Tuesday 6 June

14:00-18:00	**Registration at the Conference Venue**	
19:00-22:00	**Opening ceremony, welcome reception and dinner**	

Wednesday 7 June

08:00-08:45	**Registration**	
08:45-09:00	**Welcome and Introduction**	
09:00-10:30	**Benefit-risk profile of medicinal products**	*Chair: Oscar Della Pasqua*
09:00-09:30	*Praveen Thokala*	Overview and implementation of multi criteria decision analysis (MCDA) for benefit-risk assessment
09:30-10:00	*Andreas Kouroumalis*	European regulatory views on benefit-risk assessment methodologies - role of MCDA and other model-based approaches
10:00-10:30	*Kevin Marsh*	Current practices and gaps in benefit-risk assessment: opportunities for combining MCDA with model-based approaches
10:30-12:00	**Coffee break, Poster and Software session I**	
	Posters in Group I (with poster numbers starting with I-) are accompanied by their presenter	
12:00-12:40	**Benefit-risk profile of medicinal products, continued**	*Chair: Mats Karlsson*
12:00-12:20	*Neeraj Gupta*	Model-Informed Drug Development (MIDD) for ixazomib, an oral proteasome inhibitor
12:20-12:40	*Nadia Terranova*	Simulation analysis of absolute lymphocytes counts (ALC) and relapse rate (RR) following cladribine (re-)treatment rules in subjects with relapsing-remitting multiple sclerosis (RRMS)
12:40-12:45	**Announcement for ACoP8 (2017)**	*Jin Jin*
12:45-14:10	**Lunch**	
14:10-15:10	**Scaling of PD in paediatrics**	*Chair: Lutz Harnisch*
14:10-14:50	*Joseph Standing*	Scaling pharmacodynamics in children: Lessons from immunology, infectious diseases and critical care
14:50-15:10	*Nick Holford*	Scaling renal function in neonates and infants to describe the pharmacodynamics of antibiotic nephrotoxicity

15:10-16:40	**Tea break, Poster and Software session II**		
	Posters in Group II (with poster numbers starting with II-) are accompanied by their presenter		
16:40-17:20	**Study design**		*Chair: Marylore Chenel*
16:40-17:00	*Hanna Silber Baumann*	Using pharmacokinetic simulation to guide dose escalation decisions for targeted IL2v immunocytokines	
17:00-17:20	*Simon Buatois*	Modelling approaches in dose finding clinical trial: Simulation-based study comparing predictive performances of model averaging and model selection	
17:20-18:00	**Oncology**		*Chair: Dinesh de Alwis*
17:20-17:40	*Yuri Kheifetz*	Model-based individual managing of thrombocytopenia during multi-cyclic chemotherapy	
17:40-18:00	*Jurgen Langenhorst*	High exposure to fludarabine in conditioning prior to allogeneic hematopoietic cell transplantation predicts impaired CD4 reconstitution and lower probability of survival	

Thursday 8 June

08:30-09:50	**Lewis Sheiner Student Session**		*Chair: Kristin Karlsson, Julia Winkler, Paolo Magni*
08:30-08:55	*Elisa Borella*	Paediatric trial design optimization using prior knowledge in combination with modelling & simulations	
08:55-09:20	*John Diep*	Host-Pathogen interactions: A mechanism-based disease progression model to describe the pathogenesis of Acinetobacter baumannii pneumonia	
09:20-09:45	*Morris Muliaditan*	Model-based rationale for drug combinations in tuberculosis	
09.45-09.50	**Presentation of Lewis Sheiner student session awards**		
09:50-11:20	**Coffee break, Poster and Software session III**		
	Posters in Group III (with poster numbers starting with III-) are accompanied by their presenter		
11:20-12:20	**Estimation methods**		*Chair: France Mentré*
11:20-12:00	**Tutorial**		
11:20-12:00	*Robert Leary*	An overview of non-parametric estimation methods used in population analysis	
12:00-12:20	*Mats Karlsson*	A comparison of performance between parametric and nonparametric estimation for nonlinear mixed-effects models	
12:20-12:25	**Announcement for WCoP 2020**		*Stacey Tannenbaum*
12:25-13:45	**Lunch**		

13:45-14:45	**European regulatory issues**		*Chair: Susan Cole & Frederike Lentz*
13:45-14:15	*Kristin Karlsson*	Regulatory pharmacometrics in the EU in practice and the role of the Modelling and Simulation Working Group	
14:15-14:45	*Anna Nordmark*	The new draft EMA Guidance on PBPK – The qualification of the intended use concept	
14:45-16:15	**Tea break, Poster and Software session IV**		
	Posters in Group IV (with poster numbers starting with IV-) are accompanied by their presenter		
16:15-17:40	**Stuart Beal Methodology Session dedicated to the memory of Matt Hutmacher**		*Chair: Emmanuelle Comets & Siv Jönsson*
16:15-16:20		In memoriam Matt Hutmacher	
16:20-16:40	*Wojciech Krzyzanski*	Correction of the likelihood function as an alternative for imputing missing covariates	
16:40-17:00	*Henrik Bjugård Nyberg*	SADDLE_RESET: more robust parameter estimation with a check for local practical identifiability	
17:00-17:20	*Dmitry Onishchenko*	Joint modeling of overall survival and tumor size dynamics in non-small cell lung cancer: Clinical trial simulations and validation of predictions at study and subject levels	
17:20-17:40	*Eva Germovsek*	Handling frequent observations of composite scores: Application to PROs in COPD	
19:00-01:00	**Social event**		

Friday 9 June

09:00-10:00	**Systems pharmacology**		*Chair: Anna Nordmark & Siv Jönsson*
09:00-09:20	*Markus Krauß*	Translational systems pharmacology for acquisition of knowledge and prediction of drug pharmacokinetics across patient populations	
09:20-09:40	*Robin Michelet*	PBPK modeling of propofol using the middle out approach	
09:40-10:00	*Miro Eigenmann*	Therapeutic antibody concentrations at the biophase	
10:00-10:25	**Modelling experience!**		*Chair: Katya Gibiansky*
10:00-10:25	*Alan Maloney*	The 6 biggest pharmacometrics modelling mistakes!	
10.25-10.30	**Preview of PAGE 2018**		
10:30-11:15	**Coffee break and Software session**		
11:15-12:15	**Infection**		*Chair: Lena Friberg*
11:15-11:35	*Richard Höglund*	Pharmacokinetic-pharmacodynamic modelling of artesunate in patients with drug resistant and sensitive malaria	
11:35-11:55	*Salvatore D'Agate*	Model-based screening of compounds for the treatment of Chagas disease, a neglected tropical disease	

11:55-12:15	*Carolina Llanos-Paez*	Balancing efficacy and reduction in renal function to optimize initial gentamicin dosing in children with cancer
12.15-12.25	**Closing remarks**	
12:25-12:40	**Audience input for potential PAGE2018 topics**	

PAGE2017 Abstracts

B-03: *Praveen Thokala* Overview and implementation of multi criteria decision analysis (MCDA) for benefit-risk assessment

Praveen Thokala
University of Sheffield

Overview/Description of presentation:

Health care decisions are complex and involve confronting trade-offs between multiple, often conflicting, objectives. Multiple criteria decision analysis (MCDA) are a set of techniques that use structured, explicit approaches to decisions involving multiple criteria to improve the quality of decision making.

Value measurement MCDA models are by far the most widely used in health care and although there are many differences in the ways in which these models are used and applied, there are several main elements of the process that are common among these methods. Broadly speaking, any value measurement modelling approach entails defining the decision problem being addressed, selecting the criteria, measuring alternatives' performance, scoring alternatives and weighting criteria, aggregation, uncertainty analysis, and interpretation of results.

An example of how value measurement MCDA approaches can help benefit risk analysis (BRA) will be illustrated. The key element of preference elicitation i.e. the weighting of the different criteria and scoring of the different alternatives will be highlighted.

There is a need to consider different areas of uncertainty when using MCDA to support BRA. An important consideration is the appropriate choice of endpoints (i.e. criteria), which can be addressed using structural sensitivity analysis. Another source of uncertainty is the importance attached to criteria and performance (i.e. weights and scores captured using preference elicitation), which can be addressed using subgroup analysis or probabilistic sensitivity analysis (PSA). There is also the uncertainty that results from lack of information (for example, lack of trial data), where expert elicitation and Bayesian approaches can be used to support PSA in MCDA for BRA.

Conclusions/Take home message:

MCDA approaches are ideally suited to deal with multiple endpoints featured in benefit risk analysis. They can support transparency by making the criteria and preferences explicit. There are techniques available, such as Bayesian analyses, which can help capture the uncertainty.

B-04: *Andreas Kouroumalis* European regulatory views on benefit-risk assessment methodologies - role of MCDA and other model-based approaches

Andreas Kouroumalis
European Medicines Agency

Objectives:

- Provide an overview of the current benefit/risk assessment process of drug evaluation in the EU
- Describe past and ongoing initiatives to further improve benefit/risk analysis
- Highlight opportunities to support the shift towards quantitative models in benefit/risk

Overview/Description of presentation: Benefit-risk assessment is the cornerstone of drug licensing decisions. Increased interest in the decision making process behind drug approvals have led to significant changes by which drug regulatory authorities conduct their assessments and communicate their decisions. Over the last 10 years, there has been a clear trend towards a more explicit benefit/risk analysis, using structured frameworks, both in Europe and the USA. The European Medicines Agency has explored the possibility to use quantitative methods in its assessments however this has not yet gained support, mainly because the experience of the European regulatory network is very limited with such models as well as the perceived complexity of such methods in the European regulatory context. To gain more experience, the Agency has invited the pharmaceutical industry to explore alternative methods in their assessment of the benefit/risk balance of new medicinal products, including quantitative methods. Acceptance of such methods will depend to a large extent on their uptake by the pharmaceutical industry within their submissions and the perceived usefulness of such approaches by regulators

Conclusions/Take home message: Quantitative methods in benefit/risk assessment in Europe are currently not required. Further evidence and experience are needed to understand the role of quantitative methods in drug regulation.

B-05: *Kevin Marsh* Current practices and gaps in benefit-risk assessment: opportunities for combining MCDA with model-based approaches

Kevin Marsh
Evidera

Objectives:

- Provide an overview of the use of quantitative BRA by the FDA.
- Illustrate how quantitative BRA is undertaken by industry to demonstrate the value of technologies.
- Illustrate how quantitative BRA can be incorporated into model-based approaches to trial design.
- Identify the challenges, and potential solutions to using quantitative BRA to inform trial design.

Overview/Description of presentation: Industry's use of quantitative benefit-risk assessment (BRA) has recently received stimulus from an increased interest in its use by the FDA. Most BRA is thus undertaken by industry alongside phase 3 trials. However, there is increasing interest in undertaking BRA earlier in the development process, incorporating BRA into model-based approaches to informing the design of trials. This will allow the assessment of trial design scenarios to be based on models of the probability of achieving regulatory approval.

The presentation will be organised into four sections:

1. A definition of quantitative BRA, how this differs from other types of BRA, and how MCDA supports quantitative BRA.
2. A summary of FDA requirements and guidelines for quantitative BRA, and an illustration of a BRA used in an FDA approval decision.
3. An outline of how quantitative BRA could be incorporated into model-based approaches to trial design.
4. An outline of key considerations when designing a quantitative BRA for incorporation into model-based approaches to trial design, including dealing with uncertainty in performance ranges, and generating weights for longer lists of treatment attributes.

Conclusions/Take home message: Quantitative BRA is increasingly being used to support approval in the US. Anticipating this requirement, it is possible to incorporate quantitative BRA into model-based approaches to trial design.

B-07: *Neeraj Gupta* Model-Informed Drug Development (MIDD) for ixazomib, an oral proteasome inhibitor

Neeraj Gupta (1), Michael J. Hanley (1), Paul M Diderichsen (2), Huyuan Yang (1), Yeamin Huh (3), Alice Ke (4), Zhaoyang Teng (1), Richard Labotka (1), Deborah Berg (1), Chirag Patel (1), Guohui Liu (1), Helgi van de Velde (1), and Karthik Venkatakrishnan (1)

(1) Millennium Pharmaceuticals Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. (2) Quantitative Solutions, Breda, The Netherlands (3) Ann Arbor Pharmacometrics Group, Ann Arbor, MI, USA (4) Certara USA, Inc., Princeton, NJ, USA

Objectives: Ixazomib is approved in the US, EU, Canada, Australia, Venezuela, Israel, Singapore, and Switzerland, in combination with lenalidomide-dexamethasone (Rd), for the treatment of patients with multiple myeloma (MM) who have received at least 1 prior therapy. MIDD was used across the ixazomib development continuum, including population (pop) PK analysis, concentration (conc)-QTc analysis, exposure-response (ER) analysis, physiologically-based pharmacokinetic (PBPK) modeling, and model-based meta-analysis (MBMA), to make drug development decisions and facilitate regulatory review.

Methods: PK and clinical data from multiple studies, including the phase 3 TOURMALINE-MM1 (T-MM1) study[1], contributed to MIDD analyses. Pop PK analyses were performed using NLME modeling in NONMEM v7.2. ER relationships were examined using logistic regression analysis in SAS v9.2. The conc-QTc relationship was assessed using linear mixed-effects models in R v3.0.1. A PBPK model was developed using SimCYP v15. A MBMA framework was developed using R to predict progression-free survival (PFS) from overall response rate (ORR) in relapsed/refractory (RR)MM.

Results: A pop PK analysis (N=137) supported the switch from body surface area-based to fixed dosing in early clinical development[2], simplifying dosing and capsule strength manufacture. A conc-QTc analysis of data from 4 phase 1 studies (N=245) showed no effect of ixazomib on the QTc interval[3], obviating the need for a dedicated QTc study. Pop PK analysis of phase 1-3 data (N=755) confirmed that no dose adjustment is necessary for ixazomib on the basis of age (23-91 years), sex, BSA, or race, or for mild-moderate renal impairment (CrCl ≥30 mL/min) or mild hepatic impairment[4]. A PBPK model enabled an integrated understanding of the victim drug-drug interaction profile for ixazomib. ER analyses on data (N=347) from T-MM1 quantitatively supported the benefit-risk and regulatory review of the 4 mg starting dose[5]. Separate ER analyses supported the dose titration approach in phase 3 maintenance trials[6] and a planned phase 2/3 study in RRMM. A MBMA predicted a PFS of 20 months based on an ORR of 78% for ixazomib-Rd[7], consistent with results of T-MM1[1]. This MBMA framework can be used to inform future decision-making and the strategy for new combinations in lifecycle management.

Conclusions: MIDD played a pivotal role in the development of ixazomib, impacting internal decisions, regulatory review, and product labeling.

References:

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[2] Gupta N, Zhao Y, Hui AM, et al. Switching from body surface area-based to fixed dosing for the investigational proteasome inhibitor ixazomib: a population pharmacokinetic analysis. Br J Clin Pharmacol 2015;79(5):789-800.
[3] Gupta N, Huh Y, Hutmacher MM, et al. Integrated nonclinical and clinical risk assessment of the

investigational proteasome inhibitor ixazomib on the QTc interval in cancer patients. Cancer Chemother Pharmacol 2015;76(3):507-16.
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[5] NINLARO (ixazomib) Clinical Pharmacology NDA Review. US FDA CDER. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208462Orig1s000ClinPharmR.pdf
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B-08: *Nadia Terranova* Simulation analysis of absolute lymphocytes counts (ALC) and relapse rate (RR) following cladribine (re-)treatment rules in subjects with relapsing-remitting multiple sclerosis (RRMS)

Nadia Terranova (1), Christine Hicking (2), Fernando Dangond (3), Alain Munafo (1)
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Objectives: Cladribine's mechanism of action in RRMS involves lymphocytes. Treatment guidelines aimed at decreasing the risk of developing severe sustained lymphopenia following cladribine treatment have been developed. They imply modifications of the nominal dosing regimen based on ALC monitoring prior to the 2nd year treatment. A Clinical Trial Simulation (CTS) analysis [1] was performed to investigate the impact of such treatment rules on the occurrence of qualifying relapses.

Methods: The simulation analysis involved models and results from previously performed ALC dynamics and RR modeling. A virtual population treated with cladribine tablets total cumulative dose of 3.5 mg/kg was first generated by considering patients of a cladribine Phase 3 trial (CLARITY) as target population [2].

Alternative guidelines allowing postponements of cladribine treatment in Year 2 for up to 9 months, to allow for ALC recovery to Grade 0 or 1 before retreating, were then investigated. For each (re-)treatment scenario, lymphocyte dynamics were simulated at the patient level by allowing postponements according to the defined rules. Resulting individual dosing regimens were then used to obtain corresponding RR dynamics for each virtual patient.

The R package *mlxR 2.2.0* was employed for simulations, with models encoded in MLXTRAN.

Results: The simulation workflow was validated with a virtual population of 5000 subjects [3]. Specifically, percentages of subjects with lymphopenia grades, as well as the probability of being relapse-free in the virtual population, well reproduced those observed in the target population.

Results showed that i) only very few subjects (≤1%) would not recover to Grade 0 or 1 with postponements up to 6 months, ii) in those subjects qualifying for postponement, the proportion not experiencing Grade ≥3 lymphopenia at any time during Year 2 was increased (from 15% to 24%) when the mitigation rule was applied, and iii) such a delay of up to 6 months had essentially no effect on the probability of experiencing (1 to 6) relapses during Year 2 of cladribine treatment. This suggests that the efficacy of cladribine could be sustained if its administration needs to be interrupted to allow resolution of lymphopenia.

Conclusions: This CTS analysis supported the risk minimization measure of (re-)treatment guidelines to manage severe lymphopenia, while preserving cladribine tablets efficacy on the considered clinical endpoint.

References:
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B-11: *Joe Standing* Scaling pharmacodynamics in children: Lessons from immunology, infectious diseases and critical care

Joseph F Standing (1,2,3)
(1) Infection, Immunity, Inflammation Programme, UCL Great Ormond Street Institute of Child Health, London, UK; (2) Department of Pharmacy, Great Ormond Street Hospital for Children, London, UK; (3) Paediatric Infectious Diseases Group, St George's, University of London, UK.

Objectives: With changes to medicines regulation in recent years, under 18 year olds are no longer "therapeutic orphans" but a group of patients that all drug developers need to consider. Using examples, this presentation will consider pharmacodynamic scaling to help answer: Can we assume equal effect with equal PK exposure? How can modelling support extrapolation of PD?

Overview: The paradigm in much of paediatric PK research once centred on the philosophy "children are not small adults" and hence all possible should be known about the physiological differences with potential impact [1-4]. More useful perhaps than merely listing differences, is to know how PK scales with size and age, and this has been addressed as early as 1950 [5], then refined to account for maturation [6,7] and now explained using PBPK scaling [8]. Whilst it has been suggested that matching PK exposure in children maybe sufficient to understand PD, in practice regulatory approval requires an indication of PD equivalence [9]. Some examples of our recently published and ongoing work in PD scaling from immunology [10], infectious diseases and critical care/anaesthesia [11] will be discussed.

Conclusions: PD scaling requires a heterogeneous range of data sources and can be complicated by differing PD measures with age, but whether and how to scale will be necessary for rational paediatric drug development and dosing guidelines.

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B-12: *Nick Holford* Scaling renal function in neonates and infants to describe the pharmacodynamics of antibiotic nephrotoxicity

Nick Holford (1) Catherine Sherwin (2)
(1) University of Auckland (2) University of Utah

Objectives: 1. To use pharmacokinetic analysis methods to inform systems biology 2. To apply systems pharmacology to describe renal function (RF) in neonates and infants 3. To describe the pharmacodynamics of gentamicin (G), amikacin (A) and vancomycin (V) on RF

Methods: *"Systems pharmacology is the application of systems biology principles to the field of pharmacology."*[1]. The pharmacokinetics of the antibiotics G, A and V have been widely described. Target concentration intervention is recommended to reduce the risk of nephrotoxicity. The time course of RF in relation to antibiotic exposure has not been well defined. A systems pharmacology approach using pharmacokinetic parameters such as clearance (CL) in combination with biological data (GFR) and clinical data (weight, height, post-menstrual age (PMA), serum creatinine) has been applied to scale RF in neonates and infants. A joint model of GFR in neonates and young adults [2] and creatinine production rate (CPR) and G, A, and V pharmacokinetics was developed using NONMEM 7.4 alpha. A standard model [3] was used to describe size and maturation of all processes. RF was defined by the ratio of apparent creatinine clearance to normal GFR expected based on weight and PMA (2). We are grateful to our colleagues who shared data and/or helped with the analysis of G, A and V (Karel Allegaert, Nicolas Simon, Amicar Falcao), GFR (Malin Rhodin, Brian Anderson) and FFM (Anita Sumpter, Heshem Al-Sallami).

Results: The time course of size standardized CPR production in 108 subjects (neonates to young adults (age 20 y)) was described by a linear function of PMA. Individual GFR, CPR and PK of all 3 drugs in 2,248 neonates and young infants was described. The best size metric for all parameters was fat free mass (FFM). CL of each drug had a predominant renal component predicted by RF and GFR. There was also a substantial non-renal component of CL. Renal function in neonates and young infants (post-natal age 0-90 d, PMA 23-48 w) increased within 7 d of birth and stabilized with respect to PNA. V and A had a greater effect than G on the subsequent progression of RF.

Conclusions: Systems pharmacology can be used to inform the development of biological systems (CPR and RF) in human neonates. A common model for G, A and V precisely describes neonatal concentrations in relation to time after dose, post-natal age and weight. The nephrotoxicity of antibiotic use in early life can be described using this model.

References:

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B-14: *Hanna Silber Baumann* Using pharmacokinetic simulation to guide dose escalation decisions for targeted IL2v immunocytokines

Hanna Silber Baumann(1), Christophe Boetsch(1), Volker Teichgräber(2), Benjamin Ribba(1), Valerie Cosson(1)
Roche Pharma Research & Early Development. (1) Clinical Pharmacology, Roche Innovation Center Basel, (2) Translational Medicine Oncology, Roche Innovation Center Zurich.

Objectives: To guide dose escalation of targeted IL2v compounds with a narrow safety window through pharmacokinetic (PK) simulation, when a continuous reassessment dose escalation method (with overdose control, EWOC) did not provide sufficient flexibility due to the presence of non-linear PK behaviour.

Methods: Two targeted immunocytokines, that contain a variant of IL-2 (IL2v), are currently being investigated in clinic. Their molecular design aims to avoid preferential activation of regulatory T-cells by removing CD25 binding, to increase the therapeutic index of IL-2 therapy and to improve PK properties over wild type IL2 (Proleukin). The PK properties of the IL2v's are similar with the main elimination pathway likely mediated via interaction with the IL2 receptor (IL2R) expressed on circulating immune cells. The interaction with IL2R is also the cause of side effects which leads to a narrow safety window. A model describing the target mediated PK (TMDD) and expansion of the target pool has been presented previously [1,2]. Simulations were performed investigating different dosing intervals (e.g. QW, Q2W) and regimens for intra-patient dose escalation with the aim to find a regimen that would provide maintained peripheral exposure over several treatment cycles in order to optimize tumor uptake. We also aimed to understand the effects of dose and regimen on the expansion of the peripheral target pool.

