters were fixed from a prior PK analysis for subsequent PD modelling. Identifiability of the model was analyzed using PFIM 3.2.2 software by computing expected parameter precision of estimation using mathematical derivation of the Fisher Information Matrix, for different sampling designs [1]. The structural and experimental identifiabilities of the model were evaluated by estimating each parameter's standard errors with respectively a rich design (14 platelets samples) and the sampling design used in a clinical protocol (4 platelet samples).

Results: A *basic* model incorporating a stem cell proliferation inhibition drug effect was developed with the same structure as Friberg *et al*'s semi-mechanistic myelosuppression model [2-3]. *Extended* models were developed with an additional drug-induced megakaryocyte apoptosis. Models evaluation by individual fits analysis, goodness of fit plots and Normalized Prediction Distribution Error (NPDE) graphs, showed that both *basic* and *extended* models are able to adequately describe and predict available data [4]. All these models were shown structurally and experimentally identifiable, allowing the expectation of a good precision of estimation of model parameters for both an experimental and a richer sampling design.

Conclusions: A semi-mechanistic thrombocytopenia model, which increased pharmacological description of drug effect by mimicking the thrombocytopenic mechanism of drug S was developed. Clinical data supported a refined model, which was able to adequately describe and predict the time-course of platelets following administration of drug S.

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III-36 *Pascal Chanu* On the use of hemodynamics biomarkers to assess the benefit of high doses of sildenafil in some patients with pulmonary arterial hypertension (PAH)

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Objectives: The assessment of efficacy of pulmonary arterial hypertension treatments is mainly based on improvements in exercise capacity: six-minute walk distance (6MWD). Sildenafil (REVATIO®), 20 mg TID, received approval for the treatment of adult PAH in the US based on 6MWD data. A recent FDA analysis [1] showed a relationship between changes from baseline in 6MWD and pulmonary vascular resistance index (PVRI), an hemodynamic (HD) endpoint in the adult PAH population. The objective of this analysis was to assess whether some patients could have reached their PVRI reduction target from a higher sildenafil dose than the one currently registered according to their baseline and patho-physiological characteristics.

Methods: A previous population PK/PD analysis of PVR data from two pivotal sildenafil trials in adult [2] (n=218) and pediatric patients (n=219, 1-17 y) was performed in NONMEM 7 to characterize the relationships between PVR (=PVRI/BSA), baseline patho-physiological covariates and sildenafil exposure [3]. Simulations, based on pre-defined success criteria to achieve expected HD responses as a function of age, functional class and baseline PVR were conducted to assess the potential PVRI reduction associated with higher doses (40 and 80 mg TID) of sildenafil in some PAH patients compared to the labeled dose.

Results: The model based simulations of HD outcomes showed that while 20 mg TID provides a clear improvement over placebo, the 80 mg TID regimen provides a substantial additional improvement over the labeled dose, whereas a 40 mg TID regimen provides only a marginal additional improvement. Simulations focusing on a target PVR improvement from baseline (200 dyne.s.cm^{-5} reduction) showed that elderly patients (60 to 80 y) may expect a lower response rate with the labeled dose but a similar response rate with 80 mg TID compared to that obtained in younger patients at the labeled dose. Simulations focusing on the achievement of a target PVR value of less than 350 dyne.s.cm^{-5} showed that more severe patients at functional class 3 or 4 and/or high baseline PVR may also reach the PVR target with a 80 mg TID regimen.

Conclusions: Model based simulations of PVR outcome showed that a dose of 80 mg TID might provide additional PVR improvement in specific PAH populations (elderly, severe patients). The implication of these simulation results into 6MWD improvement remains to be further investigated.

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III-37 *Ayyappa Chaturvedula* Development of population pharmacokinetic model for Tenofovir using sparsely sampled subject data

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Objectives: The study was performed to investigate gender differences in the pharmacokinetics of Tenofovir from the Partners pre-exposure prophylaxis (PrEP) study, a double-blind, placebo-controlled, randomized trial of tenofovir disoproxil fumarate (TDF) and emitricitabine (FTC)/TDF PrEP among 4747 HIV uninfected members of heterosexual HIV serodiscordant couples from Kenya and Uganda.

Methods: A population pharmacokinetic model for Tenofovir was developed from sparse samples (1 sample per occasion, multiple occasions) collected from 1154 observation records from 268 individuals sampled at random from the active drug arms of the study using a non-linear mixed effects model. The data was supplemented with another study MTN-001 where 6 samples were collected after oral administration. Measures below the limit of detection (BQL) were included in the modeling and M3 method was used for handling BQL.

Results: Tenofovir pharmacokinetics was well described by a two compartment open model. Typical population estimates of first order absorption rate constant (Ka), apparent central distribution volume (Vc/F), peripheral distribution volume (Vp/F), intercompartmental clearance (Q/F) and plasma clearance (CL/F) were 0.493/h, 81.7 L, 3790 L, 143 L/h and 50.5 L/h respectively. Between-subject-variability (CV) on Ka, Vc/F,Vp/F , Q/F and CL/F was estimated as 26%,74%,115%,38% and 32% , respectively. We estimated Ka as a separate parameter opposed to the previous attempts that assumed Ka equals the distribution constant. It could be driven by the availability of blood samples in the absorption phase from the MTN-001 study.

Conclusions: We utilized the non-linear mixed effect model to estimate the individual pharmacokinetic parameters from sparsely sampled population. Data pooling approach helped us to estimate fixed and random effect parameters for the population. No major differences were observed in the pharmacokinetic parameters between male and female.

III-38 *Chao Chen* Quantifying the Effectiveness of Dose Personalisation by Simulation for a Drug with Moderate Pharmacokinetic Variability

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Objectives: The objective of the work described here was to quantify the potential for reducing the variability in exposure by personalising dose for a drug with moderate pharmacokinetic (PK) variability and narrow therapeutic window. Exposure (AUC) of the drug increases greater than proportionally to dose. At the same dose, the AUC is higher in women than in men.

Methods: A population PK model, including both between-subject and within-subject between-occasion variability, was developed using phase I data. Individual AUC in a large trial with a target AUC were then simulated. In the simulated trial, each subject received a test dose which was chosen to generate the target AUC for a typical person. A PK profile following this dose was obtained. Using this PK profile and the model, a personalised dose for the target AUC was derived with a pre-defined set of formulation strengths. A therapeutic AUC range was defined as +/- 20% of the target. The proportion of the people whose mean AUC was within this range was calculated for the test dose and for the personalised dose. Dose personalisation would be declared effective if the mean AUC of at least 30% more people were within this range.

Results: The model adequately described both the sex effect and the non-linear dose effect on exposure. The variability for apparent clearance was 23.8% between subjects or 14.4% between occasions. Because the AUC following the test dose was subject to between-occasion variability, this AUC could mis-inform the dose change. The simulations showed that the dose change brought the AUC, from outside the therapeutic range after the test dose, into the range for 82% of people. However, it also brought the AUC outside of this range for 20% of the people whose AUC after the test dose was already in the range. The proportion of people whose AUC was within the range increased from 62.3% with the test dose to 80.7% with personalised dose, representing a 18.4% gain by dose personalisation which was below the pre-defined success criteria of 30%.

Conclusions: Findings from this exercise provided the basis for ruling out single-profile based dose personalisation for this drug. The same simulation frame work can be applied to other situations with a defined set of conditions, such as the therapeutic exposure range, dose adjustment increments, number of profiles to inform dose change, and the success criteria.

III-39 *Marylore Chenel* In vitro – in vivo correlation by population approach applied to modified-release forms with double-peak absorption

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Introduction: According to *in vitro* - *in vivo* correlation (IVIVC) guideline [1], *in vitro* dissolution data can be used early in drug development process to help designing/refining formulations, or at later stages, as a surrogate for bioequivalence studies for qualifying formulation scale-up or post-approval changes.

Objectives: An IVIVC model, based on a population compartmental approach, was implemented to predict the *in vivo* drug concentration-time profiles (CTP) with double-peak absorption of 3 different modified release (MR) formulations from their respective *in vitro* dissolution fraction-time profiles (DFTP).

Methods: *In vivo* CTP were obtained after oral administration of one immediate release (IR) and 3 MR formulations of molecule S (with 3 different release rates: fast, intermediate, and slow, showing double-peak absorption), in a single cross-over trial, performed in 13 healthy volunteers. The IR CTP were fitted with a population PK model. Then, 6 *in vitro* DFTP of each of the 3 MR formulations were fitted with a non-linear mixed-effect model. At last, IVIVC model consisted in a unique relationship for all MR formulations between *in vitro* DFTP and *in vivo* DFTP in which individual IR PK model were plugged. Internal validation (model built with 3 formulations) and external validation (model built using slow and fast formulations only, then used to predict intermediate form) were performed by computing the percentage prediction errors (%PE) on C_{max} and AUC.

Results: IR CTP were fitted using a 2-compartment model with a first order absorption rate and a lag-time; inter-individual variability was estimated on clearance and central volume. For each MR formulation, *in vitro* DFTP were fitted with a Gompertz function, and inter-tablet dissolution variability was estimated. IVIVC model involved a 3-phase non-linear time scaling (no change in first phase, second phase with a stopped dissolution, and third phase with a delayed dissolution) and inter-individual variability on tablet dissolution and relative bioavailability terms. Internal and external validations showed good prediction abilities of the model. The non-linear scaling allowed the description of double-peak absorption.

Conclusions: This work illustrates another application of a population PK approach [2] to IVIVC model building, adding an accurate individual description of complex absorption CTP, which is valuable for evaluation of further formulation in development.

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III-40 *S. Y. Amy Cheung* An update on structural identifiability of parallel pharmacokinetic experiments viewed as constrained systems

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Background and Objectives: Structural identifiability is the property of whether an experiment can uniquely identify the unknown model parameters. The usefulness of incorporation of parallel pharmacokinetics experiments as a formal model structure for validation using structural identifiability has previously been discussed [1-3]. Also, the parallel methodology and the implication to the structural identifiability have been illustrated through a number of examples ranging from a basic one compartmental model to a mechanistic parent-metabolite model [4]. The previous focus of the development of the parallel methodology was to understand the impact and relationship of the perturbation of individual unknown parameters, due to changes in experimental conditions and the preservation of mutual parameters in between experiments to the identifiability status of the model. The objective of the present work was to develop new strategies whereby models are rendered globally identifiable by considering other types of perturbation to the model parameters via the parallel experiments.

Methods: The ‘same' experiment may sometimes be carried out several times on a system, in which it can be assumed *a priori* that some, but not all, of its rate constants change between experiments. Such a situation might arise in population PK experiments where there are covariate effects. The models representing each experimental observation thus share some common rate constant values depending on the dosing method and physiological nature of the model. This forms a much more constrained structure, encapsulates more information of the system and still can be readily analysed. The extended methodology is applied to a number of examples, including classic compartmental models and a series of mechanistic compartmental models to understand the impact of on identifiability status

Results: It is shown that by considering parallel experimental strategies, including the covariates effect perturbation, individually unidentifiable or locally identifiable models, in many cases are rendered uniquely identifiable.

Conclusions: A formulation has been presented that places the concept of parallel experiment in the context of a single constrained model structure. Incorporation of prior knowledge into parallel experiment model structures with constrained parameterization allows sufficient information to be present in the input-output behaviour to give unique parameter estimates. The results show that the parallel experiment strategy can be very powerful in providing globally uniquely identifiable models.

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III-42 *Karina Claaßen* Development and evaluation of dynamical whole body Physiologically-based Models of the Circulation and the Renin-Angiotensin-Aldosterone system

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Objectives: This work is aimed to develop a whole body physiologically based pharmacokinetic (wb PBPK) model including a dynamic circulation model and the renin-angiotensin-aldosterone system (RAAS). Furthermore a model for detailed representation of the arterial blood pressure (BP) is developed.

Methods: The PBPK model was established by usage of PK-Sim® and MoBi® based on data for physiological factors determining the RAAS and the circulation. In a first step a PBPK model was developed and physiological data of the RAAS [1-4] have been included. This results in a coupled wb PBPK model containing the temporal evolution for the main RAAS actors angiotensinogen, angiotensin 1 and 2, angiotensin 2 receptor type 1, aldosterone, renin and angiotensin converting enzyme. The influence of xenobiotics on this hormone system involved in the regulation of BP is discussed in detail. In a second step a mechanistic representation of the mean arterial blood pressure (MAP) was build based on available data [5-7] and then integrated into a wb PBPK model. Different pathological states leading to hypertension or hypotension were investigated by this pharmacodynamic (PD) model and compared to observed behavior. The impact of different physiological conditions on the MAP will be shown exemplarily.

Results: The results show in detail that the RAAS model is able to describe the circulating plasma hormone levels with sufficient agreement to experimental data. Further development of the blood pressure regulation model led to a very accurate representation of the typical behavior of the circulation and the changes in case of pathological conditions. Different realistic BP scenarios like hypertension or hypotension could be described by this approach and the modeled effects of the main physiological factors influencing the MAP are in very good agreement with knowledge gained from literature.

Conclusions: The wb PBPK model of the RAAS is able to represent the pharmacokinetics of drugs interacting with RAAS and the hormone system sufficiently well, indicating a reasonable description of the underlying physiological processes. Furthermore, the accurate prediction of the BP changes by the PD model under different healthy and pathological conditions indicates a good representation of the BP regulation. Next steps will be the coupling of both models, which could lead to a mechanistic representation of the PBPK-PD relationship in cardiovascular diseases and thus help to facilitate dose and dosing regimen decisions in the area of cardiovascular diseases.

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III-43 *Laurent Claret* Evaluation of Tumor-Size Response Metrics to Predict Survival and Progression Free Survival in First-Line Metastatic Colorectal Cancer

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Objectives: Change in tumor size from baseline at the end-of-cycle 2 has been proposed as a predictor of overall survival (OS) in metastatic colorectal cancer (CRC) (1, 2) and other tumor types (1, 3, 4). The goal of this project was to assess new metrics of tumor size response to predict clinical endpoints, i.e. OS and progression free survival (PFS), and to test for any ethnic differences in the link between tumor size response and clinical endpoints in CRC.

Methods: Various metrics of tumor size response were estimated using longitudinal tumor size models developed from two Phase III studies comparing bevacizumab plus chemotherapy vs. chemotherapy in Western (923 patients) (5) and Chinese patients (203) (6) as first-line therapy in patients with CRC. Effect of baseline prognostic factors and estimates of tumor size metrics were assessed in multivariate models to predict OS and PFS. Predictive performance of the models were assessed by simulating OS, PFS and hazard ratios (HR) of bevacizumab vs. chemotherapy in multiple replicates (n=1000) of the two Phase III studies.

Results: Time to tumor growth (TTG) was the best metric to predict OS and PFS in 991 evaluable patients. In the OS model, TTG fully captured bevacizumab effect, ECOG performance status (PS) and the number of metastatic sites were significant baseline prognostic factors. In the PFS model, TTG did not fully capture bevacizumab treatment effect and ECOG PS was a significant baseline prognostic factor. In both models, when other covariates like ECOG PS and TTG were accounted for, there was no impact of Chinese ethnicity on any of the endpoints, or on the TTG-OS or PFS relationships (no interactions). The models correctly predicted OS and PFS distributions in each study arm and each patient population as well as bevacizumab HRs (e.g. model prediction [95% prediction interval]: 0.78 [0.52 - 1.13] vs. 0.63 observed for OS in Chinese patients and 0.56 [0.39 - 0.76] vs. 0.43 observed for PFS in Chinese patients).

Conclusions: TTG is a better tumor size metric to capture drug effect and predict OS and PFS in first-line CRC patients than previously proposed ones. There is no impact of Chinese ethnicity on TTG survival or PFS relationships. Longitudinal tumor size data coupled with model-based approaches may offer a powerful alternative in the design and analysis of early clinical studies in both Western and Chinese patients (7).

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III-44 *Francois Combes* Prediction of precision of individual parameter estimates and of shrinkage via the Bayesian Fisher information matrix in non-linear mixed-effects models with application in pharmacokinetics

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Objectives: In population pharmacokinetics (PK), precision of population parameter estimates depends on design and are evaluated using Fisher information matrix [1]. Individual parameters are usually estimated by the Maximum A Posteriori (MAP) and precision of individual estimates can be evaluated using the Bayesian Fisher information Matrix (BMF) [2]. Shrinkage of individual parameters towards the mean occurs when information is sparse and can be quantified as a reduction of variance of the estimated Random Effects (RE) [3]. This study aims at 1) exploring the relationship between BMF and shrinkage in order to propose a prediction of shrinkage and 2) evaluating by simulation the prediction of individual parameter precision and shrinkage.

Methods: We first derived the BMF for additive RE and constant residual error and then extended it for exponential RE and/or combined residual error. From the formula of shrinkage in linear mixed effects models, we derived the normalized Estimation Variance (nVE) from the expected BMF as a prediction of shrinkage. Regarding the evaluation by simulation, we simulated data from sparse and rich design for two PK examples: a simple one (one compartment) with six different scenarios (additive or exponential RE, with low and high variabilities, additive or combined residual error); a more complex example derived from a real case study [4] (two compartment, dual linear and non-linear elimination). We used NONMEM 7.2 and MONOLIX 4.0 to perform individual estimation via MAP assuming known population parameters and fixed to their exact value. We also recorded individual standard errors (SE). We then compared predicted and estimated SE for each scenario and example as well as the predicted and estimated shrinkage, evaluated using the formula with ratio of variances.

Results: For the simple example, considering all scenarios and designs, predicted SE of the two parameters using BMF were close to the estimated SE with both software and varied as expected with the richness of the design and the variabilities. There were also a very good agreement (almost identity line) between estimated shrinkage (which varies from 0 to 70%) and predicted shrinkage. Similar results were observed for all the parameters of the real example.

Conclusion: The Bayesian Information Matrix allows to evaluate impact of design on precision of individual parameters and to predict shrinkage. This can be used for design optimization and will be implemented in PFIM.

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III-45 *Emmanuelle Comets* Dealing with BQL data in normalised prediction distribution errors: a new version of the npde library for R

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Objectives: Over the last few years, several new approaches including VPC (Visual Predictive Check) [1], prediction discrepancies (pd) [2] and normalised prediction distribution errors (npde) [3] have been proposed to evaluate nonlinear mixed effect models. npde are now included in the output of NONMEM and Monolix, and we created a R library to facilitate the computation of pd and npde using simulations under the model [4]. We propose a new version of this library with methods to handle data below the limit of quantification (BQL) [5] and new diagnostic graphs [6] .

Methods: BQL data occurr in many PK/PD applications, particularly in HIV/HCV trials where multi-therapies are now so efficient that viral loads become undetectable after a short treatment period. These data are generally omitted from diagnostic graphs, introducing biases. Here, we propose to impute the pd for a BQL observation by sampling in U(0,pLOQ) where pLOQ is the model-predicted probability of being BQL. To compute the npde, censored observations are first imputed from the imputed pd, using the predictive distribution function obtained by simulations, then npde are computed for the completed dataset [3].
New graphical diagnostics include a graph of the empirical cumulative distribution function of pd and npde, and prediction intervals can be added to each graph. Tests can be performed to compare the distribution of the npde relative to the expected standard normal distribution. In addition, graphs and tests to help selecting covariate models have been added [7].
These extensions were implemented in a new version of the npde library,which implements S4 classes from R to provide an easier user-interface to the many new graphs, while remaining mostly compatible with the previous version. Exceptions are that computing the pd in addition to the npde is now a default option.

Results: We illustrate the new library on data simulated using the design of the COPHAR3-ANRS 134 trial. In the trial, viral loads were measured for 6 months in 34 naïve HIV-infected patients after initiation of a tri-therapy, and up to 50% of data were BQL. Ignoring BQL data results in biased and uninformative diagnostic plots, which are much improved when pd are imputed. Adding prediction intervals is very useful to highlight departures from the model.

Conclusions: Version 2 of the npde library implements a new method to handle BQL data, as well as new graphs, including prediction intervals for distributions.

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III-46 *Damien Cronier* Population Pharmacokinetic Study of a New Humanized Anti-CD20 Monoclonal Antibody AME-133v (LY2469298) in Patients with Previously Treated Folicular Lymphoma.

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Objectives: AME-133v is a humanized monoclonal antibody that was engineered ti have increased affinity to CD20 and mediate antibody-dependent cell-mediated cytotoxicity (ADCC) better than rituximab in vitro. The safety, pharmacokinetics (PK) and preliminary efficacy of AME-133v were assessed in a phase 1/2 clinical trial in patients with previously treated follicular lymphoma (FL). The objective of this study is to characterize the PK of AME-133v in the target patient population.

Methods: 5 dose levels of AME-133v (2, 7.5, 30, 100 and 375 mg/m2) were tested in a total of 67 patients with previously treated CD20+ FL. AME-133v was administered intravenously in 4 weekly infusions. Blood samples were obtained pre-dose and 1, 3-5 days after infusion 1, pre-dose and post-dose during infusions 2, 3 and 4, and 1, 5, and 9 weeks after infusion 4. The PK database (399 data points) was analyzed by nonlinear mixed-effect modeling (NONMEM). Covariates including demographic characteristics and the FCyRIIa receptor genotype were evaluated fir their influence on the population PK parmaters of AME-133v.

Results: Owing to serum concentrations falling below the limit of detection, the 2 mg/m2 dose group was not included in the analysis. The basic model selected was a 2-compartment pharmacokinetic model with first-order elimination. However, a different typical CL value had to be estimated for each dose group. The typical values for V1, Q and V2 were 2.99 L, 0.94 L/day and 3.31 L, respectively. the typical CL value was 0.70, 0.53, 0.26 and 0.27 L/day for 7.5, 30, 100 and 375 mg/m2, respectively, which indicates a linearization of the elimination rate of AME-133v at doses of 100 mg/m2 and above. Inter-individual variability was moderate to high with CVs of 45.9, 34.1 and 50.0% for CL, V1 and V2, respectively. The only covariate found to influence the PK of AME-133v was BSA which explained 9.6% of the variability on V1. The form of the FcyRIIIa receptor did was not found to have a significant effect on the PK of AME-133v/

Conclusions: The PK of AME-133v were best described by a 2-compartment model. Clearance was found to be dose-dependent with a linearization of the elimination rate at doses of 100 mg/m2 and above. BSA has a statistically significant influence on V1 whereas the FcyRIIIa genotype does not seem to influence the disposition of AME-133v.

III-47 *Zeinab Daher Abdi* Joint model for longitudinal exposure to mycophenolic acid and rejection survival data in the first year after renal transplantation

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Objectives: Previous studies have reported conflicted results concerning the relationships between mycophenolic acid (MPA) exposure and the risk of acute rejection in the first year post-transplantation[1]. A recent randomized clinical trial[2] concluded to a significant association between very early (i.e on day 3) MPA inter-dose area under the plasma concentration *vs* time curve (AUC) and acute rejection. The present study aimed at modelling the effect of MPA exposure on rejection free survival by comparing two approaches: i) a survival model with independent-time covariate(s) and ii) a joint model for longitudinal and survival data so as to take into account the time-course of MPA exposure.

Methods: We analyzed data from adult kidney transplant recipients enrolled in the randomized clinical trial APOMYGRE[3]. All patients received mycophenolate mofetil associated with cyclosporine. MPA $AUC_{0\text{-}12h}$ were previously estimated using Bayesian methods[4]; 126 patients provided between 2 and 6 AUC values estimated at different postgrafting periods. 22 patients experienced acute rejection(s). An exponential baseline hazard model implemented in NONMEM VII was used to predict the risk of rejection with an interval censored approach. MPA exposure was incorporated in the survival model using either i) a single MPA AUC value estimated within the first week (i.e. AUC_{w1}) or ii) the longitudinal MPA exposure modelled by a non-linear mixed effect model (then the joint likelihood was maximized using the laplacian approximation). Visual predictive checks (VPC) based on simulated *vs* non-parametric estimates of survival (Kaplan-Meier plots) were used for model evaluation.

Results: The predicted time course of MPA AUC described rejection free survival better than $AUC_{w1.}$ In this joint model, the time-course of MPA AUCs over the first year post-transplantation was fitted using an exponential model with intercept. The number of HLA mismatches was the only significant independent-time covariate. The VPC based on the final joint model showed that the simulated survival curves matched the Kaplan-Meier survival estimates.

Conclusions: The developed joint model suggested that optimum MPA exposure is critical over the first year and not only in the very early post-transplantation period, highlighting the utility of monitoring MPA levels throughout the first year post-transplantation. Using this joint model, simulations can be performed leading to MPA target levels minimizing the risk of rejection.

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III-48 *Elyes Dahmane* The influence of CYP2D6 genetic polymorphism on tamoxifen and its active metabolite exposure in breast cancer patients: preliminary results from a prospective, open-label trial.

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Objectives: Tamoxifen (Tam) treated patients with null or reduced CYP2D6 activity display low endoxifen exposure and thus might experience lower benefit from their treatment [1]. The objectives of the trial are to study Tam and its major metabolites concentrations and to evaluate the influence of doubling tamoxifen dose on endoxifen levels in the different CYP2D6 genotype groups. Correlations between endoxifen concentrations and both CYP2D6 genotype and phenotype were also explored.

Methods: Patients under tamoxifen 20mg once daily (QD) were prospectively genotyped and phenotyped (dextromethorphan/dextrorphan ratio test) for CYP2D6. Patients were categorized into 4 genotype groups: poor, intermediate and extensive metabolizers (PM/IM/EM) according to their CYP26 genotype. Plasma levels of Tam, N-desmethyltamoxifen (NDTam), 4-hydroxytamoxifen (4OHTam) and endoxifen were measured [2] at baseline (20mg QD), then at 30, 90 and 120 days after dose escalation to 20 mg twice daily. Plasma levels increase and between-group differences in endoxifen levels were tested using ANOVA. Correlations between CYP2D6 genotype/phenotype and endoxifen or endoxifen/NDTam levels ratio were performed using linear regression models.

Results: 63 patients were available for this analysis. At baseline, endoxifen levels (CV %) were lower in PMs: 7 ng/mL (36%) than in EMs: 24 ng/mL (71%) ($P = 0.001$), but not statistically different from the IMs: 16 ng/mL (70%) ($P = 0.08$). After doubling tamoxifen dose, endoxifen concentration increased less than 2 fold ($P<0.0001$) and to a similar extent in PMs, IMs and EMs with respectively, 1.5 (18%), 1.5 (28%) and 1.7 (30%) fold increase from baseline ($P = 0.18$). A modest correlation between CYP2D6 genotype groups and endoxifen levels (R-squared = 28%, $P = 0.002$) and endoxifen/NDTam levels ratio (43%, $P < 0.0001$) was observed. CYP2D6 phenotype explained 31% ($P < 0.0001$) of endoxifen levels variability and 60% ($P < 0.0001$) of endoxifen/NDTam levels ratio.

Conclusions: An important interindividual and intergroup variability in endoxifen levels was observed, which was best correlated to CYP2D6 phenotype. Endoxifen concentration monitoring would thus be beneficial for individualizing tamoxifen dose. In that purpose, a population

pharmacokinetic modeling will be performed that will bring a better understanding of Tam and its metabolites disposition and variability, which would be useful for Tam dose optimization strategies.