Results: In general, the dose increase needed to maintain exposure was higher with a higher starting dose and a more frequent dosing, due to the effect on the target pool and TMDD. As an example, with a dose of 5 mg, no dose escalation was necessary to maintain exposure. By contrast, with a dose of 25 mg, a dose escalation of 60% was necessary when the regimen used was Q2W with an initial induction phase (2xQW). For the evaluated dose regimens, the median predicted exposure was in general maintained within 10% of that observed following the initial dose. With Q3W dosing, the target pool returned towards baseline in between doses and the required dose increase was lower compared to the QW/Q2W regimen. The simulations were used to guide dose escalation decisions in the clinic whilst managing safety.

Conclusions: Intra-patient dose escalation should benefit tumor uptake of the targeted IL2v's, as it allows higher doses to be administered compared to when a fixed dose regimen is applied. Simulations were used to mitigate time dependent loss of exposure and to safely explore and optimize dose and schedule.

References:
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B-15: *Simon Buatois* Modelling approaches in dose finding clinical trial: Simulation-based study comparing predictive performances of model averaging and model selection.

Simon Buatois(1,2), Sebastian Ueckert(3), Nicolas Frey(1),Sylvie Retout(1), France Mentré(2)
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Objectives: In dose finding clinical trials, modeling based approaches require selection of the model (MS) that best describes the data. However, MS ignores model uncertainty which could impair predictive performance [1,2]. To overcome this limit, model averaging (MA) might be used and has recently been applied to nonlinear mixed effect models (NLMEM) [3]. MA allows taking into account the uncertainty across all candidate models by weighting them in function of an information criterion (IC) [1].
The objective of this work is to compare predictive performances of MA and MS based on a predefine set of NLMEMs with a same disease progression model and different dose-effect relationships

Methods: Clinical trial simulations were based on a simplified version of a disease model which characterizes the time course of visual acuity (VA) of age-related macular degeneration patients [4]. The study design was set to 300 patients who were equally randomized in four different arms receiving receptively a placebo or one of the doses of a hypothetical drug. The dose-effect relationship was assumed to follow an emax function. Three scenarios were investigated assuming doses across ED50, doses lower than ED50 or no dose effect. Under each scenario, 500 trial replicates were simulated.
For each trial, parameters of four candidate models (emax, sigmoid emax, log-linear and linear) were estimated using importance sampling in NONMEM7.3 and several IC were investigated to select a model (MS) or compute weights (MA).
The estimation of the minimal effective dose (MED) and the Kullback–Leibler divergence (D_{KL}) between the true and the predicted distributions of the VA change from baseline were used as performance criteria to compare MS and MA.

Results: The overall predictive performance of the MED was better for MA than MS (up to 10% reduction of the root mean squared error). When looking at the entire dose response profile, the mean D_{KL} was reduced (up to 50%) when using MA compared to MS. Finally, regardless of the modelling approaches, AIC outperformed the others IC.

Conclusions: By estimating weights on a predefine set of NLMEMs, MA adequately described the data and showed better predictive performance than MS increasing the likelihood to accurately characterize the optimal dose.

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B-16: *Yuri Kheifetz* Model-based individual managing of thrombocytopenia during multi-cyclic chemotherapy

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Objectives: Thrombocytopenia is a major side-effect of cytotoxic cancer therapies. The development of individual therapy adaptations is a non-trivial task since thrombocytopenic risk depends on many therapy-associated and individual factors. To solve this task, we developed an individualized bio-mathematical model of human thrombopoiesis under chemotherapy and implemented it in a software-tool usable for therapy management.

Methods: We performed bio-mechanistic modelling of the dynamics of bone marrow thrombopoiesis and platelets by ordinary differential equations. Amplifications, death rates and transition times of the system are regulated by three types of biologically motivated feedback loops. The most important one is mediated by thrombopoietin for which injections can be considered by an attached pharmacokinetic and –dynamic model. Effects of cytotoxic drugs are modelled by a transient depletion of proliferating cells and a long-term depletion of osteoblasts reducing the supporting capacity of the bone marrow.

To parametrize the model, we used population data from the literature and close-meshed individual data of 138 non-Hodgkin's lymphoma patients treated with CHOP-like chemotherapies (on average 43 measurements per patient). The over-fitting issue of individual parameter estimates was successfully dealt with a virtual participation of each patient in 3 population-based experiments measuring 12 biological features.

Results: Our model qualitatively and quantitatively explains major mechanisms of thrombopoiesis such as: the role of osteoblasts in explaining long-term toxic effects, multiple regulatory functions of TPO, dynamics of megakaryocyte ploidies and non-exponential platelet degradation.

Almost all of the considered 138 individual time series data are fitted with high precision assuming only 11 parameters to be heterogeneous among patients.

We transferred the model into a user-friendly software tool which allows individual prediction of platelet-dynamics for CHOP-like chemotherapies of non-Hodgkin's lymphoma and the effect of therapy adaptations.

Conclusions: We successfully established a comprehensive mechanistic model of human thrombopoiesis under chemotherapy. It allows individual predictions of degrees of thrombopenia for the first time with superior accuracy compared to statistical or semi-mechanistic competitors. Moreover, it can be used to make clinically relevant predictions regarding individual therapy adaptations.

B-17: *Jurgen Langenhorst* High exposure to fludarabine in conditioning prior to allogeneic hematopoietic cell transplantation predicts impaired CD4 reconstitution and lower probability of survival

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Objectives: Allogeneic hematopoietic cell transplantation (HCT) is a procedure where healthy donor cells are infused to replace a diseased bone marrow. Fludarabine (Flu) is a drug widely used together with busulfan (Bu) in conditioning, a part of the procedure where high dose chemo- and serotherapy and/or irradiation are used to allow engraftment of the donor cells and to eradicate residual disease. Whilst targeting Bu to optimal exposure has been shown to increase survival(1), to date there is no optimal exposure known for Flu. As Flu has strong cytotoxic and immunosuppressive properties, this study aims to relate Flu exposures with CD4+ T-cell reconstitution (IR) and overall survival (OS).

Methods: In this retrospective single-centre study, the circulating metabolite of Flu (F-ara-A) was quantified in samples acquired for routine Bu therapeutic drug monitoring (TDM, from 2010). With these data, a pharmacokinetic model was developed in NONMEM 7.3 and the cumulative Flu area under the curve (AUC) was determined.
Main outcomes of interest were OS and IR. A value of 50 million CD4+ T-cells per litre was chosen as dichotomous measure for IR.(2-3) The time point at which a patient had the second consecutive measurement above threshold was defined as time of IR. Statistical analyses were done using Kaplan-Meier estimation (R 3.3) and parametric time-to-event (TTE) models (NONMEM 7.3).

Results: For the outcome analyses 197 patients were included (128 adults, 69 children), with a median age of 38 (0.23-73.5 years). To find an optimal cut-off for Flu exposure regarding the impact on OS, receiver-operating characteristic curves were used. A cut-off of 21.2 mg*h/L was found to be optimal, resulting in 2-year OS of 39% OS above and 65% below this cut-off. ($p<0.001$)
A Weibull TTE model, with covariates age and anti-thymocyte globulin exposure was found to best describe IR. Herein Flu AUC continuously impaired rate of IR. (OR 0-50 mg*h/L: 0.13, $p=0.01$). In a sequential analysis, where IR probability was imputed into an OS TTE model, IR was found to have an effect on OS (OR 0-100% IR: 0.41, $p<0.001$). Independently from IR, Flu exposure above cut-off further decreased OS (HR 2.2, $p=0.0035$).

Conclusions: High exposure to Flu impairs CD4+ T-cell reconstitution and reduces survival after HCT both via an IR dependent and independent manner. This is the first step in the definition of a target exposure for Flu in this setting. Dose individualization and/or TDM-based corrections towards the Flu target is warranted to reduce overexposure and improve survival after HCT.

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C-01: *Elisa Borella* Paediatric trial design optimization using prior knowledge in combination with modelling & simulations

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Objectives:
Evidence of PK/PD relationships for a new compound requires data arising from well-designed and relatively large clinical trials. Lack of attention to such requirements usually yields PK and PD parameters estimates which are biased or show poor precision. However, this prerequisite is often not possible in case of paediatric and rare diseases, where the patient population is small. In these cases, it is strongly recommended using all the available data and knowledge to design informative trials and analyse the data[1-5].

Our investigation uses clinical trial simulations based on the PK and the non-inferiority trial conducted by the DEferiprone Evaluation in Paediatrics (DEEP)[6] consortium as a case study. The main scope of the DEEP consortium trial is to characterize the PK of deferasirox (DFX) and to establish the non-inferiority of deferiprone (DFP) relative to DFX in paediatric patients with rare anaemias. Here we evaluate to what extent the use of prior knowledge can support: 1) the analysis of sparse samples collected in a (very) limited number of children when Bayesian estimation methods are used; 2) the optimisation of study design, as defined by ED-optimality, and the choice of alternative designs; 3) the development of drug-disease models to predict long-term clinical response.

Methods:
A population PK model for DFX was developed using published data from several PK studies in adults[7-11]. Allometric scaling was then used to account for PK differences in children. Scaled values of PK model parameters were used as input for the simulation of concentration-time profiles in virtual patients with same demographic covariates of the DEEP-2 study population.

1) Evaluation of the performance of Bayesian estimation methods in analysing very sparse PK data
PK trials were simulated in R, extracting randomly each time a different subset of virtual patients and one virtual sample per subject at sampling time points defined in the original clinical study protocol. For each simulated trial, the population PK model was evaluated in NONMEM with FOCE method, using the sparse simulated data, and $PRIOR when priors are defined. Three different analyses were compared: population analysis without priors, with highly-informative or weakly-informative priors. For each analysis, this simulation-estimation procedure was repeated until 100 successful runs were obtained. Probability of successful convergence and ratios of the individual exposure-related parameter estimates (AUC, Cmax) to the 'true' values were used to compare the performances of each method. A sensitivity analysis on priors was also performed to evaluate how heavily the conclusions were weighted on prior beliefs. To this aim, several scenarios including conditions in which DFX PK differences in children were not fully accounted for by allometric scaling were considered.

2) Evaluation of the impact of optimized designs on the precision of exposure extrapolation
Assuming uncertainty in PK model parameters, optimized blood sampling time-windows were obtained using the ED-optimization method in PopED. Optimized PK trials were simulated in R, extracting each time a different subset of virtual patients, who had samples collected at various points according to the optimized

sampling time-windows. For each simulated trial, the population PK model was evaluated in NONMEM with FOCE method and $PRIOR with weakly-informative priors, using the optimized simulated dataset and priors on PK model parameters. This simulation-estimation procedure was repeated until 100 successful runs were obtained. Precisions of individual exposure-related parameters estimates and convergence of the algorithm were compared for different n° of optimized samples per subject (from 1 to 4).

3) Evaluation of the impact of a model-based approach on the duration of a non-inferiority trial
Serum ferritin data retrieved from several published studies[12-23], involving both untreated and treated patients with DFX or DFP, were used to develop a PK/PD model for iron overload. Serum ferritin-time profiles in the virtual patients were simulated assuming similar mechanism of action in adults and children. Shorter trial durations with a sampling interval of one month were then tested. Non-inferiority trials were simulated for each scenario, extracting each time a different subset of virtual patients with their corresponding ferritin values. These data were used together with the PK/PD model to predict individual treatment response at 1 year. A comparison between the predicted serum ferritin values and the 'true' values was used to evaluate the predictive performance and positive predictive value for each scenario.

Results:
1) DFX PK was well described by a 2-compartment model with first order absorption and elimination. Allometric scaling was added on CL and Q with exponent 0.75, and on V1 and V2 with exponent 1. The use of priors consistently helps to obtain a successful convergence of the FOCE method, increasing the probability of successful convergence in case of sparse sampling from only 12% (no priors) to 56% and 75% for weakly- and highly-informative priors, respectively. Weakly-informative priors are more robust when there is uncertainty on the assumptions adopted in the model (e.g., scaling method).
2) It has been demonstrated that collecting only one sample per subject, even if these samples are randomly extracted from the optimized sampling time-windows, leads to a 60% chance of over/underestimating the exposure in children of more than 1.3 folds. Increasing the number of samples only from 1 to 3 shrinks this probability to less than 10%.
3) The developed PK/PD model for iron overload accurately describes the individual time-course of serum ferritin in patients undergoing life-long blood transfusions and chelation therapy. The model consists in a compartment representing the iron in excess in the body which is linked to the serum ferritin through an Emax model. The use of a model-based approach, using a PK/PD model developed starting from historical data, leads to predictive performances (e.g., positive predictive values) at 6 months that are not significantly different from those at 1 year, suggesting the possibility of shorter trial duration.

Conclusions:
The concept of prior knowledge is often highlighted in statistical research, but rarely evaluated in a systematic manner. We have used a concrete case to illustrate the implications of Bayesian principles in the context of pharmacometric analyses. Our investigation shows that Bayesian estimation methods allow integration of prior distributions as descriptors of both uncertainty and expected differences in parameter estimates, supporting the analysis of sparse samples when the population sample size is limited. Besides, we show how prior distribution can be used together with optimization and M&S techniques to inform decisions about the design of studies in small populations.

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C-02: *John Diep* Host-Pathogen interactions: A mechanism-based disease progression model to describe the pathogenesis of Acinetobacter baumannii pneumonia

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Objectives:

Pneumonia, an acute lower respiratory tract infection, is the fourth most common cause of death globally [1]. Emergence of multi-drug resistant Gram-negative pathogens, like *Acinetobacter baumannii,* complicates the selection and design of effective antibiotic therapy. The clinical outcome of such infections depends on the balance between the virulence of the bacteria, the host immune response, and drug effect.

Pneumonia due to *A. baumannii* is recognized through its lipopolysaccharide binding to the toll-like receptor-4 complex on macrophages [2, 3]. This activates NF-κB leading to production of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). These cytokines stimulate lung epithelial cells to secrete chemokines, such as cytokine-induced neutrophil chemoattractant-1 (CINC-1), resulting in the recruitment of neutrophils to the lungs to help clear infection. Prolonged proinflammatory response can cause acute lung injury, and is regulated by anti-inflammatory cytokines [4].

Current translational research primarily focuses on the interactions between antibiotics and bacteria, neglecting the host immune response. There is a critical need to integrate host-pathogen interactions into the design and optimization of antibiotic treatment regimens using a systems-based approach. The aims of this study were (i) to develop a mechanism-based model that quantitatively describes the interactions between (1) bacterial dynamics, (2) host immune response, and (3) lung injury using an immunocompetent rat pneumonia model of infection and (ii) to predict (simulate) the effects of an altered immune system on disease progression.

Methods:

Data
Pneumonia infection was introduced in Long-Evans rats via intratracheal instillation of *A. baumannii* strain 307-0294 [5]. Rats were challenged with 5 different initial inocula: $7.00x10^6$, $5.76x10^7$, $3.50x10^8$, $4.32x10^8$, and $7.65x10^9$ colony forming units (cfu)/mL with 18 animals per inoculum. During the time course of infection, terminal sampling was performed at 3, 6, 24, 48, 72, and 168 h for bronchoalveolar lavage fluid (BALF) and excision of lungs. Three animals were sacrificed at each time point. The total bacterial burden (CFU) was quantified as the sum of bacteria in the lung homogenate and BALF. Host immune response in the lung was quantified by measuring IL-1β, TNF-α, CINC-1, and neutrophil counts (NC) in BALF. Lung injury was assessed by measuring albumin concentrations (ALB) in BALF due to leakage from the vasculature into the alveolar spaces [5, 6].

Model
A mechanism-based disease progression model was developed to describe the time course of:
1) Bacterial dynamics: bacterial replication, natural death, and clearance by neutrophil response;

2) Host immune response: stimulation of proinflammatory cytokines by bacteria and stimulation of neutrophil recruitment by proinflammatory cytokines;
3) Lung injury: leakage of albumin dependent on proinflammatory cytokine expression.

Simulation
The model was used to simulate disease progression from an initial inoculum of 10^8 cfu/mL. NC was varied from 50-100% to simulate the effects of an altered immune system on disease progression.

Model development was conducted using a pooled approach with maximum likelihood estimation. ADAPT5 [7] was used for modeling and simulation.

Results:

Model Structure
All data were co-modeled: 5 different inocula with 6 different disease progression biomarkers per inoculum, CFU, expression of IL-1β, TNF-α, and CINC-1, recruitment of NC, and leakage of ALB.

1) The net of bacterial replication and natural death were described by a first-order process; bacterial killing by NC and neutrophil signaling were by second-order.

2) IL-1β and TNF-α were described by indirect response models [8] with capacity limited stimulation by CFU ($[S_{max}*CFU]/[SC_{50}+CFU]$) on the rate of production. CINC-1 was described by first order stimulation by TNF-α ($S_{TNF-\alpha}$) with first order elimination. NC was described by an indirect response model with linear stimulation by IL-1β ($S_{IL-1\beta}$) and CINC-1 (S_{CINC-1}) on rate of production. Neutrophil signaling was represented by transit compartments. An anti-inflammatory biomarker (AI) was included as an unobserved variable with capacity limited stimulation by CFU that inhibits both IL-1β and TNF-α rate of production.

3) ALB was described by an indirect response model with linear stimulation by IL-1β ($S_{IL-1\beta\_ALB}$) on rate of production.

Disease progression from initial inocula of $3.50x10^8$, $4.32x10^8$, and $7.65x10^9$ (high inocula) was markedly different from $7.00x10^6$ and $5.76x10^7$ (low inocula). Hence, the SC_{50} parameters acting on stimulation of IL-1β, TNF-α, and AI by CFU were different between high and low inocula. This biological relevant infection burden threshold enabled the co-modeling of the 5 inocula.

Model Results
The model described the observed data well. Time to maximum (T_{max}) CFU was predicted to range from ~15-18 h for the high inocula and ~3-6 h for the low inocula. Maximal stimulation of IL-1β ranged from ~22-30 h for high inocula and ~8-12 h for low inocula, with an estimated S_{max} of 96.6 (5.7% SE). Maximal stimulation of TNF-α and CINC-1 ranged from ~6-10 h and ~7-11 h with S_{max} and $S_{TNF-\alpha}$ estimates of 64.1 (5.2% SE) and 5.1 h^{-1} (12.7% SE), respectively. Stimulation of NC peaked from ~27-35 h for high inocula and ~9-13 h for low inocula with $S_{IL-1\beta}$ and S_{CINC-1} estimates of $6.51x10^{-3}$ mL/pg (39.1% SE) and $4.44x10^{-4}$ mL/pg (39.3% SE). ALB peaked from ~25-30 h for high inocula and ~9-14 h for low inocula with a $S_{IL-1\beta\_ALB}$ estimate of $9.76x10^{-4}$ mL/pg (5.0% SE). Remaining parameter estimates were within physiological ranges or agreed with values reported in the literature.

Simulations
The simulated infection with intact immune response (100% NC) predicted a CFU T_{max} of 21.0 h, with infection burden of $2.69x10^2$ cfu/mL by 168 h. With an altered immune response of 90% and 80% NC, the predicted CFU T_{max} was 23.2 and 26.4 h, with infection burden of $2.37x10^5$ and $2.08x10^8$ cfu/mL by 168 h, respectively. NC ≤ 70% showed no reduction in CFU. Proinflammatory cytokine expression and lung injury were more prolonged with decreasing NC.

Conclusions:

The model provides a reasonable description of the time course of bacterial pneumonia pathogenesis and host-pathogen interactions. It captures the maximal stimulatory effects of *A. baumannii* on proinflammatory cytokine expression, resulting neutrophil recruitment and response, and lung injury. It also allows for simulations of disease progression in hosts with altered immune systems.

The model will be expanded with additional biomarkers to validate neutrophil signaling and anti-inflammatory components and to provide a more comprehensive description of bacterial pathogenesis. Antibiotic PK/PD will be integrated to enable the design and optimization of novel treatment regimens.

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C-03: *Morris Muliaditan* Model-based rationale for drug combinations in tuberculosis

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Objectives: Pulmonary tuberculosis (TB) is an infectious disease caused by *M. Tuberculosis* (Mtb). The first-line regimen consists of rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z) daily for two months followed by R and H daily for additional four months, with doses depending on the patient's body weight. Despite the evidence of efficacy in clinical trials and clinical practice, the rationale underpinning the selection of present and novel combination therapies for TB remains empirical. Such empirical dose selection may explain the recent failure of three major phase 3 trials aimed to shorten current first-line therapy. Novel methods are hence required to better integrate pharmacokinetic-pharmacodynamic (PKPD) data arising from different preclinical experimental protocols for rational selection of drug combinations for clinical development. The availability of parametric approaches that enable quantification of the contribution of each drug in the combination therapy separately from the growth and death rate of the Mtb bacteria has remained limited. In fact, most of those methods are not readily applicable for the evaluation and ranking of combination regimens under current experimental protocols in TB. In addition, available methods describing drug interactions are not suitable to guide dose selection in clinical development. To overcome some of the current challenges in TB drug development, this analysis aimed to demonstrate how non-linear mixed effect modelling in conjunction with simulation methods can be used to integrate PKPD data from various preclinical experiments. Second, different scaling methods for selection of the dose and drug combination were evaluated.

Methods: Standard of care drugs (R, H, Z and E) were used as paradigm compounds. PKPD data of untreated BALB/c mice or treated with R, RH, RZ, RE, RZH, RZE and RZEH (5 days per week, once daily) for 8 weeks were extracted from literature (1-4). All drugs were administered via oral gavage. Mice were infected either by aerosol or intravenous route. In most experiments, the following standard doses were given: 10 mg/kg (R), 150 mg/kg (Z) and/or 100 mg/kg (E). Doses of H varied between experiments and ranged from 1.56 to 50 mg/kg. One experiment (1) studied the microbial clearance following 10-50 mg/kg R.

Disease progression, as measured by colony forming unit (CFU) counts, was described using a two-state model which assumed the existence of fast (F) and slow-growing (S) Mtb populations. Net growth rates of each population was assumed to be the same in mice as in human, whereas the inoculum and the host carrying capacity was estimated for each preclinical experiment or clinical study.

R was subsequently selected as backbone therapy and a PKPD model of R monotherapy was developed. The additional contribution of subsequent candidates was based on change in potency of the backbone regimen, as described by fast-growing (IC50-F), slow-growing (IC50-S) or both populations. Following this strategy, a stepwise covariate model building was performed. This was followed by simulations to assess the predictive performance of the PKPD models for early bactericidal activity (EBA0-14) in patients treated with R mono-therapy for which clinical data is available (5). The inoculum in TB patients was assumed to be 100 CFU/ml sputum while treatment was assumed to start approximately two months after infection. The PKPD relationship were initially assumed to be the same as in mice while differences in drug disposition and bacterial load at onset of treatment were taken into account. Published population PK of R was used to simulate exposure in TB patients (6).

Alternative scaling strategies were then explored to improve the predictive performance of the in vivo PKPD model for EBA0-14 in patients. Strategies included scaling for, but not limited to, differences in infection routes in the mouse models (intravenous vs. high-dose aerosol vs. low-dose aerosol), protein binding, F:S Mtb ratio or combination of the aforementioned factors. External validation of the selected scaling factors was subsequently performed using datasets from patients treated with R, RH, RE and HRZE (7, 8). Data analysis was performed using a non-linear mixed effect approach as implemented in NONMEM 7.3.

Results: Z was found to be the best companion for R (1.9x increase in IC50-F and IC50-S). In contrast to current clinical practice, it was found that the addition of H worsened the antibacterial effects of RZ in a dose dependent manner. Addition of E had no effect to the antibacterial activity of RZ. External validation demonstrated adequate performance for prediction of microbial clearance in mice infected via high-dose aerosol intravenous route who were treated with various combination regimens.

EBA0-14 in patients following R mono-therapy could not be predicted by scaling for difference in disposition and initial bacterial load alone. On the other hand, scaling for difference in protein binding, F:S Mtb ratio or combination of both factors did yield adequate predictions. This latter approach was chosen for subsequent simulations. EBA0-14 in patients who received either (up to 2 fold) higher doses of R or WHO recommended RHZE dosing regimens were also predicted. RH and RE data showed higher variability than predicted by the model.

Conclusion: We have shown that it is possible to systematically integrate different experimental protocols and describe the effect of combination treatments on the parameters of interest. The evaluation of drug combinations by non-linear mixed effect modelling using preclinical PKPD data provides a more robust rationale for selection of drug combinations than empirical choices. It is anticipated that the proposed parametric approach may allow for the assessment of the contribution of companion drugs in novel combination therapies. This analysis furthermore demonstrates that EBA0-14 in TB patients can be predicted from in vivo experiments. Finally, the data shows that RZ or eventually RZE are sufficient as a backbone therapy in prospective novel combination regimens against TB.

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C-06: *Robert Leary* An overview of non-parametric estimation methods used in population analysis

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Objectives: To present an overview of non-parametric (NP) estimation methods used to analyze PK/PD population models. Emphasis will be placed on current generation NP maximum likelihood (ML) methods, although semiparametric ML and Bayesian NP methods based on Dirichlet priors will be briefly described. Differences with parametric methods will be discussed, as will advantages and limitations of the NP approach. We will also discuss the range of mainstream current implementations now in use, and their various approaches to dealing with some of the limitations of earlier NP methods.

Overview: In 1986 Mallet wrote a seminal paper [1] which described an NP approach (Non-Parametric Maximum Likelihood, or NPML) for the PK/PD population estimation problem in which the assumption that the random effects (ETAs) are based on a multivariate normal distribution is discarded in favor of an arbitrary distribution. The paper described the key mathematical property of ML-based NP estimators, namely that the form of the optimal solution is a discrete distribution with support on a limited number (generally not greater than Nsub, the number of subjects) of support points. Mallet's algorithm allowed the support points to move (but only one per iteration) based on some ideas from optimal design (OD) theory, but suffered from a relatively slow algorithm for computing probabilities. In 1991, Schumitzky proposed a new NPEM (Non-Parametric Expectation Maximization) algorithm in which the support points were fixed and the probabilities computed via an EM algorithm [2]. Both NPML and NPEM were viable but slow and had a fundamental limitation in that the residual error model had to be input a priori. However, both algorithms were demonstrably successful in identifying, for example, mixtures of fast and slow metabolizers, even with relatively sparse data, in cases where standard parametric methods failed.

NPEM was ultimately succeeded by Leary's 2001 NPAG (Non-Parametric Adaptive Grid) algorithm [3], which allowed much smaller initial grids, movable support points (several per iteration), and had a far faster primal-dual probability optimization algorithm which took advantage of the convexity (in probabilities) of the negative NP log likelihood function. NPAG resolved some of the NP performance issues and is still the primary NP method in use by the Laboratory of Applied Pharmacokinetics in its Pmetrics and BestDose software as well as the method current used in Certara's Phoenix NLME software.

NP algorithms gained a great deal of exposure when a rather simple NP variant NONP appeared in NONMEM 6 in 2007. NONP fixed the support points at the EBE posthoc values of a prior parametric run, and that parametric run was also used to import covariate fixed effect and residual error model parameters. The initial NONP version was usually quite fast due to its limited grid size, but suffered to some extent from that limited grid and shrinkage effects in the sparse data case. Later work in Karlsson's laboratory at Uppsala to some extent resolved the NONP grid problem by augmenting the starting grid with several strategies [4]. These modifications have now made their way into PsN and hence are readily available to the community at large. The Karlsson laboratory also did some pioneering work on bootstrap and SSE estimation of standard errors, which appear to be the only viable approaches for the NP case [5].

NP methods are still an active area of research with an increasing user base and there are now a variety of quite effective methods available to the PK/PD population community. There are still limitations and some

performance issues, but these are gradually being overcome. We expect this trend to continue in the future and NP methods to take a more visible and effective role in the armamentarium of population methods.

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C-07: *Mats Karlsson* A comparison of performance between parametric and nonparametric estimation for nonlinear mixed-effects models

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Objectives: Nonparametric (NP) methods estimating discrete parameter distributions offer an alternative to parametric methods in pharmacometric analyses. This study aims to evaluate the performance of the NP estimation method in NONMEM 7 in comparison with the first-order conditional estimation or Laplacian method with or without interaction (FOCEI) [1].

Methods: The FOCEI and NP methods were compared for 29 PK and PD models previously developed based on real data. For the NP method both the default number of support point, which is equal to the number of individuals of the data set, and an increased number using the extended grid method [2] were tested. Model fits based on NP and FOCEI were compared based on objective function values (OFVs) and prospective OFVs using 5-fold cross-validation. For 12 out of the 29 models, reference distributions of the difference between the NP and FOCEI OFVs were created using stochastic simulation and estimation (SSE), where the original parametric models were used to generate 100 simulated data sets and then the difference between the OFV of the FOCEI and NP methods was calculated for each simulated data set.

Results: The estimated model fit to data was better for the NP compared to the FOCEI method as judged by lower OFVs. The range of difference in OFV was 12-1441. When the OFV was evaluated prospectively through cross-validation, the opposite was observed, lower prospective OFVs for the FOCEI method (range of difference 0.1-5847). SSE reference distributions of OFV differences indicated that a decrease in OFV for NP methods during fitting was larger than expected by chance in 3 of 12 models, which indicate model misspecification of the original FOCEI models. Use of the extended grid method did not change the relative performance of the two methods.

Conclusions: The better fit to data of the NP method can be expected given that more parameters are estimated and appears to be spurious in 9 of 12 investigated examples. The better predictive performance for new data of the FOCEI method in all examples can be understood from the local nature of discrete NP distributions.

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C-11: *Kristin Karlsson* Regulatory pharmacometrics in the EU in practice and the role of the Modelling and Simulation Working Group

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Objectives: To give an overview of regulatory pharmacometrics within the European Union aiming for a smoother workflow between regulators and applicants.

Overview/Description of presentation: The presentation will give a brief description of the European Medicines Agency organisation and workflow to provide an understanding of how pharmacometric analyses are evaluated. The role of the Modelling and Simulation Working Group will be explained and past and present activities of the group will be highlighted.

Furthermore the presentation will give an overview of common uses of pharmacometrics in the regulatory setting and where it plays a vital role in the development and authorization of medicinal products. The impact of pharmacometric analyses will be highlighted by examples from actual regulatory submissions. Some practical advice will be provided on how to improve communication between regulators and companies/applicants during market authorization procedures. References that can be used for good reporting standards will be included.

C-12: *Anna Nordmark* The new draft EMA Guidance on PBPK – The qualification of the intended use concept

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Objectives: Aspect regarding the Draft EMA PBPK guideline will be presented.

Overview/Description of presentation: The use of physiologically based pharmacokinetic (PBPK) modelling has been increasingly seen in applications submitted to European agencies as well as requested by regulatory agencies in Europe during assessment of marketing authorisations. At present the intended use is mainly PBPK simulations for drug-drug interaction scenarios. Available EMA guidance covers the principles and the general approach to the use of PBPK analysis. The draft EMA Guideline on the Qualification and reporting of PBPK Modelling and Simulation was released for public consultation in July 2016 [1]. During the consultation period a workshop with interested parties was held. Some highlights from this workshop will be presented in this presentation as well aspect from the draft Guideline regarding Qualification of the intended use illustrated with some case examples. Further, some aspects around reporting will as well be described.

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C-15: *Wojciech Krzyzanski* Correction of the likelihood function as an alternative for imputing missing covariates

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Objectives: Missing covariates in a population PKPD model are typically imputed in order to obtain a full data set for population analysis [1]. The major drawback of imputation is the creation of artificial data that might not reflect the actual covariate distribution. We propose a new method of handling missing covariates, where the likelihood function is corrected for missing data and imputation is not required.

Methods: Simulated plasma concentration data for N=80 subjects, based on the one compartment model after an IV bolus dose were used for testing the new method. Body weight (BW) was the only covariate related to CL and V according to power functions with exponents SCL=0.75 and SV=1. BW was log-normally distributed with mean log(65.8) and 10% CV. Individual CL and V were log-normally distributed. The plasma concentrations were log-transformed. For missing data, BWs of 20 subjects were excluded from the original dataset. The distribution of the remaining BWs was similar to the original one with logBW~N(log(65.5),0.18). The likelihood function was corrected by allowing the BW for subjects with a missing covariate to be drawn from the log-normal distribution N(log(65.5),0.18). An additional data set was generated were the missing BWs were imputed with the mean BW of 65.5 kg. The original model was fitted to the data sets with all (ALL) and imputed covariates (IMPUT), whereas the model with the corrected likelihood function was applied to the data set with missing BWs (MISS). Parameters were estimated using the FOCE method as implemented in NONMEM 7.3 [2].

Results: The estimates of typical values for CL, V, SCL, and SV were close to the original ones with relative absolute error less than 10% in all cases. The estimates of BSV for CL and V were less than 11% for the ALL and MISS models, whereas imputing BW resulted in 64% error (0.1 vs. 0.164) in the estimate of variance of V. The eta-shrinkages for CL and V were less than 17% for all models. The objective function values were -960.9 (ALL), -929.7 (MISS), and -913.1 (IMPUT).

Conclusions: Information about the distribution of the covariates can be used to correct the likelihood function for the probability of missing a covariate. This approach results in accurate estimates of the population parameters that are not different from the estimates obtained by the model with all covariates. Imputation of missing covariates with the mean value can result in biased estimates of BSV, if the distribution of the covariates is wide.

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C-16: *Henrik Bjugård Nyberg* SADDLE_RESET: more robust parameter estimation with a check for local practical identifiability

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Objectives: In the model building process finding the parameter values that best fit the data is a crucial step. Methods based on minimizing the gradient of the likelihood do not adequately evaluate the identifiability of the parameters, potentially leading to incorrect conclusions. We present an algorithm for checking local practical identifiability. The method provides higher confidence in parameter estimates, and can identify local identifiability problems for model-data combinations. We demonstrate the performance of our algorithm as implemented in NONMEM 7.4[1].

Methods:

Algorithm: Estimation utilizing gradient based optimization (e.g. FO, FOCE, LAPLACE) is performed. The result is checked for zero gradients, and if found any associated parameters are reset to their initial values. If no zero gradients are found, then the Hessian of the likelihood (R-matrix) is eigendecomposed and parameters are changed along the direction of the minimum curvature (including negative curvature) of the -2log(likelihood). Estimation is then re-initiated from the new values.

Numerical experiment: Seven example models were selected to represent likely scenarios: five published models with original data – A[2], B[3], C[4]; D – practically identifiable emax model-data, E – practically unidentifiable emax model-data, and F – structurally unidentifiable model[5]. Random perturbation using "retries" in PsN[6] was used to select 1,000 sets of initial parameter estimates within 99% of the best known estimate. Estimation was performed in NONMEM 7.4 alpha 14 from these initial values using SADDLE_RESET. An additional step was taken for models A and B to compare this new method to random perturbation within 10% of final parameter estimates instead of saddle reset in the workflow above.

Results: SADDLE_RESET improved the portion of estimations reaching lowest OFV from 81.2%, 69.8%, and 69.0% to 95.5%, 83.9%, and 77.3% for models A, B and C respectively. Random perturbation only improved percentages to 89.2% and 72.2% for models A and B. SADDLE_RESET successfully indicated local nonidentifiability by obtaining two sets of model parameters with minimum OFV in 96% and 95% of estimations for models E and F respectively.

Conclusion: Our algorithm provides an efficient and easy-to-use check for local practical identifiability of model-data combinations, thus improving confidence in parameter values. We recommend setting SADDLE_RESET to 1 whenever FO, FOCE or Laplacian estimation is performed.

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C-17: *Dmitry Onishchenko* Joint modeling of overall survival and tumor size dynamics in non-small cell lung cancer: Clinical trial simulations and validation of predictions at study and subject levels

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Objectives: Projecting survival estimates from early- to late-phase studies is a critical step in anti-cancer drug development. Surrogate endpoints such as progression-free survival (PFS) and overall response rate (ORR) are commonly used to assess efficacy in Phase 2 trials, while their association with overall survival (OS) in Phase 3 trials is known to be weak. An earlier FDA analysis modeled non-small cell lung cancer (NSCLC) tumor dynamics and OS in a 2-step approach [1], yet without considering dependencies between the two variables. Joint modeling [2] is a technique which allows to simultaneously fit a longitudinal variable (*e.g*., tumor size dynamics) and a time-to-event variable (*e.g*., OS). It enables one to convert full information from individual tumor size assessments into personalized predictions of survival, thereby avoiding dichotomization of patient response measures. To assess its predictive power, a joint model must be validated both at population and patient levels.

Methods: Clinical data from the Iressa IPASS Phase 3 study of gefitinib in NSCLC [3] were used to fit a joint model of tumor size dynamics and OS. Model validation was performed on a follow-up study data (IFUM, Phase 4 [4]). We simulated clinical trials using the model and compared mean simulated survival *vs*. observed data. A delayed effect of tumor dynamics on survival was also incorporated in the model. Model covariates were selected by performing various types of posterior predictive checks, including survival prediction for censored patients. The survival estimation method was implemented in R packages JM and JMbayes [5].

Results: The fitted model accurately estimated patient survival in the follow-up study using early data cut-off for tumor assessments. Individual odds of experiencing an event were evaluated in real time along with study-level survival estimates. Treatment, EGFR mutation status, and ECOG performance status were evaluated as covariates for the survival function. Associations between tumor dynamics (size and time derivative) and time to death were statistically significant (P-values <0.05).

Conclusions: Joint modeling of tumor size dynamics and survival allows for effective simulation of clinical trials, personalized predictions and robust validation of predictive survival models. It is applicable to different types of endpoints, including PFS and OS, and may thus provide a generalizable tool for prospective forecasting of survival in various study populations.

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C-18: *Eva Germovsek* Handling frequent observations of composite scores: Application to PROs in COPD

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Objectives: Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the lung, characterised by not-fully reversible airflow obstruction that progresses with time [1]. To record how well a disease is managed from the patient's point of view, daily questionnaires are often used; however, their analysis is challenging since the scale is composed of several individual elements, and the results contain a strong memory component. The aim of this study was to develop a model able to describe and learn from such patient-reported outcome (PRO) data.

Methods: Data were collected over a 1 year period using daily electronic diaries with 14 items (9 with 5 categories, and 5 with 4 categories) from patients enrolled in a prospective, observational study; the Acute Exacerbation and Respiratory InfectionS in COPD (AERIS) study, conducted at Southampton General Hospital, UK [2]. An item response theory (IRT) model [3] was used to relate the response data from each individual item to the underlying disease state. On the item level, Markov models (MM) were required to account for the dependence of an observation on the preceding observation. Minimal MM were used (i.e. the mean equilibrium time was assumed not to differ between compartments) and runtime reduction was explored by finding an analytical solution (AS) for the ordinary differential equations (ODEs). Since an AS for 3 compartments was obtained, some scores were initially merged; however, different combinations of scores were tested to allow for acquiring of good initial estimates for the full 5-compartment model (parameterised with ODEs).

Results: We analysed data from 127 COPD patients (median age 67 years, 54% male, 39% current smokers), providing approximately 40,000 observations per item. Parameterisation with the AS gave equivalent results to ODEs, and was about 6-times faster, therefore it was used for further model development. In this preliminary assessment mean (standard error) equilibrium time was estimated as 2.85 (0.22) days, and the slope on disease progression 0.035 (0.26) per year. Visual predictive checks on the individual item level showed satisfying fit to the data.

Conclusions: A preliminary IRT model was linked to Markov models for the first time to our knowledge and applied to real data from an observational study.

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Disclosures: EG, MOK and EP declare no conflicts of interest; CA, SY and MB are GSK employees and hold GSK shares.

D-01: *Markus Krauß* Translational systems pharmacology for acquisition of knowledge and prediction of drug pharmacokinetics across patient populations

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Objectives: Identify and translate (patho-) physiological and drug-specific knowledge across distinct patient populations for the subsequent prediction of drug PK in a specific population of interest [1].

Methods: A previously developed Bayesian population PBPK approach is used to extract information about physiological and drug-specific parameters, taking into account available prior information about corresponding parameters in the PBPK model [2]. Translation of generated posterior knowledge is possible due to the mechanistic consideration of the PBPK models, as the underlying structure and parameters allows transferring assessed parameter distributions as prior knowledge in the subsequent Bayesian-PBPK analyses. Data for the application of the translational approach was collected in a clinical study, conducted within the Virtual Liver program [3]. The study involved 103 healthy volunteers and 79 diseased patients. Both cohorts received the same cocktail of six approved and commonly used drugs at sub-therapeutic doses.

Results: In three learning steps, prior information about drug physicochemistry and individual physiology information was used together with experimental PK data to acquire posterior knowledge about a reference probe drug (midazolam) and a candidate probe drug (torsemide), respectively, both in a healthy population and an obese patient cohort. The population approach of our Bayesian-PBPK analysis allowed to consider both individualized PK profiles as well as population simulations which were both used for qualification of each step of the translational workflow. Every learning step demonstrated significant improvement in the agreement between simulations and observed data as well as in the information gained about physiological parameters of the model. The posterior knowledge about the candidate probe drug torsemide and the pathophysiological changes of the reference probe drug midazolam was then used for successful prediction of the population PK of torsemide in the obese population [1].

Conclusions: The presented systems pharmacology approach is a prototype for model-based translation across different stages of pharmaceutical development programs. It has the potential to systematically improve predictivity in drug development programs by incorporating results of clinical trials and translating them to subsequent studies.

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D-02: *Robin Michelet* PBPK modeling of propofol using the middle out approach

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Introduction: The project SAFEPEDRUG aims to provide guidelines for drug research in children, based on a combination of bottom-up and top-down approaches. Propofol, one of the drugs under study, is extensively metabolized in the liver and the kidney [1]–[3]. Furthermore, being a lipophilic molecule it distributes into the fat tissues, from where it slowly redistributes into the circulation [4]. In the past, both the bottom-up (PBPK, [5]) and top-down approach (popPK,[6], [7]) were applied to describe the PK of this compound with mixed results. In this work, a combination of the two approaches (middle-out approach) was applied to describe propofol PK.

Materials and methods: Clinical data containing different trial conditions were analyzed using a 3-compartment model in NONMEM v. 7.3, [8]. In vitro metabolism data was generated the same methodology as Gill et al. [9]. All data was then described using a full PBPK model in the Simcyp® Simulator V16 (Sheffield, UK). In vivo clearances were either obtained starting from in vitro clearance or scaled back from the in vivo clearance values estimated using NONMEM. Once an accurate in vivo clearance was obtained, the resulting model was challenged with new data.

Results: A CL of 1.07 L/h/kg and Vd of 822 L were estimated using the population approach. In vitro CLint values were consistent with literature, and an IVIVE would thus result in the same underprediction of total CL as described before. Therefore, the published model [9] was examined to see which parameters could increase the predicted CLiv. It was found that estimating the B:P and fu resulted in a predicted average CLiv of 1.01 L/h/kg compared to 0.39 L/h/kg before. Using the retrograde approach based on literature data, a match between predicted CLiv and NONMEM-derived CL was obtained. The model performed better than previous models and was able to describe PK for both long- and short-term infusions.

Conclusion: In the past, PBPK and PopPK have mostly been used side by side to describe PK. However, a better result is achieved if both are combined. When studying a complex ADME compound such as propofol, a PBPK approach is often recommended. However, current in vitro systems and IVIVE are not yet optimized for complexities such as UGT metabolism. Therefore, the best strategy is to integrate in vivo data with in vitro studies as is done in this model. Once an adult PBPK model is built, it can be scaled to children using knowledge of the ontogeny and maturation, which implies a correctly predicted contribution of each subsystem to the systemic clearance.

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D-03: *Miro Eigenmann* Therapeutic antibody concentrations at the biophase

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Objective: Concentrations of monoclonal antibodies in the different tissue compartments, vascular, interstitial and cellular, are very heterogeneous [1, 2]. PK measurements in the tissue interstitial spaces are very challenging [3] and often lacking for macromolecules. In this work we strive to improve the prediction of the interstitial PK of monoclonal antibodies in tissues using a combination of tailored *in vivo* studies and a PBPK modeling approach.

Methods: Tracer distribution studies were performed in mice in order to assess extracellular (^{51}Cr-EDTA), residual plasma (^{125}I-albumin) and derive interstitial volumes of individual tissues. In the same mouse strain, a biodistribution study of an untargeted IgG monoclonal antibody was conducted after i.v. injection of a 10mg/kg dose. Skin and muscle samples were subject to a tissue centrifugation method [4] in order to isolate native interstitial fluid and measure concentrations therein. All newly measured parameters and data were used to estimate tissue subcompartment concentrations and integrated into a PBPK model in order to predict interstitial tissue concentrations of mAbs.

Results: The PK showed a biphasic profile in plasma with a Cmax of ~210mg/mL and clearance of ~9mg/kg/d. Residual plasma fractions are high in well perfused tissues (e.g. lung=0.137) whereas lower in tissues with less blood perfusion (e.g. muscle=0.009). The interstitial volume fraction was found to be highest in skin (0.431). Corrections with tissue volume fractions enabled us to derive expected extravascular and interstitial concentrations in tissues. Measured interstitial concentrations in skin and muscle reach concentrations of about 50% of plasma concentration. The established PBPK model allowed an accurate description of the derived concentrations in the different tissue subcompartments.

Conclusion: Interstitial concentrations are highly tissue specific, dependent on the underlying capillary structure of the tissues [5, 6]. We hypothesize, that concentrations in tissues with discontinuous capillaries (e.g. liver, spleen and bone marrow) might even be equal to plasma concentrations. High concentrations (~50% of C_{pla}) were found in skin and muscle, tissues with continuous capillaries. In kidney and brain however, extravascular concentrations seem negligible. Integration of such data and parameter values into a PBPK model allows a physiologically more realistic and accurate description of the PK in the tissue interstitial space.

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D-04: *Alan Maloney* The 6 biggest pharmacometrics modelling mistakes!

Alan Maloney
Equation AB

Objectives:

Applied pharmacometrics is very difficult. From ensuring the designs of clinical studies are sound, through to analyses using non-linear mixed effect modelling, there are many opportunities for things to go wrong.

The objective of this presentation will be to highlight a number of the main technical mistakes I have made (or have seen) in applied pharmacometrics, and offer potential solutions.