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III-49 *Adam Darwich* Development and application of a mechanistic physiologically based pharmacokinetic model to assess oral drug bioavailability post bariatric surgery in morbidly obese patients

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Objectives: The invasive nature of bariatric surgery, partially restricting the gastrointestinal (GI) tract, has led to observed changes in oral drug bioavailability (Foral) [1]. This study aimed to develop a mechanistic pharmacokinetic in silico model based on known physiological alterations, applying it to clinically relevant drugs.

Methods: A set of GI and 'whole body' physiological parameters were identified based on factors influencing Foral post bariatric surgery, including: GI dimensions, pH, GI drug metabolising enzyme abundances, gastric emptying, small intestinal transit (SIT) and bile delay. Using the Advanced Dissolution, Absorption, Metabolism (ADAM) model in Simcyp® Simulator, the morbidly obese population template [2, 3] was altered to mimic the characteristics of Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) and biliopancreatic diversion with duodenal switch (BPD-DS) and jejunoileal bypass (JIB). A set of drugs (e.g. simvastatin, atorvastatin, omeprazole, diclofenac, cyclosporine, fluconazole and ciprofloxacin) were simulated over therapeutic dose ranges and varying SIT, comparing pre to post surgery AUC, plasma concentration-time profiles, fa (fraction absorbed in the gut wall) and FG (fraction escaping gut wall metabolism).

Results: Different drugs showed variation in sensitivity to surgery. Simvastatin immediate release (IR) displayed a post/pre surgery AUC ratio of 1.14 (±0.18) following RYGB (SIT=3.0h) at a low therapeutic dose, becoming less apparent at a higher dose, due to an increase in FG counteracted by a reduction in fa. Diclofenac enteric-coated (EC) post/pre surgery AUC ratio displayed a minor reduction following RYGB (SIT=3.0h). Following BPD-DS a more extensive reduction in fa resulted in a lower AUC ratio as compared to RYGB. Post JIB, drugs displayed an extensive reduction in AUC due to a more apparent reduction in fa. Simulated cyclosporine displayed a dose dependent reduction in plasma concentration post JIB (SIT=0.7h) in magnitude of observed data [4]. Simulations post SG did not significantly alter the drug exposure.

Conclusions: Trends in Foral pre to post bariatric surgery seem to be highly dependent on drug specific parameters such as affinity to CYP3A4, solubility and permeability issues, where the extent of these effects will be dependent on the surgery in question. Current limitations in simulating the impact on Foral following bariatric surgery include the lack of clinical and physiological data.

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III-50 *Ruben de Kanter* The impact of using the well-stirred liver model in PBPK modelling for high-clearance compounds

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Objectives: The well-stirred liver model is a widely used standard in Physiologically-based pharmacokinetic (PBPK) modelling. This analysis aimed at assessing the food effect observed for a high-clearance oral drug, assumed to be caused by a change in hepatic blood flow due to the presence of food.

Methods: PBPK modelling was performed using GastroPlus v.7 (Simulations Plus Inc.). Healthy human physiology was applied for all variables, including blood volume and flow values. In fed state (GastroPlus allows entering fed or fasted but no gradual switch between states), the liver blood flow was increased by 25%. Volume of distribution and tissue-to-blood partitioning were predicted. The clearance was fitted to the observed human plasma concentration-time profile after a single dose in either fasted or fed subjects.

Results: Clearance was estimated as 12.5 mL/min/kg (fasted) and 15.6 mL/min/kg (fed), volume of distribution was predicted to be 283 L. The observed food effect was a 15-fold increase in both C_{max} and AUC. The observed concentration-time profile could not be described by the PBPK model for both fed and fasted state while keeping the intrinsic clearance (CL_{int}) constant (which is assumed to be the case). Additional analyses using either the well-stirred and parallel tube liver models were performed to find a constant value for CL_{int} in fasted and fed state that better described the observations. The parallel tube liver model, but not the well stirred model, was able to characterise the observed data substantially better, assuming the food effect is caused by a change in liver blood flow.

Conclusion: A limitation of the well-stirred liver model is that, for high-clearance compounds, the effect of a changed blood flow due to food is not correctly translated into a change in extraction ratio. This artefact, caused by an inappropriate model assumption, should be kept in mind when using commercial PBPK software packages that have the well-stirred model implemented as the only option.

III-51 *Giuseppe De Nicolao* PCA-based modelling in antidepressant trials: a pre-mechanistic approach

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Objectives: For many diseases, such as psychiatric ones, mechanistic knowledge of the progression of the disease and the interaction between disease and drug action is often very limited or absent. The empirical models, adopted to describe the evolution of clinical endpoints [1], are characterized by arbitrarily chosen basis functions and are usually dataset-specific. This motivates the development of a flexible and general-purpose "pre-mechanistic" technique to be used for exploratory analysis and as a touchstone for subsequent mechanistic model building. Along this direction, the aim of this work is to introduce a method, based on Principal Component Analysis (PCA), that automatically provides regression functions reflecting the informative content of the data: the PCA-based approach [2].

Methods: Population analyses of simulated and experimental datasets were performed. Three parametric models were used to simulate 50 datasets (100 subjects per dataset): Weibull, Inverse Bateman and Weibull + linear models. The experimental dataset was obtained from a Phase II depression trial. The proposed approach provides the principal functions of the unobservable true signal through the singular value decomposition of the covariance matrix of data. The number of components was selected through either Mallows' Cp criterion [3] or random crossvalidation. The new PCA-based approach and the three parametric models were compared in simulation in terms of "denoising", i.e. the ability to reconstruct the true individual profiles. Moreover, we evaluated the crossvalidatory RMSE on both simulated and experimental data. Parameter estimation was carried out with R 2.13.1 [4], according to the empirical Bayes paradigm.

Results: The PCA-based approach provided satisfactory denoising perfomances and good predictive ones, in all the 150 simulated datasets. In the experimental scenario, the PCA-based model with 3 principal functions was chosen according to the order selection procedure. The proposed approach achieved very satisfactory individual fittings and crossvalidatory performances.

Conclusions: The proposed PCA-based approach can be valuable when the mechanistic knowledge of the disease is limited or absent. It automatically provides basis functions suitable to develop parsimonious population models and yields reliable reconstructions of individual profiles. This approach is useful for exploratory analysis and as a touchstone in order to benchmark the performances of mechanistic models.

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III-52 *Ivan Demin* Posterior predictive check to assess similarity of systemic exposure profiles of an inhaled drug product pre- and post- manufacturing modification.

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Objectives: To assess similarity of tobramycin concentration-time profiles in serum of Phase III product (TIP-PhIII) and the marketed product (TIP-Mkt).

Methods: The population PK analysis was based on a two-compartment model with first-order absorption and first-order elimination and was implemented in NONMEM VI. Predictive simulations of the model were performed in R 2.10.1 software. Visual predictive check (VPC) plots were constructed to assess the overall agreement between simulated and observed concentration data. The NPDE tests were performed with R package npde version 1.2.1. All tests were performed at the pre-specified significance level of 0.05.

Results: Predictive simulations of serum concentration profiles using the population PK model for TIP-PhIII showed that the majority of observed concentrations for TIP-Mkt fall within the 90% predictive interval; proportion of data points outside the interval (13%) is close to expected 10% if the procedure was repeated on independent realizations of PK data with identical study design. Model adequately described the central tendency and variability of observed concentrations of the modified product. Diagnostic plots and results of tests for normality of the NPDE distribution showed that null hypothesis that the distribution is normal is not rejected at pre-specified level of 0.05.

Conclusions: Serum exposure profiles of tobramycin after inhalation of TIP-Mkt are not statistically significantly different from exposure after inhalation of TIP-PhIII expected based on the population PK model of TIP-PhIII. Statistical equivalence of exposures implies that estimates of PK model parameters and effect of covariates reported in the existing population PK model apply to TIP-Mkt as well.

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III-53 *Paolo Denti* Population pharmacokinetics of ritonavir-boosted darunavir together with efavirenz in healthy volunteers

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Objectives: Ritonavir-boosted darunavir (DRV/r) with efavirenz (EFV) is an alternative nucleoside-sparing regimen for HIV treatment. The metabolic pathways involved in the pharmacokinetics of these drugs are intertwined and complex drug-drug interactions are expected. We have previously shown that efavirenz induces the metabolism of darunavir but the inhibitory effects of ritonavir ensure that the drug concentrations are still adequate to treat patients without darunavir drug resistance mutations, at a once daily dose [1]. We aim to develop a population model to characterize these interactions and help make predictions about possible dosing regimens.

Methods: Twelve healthy volunteers were included in the study and blood samples were collected across 38 days. DRV/r (900/100 mg once daily) was administered alone for 10 days, on day 11 EFV (600 mg once daily) was started, and on day 24 DRV/r was stopped and EFV continued for another 14 days. Intensive blood sampling was performed on day 10, 11, 24, and 38, and additional trough samples were collected every 4-5 days in between [1]. An integrated population pharmacokinetic model describing the interaction of darunavir (DRV) and ritonavir (RTV) was created in NONMEM 7, characterising between-subject (BSV) and -occasion variability (BOV) in the PK parameters. An independent model was also designed for EFV, whose effect on DRV and RTV was modelled as dichotomous. Allometric scaling was applied to adjust for body size [2]. Visual predictive checks and the objective function value were used during model development.

Results: For all three drugs the structural model was a 2-compartment disposition with transit compartment absorption [3]. There was a strong correlation between the variability for absorption and elimination parameters at BOV level for DRV and RTV. The dynamic effect of RTV concentration on DRV CL was modelled with a sigmoidal function, which improved the model fit and provided DRV CL values of ~6L/h for the range of observed RTV concentrations. The typical value of DRV CL in absence of RTV (a scenario not observed in this dataset) was fixed to the value of ~33 L/h, reported by Sekar et al. [4], and the model estimated a low value of RTV EC50 (<70 ng/mL, the assay limit of quantification). EFV co-administration was found to increase the CL of DRV and RTV by more than 15%. CL of EFV decreased by about 30% for each CYP2B6 *6 allele, with respect to homozygous wild type.

Conclusions: The low value of RTV EC50 indicates the potency of RTV as an inhibitor, which was already highly active at low concentrations. This suggests that a reduction in RTV dose could preserve its inhibitory effect on DRV CL, as long as the concentration is kept above the (low) active concentration. A RTV dose reduction in DRV/r has been previously advocated by Hill et al. [5]. This strategy could be possible as RTV is now a generic drug and future RTV formulations may

include lower doses like 50 mg. The further integration of EFV in the combined model could help separate the expected RTV inhibition effect on EFV CL and the EFV auto-induction effect.

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III-54 *Kristin Dickschen* Evaluation of CYP2D6 Phenotype-Guided Tamoxifen Dosing in European Female Breast Cancer Patients using a PBPK-Model

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Objectives: Tamoxifen is a first-line agent in the treatment of estrogen-receptor positive breast cancer [1]. Endoxifen is a secondary metabolite of tamoxifen and regarded as a major contributor to its anti-tumoral activity [2]. Patients with the intermediate or poor metabolizer (IM, PM) phenotype of cytochrome P450 2D6 (CYP2D6), one major enzyme involved in biotransformation, exert a decrease in endoxifen steady-state plasma concentrations [3].
The impact of reduced CYP2D6 activity resulting in decreased endoxifen steady-state plasma concentration on treatment outcome remains to be elucidated [4]. However, there is evidence that IM and PM may not fully benefit from regular therapy [5].
Thus, a possible treatment strategy for IM and PM patients might be phenotype-guided dose escalation of tamoxifen to achieve endoxifen steady-state plasma concentrations comparable to extensive metabolizers (EM) [6].

Methods: A physiologically-based pharmacokinetics (PBPK)-model of endoxifen formation out of tamoxifen was developed for populations of European female individuals of EM, IM, and PM phenotype comprising physiological variability [7] and using prior knowledge of CYP2D6 activity [8].
The populations of PM and IM were adapted to a dose regimen of 4 months of 20mg tamoxifen daily followed by 4 months of 20mg tamoxifen twice daily [6]. Additionally, 4 months of 20mg tamoxifen daily followed by 4 months of 40mg tamoxifen once daily were simulated in both populations.

Results: Dose escalation from 20mg once daily to twice daily led to increased endoxifen steady-state plasma concentrations in both populations. However, only the IM population reached levels comparable to average EM endoxifen steady-state plasma concentrations.
Simulation experiments show that 40mg tamoxifen once daily achieved comparable results regarding plasma profiles to 20mg twice daily in both populations.

Conclusions: Dose escalation might prove a preferable treatment strategy for IM breast cancer patients, as model and experimental data [6], indicate comparable endoxifen steady-state plasma concentrations to EM. In terms of patient compliance, once daily 40mg is superior to twice daily 20mg.
Nevertheless, phenotype-guided dose escalation does not enable an exposure for PMs comparable to EMs up to doses of 60mg daily and may therefore not be the preferred dosing strategy. Possibly, direct endoxifen dosing to PM could be a suitable option of treatment. First-in-man studies have already been published [9].

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III-55 *Christian Diestelhorst* A Physiologically-Based Pharmacokinetic Model for Busulfan

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Objectives: Busulfan (Bu), a DNA-alkylating agent, is used widely for conditioning prior to bone marrow transplantation in both children and adults for haematological malignancies and non-malignancies. Despite years of investigation there are still open questions regarding intravenous (i.v.) Bu chemotherapy, e.g. an optimal area under the curve (AUC) target to reduce toxicity and optimize efficacy, the best schedule of administration as well as the optimal dosing in children. Therefore, a Physiologically-based pharmacokinetic (PBPK) model for adults was developed with the aim to predict plasma concentration-time curves, e.g. in children and other special patient groups.

Methods: PK-Sim® (Bayer Technologies, Leverkusen, Germany) was used to build a PBPK model. We implemented several physicochemical parameters of Bu and also considered particular properties, e.g. both plasma protein binding (reversible and irreversible) and red blood cell binding [1,2]. Metabolism is implemented in the liver and the small intestine using the activity of Glutathione S-transferase (GST) A1, the predominant isoform of GST catalysing Bu [3,4,5]. A fixed combination of K_m and V_{max} values for GST-A1 in all simulations was applied. For model development, simulations were computed and compared to raw pharmacokinetic data from 108 adults (13 patients received i.v. Bu four times daily, 95 patients received i.v. Bu once daily). Subsequently, model appropriateness was evaluated with an external dataset consisting of 95 adults [6,7], whom had 5 pharmacokinetic samples drawn about the first once daily dose.

Results: For the evaluation dataset parameters calculated by PK-Sim® were as follows: AUC (after the first once daily dose of 2.94 ± 0.26 mg/kg) 1.16 ± 0.15 mg*min/ml, clearance 0.16 ± 0.03 l/h/kg and volume of distribution at steady state 0.65 ± 0.06 l/kg (mean ± standard deviation). Mean Percentage Error (MPE) was less than 30% for each parameter compared with data from non-compartmental analysis [6,7].

Conclusion: Our PBPK model appears to accurately characterize i.v. Bu pharmacokinetics compared to non-compartmental analysis. Further investigations, e.g. distribution processes in different organs, the influence of different comedication and clearance scaling to predict the pharmacokinetics in children, are ongoing.

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III-56 *Nassim Djebli* Pharmacokinetic/pharmacodynamic (PK/PD) Analysis of Teriflunomide in Patients with Relapsing Forms of Multiple Sclerosis (RMS)

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Objectives: To explore the relationship between 12 safety and 6 efficacy variables and steady-state mean Teriflunomide trough concentrations (MCONC) in RMS patients with the inclusion of significant covariates, after 7 and 14 mg once daily (OD) Teriflunomide administration.

Methods: Data were collected in 2 clinical studies (Phases II and III) for the evaluation of safety (up to 1265 patients) and in 1 Phase III study (up to 1036 patients) for efficacy. The PK/PD models were developed and validated with R following: (a) Exploratory plots: PD variables were plotted vs. MCONC to assess possible relationship between MCONC and PD; (b) Statistical model (inter-individual variability) both additive and proportional, were tested; (c) MCONC effect model: linear, exponential, Emax (and Sigmoidal Emax models when necessary) were tested - logistic regression (binomial R function) or quasi-Poisson distribution models were used to evaluate categorical variables; (d) Covariate Screening: a minimum increase of the ΔOFV of 15.1 (p

Results: Regarding safety variables, final PK/PD models were mainly Emax models with an inter-individual variability and covariate inclusion on baseline for ALT (Alanine aminotransferase), Neutrophils, Lymphocytes, White Blood Cells, Diastolic Blood Pressure, Phosphate and Uric Acid. A linear model was selected for Amylase and a logistic regression model for Hair thinning. No significant relationship between MCONC and Lipase, Systolic Blood Pressure and CLCR was found.
Regarding efficacy variables: (a) A survival analysis model (Kaplan-Meier method) by MCONC category was performed and the Cox regression model showed a significant (p=0.033) decreased risk for disability progression as MCONC increased; (b) Number of Gadolinium-enhanced T1 lesions and number of unique active lesions per number of scans: quasi-Poisson models were selected with a low predictive performance; (c) Number of patients free of active lesions: a logistic regression model was selected; (d) Annual Relapse Rate: a trend was observed regarding relationship with MCONC; (e) Burden of disease: no significant relationship was observed.

Conclusions: This analysis allowed the development and qualification of PK/PD models (safety and efficacy) for OD Teriflunomide administered to RMS patients at doses of 7 and 14 mg.

III-57 *Jennifer Dong* Assessment of Mechanism of Action and Drug Effects in Early Signal of Efficacy Trials Using Integrated Glucose-Insulin Modeling: A Simulation-Estimation Approach

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Objectives: An integrated glucose-insulin (IGI) model describing glucose and insulin regulation during oral glucose tolerance tests (OGTT) has been proposed in both healthy and type 2 diabetes (T2DM) subjects [1-3], which could be integrated to simulate the outcome of longer duration trials for anti-diabetic agents [4-5]. The object of this work was 1) to understand if the IGI model can be used to gain insight in the main mechanism of action (MOA) of a test anti-diabetic agent and 2) to assess the precision and bias of the IGI model in estimating quantitatively the main drug effects.

Methods: A typical early signal of efficacy trial was simulated in which a cohort of 12 T2DM subjects received a 75 g oral glucose load at baseline and at the steady state of drug effect. This sample size allowed to detect a clinically meaningful drug effect of 20% reduction in glucose excursions after an OGTT. Four categories of MOA were simulated to represent: hepatic glucose production lowering (HGP 65%↓), glucose dependent insulin secretion increase (IPRG 300%↑), overall insulin secretion increase (ISEC 130%↑), and insulin sensitivity increase (ISEN 200%↑). For each MOA, 50 realizations of the study design were simulated with intensive glucose and insulin sampling over 3 hours. During Part 1 (identifying correct MOA) of the model estimation step, inclusion of different MOA factor in the model was applied to the baseline and post drug data simultaneously in a one-by-one manner. Goodness-of-fit plots and the Objective Function Value (OFV) provided by NONMEM (v7.1.2) were used for selecting the correct MOA. For part 2 (quantifying drug effects), percent Relative Estimation Error (REE%) for the specific MOA factor was determined.

Results: The IGI model without incorporation of drug effect was used as the reference run for the calculation of delta OFV. For each of the 4 MOA categories, the model incorporating the correct drug effect generated the lowest OFV (typically a difference in OFV of 750-1300). The difference to the second best MOA model was generally 300-500. Goodness-of-fits plots also supported correct model selection. In addition, the correct model consistently provided accurate estimation of the drug effect with the median REE < 5% (90% CI < 10%) for each MOA factor.

Conclusions: The IGI model was able to both correctly categorize and quantify the MOA responsible for the glucose and insulin response following simulated standard OGTT protocols in T2DM patients.

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III-58 *Pinky Dua* A Systems Pharmacology model of the nerve growth factor (NGF) pathway to aid drug discovery and development

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Objectives: The aim of this work was to integrate the knowledge of the biology of NGF response in a Quantitative Systems Pharmacology (QSP) framework to guide drug discovery and development programs, for novel drug target identification, target validation, biomarker and biomeasure [1] selection, dose prediction and ultimately patient selection ("precision medicine").

Methods: In sensory neurons, NGF engages with its receptor known as tropomyosin receptor kinase A (TrkA) causing an accumulation of diphosphorylated extracellular signal regulated kinase (dppERK) in the nucleus and subsequently the expression of numerous genes related to neuronal survival and pain sensation; dppERK concentration could therefore be regarded as an upstream biomarker linked to pain response. Two Systems Biology models for describing the events leading to dppERK migration [2] and nuclear-cytoplasmic shuttling of ERK [3] were coupled and the resulting ordinary differential equation model (59 molecular species and 233 parameters) was converted into a QSP model by expressing it in three inter-connected compartments and integrating a pharmacokinetic component, allowing for investigations of small molecules as well as monoclonal antibodies. The model was calibrated using in-house and external preclinical and clinical data.

Results: Using sensitivity analysis it was concluded that after NGF itself, TrkA was one of the more sensitive druggable targets (**target selection**). With the focus on TrkA, the initial model was used to develop a reduced model to explore the characteristics required for a successful hypothetical TrkA inhibitor (**target validation**). The model could then be used to provide **dose predictions** for new entities without the need for any data from animal models of ‘disease'.

Conclusions: Using the model, a hypothetical drug with typical characteristics could inhibit the NGF pathway at conceivable plasma concentrations. Given the importance of the TrkA concentration to the observed response, TrkA concentrations were experimentally determined in a range of cell types including a mammalian neuronal cell line. Levels varied markedly between cell types, highlighting the need for a reliable estimate in a relevant human cell type. QSP models incorporating such biomeasure data could be of great utility at all stages in drug discovery and development.

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III-59 *Vivek Dua* Multi-objective Optimal Control of Non-Viral Gene Delivery

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Objectives: Obtain optimal cellular exposure and transfection by formulating and solving a constrained multi-objective optimal control problem to compute the optimal dosage injection rate in the presence of constraints on the injection rate and cytotoxicity.

Methods: Gene therapy can potentially become a viable tool for the effective treatment of diseases. For effective gene therapy a gene delivery system has to balance between the two main objectives: high efficacy and low toxicity. However, usually these two objectives conflict with each other, i.e. one objective can not be improved without sacrificing the other. Several mathematical models have emerged recently to quantify the rates of transfer across various biological barriers. These models are based upon *in vitro* experiments where plasmid concentration in the medium at the start of the experiment is given and no additional plasmid is added to the medium during the experiment. For *in vivo* applications, the initial plasmid concentration can be initially zero and then plasmid is infused over a period of time. To take infusion into account we have modified the model and then use it to ask the question - what is the optimal gene delivery rate?

Polymeric carriers can assist delivery of genetic material to cross various biological barriers including cell membrane binding, endocytosis, endosomal escape, and nuclear entry. Some high molecular weight polymeric carriers have high transfection efficiency but are also highly cytotoxic. To manifest the desired therapeutic effect, optimal cellular exposure and transfection must be achieved. In this work, optimal cellular exposure and transfection are obtained by formulating and solving a constrained optimal control problem to compute the optimal dosage injection rate in the presence of constraints on the injection rate and cytotoxicity.

Results and Conclusions: The proposed gene delivery optimal control problem (GENOCT) problem explicitly takes into account the dynamic model of the transport across the biological barriers. The solution of the GENOCT problem provided some very interesting insights on what gene delivery profile might look like in a clinical setting and also on how these profiles are affected by the trade-offs between efficacy and toxicity.

III-60 *Anne Dubois* Joint modelling of the placebo response and the dropout mechanism using clinical data from a trial performed in patients suffering from major depressive disorder

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Context: The high rate of failure observed in clinical trials evaluating antidepressant agents is mainly explained by a marked placebo response and a high rate of dropout. There is no universally applicable method of handling such missing data. Traditionally, they were handled by carrying forward the last observation but this method could result in biased estimates of treatment efficacy. Most recently, the joint nonlinear mixed effects modelling (NLMEM) of longitudinal and time-to-event (TTE) data was developed [1-4]. Our objective was to describe the time course of the Hamilton depression rating scale score (HAMD) under placebo for patients suffering from a major depressive disorder, using joint NLMEM approach.

Methods: Placebo data from a 8-week (with an optional 16-week extension) phase II trial were used. HAMD was measured before the start of placebo treatment, at week 2, 4, 6, 8, and optionally at week 12, 16, 20 and 24. We tested several structural models to describe the HAMD time course using NLMEM [5-6]. We also tested different random effect models for the inter-individual and residual variability. Then, we added TTE data to HAMD data in the NLMEM, using a parametric TTE model to describe them. We tested different dropout mechanisms (completely random, random and informative [3]). As adding dropout into the model may influence the HAMD parameter estimates, all parameters (for HAMD and TTE data) were estimated for joint NLMEM. Furthermore, there were 3 types of TTE data (right-censored, exact or interval time event); we distinguished them during the estimation.

Results: The inverse of the Bateman function better described the HAMD data [6]. However, as expected, the analysis of the longitudinal data alone did not allow us to correctly predict HAMD at population level. Taking into account dropout data to develop a joint model was essential to improve the prediction. The final TTE model was an exponential model which considered the last observation of the HAMD score as a covariate. A specific covariate effect was also added to take into account the study design as only well-improved patients could continue after the 8^{th} week

Conclusion: The results of the joint modelling showed that taking into account the TTE data improved the model capacity to predict HAMD in patients under placebo. This method could also be applied to clinical data from patients under active treatment and, hence, help to better distinguish the treatment effect from the placebo one [1].

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III-61 *Cyrielle Dumont* Optimal two-stage design for a population pharmacokinetic study in children

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Objectives: Pharmacokinetic (PK) studies in children are mainly analysed by nonlinear mixed effect-models [1,2] as recommended in guideline [3]. Approaches based on the Fisher information matrix (M_F) [4] can be used to optimize their designs and are based on *a priori* information. However, PK data in children are often not available and methods as allometry or PBPK are used to predict 'initial' PK parameters. Therefore adaptive designs [5,6], among which two-stage designs, are useful to provide some flexibility. Our aims are: i) to analyse concentration-time data obtained from PBPK simulations in children after oral absorption of a drug X in development; ii) to develop and evaluate the impact of two-stage designs when children 'true' parameters are different from initial ones.

Methods: Concentration of drug X are generated by PBPK with SIMCYP [7] for 100 children from 6 months to 18 years. PK model and parameter estimates are obtained using NONMEM 7 [8]. Optimal one-stage and two-stage designs are derived assuming a total of N=60 children with identical 5 sampling times using PFIM [9,10]. The two-stage design is defined as follows. From initial parameters Ψ_0, we optimize design ξ_1 for the first cohort of N_1 children. From the obtained data set Y_1, population parameters Ψ_1 are estimated. The design ξ_2 of the second cohort of N_2 children, is optimized using a combined information matrix. The study is then performed in N_2 children with design ξ_2 and, finally, data Y_1 and Y_2 obtained from each cohort are analysed together. We evaluated one and two-stage designs for drug X assuming that the true CL is moderately or strongly higher than the initial one. A simulation study is on-going to evaluate the impact of the size of each cohort on the precision of population parameters estimation.