Whilst I am hugely indebted to my educators, a number of mistakes can be traced back to my early education, where the desire of my tutors to provide a concise framework for modelling resulted in subtle, but important, factors being omitted. The “cookbooks” are not always right.

Methods:

The 6 mistakes that will be covered:

- Mistakes in experiment design (complex models versus weak data)
- Mistakes in model selection (significance testing and parsimony)
- Mistakes in model assessment (how sound are DV v PRED/IPRED?)
- Mistakes in model qualification (useless predictive checks)
- Mistakes in model uncertainty (or why didn’t we learn this!)
- Mistakes in parameter uncertainty (say no to the NP bootstrap!)

Advice or alternative methods and approaches will be suggested.

Conclusions:

The presentation will hopefully be enlightening, and help stimulate discussion on improving how we design, execute and evaluate our pharmacometric projects. It is also hoped the audience will be inspired to challenge their own education “cookbooks”.

D-07: *Richard Höglund* Pharmacokinetic-pharmacodynamic modelling of artesunate in patients with drug resistant and sensitive malaria

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Objectives: Today our current arsenal of antimalarial drugs are quickly becoming obsolete with the emergence of antimalarial drug resistance [1]. Multi-drug resistant malaria is now emerging and spreading quickly in Southeast Asia [1,2]. It is therefore crucial to optimise the treatment of currently available drugs to contain the spread of resistance and maximise therapeutic efficacy. The objective of this project was to develop a pharmacokinetic-pharmacodynamic model for artesunate and its active metabolite, dihydroartemisinin, and investigate the impact of drug resistance.

Methods: A total of 1,151 patients with uncomplicated *falciparum* malaria in 10 different countries in Africa and Asia were enrolled and received standard oral artesunate treatment (NCT01350856). Hitherto, this is the largest study conducted, investigating the pharmacokinetic and pharmacodynamic properties of artesunate and the influence of antimalarial drug resistance. Densely collected plasma concentrations of artesunate and dihydroartemisinin, microscopy parasite counts and molecular markers for drug resistance were collected in all patients. Pharmacokinetic and pharmacodynamic data were analysed using nonlinear mixed-effect modelling (NONMEM v.7).

Results: The pharmacokinetics of artesunate and dihydroartemisinin were well-described by a joint parent-metabolite model, assuming 100% *in-vivo* conversion of artesunate into dihydroartemisinin. One-compartment disposition models for both artesunate and dihydroartemisinin were sufficient with no further improvement of additional peripheral compartments. Parasitemia at enrolment, sex, and body weight were found to influence the pharmacokinetic properties significantly.

Total parasite biomass was modelled by a parasite compartment with a fixed 10-fold multiplication rate per parasite life-cycle (i.e. 48 hours). The drug-dependent elimination of parasites was dependent on the concentration of dihydroartemisinin and was incorporated with an E_{MAX} model. Molecular markers, associated with reduced drug susceptibility, had a significant impact on the E_{MAX}-value, resulting in a slower killing of parasites in patients with drug resistant infections.

Conclusions: A pharmacokinetic-pharmacodynamic model describing artesunate and dihydroartemisinin concentrations and their relationship to the elimination of malaria parasites were successfully developed. This model quantified the impact of molecular markers associated with drug resistant malaria infections.

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D-08: *Salvatore D'Agate* Model-based screening of compounds for the treatment of Chagas disease, a neglected tropical disease.

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Objectives: The aim of the investigation was to develop a drug-disease model with suitable parameterisation for the screening and selection of compounds against *T. cruzi*. A model parameterisation was chosen that allows the description of parasite growth and clearance in a standard *in vitro* protocol. This screening protocol enables the evaluation of multiple compounds, but empirical metrics of drug effect have shown to be misleading. Our approach provides insight into system- and drug-specific properties as distinct parameters, which in turn allows ranking of compounds considering different mechanisms of action.

Methods: A population modelling approach was applied for the estimation of systemic and drug-related parameters to describe data from an in-vitro experiment performed on H9c2 cells (rat cardiomyocytes) infected with Trypanosoma Cruzi based on previous literature models[1, 2]. Data was obtained from experiments in which different anti-parasitic compounds were tested using high-throughput screening (HTS) assays[3]. The analysis was performed using NONMEM V7.3. Model performance was assessed by diagnostic and GOF criteria. Statistical analysis, dataset handling and graphic visualisation were performed in R. The ranking was based on the estimated efficacy of compounds and was validated by comparison of standard compounds with previous literature data[4].

Results: A four-transit-compartments pharmacodynamic model was found to describe screening data with parallel analysis of multiple compounds per experimental protocol. The model predicts the time course and number of healthy and infected cells along with the number of intracellular amastigotes/trypomastigotes. An exploratory analysis showed the drugs to affect: 1) the duplication rate of intracellular parasites; 2) the premature lysis of H9c2 cells by the parasites, leading to re-infection; 3) the death rate of intracellular amastigotes; and 4) the growth rate of H9c2 healthy cells. It was also possible to show that the use of this model developed in conjunction with PK information allows the prediction of the therapeutic dose in humans.

Conclusion: The use of a drug-disease model allows screening and ranking of novel molecules against *T. cruzi*. Our analysis shows that the model can be applied prospectively for a more accurate classification of compounds. Despite the limited number of compounds tested so far, model parameterisation seems to provide the basis for the dose rationale in humans.

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D-09: *Carolina Llanos-Paez* Balancing efficacy and reduction in renal function to optimize initial gentamicin dosing in children with cancer

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Background: Children with cancer often receive long courses of gentamicin on multiple occasions alongside nephrotoxic chemotherapy. Achieving sufficient exposure for optimal efficacy is crucial in this immune-compromised population. Pharmacokinetic (PK) exposure targets are currently not achieved by 54% of patients, even after dose adjustment (1). Use of gentamicin is associated with nephrotoxicity and ototoxicity as a result of drug accumulation in the renal cortex and inner ear, which may be complicated by concurrent chemotherapy. Our research team previously developed a population PK model of gentamicin in 423 children with cancer (median body weight: 19.4 kg and age: 5.2 years) (2).

Objectives: To apply our population PK model in i) a utility function approach that balanced the probability of efficacy against potential reduction in renal function related to gentamicin accumulation in the renal cortex and ii) in semi-mechanistic pharmacodynamic (PD) models to simulate bacterial killing over time; to predict optimal initial dosing of gentamicin in this population.

Methods: Our previously developed population PK model (2) included an influence of patient age, fat-free mass (FFM) and serum creatinine concentration on gentamicin clearance (CL); and an influence of FFM on gentamicin central (V_1) and peripheral (V_2) volume of distribution and inter-compartmental CL (Q). Typical PK parameter estimates were: CL (L/h/70kg) = 5.77; V_1 (L/70kg) = 21.6; Q (L/h/70kg) = 0.62 and V_2 (L/70kg) = 13.8 (2), when standardised for FFM of 70 kg and serum creatinine of 37.4 µmol/L. The PK model was used to predict gentamicin exposure over 24 hours after a single IV-infusion (30 min) after drug administration and this information was then incorporated into a utility function and two semi-mechanistic PD models (3, 4).

Within the utility function the probability of efficacy (P_{EFF}) was balanced against the extent of gentamicin accumulation in the renal cortex and potential reduction in renal function. Efficacy probability at different C_{max}/MIC and AUC_{24}/MIC values were obtained from previous publications (5, 6). Patients were considered to have a 100% chance of efficacy when C_{max}/MIC reached 10 and AUC_{24}/MIC reached 100. The importance of achieving both C_{max}/MIC and AUC_{24}/MIC targets was weighted equally according to equation 1:

P_{EFF} = (Probability of C_{max}/MIC ≥ 10 + Probability of AUC_{24}/MIC ≥ 100)/2 Equation 1

Accumulation of gentamicin in the renal cortex (C_R) (mg/kg kidney weight) was predicted using a previous model which allowed for non-linear uptake (7) and linear elimination of gentamicin from the kidneys (8). A threshold concentration ($C_{Rthreshold}$) of accumulated gentamicin (8) (42.5 mg/kg kidney weight) was allowed based on patient age-predicted kidney weight (9), below which no side effects occurred. Gentamicin accumulation beyond this threshold had a detrimental effect on renal function, which was described by E_{GFR} (mM) and was calculated using equation 2 (6). Patient's baseline renal function prior to gentamicin usage (GFR_0, mL/min) was calculated using an equation proposed by Rhodin *et al*. (10). Patient renal function after gentamicin exposure (GFR_{new}) was predicted based on patient renal function prior to gentamicin usage and the detrimental effect of gentamicin accumulation given by another E_{max} model (equation 3). The percentage reduction in renal function (P_{GFR}) calculated according to equation 4 was included in the utility function.

If $C_R < C_{Rthreshold}$ $E_{GFR}(t) = 0$ Equation 2

If $C_R > C_{Rthreshold}$ $E_{GFR}(t) = E_{max} \times C_R^{\gamma}/(A_{R50}^{\gamma} + C_R^{\gamma})$

$GFR_{new} = GFR_0 - (GFR_{max} \times E_{GFR}^{\delta}/(E_{GFR50}^{\delta} + E_{GFR}^{\delta}))$ Equation 3

$P_{GFR} = (GFR_0 - GFR_{new})/((GFR_0 + GFR_{new})/2)$ Equation 4

Where E_{max} is the maximum accumulation effect observed and was fixed to 190 mM; A_{R50} is the amount of gentamicin in the renal cortex when E_{GFR} is equal to $E_{max}/2$ and was fixed to 55.4 mg; γ is the Hill coefficient and was fixed to 2.5; GFR_{max} is the maximum decrease in renal function and was fixed to 41 mL/min; E_{GFR50} is the accumulation effect value for which GFR_{new} is equal to $GFR_{max}/2$ and was fixed to 33.5 mM; δ is the Hill coefficient and was fixed to 5.5.

NONMEM® version 7.3 was used to estimate an optimal dose of gentamicin for different microorganism's MICs using a logit function (equation 5) under which P_{EFF} was maximised towards 1, while P_{GFR} was minimised towards 0.

$f(P) = \log(P_{EFF}) - \log(1 - P_{GFR})$ Equation 5

Bacterial kill curves for the estimated optimal initial gentamicin doses were then evaluated, given different microorganism MICs using two semi-mechanistic pharmacodynamic (PD) models (3, 4). R© studio software version 3.1 (http://www.r-project.org./) was used to simulate bacterial count over time.

Results: Based on the utility function, the optimal initial dose for gentamicin ranged from 7.2 mg/kg/24 hours (MIC = 0.5 mg/L) to 9.6 mg/kg/24 hours (MIC = 1, 2 and 4 mg/L). These doses provided a 92% (MIC = 0.5 mg/L), 87% (MIC = 1 mg/L), 79% (MIC = 2 mg/L) and 72% (MIC = 4 mg/L) probability of achieving $C_{max}/MIC \geq 10$ and $AUC_{24}/MIC \geq 100$. Baseline GFR prior to gentamicin usage was on average 40.8 mL/min. An average reduction in the GFR of 0.51% and 1.6% was predicted with an initial dose of gentamicin of 7.2 mg/kg and 9.6 mg/kg, respectively. Our utility function model predicted that the currently commonly administered initial gentamicin dose of 7.0 mg/kg/24 hours (1) achieved probability of efficacy of 91%, 83%, 76% and 67% for microorganisms with an MIC of 0.5, 1, 2 and 4 mg/L. When tested in the semi-mechanistic PD model (MIC = 2 mg/L) the estimated optimal dose of 9.6 mg/kg/24 hours given to the typical patient produced rapid initial bacterial eradication with 11 log killing and no bacterial regrowth for at least 11 hours. A dose of 7.0 mg/kg/24 hours produced initial bacterial eradication with 10 log killing and no bacterial regrowth for at least 9 hours. The bacterial count did not reach the starting initial inocula at 24 hours post-dose with any of the two doses.

Conclusions: This study utilised the first population pharmacokinetic model for gentamicin in oncology children with febrile neutropenia to obtain data that will assist in the personalisation of therapy. Using a novel utility function, an initial dose of 9.6 mg/kg/24 hours was identified as optimal to fight microorganisms with an MIC of 1, 2 and 4 mg/L providing 87%, 79% and 72% probability of efficacy, respectively, with a predicted 1.6% reduction in GFR. Simulations from two semi-mechanistic PD models showed that this dose provides acceptable bacterial killing in the typical patient.

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I-01: *Martina Liebich* Modelling of Dexamethasone in Paediatric Leukaemia Patients using a Population Pharmacokinetic Approach

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Objectives: Dexamethasone has been used as a central component in the treatment of childhood acute lymphoblastic leukaemia patients for several decades. However, relatively limited information about its pharmacokinetics in children has been published [1]. We conducted the current study to gain a deeper insight and understanding of dexamethasone pharmacokinetics in this vulnerable patient group.

Methods: Blood samples were collected from children enrolled in the UKALL 2011 Trial (EudraCT number: 2010-020924-22). Dexamethasone was administered orally at doses of 6 or 10 mg/m²/day. A total of 107 patients, 163 occasions and 668 blood samples were available for pharmacokinetic analysis. Modelling was performed using NONMEM 7.3 and diagnostic plots were created using R 3.3.2 and the xpose4 package.

Results: Median age and median weight for the studied population were 4.85 years and 19.0 kg, respectively. A one-compartment model with first-order absorption and elimination and proportional residual variability described the pharmacokinetics of dexamethasone adequately. As only oral data was available, volume of distribution and clearance were calculated as apparent volume of distribution and apparent clearance. Inter-individual variability was implemented on the apparent volume of distribution and the apparent clearance. Inclusion of allometric scaling was used to account for maturation processes among this patient population and substantially improved the model fit. Moreover, inter-occasional variability on clearance of dexamethasone was incorporated in the model explaining about half of inter-individual variability.

Conclusions: The pharmacokinetics of dexamethasone could be adequately described with our established model. The analysis provided a robust population pharmacokinetic model, which can be used to evaluate dosing regimens and covariate effects in children.

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I-02: *Klaus Lindauer* Model Simplification

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Objectives: In the course of the development of population pharmacokinetics and - dynamics models often multiple structural different models are able to describe and predict the experimental data nearly equally well. Often the obtained models can be distinguished only by their differences in the respective objective function value (OFV). Even though a more complex model might be favourable based on a lower objective function value compared to a structurally more simple model, the reproducibility of the complex model might be questionable. Therefore we developed a fast and elegant method to evaluate the robustness of the obtained model in varying the initial parameter set. We applied our newly developed method to a one - and two-compartment population pharmacokinetic model of a Glp1 agonist analog.

Methods: The results of the fitting procedure are often dependent on setting of initial values. Therefore the successful NONMEM (version 7.3) [1] run of the one- & two-compartment model was used as a reference of a successful path for the identification of the model parameter respectively. Along this path the model that resulted previously in an OFV with at least 10 points larger than the one of the successful fitting, is used as a starting model for re-fitting purposes. The identified parameter values were modified based on a multivariate normal distribution $\cal N(\theta,\sigma \textrm{= 0.01})$ and used as an initial parameter sets for the re-fitting approach. The procedure was repeated 25 times. Therefore we obtained 25 models (NONMEM runs) and respective parameter sets.

Results: Our newly developed method for evaluating the robustness and validity of the model parameter obtained, was applied to a Glp1 receptor agonist analog. For the one-compartment model all 25 fitting attemps converged into the same parameter set, whereas less than 1/2 (12) of the 25 re-fitting runs converged in case of the two-compartment model. Although the OFV was significantly lower for the two-compartment model, due to the lower robustness of the model, the simplier PK model was selected for our further analysis.

Conclusions: Even though a more complex model seems to be favourable based on its OFV, the one-compartment model resulted in more robust parameter sets.

References:
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I-03: *Dan Liu* Application of Global Sensitivity Analysis Methods to Determine the most Influential Parameters of a Minimal PBPK Model of Quinidine

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Objectives: Sensitivity analysis is used to evaluate the effect of model parameters on its outputs in various areas including systems biology and systems pharmacology [1-2]. Global sensitivity analysis (GSA) evaluates the relative contributions of each parameter as well as their interactions to the model outputs by simultaneously varying all parameters. We present an application of GSA methods to a minimal-Physiologically-Based PK (mPBPK) model of Quinidine, a model drug, to identify the most influential model parameters affecting the PK properties of interest.

Methods: Elementary effect GSA method (Morris screening) and variance-based GSA methods (extended Fourier Amplitude Sensitivity Test (eFAST) and Sobol sensitivity analysis) [2] were used to study the model parameters influence on the simulated PK properties, i.e. on C_{max}, T_{max}, and AUC, of a mPBPK model [3] of Quinidine given orally. For eFAST and Sobol methods, two sensitivity indices were calculated, i.e. first-order sensitivity index evaluating the effect of each parameter without considering its interaction with others, and total sensitivity index assessing the impact of parameters considering their potential interactions. The performance of GSA methods was also evaluated on non-linear and non-monotonic Ishigami-Homma function and g-function [4] by comparing the estimated sensitivity indices/importance with analytical solutions.

Results: In the mPBPK model of Quinidine, GSA sensitivity indices suggest that 1) Dose, Vss, BW, BP, fa, and Fg are the key parameters to influence C_{max}; 2) ka and fu are the influential parameters for T_{max}; 3) Dose, BP, Vss, BW, fa, Fg, fu, and CL_{uint}, have high impact on AUC_{24h}. Qualitative Morris screening can be as sufficient as quantitative Sobol and eFAST methods to identify the importance of model parameters when comparing with analytical solutions for both Ishigami-Homma function and g-function.

Conclusions: GSA methods were applied to identify the most influential parameters of a mPBPK model of Quinidine. Knowing the physicochemical and plasma/blood binding properties of Quinidine the determined ranking is as expected. Further, in this case, the qualitative Morris screening was as informative of the quantitative methods. Some of the model parameters can be inter-dependent; hence in the next step GSA methods capable of handling such cases (e.g. exSobol) will be used.

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I-04: *Rocio Lledo* PK/PD modelling of an anti-FcRn mAb to optimise FIM design - translation from cyno to human

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Objectives: UCB7665 is a mAb that aims at reducing levels of pathogenic IgG in autoimmune/alloimmune diseases by blocking FcRn receptor. Our objectives were: a) to develop a PK/PD model characterising the relationship between UCB7665 PK-IgG in cynomolgus monkeys (cynos); b) following its translation into humans, to optimise the FIM study design characterising the safety/tolerability at clinically relevant doses, and to prove the mechanism of action; and c) to update the model with FIM data and further understand cross-species differences.

Methods: Data from a PK/PD study in cynos was analysed by non-linear mixed-effects modelling. The model described by Lowe 2009 for drugs with target mediated disposition (TMDD) and an indirect effect model were used to describe PK and effects on IgG.

System and drug related parameters were translated from cyno to human using a combination of literature, in vivo and in vitro data. Uncertainty in the translation was included in the simulations of possible FIM scenarios. The model was updated with the FIM data.

Results: A two-compartment model with TMDD in the central compartment and an indirect-effect model where the free drug stimulates IgG catabolism characterised the PK-IgG relationship in cynos. Simulations from the cyno-to-human translated model were used to optimise the FIM design. A range of doses between a starting dose corresponding to MABEL (<10% IgG reduction) and a maximum dose providing a -70% mean change from baseline IgG, were chosen. Intermediate IV doses were predicted to provide a mean -32% and -52% change from baseline IgG. The observed FIM data shown mean (±SD) reductions on IgG of -15.06±3.95%, -36.04±5.98% and -47.6±3.16% (6-9 days post-dose) for the 3 first doses in the escalation. The alignment between predictions and observations increased at higher doses, as the system moved towards linearity. The model adequately described the human data. The linearly-related parameters where well translated by allometry, whereas some differences on the parameters driving the TMDD process were observed between human and cynos.

Conclusions: The PK/PD model allowed the combination of different sources of data to optimally inform the FIM design. It displayed alignment between human predictions and observations, and correctly characterised the non-linear and complex system in a simplified mathematical description.

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I-05: *Florence Loingeville* Using Hamiltonian Monte-Carlo to design longitudinal count studies accounting for parameter and model uncertainties

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Objectives: Nonlinear mixed effect models (NLMEM) are widely used for the analysis of longitudinal data. To design these studies, optimal design based on the expected Fisher information matrix (FIM) can be used instead of performing clinical trial simulations. A method evaluating the FIM, without any linearization, based on Monte-Carlo Hamiltonian Monte-Carlo (MC/HMC) has been proposed and implemented in the R package MIXFIM [1] using Stan for HMC sampling [2]. This approach however requires a priori knowledge on models and parameters, which lead to designs that are locally optimal. The objective of this work was to extend this MC/HMC-based method to evaluate the FIM in NLMEM accounting for uncertainty in parameters and in models. We showed an illustration of this approach to optimize robust designs for repeated count data.

Methods: When introducing uncertainty on the population parameters, we evaluated the robust FIM as the expectation of the FIM computed by MC/HMC on the population parameters. Then, the compound D-optimality criterion [3, 4] was used to find a common CD-optimal design for several candidate models. Finally, a compound DE-criterion combining the determinants of the robust FIMs was calculated to find the CDE-optimal design which was robust with respect to both model and parameters. These methods were applied in a longitudinal Poisson count model where the event rate parameter ($\boldsymbol{\lambda}$) is function of the dose level. We assumed a log-normal a priori distribution characterizing the uncertainty on the population parameter values as well as several candidate models describing the relationship between log($\boldsymbol{\lambda}$) and the dose level (linear, log-linear, Imax, full Imax, or quadratic functions). Assuming the first dose fixed to 0, we performed combinatorial optimization of 2 among 10 doses between 0.1 and 1, corresponding to 45 possible elementary designs.

Results: We found that accounting or not for uncertainty on parameters does not have a striking impact on the allocation of optimal doses in this study. However misspecification of models could lead to low D-efficiencies of only 30%. The CD- or CDE-optimal designs provided then a good compromise for different candidate models, with D-efficiencies of at least 80% for each model.

Conclusions: MC/HMC is a relevant approach allowing for the first time optimization of design for repeated discrete data accounting for uncertainty in parameters and in candidate models.

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I-06: *Amelia Deitchman* Tigecycline-Tetracycline Combination Modeling against Pseudomonas aeruginosa: Application of the General Pharmacodynamic Interaction Term in Various Interaction Models

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Objectives: The enhanced activity of combination tigecycline (TIG) and tetracycline (TET) against *Pseudomonas aeruginosa* has been previously described in *in vitro* static time kill curve experiments [1]. We aimed to develop a PK/PD model based on this data to comprehensively describe the antibacterial interaction and effect for this drug combination. This analysis also aimed to explore the use of an interaction term (previously presented as the general pharmacodynamic interaction (GDPI) model [2]) applied to empiric and mechanism-based models.

Methods: Static time-kill curve modeling was performed with NONMEM (Ver.7.3). Using previously developed models for the TIG and TET alone [3,4] as base models, a collective model was developed to describe a combined dataset of mono and combination therapy. Change in objective function value, visual predictive checks, and goodness-of-fit plots were utilized to evaluate fit of standard and modified Bliss Independence, Loewe additivity, and competitive inhibition models. GDPI terms were incorporated into models on EC50 or Emax terms to improve interaction description.