Results: The PK model is a 2-compartment model with first-order absorption. One-stage design from initial parameters shows a loss of efficiency when true CL is different. The two-stage design, with $N_1=N_2=30$, allows to partly compensate this loss of information and we show that the second stage design ξ_2 is different from ξ_1. The respective size of each cohort influences the gain in efficiency of the two-stage versus the one stage design.

Conclusions: Two articles in other contexts [11,12] discussed that two-stage designs could be more efficient than fully adaptive designs. Two-stage designs, which are easier to conduct, is a good alternative for designing PK studies in children.

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III-62 *Jeroen Elassaiss-Schaap* Pharmacokinetic-Pharmacodynamic Modelling & Simulation of Org 52186, a V3 antagonist, in Support of a Challenge Agent Trial Design with dDAVP

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Objectives: Org 52186, a V3 antagonist, was in development as an agent against depression before being discontinued. The objective of this analysis was to design a Proof-of-Principle trial to show antagonism of the V3 receptor of Org 52186 in vivo in humans, optimizing for trial cost. This trial should follow up on a single rise dose trial of Org 52186.

Methods: The pharmacokinetic-pharmacodynamic (PK-PD) properties of dDAVP were richly sampled in an experimental medicine study in healthy volunteers on the V2- and V3-selective agonist desmopressin (dDAVP). ACTH levels were determined as described by a PK-PD model developed in NONMEM 6. A population PK model of Org 52186 was built on data from healthy volunteers in a first-in-man single ascending dose study. In vitro affinity and plasma protein binding of Org 52186 were used to predict the antagonism of dDAVP-induced ACTH release. Simulations were performed using resampling of residuals of dDAVP PK-PD analysis. The simulated values were used to reconstruct trials of varying designs and analysis approaches in R, to determine an acceptable design of the challenge trial.

Results: The ACTH-releasing activity of dDAVP was quite variable as can be expected for such a pituitary hormone and in light of the dose limiting V2 effects of dDAVP. The PK-PD model that was developed described a subset of healthy volunteers not responding to dDAVP whereas substantial between-subject variability in maximal effects was observed among the other subjects. The resulting model was not yet flexible enough to capture all trends in the longitudinal responses and therefore the residuals were taken into account in subsequent simulations. The exposure to Org 52186 was readily captured by a pop-PK model.
Simulations showed that a classical cross-over trial design was not acceptable due to the variability in ACTH response to dDAVP. The designed screening phase was therefore expanded to include an evaluation of responsiveness to dDAVP, increasing the cost of screening but decreasing over-all cost. An apparent optimum was found when screening for an average ACTH response of 8 ng/ml and including n=12 subjects in the final challenge test. Inclusion of resampled residuals was determined to be essential for conservative estimation of trial sample size.

Conclusions: Innovative resampling approaches and trial design element evaluations were able to select an acceptable design for a dDAVP-challenge trial of Org 52186.

III-63 *Farkad Ezzet* Power Calculation Based on Pharmacokinetic Sampling Designs of ELND005 in a Phase 3 Clinical Trial Design in Mild Alzheimer Disease Patients

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Introduction: Sample size of a clinical trial is aimed at appropriately powering the study on the basis of one or more primary efficacy and/or safety endpoints. The calculation typically assumes a given effect size and variance of the response variable. For a phase 3 clinical trial investigating ELND005 250 mg twice daily (BID) versus placebo for 78 weeks, various PK sampling designs were compared and selected on the basis of the predicted accuracy of the PK model and impact on PK/PD model estimates.

Objective: To determine and compare power of alternative sampling designs in a Phase 3 clinical trial to detect the difference in clinical endpoints between ELND005 and placebo

Methods: Sample size was fixed at 450 patients per treatment arm, assuming 30% dropout rate by the end of the study. The primary clinical endpoints were expressed as a function of the drug exposure model previously developed. Power was calculated by simulating a large number of clinical trials (1000) and counting the proportion of trials with a statistically significant difference from placebo. For each simulated trial, response was calculated using the PK/PD model, incorporating uncertainty in its estimates as well as uncertainty in the PK model due to its design. Using a base design as a reference: 1 sample collected at pre-dose and 2 post-dose collected with at least 1 hour apart from each other during baseline visit, and 2 blood samples drawn at approximately 5 to 9 hours post-dose with at least 1 hour apart from each other post dose during follow-up clinical visits at weeks 6, 12, 24, 48. Three alternatives A, B and C revised to 2 post dose samples with one soon after dosing (0.5 hours) and the other at ~2 (Design A), ~3 (Design B), or ~4 (Design C) hours post-dose during baseline visit and to 1 sample post dose sample during the rest of the visits were compared.

Results and Discussion: Base design yielded power of ~74-79% for clinical endpoints. Although design C, followed by B then A, had the smallest variance of clearance, they achieve very similar power. Power calculated from all 3 Designs A, B, C was higher by at least 10% in all designs in a slightly increasing order (84-91%, 90-95%, and 90-97%, respectively).

Conclusion: Design B provides an efficient and practical sampling plan with a higher power than the base design, and hence preferred for future Phase 3 study of ELND005.

III-64 *Iñaki F. Trocóniz* Exploratory analysis to evaluate the relevance of different mechanism involved in a bivariate response target mediated disposition model characterizing the IL12 – IFNγ relationship.

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Objectives: Interleukin-12 (IL12) has shown to have a great therapeutical potential for the treatment of chronic hepatic diseases [1]. Nevertheless its in vivo efficacy is hampered by a negative feedback mediated by the interferon γ (IFNγ) produced in response to this cytokine [2]. A target mediated drug disposition model [3,4] able to describe the relationship between IL12 and IFNγ, after administration of a viral vector (DNA) codifying for the IL12 gene under the control of Mifepristone (RU) inducible promoter, has been developed for wild type mice (WT) and knock-out mice for the IFNγ receptor (KO). The aim of this work is to explore the role and importance of the different processes considered in the model to increase the understanding of the system.

Methods: The impact of the different model processes on free and bound IL12 and IFNγ, as well as on their receptors was evaluated by temporal modification of different model parameters. Different initial viral loads and daily administration of a single RU dose (250µg/kg) were explored. The implementation and evaluation has been performed by Matlab® software.

Results: The analysis of the model has revealed an important coupling between the different kinetics involved in the processes. Because of this feature, the changes on some parameters reveal behaviours which are hard to extrapolate without this exploration. Moreover, the results show a great influence of the parameters related to the bound IL12 and IFNγ on the dynamics of the system.

Conclusions: A better understanding of the role of the different model processes has been obtained. This approach can be used to propose new therapeutic goals to achieve sustained levels of IL12 minimizing the negative feedback triggered by IFNγ.

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III-65 *Christine Falcoz* Population PKPD modeling of an anti-diabetic compound with a new mechanism of action in ob/ob mice to predict the human dose

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Objectives: The aim was to predict a likely clinical efficacious dose for PXL, a compound with a new mechanism of action developed in type 2 diabetes, based on in vitro (IVT) efficacy data, PKPD modeling in ob/ob mice, one of the disease models, and a single endpoint, glucose.

Methods: The exploration of early and sparse PK and glucose data justified a PKPD approach based on glucose only levels. Specific PK and PKPD studies were designed under experimental constraints, and population PK and PKPD (PopPK, PopPKPD) models developed in normal and ob/ob mice. Phoenix® was used for exploratory analysis and Phoenix® NLME^{TM} for nonlinear mixed-effect modeling. Simple allometry was used to predict human clearance (CL). A likely clinical efficacious dose was predicted using the IC50 estimated in mice, scaled to man based on IVT differences between species and plasma binding.

Results: Data from the first pharmacological experiments showed that glucose levels 1 h post dose after 8 days of treatment were correlated to PXL concentrations. Glucose and PXL concentrations were available from the new studies over 8 h following the morning dose (0, 25, 50 or 100 mg/kg BID). *PopPK.* A two-compartment model was developed, with between-subject variability on CL, V and V2; the kinetics was proportional with dose. *PopPKPD.* There was an apparent diurnal pattern for glucose; however data were not available over 24 h and a constant baseline was used. The best model was an indirect-response model with inhibition of glucose production. Some model-misspecification was partly due to the circadian baseline which could not be accounted for. Using individual PK parameters allowed a better estimation of IC50. *Allometric scaling.* Scaling with unbound concentrations led to lower and tighter predictions of human CL (1.1 L/h). *Human dose.* The IVT difference in sensitivity between human and animal was 8 fold. The human dose providing on average 50 and 80% of maximal effect was predicted at 25 and 100 mg/d, respectively.

Conclusions: Integrating early sparse and literature information allowed designing studies which led to successful modeling. A two-compartment PK model was adequate. Using a population PKPD approach and IVT data in animal and man, human doses likely to produce a defined lowering effect on glucose were predicted, which should guide the FTIM study.

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III-66 *Mathieu Felices* Dose Regimen Assessement For Oral Fexinidazole

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Objectives: Fexinidazole, a 5-nitroimidazole, is being developed as a new oral treatment for Human African Trypanosomiasis. The aim of the present study was to determine the efficient dosing schedule for a phase II/III study based on a population pharmacokinetic (PK) model.

Methods: The population PK analysis was performed using NONMEM VI and SAS 9.2 based on plasma samples from data collected through three phase 1 studies, validated using the data of a fourth study (Multiple Ascending Dose over 10 days under fed condition using two different loading dose regimen).

Results: The PK of fexinidazole was best described by a two compartment model with a zero order absorption process. Integration of M1 and M2 metabolites in the model was successful and allowed simultaneous fitting of the three compounds. Population PK parameters of the parent drug estimated in the complete model were in agreement with those reported by non-compartmental analysis. The model simulates the time course of concentration of fexinidazole, M1 and M2 in a typical subject, following multiple once daily oral administration of fexinidazole under fasting and fed conditions. The following dosing regimens under fed conditions were determined from the simulations and implemented in the fourth phase I study:
-1800 mg fexinidazole or placebo from Day 1 to Day 4, and 1200 mg fexinidazole or placebo from Day 5 to 10
-2400 mg fexinidazole or placebo from Day 1 to Day 4, and 1200 mg fexinidazole or placebo from Day 5 to 10. This treatment regimen was found to be poorly tolerated and was stopped
Observed data of the first dosing regimen were in agreement with simulated data obtained with the first treatment schedule. Safety and tolerability were acceptable. Active metabolite M2 plasma concentration was reached rapidly and maintained for 3 to 4 days in all cases and more than 80% of the subjects had pre-dose plasma levels above 10 mg/L.

Conclusions: Based on these results, the dosing regimen of phase II study was defined and is about to be tested.

III-67 *Gregory Ferl* A mixed-effects simulation approach to quantifying the impact of missing pre-treatment baseline clinical DCE-MRI data on estimated population parameters

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Objectives: Our objective is to model the time course of an imaging biomarker in malignant tumors following a single dose of bevacizumab. The biomarker, K^{trans}, is monitored by Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) and reflects vascular permeability, surface area and rate of perfusion within each lesion. Patients underwent DCE-MRI at two timepoints before treatment and four time points after treatment; we subsequently used a mixed-effects model to describe true individual baseline values [1,2] and response to treatment [3]. Assessment of intra-patient variability via multiple baseline scans is important when comparing pre-treatment levels to a single post-treatment scan. Here, we assess the impact of multiple baseline scans when not one, but four, post-treatment scans are obtained, by fitting the model to simulated data with either one or two pretreatment timepoints.

Methods: DCE-MRI data was collected from 10 patients with liver metastasis from primary colorectal cancer, where each patient received two pretreatment scans and four additional scans subsequent to a single dose of the anti-VEGF antibody bevacizumab [4]. K^{trans}, a PD parameter that reflects vascular permeability, surface area and rate of perfusion within each lesion was estimated for each imaging time point. We developed a modified indirect response, mixed-effects model to describe the population change in K^{trans} after treatment. 1000 data sets were simulated in NONMEM using population parameters estimated by fitting our modified indirect response model to the full data set. The mixed effects model was then fitted to two variations of the 1000 simulated data sets, where: 1) each patient received 2 baseline scans (each simulated data set is unmodified) and 2) each patient received only a single baseline scan (the first baseline scan from each simulated data set was removed).

Results: The model that was fitted to the original data and was used to generate the simulated data is characterized by three structural parameters [k_{out} (time^{-1}), k_{tol} (time^{-1}) and *loss* (dimensionless)], three interindividual variance parameters, and one overall residual variance parameter. The parameter estimates obtained from the simulated data varied widely, likely due to data sparsity in the presence of large residual variability. The quality of the parameter estimates obtained from the simulated data was slightly improved in the two-baseline scenario as shown by the following root mean square errors (RMSE):

Root Mean Square Errors			
	k_{out}	k_{tol}	*loss*
mean	111 (133)	43 (45)	14 (15)
%CV	155 (225)	78 (108)	105 (113)

where RMSE's are expressed as percentages of the true parameter values underlying the simulation and numbers in parentheses are for the one-baseline scenario. %CV refers to variability of each parameter between individuals.

Conclusions: The results observed here suggest that double baseline scans, which are costly and a burden to patients, may not be required for everyone enrolled in the study if multiple (≥ 4) post treatment scans are obtained.

Acknowledgements: The authors thank Michel Friesenhahn, Ph.D. (Genentech) for statistical guidance.

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III-68 *Eric Fernandez* A database of PK-PD parameters and information for the modelling of anti-cancer drug regimen and combinations

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Physiomics, Pharmacometrics

Objectives: Physiomics and Pharmacometrics have collaborated to design a new database of anti-cancer drugs and therapeutic treatment information aimed at researchers in oncology and clinicians.

Methods: This database, accessible through the web, offers data on more than 130 anti-cancer drugs (small molecules and biologics) used in research and in the clinic. It contains information on drug combination as well as a several hundreds of cancer chemotherapy regimens routinely used in the clinic. Furthermore, these data are classified according to tumour type, species, in vitro or in vivo. It will be constantly expanded and curated with the most recent information.

Results: Individual drug information covers pharmacokinetic profiles, mechanism of action and of resistance, dose-response effect, dosing limits, therapeutic index, and immunosuppression data. Drug combinations are also referenced. The database covers synergy or antagonism, as well as a combination therapeutic index and cross-resistance information. Some drug combination having level of synergy depending on the drug schedule, drug sequence and administration timings are also referenced and thoroughly discussed. The user can also browse and compare chemotherapeutic regimens, analyse the overall drug dose over a course of treatment, by tumour type, in animal and clinical models. Advanced functions include the ability to do statistical analysis on drug usage and dosing in various contexts. It can also help determine which drug candidates are likely to be used in combination with a new chemical or biological entity, given the mechanism of action and other PK/PD data. Finally, data can be exported and used in spread sheets, modelling software or simulation packages.

Conclusions: This database will allow users to design new combinations and regimens, which obey dosing constraints, such as MLD and MTD. Furthermore, it provides ways to standardize the expression and nomenclature of chemotherapy regimens unambiguously and uniformly is of paramount importance to improve efficacy, as well as to reduce medication errors [1].

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III-69 *Martin Fink* Population pharmacokinetic analysis of robenacoxib in dogs with chronic osteoarthritis

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Objectives: A previous population analysis showed the preferential distribution of the coxib NSAID robenacoxib to inflamed joints in dogs [1]. The objective of this analysis was to further study the pharmacokinetic properties of robenacoxib in the target animal population (dogs suffering from chronic osteoarthritis) and to assess the influence of covariates such as age, weight, sex, and breed categories and the subsequent need of any dose adjustment.

Methods: Data was pooled from three different clinical studies including a total of 208 adult dogs with chronic osteoarthritis. Robenacoxib was administered orally as tablets and was quantified in blood using LC-MS analysis. A population pharmacokinetic model was developed using NONMEM and stepwise covariate search was performed with scm from the PsN. Figures were produced in R based on the empirical Bayes estimates from the final model.

Results: A two-compartment population model was identified to fit the pooled data well with sequential 0- and 1st-order absorption. Statistically significant effects on apparent clearance (and thus exposure) and central volume of distribution was found for weight only ($p<0.01$). Age, sex, and breed group were not found to significantly explain part of the remaining variability.

Conclusions: The presented population pharmacokinetic analysis provided insights in the necessary adjustment of dose for robenacoxib in the patient population, which would have been impossible using standard statistical approaches. The analysis supports the current recommended dose of 1-2 mg/kg body weight. The remaining unexplained variability in apparent clearance is minor compared to the approximately 2-fold range of exposure in the present dose range of 1-2 mg/kg body weight. No significant effects of age and breed on exposure support that no further dose adjustment is necessary.

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IV-01 *Nicolas Frances* A translational threshold model to assess exposure-driven QTc changes

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Objectives: QT prolongation in the electrocardiogram is a surrogate marker of 'torsade de pointes' (fatal arrhythmias). This QT parameter is investigated during pre-clinical cardiovascular telemetry studies and it is critical, in case of QT prolongation, to define the safety margin for initiation of human trials. The objective of this study was to evaluate a threshold model to link QT with exposure and explore its translational capability.

Methods: The threshold model described below was applied to 3 compounds in pre-clinical development and for one compound for which clinical data was available. QTc (heart rate corrected QT) [1] change was linked to exposure by a threshold model using a population approach (Monolix® 3.2 [2]). This model combines a baseline parameter (QTc baseline value), a threshold parameter which corresponds to the concentration below which there is no drug induced changes in QTc expected, and a slope parameter which corresponds to the QTc increase rate according to exposure above the threshold parameter value. Inter-individual variability was estimated on baseline and slope parameter. The pre-clinically assessed threshold parameter is then used for human prediction in combination with the predicted PK profile in man by PBPK modeling (GastroPlus® [3]).

Results: The threshold model effectively described the relationship between exposure and heart rate corrected QT when data show a range of exposure with no effect on QTc and no saturation in effect. Under these circumstances, the threshold model can be used as an alternative to other existing models [4, 5]. The approach successfully described QTc change in human and showed translational properties of model parameters.

Conclusions: QTc and exposure can be linked by a threshold model and demonstrate translational properties from pre-clinical to clinical studies. In case of a QTc prolongation, this model predicts the exposure where effects are expected to occur (threshold parameter, which will likely be higher than the otherwise used No Effect Level). By using the threshold model to describe the exposure response relationship and translate the model to humans, a better prediction of where QTc prolongation is likely to occur can be estimated which provides more confidence in the dose escalation strategy.

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IV-02 *Ben Francis* Using Stochastic Control Methods and Pharmacokinetics to Individualise Drug Therapy: A Case Study with the Enzyme Inhibitor Imatinib.

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Objectives: The list of drugs which exist in healthcare to treat various conditions and diseases is vast with new drugs added every year. Many drugs cause adverse events which are dose dependent, consequently there is a need to identify the correct dose for each specific patient, which minimises their risk of having an adverse drugs reaction, whilst at the same time maximising the efficacy of the drug. The benefits of personalised medicine include more optimal treatment for the patient and the potential reduction in treatment costs from minimising the occurrence of adverse events [1]. However, the objective of a drug dose algorithm, finding the optimum dose, is complicated by the inter-individual variability in the response of each individual patient to a specific drug [2].

Population pharmacokinetics are often established in either drug trials or by similar research undertaken on drugs already in use. Population pharmacokinetic parameters are indicative of population dosing which will derive optimum dosage regimens for the average patient. Although, with large amounts of variability between patients, population dosing would be sub-optimal to provide therapeutic effect for most patients [3]. Post population analysis is required to classify and account for all the sources of variability in drug dose response. Thus enabling greater individualisation of drug therapy for patients and providing informed doses which aim to induce therapeutic plasma concentration levels as quickly as possible.

Using stochastic control methods, which utilize information on pharmacokinetic parameters and allow feedback of plasma concentration values from samples, creates an interactive drug dosing algorithm. The drug dose algorithm is also adaptive as factors which affect pharmacokinetic parameters can be inputted at anytime to update drug dosage regimens. This is particularly useful as the algorithm can derive dosage regimens based on probabilities of multiple models [4] whilst waiting for factors which require processing time, such as, pharmacogenetic information.

An example using the drug imatinib is provided, which is used to treat chronic myelogenous leukaemia. Imatinib is often administered as a 400mg dose regardless of patient dosing needs with 800mg doses prescribed if there is an apparent resistance to the drug [5]. In this example, seven day dosage regimens will be derived for twelve patients to demonstrate the effectiveness of the algorithm - the ability of the dosage regimen to guide the patient's plasma concentration levels to maintain a therapeutic trough level of 1000ng/ml [6, 7]. Further, the ability of the drug dose algorithm to respond to varying degrees of non-compliance will be tested.

Methods: The drug dose algorithm is developed from stochastic control methods utilising data from a population pharmacokinetic model to make drug response estimates which can then be compared against noisy measurements (e.g. plasma concentration samples) of the response from each specific patient [8]. Using noisy measurements to update the analysis allows the system to become interactive; ultimately seeking to reduce the overall uncertainty of prediction and providing dose estimates which are tailored to the patient's requirements. The pharmacokinetic system must

first be presented as a stochastic control problem this involves determination of possible treatments, desired therapeutic outcome, time scale of treatment and expected responses from the system.

The pharmacokinetic compartmental model can be expressed as a set of differential equations or analytical solutions [9]. A stochastic component is then added to model to model small fluctuations that occur in patient's plasma concentrations not explained by sources of variability. Traditionally the Weiner process has been added to an ordinary differential equation to show fluctuation in plasma concentration level [10]. However recently an alternative method has been proposed by Delattre et al. (2011) [11] where parameters are constantly perturbed around their mean value by the Weiner process thus leading to a variable gradient of the plasma concentration level. The later method is applied in the Imatinib case study. We simulated patient non-adherence to their prescribed drug dose regimen and then determined how well the drug dose algorithm responded with 'days to return to therapeutic trough level' as the primary outcome.

Results: In the Imatinib case study, firstly forecasting the plasma concentration of a patient taking the prescribed dose showed that patient trough levels were between 2.1 and 48.9% away from the therapeutic trough level. Dosage regimens derived by the drug dose algorithm advised alterations in ten out of the twelve patients included in the study. Dose adjustments in all but one patient (advised an average daily dose reduction of 129mg) advised an increase in their prescribed dosing, with average daily dose increases between 114 and 400mg. In simulation, the new dosage regimens kept patient trough levels between 0-5.4% away from the required therapeutic trough level of 1000ng/ml. Running the algorithm through compliance situations showed that 'recuperation dosage regimens' were derived which would restore the patient's tough level to the required therapeutic trough level.

Conclusions: There is an important need for individualised dosing regimens that maximise efficacy of the drug, whilst at the same time minimising the risk of adverse drug reactions. The results from this case study show that patients who continue on the standard dosing protocol, in all but two cases, will fail to achieve a therapeutic trough level; whereas, stochastic control methods have been shown to estimate a dosing regimen which will induce a therapeutic trough level. This methodology can be applied to almost any drug with an established compartmental pharmacokinetic model. Additionally various clinical targets, other than therapeutic trough level, can be given to the drug dose algorithm. These include therapeutic concentration windows, concentration maximum targets and area under the curve targets. The main intention of this research is to compliment the clinician decision making process, therefore, further work will be undertaken to provide clinicians with percentage risks of therapeutic effect and adverse event. This further work will allow the clinician to make decisions based on information patient demographics, co-morbidity, co-medication, treatment risk factor and the drug dose algorithm output further combining clinical judgement with statistical models.

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IV-03 *Chris Franklin* Practical Implications of Ontology and Global Standards for Model-based Data Analysis

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Objectives: The development of a semantic metadata infrastructure is required to support the sharing and reuse of model libraries. The DDMore consortium is delivering an infrastructure based on the RICORDO approach to model annotation and data resources with shared ontologies. Ontologies consist in classes of entities found in a given domain as well as relationships between them. They can be used for the machine processable classification of information contained in model specifications, ensuring the shared clarity of these specifications. The approach enables the application of ontology-based knowledge management to model and data library. We illustrate the concepts with a real-life case study.

Methods: Models will be selected representing typical modelling approaches and languages drawing from examples of PK, PBPK and PKPD analyses. These will be inspected in relation to their parameters and variables (deterministic and stochastic components). Ontologies will be drawn from those in the public domain as well as the ongoing knowledge representation efforts from within the modelling community including the DDMoRe consortium. The results will allow comparable models to be used across different software applications and across different statistical methods.

Results: The case studies illustrate how the availability of standards for model specification permits improvement in model reusability on the basis of clear, explicit and shareable model descriptions in support of model libraries. The availability of specification standards for models coupled with standardised semantic annotation also implies that some models can be converted into a model definition language to provide interoperability. Furthermore these standards allow workflows for modelling and simulation within the DDMoRe framework.

Conclusions: Our work shows the need and relevance for community standards in model representation and model annotation for effective collaboration and workflow. The examples offer insights to the potential impact for both modellers and software development. This work shows that ontologies for model specification can support model reuse and establish crucial interoperability between models and experimental or clinical trial data (e.g. CDISC).

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IV-04 *Nicolas Frey* Short- and Long-Term Effects of Tocilizumab on Neutrophil Counts in Pediatric Patients with Systemic Juvenile Idiopathic Arthritis

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Objectives: Tocilizumab (TCZ) is a recombinant humanized IL-6 receptor monoclonal antibody that inhibits binding of IL-6 to its receptors. The aim of the analysis was to describe the time course of peripheral neutrophil counts (NTC) after TCZ administration in a pediatric population.

Methods: Serum TCZ concentrations and NTC were available from 75 patients with active systemic juvenile idiopathic arthritis (sJIA) who received 12 mg/kg (for patients < 30 kg) or 8 mg/kg (for patients ≥ 30 kg) infusions of TCZ every 2 weeks (total of 6 doses). Neutrophil counts were assessed at screening, baseline (week 0), and at 1, 2, 3, 6, 8, 10 and 12 weeks. A previously developed two-compartment model with parallel linear and Michaelis-Menten elimination described TCZ concentrations [1, 2]. Different PKPD models with direct and indirect response were tested to characterize the TCZ-NTC relationship.

Results: The TCZ-NTC relationship was described by a model that included an immediate TCZ effect on NTC decline (possibly, neutrophil margination [3]) and a longer term TCZ effect on NTC decline (toward normal levels) due to the improvement of patients' condition (e.g. decrease of inflammation). The immediate effect was described by a direct sigmoid E_{max} model (E_{max} = 0.724 (%RSE 14.8%) and EC_{50} = 6.38 µg/mL (%RSE 15.8%)). The PKPD parameters were very similar to the respective values obtained earlier for adult patients [2] (E_{max} = 0.788 and EC_{50} = 7.49 mcg/mL). The maximum rate of decline of the long term effect was 0.166 day^{-1} and the TCZ concentration corresponding to half of this rate was 151 µg/mL. The corresponding NTC decline for a typical patient was estimated to go from 8.12×10^9/L to 5.72×10^9/L. Diagnostic plots and predictive check simulations indicated a good agreement of model predictions with the observed data.

Conclusions: The NTC time course following TCZ administration in pediatric patients with sJIA was characterized by a combination of an immediate response corresponding to the direct blockade of the IL-6 signaling pathway and a slow decline possibly related to the improvement of the patients' condition (e.g. decrease of inflammation)

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IV-05 *Lena Friberg* Myelosuppression as a Biomarker of Tumor Response in Docetaxel Treated Metastatic Breast Cancer Patients

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Objectives: Toxicity and treatment outcome varies considerably between cancer patients and new strategies for dose individualisation are needed. The aim of this project was to investigate if myelosuppression, characterized by a semi-mechanistic model, is correlated with the change in tumor size and thereby could be used as a biomarker to earlier evaluate the treatment and guide dose adjustments to increase the chance of a successful therapy.

Methods: Data on haematological toxicity and tumor size were available from 244 metastatic breast cancer patients treated with single agent docetaxel (75-100 mg/m^2) [1]. The change in tumor size, i.e. the sum of longest diameters (SLD) of target lesions according to RECIST, as a function of time, was described by applying a longitudinal model for tumor growth inhibition [2]. The time-course of absolute neutrophil counts (ANC) was predicted by individual parameter estimates obtained from an earlier characterization using a semi-mechanistic myelosuppression model [3]. Docetaxel dose (in mg), individual myelosuppression model parameters [neutrophil baseline (BASE), maturation time (MTT) and drug sensitivity (SLOPE)], and the absolute [ANC(t)] and relative change in myelosuppression over time [(ANC(t)-BASE)/BASE], were evaluated separately or in combination to describe the change in tumor size. The myelosuppression descriptors were linked to changes in tumor size in the same manner as dose [2]. Model development was performed using the FOCE method with INTERACTION in NONMEM 7.

Results: The change in tumor size following treatment with docetaxel was adequately described by the tumor growth inhibition model. The relative change in ANC over time [(ANC(t)-BASE)/BASE] was the best predictor of tumor size dynamics and statistically significant better than dose (Δ OFV = -22).

Conclusion: The identified relationship between the relative change in ANC and tumor size indicates a potential use of ANC as an early predictor of tumor response and may thereby be used for dose individualisation to maximize treatment efficacy.

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IV-06 *Anne-Kristina Frobel* A time-to-event model for acute rejections in paediatric renal transplant recipients treated with ciclosporin A

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Objectives: Ciclosporin A (CsA) immunosuppression after paediatric renal transplantation remains challenging due to a narrow therapeutic range and limited information in children. Also, the target CsA exposure (AUC) is under debate. The aim of this study was to develop a model for the time to first acute rejection (AR) and to explore predictive factors for therapy outcome.

Methods: Data was extracted from patient records at the hospital for Children and Adolescents in Helsinki, Finland (1995-2006). A parametric survival model implemented in NONMEM 7.2 was used to describe the time to first AR. The influence of AUC and other covariates on the hazard were explored using stepwise covariate modelling (SCM), bootstrap-(boot-) SCM (1) and cross-validated (XV-) SCM (2). The clinical relevance of the potential effects was assessed with the time at which 90% of the patients were AR-free (T90), taking into account parameter uncertainty and covariate distributions.

Results: Data on 87 patients (0.7-19.8 years), whereof 54 experienced an AR, was analysed. An exponential survival model based on a function of discrete constant hazards changing in steps over time, (peak hazard day 5-8 after transplantation), described the data best. Dialysis time, sex and baseline weight were identified in the SCM as potential, but were not statistically significant covariates ($p>0.01$), which was confirmed by boot- and XV-SCM procedures. The boot-SCM demonstrated low inclusion rates for all relationships and selection bias in covariate effect sizes. The XV-SCM showed the best predictive performance for a model without covariates. The median T90 changed by about 1 day for different covariate values; for the strongest covariate found, dialysis time, median T90 was 5.8 days (90% confidence interval 5.1-6.8) for long (90. percentile) and 7.4 (6.4-11.7) days for short (10. percentile) times.

Conclusions: The data was described in a survival model based on a step function of hazards. Covariate effects were not statistically significant and the predicted clinical relevance of the effects was low. Boot-SCM and XV-SCM methods were successfully applied and discouraged inclusion of any covariates into the model. Daily CsA AUC was not identified as a covariate, suggesting that within the observed range (90% interval 1.13–8.40 h*mg/l), an increase in AUC did not increase protection from AR. This feedback on current therapy may help avoiding unnecessarily high, potentially toxic dosing of CsA in children.

IV-07 *Ludivine Fronton* Relevance of Endogenous IgG Binding to FcRn in PBPK Models of Therapeutic mAbs

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Objectives: There is a high interest in developing mechanistic pharmacokinetic models to describe the disposition of monoclonal antibodies (mAbs). Physiologically-based pharmacokinetic (PBPK) models represent a primary choice because they allow one to integrate in-vitro data (e.g. the neonatal Fc Receptor (FcRn) affinity, KD), physiological data (e.g. plasma and lymph flows, plasma and tissue volumes) and in-vivo data (e.g. plasma and tissue concentrations). So far, existing PBPK models in mice are not satisfactory because they either do not take into account tissue data or the endogenous immunoglobulin type G (IgGendo) for model building. We developed a PBPK model for mAb and IgGendo, in mice, in the absence of target which accounts for available plasma data, tissue data including the correction for residual blood and tissue-dependent FcRn expression.

Methods: We used the physiological parameters reported in [1]. The experimental venous plasma and tissue data of the mAb (7E3), administered intravenously at 8 mg/kg, were extracted from [1] for FcRn-knockout and wild-type mice using the software DigitizeIt, version 1.5.8a. The steady-state plasma concentration of total IgGendo was reported in [2]. The tissue concentrations of total FcRn were considered to be tissue-dependent and scaled from the whole-body FcRn concentration according to the different tissue expression levels of FcRn reported in [3]. MATLAB R2010a was used for modelling (lsqcurvefit) and simulations (ode15s solver with default options). The 5 unknown parameters were fitted simultaneously to all data.

Results: To assess whether FcRn-binding can be considered in quasi-steady state, we analytically assessed the concentration of mAb in the endosome considering explicitly the association and the dissociation to FcRn (detailed model) and under the quasi-steady-state assumption (QSSA), based on the association (kon) and dissociation (koff) constants values proposed in [4]. Given the data, the model based on QSSA resulted in excellent approximation of the detailed model due to the relative slow degradation rate constant (kdeg) of mAb compared to the fast association to FcRn. We previously showed [5] that the endosomal IgGendo level solely sets the saturation level of FcRn. Hence, it is essential to consider it in the PBPK model. However, the parameter estimates are highly sensitive to the IgGendo-binding to FcRn. We used these insights to translate the explicit IgGendo- and FcRn-model dependence into an implicit dependence which makes it possible to reliably perform the parameter estimation process.

Conclusions: To explain mechanistically the elimination process of IgGs (i.e. mAb and IgGendo), it is critical to integrate the saturable binding to FcRn in the PBPK model. However, the induced sensitivity of parameter estimates necessitates considering the FcRn-binding implicitly.

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IV-08 *Aline Fuchs* Benchmarking therapeutic drug monitoring software: A systematic evaluation of available computer tools

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Objectives: Therapeutic drug monitoring (TDM) aims at optimizing treatment by individualizing dosage regimen based on blood concentrations measurement. Maintaining concentrations within a target range requires pharmacokinetic (PK) and clinical capabilities[1,2]. Bayesian calculation represents a gold standard in TDM approach but requires computing assistance. The aim of this benchmarking was to assess and compare computer tools designed to support TDM clinical activities.

Methods: Literature and Internet were searched to identify software. Each program was scored against a standardized grid covering pharmacokinetic relevance, user-friendliness, computing aspects, interfacing, and storage. A weighting factor was applied to each criterion of the grid to consider its relative importance. To assess the robustness of the software, six representative clinical vignettes were also processed through all of them.

Results: 12 software tools were identified, tested and ranked. It represents a comprehensive review of the available software characteristics. Numbers of drugs handled vary from 2 to more than 180, and integration of different population types is available for some programs. Nevertheless, 8 programs offer the ability to add new drug models based on population PK data. 10 computer tools incorporate Bayesian computation to predict dosage regimen (individual parameters are calculated based on population PK models). All of them are able to compute Bayesian *a posteriori* dosage adaptation based on a blood concentration while 9 are also able to suggest *a priori* dosage regimen, only based on individual patient covariates. Among those applying Bayesian analysis, MM-USC*PACK uses a non-parametric approach. The top 2 programs emerging from this benchmark are MwPharm and TCIWorks. Others programs evaluated have also a good potential but are less sophisticated or less user-friendly.

Conclusions: Whereas 2 software packages are ranked at the top of the list, such complex tools would possibly not fit all institutions, and each program must be regarded with respect to individual needs of hospitals or clinicians. Programs should be easy and fast for routine activities, including for non-experienced users. Although interest in TDM tools is growing and efforts were put into it in the last years[3], there is still room for improvement, especially in terms of institutional information system interfacing, user-friendliness, capability of data storage and automated report generation.

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IV-09 *Samira Garonzik* Development of PK/PD Models to describe Pharmacokinetics and Biomarker Responses for Dovitinib (TKI258)

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Objectives: Dovitinib is a potent oral inhibitor of Receptor Tyrosine Kinases (FGFR, VEGFR, PDGFR). It is expected to be effective in patients with tumors with FGF-activated pathways (mutation, amplification or overexpression), especially since FGF is considered a mechanism of resistance to anti-VEGF therapies. The objectives of this analysis were to improve upon an existing PK model [1], and to develop a PD model to describe the response of FGF23 to both dovitinib and VEGF, considered a marker of hypoxia. Inhibition of FGFR has been shown to cause acute FGF23 mRNA decrease, causing serum levels to drop, followed by rebound upon discontinuation of blockade.[2] Continued blockade of angiogenesis leads to increased FGF signaling.[3]

Methods: PK/PD data from 127 patients receiving dovitinib, 50 – 600 mg daily or intermittently over 15 – 859 days was available. Plasma concentration-time data + sparse biomarker (BM) data was available after the first dose and at steady state (SS). Data was modeled to characterize nonlinearities in PK as well as FGF23 response.

Results: Prolonged absorption, linear clearance after the first dose, but dose dependent decrease in clearance beyond day 7 at doses > 400 mg qd (leading to over-proportional accumulation)was observed in the data. The earlier PK model modeled the accumulation as a Michaelis Menten process, implying the greatest potential for accumulation was after the first dose rather than after auto-induction had set in. In the current model, two parallel clearance terms allow for either auto-induction or accumulation to manifest. Both processes depend on cumulative exposure through a single time dependent process. Transit compartments were used to describe absorption lag. Median (10th – 90th percentile) total clearance was 30 (17 – 80) L/h on Day 1, and 96 (51 – 185) L/h at SS. A PD model for FGF23 used a precursor dependent indirect response model to characterize the acute drop and rebound/tolerance. The observed increase of FGF23 levels to a new steady state was modeled as a feedback response to increased VEGF in the system. The model predicted 36% and 57% increase in VEGF and FGF23 respectively at SS, for median exposure at a dose of 400 mg daily. Simulations of PK and BM responses with different dosing regimens quantified relative safety and target effects.

Conclusions: PK/PD model developed described data well. Simulations suggest intermittent dosing may be preferred to minimize over-proportional accumulation.

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IV-10 *Peter Gennemark* Experimental design based on mechanistic mathematical modeling of body composition and energy turnover

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Objectives: Experimental studies of drugs related to appetite, metabolism, and energy expenditure often require rigorous monitoring of food intake and body weight. Obviously, such studies are complicated to administrate and associated with high cost. Experimental design is therefore an important issue. Here, we explore how mechanistic dynamic mathematical models of energy balances and body composition can improve the analysis and experimental design of such studies in both pre-clinical and clinical settings.

Methods: We consider a class of dynamical mathematical models of energy turnover that are based on the law of energy conservation and explicitly connected to physiological variables [1-2]. Key model variables include food intake, body weight and composition, energy expenditure (including resting metabolic rate and physical activity) and metabolic fuel selection under various dietary conditions.

Results: Using the models we first confirmed their flexibility to fit data generated for both food intake and body weight. We then investigated under what assumptions time profiles of food intake can be inferred from body weight data only. We identified two main sources of uncertainty: model choice for representing noisy body weight time profiles and empirical based estimation of energy expenditure. We finally investigated how the models can predict long-term (weeks) effect on body weight based on short-term (days) food intake studies. Our analyses indicate that more cost efficient experimental designs are plausible, in particular for scenarios with no or only minor unmonitored drug tolerance development.

Conclusion: Key advantages of a mechanistic model based analysis include improved understanding of the system dynamics, improved ability to predict beyond the data ranges, and potential to significantly improve the experimental design by reducing the study length. For the latter, the risk of tolerance development must be assessed.

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IV-11 *Cecile Gerard* Determination of the most influential sources of variability of tacrolimus trough blood levels in adult liver transplant patients: a bottom-up approach

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Objectives: Tacrolimus (TAC), an immusuppressive drug used for the prevention of graft rejection after liver transplantation, presents a large pharmacokinetic variability. Blood concentration of TAC are routinely measured to achieve and maintain target trough blood concentration (TBC). Most part of the interindividual variability remains unexplained. The objective was to identify predictive factors influencing TBC of TAC using a bottom-up approach.

Methods: A physiologically-based pharmacokinetic (PBPK) model of TAC was proposed, taking into account the body weight (BW), the proportion of adipose tissue, hematocrit, lipid fraction of organs, liver function, CYP3A5 genotype of patient and concomitant drugs (CYP3A4 inhibitors). TAC concentration profiles were simulated in a virtual population defined by a set of covariate values similar to those from a real population of 66 transplanted patients included in a multicentric PK study. Correlations between covariates were accounted for. For the validation of the PBPK model, TBC were compared with those observed in the real population. Then, the impact of each covariate has been tested on TBC of TAC in order to identify the most influential ones.

Results: For CYP3A5 *3/*3 genotype (non-expressor) of liver donor and three levels of drug-drug interaction (without inhibition, low and moderate inhibition), means were 7.84 *vs* 7.80, 8.22 *vs* 8.25 and 10.30 *vs* 9.97 ng/ml for observed *vs* simulated TBC of TAC.
With a dosage regimen of 0.04 mg/kg every 12 hours, significant increase of the TBC of TAC (6.61 to 17.1 ng/mL) has been found when the BW increase (50 to 110 kg). For the liver function (degrees of cirrhosis with Child Pugh score of A to C), hematocrit (0.19 to 0.43), proportion of adipose tissue (0.10 to 0.30), the same trend in TBC was found: means of 9.48 to 14.39, 4.92 to 11.8 and 6.00 to 8.83 ng/mL, respectively. Without drug-drug interaction, mean TBC of TAC were 3.68, 5.21 and 7.80 when CYP3A5 genotypes of the liver donor were *1/*1, *1/*3 and *3/*3, respectively.

Conclusions: Bottom-up approach allowed taking into account the influence of relevant covariates on TBC of TAC. The most influential covariates were BW, hematocrit, liver function and CYP3A5 genotype of the liver donor. These covariates should therefore be taken into account in therapeutic drug monitoring to adjust dosage regimen for each transplant recipient patient.

IV-12 *Massimiliano Germani* Population pharmacokinetic analysis in healthy volunteers treated with different oral formulations of riluzole.

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Objectives: The aim of the current study was to develop a population model to assess the PKs of riluzole administered orally as a suspension (50 mg/10 mL oral suspension, Italfarmaco S.p.A., Italy; test compound) and as tablets (Rilutek® 50 mg film coated tablets; reference compound) in healthy subjects (HS). Once the population PK model was established, it was used to simulate 50 mg/10 mL oral suspension of riluzole and 50 and 100 mg oral treatment of Rilutek® at steady-state following a twice a day administration in order to characterize the population exposure-response relationships on tolerability endpoints in humans.

Methods: 53 HS in three clinical studies were treated with both riluzole as oral suspension and as tablets. The different formulations of riluzole were simultaneously analyzed using a two-compartment model (ADVAN4 TRANS4 subroutines in NONMEM) with sequential zero/first-order absorption. Parameters related with the absorption process (ALAG1, k_a) were assumed to be different for test and reference. The effect of covariates (body weight, height, BMI, age and gender) on PK parameters was assessed using a stepwise regression model with a forward additive and a backward elimination step.
Providing the final model, 1000 concentration profiles were generated for each simulation scenario. C_{max} and AUC_{0-12}, were computed and summarized with descriptive statistics (i.e. median, quartiles, 5^{th}, 95^{th} and 99^{th} percentiles).

Results: The final riluzole model, including body weight on CL/F, V_2/F and V_3/F as covariate, minimized successfully with the covariance step. Typical parameter estimates were: CL/F=55.5 L/h, Q/F=42.5 L/h, V_2/F=154 L, V_3/F=208 L, D_1= 0.269 h, $k_{a,test}$=18.5 h^{-1}, $k_{a,ref}$=8.22 h^{-1}, $ALAG1_{test}$=0.0650 h, $ALAG1_{ref}$=0.134 h.
Following 50 mg/10 mL riluzole oral suspension, a median C_{max} value of 303 ng/mL (5^{th}-95^{th} percentile interval: 130-637 ng/mL) was obtained The corresponding median values for 50 mg and 100 mg Rilutek® were 266 ng/mL (88.3-642 ng/mL) and 532 ng/mL (177-1284 ng/mL), respectively.

Conclusions: The results of the present investigation are in agreement with previous ones reported in [1,2]. The simulated results show that the expected distribution of C_{max} and AUC of 50mg riluzole oral suspension and of 50 mg Rilutek® film coated tablets in the patient population are fully overlapping. Moreover, the distribution of C_{max} and AUC of 50mg riluzole oral suspension are far below those of 100 mg Rilutek® film coated tablets.

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IV-13 *Leonid Gibiansky* Monoclonal Antibody-Drug Conjugates (ADC): TMDD Equations, Approximations, and Identifiability of Model Parameters

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Objectives: To derive equations that describe antibody-drug conjugate (ADC) distribution, deconjugation, elimination and interaction with the target; to derive Michaelis-Menten approximation of these equations; to investigate identifiability of model parameters given typically available measurements and clinically feasible sampling scheme.

Methods: Equations of that describe concentration-time course of the ADC - target system that includes the naked antibody, ADCs with various loads, free drug, free target, and various antibody ADC-target complexes were derived. Michaelis-Menten approximation of these equations was derived based on the assumption of fast internalization of the ADC-target complex. Identifiability of the model parameters was investigated using optimal design PFIM software [1]. The parsimonious model flexible enough to describe the typically available measurements yet simple enough to be identifiable was suggested. Various generalizations of the proposed model were discussed.

Results: The ADC system can be described using the general TMDD framework with an additional element that accounts for the deconjugation process. Given the typically available measurements, parameters of the individual ADC species (ADCs with specific drug loads) are not identifiable. Assumptions that relate ADC and ADC-target parameters with different drug loads are required. In particular, the system where ADC model parameters do not depend on the drug load is identifiable. The system where parameters linearly depend on the drug load also can be identifiable. Similarly, deconjugation rate of individual ADC species can be identifiable only under specific assumptions on how deconjugation rate depends on the drug load; the individual ADC deconjugation rates cannot be estimated from the typically available data.

Conclusions: Michaelis-Menten approximation of the TMDD model can be used to describe the interaction of ADC with the target when internalization rate is fast. Assumptions that describe dependence of the ADC parameters on drug load are necessary to make the system identifiable. In particular, the system with ADC parameters linearly dependent on the drug load can be identifiable.

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IV-14 *Bill Gillespie* From Evidence Synthesis to Trial Optimization: The adsim Package for Model-based Simulation in Alzheimer's Disease

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Objectives: Model-based drug development is ideally characterized by both comprehensive synthesis of available evidence as well as realistic simulation of future scenarios. To this end, a disease-drug-trial model for Alzheimer's Disease has been developed based on joint modeling of literature meta-data and individual patient data, summarizing available evidence with regard to rates of natural progression, placebo effects, and drug effects for marketed therapeutics [1,2]. Our objective was to facilitate the broad use of this model for the purpose of clinical trial simulation.

Methods: An R package was developed to provide a flexible framework for trial simulation based on the fitted model. The starting point for all package operations is a data matrix representing the posterior samples from the fitted model. Trial simulation proceeds by successively applying three core functions that "recruit", "randomize", and "run" the trial. The "recruit" function is used to generate covariate settings for individual patients, optionally using an included covariate imputation model. The "randomize" function is used to assign treatment sequences. Finally, the "run" function generates longitudinal response data for each individual, based on model-estimated parameters as well as user-specified treatment properties. Additionally, a function is provided to utilize a fitted drop-out model to generate missing data patterns. The robustness of the package design was assessed using several disparate use cases.

Results: The package architecture was sufficiently robust to accommodate all three attempted use cases: a 12 week cross-over design for assessing proof of concept of a symptomatic agent, an 84 week parallel group design for assessing efficacy of a disease modifying agent, and a 91 week delayed-start design for assessing efficacy of a disease modifying agent. Simulation-based estimates of operating characteristics were in approximate agreement with theoretical results in cases where the latter were available (e.g. simulation based estimates of assurance [4] were in approximate agreement with theoretical estimates of power for parallel group designs). The adsim package has also been used to explore trial designs in a real development program [3].

Conclusion: The adsim package enables simulation of a diverse class of clinical trial designs in Alzheimer's Disease, based on a comprehensive synthesis of available evidence.

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IV-15 *Pascal Girard* Simultaneous Ocular Adverse Event and Treatment Discontinuation Model of Pimasertib

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Objectives: Pimasertib is an oral inhibitor of MAPK/ERK Kinase, currently developed for treatment of pancreatic cancer and melanoma, that was given to patients with solid tumors and hematological malignancies in 2 phase I dose escalation studies. All patients were monitored for tolerability (diarrhea, skin rash, ophthalmology, etc). Since ocular adverse events (OAE) were the main dose-limiting events, the objective of present analysis was to develop a joint model for exposure, OAE and treatment discontinuation (TD).

Methods: Population PK yielded estimates of individual exposure. A proportional odds model, with Markov components, was build for OAE weekly highest grade. The logits of the different cumulative probabilities (P) were a non linear function of AUC accumulating in a KPD compartment [1]. In addition, Cmax was tested as acting either continuously or on 1st month. Other covariates were schedule (QD/BID), hypertension history, comedications and demographic covariates. Time to TD and OAE were jointly modeled using Weibull hazard and completely at random, random and informative TD assumptions were tested [2]. All models were built using NONMEM (FOCEI for PK, Laplacian for OAE and TD).

Results: 199 patients, receiving total daily dose ranging from 1 to 255 mg contributed to 4766 PK, OAEs or TD observations. A 3 compartment PK model with 1st order absorption and lag time provided individual Cmax and weekly AUC estimates. OAEs were fitted to the odds model. Markov parameters and AUC mediated through a KPD Emax model were highly significant. BID regimen was associated with a reduction in P(OAE), while higher Cmax was significantly but transiently increasing them on 1st month. For TD, Kaplan Meier curves showed that patients with either OAEs or highest doses were more likely to stay on treatment. Neither the random nor the informative TD models were successful and a simpler TD model with daily dose was found significant.

Conclusion: This analysis showed that OAE are related to higher exposure (AUC, Cmax) and to QD administration. Presumably, BID regimen reduces P(OAE) by reducing peak concentrations, as indicated by higher P(OAE) linked to higher Cmax during 1st month of treatment. High TD rate was found to be dose related, with higher doses leading to less TD. This suggests a potential treatment benefit but needs to be tested further using efficacy data. Model results and simulations are being used to support the choice of dosing regimen for future studies.

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IV-16 *Sophie Glatt* A population pharmacokinetic analysis and pharmacokinetic/adverse events analysis of a sodium channel blocker in healthy subjects.

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Objectives: The objective of this work was to assess the safety, tolerability and pharmacokinetics of an oral sodium channel blocker in healthy subjects and also to explore the relationship between the predicted exposure and adverse events of interest.

Methods: Two Phase I studies were conducted in healthy subjects. The first study was a double-blind, randomized, placebo-controlled dose escalation study. The sodium channel blocker was administered as two different oral formulations. The primary formulation was a spray-dried dispersion (SDD) formulation of the free base. An alternative tosylate salt (TS) suspension formulation was also investigated. 12 single oral doses were investigated from 10 to 2400 mg. The effect of food and of another formulation on the pharmacokinetics of the compound was also investigated. The second study was a double-blind, randomized, placebo-controlled, parallel-group study. Dose regimens of 100 mg, 300 mg and 600 mg twice daily (BID) for 14 days were investigated. The pharmacokinetics were characterized with the use of a population modelling approach and were described by a two-compartment model with first order absorption and first order elimination. The relationship between the adverse events of interest (severity of paraesthesia/hypoesthesia episodes) and predicted exposure was characterized by logistic regression analysis.

Results: Pharmacokinetic analysis showed a dose dependent effect of the food and of the formulation on the PK of the compound. Logistic regression analysis showed that at exposures that exceeded approximately 21000 ng/mL, the severity of paraesthesia/hypoesthesia events increased and also the percentage of subjects with these events increased

Conclusions: Our preliminary results show that the incidence model described the data well. Further work is ongoing to assess the influence of covariates on adverse events of interest in patients.

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IV-17 *Martin Gnanamuthu Johnson* Title: Pharmacokinetic-Pharmacodynamic Modeling of the relationship between D2 receptor occupancy and Catalepsy in Rats: Predicting Extrapyramidal Side Effects in Humans

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Objectives: Dopamine D_2 receptor occupancy (D_2RO) is the major determinant of efficacy and safety in schizophrenia drug therapy (1,2). Excessive D_2RO (>80 %) is known to cause catalepsy (CAT) in rats and extrapyramidal side effects (EPS) in human(3). The relationship between CAT scores in rats and EPS events in human is not yet clear. The objective of this study was to use pharmacokinetic and pharmacodynamic (PK-PD) modeling tools to relate CAT with D_2RO in rats and compare that with the relationship between D_2RO and EPS in human.

Methods: Severity of CAT as an ordered categorical observation was assessed in rats at hourly intervals over a period of 8 hours after antipsychotic drug treatment. D_2RO was predicted using previously developed hybrid physiology-based pharmacokinetic and pharmacodynamic (PBPKPD) models to describe the relationship between drug exposure in plasma and brain with D_2RO in rats for olanzapine (OLZ), paliperidone (PAL), risperidone (RIS) (4,5). An indirect response model (IDR) combined with Markov element was used to describe the relationship between D_2RO and CAT scores. We also compared the probability of CAT with the probability of EPS events in humans at steady-state conditions, as predicted using the PK-PD model proposed by Reddy *et al (6).* The relationship between D_2RO and probability of CAT in rats was related to the D_2RO-EPS relationship in humans using a polynomial equation.

Results: The IDR model with Markov elements explained the CAT data well. K_{in}, K_{out}, RO_{50} and baseline probabilities were estimated with good precision. The relationship between CAT scores in rat and EPS scores in humans was elucidated in a quantitative manner. The probability of having EPS for 0% D_2RO is approximately 5%, which shows the effect placebo on EPS. The risk of EPS does not exceed 10% over placebo correlates with less than 86% D_2RO and less than 30% probability of CAT events in rats.

Conclusion: The relationship between D_2RO and CAT scores was elucidated using IDR with Markov elements. A quantitative relationship between CAT as observed in rats and EPS as observed in humans was elucidated and may be used in drug discovery to predict the risk of EPS in humans from D_2RO and CAT scores in rats.