Results: Generally, many GDPI models had improved performance compared to their respective parent models. A competitive inhibition model with a GDPI term on Emax (INT 0.415) best described the TIG-TET interaction and was selected as the model to move forward for future analyses (EC50 2.7 mg/L TIG and 8.86 mg/L TET, $Kmax_{TIG}$ 1.49 h^{-1}, $Kmax_{TET}$ 1.35 h^{-1}, Hill factor 1.88). The final model was a two subpopulation (susceptible and persistent resting) bacterial model with load dependent transfer from the susceptible to persistent state (k_{SR} 1.25 h^{-1}), and drug degradation for both TIG ($kdeg_{TIG}$ 0.0909 h^{-1}) and TET ($kdeg_{TET}$ 0.0539 h^{-1}). Relative standard errors of estimates were below 30%.

Conclusions: TIG and TET effects alone and in combination *in vitro* against *P. aeruginosa* were described using a semi-mechanistic GDPI competitive inhibition model, which will be combined with clinical pharmacokinetic information to evaluate combination dosing regimens. This exploration has also demonstrated the flexibility of the GDPI term as well as its ability to generally improve model fit of empiric or mechanism-based interaction models.

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I-07: *Dominik Lott* Tolerance modeling: effects of the selective S1P1 receptor modulator ponesimod on heart rate

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Objectives: Development of a population pharmacokinetic/pharmacodynamic (PK/PD) model to characterize the effect of the selective $S1P_1$ receptor modulator ponesimod on heart rate (HR), including the development of tolerance upon repeated dosing.

Methods: ECG HR data from 280 subjects in 9 phase 1 studies (42500 measurements in total) were pooled (single doses of up to 75 mg and multiple once-daily doses of up to 100 mg).

The PK/PD model was built sequentially. Based on the PK model (1), PD model selection started with the analysis of placebo data. Presence of a circadian rhythm and placebo effect(s) were investigated. Subsequently, all data were used to include the drug effect and the development of tolerance. With HR as safety parameter, particular focus was placed on adequate capturing of the variability to predict the occurrence of bradycardia (HR < 40 bpm).

Results: A direct-effect I_{max} model with tolerance compartment and circadian rhythm was found to best describe the effect of ponesimod on HR. Baseline HR was estimated as 67.2 bpm and found to vary with an amplitude of 6.6% during the day. The circadian maximum was estimated to be reached at 5 PM. Although suggested by individual subjects' data, a placebo effect could not be identified. The maximum possible reduction in HR was estimated as 50% (from baseline), decreasing with development of tolerance with multiple doses. The appearance of tolerance was fast (0.41/h) compared to its decrease (0.011/h) indicating rapid onset and sustained maintenance of tolerance, allowing for multiple days of treatment interruption without complete loss of tolerance.

The effect of the first dose of ponesimod on HR including inter-individual variability was simulated using the final model. The median HR (10^{th} to 90^{th} percentile) at the time of maximum decrease was estimated as 59 (50-70), 53 (44-66), 48 (38-62), and 44 (34-59) bpm for doses of 2, 5, 10, and 20 mg, respectively. These results show that the risk of eliciting HR values < 40 bpm is minimal following an initial dose of 2 mg, the dose selected as starting dose for phase 3 clinical development (2-4), followed by gradual up-titration.

Conclusions: This analysis quantifies the effect of ponesimod on HR including the development of tolerance. A large number of measurements from 9 phase 1 studies provide robust data, allowing to simulate up-titration regimens to minimize the risk of bradycardia. In turn, these regimens can be clinically investigated in patients.

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I-08: *Rubin Lubomirov* Population pharmacokinetic-based interspecies allometric scaling and prediction of first-in-human (FIH) pharmacokinetics of a new anticancer agent

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Objectives: To develop a population pharmacokinetic model for simultaneous interspecies allometric scaling of individual preclinical pharmacokinetics and to predict the pharmacokinetic (PK) parameters and concentration-time profiles of a new anticancer agent in humans.

Methods: Preclinical PK studies conducted on mice, rats, dogs, mini-pigs and monkeys involving 122 animals with 387 plasma concentrations were available for interspecies scaling. In mice and in rats, each plasma concentration corresponds to a unique animal, whereas in the remaining species the individuals contributed with several plasma concentrations. The new anticancer compound was administered intravenously over wide range of doses (0.005 to 1.25 mg/kg) to animals with body weight ranging from 0.02 kg in mice to 20 kg in mini-pigs. Animal plasma concentrations were pooled and fitted in one step to a PK model using non-liner mixed-effects modelling implemented in NONMEM v7.3. Allometric equations were contained into the PK model to allow individual body weight PK parameters scaling. The incorporation into de model as covariates of gender, brain weight (BrW), maximum lifespan (MLS) and unbound plasma fraction (fu) was investigated.

Results: A three-compartment mammillary model with linear elimination from central compartment and additive residual error in log domain was shown to adequately describe four-species pooled concentration-time data. Including all five preclinical species resulted in a deficient fit, thus mini-pigs were excluded from the final model. Further model fit improvement was archived accounting for the presence of a small subpopulation of monkeys with low clearance and low central compartment volume of distribution. No other covariates (gender, BrW, MLS or fu) were retained in the final model. The final PK model allowed extrapolation of PK parameters from preclinical mammals to man. Subsequent simulations performed using an in-house dataset of phase I trials patients were used to inform the design of FIH dose-scaling clinical trial and to assist bioanalytical method development.

Conclusion: Population PK model for simultaneous interspecies allometric scaling was successfully used to describe plasma concentration-time profiles from four animal species administered intravenously over wide range of doses accounting for the presence of potential bimodal exposure. This approach provides valuable information that cannot be provided by “two-stage” allometric scaling methods.

I-09: *Inga Ludwig* Correlative analysis of response to treatment and biomarker levels in a setting with a time-to-event efficacy outcome and sparse biomarker data

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Objectives: The identification of reliable pharmacodynamic markers of drug efficacy can be of great value, e.g. to explore optimal drug schedule options in oncology applications. However, correlative analysis of biomarker levels and efficacy outcomes can be challenging in settings with time-to-event based efficacy endpoints and limited availability of biomarker samples. The goal of this analysis is to assess a potential correlation between biomarker levels and tumor response as characterized by time to progressive disease in patients treated with an investigational drug, making use of predicted biomarker response.

Methods: Data from 230 patients were evaluated for this analysis. Only few biomarker samples per patient were collected, therefore biomarker levels could not directly be related to efficacy outcomes (time of progressive disease observation). Instead, biomarker levels at the time of disease progression were estimated from an E_{max} response model established from earlier studies, using C_{trough} estimates from an existing population PK model. Exploratory graphical analysis of these predictions was performed to compare predicted biomarker levels at the time of disease progression with the levels of a corresponding at-risk population.

Results: The analysis approach allowed to further assess hypotheses initially generated upon visual inspection of patient-level data, summarizing and putting in context information from the whole study population. E.g. whether, after treatment discontinuation, elevated biomarker levels may be associated with an increased risk of disease progression. In the studied case, this hypothesis was supported, which encourages further exploration of the biomarker as a potential marker of drug efficacy.

Conclusions: Model-based prediction of biomarker levels using prior knowledge from population PK and PK-biomarker models allowed assessment of a potential correlation with tumor response outcomes (time of progressive disease) despite limited availability of biomarker data. The proposed graphical analysis is a well suited means to explore general trends in the data, support hypothesis generation and make a basis for fruitful discussions with the clinical team. We conclude that this approach may be valuable also in a wider setting of exposure-response analyses with time-to-event endpoints.

I-10: *John C Lukas* Order in patch absorption rates?

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Objectives: Transdermal delivery systems ("patch") achieve steady "infusion-like" delivery avoiding sharp peaks & first pass metabolism, eliminating multiple dosing, increasing bioavailability and improving compliance. Absorption rates of patches are reported as zero-order, possibly not to their true complexity. The single dose PK for four compounds were extracted from the public domain and their absorption rates qualified vs. the zero-order assumption.

Methods: Patch PK in human from Rivastigmine[1], Nicotine[2], Estradiol[3] and Rotigotine[4] were extracted covering most patch types. The Wagner-Nelson method was used to obtain partial areas up to all profile times with lamda-extension to AUC[0-inf] and for Kel. The slope of the "log-amount vs. time" plot was used for evaluating actual absorption rates. This is assumed to be linear if absorption is first order ("ka"), i.e. passive. Visual estimation of levels of linearity in the calculated slopes was used to evaluate first to zero-order or mixture of rates transitions in the patch absorption PK.

Results: 17 profiles across multiplicities by dose and patient type of the 4 drugs were extracted. The listed zero-order rates were for Rivastigmine (e.g. 9 mg dose; 4.6 mg/day); Nicotine (40 mg; 27 mg/day); Rotigotine (4.5 mg; 2 mg/day). However, the absorption rates, independent of flip-flop kinetics and patch types, were complex for all drugs analyzed. Absorption appeared as zero order in the first quarter of total application time but became more complex in later times. Dose-dependencies existed for amount and rate partitioning.

Conclusions: Actual patch absorption rates appear to be far from single order and may have complex dependencies with patch formulation types, dose and patch size. There are limitations in this analysis in the small number of single dose profiles tested. Although in multiple applications, the absorption rate is not essential in determining exposure, in flip-flop kinetics this rule fails. The impact of gaining such knowledge as early as possible in drug development, for formulation design, bioequivalence and forward modeling and simulation in development is evident.

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I-11: *Sreenath M Krishnan* Influence of the number of tumor size measurements on model-derived tumor size metrics and prediction of survival

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Objectives: The tumor size ratio (TSR), time-to-tumor growth (TTG) and tumor growth rate (KG) are frequently suggested predictors of overall survival (OS) for different types of tumors[1,2]. It should however be acknowledged that all available measurements are typically used to estimate these metrics for an individual patient. This study aims to investigate how the number of available tumor size measurements may influence the accuracy of predicting the true tumor size metrics for an individual patient, which in turn could influence the metrics' value in predicting the hazard of death.

Methods: Tumor size data for 1000 subjects were simulated using a simplified tumor growth inhibition model for bevacizumab+chemotherapy in colorectal cancer[3], at baseline, and at 6,12,18,24,36,48,60,72,84 and 96 weeks. The 'true' TSR at week 6 (TSRw6), TTG and KG were derived from the simulated individual profiles and the prospective evaluation function in PsN[4] was applied to investigate the accuracy of the predicted metrics and the OS estimation.

Results: As expected, the accuracy of the tumor size metrics improved as the number of measurements increased. When only baseline and w6 measurements were used in the predictions of TSRw6, about 70% of individuals had <10% deviation from 'true' TSRw6. By adding a w12 measurement, the corresponding percentage was 78%. The accuracy in the individuals' predictions was little affected with addition of later observations. The accuracy in TTG predictions was in general low; the percentage of individuals with <30% deviation from 'true' TTG was increased from 32% to 39% when increasing from 2 to 4 observations, while additional measurements only marginally affected the accuracy. The percentage of individuals with <10% deviation from 'true' KG improved from 41% (2 observations) to 77% when all 11 observations were used. As the number of tumor size measurements increased, the OS predictions improved as determined by the model fit and the parameters uncertainty. However, to predict the 'true' hazard of death, 6 tumor size measurements were needed.

Conclusions: This simulation study demonstrates that TSRw6 is a more promising metric than TTG or KG for early prediction of treatment outcome for an individual patient, since fewer measurements are needed for adequate estimation of the metric and hence for predicting OS, in line with its lower shrinkage [5]. In addition to baseline and a w6 measurement, a w12 measurement appears beneficial for estimating an individual's TSRw6.

Acknowledgements: This work was supported by the Swedish Cancer Society.

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I-12: *Lei Ma* Dupilumab dose selection for a phase 3 study in asthma patients: pharmacokinetic/pharmacodynamic (PK/PD) modelling and clinical trial simulation

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Objectives: Dupilumab, an anti-IL-4Rα monoclonal antibody, is under development for multiple indications, including asthma. To select phase 3 doses in asthma, a phase 2b dose-ranging study was completed in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta agonist, randomized to dupilumab 200/300 mg every 2/4 weeks (q2w/q4w), or placebo (PBO) (NCT01854047).[1] Exposure-response (PK/PD) modelling and clinical trial simulation (CTS) were conducted to aid optimal dose selection in the intended patient population, understand PK/PD relationships, and identify influential baseline covariates.

Methods: Functional dupilumab was measured by serum immunoassay. PK/PD models of severe exacerbation events and forced expiratory volume in 1 second (FEV_1) were established based on observed efficacy data and dupilumab exposure (model-predicted area under the curve) from the phase 2b study, then used to predict the efficacy of various dose regimens, including those not clinically evaluated (e.g.200 and 300 mg weekly). Various phase 3 design scenarios were compared and their probability of success (POS) evaluated by CTS.

Results: The PK/PD relationship for recurrent severe exacerbation events and FEV_1 were best described by a negative binomial Emax regression model (offset by patient treatment duration and accounting for over-dispersed event rates across patients) and by a non-linear Emax regression model, respectively. The model-predicted annual exacerbation rate ratios (95% CI) vs PBO were 0.365 (0.229–0.583) for 200 mg q2w and 0.314 (0.186–0.530) for 300 mg q2w. At Week 12, FEV_1 change from baseline predicted differences (95% CI) vs PBO were 0.146L (0.078–0.213) for 200 mg q2w and 0.159L (0.087–0.23) for 300 mg q2w. The empirical models indicated a near-plateau effect at the study's high dose (300 mg q2w) for both endpoints; and predicted very limited additional clinical benefit with doses [300 mg weekly with 0.270 exacerbation rate ratio and 0.170L for FEV_1 change] greater than 300 mg q2w. Of the 4 studied doses, the q4w regimens were predicted to be less efficacious vs q2w regimens. The model predicted results were similar to those observed. CTS provided quantitative POS for efficacy assessments with various doses.

Conclusions: PK/PD and CTS predictions were consistent with observed efficacy results in the phase 2b study. Modelling and simulation indicated the 200 and 300 mg q2w doses with highest POS for efficacy, thus supporting selection of doses for phase 3 asthma trials.

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I-13: *Vincent Madelain* Modeling viral kinetics predicts a rapid establishment of the cytotoxic immune response targeting distinct infected cell compartments in SIV controller macaques (ANRS SIC study)

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Objectives: Our group recently demonstrated that long term control of SIV infection can be obtained in cynomolgus macaques presenting a H6 MHC haplotype or in non-H6 animals infected with a low dose inoculum of SIVmac251 by mucosal route [1]. Here we applied mathematical modeling to viral kinetics in this model to help unraveling the determinants of viral control.

Methods: The kinetics of SIV RNA and SIV DNA was obtained for 18 months in 16 macaques in 3 groups: i) H6 macaques infected with 50 AID50 (n=6) ; ii) non-H6 macaques infected with 5 AID50 (n=4) ; iii) non-H6 macaques infected with 50 AID50 (n=6, controls). SIV RNA and DNA data were jointly fitted with a mechanistic model of viral infection, using nonlinear mixed effect models (SAEM algorithm, implemented in Monolix software).

Results: The rapid viral decline after the peak in controllers could be best reproduced assuming a cytotoxic immune response with a saturable infected cells-dependent growth rate, as previously described in [2]. Interestingly, simulation and Sobol global sensitivity analysis suggested that in our model viral control was mostly driven by an early effective response after peak viremia, and to a lesser extent by the strength of the immune response *per se*. This result corroborated independently by longitudinal ex-vivo assessment of CD8 T cells cytotoxic activity. Further, SIV-DNA after the peak declined slowly in a biphasic manner, suggesting that SIV-DNA after the peak largely originates from not or low actively productive cells. In fact, best fit to SIV-RNA and SIV-DNA kinetics was obtained assuming 3 compartments of infected cells: highly productive cells with a short half-life decreasing from 5.5 days (early infection) to 0.3 days after peak viremia, and two populations of weakly or nonproductive cells, with half-life of 5.1 and 118 days. Thus one predicts that these compartments respectively account for about 1, 5 and 96% of circulating infected cells, in typical controllers at the setpoint viremia.

Conclusions: In conclusion modeling predicts that an early establishment of an effective CD8 response is key to achieve viral control. Discrepancy between SIV-RNA and SIV-DNA kinetics reveals that more than 90% of SIV-DNA containing cells are not highly producing and not highly targeted by the immune response in these controllers.

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I-14: *Paolo Magni* Execution of complex Bayesian workflows with the DDMoRe Interoperability Framework: a case study in the diabetes area

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Objectives: The DDMoRe Interoperability Framework (IOF)[1] is an integrated infrastructure that enables the exchange and integration of models across different modelling languages and tools. The IOF is based on two interchange standards: Pharmacometrics Markup Language (PharmML)[2] and Standard Output (SO)[3]. It allows users to encode models via Modelling Description Language (MDL)[4], convert them into PharmML, run different tools via R script, and store and reuse results via SO. We updated the previously developed PharmML-to-BUGS converter, NMTRAN-to-BUGS data converter, and the WinBUGS connector[5,6] to support new features. The public-released IOF[7] was updated with this new software suite. The objective of this work is to demonstrate its use to design and execute a complex interoperable workflow based on two diabetes-related models.

Methods: The selected case study is here summarized: 1) identification of a multivariate regression model, relating demographic covariates with the parameters of a linear 2-compartment model of C-peptide (CP) kinetics, on a 207-subject dataset[8]; 2) estimation of the CP kinetic parameters for a new subject by using the identified regression model; 3) identification of the glucose-insulin minimal model (MM) and estimation of insulin secretion rate (ISR) by using the estimated CP kinetic parameters, and CP and glucose plasma concentration data collected in the considered subject after an IVGTT[9]. The IVGTT data have been analysed by testing in the DDMoRe IOF three modelling approaches, whose results have been compared to those reported in literature: i) a full non-Bayesian approach, providing point estimates of MM parameters in a given individual; ii) a mixed approach where a Bayesian identification of the MM was considered; iii) a full-Bayesian approach where also the uncertainty on CP kinetics parameters was taken into account in the MM identification. NONMEM and PsN were used for non-Bayesian tasks, whereas WinBUGS was used in the Bayesian approaches.

Results: Parameters estimates obtained at points 1) and 3) were consistent with the published values, which were originally obtained via Matlab.

Conclusions: This work demonstrates the usefulness of the IOF to execute complex Bayesian workflows, using standard languages for model encoding and task execution, even running target tools with different estimation methods. This also overcomes the encoding difficulties of complex PK-PD models in WinBUGS that are normally written via a nontrivial combination of BUGS and Pascal code.

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I-15: *Corinna Maier* Robust parameter estimation for dynamical systems from outlier-corrupted data

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Objectives: Dynamics of cellular processes are often studied using mechanistic mathematical models. These models possess unknown parameters which are generally estimated from experimental data assuming normally distributed measurement noise [1]. Outlier corruption of datasets often cannot be avoided. These outliers may distort parameter estimates, resulting in incorrect model predictions. Robust parameter estimation methods are required which provide reliable parameter estimates in the presence of outliers.

Methods: We propose and evaluate methods for estimating the parameters of ordinary differential equation models from outlier-corrupted data. As alternatives to the normal distribution as noise distribution, we consider the Laplace, the Huber, the Cauchy and the Student's t distribution. Therefore, we derive the necessary gradients and Hessian matrices of the objective function to ensure an efficient optimization.

Results: We assess accuracy, robustness and computational efficiency of estimators using these different distribution assumptions. To this end, we consider artificial data of a conversion process, as well as published experimental data for Epo-induced JAK/STAT signaling [2]. We study how well the methods can compensate and discover artificially introduced outliers.

Conclusions: Our evaluation reveals that using alternative distributions improves the robustness of parameter estimates [3].

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I-16: *Victor Mangas-Sanjuan* Semi-mechanistic Pharmacodynamic model of complex receptor-hormone dynamics

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Objectives: The objective of this work is to develop a pharmacodynamic model describing hormone time-course after the administration of a receptor agonist at different rates-.

Methods: A simulation exercise was developed in order to characterize the complex and flexible behavior of hormone levels in vivo. Different structural models were proposed incorporating a receptor, hormone and modulator compartments. Several mechanisms were adopted: a down-regulation mechanism, tolerance phenomenon, stimulation of hormone levels through endogenous/exogenous agonist, the rate of change of receptor/hormone levels as an activator of feedback kinetics, a modulator-mediated effect on the receptor/hormone levels. All analyses were performed with Simulx (mlxR package) in R 3.3.1.

Results: Due to the great time-scale between IV (measurements up to 2 days) and SR (measurements up to 300 days) formulations, a standard receptor-agonist model could not characterize the observed outcome. Therefore, the final model includes a modulator cascade (MTT=0.7 days) non-linearly activated by the rate of change of hormone levels, which stimulates hormone loss through an exponential function based on the concentrations of modulator in the last compartment (CMT=5). Deterministic and stochastic simulations were implemented in Simulx.

Conclusion: A semi-mechanistic pharmacodynamic model able to simulate the extent and flexibility of receptor and hormone dynamics was developed. After IV administration, the large amount of exogenous agonist perturbs in a greater extent the hormone synthesis and loss, which could not be characterized with standards models available. The rate of change of hormone and a feedback effect on hormone levels through a delayed modulator synthesis allowed to predict the different hormone dynamics after IV and SR administration.

I-17: *Ben Margetts* Modelling Cytomegalovirus Growth Kinetics in Immunocompromised Children

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Objectives: To produce a three compartment cytomegalovirus (CMV) viral kinetic (VK) model that is able to accurately predict viral loads (VL) whilst maintaining parameter identifiability.

Methods: 69 VK profiles containing a total of 1598 CMV qPCR observations were extracted from haematopoetic stem cell transplant (HSCT) patients treated between 2010 and 2014. In addition to these profiles, we also extracted all drug administration and lymphocyte count data available for these children.

A single compartment model assuming logistic growth inhibited by antiviral treatment and immune response was initially fit to these data, but was not able to account for many of the defining features in the VK profiles. In response to this, a traditional 3 compartment VK model [1] was fitted to these data (using NONMEM 7.3), with antiviral treatment as a covariate on viral replication, and age-scaled total lymphocyte count as a covariate on total VL and infected cell reservoir. In order to confer parameter identifiability in this model, uninfected cell parameters were fixed to endothelial cell estimates.

Results: Model diagnostic plots were promising, demonstrating clear improvement in the model's predictive power, with it able to consistently predict key disease progression events for the majority of patients. Simulations produced from the 3 compartment model were a substantial improvement over those produced by the single compartment model. It was able to capture a wide range of VK profiles, including slow exponential increases in VL, rapid decreases, and sharp oscillatory reactivation-like events. Parameter estimates were appropriate, demonstrating highly variable drug efficacy, a fast literature-supported [2] viral doubling time of ~ 1.1 days, and a potent immune response.

Conclusions: We have improved upon our single compartment CMV VK model, producing a more predictive, clinically applicable, three-compartment CMV VK model. This model can now be used to better inform us of the VK risk factors for developing drug resistant strains, allowing us to study the growth kinetics leading to CMV inter-host strain competition and viral persistence. Alongside these studies, we can now investigate the use of this model and its covariates for modelling other serious post-HSCT infections including Adenovirus and Epstein-Barr Virus.