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IV-18 *Daniel Gonzalez* Population Pharmacokinetics of Two Volatile Markers Used for Assessment of Definitive Adherence

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Objectives: The availability of a breath test to measure medication adherence in real-time, either at home or in a clinic, may facilitate medical decision making, streamline clinical trials, and improve therapeutic outcomes. Recent studies indicate that both 2-butyl acetate and 2-pentyl acetate, safe food flavorants, are rapidly converted to volatile alcohol and ketone metabolites which can be measured in breath [1,2]. The goal of the analyses described herein was to conduct a population pharmacokinetic analysis for two volatile markers, 2-butanone and 2-pentanone, measured in exhaled breath, after the oral ingestion of 2-butanol and 2-pentanone.

Methods: Five fasting, healthy subjects were administered a size zero hard gel capsule (Capsugel, Inc., Greenwood, SC) containing 2-butanol (60 mg), 2-pentanone (60 mg), and L-carvone (30 mg) on six separate occasions. Breath concentrations of 2-butanone and 2-pentanone were measured at 0, 5, 10, 15, 20, 30, 45, and 60 minutes post-ingestion of the capsule using a miniature gas chromatograph (Xhale, Inc., Gainesville, FL, USA). A population pharmacokinetic analysis was conducted using the software NONMEM (Version 7.2, Icon Development Solutions, Ellicott City, Maryland) and a first-order conditional estimation method with interaction.

Results: A one-compartment body model with first-order absorption and elimination adequately described the breath pharmacokinetics of 2-butanone and 2-pentanone. For 2-butanone, the typical model estimates for the first-order absorption (KA) and elimination (K) rate constants were 0.034 and 0.129 minutes^{-1}, respectively. Inter-individual variability was moderate and more pronounced for K (73.7% K and 39% KA); whereas the opposite was true for the inter-occasion variability (27.7% K and 62.2% KA). For 2-pentanone, the typical model estimates for KA and K were 0.061 and 0.078 minutes^{-1}, respectively. A similar pattern was observed with the inter-individual and inter-occasion variability. Inter-individual variability was more pronounced for K (56.5% K and 38.7% KA), but the opposite was true for the inter-occasion variability (36.3% K and 85.6% KA).

Conclusions: The results of this pilot study demonstrate that 2-butanone and 2-pentanone could be quantified in breath following oral administration of food flavorants. The availability of a validated method which uses a portable device for detection of these volatile markers can allow for a real-time assessment of medication adherence.

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IV-19 *Linus Görlitz* Physiological modeling of interindividual variability: PBPK-NLME vs. compartimental modeling

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Objectives: The assessment of inter-individual variability is a key aspect in PK modeling which is usually performed using compartmental models combined with covariate mixed effect models. They are not capable of identifying physiological sources of variation. Physiology-based pharmacokinetic (PBPK) models enable a comprehensive simulation of drug pharmacokinetics at the whole-body scale based on drug distribution models and extensive collections of physiological parameters. By integration of specific experimental data, models are used to analyze and represent the key processes leading to the observed behavior and to investigate the expected pharmacokinetics in groups of healthy volunteers or patients by processing population simulations. A combination of nonlinear mixed-effects modeling and PBPK would allow identification of main sources of inter-individual variability.

Methods: We apply a PBPK-model of Theophylline, an anti-asthmatic drug, built in PK-Sim/MoBi [1] combined with a nonlinear-mixed effects model [2] written in R [3] to the data described in [4]. The data contain urine and plasma samples of 8 healthy male volunteers after PO-administration of 185 mg and after IV-administration of 208 mg Theophylline. Each individuals' PBPK-model contains BMI- and age-adjusted organ volumes and blood flows derived from PK-Sims built in database. Starting with a no-random-effects model the NLME-PBPK is iteratively enriched by adding random effects found after visual inspection of the residual plots. The final model is identified if no further random effect can be added to the model (based on p-values).

Results: The approach is capable of identifying a model nicely representing the Theophylline plasma and urine concentrations. Inter-individual variation can be attributed to different glomerular filtration rates, different degrees of enterohepatic cycling, metabolization in the liver and absorption of the PO-administered drug in the GI-tract.

Conclusions: We showed that combining PBPK-modeling with nonlinear mixed effects approaches allows the identification of sources of inter-individual variation. Although generating comparable results on the population variation level, only this approach allows the explanation of this variation which is a highly valuable information for study planning as it e.g. provides hypotheses for population stratification.

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IV-20 *Nathalie Gosselin* Simultaneous Optimization of Sampling Strategies for Parent and Metabolite Data Taking into Account a Body Weight Distribution: Applications to Paediatric Studies

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Objectives: A study design of a drug with an active metabolite must assess the pharmacokinetics (PK) of the parent drug (PG) and its active metabolite (MET) to understand its contribution to the therapeutic effects. The purpose of this study was to determine a trial design aimed of optimizing the precision on PK parameters of a PG-MET model in a pediatric population from age 2-18 years.

Methods: Adult PK data were used to develop a population PK model that links the parent drug (PG) and its active metabolite (MET) with NONMEM. The model included an allometric function with body weight (WT) and a biotransformation rate with the corresponding variability. The apparent clearance (CL/F) of PG and its MET were markedly different. To account of the complexities of the PG/MET model and the covariate distributions, a simulation/re-estimation approach (SIM-RE) was deemed the most appropriate. To reduce the number of the scenarios and iterations, the initial sampling schedule for PG was determined based on the optimization of population Fisher information matrix in WINPOPT using the mean WT values for each age group. The precisions of the PK parameters of PG and its MET, derived from this optimal design were re-assessed using SIM-RE in NONMEM using 50 replicates for each scenario. Realistic weight-age distribution were incorporated into the simulated data for patients 2 to 18 years using a generalized additive model for location scale and shape (GAMLSS)[1] built on available data from CDC[2]. The asymptotic RSE derived from NONMEM covariance step of the 50 replicates were summarized. This procedure was tested for several possible N to determine the minimum number of subjects that would meet the desired precision.

Results: Optimal sampling schedule for the PG from WinPOPT gave RSE on CL/F and central volume of distribution (V/F) of approximately 12% and 23%, respectively (with N=25). The same trial design tested with the simulation and re-estimation approach using NONMEM resulted in similar values for RSE of the PG (i.e., mean [95%CI] 10% [9.4-10.6] for CL/F and of 24% [22.3-25.6] for V/F). The precision obtained with N=36 resulted in RSE (lower than 20%) for CL/F and V/F of the PG and its MET that met FDA recommendation.

Conclusions: Using optimal design software reduces the number of possible time points and accelerates applying the SIM-RE analysis which is the best method that account for the covariate distributions in the target population.

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IV-21 *Verena Gotta* Probability of achieving optimal molecular response to imatinib in chronic myeloid leukemia (CML) patients: Pharmacokinetic/Pharmacodynamic (PK/PD) relationships observed under field-conditions

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Objectives: Imatinib has been increasingly proposed for therapeutic drug monitoring (TDM), as trough concentrations (Cmin) correlate with response rates in CML patients[1]. This analysis aimed to evaluate the impact of imatinib exposure on optimal molecular response[2] rates in a large European cohort of patients followed by centralized TDM[3].

Methods: Sequential PK/PD analysis was performed in NONMEM 7 on 2230 plasma (PK) samples obtained along with molecular response (PD) data from 1299 CML patients. Model-based individual Bayesian estimates of exposure, parameterized as to initial dose adjusted and log-normalized Cmin (log-Cmin) or clearance (CL), were investigated as potential predictors of optimal molecular response, while accounting for time under treatment (stratified at 3 years), gender, CML phase, age, potentially interacting comedication, and TDM frequency. PK/PD analysis used mixed-effect logistic regression (iterative two-stage method) to account for intra-patient correlation.

Results: In univariate analyses, CL, log-Cmin, time under treatment, TDM frequency, gender (all $p<0.01$) and CML phase ($p=0.02$) were significant predictors of the outcome. In multivariate analyses, all but log-Cmin remained significant ($p<0.05$). Our model estimates a 54.1% probability of optimal molecular response in a female patient with a median CL of 14.4 L/h, increasing by 4.7% with a 35% decrease in CL (percentile 10 of CL distribution), and decreasing by 6% with a 45% increased CL (percentile 90), respectively. Male patients were less likely than female to be in optimal response (odds ratio: 0.62, $p<0.001$), with an estimated probability of 42.3%.

Conclusions: Beyond CML phase and time on treatment, expectedly correlated to the outcome, an effect of initial imatinib exposure on the probability of achieving optimal molecular response was confirmed in field-conditions by this multivariate analysis. Interestingly, male patients had a higher risk of suboptimal response, which might not exclusively derive from their 18.5% higher CL, but also from reported lower adherence to the treatment[4]. A prospective longitudinal study would be desirable to confirm the clinical importance of identified covariates and to exclude biases possibly affecting this observational survey.

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IV-22 *Navin Goyal* Kinetic-Pharmaco Dynamic (K-PD) Modeling of a Novel Oral 5-Lipoxigenase Activating Protein (FLAP) Inhibitor for Asthma and its Comparison with a PK-PD Approach

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Objectives: To develop a K-PD model to describe the kinetics of effect of a novel FLAP inhibitor (GSK2190915) on the functional biomarker-cysteinyl leukotriene LTE4, as measured in urine samples. Compare performance of this K-PD model to a corresponding PK-PD model using data from single and repeat dose escalating study in healthy volunteers [1].

Background: K-PD modeling presents an appealing methodology to support clinical drug development especially where it may not be feasible or possible to obtain time course of systemic drug concentrations to correlate with biomarker or clinical endpoints [2-5].

Methods: Data: Serial drug samples (PK) and urine biomarker samples of LTE4 (PD) were available from healthy volunteers receiving 50,150,300,600 or 1000 mg single dose (n=40) and 10,50,150 or 450 mg once daily oral repeat dose (n=32) of GSK2190915 for 11 days.

Model: The PK-PD model was a two compartment PK model with first order absorption and an indirect PD response model with inhibition of rate of synthesis of LTE4. The K-PD model completely ignored the PK data and utilised only PD information. The modeling was performed with NONMEM (NMVI) [6].

Results: The K-PD model described the data with similar efficiency as the PK-PD model. The parameter estimates are presented in the table below. The EDK50 represents the drug's *in vivo* apparent potency at steady state. This EDK50 estimate when adjusted for the systemic clearance is comparable to the IC50 estimate calculated from the PK-PD model. The K-PD model run time was 4 times faster than the PK-PD model.

Parameter	PK-PD Population Estimate (Inter Subject Variability %CV)	K-PD Population Estimate (Inter Subject Variability %CV)
CL (L/hr)	7.7 (52.1)	
V2 (L)	82.2 (65.7)	
IC50 (ng/ml)	25.6 (152.3)	
Kin (pg/mg Cr/hr)	7.83 (63.3)	11.7
Kout (1/hr)	0.213 (28.6)	0.28 (70.8)
KDE (1/hr)		0.03 (107.2)
EDK50 (mg/hr)		0.16 (101.9)
NMVI Run Time (mins)	58	14

Conclusions: This work demonstrates the value of K-PD modeling in providing a good description of kinetics of drug effect even in absence of systemic drug concentrations. The K-PD model for GSK2190915 provides a valuable tool to support its clinical drug development; e.g. paediatric studies where plasma samples may not be available. Certain limitations exist with generalizing the K-PD approach across untested dosing routes or regimens. Diligent use of K-PD methodology may obviate requiring systemic concentrations in clinical studies where appropriate..

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IV-23 *Iztok Grabnar* Enterohepatic Recirculation of Free and Conjugated Silybin Following Administration of a Chewing Gum with Milk Thistle Extract

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Objectives: Silybin is the main ingredient of silymarin, a milk thistle extract, with recognised anti-hepatotoxic and free radical scavenging activity. Due to low oral bioavailability, a new chewing gum device 3TabGum has been developed. Silybin is rapidly metabolised to sulphate and glucuronide conjugates. Enterohepatic recirculation has been previously described; however, pharmacokinetics of the free and conjugated silybin is poorly studied [1]. To characterise bioavailability of silybin from 3TabGum and to better understand its enterohepatic recirculation we studied pharmacokinetics of the free and conjugated silybin in a group of healthy volunteers.

Methods: Fifteen subjects provided 90 blood samples (6 per individual, range 0.5 to 5 h after administration). Total and free silybin A concentration has been determined by LC-MS. The population pharmacokinetic analysis was performed using NONMEM based on previously described quantitative enterohepatic circulation model [2].

Results: Oral clearance of silybin A was 600 L/h, oral volume of distribution was 57.2 L, absorption rate constant was 2.25 h-1, and absorption lag-time was 0.449 h. Elimination clearance of silybin A conjugates was 177 L/h, distribution volume was 12.5 L. 27.9% of silybin A conjugates entered into enterohepatic circulation with a period of sine function of 10.6 h and a shift of 2.69 h.

Conclusion: The model adequately described multiple peaks in plasma concentration of Silybin A and was successfully applied for simultaneous evaluation of free and conjugated Silybin A pharmacokinetics.

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IV-24 *Joachim Grevel* Response type modelling and clinical trial simulation.

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Objectives: Drug development in depression is a particular challenge since high apparent variability in response is obscuring a clear dose-response against placebo. New drugs are often interacting at multiple targets, and it seems appropriate to identify patients that share a common response type. We present a statistical model for response type analysis.

Methods: A between subject model mixture (BSMM) was implemented in Monolix 4.1 [1] that estimated the probabilities of four different response types. The types were: no response, short, long, and continued response. Considering dose as a categorical covariate, the probability distribution of the response type was estimated as a composite of the probability distribution in each treatment arm. The population parameters of the model were estimated using the SAEM algorithm for BSMM. The prediction distribution of the response in each treatment arm was estimated by simulation using the population parameters.

Results: A clinical anti-depression trial was simulated using the first prototype of the clinical trial simulator developed by Inria for DDMoRe [2] with 200 patients being randomly allocated to four equal treatment arms: placebo, 50, 100, and 150 mg. The treatments were administered for 3 weeks and response was simulated up to 8 weeks. Without a response type analysis all three active treatments seemed to be equally effective in comparison to placebo. The distinct probability distributions for the response type under each treatment demonstrated a clear dose-response. The prediction distribution of the response in each treatment group demonstrated the superiority of the 100 mg dose over the two others. Minimal group sizes could be determined according to outcome expectations.

Conclusions: A between subject model mixture estimated the probabilities of different response types in the treatment arms. The response type analysis paired with trial simulation elucidated a dose-response where a standard analysis failed.

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IV-25 *Zheng Guan* Population PK/PD modeling to compare cannabinoid receptor antagonists in the THC challenge test

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Objectives: To explore the PK/PD relationships of 4 cannabinoid receptor antagonists after a Δ9-tetrahydrocannabinol (THC) challenge. To compare the inhibition potential and target site equilibration of these antagonists in the THC challenge test.

Methods: 4 different CB1 antagonists (drinabant (AVE1625), surinabant, rimonabant, and TM38837) were studied in volunteers after multiple administrations of THC. First, the PK models of THC after multiple dosing and of the 4 antagonists after single dose were developed separately. Next, the THC-induced effects, including changes in heart rate (HR), body sway (BS) and visual analogue scale for feeling high (FH) were modeled by a PK/PD link model. Then, the reversal of the THC-induced effects by the antagonists was also quantified by incorporating terms representing the inhibition effect in the model.

Results: Two-compartment models were selected to describe the THC and antagonists' PK profile. For the PD model, HR and BS were modeled using an E_{max} model. FH was first translated into binary data, and then modeled applying logistic regression. The delay between drug concentration and drug effect was described using a biophase compartment [1] [2]. The inhibition potential (IC_{50}) to reverse the effects of the THC challenge was compared based on the differences in THC EC_{50} shifts and equilibration half-lifes among the antagonists. The compounds showed marked differences in their IC_{50} and penetration half-life for the PD variables. The estimated IC_{50} of HR, BS and FH for the 4 antagonists varied from 9.13 to 438ng/ml, 12.7 to7560ng/ml and 12.1 to 376ng/ml respectively.

Conclusions: PK/PD models could be used to predict the concentrations and HR, BS, and FH profiles of THC alone and with antagonists. Modeling also provided quantitative insights for understanding the target site equilibration and antagonizing potency of antagonists working on the cannabinoid system.

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IV-26 *Ivelina Gueorguieva* Development Of Integrated Pharmacokinetic/Pharmacodynamic (PK/PD) Model For The Novel TGF- β Inhibitor LY2157299 Monohydrate: Preclinical To Phase II

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Objectives: To prospectively identify a safe therapeutic window, based on a PK/PD model, for administration of the novel oral TGF-b inhibitor LY2157299 monohydrate. This PK/PD model was updated after completion of each cohort during the First-in-Human Dose (FHD) study. Simulations of population plasma exposures and biomarker responses in tumor were performed, and optimal sampling windows for future trials in glioblastoma and other cancer populations were calculated. Exploratory Bayesian inferences with exposure, biomarker and tumor size change were also carried out.

Methods: The PK/PD model was updated after completion of each cohort during the FHD study. The flexible design, with dose escalation starting at a total daily dose of 40 mg and increasing up to (potentially) 360 mg, allowed continuous assessment of PK variability by recruiting the required number of patients in each cohort. NLME analysis, with exposure, target-linked biomarker and tumor size under Bayesian inference, were performed in WinBUGS [1] with informative priors on biomarker and vague priors on exposure and tumor size. Component WBDiff, with "Adjust" procedure was used.

Results: During the course of the FHD study no medically significant safety issues were observed and no dose limiting toxicities were established. Based on 30% inhibition of pSMAD [2], biologically effective exposures were anticipated to be reached from Cohort 3 (160 mg) onwards. Additionally, doses above 360 mg/day were predicted to have an unacceptable risk of an individual patient exceeding a potentially toxic exposure. Therapeutic widow was identified to be between 160 and 300mg/day [3]. We predicted, based on clinical exposure, that doses above 300 mg/day to have an unacceptable risk of an individual patient exceeding a potentially toxic exposure.

Conclusions: A therapeutic window for the clinical investigation of LY2157299 in cancer patients was defined using a targeted PK/PD approach, which integrated translational biomarkers and preclinical toxicity. Using modelling can help define a therapeutic window for other TGF-beta inhibitors. Further, integrating exposure, biomarker and tumor size change in the same model, using Bayesian inference, can provide insights for future drug development in Phase 2 and 3 studies.

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IV-27 *Monia Guidi* Population Pharmacokinetics of Risperidone and 9-hydroxy-risperidone in psychiatric patients.

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Objectives: A therapeutic range has been proposed for risperidone (RISP) and 9-hydroxy-risperidone (9OHRISP). Their pharmacokinetics is subject to a high inter-variability, mainly due to polymorphic enzymes, which can contribute to the variability of treatment response and sides effects. The aim of this analysis was to characterize the population pharmacokinetics of RISP and 9OHRISP, to test the influence of genetic polymorphism along with non-genetic factors on drug and metabolite levels and to compare the active moiety (RISP + 9OHRISP) expositions between the metabolic groups.

Methods: A one-compartment model with first-order absorption and elimination was used to describe the pharmacokinetics of both RISP and 9OHRISP, with linear metabolisation from drug to metabolite (NONMEM®). Total RISP (CL_{RISP}) and 9OHRISP ($CL_{9OHRISP}$) clearances, drug over metabolite concentrations ratio (D/M), drug and metabolite AUC_{0-24} were derived from the model. The AUC_{0-24} of the active moiety was obtained by summing RISP and 9OHRISP AUC_{0-24}. Co-administered drugs and demographic, clinical variables, CYP2D6 phenotypes and genetic polymorphisms in CYP3A4 rs4646437 C>T, CYP3A4*1B, CYP3A5*3, CYP3A7*1C, POR rs1057868 (*28 C>T), PXR rs7643645, PXR rs1523130 and PXR rs2472677 were tested as covariates.

Results: A total of 144 concentrations of both RISP and 9OHRISP were available from 126 patients. Among all the evaluated covariates, CYP2D6 phenotype had the most significant impact on both drug elimination (k_{20}) and metabolism (k_{23}) rate constants, which was also affected by CYP2D6 inhibitors. These covariates explain altogether 29% and 54% of the interpatient variability in k_{20} and k_{23}, respectively. No difference between CYP2D6 intermediate (IM), extensive (EM) and ultra (UM) metabolizers were observed. CL_{RISP} and D/M ratio were estimated to be respectively 4.9 L/h and 2.82 in PM and 22.2 L/h and 0.27 in IM/EM/UM patients. The AUC_{0-24} of the active moiety derived by simulation of the final model was 1270 ng·h/ml (90%PI: 370-2760 ng·h/ml) for the CYP2D6 PM vs. 890 ng·h/ml (90%PI: 320-1570 ng·h/ml) for the IM/EM/UM ($p< 0.001$).

Conclusions: CYP2D6 polymorphism accounts for the majority of the variation in risperidone and its active metabolite drug levels. The significant difference found in the active moiety exposure between poor and intermediate or good metabolizers might explain reported higher rates of side-effects and drop-out in risperidone poor metabolizers [1].

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IV-28 *Emma Hansson* PKPD Modeling of Predictors for Side Effects and Overall Survival in Patients with Gastro Intestinal Stromal Tumor Treated with Sunitinib

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Objectives: To describe the association between sunitinib exposure, candidate biomarkers (VEGF, sVEGFR-2, sVEGFR-3, sKIT) and side effects (myelosuppression, hypertension, fatigue and hand-foot syndrome) by the development of longitudinal pharmacokinetic-pharmacodynamic (PKPD) models. A further objective was to investigate relationships between side effects and overall survival (OS) in a model based analysis.

Methods: Neutropenia was well characterized by a semi-physiological model [2] and hypertension with an indirect response model [3]. Proportional odds models with a first order Markov model [3,4] described the time-course of the incidence and severity of fatigue and hand-foot syndrome (HFS). The relative change in sVEGFR-3 over time best described myelosuppression, fatigue and HFS. Hypertension was best predicted by sunitinib exposure. Baseline tumor size, neutropenia and the relative time-course of diastolic blood pressure (dBP) were identified as predictors of OS using a parametric time-to event model with a Weibull distribution.

Results: Neutropenia was well characterized by a semi-physiological model [2] and hypertension with an indirect response model [3]. Proportional odds models with a first order Markov model [3,4] described the time-course of the incidence and severity of fatigue and hand-foot syndrome (HFS). The relative change in sVEGFR-3 over time best described myelosuppression, fatigue and HFS. Hypertension was best predicted by sunitinib exposure. Baseline tumor size, neutropenia and the relative time-course of diastolic blood pressure (dBP) were identified as predictors of OS using a parametric time-to event model with a Weibull distribution.

Conclusions: The relative change in sVEGFR-3 over time was identified as a predictor of the occurrence and severity of myelosuppression, fatigue and HFS following sunitinib treatment. Furthermore, sunitinib induced elevation of dBP and neutropenia were identified as predictors of OS in GIST. The developed model has a potential to be used for early monitoring of treatment response thereby facilitating dose individualization.

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IV-29 *Eva Hanze* Comparison of longitudinal data analysis to end of treatment data analysis when evaluating precision in dose-exposure-response in neuropathic pain studies.

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Objectives: In neuropathic pain, the primary endpoint for detecting the presence of dose-response has typically been the end of treatment (EOT) response in the Numeric Rating Scale (NRS) [1]. The objective of this simulation study was to evaluate the precision in the dose-exposure-response relationship when using change from baseline at end of treatment as compared to when longitudinal data, i.e. all individual data from all time points are used. In addition the impact of introducing an effect delay in the longitudinal model was evaluated.

Methods: For the longitudinal data analysis a simulation model was developed based on placebo-response (NRS) data from a phaseIIa study in patients with Painful Diabetic Neuralgia. For both the longitudinal and EOT model an assumed dose-exposure-response relationship was applied with a sigmoid E_{max} model driving the response. The estimation models were simplified compared to the simulation model and was not fully identifiable. A no effect model, a linear model, an E_{max} and sigmoid E_{max} model was fitted to data and model selection was based on likelihood ratio test. Different study-designs with varying number of dose arms and number of patients were evaluated. For the longitudinal analysis, a direct response model was compared to a model with a time-delay in response reaching maximum effect half-way in the study. The precision in dose-exposure-response was evaluated by estimating the percentage of studies with an estimated delta NRS within 0.7-1.3 of given a true effect (simulated effect) of delta NRS equal to 1.

Results: In a simulated study with 4 dose arms and 54 patients in each dose arm the precision in dose-exposure-response was increased from 33% to 97% when using longitudinal data as compared to EOT. Introducing a time-delay in the efficacy reduced the precision from 97% to 83%.

Conclusions: Including all time point of efficacy assessments increased the precision in dose-exposure-response to a large extent. When performing a simulation based evaluation of a longitudinal analysis it is important to identify considerations that can lead to overestimating the precision.

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IV-30 *Lutz Harnisch* Determining the Pharmacokinetic (PK) Profile of Sildenafil in One Month to One Year Old Pediatric Pulmonary Arterial Hypertension (PAH) Patients Using Interpolation of Two Population Pharmacokinetic Models of Sildenafil in PPHN population (3 to 10 Days Old) and in Pediatric PAH population (1 to 17 Years Old)

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Objective: To predict the sildenafil PK in children with PAH 1 to 12 months old and to derive corresponding dosing recommendations.

Methods: Sets of predicted PK exposure data were generated in children 1 to 12 months old by two PK models developed previously: 1) a Persistent Pulmonary Hypertension of the Newborn (PPHN) PK model (1) (11 hours to 10 days old) to project forward to 1 year and 2) a PAH PK model (2) (1 to 17 years old) to project backwards to 1 month.
To qualify either model for selection, two simulation schemes were conducted: 1) a weight based regimen (0.4 to 4 mg/kg), commonly used in clinical practice; and 2) a fixed dose regimen (2 to 20 mg). The ontology of CYP3A, responsible for sildenafil clearance, provided additional scientific basis for the model selection. The results were compared to the PPHN PK exposure at one month, and the PAH PK exposure at one year, with the better PK model chosen based on the closeness of its generated PK exposure to these two reference points. A sensitivity analysis with alternative models and a limited external validation were performed to justify the model selection. The selected model was finally used to derive the dose recommendation for pediatric PAH patients, one month to one year old.

Results: Under the two simulation schemes, the CL/F and Css values extrapolated back to 1 month, using the PAH PK model, were very close to the 1 month values predicted by the PPHN PK model; whereas the CL/F and Css values extrapolated to 1 year from 1 month by the PPHN PK model deviated substantially from the 1 year values predicted by the PAH PK model. Hence, the PAH population PK model was chosen to predict the PK for children from 1 month to 1 year. Subsequently, two dose regimens, 1.2 mg/kg or 7 mg TID, were proposed for the treatment of PAH pediatric patients from one month to one year old as they would predict to produce a similar exposure compared to the labeled dose in PAH pediatric patients. The sensitivity analysis revealed that if the alometric scaling would have been used, there were no substantial differences between the selected model and alternative scaling methods. A limited external validation using data extracted from literature (3) showed that the selected model described the observed data quite well.