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I-18: *Dimitris Maris* Asymptotic Analysis on a TMDD model: Control of the process

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Objectives: A detailed analysis of a multi-scale pharmacokinetic-pharmacodynamic (PKPD), one compartment, target mediated drug disposition model (TMDD) is performed. This TMDD model incorporates the interaction of a drug with its target, the binding of the compounds (generation of the complex) and the outcome of their interaction. The purpose of this analysis is to identify methodologies for the control of the process by acquiring a full system-level understanding.

Methods: The analysis is based on the Computational Singular Perturbation (CSP) algorithm [1]. CSP provides (i) an approximation of the Slow Invariant Manifold (SIM), which is the surface created by the constraints of the system (the emerging equilibria), (ii) the reduced model, that drives the system along the SIM and (iii) a number of diagnostic tools, that can be employed for the identification of the reactions that are responsible for the formation of the SIM and the reduced model. Among others, this method can identify numerically the stages in the evolution of the process where Quasi Steady State (QSS) or Partial Equilibrium (PE) approximations are valid [2].

Results: The reactions in the model that (i) generate the fast time scales, (ii) contribute to the formation of the SIM and (iii) drive the slow system, were identified. The analysis concluded that there are two distinct stages in the evolution of the process where QSSA and PEA are valid. The parameters of the model that (i) affect the formation of the SIM and (ii) the way the solution lands and then evolves on it were identified.

Conclusions: The present analysis systemizes the findings in the literature for the one-compartment TMDD model and provides some new insights about the control of the process. These findings are very important in order to i) propose improvements in the design of new TMDD models and ii) find ways to control the evolution of the process on existing TMDD models by identifying the correct parameters that must be more accurately specified [3].

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I-19: *Emma Martin* Using mixed effects modelling improves detection of drug-gene interactions in mouse trials

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Objectives: Mouse trials use multiple patient derived xenografts (PDXs) in order to reflect the heterogeneity in clinical cancer trials and to allow identification of subgroups of patients for treatment. Each PDX is treated once with each of the drugs being investigated, in a 1x1x1 design. These studies allow for the detection of drug-gene interactions, where gene mutations have an effect on drug-sensitivity. We aim to identify the best metric for measuring drug-sensitivity in order to identify drug-gene interactions.

Methods: The breast cancer PDXs from the data published by Gao *et al*. [1] was used to develop and test the methods. Three metrics considered were final tumour volume [2], mRECIST criteria [1] and growth rate in an exponential growth model. A mixed effect modelling approach with the interaction estimated as a parameter was also tested. The estimates of the interactions using each of the methods were compared to those found in a systematic literature review.

Results: Using a mixed effects modelling approach gave the most power to detect interactions. Both the modelling and growth rate approaches could be used to evaluate all interactions, even when data for a given animal was sparse, whereas missing data and drop outs led to a large number of interactions being non-evaluable for the other two methods. When compared to the 16 interactions found in the literature, 14 were correctly identified by the modelling and growth rate methods, the other two methods had a lower success rate, with fewer interactions available to compare.

Conclusions: Using modelling can help to identify interactions when using a mouse trial design. Changes to the design could potentially further aid in the identification of interactions. These include more replicates per patient tumour, particularly in the control group, and the inclusion of more dose levels for each treatment instead of a single clinically relevant or maximum tolerated dose per drug. Comparing the results to previously reported interactions in the literature allows for investigation into whether the results of mouse trials could be used to predict interactions which will later be confirmed clinically or preclinically, however there are potential issues with reproducibility [3] and publication bias [4].

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I-20: *Paolo Mazzei* Translational model-based approach to assist the dose-range selection of an antibody-drug conjugate entering Phase I

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Objectives: MEN1309 is an antibody-drug conjugate (ADC) specifically targeting cells expressing CD205/Ly75 antigen, inducing potent cytotoxic and antitumoral effect in preclinical models. This analysis aimed to propose a model-based strategy to support the design of the dosing regimen for the first-in-human (FIH) study, leveraging available data from toxicokinetic studies in monkey and in-vivo tumor growth experiments in mouse xenograft.

Methods: First, allometric approaches were applied to monkey PK data to predict the human PK profile. Second, a population PK/PD model was developed to scale the time-course of MEN1309-induced neutropenia from monkey to patients. Third, tumor growth inhibition data in mice were modelled to define the target exposure in human. Finally, the risk-benefit profile of the proposed dosing schedule was evaluated based on predicted neutropenia and expected antitumor activity in patients. Clinical trial simulations (CTS) were also performed to explore plausible scenarios for the FIH study (e.g., sample size and dose limiting toxicity occurrences). Data analysis was performed in NONMEM, Matlab and R software.

Results: MEN1309 monkey PK were described by a 2-compartment model with linear and non-linear elimination from the central compartment; both linear and non-linear clearance were scaled based on body weight using an allometric exponent of 1 [1]. Myelosuppression in monkey was modelled by the Friberg model [2] that adequately described the observed neutropenia after single and repeat dose; time-courses of neutropenia in patients were then predicted based on expected PK in human, typical human system-related parameters reported in the literature and drug-effect parameters estimated in monkey [3]. Tumor growth dynamics in mice was described by the Simeoni TGI model [4], from which the concentration threshold and target exposure in human were computed. Finally, CTS enabled the computation of several quantities of interest that supported the feasibility of the proposed accelerated titration design with 100% dose escalations that reverts to a more conservative design with smaller dose escalations once Grade ≥ 2 toxicity is observed.

Conclusions: By effectively allowing a model-based “humanization” of preclinical efficacy and toxicity data that otherwise are difficult to interpret from a clinical point of view, the proposed translational strategy supports the regimen design for the FIH study.

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I-21: *Nicola Melillo* Multiscale mechanistic models in Systems Pharmacology: development of a model describing Atorvastatin pharmacokinetics through integration of metabolic network in Physiologically Based Pharmacokinetic models.

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Objectives: This work aims to develop a Whole Body Physiologically Based Pharmacokinetic (WB-PBPK) model of Atorvastatin (AS), an HMG-CoA reductase inhibitor, and its metabolite AS-lactone (ASL) to predict drug plasmatic concentration in human through integration of *in vitro* experiments and prior physiological knowledge. Drug hepatic metabolism was described using a rescaled *in vitro* derived metabolic network coupled with the PBPK model.

Methods: An adaptation of the Compartmental and Transit (CAT) model was built to describe dissolution, transit and absorption of AS in the intestine following an oral dose. Metabolism due to CYP3A activity in enterocytes was added using an intrinsic clearance derived from *in vitro* experiments [1] as in [2]. This model was then coupled with a PBPK model describing AS distribution in organs. AS hepatic metabolism was described by using a metabolic network modelled through a set of differential equations representing the dynamic of the enzymatic reactions involved in the drug metabolism process. A metabolic network parametrized through *in vitro* experiments with hepatocytes was taken from the literature [3] and was integrated in the PBPK model upon appropriate parameters rescaling. The network includes reactions catalysed by the enzymes CYP3A4, UGT1A3 and membrane transporters. Finally, was also developed a PBPK model for ASL and was coupled with the previous one supposing that the formation of ASL can be attributed only to the activity of UGT1A3 in liver.

Results: Predicted *Cmax*, *AUC* and *tmax* of AS venous plasma concentration for 40mg oral administration are in the range of one standard deviation from the mean of clinical data collected by [4]. For the dose of 20mg predicted AS *Cmax* remains in the range of one standard deviation from the mean of the data [4] but *tmax* and *AUC* are underpredicted. Concerning ASL the model under -predicts all the metrics.

Conclusions: This model is a good instrument for the prediction of human *in vivo* concentration of AS, however, does not well explain the pharmacokinetics of ASL. This happens maybe because the conversion from AS to ASL occurs in other sites than liver where UGT enzymes are expressed, for example gut wall [5] and kidney [6]. In conclusion, these types of models provide a way to describe drug absorption, distribution and metabolic processes in an integrated manner. These models could be useful to understand how the current knowledge supports data explanation.

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I-22: *Sandrine Micallef* Evaluation of tumor kinetics metrics as early endpoint to support decision making in early drug development

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Objectives: In the process of drug development in oncology, moving from early to late phase is a critical and complex step. Usually, decisions are based on the overall response rate (ORR) derived from RECIST[1] criterion, and assessed on a limited number of patients (often 20-40 with more or less similar tumors). Because of variability and the limited amount of information obtained, good decision making can be difficult. We explored the benefits of metrics based on longitudinal tumor kinetic modeling to inform decision making in early drug development.

Methods: We used a bi-exponential tumor kinetics model previously proposed by Stein[2] and implemented as a nonlinear mixed effect model by Claret[3] to fit longitudinal tumor size data simulated from a real study in NSCLC patients treated with an immunotherapy. Predicted Tumor Kinetic Metric (pTKM) were derived from the model, including maximum tumor shrinkage, time to growth and time to progression. We defined decision criteria based on these pTKM to determine trial outcome (success/failure), mimicking the decision process based on ORR. The TKM based criteria were evaluated for consistency with truth and ORR using a simulation study. We compared TKM for decision making in simulated clinical trials of different scenarios (different number of patients, or different tumor assessment periods of time).

Results: Model based TKM required a minimum amount of data to allow model fitting while observed TKM can be derived from any dataset. Globally, predicted TKM had performed at least as well as observed TKM. However, when data were limited (low number of subjects, for example), decision criteria based on observed TKM had high risk of producing incorrect decisions. In this case, predicted TKMs were more likely to give correct decision.

Conclusions: At the end of a phase I clinical trial, when there is enough tumor kinetic data to allow population tumor kinetic model fitting, decision criteria based on predicted TKM support better decisions than observed TKM. Predicted tumor kinetic metric should be further explored as a quantitative support for decision making in early drug development.

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I-23: *Joske Millecam* A new approach in pediatric drug design: the development of a pediatric pig model. Part II: The maturation of hepatic cytochrome P450 enzymes using enzyme activity and proteomics

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Objectives: Development of appropriate animal models taking growth and maturation into account is pivotal for pediatric preclinical pharmacokinetic and pharmacodynamic (PK/PD) research. To determine if the conventional pig is such a potential animal model, the ontogeny of the different eliminating organ processes needs to be unraveled. The liver plays a key role in the biotransformation of drugs due to the presence of the cytochrome P450 enzyme system. Literature reports have demonstrated a high homology between human and porcine CYP450 enzymes in adults, suggesting the pig as a suited animal model for PK/PD and safety studies [1]. However data regarding the ontogeny of porcine hepatic CYP enzymes are lacking.

Methods: The *in vitro* CYP450 enzyme activity of the following probe substrates was measured in microsomes: midazolam, tolbutamide and chlorzoxazone. The microsomes were prepared of each time 16 pigs (8 ♂and 8 ♀, Hybrid sow x Piétrain boar) aging 2 days, 4 weeks, 8 weeks and 6-7 months. The corresponding metabolites, namely 1-hydroxy-midazolam, 4-hydroxy-tolbutamide and 6-hydroxy-chlorzoxazone, were quantified using a validated UHPLC-MS/MS method [2]. Furthermore, the microsomal protein per gram liver (MPPGL) was determined as it is a scaling factor in the extrapolation of the obtained enzyme activities to *in vivo* [3]. In addition to these *in vitro* activity experiments, the CYP isoenzymes in the same microsomes were determined by high definition data directed analysis (HD-DDA) mass spectrometry. The data analysis was performed using Progenesis QI.

Results: The microsomal activity of the three substrates increased with age. Significant sex differences were observed at 8 weeks of age for the three substrates and at 6 months of age for chlorzoxazone. The activity per gram liver, as calculated with the MPPGL, also showed a maturation profile. The increase in microsomal activity is reflected in an increase in CYP450 proteins in the microsomes. A total of 17 CYP isoenzymes was identified from which 10 had 2 or more unique peptides.

Conclusions: The maturation of porcine CYP450 enzymes shows a growth profile comparable to humans. The increase in activity suggests maturation of the enzymes as well as an increase in the absolute amount of the different CYP450 proteins.

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I-24: *Jonathan Mochel* One Health: Translational and Reverse Translational Modeling of Inflammatory Bowel Disease using an advanced Boolean Network

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Objectives: Recent literature [1,2] suggests that the purinergic receptor P2X7 is a relevant target for treating inflammatory bowel disease (IBD). IBD is a highly prevalent chronic intestinal disorder in both humans and dogs, such as clinical trials with naturally occurring cases of canine IBD are particularly relevant to study the efficacy and safety of P2X7 receptor antagonists (P2X7A). A model-based approach was used to predict the effect of a candidate non-competitive P2X7A on biomarkers known to be associated with chronic intestinal inflammation (IL1b, IL18) and tissue damage (i.e. Matrix Metalloproteinases, MMPs), as well as to guide dose selection for an upcoming clinical trial in IBD dogs.

Methods: A semi-quantitative Systems Pharmacology (SP) model, based on Boolean equations of IBD (including 43 nodes and 240 interactions), and implemented in the SP platform SPIDDOR [3], was used to simulate the effect of the candidate P2X7A. Simulations were performed assuming chronic response to 3 different microbial antigens (Lipopolysaccharide, Muramyl dipeptide and Peptidoglycan), and a direct effect of P2X7 antagonism on the inflammasome. Results were expressed as relative percent change from control for an increasing fraction of P2X7 being antagonized (from 25% to 100%, with 25% increments).

Results: In silico simulations showed a reduction by ca. half of IL1b and IL18 systemic levels when antagonizing 50% of P2X7, with only moderate effect on MMPs. A more substantial decrease in MMPs (>20%) can be expected with 75% and higher blockade of the target receptor.

Conclusions: Assuming that MMPs levels are associated with clinical activity, the selected dose of the P2X7A candidate should antagonize at least 75% of the target receptor. This approach has apparent translational medical impacts due to similarities in the pathophysiology of IBD between humans and dogs.

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I-25: *Daniel Moj* Application of a physiologically-based pharmacokinetic and pharmacodynamic (PBPK/PD) model of the histone deacetylase (HDAC) inhibitor vorinostat to improve dosing regimens in adults

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Objectives: First, to develop a PBPK model of the HDAC inhibitor vorinostat for adults [1]. Second, to link the PBPK model with (i) an HDAC-activity PD model (efficacy marker) and (ii) a thrombocytopenia PD model (safety marker). Third, to use the developed PBPK/PD model to identify vorinostat dosing regimens possibly superior to the standard treatment.

Methods: PK, PD, physicochemical, and ADME data were obtained from published literature and unpublished in-house data. For the PBPK model, 11 clinical studies (355 patients) administering single intravenous (75–900 mg/m^2) or single/multiple oral doses (100-800 mg) of vorinostat were split into a development and an evaluation dataset. When necessary, parameters were estimated based on the development dataset. For the PD models, 2 clinical studies after single and multiple doses of 400 mg daily were available including 73 patients. Both PD models were linked to intracellular bone concentrations of vorinostat. An indirect response model was used to model the HDAC-activity with vorinostat increasing k_{out}. Thrombocytopenia during a 36 weeks treatment was modelled using an expanded Friberg model [2]. Model parameters were based on literature results of 8 studies, mean parameter values were used for simulation and the vorinostat slope parameter was estimated. The full PBPK/PD model was used to simulate various dosing regimens. Modeling and simulation was performed using PK-Sim® 6.3.2, MoBi® 6.3.2, and Matlab® 2013b.

Results: A vorinostat PBPK/PD model was successfully developed. Development and evaluation datasets were excellently described and predicted. The ratios of predicted vs. reported $AUC_{0->inf}$ (n=52), C_{max} (n=54), T_{max} (n=41), and half-life (n=49) were 1.00, 1.00, 0.99, and 1.06, respectively. The standard vorinostat dosing scheme of 400 mg daily led to a steady-state thrombocyte count of $193*10^9$ cells/L and a maximum HDAC-activity reduction to 37%. The most favourable dosing regimen (2 h intravenous infusion, 7 daily doses, every second week) resulted in a maximum HDAC-activity reduction (E_{max}) to 23%, without altering the thrombocyte count. In general, single oral daily doses were superior to two and three daily doses.

Conclusions: The successfully developed PBPK/PD model of vorinostat identified new dosing regimens for vorinostat chemotherapy, which could significantly increase HDAC inhibition and thus possibly treatment effectiveness without increasing the risk of thrombocytopenia.

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I-26: *Tadakatsu Nakamura* Population Pharmacokinetic Analysis of Compound A and Its Metabolite in Healthy Subjects and Patients with Diabetic Nephropathy

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Objective: Compound A is a potent and highly selective non-steroidal mineralocorticoid receptor (MR) antagonist being developed for the treatment of diabetic nephropathy and other potential indications. Richly sampled PK data collected in phase 1 studies exhibited complex PK profiles for Compound A (secondary and tertiary peaks as well as prolonged absorption profiles following initial peak concentrations in conjunction with dose-dependent reductions in exposure with increasing doses) and its major metabolite (Metabolite B; slow formation and elimination). The objectives of the analyses were to develop population pharmacokinetic models that describe these characteristics of Compound A and Metabolite B.

Methods: PK data were pooled from 6 Phase 1 studies conducted in healthy subjects and 3 Phase 2a studies in patients with type 2 diabetic nephropathy. Plasma concentrations of Compound A and Metabolite B were sequentially fit by population pharmacokinetic models using nonlinear mixed effects modeling implemented in NONMEM 7.1.2.

Results: Exploratory models incorporating enterohepatic recirculation were tested to describe the multiple peak phenomenon, but were not adopted because they conferred limited improvement in the characterization of overall Compound A PK disposition. Compound A concentration-time profiles were best described by a 2-compartment model with 2 parallel absorption inputs (a first-order process to describe initial peaks and a zero-order process to describe prolonged absorption), dose-dependent relative bioavailability (described by a sigmoid Hill function), and first-order elimination. Metabolite B concentration-time profiles were best described by a 1-compartment model with linear elimination. The formation of metabolite was characterized by 2 input processes, with 1 formation pathway described as a fraction of the systemic elimination of Compound A and the second formation pathway described as a proportion of Compound A lost to apparent first-pass effect.

Conclusions: The atypical PK profiles observed in these data were adequately described by modeling the absorption of Compound A via parallel input processes as well as modeling the formation of Metabolite B as a function of both first-pass and systemic parent drug elimination.

I-27: *Srividya Neelakantan* Population Pharmacokinetic Analysis of Recombinant Factor VIII Fc Fusion Protein in Subjects with Severe Hemophilia A Across All Ages

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Objectives: To develop a population pharmacokinetic (PK) model that characterizes the PK of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with severe Hemophilia A across all ages and to identify factors that determine the PK variability.

Methods: The FVIII activity data from 3 clinical studies, measured by one-stage clotting assay, was used as marker for rFVIIIFc PK. Mixed-effects modelling with maximal likelihood parameter estimation methods were used to evaluate the population characteristics of rFVIIIFc. Since the proportion of observations below the lower limit of quantification (BLQ) was greater than 10%, the M3 method was used to account for the BLQ values. The effect of covariates was evaluated using a forward inclusion, backward elimination process. Diagnostic plots, standard errors of model parameters, evaluation of shrinkage, and visual predictive checks were used to guide model building and assess goodness-of-fit.

Results: The final population PK model for rFVIIIFc was a two compartment model with covariates weight (WT) and von Willebrand Factor (VWF) on CL; WT on V1. The population estimates of CL for this model was 1.59 dL/h (95% CI 1.53 – 1.65 dL/h); while the V1 was 32.2 dL (95% CI 31.3 –33.1 dL), the intercompartmental clearance Q was 1.01 dL/h (95% CI 0.44 – 1.58 dL/h), and V2 was 4.89 dL (95% CI 3.70–6.08 dL). Weight was identified as a major covariate of both the clearance and volume terms. The single allometric exponent that describes the relationship between weight and the clearances is 0.690, while the exponent for the volume terms is 0.932. Consistent with the mechanistic understanding of rFVIIIFc clearance, VWF explained additional 6% inter-individual variability in rFVIIIFc clearance in adults and adolescents ≥ 12 years of age. The negative exponent on VWF (-0.408) indicates that the higher the measured level of VWF, the lower the rFVIIIFc clearance. It should be noted that VWF data was not available in children <12 years of age and therefore, the relationship between VWF and rFVIIIFc clearance could not be ascertained in this population.

Conclusion: The kinetics of rFVIIIFc activity displays a two-compartmental behavior. The covariate for FVIII activity identified was Weight and VWF on Clearance; Weight was identified as a major covariate on the volume of distribution.

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I-28: *Asuka Nemoto* A Bayesian approach for population pharmacokinetic modeling of alcohol in Japanese Subjects

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Objectives: To explore significant covariates for the population pharmacokinetic analysis of alcohol by incorporating external data using a Bayesian method, and estimate effects of the covariates.

Methods: Blood alcohol concentration (BAC) data that were previously obtained from 34 Japanese subjects with limited sampling times [1] were re-analyzed. Characteristics of the data were that the concentrations were obtained from only the early part of the time-concentration curve. The data were analyzed using a Markov chain Monte Carlo Bayesian estimation with NONMEM 7.3. Informative priors were obtained from the external study [2]. Namely, a 1-compartment model with Michaelis-Menten elimination, which includes subject characteristics (body weight, sex and the genotype for ADH1B) as covariates, was fitted to our data. Age and the genotype of ALDH2 were investigated in an additional covariate modeling. Uninformative priors were used for scale factors of age on population mean pharmacokinetic (PM-PK) parameters and for the change in the PM-PK parameter values for the genetic variant of ALDH2. Predicted concentration was simulated using estimated values for PM-PK parameters and the area under the time-BAC curve (AUC) was calculated.

Results: The typical value for the apparent volume of distribution was estimated to be 49.3L in subjects with *ALDH2*1/*1* (the wild-type) and was 20.4 L smaller in subjects with *ALDH2*1/*2* (the genetic variant). The AUC for the subjects with *ALDH2*1/*2* was calculated 1.34 times higher than the subjects with *ALDH2*1/*1.* Age was shown to be positively correlated with the absorption rate and shown to be negatively correlated with the apparent volume of distribution.

Conclusions: A population pharmacokinetic model for alcohol was updated. A Bayesian approach allowed interpretation of significant covariates relationships, even if the current dataset is not informative about all parameters. This is the first study reporting an estimate of the effect of the ALDH2 genotype in a PPK model.

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I-29: *Thu Thuy Nguyen* Population pharmacodynamic model of bronchodilator response to salbutamol in wheezy preschool children

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Objectives: Inhaled short-acting beta2-agonists such as salbutamol are used to relieve acute symptoms of asthma in clinical settings and to measure airway reactivity during routine lung function testing. Preschool wheezing is a heterogeneous condition characterised by inconsistent effect of asthma medications [1], therefore it is not known whether the dose-response of salbutamol specific of asthma in adults exists in young children. We studied for the first time the population dose-response relationship of salbutamol in preschool wheezers using interrupter resistance (Rint) measurements [2]. A simulation study was performed to determine the appropriate salbutamol dose to administer for this age group.

Methods: Children (3 to 6 years) with wheezing episodes in the previous year were enrolled in a multicenter study. Each child received two successive doses of salbutamol in four groups (100, 400), (100, 600), (200, 600), and (200, 800) µg. Design evaluation was performed using PFIM3.2 [3]. Rint measured after each dose were described with a sigmoid Imax model. Data were analysed by nonlinear mixed models using SAEM algorithm [4] in MONOLIX4.3. A covariate analysis was performed to study the effect of several factors (asthma symptom control, treatment, allergy, tobacco exposure, etc.) using forward selection based on likelihood ratio test. Using the final model, individual Rint values (expressed in % of the expected Rint for a given height [5]) were simulated for 5000 children at progressive doses from 0 to 800 µg. We predicted at each dose the proportion of children with significant Rint reversibility (decrease ≥35% of predicted Rint).

Results: Data from 99 children were available for analysis. The Imax model adequately fitted the data with satisfactory goodness-of-fit plots. Children with uncontrolled symptoms had lower Imax compared to those with totally or partly controlled symptoms (0.23 vs 0.31, $p<0.001$). Dose to reach 50% of Imax (D50) was 51 µg. According to simulation, 88.1% of children with significant reversibility at 800 µg would already show significant reversibility at 400 µg.

Conclusions: Interrupter resistance could measure a dose-response curve to salbutamol in wheezy preschool children, which was similar to that of older patients. These young children require a high dose of salbutamol to correctly assess airway bronchodilator response (at least 400 µg). Poor symptom control was associated with reduced bronchodilation.

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I-30: *Rikard Nordgren* Calling C functions from NONMEM

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Objectives: Some PK-PD modelling activities require the use of root finding techniques when an explicit solution of a function is not available. In a recent pharmacometric study [1], Loewe additivity [2], a criterion to define a pharmacodynamic additive interaction, was required, which only has an implicit solution. A C function had previously been developed to solve this equation using the GNU scientific library [3]. When implementing the model in NONMEM, we needed either a rootfinder written in Fortran or a way to be able to call the C function from NONMEM. We choose the second option to be able to reuse our code.

Methods: The rootfinder C function was a function of double precision type variables returning a double, which should be called from an NM-TRAN abbreviated function [4]. Fortran 2003 introduces a standardized way of interoperability between C and Fortran via the iso_c_binding intrinsic module. This module was used to create a Fortran function interface to the C function. The C function could now be called via the Fortran function interface from an abbreviated NM-TRAN function, which in turn can be called from an NM-TRAN control stream. An additional difficulty was due to the fact that our C function took 12 arguments and the abbreviated functions of NONMEM 7.3 could maximum take 9 arguments. This was solved by introducing an additional function off-loading the extra arguments to global variables. For the control stream to be able to compile and link correctly a $SUBROUTINE for the Fortran code needs to be included in the control stream and an addition of the C object code file and gsl libraries in the link step of the nmfe script had to be made.

Results: The C function could be called from a NM-TRAN control stream via an NM-TRAN abbreviated function and the result of the implicit function could be directly used in $DES defined items. The approach is applicable to any other interoperable C function.

Conclusion: The Fortran 2003 iso_c_binding intrinsic module allows for many different types of C functions to be called from Fortran and therefore also NM-TRAN in a portable way. A slightly specialized nmfe script is needed to add the C file and dependencies to the linkage. The possibility to add files for linkage to nmfe without changing the script would simplify the future use of C together with NONMEM.

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I-31: *Ana Novakovic* A longitudinal model linking absolute lymphocyte count (ALC) and volume of T2 lesions to expanded disability status scale (EDSS) in patients with relapsing-remitting multiple sclerosis (RRMS)

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Objectives: Treatment of patients with MS and development of new therapies have been challenging due to the complexity of the disease, its slow progression, and the limited sensitivity of available clinical assessment outcomes. The utility and pressing need for biomarkers in MS has been extensively demonstrated, but so far no single endpoint/biomarker has fulfilled all the requirements [1]. The aim of this analysis was to establish the relationship between three clinical markers: ALC, a marker of the pharmacological effect of cladribine tablets; total volume of T2 lesions, an MRI (Magnetic Resonance Imaging) readout representing the burden of disease and EDSS, a long-term marker of disease progression.

Methods: The analysis included ALC, total T2 volume and EDSS data from two phase III trials investigating the efficacy of cladribine tablets in 1319 patients with RRMS [2, 3]. A biomarker-driven model for EDSS was developed using IRT (Item Response Theory) methodology by linking ALC and total T2 volume to the latent IRT disability of EDSS. A sequential modeling approach was applied in the analysis [4].

Results: Inclusion of total T2 volume as mediator of IRT latent disability improved the EDSS model fit in presence of the relative change from baseline ALC (DALC) ($p<0.001$). However, DALC remains the single most predictive variable for EDSS time-course ($p<0.001$), the higher the reduction in ALC, the lower the increase in EDSS. The final IRT model allowed adequate description of EDSS data on both the item and total score level.

Conclusions: Our findings confirm the well-documented lack of proof of surrogacy of total T2 volume for EDSS [5]. However, they indicate that lesions progression (as assessed by MRI) is nevertheless associated with disease progression (as measured by EDSS). The proposed model is the first dose-exposure-biomarkers-clinical endpoint model integrating the IRT methodology. It offers a platform for the quantitative understanding of the biomarker(s)/clinical endpoint relationship in RRMS.

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I-32: *Kayode Ogungbenro* Sparse sampling design for characterizing individual PK of recombinant factor VIII fusion protein (rFVIIIFc) in prophylactic treatment of Hemophilia A

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Objectives: To determine sparse sampling times for estimating individual rFVIIIFc maximum a priori (MAP) Bayesian estimates in children (<12yr) and adults/adolescents (≥12yr) and to evaluate the effectiveness of the recommended times to estimate individual pharmacokinetic (PK) parameters.

Methods: Fisher information matrix (FIM) for Bayesian MAP estimator [1] was implemented in PopDes, determinant of the FIM was optimized to derive optimal sampling times, assuming a dose of 50 IU/kg and 10 minutes intravenous infusion, and were also used to evaluate designs. Previously developed population PK model provided prior information. Robust three and two time points were proposed to estimate individual PK based on Bayesian methodology and their effectiveness was investigated using simulations. Plasma FVIII activities of 1000 random individuals were simulated using the population PK model for different designs, individual MAP Bayesian estimates and their relative errors were determined.

Results: Optimal three sampling times for children and adolescent/adults identified were all in the terminal phase due to the relatively weak prior on clearance. Despite informative prior on volume, an earlier timepoint at 0.5h was explored for the robust, practical sampling design to better estimate individual volume. Robust and practical three and two time points designs were identified for children and adults/adolescents with efficiencies relative to the optimal time points of approximately 91 and 83% for three and two time points respectively. Due to possible loss of information to data below lower limit of quantification at later timepoints for those robust sampling designs, alternative three and two time points were also derived; 0.5, 24, 48h and 0.5, 48h for children and 0.5, 48, 72h and 0.5, 72h for adults/adolescents. Relative to the optimal time points, the efficiencies of these designs were approximately 85 and 79% for three and two time points respectively. Simulation results showed adequate MAP Bayesian parameter estimation by both robust designs; mostly with relative errors within ±25 to 30% for the parameters.

Conclusions: Robust three and two sampling times for estimation of individual MAP Bayesian estimates were successfully derived and the simulations indicated that these allowed adequate estimation of individual PK of rFVIIIFc which could then subsequently be utilized for dose individualization.

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I-33: *Boram Ohk* Population Pharmacokinetics of Tacrolimus in Healhty Korean Subjects:role of CYP3A5 genotype and metabolite

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Objectives: Tacrolimus, an immunosuppressive agent that has been commonly used to prevent rejection after organ transplantation, is known to have substantial inter-individual pharmacokinetic (PK) variability and narrow therapeutic range. The aim of this study was to develop a population PK model of Tacrolimus in healthy Korean subjects.

Methods: This study was conducted in 29 healthy Korean subjects. All subjects received a single 0.075mg/kg oral dose of tacrolimus. Blood samples were drawn at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours after dosing. Plasma tacrolimus concentrations were analyzed using liquid chromatography mass spectrometry (LC/MS). A population PK analysis was conducted using NONMEM (Ver. 7.2).

Results: A 2-compartment model with first-order absorption provided the best fit from healthy subjects. Estimates of the population PK parameter were as follows; CL, 12.5 L/h; Vc, 19.6 L; Ka, 0.545 h-1; ALAG, 0.363 h-1; Vp, 359 L/h; Q, 26.4 L/h. The visual predictive check (VPC) was performed and the result exhibited the acceptable predictive performance of the final model.

Conclusions: A population PK model was successfully developed and reasonable parameters in agreement with previously published datawere obtained. Further study will be required to find out covariates affecting the PK parameters.

I-34: *Olafuyi Olusola* The Use of Physiological Based Pharmacokinetic Modelling in Assessing Drug–drug Interactions Associated with Antimalarial Treatment in Paediatrics

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Objectives: Drug-drug interactions (DDIs) between the antimalarial–Artemether/lumefantrine (AL) and anti-tuberculosis (TB) or antiretorvirals are likely. This DDI impact in children is unknown. Physiological based pharmacokinetic (PBPK) modelling technique can be used to describe the pharmacokinetics of drugs where clinical data is either unavailable or limited. This study aims to investigate the impact of AL co-administered with anti-TB drugs in paediatrics using physiological based pharmacokinetic (PBPK) modelling techniques.

Methods: Oral PK profiles as well as physico-chemical data of AL was collated from literature and used to develop adult oral PK models in the presence and absence of interactions with ketoconazole on SimCYP®. These models were validated with published clinical data. Paediatric oral DDI with rifampicin and isoniazid where then simulated followed by prediction of paediatric dose evaluations of AL in the presence of DDI with anti-tuberculosis drugs.

Results: Cmax and AUC_{last} of artemether and lumefantrine (include the lumefantrine day-7 concentrations) were within 2-folds of published clinical data. In children, the model-predicted mean artemether plasma concentration for 20mg dose (293.5 ± 98.6 µg/mL) and 40mg dose (221.3 µg/mL ± 104.5 µg/mL) were within the 2-fold of the literarture reported plasma concentrations for the 20mg dose (150 ± 206 µg/mL) and 40mg dose (196 ± 204 µg/mL). Also the day 7 lumefantrine concentrations 389.7 [0.1-7544] ng/ml were predicted within 2-folds of reported clinical studies 367 [0.12-768] ng/ml. The DDI in the presence of a combination of rifampicin and isoniazid significantly reduced the C_{max} and AUC to give a C_{max} ratio and area under concentration time profile curve ratio (AUC_r) of 0.21 and 0.22 respectively while for the lumefantrine day 7 concentrations the same DDI resulted in C_{max} ratio and AUC_r of 0.41 and 0.40 respectively significantly falling below the 280ng/ml threshold. An adapted AL 7-day dosage regimen resulted in between 63% and 75% of subjects attaining the 280ng/ml day 7 concentration target.

Conclusions: AL concentrations decreases significantly in presence of interaction with anti-tuberculosis (TB) regimen (rifampicin and isoniazid)**.** An increase in dosing frequency increased the percentage of subjects within the 280ng/ml C_{d7} target. An increase AL dosing frequency to a 7-day regimen from the regular 3-day regimen may overcome the impact of DDI in most TB co-infected malaria patients between 2 and 5 years old.

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I-35: *Sean Oosterholt* PKPD modelling of MYCN-inhibition in vitro and in vivo in a mouse model of neuroblastoma

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Objectives: This work evaluates the PK-PD relationships of a NCE aimed at the inhibition of oncogene amplification through *in vitro* models for cell viability and mRNA transcription, and in-vivo PK and tumor growth experiments in mice and rabbits. Model-derived parameters are then used to propose a starting dose in children and a suitable trial design for assessing the safety, tolerability and pharmacological profile of the NCE in patients with relapsed refractory neuroblastoma.

Methods: First, *in vitro* experiments exploring cell viability and mRNA inhibition levels were analyzed and characterized. Next, *in vivo* data containing 7 different dose groups ranging from 2.5 to 50 mg/kg was pooled together to describe the plasma concentration over time. Tumor concentration measurements were linked to the plasma PK model. The PK model in combination with the *in vitro* models were used in describing the drug effect on tumor growth in mice following 2 weeks of treatment. Finally, several scenarios were simulated to explore the effect of the drug on tumor growth in humans. PK data were extrapolated based on allometric scaling concepts.

Results: The PK of the drug after IV or SC administration was best described by a two-compartment model with first order absorption and elimination. Solubility issues resulted in non-linear exposure and was described by variability on bioavailability. *In vitro* cell viability and mRNA transcription inhibition experiments revealed the minimum inhibition level of 80% for the drug to have an effect. The combined PKPD model describing plasma PK and tumor weight was used in simulations of a range of drug exposure levels, this suggested a target range from 50 h*ng/ml to 1400 h*ng/ml. For a 70 kg human, equivalent exposures would be reached by a predicted dose range starting at 0.08 mg/kg up to 2.2 mg/kg.

Conclusion: The use of a model-based approach allows effective integration of *in vitro* and *in vivo* data. It does not only allow for the characterization of the parameters of interest, but also for the optimization of dose rationale in oncology trials, where the principle of target attainment is still replaced by the use of toxicity as marker for dose escalation in humans (i.e., MTD).

I-36: *Shan Pan* Investigation of Bayesian inference in predicting tissue concentrations using RStan

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Background & Objectives: A full PBPK model representing physiological profiles may not be available due to limited data. Minimal PBPK models can be an alternative to evaluate the target tissue concentrations. In this work we aimed to investigate the prediction of tissue concentrations using Bayesian approach, for compound X that is intended for the treatment of inflammatory liver disease.

Methods: A full PBPK model for compound X is available from a pre-clinical study, with the liver as the site of elimination. Using the full PBPK model scaled from pre-clinical species to humans, 1,000 subjects aged between 20 and 80 were simulated in R. Volume and blood flow in the liver were correlated and decreased by 20-40% with increase in age, and approximately one-fold decline in liver function with increase in age was considered [1]. Distributions of steady-state drug concentrations, volume, blood flow and clearance in the liver were obtained and referred to as true distributions.

Random sampling from the 1,000 subjects was conducted for the following two testing scenarios: (1) plasma data only, and (2) plasma and liver data. In each scenario, both sparse and rich samples were considered for 10 and 100 subjects, respectively. In total three runs of random sampling were considered.

Bayesian modelling with a minimal PBPK [2] was performed in RStan, with prior distributions defined on tissue volume, blood flow and clearance. Due to the structural identifiability with plasma data only, the minimal PBPK model was simplified into the classical two-compartment model via re-parameterisation. Posterior distributions of liver volume and clearance were compared with true parametric distributions. Posterior predictive distributions of steady-state concentrations in the liver were compared with true concentrations distribution.

Results: When plasma data was available only, rich or sparse plasma data had little impact on the prediction of drug concentrations in the liver. Strong prior distributions of liver clearance and volume, however, predicted close to true drug concentrations in the liver. When both plasma and liver data were available, even sparse samples in the liver gave good predictions of drug concentrations in the liver using the minimal PBPK.

Conclusions: The current study explored scenarios where Bayesian interference may be useful in predicting drug concentrations in tissue, and this in return may increase the predictive power of target engagement in tissue.

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I-37: *Maria Panselina* Dose-saturable model for amoxicillin used to predict probability of response in normal and obese pediatrics

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Objectives: Amoxicillin ("AMOX"), a beta-lactam hydrophilic antibiotic is used extensively against *Streptococcus pneumoniae* ("STREP") in pediatric adult pneumonia and acute otitis. Five in 1000 persons each year contract pneumococcal pneumonia and incidence is increasing. Revised breakpoints for p.o. AMOX against resistant STREP are at minimum inhibitory concentration (MIC) ≥2 mg/L [1]. Due to the dose-saturable kinetics of AMOX [2] and increasing prevalence of obesity in children, efficacy between 6 and 12 year olds may be reduced. The %T>MIC efficacy is obtained for normal weight and obese (50% increase) children.

Methods: PK profiles in healthy normoweight adults were extracted from Sjovall [2] for four AMOX single oral adult doses and a combined first-order and dose saturation-impacted zero-order absorption model was developed for AMOX in NONMEM. Mono-compartmental AMOX parameters were within literature estimates, higher doses becoming infra-bioavailable and represented by an ellipsoid saturation function with a KD = 1500 mg. The model was used to simulate the standard regimen PK of 40 – 50 mg/kg/day AMOX in children of 6 to 12 yr. Allometry for volume of distribution was by weight. The GFR is mature at 6 yr so clearance was assumed unchanged. The total, by-weight, daily dose varied between 750 and 3000 mg/day. In obesity (BMI > 50), the increase in kidney size follows a ¾ law with increasing weight [3]. A 50% increase in nominal weight led to a 37% increase in CL and a similar increase in V due to increasing extracellular fluid. Simulations were performed for a Q3D multiple dose regimen for AMOX 750, 1200, 2250, 3000 mg daily, covering nominal to obese 6 and 12 yr-olds. The 3rd day profile was extracted and the %T>MIC efficacy across N=150 virtual subjects calculated (threshold taken as T>MIC = 50%). Protein binding for AMOX is 18%.

Results: The recommendation per weight AMOX dosing is expected to provide adequate coverage in resistant STREP for pediatric patients (6 to 12 yr) with near 70% T>MIC attainment at over 90% proportion of patients (given assumptions on pediatric PK parameters).

Conclusions: The 40-50 mg/kg/day plan seems likely to provide coverage of therapy even for obese children. However, the assumption of pediatric clearance been similar to the adult may not hold. According to bedside reports it possibly represents the lower limit for CL, then true coverage will be reduced yet remain efficacious for non-resistant strains.

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I-38: *Sang-In Park* Population pharmacokinetic analysis of evogliptin in subjects with varying degrees of renal function

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Objectives: Evogliptin is a potent and selective dipeptidyl peptidase-4 inhibitor developed for treatment of type 2 diabetes mellitus (T2DM) patients. Renal impairment, one of the complications of T2DM, can alter the pharmacokinetics (PK) of evogliptin [1]. The objective of this study was to develop a population PK model of evogliptin in subjects with varying degrees of renal function and to evaluate the effects of the factors including renal function on the PK of evogliptin.

Methods: Plasma concentrations of evogliptin obtained from 30 subjects who received a single oral dose of 5 mg evogliptin were included for population PK analysis. The analysis was performed using non-linear mixed-effects modelling as implemented in NONMEM version 7.3. Renal function of the subjects were estimated based on the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula. Covariates including eGFR, body weight, age, and height were evaluated and the final model was selected based on decrease in objective function, diagnostic plots, and visual predictive checks.

Results: A two-compartmental model with first order-absorption was selected as the final PK model. Inter-individual variability (IIV) was modeled using an exponential error model and residual variability was modeled using a combined proportional and additive random effects model. The eGFR had a significant influence on apparent clearance (CL/F), and both the eGFR and body weight had a significant influence on apparent volume of distribution for central compartment (V2/F) which were described in the final model as follows: CL/F (L/h) = $18.8 \times (\text{eGFR}/63.7)^{0.529}$; V_2/F (L) = $757 \times (\text{body weight}/61.4)^{0.667} \times (\text{eGFR}/63.7)^{0.284}$. The typical value of absorption rate constant (Ka) was 1.03 h^{-1}. The IIV (CV%) for CL/F, V2/F, and Ka were 27.3%, 18.0%, and 53.2%, respectively. Model evaluation by goodness-of-fit plots and visual predictive checks suggested that the proposed model adequately described the observed data.

Conclusions: The population PK model for evogliptin was used successfully to select the significant covariates for the PK parameters of evogliptin. This model can be utilized to guide evogliptin therapy by explaining the effects of renal impairments on the PK of evogliptin.

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I-39: *Zinnia Parra-Guillen* Exploring the impact of study design on unperturbed tumour growth inhibition modelling

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Objectives: Xenograft and syngenic models are being increasingly used in drug development to evaluate the antitumour effects of oncological compounds. To characterise the pharmacokinetic/pharmacodynamic drug effect, the Simeoni tumour growth inhibition (TGI) model [1] is commonly used. An accurate description of the tumour dynamics in the absence of drug is a key step before characterising TGI drug effects. However, experimental designs are frequently limited both in duration and number of animals, potentially influencing parameter estimation. The objective of this study was to evaluate the impact of sampling schema and number of animals on the precision of parameter estimates, as well as exploring alternative sampling schemas.

Methods: Longitudinal tumour volume from 28 different cell lines corresponding to 10 different tumour types- was modelled using the Simeoni TGI model in NONMEM 7.3. Parameter precision of the different studies was evaluated considering (i) the standard schema of measurements every two days (Q2D), (ii) twice per week (BIW) or once per week (QW) in PFIM [2] and keeping the original number of mice per study (from 7 to 287). Additionally, parameter precision was evaluated when optimising the sampling times assuming 8 and 10 samples per study.

Results: Good precision was observed for the typical parameters (mean relative standard error, RSE, below 10%) in all evaluated scenarios. Largest imprecision was detected on the linear growth rate for those tumours with a low exponential growth rate. Moreover, precision on the interindividual variability (IIV) parameters was highly dependent on the number of experimental mice, with a RSE between 50-60% for standard experiments of 8-10 mice. The BIW sampling schema was proven adequate, showing little impact on parameter precision with a mean absolute loss <5% and a relative loss <25% for all parameters except for residual error estimate. When performing optimal design, clusters of sampling points around the initial and latest possible collection designtimes was observed, highlighting the importance of early and late measurements on parameter precision.

Conclusions: Measuring tumour volume twice per week allows for an adequate estimation of population parameters. However, precision of IIV parameters highly depended on the number of mice in the study rather than number of measurements. The results can be generalized to any tumour type cell line regardless of the dynamics of growth and variability.

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I-40: *Christophe Passot* In-depth assessment of the influence of anti-drug antibodies on adalimumab pharmacokinetics and concentration-effect relationship in rheumatoid arthritis

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Objectives: To assess the influence of free and total (free + complexed with adalimumab) anti-adalimumab antibodies on pharmacokinetics (PK) and pharmacokinetic-pharmacodynamic (PK-PD) relationship of adalimumab in rheumatoid arthritis (RA).

Methods: PK and PK-PD data were obtained from a prospective, observational, open, multicentric 26-week study (NCT01382160). Patients received 40 mg adalimumab subcutaneously every other week with or without methotrexate. Adalimumab concentrations and RA disease activity score (DAS28) were measured at inclusion visit, then at weeks 4, 8, 12 and 26. Adalimumab concentrations were measured using a validated enzyme-linked immunosorbent assay [1]. Anti-drug antibodies (ADA) were measured using two assays: Antigen binding test (ABT) and Acid dissociation radioimmunoassay (ARIA) [2], measuring free and both free and adalimumab-complexed ADA, respectively. The PK of adalimumab was described using a one-compartment model with first-order absorption and elimination rates. The relationship between adalimumab concentrations and DAS28 was described using a direct model. Body weight, sex, age and methotrexate cotreatment and ADA measured with both techniques were each tested as covariates on PK and PK-PD parameters. Data were fitted to a PK-PD model using non-linear mixed-effects modelling using Monolix 4.3.3 software (Lixoft).