Conclusions: The PAH PK model adequately predicts the sildenafil PK in PAH patients aged one month to one year. Using this model, an oral dosing regimen of 1.2 mg/kg TID or a fixed dose of 7 mg TID can be recommended for this age group for the treatment of PAH.

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IV-31 *Tomi Hendrayana* Population pharmacokinetic (PK) model for fluorouracil (5-FU) accounting for irregularities in infusion rate

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Objectives: To develop a population PK model of 5-FU accounting for deviating infusion rates at the end of infusion and identify potential covariates explaining PK variability of 5-FU exposure during continuous intravenous (c.i.v.) infusion.

Method: A total of 1023 plasma concentrations from 93 patients after administration of 5-FU c.i.v for more than 18 hours, were analyzed using NONMEM 7.1.2. 5-FU concentrations were determined using HPLC or immunoassay. Population PK parameters were estimated, a flexible infusion rate was included and potential covariates such as sex, age, BSA and dose were tested. Model evaluation was performed using visual predictive checks, bootstrap methods and by Bayesian prediction of 272 plasma concentrations from 25 patients.

Results: A one-compartment model was successfully fitted to the data. Since in clinical routine deviations from the infusion rate frequently occur at the end of infusion, a flexible infusion rate was introduced during the last 10% of the infusion duration leading to a smaller objective function value. Sex was the only covariate found: Clearance (CL) of female patients was estimated to be 74% (95% CI: 63-87%) of male patients' CL. The inter-occasion variability (IOV) of CL was 13.3% (95% CI: 9.3-17.1%) and the inter-individual variability (IIV) of CL was 35.4% (28.4-41.5%). The fact that IOV of CL is lower than IIV suggests that 5-FU target exposure may be achieved by adapting the dose in subsequent cycles based on measured plasma concentrations from previous cycles. Model evaluation and Bayesian estimation using the estimated population PK parameters predicted individual plasma concentrations with satisfactory precision.

Conclusion: Accounting for irregularities of infusion rates is a promising approach to improve estimation of PK parameters of 5-FU during continuous intravenous infusion. Our model should be further evaluated for its potential to individualize 5-FU dosing maximizing efficacy and minimizing toxicity.

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IV-32 *Emilie Hénin* A latent-variable model for Sorafenib-induced Hand-Foot Syndrome (HFS) in non-selected patients to predict toxicity kinetics according to sorafenib administrations

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Introduction & Objectives: Sorafenib is a multi-kinase inhibitor, targeting especially Ras-ERK and VEGFR pathways, for the treatment of advanced renal cell carcinoma (RCC) and unresectable hepatocellular carcinoma (HCC). Sorafenib was found to induce cutaneous, hematological and metabolic toxicities. Hand-Foot Syndrome (HFS) is characterized by an inflammation of the skin on palms and soles. Its physiopathological mechanism has not been fully understood yet, but several hypotheses suggested the accumulation of a toxic compound in skin cells. The objective of our work was to propose a physiologically coherent model for the sorafenib-induced HFS on a long-term basis in non-selected patients and to quantify the risk dynamics, linked to sorafenib doses.

Patients & Methods: 89 patients treated with sorafenib were unselectively considered for the modeling work. Treatment duration, sorafenib regimen and number and frequency of HFS observations were highly variable.
A non-linear mixed effect model was built to link sorafenib administrations to the risk of each HFS score. The drug, whose PK was described by a saturable absorption one-compartment model as proposed by Hornecker et al, was considered as impacting the kinetics of a latent variable (LV). The probability of each HFS score is computed from a probit function of the LV level and corresponding threshold parameters. Parameters were estimated in NONMEM7.1.2. Model evaluation was driven by goodness-of-fit and simulation-based diagnostics, using Xpose package in R.

Results: A physiologically coherent model, relating sorafenib administrations and, per se its exposure, to HFS dynamics has been built. The latent variable can be interpreted as an unobserved quantity (e.g. a non-identified biomarker), which would be directly related to the resulting HFS score. The latent variable has a half-life of 7 days, whereas sorafenib has a plasma half-life of 35 hours. Our model allows taking into account the differences between the kinetics of the drug concentration, and the kinetics of the toxicity. HFS toxicity is of great inertia: HFS development and resolution are generally slow processes compared to sorafenib kinetics.
Understanding the dynamic relationship between drug administrations and an induced adverse event is essential to control toxicities and adequately adjust treatment modalities. A pharmacokinetic-pharmacodynamic model for sorafenib-induced HFS can be used as an early predictor of severe toxicity risk in patients.

IV-33 *Stefanie Hennig* Pharmacokinetics of tobramycin do not differ in patients with and without cystic fibrosis

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Objectives: While several studies have examined the pharmacokinetics (PK) of tobramycin in patients with cystic fibrosis (CF) (1-3), there is no common consensus on the following questions: do the PK of tobramycin differ in patients with and without CF; if so, can PK differences be explained by patient characteristics?

Methods: To answer these questions, a PK meta-analysis was undertaken of data from adults and children with and without CF, who received tobramycin by short intravenous infusion or bolus. A population PK approach was employed, utilising NONMEM 7, to establish PK parameters and identify potential covariates to explain between subject variability. Data were available from 4 published studies (3-6) and collected at 3 additional sites (Royal Children's Hospital, Brisbane Australia; Cincinnati Children's Hospital, Cincinnati, USA; and Gartnavel General Hospital, Glasgow, UK). Data from 732 patients were included providing 5605 tobramycin concentration-time points from 0.17 to 15 hours post-infusion.

Results: Tobramycin disposition was best described by a two-compartment model with first-order elimination. Patient gender significantly influenced tobramycin clearance (CL) and volume of the central compartment (Vc). CL was 7.4 L/h/70kg and 9.5 L/h/70kg and Vc was 21.4 L/70kg and 27.3 L/70kg in females and males, respectively. Inter-compartmental clearance (Q) and peripheral volume of distribution (Vp) were 0.486 L/h and 4.9 L respectively. Lean body weight (LBW) was superior to total body weight as a descriptor of CL (allometrically scaled with estimated exponent of 0.85) and of Vc (fixed exponent of 1). Patient age (modelled using a piece-wise linear model with a breakpoint at 18 years) and creatinine clearance (modelled using a power model) were also included as significant covariates in the final model. CF as an independent disease specific factor was not significant at any stage during covariate model building on CL, Vc or Vp. Model residual error was 20.5%. The final model showed excellent predictive properties in a VPC and no flaws in GOF plots.

Conclusions: The PK of tobramycin does not differ significantly in CF patients compared to patients without CF when subject age, LBW, gender and renal function are taken into consideration. Any differences in tobramycin dosing between CF and non-CF patients should be based on differences in expected pathogen sensitivity and can be optimised using an efficacy/toxicity utility function(6).

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IV-34 *Sarapee Hirankarn* Pharmacokinetics Of High-Dose Methotrexate In Children With Cancer: A Mechanism Based Evalution Of Clearance Prediction

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Objectives: The current management of high-dose methotrexate (HDMTX) therapy typically involves a complex process to reduce toxicity. Nonetheless, the incidence of life-threatening toxicity continues to occur in approximately 1%. Better understanding of MTX pharmacokinetics (PK) could be helpful in improving the management of MTX therapy. The objectives of this analysis were 1) to develop a population pharmacokinetic model of HDMTX in pediatric cancer patients from routine clinical data and 2) to evaluate the predictable components of variability in MTX PK.

Methods: A total of 956 concentrations collected from 56 patients administered MTX by IV infusion of 1 to 12 g/m2 over 20 min to 24 h). Data were analyzed using NONMEM® 7.2. A two compartment model was parameterized in terms of clearance (CL), central volume of distribution (V1), intercompartmental clearance (Q) and peripheral volume of distribution (V2). Size related differences in CL, V1, Q and V2 were predicted by theory based allometric scaling using total body weight (TBW) and fat free mass (FFM). Creatinine clearance (CLcr) was predicted using the Schwartz formulae. CL was split into a component that varied with urine pH (renal clearance tubular, CLtub) and a component that varied with renal function (renal clearance glomerular, CLgfr) predicted from the ratio of CLcr to normal glomerular filtration rate based on age, TBW and FFM. Random between subject (BSV) and between occasion variability (BOV) were estimated assuming log-normal distribution of the CL, V1, Q and V2. The covariance between CL, V1, Q and V2 for BSV and for BOV were estimated. Residual unidentified variability was described by a proportional residual error model.

Results: CL were predicted by TBW and renal function. There was no significant improvement from using urine pH to predict clearance. The population mean parameters (%RSE) for CLtub, CLgfr, V1, Q, and V2 were estimated to be 19.0 (19.1%) L/h/70kg, 5.4 (28.6%) L/h/70kg, 145.0 (20.8%) L/70kg, 0.9 (26.1%) L/h/70kg and 22.3 (33.7%) L/70kg, respectively. The BSV in CL was 65% and BOV in CL was 56%. 20% of total population variance in CL (BSV and BOV) was explained by differences in TBW. Only 3% of variance in CL was explained by differences in renal function.

Conclusion: TBW but not body composition differences can predict some of the differences in MTX clearance. CLcr has no clinically relevant value in predicting MTX clearance in a typical population requiring HDMTX.

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IV-35 *Richard Höglund* A population pharmacokinetic model of piperaquine in pregnant and non-pregnant women with uncomplicated P.falciparum malaria

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Objectives: Pregnancy has been associated with an increased risk of contracting a malaria infection and with higher risk of severe malaria. The pharmacokinetic properties of many antimalarials are also altered during pregnancy, often resulting in a decreased drug exposure. Piperaquine is a promising antimalarial partner drug used in a fixed-dose combination with dihydroartemisinin. The aim of this study was to investigate the population pharmacokinetics of piperaquine in pregnant and non-pregnant Sudanese women with uncomplicated *P. falciparum* malaria.

Methods: Patients received a standard dose regimen of the fixed oral piperaquine-dihydroartemisinin combination treatment. Dense plasma samples were collected and analysed using a previously published LC-MS/MS method. Data from 12 pregnant and 12 non-pregnant women were analysed using non-linear mixed effects modelling. A Monte Carlo Mapped Power (MCMP) analysis was conducted based on a previously published study to evaluate the power of detecting covariates in this relatively small study population.

Results: A three-compartment disposition model with a transit-absorption model described the observed data well. Body weight was added as an allometric function on all clearance and volume parameters. A statistical significant difference in terminal half-life between pregnant and non-pregnant women was found, but there were no differences in total drug exposure. The MCMP analysis indicated a minimum of 13 pregnant and 13 non-pregnant women to identify pregnancy as a covariate on relevant pharmacokinetic parameters. Pregnancy was therefore evaluated as a categorical and continuous covariate (i.e. estimate gestational age) in a full covariate approach.

Conclusions: The population pharmacokinetic properties of piperaquine were well described by a three-compartment disposition model in pregnant and non-pregnant women with uncomplicated malaria. The full covariate approach resulted in no major difference in piperaquine clearance and post-hoc estimates of piperaquine exposure were similar in the two groups. Data presented here is reassuring and do not warrant a dose adjustment on account of pregnancy in this vulnerable population.

IV-36 *Nick Holford* What is the between cycle variability in methotrexate clearance?

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Objectives: High dose methotrexate (MTX) is administered on repeated occasions known as 'cycles'. Individualization of future doses based on a target area under the curve has been shown to improve survival. BOV determines the size of the unpredictable variation in PK between cycles. In 8 previous reports only the BOV for CL was estimated (in one BOV for V1 was also reported but without correlation with CL). BOV estimates were 12%, 16.6%, 13.3%, 8.2%, 13.3%, 13.2%, 17% and 0%. The objective was to evaluate the reliability of these estimates.

Methods: Using data from 56 children with cancer three pharmacokinetic models were selected for a simulation study. The three models are a model including BSV and BOV and their covariance (Full model), a model including BOV only on CL and without any covariance (BOVCL model as used in literature reports), and a model that estimated BOV for CL, V1, Q and V2 but without covariance between BSV or BOV parameters (BOV4 model). Details of the full PK model are described elsewhere (1). The full model MTX parameters including BSV and BOV and their correlations was used to simulate 100 data sets using the same covariates and sampling times as in the original data. A parametric bootstrap was performed with each of these data sets by fitting the Full model and the two simpler models (BOVCL and BOV4).

Results: Using the full model, the estimate of BOV for CL (56%) was accurately estimated (bias 2% larger variance) but seriously underestimated when BOV in the other PK parameters was ignored (BOVCL=91% smaller variance) or if covariance in BOV was ignored (BOV4=71% smaller variance). The empirical Bayes estimate of BOV for CL was 35% when each occasion was treated as if it came from a different subject. When the BOVCL model was applied to the original data set the BOV in CL was estimated to be 16%. The residual error parameter was estimated with negligible bias with the Full model but was overestimated with the simpler BOVCL (75% larger variance) and BOV4 (49% larger variance) models.

Conclusions: We conclude that literature estimates of BOV of CL are substantial underestimates of the true BOV. The BOV values overestimate the usefulness of estimating CL during one cycle of MTX in order to predict the dose needed to achieve a target exposure in subsequent cycles.

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IV-37 *Andrew Hooker* The Kaplan-Meier Mean Covariate plot (KMMC): a new diagnostic for covariates in time-to-event models.

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Objectives: When building time-to-event (TTE) models it is often difficult to screen for covariates (or predictors) and it can be especially challenging to understand, and illustrate, how covariates should be included in the model. For example, to understand the influence of a continuous covariate, one might stratify the covariate and plot multiple Kaplan-Meier visual predictive check (VPC) plots along the various strata. Time-varying covariates represent another challenge that is not well handled by present graphical diagnostics. In this work we present a new graphical tool that can overcome these problems; the Kaplan-Meier Mean Covariate (KMMC) plot.

Methods: The plot is created by computing the mean (or any other function) of a covariate for all of the individuals still in a study at every inflection point of a Kaplan-Meier survival curve. This "running" mean of a covariate that is influential on survival would be expected to increase or decrease as a study progresses. Simulating from a model numerous times will give numerous simulated KMMC curves, and a VPC of the KMMC can thus be created, allowing for comparison between model predictions and the true data. The plot is easily created using the latest versions of PsN [1] and Xpose [2].

Results: KMMC plots for both before and after a covariate is included in a TTE model are shown to identify the covariate effect and show when a model adequately describes that effect.

Conclusions: From a base TTE model all covariates can be screened right away using the KMMC plot. The plot works well for continuous as well as categorical covariates and can easily handle both time-constant and time-varying covariates. The KMMC plot can filter out or stratify individuals that are censored in the study so that covariates influencing both censoring and event can be visualized.

Acknowledgement: This work was part of the DDMoRe project.

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IV-38 *Daniel Hovdal* A mechanism-based population model for estimation of system parameters, vehicle effects and drug-induced body weight changes in diet induced obesity mice

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Objectives: To present a mechanism-based turnover model of body weight change in diet induced obesity (DIO) mice. The model discriminates between system parameters, handling effects (e.g. stress) and drug parameters (affinity, capacity).

Methods: Growth curves of body weight gain were obtained in mice after varying periods on different diets and vehicle and drug (Taranabant) treatment. The drug doses ranged from 0.2 to 20 µmol/kg. The drug exposure was modeled using a two-compartment model with first order absorption. The derived pharmacokinetic parameters were then fixed in the subsequent PKPD analysis of body weight data. Total body weight was analyzed simultaneously with body composition data derived from Dual Energy X-ray Absorptiometry (DEXA) determinations. The mechanism-based turnover model included a first order growth of lean body weight moderated by a physiological limit and a peripheral compartment of tissues readily induced by diet. The vehicle effects were added on parameters reflecting energy intake and the drug induced effects were added on the energy expenditure. All analysis was performed using NONMEM.

Results: A total of 1099 mice, including 20482 observations, were used in the analysis. 102 of these mice were vehicle control animals and another 55 mice were given various doses of drug. The population estimate of *in vivo* potency of drug was 37 nmol/L (95%CI 12-61 nmol/L) and the half-life of the rapidly induced cells was approximately 17 days in DIO mice.

Conclusions: The proposed mechanism-based turnover model provides practical means of separating vehicle and drug induced changes in body weight and body composition. The model allows analysis of drug- and vehicle (handling) mediated effects via different routes of provocations, such as drugs impacting food intake or energy expenditure. The model can handle different dietary conditions and can account for mice of different strains, age and body compositions.

IV-39 *Xiao Hu* Comparison of Tolerance Models for Neopterin Elevation Following Interferon beta-1a or PEGylated Interferon beta-1a treatment in Rhesus Monkeys

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Biogen Idec Inc, sponsor of the study.

Objectives: Seven tolerance models were compared to describe neopterin response as a pharmacodynamic marker and to explore the mechanisms of tolerance development in Rhesus monkeys after administration of interferon beta-1a (IFN) or PEGylated IFN.

Methods: PEG-IFN and IFN concentration data and neopterin concentration data were collected in two single-dose PK/PD studies and one multiple-dose toxicity study, from a total of 76 monkeys. A two-compartment PK model and an indirect stimulatory PD model were developed [1]. Seven tolerance models were compared, including indirect moderator tolerance model, direct moderator model, tolerance pool model, tolerance adaptive model, partial agonist model, competitive antagonist model, and noncompetitive antagonist model [2], to select the best model to describe the data. The analysis was performed using nonlinear mixed effect modeling tool, NONMEM 7.2.

Results: All tolerance models fit the data better than the base model which did not include tolerance, with the indirect moderator tolerance model providing the best fit and the tolerance pool model the least fit. Based on the indirect moderator tolerance model, BASE (neopterin baseline) was 2.88 ng/mL, the LOSS (first-order elimination rate) was 0.0095 h^{-1}, the MRT (mean resident time for the delayed neopterin response) was 8.24 h for IFN and 7.85 for PEG-IFN, the K_{TOL} (the rate constant for tolerance compartment) was 0.0593 h^{-1}, the TC50 (concentration in tolerant compartment to achieve 50% of tolerance) was 0.0261, the E_{max} (maximum stimulating effect) was 1710, the EC_{50} (concentration to achieve 50% of E_{max}) was 574 pg/mL for IFN and was 8220 pg/mL for PEG-IFN. The results suggest that the development of tolerance, which resulted in similar neopterin response between PEG-IFN and IFN, is more likely due to negative feedback of neopterin or down-regulation of IFN receptors than due to exhausted neopterin precursor pool.

Conclusion: An indirect moderator tolerance model was selected as the best model from seven tolerance models to describe the development of tolerance in neopterin elevation following IFN or PEG-IFN treatment in Rhesus monkeys.

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IV-40 *An Hyungmi* The Modified Bland-Altman Method to Measure Agreement with Repeated Measures Data using Random Effects Model

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Objectives: This study aimed to modify the Bland-Altman method which is used for evaluating agreement between two measurement techniques with repeated measures data through the random effects model.

Methods and Results: The Bland-Altman analysis using a graphical method to plot the difference of two measurement techniques against the mean for each subject is most frequently used to assess agreement between two techniques. However, with repeated measures data, the standard Bland-Altman method ignores the time profiles of repeated measurements by summarizing them as a mean on each subject [1]. Random effects model using SAS (v.9.2) which considers correlations between repeated measurements in each subject reduced information loss of the standard Bland-Altman method which sums up repeated measurements as a mean.

Conclusions: we analyzed agreement of two measurement techniques using the modified Bland-Altman method which utilized all the data and exposed the time profiles of differences between two measurement techniques. In addition, we outlined how our random effects model could account for the dependent nature of the repeated measures data, and additional explanatory variables, to provide reliable estimates of agreement in this setting.

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IV-41 *Laura Iavarone* A population PK model combined with PK/PD model for analysis of headache in clinical trials

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Objectives: Headache is a common adverse event in clinical studies [1]. The objective of this analysis was to examine the effect of systemic exposure to drug X on the incidence of headaches with the final aim of proposing a better tolerated dosing regimen for future trials with this drug.

Methods: The overall analysis consists of two sections: (1) a population PK model to estimate individual exposure, (2) a PK/PD model to correlate individual exposure to severity and duration of headache. For the development of the PK model a dataset of 168 subjects (from either single and repeat dose studies) was used. For the implementation of the PK/PD model of headache the subset of data coming from the repeat dose studies only have been considered.
Two and three compartment models with first-order and zero order absorption were evaluated. The effect of covariates such as dose, fed/fasted conditions, formulation (either suspension or tablet) and body weight have been assessed.Individual PK parameter (Cmax, AUCt, cumulative Cmax and cumulative AUCt) values have been estimated for the inclusion in the PK/PD model.
The probability of getting a moderate headache was modelled using a mixed effects ordinal logistic regression model with concentration and time as covariates and subject as a random effect.

Results: The disposition kinetics were best modelled with 2 compartments with first order absorption rate constant (ka) and a lag-time parameter (Tlag) to characterize the absorption process. Allometric factors on CL/F and Vc were included in the final model. Different ka have been estimated for suspension and tablet and, within suspension, different ka's have been estimated for dose below and above 600mg. There was a statistically significant relationship between the severity of headache and both concentration and the rate of exposure. It was shown that the probability of a moderate headache increased with concentration but was reduced when concentrations were increased at a slower rate.

Conclusions: The innovative modelling of the relationship between the headache and pK data has provided an understanding of how to improve tolerability through use of titration.

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IV-42 *Vijay Ivaturi* Individual Observation-Shrinkage Scaling of Residuals in a Generalized Least Square Type of Estimation in NONMEM

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Objectives: A generalized least square (GLS) type of approach is often used in regression analysis where the predictions from a first model fit are used to weigh the residuals in a subsequent fit, thus making the estimation of the residual variance component independent of the structural model predictions. This approach is useful when the underlying data distribution is not known or deviates heavily from normality, and thus relies only on the relation between the mean and the variance function (1). The objective of this work is to introduce the concept of an individual data point shrinkage (ISHR) scaled GLS approach (GLS-ISHR) and evaluate this method with respect to different estimation algorithms (FO, FOCE/FOCE-I) , bias of parameter estimates and robustness to residual error model misspecification.

Methods: 100 replicates of sparse (n=2), moderate (n=5) and rich designs (n=11) with 100 individuals each were simulated for estimation from a one-compartment first-order absorption and elimination model with proportional RE (30% CV) and exponential parameter variability (50% CV). This is an extension of a previous work which used GLS where residual weighting from previous model prediction was done by scaling with population shrinkage (GLS-PSHR) (2). Within NONMEM, GLS estimation algorithms were reproduced by fitting sequential models. The IPREDs and PREDs obtained from a first model fit are used to model the residual error in a second step. GLS-ISHR was fit with a mixture (MIX) of IPRED and PRED weighted by average individual data point shrinkage across 30 replicates computed as $\Sigma(1\text{-}SD(IWRES))_{ij}/30$, where $IWRES= (DV_{ij}\text{-}IPRED_{ij})/\sigma_{ij}$; $GLS\text{-}ISHR = PRED_{orig}\cdot iwres\_shrinkage_{orig} + (1\text{-}iwres\_shrinkage_{orig})*IPRED_{orig}$. Parameter estimate bias and robustness to model misspecification were computed for the GLS-ISHR approach, the GLS-PSHR approach and two other GLS methods (GLS-PRED, GLS-IPRED) and was compared to the regular FO/ FOCE/FOCEI estimation algorithms.

Results: In general there was an improvement of parameter precision and bias using the GLS-ISHR approach compared to FO and FOCE, but was not always the case when compared to FOCE-I. Population shrinkage obtained from the model fit was lowered using the GLS-ISHR approach compared to FO, FOCE and FOCE-I. Robustness to model specification was both design and magnitude of misspecification dependent. The greater the deviation of the underlying data from normality, the better GLS-ISHR performed compared to the FOCE(I) methods.

Conclusions: GLS-ISHR improved on all other GLS methods previously reported and was sufficiently robust to residual error model misspecification. Further work on testing GLS methods on real datasets will serve to confirm the robustness of this method.

Acknowledgement: This work was part of the DDMoRe project.

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IV-43 *Masoud Jamei* Model-Based Prediction of Domperidone and Ketoconazole Interaction and its Impact on QTc Prolongation

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Objectives: To investigate the application of modelling and simulation in predicting the extent of the increased proarrhythmic potency of domperidone (DOMP) in the presence of a CYP3A inhibitor, ketoconazole (KETO). Early studies of high-dose DOMP showed QTc prolongation and arrythymias as a side-effect [1].

Methods: Physiologically-Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) models within Simcyp® (v11.1) were used to predict population PK/PD behaviour in healthy volunteers. A library compound file for DOMP was developed within Simcyp using published sources [2, 3]. Subsequently, the observed clinical data [4] were fitted by obtaining optimal values for the intestinal permeability, intrinsic clearance and renal clearance (Parameter Estimation module within Simcyp). DOMP and KETO interaction was simulated replicating the clinical study design of Boyce *et al.* 2012 [5]. ToxComp platform (v1.3) was used to simulate the drug induced QTc interval change (Fridericia correction). In vitro IKr ionic current inhibition data for both drugs were taken from the literature [6, 7], IKs current inhibition was predicted with the QSAR model [8].

Results: The simulation results at the steady state (day 7) following DOMP alone and DOMP+KETO [5], together with the corresponding observed values are summarised in Table 1.

Table 1: Observed vs. Simcyp simulated PK parameters for single DOMP and DOMP+KETO combination.

Dose	Cmax (ng/mL)	SD	Tmax (hr)	SD/Range	AUC (ng*hr/mL)	SD	AUC Ratio	SD
Obs DOMP	23.5	7.4	9.0	0.5 to 14	249	65		
Sim DOMP	23.3	2.6	12.7	0.04	260	38		
Obs DOMP+KETO	67.9	21.1	5.0	0.5 to 14.1	878	268	3.53	
Sim DOMP+KETO	56.7	4.4	12.8	0.03	738	71	2.88	0.44

Predicted concentration values were further utilized to predict QTc [ms] for males (M) and females (F) following DOMP alone and DOMP+KETO combination. The average QTcF[obs] / QTcF[sim] ratios at various time points were close to unity: DOMP-M = 1.11, DOMP-F = 0.97, DOMP+KETO-M = 1.09, DOMP+KETO-F = 0.95.

Conclusion: The combination of mechanistic PBPK and Tox modelling and simulation tools (Simcyp+ToxComp) was able to recover PK and toxicological effect of the single drug and its combination with pharmacokinetically and pharmacodynamically interacting drug (ketoconazole).

ToxComp tends to underpredict QTc for males and overpredict QTc for females what can come from the heart rate variability. In general model-based drug development proved to be a valuable cardiac safety assessment tool.

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IV-44 *Candice Jamois* Pharmacokinetic-Receptor Occupancy Modeling to support Phase 2 Dose Selection

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Objectives: To develop a population pharmacokinetic-receptor occupancy (PKRO) model describing the relationship between receptor occupancy (RO) in a defined region of interest in brain and drug X plasma concentrations in healthy volunteers to support Phase 2 dose selection by simulating the expected receptor occupancy at steady-state.

Methods: Rich PK profiles from the SAD and MAD studies were used to characterize the PK of Drug X in 96 healthy volunteers. Sparse PET measurements collected in 36 subjects in two PET studies were used to investigate the relationship between drug X plasma concentrations and RO following single and multiple doses.
Non-linear mixed effect approach, using NONMEM 7, was used to characterize the pharmacokinetics (PK) and the exposure-RO relationships of Drug X. PK and PD data were modeled sequentially. After qualification of the models, simulations were performed to illustrate in a large population the expected RO after given doses at steady-state, 24 h post dose, as well as the percentage of subjects above defined thresholds of RO.

Results: PK profile of drug X was accurately described by a one-compartment disposition PK model with first-order elimination and a saturable capacity limited binding. The absorption was described by a sequential zero and first-order process. The PKRO was modeled with a slowly reversible receptor binding model. To support the phase 2 dose rationale, RO were simulated following treatment with several doses of Drug X, until PK steady-state. Based on the results of those simulations, one top dose with maximum RO, one dose with maximal RO in approximately 50% of the simulated subjects and one dose with lower RO were proposed. Among the large simulated population, the maximal RO and the percentages of subjects with RO above thresholds ranging from 40 to 80% were impacting the choice of dose for Phase 2.

Conclusion: In the absence of information on RO differences between healthy volunteers and patients, and on the relationship between RO and clinical endpoints, the modeling of RO in healthy volunteers together with assumption on the level of occupancy required to obtain clinical efficacy is still a valuable tool to support phase 2 dose selection. The population PKRO model will be re-evaluated with upcoming data in patients. Data from the phase 2 study will allow the characterization of the link between target RO and clinical efficacy.

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IV-45 *Alvaro Janda* Optimization of pharmacokinetics and pharmacodynamics profiles by optimal control methods. Application to a triptorelin-testosterone PD model.

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Objectives: Triptorelin is a gonadotropin-releasing hormone agonist indicated mainly for the treatment of hormone-dependent prostate cancer. Its testosterone (TST) effects shows a complex dynamic profiles. Based on a semi-mechanistic pharmacokinetic/pharmacokinetic (PK/PD) model already developed[1], the aim of the current work is to derive pharmacokinetic profiles of triptorelin in plasma dealing with optimal TST profiles. This objective is motivated by previous works [2-3] but we apply a more flexible method based on optimal control techniques [4].

Methods: The typical testosterone profile is characterized by an undesired initial flare-up where concentrations of testosterone are greater than baseline (~4 ng/mL). Once testosterone reaches its maximum value, its level decreases to the castration limit (due to a receptor down-regulation phenomena) and keeps below it for a finite period of time. Based on the mentioned PD model, we applied optimal control methods [2] to obtain a pharmacokinetic profile that: (i) minimizes the highest levels of testosterone during the flare-up, (ii) minimizes the time to reach the castration limit and (iii) prolongs the efficacy of the drug (i.e., time below castration limit). This analysis has been performed including the variability in model parameters.

Results: Results form the optimal control analysis reveals that minimum time to reach castration (Tmin_ct) is 19 days, and to achieve Tmin_ct a flare-up of 11 ng/mL is required. Additional results have shown that cab reached at early times of 23 days after drug administration, without almost any flare-up based on a certain PK profile, characterized by a small rate of increase plasma concentration of triptorelin (Tmax = three weeks) up to a 6 ng/mL. Those results together with the value of the CTRP_min descriptor obtained previously [1] allowed to generate an optimal PK profile of triptoreline satisfying the pharmacological imposed constraints.

Conclusions: The optimal control methods is an useful technique that allows to derive from a PD model the desired effect profiles and the corresponding pharmacokinetics to obtain them. Therefore, it can be a very helpful tool to optimized and design new drug formulations.

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IV-46 *Juliette Janson* Population PKPD Modeling of BACE1 Inhibitor-Induced Reduction in Aβ Levels in vivo.

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Objectives: The transmembrane aspartic acid protease BACE1 cleaves amyloid precursor protein (APP) to generate soluble APPβ. The remainder of APP in the cell membrane is in turn cleaved by γ-secretase to form beta amyloid (Aβ). *In vivo*, pharmacologically induced Aβ reduction is dependent on compound- and system-parameters, i.e. potency and Aβ clearance respectively. Preclinical PKPD modeling was applied 1) to gain insight in the time-course between oral dose, plasma and brain exposure and inhibitory effect on Aβ in brain and CSF of novel BACE1 inhibitors as well as system constants, 2) to quantify the *in vivo* potency using population pharmacokinetic and pharmacodynamic (PKPD) modeling, and 3) to investigate the correlation between *in vitro* and *in vivo* potency.

Methods: BACE1 inhibitors were characterized *in vitro* in human SH-SY5Y cells, mouse N2A cells, and in mouse and guinea pig primary cortical neurons (PCN). The PKPD properties of 28 compounds were evaluated *in vivo* using female C57BL/6 mice in single dose, dose- and/or time-response studies (10 compounds). Four compounds were studied in male Dunkin-Hartley guinea pigs. Plasma exposure was converted to free brain exposure using brain exposure, plasma protein and brain binding. Free brain concentrations were used as input to inhibition of brain Aβ production rate. For both species, population modeling of all *in vivo* data was performed using an indirect response model with inhibition on the Aβ production rate to estimate the unbound brain concentration giving 20% inhibition from baseline (IC20%).

Results: *In vitro* potency in human SH-SY5Y cells was correlated to potency in mouse PCN with a 4.5-fold lower IC50 value than in SH-SY5Y cells. *In vivo* BACE1 inhibitors exhibited concentration- and time-dependent lowering of plasma, CSF (guinea pig) and brain Aβ levels. In mouse the population estimate of turnover of Aβ40 in brain was 26 minutes. In guinea pig this population turnover rate was estimated at 1 hour.

Conclusions: A good correlation between mouse and guinea pig *in vitro* and *in vivo* potency and an excellent correlation between mouse PCN and human SH-SY5Y, increased the confidence in using human cell lines for screening and optimization for effect of novel BACE1 inhibitors. The established *in vitro-in vivo* correlations could thereby reduce the number and change design of preclinical *in vivo* effect studies.

IV-47 *Roger Jelliffe* An Improved Population Model Prior for Nonparametric Sequential Interacting Multiple Model (IMM) Bayesian Analysis.

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Obtectives: A current limitation of IMM Bayesian sequential analysis [1] is that the changing parameter distributions which take place during the period of data analysis may lie in a region of the nonparametric population model which has few support points.

Methods: To improve this situation. our group has added extra support points from the augmented population model currently used for our hybrid Bayesian analysis of fixed parameter distributions during the data analysis The hybrid procedure starts with a maximum aposteriori probability Bayesian analysis. Extra support points were added near the MAP Bayesian estimate to form a 4 x 4 grid of support points. This has now been upgraded to 10 x 10 points, with an adjustable percent change between them, ranging from 5 to 20 percent.

Results: This augmented population model now provides a much larger set of points for the changing parameter values of the unstable patient to attach to, and provides a richer set of support points from which to compute the next adjustment of the dosage regimen to achieve the desired target goal most precisely, with minimum expected weighted squared error.

Conclusions: Past versions of this software have tracked drug behavior in patients better that other Bayesian methods [2]. This new improved population model prior enhances this capability.

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IV-48 *Lee Jongtae* Population pharmacokinetic analysis of colistin in burn patients

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Objectives: Colistin is increasingly used as salvage therapy of nosocomial infections caused by multidrug-resistant gram-negative bacteria such as *Psuedomonas aeruginosa* and *Acinetobacter baumannii*. However, the available pharmacokinetic (PK) data of colistin are limited to guide dosing. The aim of this study was to develop a population PK model for colistin in burn patients.

Methods: Fifty patients with burns ranging from 4% to 85% of total body surface area treated with Colistimethate sodium (CMS) were studied. CMS which is hydrolyzed in vivo to the active metabolite was intravenously administered at a dose of 150mg every 12 h. Blood samples were collected right before and at 1, 2, 4, 6 and 8 h after more than five infusions. The population PK model was developed using a mixed effect method (NONMEM, ver. 6.2).

Results: A one-compartment linear PK model for colistin best described the data. Covariates included in the final model were creatinine clearance on the fraction of CMS converted into colistin and body weight on the central volume of colistin. The mean population pharmacokinetic parameters were clearance (5.79 L/h), volume of distribution (53.7 L), the turnover rate of CMS converted into colistin (0.766 - EDEMA x 0.429), the fraction of CMS converted into colistin (1 - 0.203 x EXP(CL_{cr} /120)) with interindividual variability (CV%) of 35.4%, 25.5%, 68.6% and 0, respectively.

Conclusions: The PK of colistin have been characterized for the first time in burn patients after i.v. administration of CMS. The model-fitted parameter estimates may be applied to determine the optimal dosage regimens of colistin in burn patients.

IV-49 *Amita Joshi* A physiologically-based pharmacokinetic (PBPK) approach to evaluate differences in pharmacokinetics between healthy subjects and cancer patients

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Objectives: Simcyp®, a population-based ADME simulator, allows investigating the differences in pharmacokinetics (PK) between different populations by integrating demographic and physiologic data [1-3]. This study is aimed at investigating potential differences in PK between healthy subjects and cancer patients using physiologically-based pharmacokinetic approach.

Methods: Demographic data such as age, sex, body weight, and body surface area and laboratory measurements such as albumin, alpha-1 acid glycoprotein, and hematocrit were collected in ~2100 cancer patients. A custom oncology population profile was built using the observed relationships between demographic variables and laboratory measurements in Simcyp®. The healthy volunteers profile in Simcyp® was used for comparison.

Results: Cancer patients were generally older when compared to healthy subjects age distribution in the Simcyp® healthy volunteers profile. The plasma protein albumin levels were lower and alpha-1 acid glycoprotein levels were higher in cancer patients. The custom oncology profile was used to investigate the differences in PK of two probe drugs, saquinavir and midazolam. The exposure of saquinavir is higher in cancer patients whereas the midazolam exposure was similar in cancer patients and healthy subjects. Differences in saquinavir PK are expected due to altered drug binding because of elevated alpha-1 acid glycoprotein levels in cancer patients. Similarly, lack of differences in midazolam PK supports the hypothesis that the CYP3A activity is not altered in cancer patients.

Conclusions: The above results suggest that the custom oncology profile in Simcyp® can be used to obtain reliable predictions of PK of drugs in cancer patients.

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IV-50 *Matts Kågedal* Improved dose selection for PET occupancy studies

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Objectives: Receptor occupancy can be assessed by Positron Emission Tomography (PET). Since PET measurements are very expensive it is important to ensure that the study is optimized to provide sufficient information based on only a few experiments. Generally, doses targeting 50% occupancy is perceived as most informative. The objective of the present work was to investigate how the doses in a PET-occupancy study should be allocated in order to maximize the precision of the derived relationship between exposure and occupancy dependent on the distribution of specific uptake in the brain.

Methods: Based on each PET-measurement, the partition coefficient, brain/plasma (KPt) can be derived for each region. Displacement of the radioligand from the receptor by a drug competing for the same binding site will result in a reduced KPt. The relationship between KPt and plasma concentration can be estimated by a saturation function where the affinity (Ki) is estimated as a parameter in the model. The occupancy can then be derived from the exposure and the estimated value of Ki. The study design considered included 6 volunteers with three PET-measurements in each volunteer.

The following situations were considered. a) A reference region void of receptors is included in the analysis. b) Two regions with different receptor densities are included. c) A single region of interest is included. In addition different random effects models were investigated. The D-optimal design criterion was compared to Ds with Ki as the parameter of interest. The optimal dose allocation was estimated using the optimal design tool PopED [1].

Results: If a reference region exists the precision of the Ki is less sensitive to the selected doses and no high dose with full saturation is needed. If no reference region exists, doses that result in close to full saturation improve the precision of the Ki estimate. When only a single region is included, near full saturation measurements are essential. With proportional residual error the optimal doses are higher compared to an additive residual error. Ds-optimal designs include more doses near the Ki value as compared to D-optimal designs.

Conclusions: The optimal dose allocation depends on assumptions regarding nonspecific brain uptake, distribution of receptors in the brain and the residual error. Targeting an occupancy of 50% is not always most informative. Ds-optimal design provides a mean to focus on the parameter of interest in the model.

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IV-51 *Friederike Kanefendt* Modeling Sunitinib and Biomarker Response as potential Predictors of Time to Progression in Patients with Metastatic Colorectal Cancer

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Objectives: Sunitinib is a multi-tyrosine kinase inhibitor inhibiting angiogenesis which is essential for tumor growth. The concentrations of several circulating proteins are influenced by sunitinib and may serve as biomarkers in PK/PD models to predict tumor response. The aim of this investigation was the development of PK/PD models to describe the anti-angiogenic response to sunitinib and to identify potential predictors for the time to progression (TTP) in patients with metastatic colorectal cancer (mCRC).

Methods: 21 patients receiving a daily dose of 37.5 mg sunitinib on a 4-weeks on/2-weeks off treatment schedule in addition to FOLFIRI participated in this study. Blood samples were drawn at baseline and every two weeks for two therapy cycles. Sunitinib and the active metabolite SU12662 (the sum is referred to as ‘active drug') concentrations were measured using LS-MS/MS. Both circulating biomarkers, sVEGFR-2 and sVEGFR-3, were determined by validated immunoassays. Furthermore, TTP defined as day from first study medication to first assessment of progression was selected as clinical endpoint. If no information was available data were censored to the last date the patient was confirmed to be progression-free. A sequential PK/PD analysis was performed using NONMEM (version 7.1.2). Potential predictors for TTP were analyzed using Cox regression and a model-based approach.

Results: Biomarker concentration-time courses could be well described by an indirect response model. Minimum concentrations relative to baseline were estimated as 0.63 and 0.59 for sVEGFR-2 and sVEGFR-3, respectively. Concentrations of both biomarkers were highly correlated, however did not predict TTP in this data set. Higher exposure to unbound active drug was instead identified as positive predictor for TTP (HR: 0.49 (95% CI: 0.27-0.88), p=0.013).

Conclusions: The concentration-time profile of both active drug and biomarkers could be well described by the PK/PD model. The extent of biomarker response was comparable with healthy volunteers [1] but did not predict tumor response in patients with mCRC. In contrast, TTP was correlated to active drug pharmacokinetics . However, more patients have to be studied to confirm this relationship.

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IV-52 *Helene Karcher* Therapeutic drug monitoring : modeling to assess risk and benefit for a novel drug used in combination

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Objectives: Therapeutic drug monitoring (TDM) enables to adjust dosage to the needs of a particular patient. It circumvents inter-patient variability in PK though it cannot palliate to intra-patient variability [1]. Its particular usefulness in widening the therapeutic window for a new drug A used in combination was explored trough modeling of Phase II data.
The Phase II trial combined drugs A and B at various levels of fixed doses (drug A) or target concentration ranges (drug B) and explored the efficacy endpoint in terms of event rate. Safety profiles for both drugs had been previously characterized.

Methods:
1. A range of mixed-effects models were fitted to drug A's plasma trough concentration data, including inter-patient variability to characterize the relationship between drug A's dose and exposure. This model was used to investigate TDM feasibility and its impact on PK variability.
2. A mixed-effects exposure – response model was built on longitudinal trough concentrations for both drugs and event rate of the efficacy endpoint. The model extracted the exposure-event probability relationship and took into account inter-patient variability in event probability under same levels of A and B.
3. Simulations using the above models enabled to quantify the benefits of TDM on drug A in terms of PK variability reduction compared to fixed dose regimens. The frequency of dose changes for drugs was also investigated.

Results: A log-linear model structure with a random effect on intercept yielded the best fit of the dose-trough data in terms of AIC and BIC. Inter- and intra-patient variability in drug A troughs was found to change over time. At steady-state, the values were ~64% inter-patient and ~48% intra-patient variability. The smallest possible TDM window for drug A troughs at steady-state was derived from these values.
Event probability was found to clearly depend on drug A exposure in the first trial period. The rarity of late events prevented the establishment of such a relationship at steady-state. While no efficacy gain from increasing drug B levels could be extracted within the explored range, drug B was indispensable to maintain efficacy since higher event rates were observed in a previous trial without B.
A simulation showed that TDM enabled to maintain trough levels within a defined window after only a few dose adjustments. The starting dose of A was found to have an impact on the final trough distribution though it had no impact on the percentage of troughs that remained outside of range at steady state.

Conclusions: Therapeutic drug monitoring was shown to be feasible and useful for drug A in combination with drug B.

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IV-53 *Tatiana Karelina* Kinetic Model of Amyloid Beta Distribution and Allometric Scaling from Mouse to Monkey and Human

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Objectives: Abnormal accumulation and deposition of amyloid beta (Aβ) in the brain is considered one of the causes of Alzheimer's disease. Decreasing Aβ levels in brain could be a potential therapy, it is thus important to understand how Aβ distributes among different compartments. Here we present an updated model, describing Aβ kinetics in mouse and its allometric scaling to monkey and human.

Methods: The model describes three types of Aβ ($Aβ_{40}$, $Aβ_{42}$ and $Aβ_r$, all other forms), which distribute in compartments for brain cells (BC), brain interstitial fluid (BIF), cerebrospinal fluid (CSF), plasma, and peripheral tissues (PT). Aβ is generated in BIF and PT. Aβ concentrations in each compartment change due to transport or degradation. Bulk flow from BIF to CSF and to lymph is also taken into account. All the calculations and fitting were done in DBSolve Optimum software. Most of the kinetic data for model calibration have been obtained in wild-type mouse, so aggregation of Aβ was not considered. Allometric scaling of mouse model was used to describe CSF ^{13}C-Aβ in the monkey and human in the stable isotope labeling kinetic (SILK) studies. The mouse model was also tested against reported CSF and brain Aβ time courses after a dose of a γ-secretase inhibitor (GSI).

Results: The model satisfactorily describes most of the literature Aβ kinetics data. The set of parameters obtained for mouse allowed adequate allometric scaling to monkey and human, with Aβ production fitted for each species. The mouse model qualitatively reproduced the time shift between the effects of the GSI on brain and CSF Aβ, but with additional fitting of some parameters controlling Aβ distribution between BIF and BC. Local sensitivity analysis also has shown that the shape of time course of the brain Aβ concentration is sensitive to these parameters.

Conclusions: Parameter values in the updated model provided better descriptions of existing data. Difficulty in achieving better fitting of the GSI data likely stems from poor understanding of Aβ distribution in brain, partly due to lack of quality data on BC and BIF concentrations. Such information would be important for further improvement of the model.

IV-54 *Mats Karlsson* A full model approach based on the covariance matrix of parameters and covariates

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Background: A full covariate model approach has been presented [1,2] where all parameter-covariate relations of interest to characterise are added into the model as fixed effects and the posterior distribution of these effects are used for decision-making. The approach has several advantages including no bias based on data-driven model selection and rapid model building. However, there are also disadvantages, including: (i) sensitivity to correlated covariates, (ii) non-included parameter-covariate relations may bias estimates of included relations [3], and (iii) model stability may be an issue when parameter-covariate relations to be characterized are many.

Objective: To propose a new approach to a full model characterization that addresses the above-mentioned disadvantages.

Methods: In the proposed approach, selection of covariates of interest to characterize is made without concern regarding their correlation. Covariates are entered into the data set as observed variables, and their distribution are modelled as random effects. A full covariance matrix between random effects for parameters and covariates is estimated together with the other model components. The method was assessed using simulated data where covariate-parameters were defined as fixed effects in a one-compartment pharmacokinetic simulation model. Analyses were made using covariate-parameter relations either as fixed effects ("traditional" full fixed effects model - FFEM) or as a full covariance matrix of random effects (full random effects model -FREM) including both continuous and binary covariates.

Results: The two approaches described data equally well and the decrease in the objective function value was equally large compared to a base model without parameter-covariate relations for models with or without any true relations, and for both continuous and binary covariates. For a 2-parameter (CL, V) and 3 covariate model (modestly correlated covariates, r=0.4), the imprecision in the estimates of the true parameter-covariate relations were typically higher for the FFEM compared to the FFRM by a factor 1.16. This factor increased as the number of covariates and/or correlation increased.

Discussion: The FREM is a promising approach which improves on some shortcomings of the FFEM. It may also serve as a first step in an exploratory analysis as it provides the maximal benefit of the considered covariates to goodness-of-fit.

Acknowledgement: This work was part of the DDMoRe project.

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IV-55 *Nastya Kassir* A Modelling and Simulations Framework to Optimize Paediatric Studies and Facilitate Decision-Making

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Objectives: Paediatric drug development is challenging and unique in several aspects. FDA recently provided new recommendations for designing optimal paediatric studies [relative standard error (RSE) and 90% confidence intervals (CI) <20%]. A modelling and simulations framework was developed to simultaneously determine an optimal pharmacokinetic (PK) sampling strategy and sample size of paediatric subjects that would result in robust PK parameters and ultimately identify a dose level that would result in drug exposure within the targeted range of efficacy and safety of the product.

Methods: The framework consists in the following steps: 1) perform simulations using a population PK model (Trial Simulator®) to determine dose levels that would result in exposure within the targeted range in different age groups, 2) optimize sample size of patients and PK sampling (2 or 3 blood draws) using WinPOPT®, 3) confirm the best study design using a simulation-fitting approach, which accounts for the covariate distribution in the target population, 4) determine the optimal design that provides RSE and CI <20% with the smallest sample size and limited number of PK samplings across age groups.

Results: The framework was used to optimize a paediatric study for a small molecule currently under development. A population PK model including an allometric function was used to predict PK parameters in paediatric patients. Simulations were performed in all age groups (1-2, 2-4, 4-6, 6-8, and 8-12 years) to determine dose levels that would result in drug exposure within the targeted range of efficacy and safety. A total of 25, 30, 40 and 50 subjects between 1 and 12 years were randomly selected and concentrations for the optimal time points (1 and 6 h vs. 1, 4 and 6 h) were predicted with the population PK model. Sampling strategies involving 2 and 3 samples and 25 patients (5 per each age group) resulted in RSE of CL/F and Vc/F with their relative CI <20%.

Conclusions: A modelling and simulations framework was developed to rapidly identify optimal study designs in paediatrics patients and allowed a precise estimation of RSE to ensure robustness of PK parameters and meet FDA's requirements for clinical studies in paediatrics. Although EMA did not provide regulatory requirements to define the level of robustness required in paediatric studies, the above modelling and simulations framework may be considered for optimizing paediatric studies in Europe.

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IV-56 *Takayuki Katsube* Characterization of Stepwise Covariate Model Building Combined with Cross-Validation

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Objectives: We reported on a stepwise covariate model building combined with cross-validation (XV SCM) [1]. This method is useful to determine suitable model size based on prediction error using multiple data subsets.

Methods: The objective of this study is to further characterize XV SCM and make comparisons of estimated model sizes and predictive performance of developed models with other covariate modeling methods, e.g. standard SCM and lasso.

Results: All model building strategies improved the prospective OFV compared to the base model regardless of data set size and number of covariate relations used in the simulation. The prospective performance, in percent of the true-base model OFV difference, was for the small, medium and large data set: 41%, 92% and 99% (non-linear XV SCM), 52%, 91% and 99% (linearized XV SCM), 55%, 92% and 99% (SCM) and 71%, 91% and 97% (lasso) on average. The number of covariates in the final model relative to the true model was on average -0.5 (non-linear XV SCM), -0.04 (linearized XV SCM), -1.3 (SCM) and 2.4 (lasso). The predictive performance of the XV methods was similar regardless of number of splits.

Conclusions: These results suggested XV SCM provides a suitable model size with good predictive performance except for extremely small data and XV SCM using the fewer splits might be a good compromise.

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IV-57 *David Khan* In silico predictions of in vitro growth competition experiments between wild type and resistant mutants of E. coli MG1655 exposed to ciprofloxacin

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Objectives: The developing problem of antibiotic resistance due to overuse of antibiotics is threatening public health. Valuable information on optimal dosing strategies can be obtained from *in silico* models based on *in vitro* time-kill curve experiments [1]. We have previously developed an *in silico* model for *E. coli* MG1655 and three mutants thereof exposed to ciprofloxacin [2]. This model has been expanded to fit three additional mutants and include filamentation effects. The aim of this work was to predict the outcome of competition experiments between *E. coli* MG1655 wild type (wt) and three of the mutants following ciprofloxacin exposure and to predict the time-course of bacterial kill for different dosing regimens.

Methods: Experimental data was obtained from 24h *in vitro* experiments with *E. coli* MG1655 (ΔaraB) in competition with different well characterized MG1655 mutants (MIC of ciprofloxacin 2-12 times the wt) in starting ratios of wt:mutant ranging from 10:1 to 10000:1. Ciprofloxacin concentrations were constant and chosen to be below, between and above the MICs of the wt and the mutant. Bacteria were quantified on MacConkey agar. The *in silico* model included compartments for susceptible, persister, preexisting resistant and filamented bacteria. The drug effect on the susceptible bacteria was described by an Emax-model. The competition experiments were predicted from the model and compared to the observed data. Additionally, predictions of different once- and twice-daily dosing regimens of ciprofloxacin were performed.

Results: The model successfully predicted the time course of bacterial kill and growth in the competition experiments except for the one experiment where the MIC of the wt and the mutant only differed two-fold, and the ciprofloxacin concentration was between the two MICs. For all mutants, dose sizes, half-lives, and wt:mutant ratios, the model predicted once-daily dosing regimens to be as efficient or superior compared to the twice-daily regimens of the same total dose amount in overcoming resistance and resulting in an overall bacteria kill.

Conclusions: The model was shown to adequately predict *in vitro* competition experiments and can thus be a valuable tool in the search for dosing regimens that minimize the growth of resistant mutants existing in a bacterial population. Over a range of doses and half-lives, once-daily dosing was found to be superior over twice-daily dosing by more efficiently suppressing emergence of resistance.

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IV-58 *Frank Kloprogge* Population pharmacokinetics of lumefantrine in pregnant and non-pregnant women with uncomplicated Plasmodium falciparum malaria in Uganda

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Background: Pregnancy alters the pharmacokinetic properties of many antimalarial compounds which might result in lower drug exposure and increased risk of treatment failure. The objective of this study was to evaluate the pharmacokinetic properties of Lumefantrine in pregnant and non-pregnant women with uncomplicated *P. falciparum* malaria in Uganda after a standard fixed oral artemether-lumefantrine treatment (Coartem®).

Methods: Dense (25 samples/patient) venous lumefantrine plasma concentration-time data from 26 pregnant women and 17 non-pregnant women was collected. Sparse (5 samples/patient) capillary lumefantrine plasma concentration-time data from another 89 pregnant women was also collected. The population pharmacokinetic properties were evaluated with different distribution, absorption, error and covariate models. Capillary and venous data was modeled separately and simultaneously using an empirical or semi-mechanistic model structure. The final model was compared to a previously published model of pregnant women in Thailand [1].

Results: Lumefantrine absorption was best described by transit-compartment absorption followed by two distribution compartments and first-order elimination from the central compartment. Capillary and venous data could successfully be modeled simultaneously with both a semi-mechanistic model and a more simplified model using a correction factor for capillary concentrations in the error structure. The simplified model using a correction factor was more stable and with no advantage of a more complicated semi-mechanistic model. However, the correction factor could only be estimated on a population level since no patients were sampled for both venous and capillary plasma. The final model included pregnancy as a categorical covariate on inter-compartment clearance and body temperature on mean transit absorption time.

Conclusions: Lumefantrine concentrations were well described in pregnant and non-pregnant women with uncomplicated *P. falciparum* malaria in Uganda using a population pharmacokinetic approach. The proposed model could successfully link capillary and venous sampling matrices, thereby enabling a comparison of previously published pharmacokinetic studies in different matrices. Lower day 7 concentrations were found in pregnant women compared to non-pregnant women, which might have an impact on treatment efficacy and the development of resistance.

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IV-59 *Magdalena Kozielska* Sensitivity of individual items of the Positive and Negative Syndrome Scale (PANSS) and items subgroups to differentiate between placebo and drug treatment in schizophrenia

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Objectives: In recent years schizophrenia trials suffer from diminishing differences in effects of drug and placebo treatment even for established antipsychotics [1]. While there are multiple factors which can lead to difficulties in differentiating between placebo and drug treatment, one of them could be that the available rating scales, e.g. Positive and Negative Syndrome Scale (PANSS) [2] are not optimal for measuring the effect of drug treatment. The goal of this study was to analyse the responses of the individual items of PANSS and item subscales to drug and placebo treatment in order to find the ones which are most sensitive to differentiate between placebo and drug effect.

Methods: We analysed data from seven clinical trials of different antipsychotics. “Mini-PANSS” scales consisting of the most sensitive items identified in exploratory analysis were created and analysed statistically. The power of these scales to show a statistically significant difference between the placebo and drug treatment was then compared with the power of total PANSS and its positive, negative and general psychopathology subscales. Additionally, pharmacokinetic-pharmacodynamic analysis was performed in order to determine which of these (sub)scales shows the highest drug effect on top of the placebo effect.

Results: All 30 items of the PANSS scale show a therapeutic drug effect. Mini-PANSS scales consisting of items with the largest drug treatment response are somewhat better in differentiating between placebo and drug treatment than the total PANSS. However, the difference between the tested mini-PANSS scales and total PANSS is generally very small.

Conclusions: None of the studied scales can replace PANSS total in the analysis of primary endpoints.

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IV-60 *Elke Krekels* Top-Down Modeling Meets Bottom-Up Modeling: The Physiological and Physicochemical Basis for the Ontogeny of UGT2B7-Mediated Drug Glucuronidation.

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Objectives: Despite the multi-factorial nature of the ontogeny of drug clearance, paediatric population models often describe this process with a limited number of covariates in descriptive relationships. These covariate models quantify the influence of the sum of all underlying physiological changes for a given drug and preliminary proof-of-concept studies suggest that these covariate models can, in specific cases, be used for between drug extrapolations [1,2]. The current study examines the physiological and physicochemical basis of a paediatric covariate model for the ontogeny of UGT2B7-mediated glucuronidation in young children (top-down model) [1,3], by untangling the underlying maturational processes with a physiologically-based model (bottom-up model).

Methods: The physiologically-based modeling software Simcyp version 11 was used to simulate the glucuronidation clearance of morphine and zidovudine, both selective UGT2B7 substrates with intermediate hepatic extraction ratios, in 1000 children younger than 3 years. The main physiological and physicochemical drivers of the ontogeny profile of UGT2B7-mediated in vivo clearance were identified by changing system and drug parameters and evaluating the influence of these changes on the clearance ontogeny profile.

Results: Liver volume and UGT2B7 ontogeny influenced the ontogeny profile of in vivo morphine and zidovudine glucuronidation the most. Of the physicochemical drug parameters, logP and pKa both influenced the magnitude of glucuronidation clearance, but not the ontogeny pattern. A linear relationship was found between the unbound drug fraction, which is influenced by logP and pKa, and the magnitude of total clearance.

Conclusions: For drugs with intermediate extraction ratios liver volume and UGT2B7 ontogeny drive the ontogeny of in vivo glucuronidation. For drugs with similar extraction ratios, physicochemical drug properties do not influence the ontogeny profile, but only the magnitude of clearance, allowing for the extrapolation of paediatric population covariate models between these drugs. Situations involving extrapolation between drugs of varying extraction ratios and situations with non-linear drug metabolism need further investigation.

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IV-61 *Anders Kristoffersson* Robust optimal design of ciprofloxacin time-kill curve experiments with respect to autocorrelation

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Objectives: Residual autocorrelation (AC) is shown to be of importance in optimal experimental design with different magnitudes of correlation resulting in markedly different designs [1]. While always present to some degree, the magnitude of AC in experimental data may be hard to estimate accurately [2]. This work aims to design efficient ciprofloxacin time-kill curve experiments robust in the vicinity of AC earlier quantified in similar experiments [3].

Methods: A previously developed model describing the kill and growth of a wildtype E. coli strain under exposure of ciprofloxacin [4] was implemented in the optimal design software PopED [5]. The model features two proportional errors, one independent and one shared either across replicate observations only (L2 correlated), or AR(1) correlated [2]. The D-optimal design of the sampling schedule over 24 h was investigated for AC half-lives ($t_{1/2}$) ranging from 0 to 60h. In the case of no AC both a reduced model with one independent error and a full model with L2 correlated duplicate samples were investigated. Assuming an AC $t_{1/2}$ of 7.5h [3] the design was further optimized for the variables study length, time of night pause, and the number of experimental concentrations vs. the number of samples per concentration.

Results: The scenarios of L2 correlated duplicate samples and no replicate samples resulted in identical designs. Higher AC resulted in less clustering and a wider spread of the sampling times, the design was constant for AC $t_{1/2}$ of 1.5 h or greater. Evaluating models assuming AC for designs optimized without AC resulted in a distinctly larger information drop than the reverse case. At an AC $t_{1/2}$ of 7.5 h, and an experimental duration of 32h, an optimal design including a 14h nighttime pause was computed. Compared to the current study design, the optimized design prolonged the night time pause and decreased the number of samples per concentration from 8 to 6 without an increase in parameter variance.

Conclusions: L2 correlated replicate errors may in optimal design be substituted by a single suitably scaled variance. Acknowledging AC resulted in a change of the optimal design and designs produced with AC were more robust to the lack of AC than the reverse. The optimal design remained stable across a wide range of AC $t_{1/2}$, including the 7.5h $t_{1/2}$ found in similar experiments [3]. An optimized design was proposed decreasing the number of samples by 25% while maintaining parameter precision.

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IV-62 *Wojciech Krzyzanski* Methods of Solving Rapid Binding Target-Mediated Drug Disposition Model for Two Drugs Competing for the Same Receptor

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Objectives: The target mediated drug disposition (TMDD) model [1] has been adopted to describe pharmacokinetics for two drugs competing for the same receptor. A rapid binding assumption introduces total receptor and total drug concentrations while free drug concentrations C_A and C_B are calculated from the equilibrium (Gaddum) equations [2]. The Gaddum equations are polynomials in C_A and C_B of second degree that have explicit solutions involving complex numbers. The aim of this study was to develop numerical methods to solve the rapid binding TMDD model for two drugs competing for the same receptor that can be implemented in pharmacokinetic software.

Methods: Algebraic calculations and computer simulations were used to develop algorithms and investigate properties of solutions to the TMDD model with two drugs competitively binding to the same receptor. A general rapid binding TMDD model for two competing ligands incorporating new methods was coded in MATLAB 7.2. The applicability of these algorithms was demonstrated by simulating concentration-time profiles resulting from exogenous and endogenous IgG competing for the neonatal Fc receptor (FcRn), and darbepoetin competing with endogenous erythropoietin for the erythropoietin receptor. These models were implemented in Phoenix WinNonlin 6.0 and ADAPT 5, respectively.

Results: A rapid binding approximation of the TMDD model for two drugs competing for the same receptor has been proposed. The explicit solutions to the equilibrium equations employ complex numbers, which cannot be easily solved by pharmacokinetic software. Numerical bisection algorithm and differential representation were developed to solve the system instead of obtaining an explicit solution. The numerical solutions were validated by MATLAB 7.2 solver for polynomial roots. These methods were applied to solve the TMDD model for two case studies.

Conclusions: Numerical methods have been developed for solving of the rapid binding TMDD model describing two drugs competitively binding to the same receptor that can be easily implemented in any pharmacokinetic software. Two case studies involving monoclonal antibodies and growth factors have been presented.

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IV-63 *Steve Kuan* Population Pharmacokinetic (PK) Modelling of Bortezomib After Bolus Intravenous Injection in Cancer Patients

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Objectives: Bortezomib is an ubiquitin-proteasome inhibitor indicated for the treatment of multiple myeloma and for patients with mantle cell lymphoma who have received at least one prior therapy. The population modelling approach was used to further understand the pharmacokinetic (PK) differences observed after first and repeated dosing.

Methods: Population models were fitted to bortezomib plasma concentration-time data using NONMEM 7.2. Various models were examined including linear disposition, empirical time dependent systemic clearance (CL), and combined linear and nonlinear distribution for a peripheral compartment. A log transform both sides approach was used with concentrations below the lower limit of quantification handled as censored observations[1]. Model goodness-of-fit and performance were evaluated by common diagnostic tools. For the full Markov Chain Monte Carlo Bayesian analysis (BAYES) method, model qualification was additionally performed using burn-in termination and post-run convergence testing.

Results: 142 patients receiving first (1-2mg/m^2) and repeat (1-1.3mg/m^2) dosing on days 1, 4, 8 and 11 of 21-day cycles in 5 Phase 1 studies provided 3004 concentration. A 3-compartment model in which the distribution from compartment 2 (peripheral) to compartment 1 (central) was parameterized by a Michaelis-Menten function was considered most adequate based on the BAYES method. Parameter estimates (inter-individual variability as CV) by this model were 10.8L/h (43%) for CL, 14.1L (81%) for central volume of distribution (V1), 349L (304%) and 895L (114%) for peripheral volumes of distribution (V2 and V3, respectively), 46.3L/h (93%) for clearance to compartment 2 (Q2), 0.06ng/mL (93%) for Michaelis constant (Km) with the maximum velocity (Vm) fixed at 0.0926ng/mL/h, 51.7L/h (70%) for clearance to and from compartment 3 (Q3). The residual variability was estimated to be 42% or 62% depending on the assay used to determine plasma concentrations.

Conclusions: The developed model attributes previously reported time dependence in bortezomib PK [2] to saturable distribution to rather than nonlinear elimination from the central compartment. All parameters except V2 are estimated with good precision. Moreover, V2 is found to exhibit the largest variability among patients. Visual predictive checks demonstrate that this model describes bortezomib disposition well and may be used to predict bortezomib plasma exposure following alternative dosing schedules.

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IV-64 *Brigitte Lacroix* A single population pharmacokinetic model for oral levetiracetam in various populations – dose investigation for Japanese children

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Objectives: This population pharmacokinetic (PK) analysis aimed i) to assess the PK of levetiracetam (LEV) in Japanese children and adults, ii) to assess dose recommendations in Japanese children to support the pediatric submission in Japan and iii) to compare the PK of LEV in the Japanese and Caucasian population.

Methods: The population PK analysis was performed using NONMEM based on plasma LEV concentrations from Japanese children and adult with partial-onset seizures who received adjunctive LEV BID during more than10 weeks in 3 studies. The doses administered as dry syrup or tablet were 10mg/kg bid to 30mg/kg bid for the children, capped to the adult dose of 500mg bid to 1500mg bid. Bodyweight (BW) was included in the base model on clearance (CL/F) and distribution volume (V/F). Age, formulation and concomitant anti-epileptic drugs (AEDs) were examined as possible covariates to explain inter-individual variability in pharmacokinetic parameters of LEV. The model was used to simulate and compare concentrations in Japanese children and adults following various dosing regimens with the 2 formulations. The similarity of the PK in Caucasian and Japanese children was assessed through external validation.

Results: 1840 concentration-time records were available from 259 Japanese subjects (73 children and 186 adults). LEV plasma concentrations were adequately described by a one-compartment model, with low residual variability (20.0% CV). Only concomitant enzyme inducing AEDs was a significant covariate on CL/F, in addition to BW with allometric exponents on CL/F and V/F. Simulations of the dosing regimens expected in clinical practice for Japanese children lead to similar concentrations as those simulated in Japanese adult with the currently recommended regimen. The model developed in Japanese subjects with no modification gave a good prediction of the concentrations obtained in Caucasian children (historical data).

Conclusions: i) The population PK model gave a good description of the PK of LEV both in Japanese children and adults. ii) The appropriateness of the dosing regimens expected in clinical practice for Japanese children to reach concentrations in the ranges of those predicted in Japanese adults was confirmed. iii) The PK between Japanese and Caucasian children was similar.

IV-65 *Celine M. Laffont* Application of a new method for multivariate analysis of longitudinal ordinal data testing robenacoxib in canine osteoarthritis

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Objectives: Robenacoxib is a coxib non-steroidal anti-inflammatory drug approved for the treatment of osteoarthritis in dogs. In clinical trials, multiple scores were measured and as we have shown in previous work [1], a multivariate analysis is usually more appropriate than a traditional score by score analysis as it accounts for the potential correlations between ordinal responses. We have developed a new method for that purpose [1] and propose to apply this method to the analysis of robenacoxib data with two objectives: a better understanding of drug effect and the identification of possible redundancies between the scores.

Methods: Data were obtained from three clinical studies in osteoarthritic dogs where robenacoxib was given once or twice a day over 28 to 84 days at one or three different daily doses. Five scores ordered to a 3 to 4 levels were measured over time but one score was excluded from the analysis due to a high amount of missing data. In the end, the analysis was carried out on four scores documented at 1191 time points in 236 subjects. The model we used was a multivariate probit mixed effects model and model estimation was performed with a SAEM [2, 3] -like algorithm implemented in C following a pairwise approach [4] (to circumvent the computational difficulties related to the high number of scores). A principal component analysis was done to summarise the correlations between scores.

Results: The multivariate model was found to correctly predict the observed data with respect to both marginal and joint distribution. Especially, we were able to predict the percentage of dogs with complete cure at steady-state, while separate univariate analyses (assuming the independence between scores) severely underestimated this percentage by 60%. Finally, our analysis revealed that three scores were highly correlated while one was apparently independent from the others, thus giving different information on the disease.

Conclusions: Overall, the multivariate analysis appears more complex than traditional univariate analyses but provides additional insights that are worthwhile. First, it allows a better evaluation of drug effect on meaningful clinical endpoints (ex: a percentage of patients reaching the clinical target). Secondly, it provides information on the scoring system itself independently of drug effect: in the present case, what we actually measure looks more like 2 sub-scores with very different weighting 3:1.

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IV-66 *Cédric Laouenan* Modeling hepatitis C viral kinetics to compare antiviral potencies of two protease inhibitors: a simulation study under real conditions of use

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Objectives: 2011 has marked a milestone in HCV therapy with the approval of two protease inhibitors (PI), telaprevir (TVR) and boceprevir (BOC), in addition to current treatment. However the antiviral potency of BOC has never been estimated. Ongoing MODCUPIC - ANRS trial will provide for the first time a precise description of viral kinetics under tritherapy in real conditions of use. The objectives of our study were to evaluate by simulation i) the estimation performance for the chosen MODCUPIC's design ii) the power to detect a difference of potency between TVR and BOC using an HCV dynamic model.

Methods: The Neumann *et al.* [1] biphasic viral kinetics model considers initial viral load (VL), free virion and infected cells clearance rate (c and δ), and antiviral potencies (ε) which is the percentage of blockage of virion production. Values of parameters and their inter-individual variations were those proposed by Guedj *et al.* [2]. A treatment effect was added on ε (assuming $\varepsilon^{TVR} = 99.9\%$ and $\varepsilon^{BOC} = 99\%$, 99.5% or 99.8%). We simulated 500 datasets with additive error for $\log_{10}$ VL using MODCUPIC's design (30 patients per PI and VL measurement at 0, 0.33, 1, 2, 3, 7 and 14 days). Nonlinear mixed-effects models (NLMEM) were used to estimate parameters using the extended SAEM algorithm in MONOLIX v4.1 that take into account below limit of detection data [3-4]. Relative bias (RB) and relative root mean square error (RRMSE) of the estimated parameters were computed. We performed a Wald test to detect a difference between PIs.

Results: With 30 patients per PI, all parameters were well estimated with small RB and RRMSE. For example, with $\varepsilon^{TVR} = 99.9\%$ and $\varepsilon^{BOC} = 99\%$, c was estimated with RB = 0.2% and RRMSE = 4.1% and ε with RB = -0.01% and RRMSE = 0.2%. Power to detect a difference between ε were 100%, 100% and 94% with $\varepsilon^{BOC} = 99\%$, 99.5% and 99.8% respectively. With $\varepsilon^{TVR} = 99.9\%$ and $\varepsilon^{BOC} = 99\%$ but in absence of datapoints at 0.33 and 1d, ε remained precisely estimated with RB = -0.02% and RRMSE = 0.2%, but the estimation of c was degraded with RB = 35.9% and RRMSE = 80.9%. However, without these datapoints power remained very high (100%, 100% and 89% respectively).

Conclusions: The use of viral dynamic modeling approaches along with NLMEM in our simulation study validates *a priori* the design of MODCUPIC's trial to estimate parameters and to compare the antiviral potency of TVR and BOC, even with sparse initial sampling. The study of the test properties is ongoing.

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IV-67 *Anna Largajolli* Visual Predictive Check (VPC) in models with forcing functions

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Objectives: VPC [1] is commonly used to evaluate the performance of PK and PKPD models. However this diagnostic tool presents some pitfalls in the simulation step when models with forcing functions (FF) are evaluated. In fact in this case there is a mismatch between each set of simulated parameters and the associated individual FF which can cause an incorrect profile simulation. This study aims to overcome this VPC limitation by taking into account in the simulation step a correlation term that bounds the set of simulated parameters with the most appropriate FF. This is a non-trivial aspect since FF exhibit a large inter-individual variability. We assessed the technique on four nonlinear models that present one or two FFs: the IVGTT and the ORAL glucose and C-peptide minimal models (MM) [2-3-4-5].

Methods: To introduce the correlation term in the simulation step of the VPC we calculated for each set of simulated parameters (SIM) the Mahalanobis distance (MD) between the SIM and the previously estimated parameters (EST). This helped us to find the vector of EST parameters that was closer to SIM and consequently to match the EST corresponding FF to the SIM parameters in the simulation step.

Results: When VPC was used in its original formulation, we found implausible simulated curves especially with the oral glucose MM. This is essentially due to the fact that the large variability between the FFs makes the match between the simulated parameters and the associated FF critical. With the newly proposed approach to VPC the oral glucose MM results show plausible simulated curves and consequently a better agreement with the real data. Also results on the other three models with FFs [2-3-4] show an improved pattern of simulated curves but its impact was less evident with respect to the oral glucose MM where there are two independent FFs.

Conclusions: This work proposes a refinement of the simulated based diagnostic VPC which is relevant for a particular subset of models. Despite the simplicity of the method, the results show an evident improvement of VPC. Another approach has also been developed in case of a low FF variability that is a common situation in PK/PD experiments. This method adds an elaboration step before applying the MD. A clustering analysis detects the most important FF kinetics that are used to simulate a new dataset whose parameters are estimated, then the MD is applied. The VPC performance further improves since there is no error in the association of FF with the set of SIM.

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IV-68 *Christian Laveille* Use of an exposure-response model for lacosamide in adults with partial onset seizures to analyze preliminary data from a pediatric trial

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Objectives: To analyze preliminary data obtained from children aged 3−17 years with partial-onset seizures (POS) to support the design of phase III trials.

Methods: A retrospective exposure-response model was built for lacosamide based on daily seizure counts (N=210,234) of 1308 adult patients who participated in three double-blind, placebo-controlled clinical trials in adjunctive treatment of POS (SP667, SP754, SP755). A negative binomial distribution with zero-inflation and Markovian element associated with a mixture model, stratifying patients according to reduced or increased seizure frequency (SF), provided the best fit. Preliminary SF data from a multicenter, open-label trial designed to investigate the safety and pharmacokinetics of lacosamide as adjunctive therapy in children with POS (SP847) were analyzed using the exposure-response model developed in adults. In addition to an empirical Bayesian feedback estimation, simulations (VPC-like with 1000 replicates) were performed in order to evaluate the performance of the exposure-response model of lacosamide developed in adults to predict the median percentage reduction from baseline in SF and the responder rate (≥50% reduction in SF from baseline). Model development and simulations were performed using non-linear mixed-effects modeling implemented in NONMEM V7.1.0 with the Laplacian method.

Results: At the preliminary cut-off date, 28 pediatric patients aged 3−17 years had completed the dose-finding study. Their daily seizure count data (N=1,360) were satisfactorily described by the model developed in adults. Furthermore, the simulation results showed the ability of the adult exposure-response model to correctly predict the median percentage reduction from baseline and the responder rate in the study sample.

Conclusions: Based on the preliminary results, and on the limited information from the SP847 trial, no signal was seen in the present pediatric study suggesting a possible alteration of the exposure-response relationship established in adults. Therefore, the lacosamide dosing strategy in the pediatric population will probably be driven only by lacosamide pharmacokinetics.

IV-69 *Marc Lavielle* On the use of stochastic differential mixed effects models for modeling inter occasion variability. Models and methods

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Objectives: One objective of WP6.4 of the DDMoRe project is to develop new methods for complex NLMEM. We consider here stochastic differential mixed-effects models used for describing intra-subject variability of certain PK parameters.

Methods: A commonly used model for describing intra-subject variability of PK parameters assumes that each individual parameter is piecewise-constant over time and can randomly change between occasions. This Inter Occasion Variability model does not really make sense biologically if we consider short consecutive periods, since it allows discontinuities in PK parameters. Nevertheless, we show that a SDE model is the limit of the IOV model when the length of each period tends to 0 and with an appropriate autocorrelation structure which ensures the continuity of the process.
In this model, some PK parameters are random processes described with SDEs. We propose different volatility models that respect biological constraints.
In a mixed effects context, the SAEM algorithm and the Extended Kalman Filter (EKF) can be efficiently combined for estimating the population parameters of the model. EKF can also be combined with an Importance Sampling Monte Carlo procedure for estimating the likelihood function.

Results: We investigated the properties of the proposed method through simulations. The model used for the simulations is an IV bolus model with an elimination rate process k(t) defined as a stochastic process.
First, we show that the proposed model faithfully mimics biological dynamics. Indeed, even if the elimination rate process is extremely erratic (which is biologically relevant), the random fluctuations of the concentration profile are smooth and satisfactorily describe real PK profiles.
The statistical issues are twofold: recovering the dynamics of the system and estimating the population parameters. Numerical results confirm what we would expect: *i)* the dynamics of the system are correctly recovered with rich data. On the other hand, it becomes extremely difficult to distinguish the random fluctuations of the dynamical system from the residual error when the data is sparse, *ii)* the accuracy of the population parameters estimate depends on the number of subjects.

Conclusions: We have shown that stochastic differential mixed-effects models can satisfactorily model the inter occasion variability of PK parameters. The use of the Extended Kalman Filter allowed us to efficiently develop several extensions of methods used for NLMEM.

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S-01 *Roger Jelliffe* The MM-USCPACK Pmetrics research software for nonparametric population PK/PD modeling, and the RightDose clinical software for individualizing maximally precise dosage regimens.

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The **Pmetrics** population modeling software is embedded in R, called by R, and output into R. It runs on PC's and Macs. Minimal experience with R is required, but the user has all the power of R for further analyses and displays, for example. Libraries of many structural models are available. In addition, differential equations may also be used to describe large models of multiple drugs, with interactions, and with multiple outputs and effects. Analytic solutions may also be used if applicable. The model is compiled with GFortran. Runs are made with simple R commands. Routines for checking data and displaying results are provided. Likelihoods are exact. Behavior is statistically consistent - studying more subjects yields parameter estimates closer to the true ones. Stochastic convergence is as good as theory predicts. Parameter estimates are precise [1].The software is available freely for research uses. In addition, prototype new nonparametric Bayesian (NPB) software has been developed. Standard errors of parameter estimates and rigorous Bayesian credibility intervals are now available. This work, presented at this meeting, is progressing.

The **RightDose** clinical software [2] uses Pmetrics population models, currently for a 3 compartment linear system, and develops multiple model (MM) dosage regimens to hit desired targets with minimum expected weighted squared error, thus providing maximally precise dosage regimens for patient care. If needed, hybrid MAP and NP Bayesian posteriors provide maximum safety with more support points and more precise dosage regimens. In addition, the interacting multiple model (IMM) sequential Bayesian analysis when model parameter distributions are changing during the period of data analysis [[3] has been upgraded by using the hybrid analysis in advance to provide more support points than were present in the original population model, again for more capable Bayesian parameter distributions and more informed dosage regimens than were available before. This work was also presented at this meeting. IMM has tracked drug behavior better than other methods in unstable post surgical cardiac patients [4]. In all the software, creatinine clearance is estimated in either stable or changing clinical situations, based on analyzing pairwise serum creatinine values, age, gender, height, weight, muscle mass, and dialysis status [5]. The software now also runs on IPads and IPhones as virtual machines to access and run the software on a PC.

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S-02 *Coen van Hasselt* Pirana: The flexible modeling environment for NONMEM

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Introduction
Pirana is a modeling environment for NONMEM and PsN, and provides an easy-to-use toolkit for both novice and advanced modelers. It supports modeling on a local system or on computer clusters. Pirana can be utilized to run, manage and edit models, interpret output, and manage NONMEM installations. It is easily extendible with custom scripts, and integrates smoothly with R, Xpose4, Excel and other software. Pirana fully supports NONMEM version 7.2 and runs on Windows, Linux and Mac OSX.

Recent major improvements

- Full support of NONMEM 7.2, including parallelization
- Wizard functionality to easily create NONMEM model files, PsN configuration files, and parallelization files for NM 7.2
- Extended output functionality and improved report generation (HTML, CSV, LaTeX)
- Version control of models and results
- Model translator: convert any NONMEM model to R or Berkeley Madonna code

Model and results management

- Logbook-like interface for comprehensive model management.
- Full model manipulation support (create, edit, duplicate, remove model files).
- Create customizable run reports (HTML / LaTeX) containing relevant results (e.g. parameter estimates, parameter precision, shrinkage, errors and warnings)
- Extend Pirana with custom R scripts for creation of customizable posthoc run processing (e.g. diagnostic plots), with automatic loading of created plots or files. A base library of scripts is included.
- Built-in Data Inspector for quick graphical evaluation of model output files.
- Quickly open, edit any data file in your preferred spreadsheet application, code editor or in R.
- Model translator: NONMEM analytical solutions or $DES (ADVAN1-6) to Berkeley Madonna, Matlab and R-deSolve code for simulation purposes.

NONMEM, PsN and Xpose

- Install, manage and utilize multiple local and cluster NONMEM installations simultaneously.
- Monitor intermediate progression of NONMEM runs (gradients, parameters).
- Full support of all PsN commands with full access to associated help files.
- Support for PsN run record syntax

- Interface for Xpose commands: automatically creation of PDFs or export to the R GUI

Cluster support

- Wizards for creation of configuration files for parallel computation features of NM7.2.
- Support for SGE and Torque clusters.
- Clusters running NONMEM can be accessed through SSH.
- Pirana can also be installed on a server and accessed through SSH-X-window tunneling.

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