Results: A total of 251 adalimumab serum trough concentrations and 319 ADA measurements were available in the 66 eligible patients. The following PK and PK-PD parameters were estimated: apparent volume of distribution (Vd/F=9.4 L) and clearance (CL/F=0.38 L/day), and adalimumab concentration leading to 50% decrease of initial DAS28 (C_{50}=16.3 mg/L). Body weight and methotrexate cotreatment respectively increased Vd/F and CL/F. Presence of ADA was strongly associated with increased CL/F, but this association was stronger with free ADA (Δ-2LL=-25) than total ADA (Δ-2LL=-15). The presence of ADA was not associated with altered C_{50} and therefore seems not to be associated with altered adalimumab potency.

Conclusions: Adalimumab clearance variability is better described using free than total ADA measurement, which corroborates with a previous study showing free ADA as a better predictor of treatment failure than total ADA [3]. In addition, our results suggest that ADA-triggered treatment failure is only due to an alteration of adalimumab pharmacokinetics.

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I-41: *Dimple Patel* Informing modeling and clinical trial simulation using the real world data: data content, quality and availability assessment

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Objectives: Model-informed drug discovery and development approaches are increasingly utilized and recognized in the pharmaceutical industry. Clinical trial simulations are essential to leverage models/knowledge accumulated through early stage data and extrapolate the quantitative assessment and decision making to a wider and targeted patient population. To better reflect targeted patient population variability and diversity/heterogeneity,CTS often utilize historical clinical data. Real world databases have the advantages of containing large number of patients and information content, and they become even more valuable when historical clinical databases are limited by trial specific enrollment criteria selection or transition is needed from the clinical study setting to a real world study setting. We aim to investigate whether real world databases, such as EMR or EHR, provide another valuable source of such information.

Methods: We took into account that the real world data usage could be constrained by the nature of its data reporting. The lack of systematic and comprehensive collection of measurements required can lead to either inconclusive or biased population representation. Also, data quality and lack of cleaning could be of concern. To assess these issues, we investigated whether event data obtained from a real world database would be comparable to data obtained from a clinical trial. Data from a recent outcome study[1] for empagliflozin, an SGLT2 inhibitor, was used in this investigation. The study enrollment criteria were used to identify relevant patients in a GE Quintiles EMR diabetes patient database consisting of approximately 3.8 million patients. Patients in the database with medical records within the clinical study timeframe were considered for the inclusion. Similar follow-up period in the database as the study exposure time was used. Relevant patient event records were reviewed and regrouped to match the publication events using ICD9 and ICD10 codes.

Results: The populations were matched to the extent possible on demographic factors and baseline parameters. Selected patient characteristics and cardiovascular event rates (myocardial infarction, stroke and CV death) and overall death rate were summarized and compared to the empagliflozin publication results. % missing data for relevant enrollment criteria, such as eGFR and HbA1c, were summarized.

Conclusions: The differences were attributed to information uncertainty, incomplete data, and population differences. We need to proceed with caution on the utilization of RW data in CTS.

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I-42: *Dimitrios Patsatzis* Construction and evaluation of "global" Micahelis-Menten reduced models

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Objectives: Multi-compartmental models in non-linear pharmacokinetics are largely based on the enzyme kinetics of Michaelis-Menten mechanism, which is characterized by multi-scale dynamics. The traditional approaches for the analysis of this mechanism fail from constructing reduced models that reproduce the dynamics of the full mechanism in a wide parametric domain. The aim of this work is to construct and evaluate, stable and accurate reduced models with global validity and compare them with the existing *Quasi Steady-State* (QSSA) and *Partial Equilibrium* (PEA) approximations. In addition, validity criteria will be presented for the stability and the accuracy of the QSSA and PEA approximations.

Methods: The analysis is based on the algorithmic *Computational Singular Perturbation* (CSP) methodology [1]. Among others, CSP identifies the variables and reactions that relate the most with the fast timescales in the dynamics of the multi-scale model. Reduced models are constructed that guarantee stability and accuracy, by the use of CSP. The traditional QSSA and PEA approaches are studied in the context of CSP [2]. Algebraic criteria of the validity of each reduced model are derived, regarding the stability and the accuracy of the traditional approaches QSSA and PEA.

Results: The validity of the CSP-generated reduced models is examined for a wide range of values for the initial enzyme/substrate concentrations and for kinetic constants. The QSSA/PEA-generated reduced models are shown less accurate and stable, when compared to the CSP-generated ones, in a large number of cases. New criteria for the validity of QSSA and PEA were produced, which are shown more valid than the existing ones.

Conclusions: The availability of trustworthy reduced Michaelis-Menten models is very important for the experimental investigator in the fields of biology/pharmacokinetics, especially of parameter estimations purposes. CSP provides such models, which are more robust than the existing ones. Regarding the qualitative understanding of the process, the present analysis systematizes the findings in the literature and provides some new insights.

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I-43: *Sophie Peigne* How to handle non-linearity in absorption: a case study in oncology

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Objectives: Drug S is an orally administered compound, with a complex absorption due to a low solubility, currently in clinical development for cancer therapy. Two dose escalation phase I clinical studies with drug S taken once per day, without food, during a 21 days cycle, are ongoing to determine the safety profile and the tolerability of this drug. In addition, the influence of food intake was assessed in a cohort of one of the 2 clinical studies after single oral administration of drug S. Using data from those 2 studies, a population pharmacokinetic (PK) model was built in order to characterize the PK of drug S and investigate potential non-linearity, to quantify its variability in patients and to identify the sources of variability.

Methods: For the 2 clinical studies, PK measurements were available for 73 patients, including 5 patients in the food interaction cohort. A total of 22 PK samples were collected at D1 and D8. Between the 2occasions, trough concentrations were also collected. A population modelling approach was used to characterize the PK of drug S in the patient population using MONOLIX version 4.3. Several absorption models were investigated as well as different elimination processes (i.e linear or non-linear elimination). A covariate analysis was also performed, investigating the impact of demographic characteristics as well as food effect. Due to the solubility issues of this compound, a dose effect was tested on absorption parameters.

Results: A 2 compartment model with a linear elimination best described the disposition of drug S. For the intestinal absorption, a model with transit compartments, parameterized with mean transit time (MTT) and transit rate constant (Ktr), was used. A large inter individual variability was observed for most of PK parameters. The effect of dose, implemented as continuous covariate, was found on absorption parameters (MTT and Ktr), indicating that a longer absorption for the higher doses, likely due to the number of tablets administered. The food intake increased the bioavailability by a 6 fold factor and the MTT parameter by a 3 fold factor.

Conclusions: The current developed model allowed a good description of the PK data for the drug S. During model building, a dose effect on absorption parameters was identified, which could be related to the solubility and the number of dosage forms administered. As soon as PD data will be available, they will be added to build a PK/PD model.

I-44: *Nathalie Perdaems* Multi-species translational PK/PD modelling in type 2 diabetes

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Objectives: In preclinical research, pharmacokinetic/pharmacodynamic (PK/PD) modelling is very helpful in the drug development. The PK/PD model developped in mice was used to support the dose-efficacy relationship assessment in other species (diabetic monkeys and patients).

Methods: A PK/PD model was built in mice using data from an efficacy study including oral glucose tolerance test (OGTT) with a reference compound (rosiglitazone) and a S compound, describing the time-course of 3 biomarkers (glucose, insulin and HbA1c). The distinction between drug related parameters and system related parameters allowed a physiological inter-species translation. A population PK model was built in diabetic monkeys. This PK model was used in the transposed PK/PD model, and the system related parameters were transposed from mice to monkeys using allometric scaling. This approach allowed to choose different doses for a PD study in diabetic monkeys. To improve the predictability in translated PK/PD models in type 2 diabetes, the mice PK/PD model was also transposed in patients using the rosiglitazone as proof of concept.

Results: The population PK/PD model developed in mice allowed to well describe plasma concentrations of rosiglitazone and the S compound and the 3 biomarkers (glucose, insulin and HbA1c) with and without treatment. A linear effect for the rosiglitazone and an Emax effect for the S drug were applied to describe the stimulation of the glucose use. All the system and drug related parameters were well estimated (RSE < 30 %), except drug effect and Ke0. The Kin was 0.017 g/h for glucose and 0.558 µg/h for insulin. A dose of 15 mg/kg was predicted as an active dose in diabetic monkeys using the scaled model. Data from literature [1] [2] [3] allowed comparing the PK/PD predictions and the observations. Modifications were necessary to well describe the dynamics of biomarkers in patients (for instance, slower absorption of glucose during OGTT (in addition to the Ka from intestinal compartment at 1.1 h^{-1}, a stomach compartment was added with a Kdiss at 1.6 h^{-1}) and then to well predict the antidiabetic effect in patients.

Conclusions: To propose a modelling strategy for the translational drug development from animal to human, the disease should be well understood and its specificities modelled in each species. Reference compounds are very useful to characterise the disease in each population.

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I-45: *Belén Pérez Solans* Modelling tumour growth and progression free survival of breast cancer patients treated with neoadjuvant therapy

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Background: Breast cancer (BC) is the most commonly diagnosed malignancy in the US and European women, with 23% (231,840) of new cases and 40,730 estimated deaths in 2015 (1), ranking 5th as cause of death worldwide(2). Although early diagnosis offers the best chance for survival, the identification of new prognostic factors is crucial. Early change in tumour size (CTS) has been related to Progression Free Survival (PFS) and Overall Survival (OS) for a number of malignancies (3–5) and may offer a chance for early evaluation of potential clinical benefit.

Objectives: The aim of this evaluation was to I) establish a semi-mechanistic model for tumour-shrinkage for the period lasting from diagnosis to tumour resection and ii) to evaluate predictive and prognostic factors (including model predicted tumour size related metrics) in relation with PFS.

Methods: Information related to tumour size and survival was obtained from 218 patients diagnosed with BC at the University Clinic of Navarra where neoadjuvant chemotherapy was administered. Tumour size and survival versus time data were linked and described using the population approach with NONMEM 7.3. Model evaluation was performed through predictive checks.

Results: Drug exposure was dealt using the KPD approach. The model used to describe the tumour size dynamics incorporates a drug efficacy part that depends on drug exposure and the administration of immune therapy. However, the incorporation of a disease progression argument or resistance development was not possible. Covariates tested included patient's characteristics (age, BSA), tumour infiltrating lymphocytes, KI67% and tumour subtype among others. The tumour growth inhibition model was able to individually and accurately describe tumour shrinkage. Patients receiving immune therapy had a shrinkage rate of 29% higher than those who did not receive this treatment. Predicted tumour dynamics over time were linked to the probability of survival as an argument of the hazard function, which was best described using a Weibull model. Predicted 5-year PFS was 84.7% vs observed - 85.35%. The survival model also included tumour subtype and tumour size at diagnosis as covariates.

Conclusions: The modelling exercise predicts the efficacy of the neoadjuvant therapy in terms of tumour growth inhibition and survival of patients with breast cancer. It is expected to have a potential benefit in optimising the standard treatment of patients receiving neoadjuvant therapy, predicting the likelihood of treatment success.

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I-46: *Jonás Samuel Pérez-Blanco* Population PK and exposure-response analysis of sleep parameters for JNJ-42847922, a novel Orexin 2 receptor antagonist

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Objectives: The orexin system regulates wake-sleep states. [1] Orexin 2 receptor (OX2R) blockade may be a novel pharmacological approach to treat insomnia. JNJ-42847922 is a novel, high affinity OX2R antagonist under investigation for insomnia treatment. [2, 3] The objectives of this work are: (i) to characterize JNJ-42847922 pharmacokinetics (PK) in healthy volunteers and insomnia patients, (ii) to model exposure-response (E-R) of sleep parameters (latency to persistent sleep, LPS; wake after sleep onset, WASO) in insomnia patients, with/without major depressive disorder (MDD), and (iii) to assess the impact of differences in PK (e.g. due to weight or age) on sleep parameters.

Methods: Population PK modeling was conducted on two phase 1 studies and one phase 2 insomnia study in Caucasian and Japanese subjects dosed once-daily 3-5 hours after dinner with tablet formulation of 10, 20 or 40 mg. Physiologically plausible PK covariates were tested via stepwise covariate modeling. E-R modeling was conducted on LPS and WASO data collected via 8-hour polysomnography from three patient studies (one in insomnia patients, two in MDD patients with insomnia) using similar dosing conditions and dose range. Model building and simulations were performed in NONMEM v7.2. [4]

Results: The PK of JNJ-42847922 was dose-proportional, with rapid absorption (Tmax ~ 1-2h) and linear elimination characterized by a 2-3h terminal half-life. Healthy volunteer and patient PK were similar. In the studies included in this analysis, a 5% decrease in clearance per 10-year age increment (from a median of 40 years) and a 30% increase in volume of distribution when doubling body weight were found. Japanese PK was similar to Caucasian PK except for 50% smaller absorption rate constant in Japanese, which resulted in slightly delayed and lower Cmax. E-R on LPS was detected in insomnia patients and in one MDD study. A 20 mg dose is expected to result in 60% LPS reduction from placebo. WASO analysis showed evidence of an E-R signal (driven by average plasma concentration) in the insomnia study (about 14 min reduction from placebo at 40 mg).

Conclusions: The short half-life of JNJ-42847922 results in relatively low plasma concentrations at 8h post-dose, with negligible accumulation after multiple daily dosing. In insomnia patients, JNJ-42847922 administration potently reduced LPS. E-R simulations show that differences in PK identified by the covariate analysis result in limited impact on drug effects.

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I-47: *Carlos Perez-Ruixo* Identifying lack of adherence to antipsychotic treatment using plasma concentrations measurements

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Objectives: To evaluate if measuring antipsychotic plasma concentrations using a diagnostic test can be used as a predictor of treatment adherence, and to identify the best plasma concentration threshold to reliably discriminate between adherent and partially non-adherent patients with schizophrenia.

Methods: A population pharmacokinetic model for risperidone was used to simulate plasma risperidone active moiety (risperidone + active metabolite 9-hydroxyrisperidone) trough concentrations (C_{trough}) for an oral dose of 4 mg under two different scenarios. The first scenario assumed that all subjects had been adherent to their medication all of the time, whereas the second scenario assumed that 40% of the subjects had been non-adherent to their treatment, and randomly missed 20% to 50% of their doses over time at steady-state.[1] Based on C_{trough}, measured 24 hours after the last dose, the probability of being an adherent patient was calculated and assessed as a predictor of drug-treatment adherence by performing a receiver operating characteristic (ROC) analysis among the simulated patients under the two scenarios.[2,3] The area under the ROC curve (AUC_{ROC}), sensitivity (SEN), specificity (SPE), positive (PPV) and negative (NPV) predictive values were calculated and an assessment of the utility of multiple (vs single) drug concentrations of the diagnostic test was conducted.[4]

Results: The median (CV%) C_{trough} for the non-adherent cohort was 9.5 ng/mL (81.7%) while the median (CV%) C_{trough} for the adherent cohort was 16.3 ng/mL (64.1%). The $AUC_{ROC,}$ SEN, SPE, PPV and NPV (95%CI) were estimated to be 0.71 (0.69-0.72), 0.71 (0.69-0.73), 0.60 (0.58-0.63), 0.74 (0.72-0.76) and 0.56 (0.54-0.59) respectively, while the optimal predictive C_{trough} threshold accounting for the lowest number of misclassifications was 11.9 ng/mL. After the inclusion of 2 additional steady-state C_{trough} measurements as predictors, the $AUC_{ROC,}$ SEN, SPE, PPV and NPV (95%CI) were estimated to be 0.85 (0.84-0.87), 0.92 (0.91-0.93), 0.66 (0.63-0.68), 0.81 (0.79-0.83) and 0.83 (0.81-0.85) respectively, while the optimal predicted probability threshold to reliably discriminate between adherent and non-adherent patients was estimated to be 0.51.

Conclusions: The inclusion of 3 drug concentrations measurements provides an accurate and precise diagnostic test which enables to properly discriminate between adherent and non-adherent patients, if the non-adherent patients are missing at least 20% of the dose intakes.

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I-48: *Chiara Piana* A model-based approach to extrapolate drug-drug interactions from rats to humans

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Objectives: The first objective of the present analysis is to develop a population pharmacokinetic (PK) model able to quantify in vivo in rat the interaction between azathioprine (AZA), a pro-drug of 6-mercaptopurine (6-MP), and febuxostat (FBX) or allopurinol (ALL). The second objective is to build a modelling and simulation (M&S) framework capable of extrapolating to humans the findings from the preclinical study.

Methods: Non-linear mixed effects modelling was applied to describe 6-MP PK in rats after administration of AZA with and without FBX or ALL. Data below the limit of quantification were handled with the M3 method [1, 2]. The inhibitory effect of FBX/ALL on 6-MP apparent clearance (CL/F) was modelled as a multiplicative constant on the clearance of the single drug administration. For the prediction of human PK, final PK parameters in rats were scaled based on weight by using standard allometric exponents (0.75 for CL/F, 1 for volumes and -0.25 for rate constants). Allometric scaling was also applied to predict 6-MP CL/F in human following the co-administration of AZA with FBX/ALL based on the inhibited CL/F estimated in rats. NONMEM and R were used for PK data analysis and data manipulation, respectively.

Results: The final model was a one compartment model with first order absorption and elimination. Inter-individual variability was estimated for CL/F (21.9%) and absorption rate constant (119.6%). According to the model, 6-MP CL/F in rats is reduced from 11.34 L/h to 3.30 L/h and 2.09 L/h in presence of ALL and FBX, respectively. Internal and external validation satisfactory qualified the model.
The predicted AZA dose reduction in human was of 80% and 70% of the standard dose when co-administered with FBX and ALL, respectively. The model developed was deemed to be fit-for-purpose considering that both ALL Summary of Product Characteristics [3] and AZA Product Information Leaflet [4] recommend a dose reduction of AZA to 25%-30% of the usual dose when co-administered with ALL.

Conclusions: The proposed M&S analysis provided a reliable framework for translating into human species the AZA-FBX interaction observed in rats. Due to feasibility and ethical hurdles in performing a clinical drug-drug interaction study, the possibility to use the current model-based approach to provide AZA treatment recommendations when co-administered with FBX is under discussion with the European Medicine Agency.

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I-49: *Philippe Pierrillas* Application of Model-Based Adaptive Optimal Design to determine a recommended dosing regimen for combination therapy in oncology

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Objectives: Phase 1 trials in the context of combination therapy is a complex question differing from the case of single therapy. Instead of a simple linear dose range, both drug dosages can be changed resulting in a continuum of potential maximum tolerated doses (MTD), i.e. an MTD curve. This complexity can, potentially, be better explored using model based-approaches. Model-based adaptive optimal design (MBAOD) has shown to be less sensitive to initial model misspecification and can therefore be useful in bridging preclinical and clinical studies where prior information on model and parameters might differ [1,2]. In this work, MBAOD was applied for a First in Human study in oncology to determine the best dosing regimen for a phase 2 trial.

Methods: An adaptive optimal design was computed using the MBAOD R package [3]. The method was illustrated by the combination of paclitaxel and a hypothetical compound in development to be added on top of paclitaxel. Dose limiting toxicity was defined as grade 4 neutropenia and was simulated using a hematological toxicity model [4]. Two-compartment models with linear elimination were assumed as the true PK models for both drugs of the combination [5]. Information from preclinical studies on drug effect scaled up to human was used as prior information [6]. Optimization between dosing cohorts was made to target a reasonable probability of grade 4 neutropenia and maximal efficacy based on preclinical studies.

Results: MBAOD was successfully implemented with both 3+3 rules as stopping criteria and dose constraints for dose escalation strategy (increase by 50% at a time) for the new compound. MBAOD process allowed the change of paclitaxel dose amount and changes for both dosing schedule and dose amount for the hypothetical drug. MTD variability appears to be around 76% for the new drug (based on the total administered drug amount in a 4-week cycle) and 28% for paclitaxel. In most of the cases, the number of cohorts involved in the MBAOD didn't exceed 5, meaning the enrolment of less patients compared to classical strategies considering separate trials for each of the potential dosing schedules.

Conclusions: Combining information from preclinical and clinical studies, this adaptive approach could improve the ability and the efficiency of phase 1 trials to identify the MTD curve for drug combinations and be applied to propose the best dosing regimen efficacy information available at the current stage of drug development.

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I-50: *Nikhil Pillai* Estimating Nonlinear Dynamic Systems in Pharmacology using Chaos Synchronization

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Objectives: Bridging fundamental approaches to model optimization for pharmacometricians, systems pharmacologists and statisticians is a critical issue. Currently, these fields rely primarily on Maximum Likelihood and Extended Least Squares metrics with iterative estimation of parameters. Our research utilizes chaos synchronization to estimate physiological and pharmacological systems with emergent properties by exploring methods with potentially superior performance to stochastic estimators.

Methods: We analyze the structural identifiability of the Dokoumetzidis cortisol model [1] using the DAISY software and apply adaptive chaos synchronization (ACS) according to Huang [2] to track the system and estimate its linear parameters. We compare the performance of this chaos synchronization method to non-linear least squares (NLS) regression solving the ordinary differential equations via MATLAB/ode15s.

Results: We evaluated noiseless, sparse noisy and dense noisy data. With ACS according to Huang [2,]the input and output rate constants rapidly converged to their nominal values and the predictions tracked the system with high fidelity without appreciable offset. NLS regression was unable to provide accurate estimation of the parameters with a substantial offset that increased with noise and sparsity of sampling.

Conclusions: The analysis shows that ACS according to Huang [2] is a highly effective and robust approach to estimating a noisy and sparsely-sampled chaotic system. Moreover, ACS provided accurate estimation with less computational resource than NLS. The overall approach is systematic and relatively easy to implement.

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I-51: *Italo Poggesi* A Shiny App for the Probability of Technical Success of a New Molecular Entity in the Preclinical to Clinical Translational Phase

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Objectives: Having confidence in exposure and pharmacology [1,2] is important when drug candidates are transitioning from preclinical to clinical development. Differences between animals and humans, inherent uncertainties and inter-individual variabilities should be assessed in a quantitative manner, resorting to appropriate statistical and probabilistic models. An R-Shiny application was developed to allow the computation of the probability of technical success (PTS), defined as the probability of achieving a predefined target concentration or effect using information from preclinical experiments (e.g. estimates of PK, efficacy and/or safety). The PTS application aims to inform the transition from preclinical to clinical development and the selection of the clinically relevant doses and dosing regimens.

Methods: The tool was developed as an R-Shiny application [3] (version 0.13.2), written in R code [4] (version 3.2.4). PTS can be computed based on:

- target PK or PD endpoint to ensure drug efficacy or limit toxicity (such as: “CaverageSS > 25 ng/mL” or “CmaxSS < 50 ng/mL”);
- selection of appropriate PK or PK-PD models;
- range of dose levels and/or dosing regimens (e.g., QD vs. BID);
- relevant model parameters and respective uncertainty and inter-individual variability (with the appropriate probability distributions).

PTS for each dose is estimated as the proportion of times when the desired endpoint is achieved.

Results: To restrict computational time, only PK endpoints and 1 or 2 compartment models with 0^{th} or 1^{st} order input were considered. In the app, different thresholds for PK metrics can be simulated and compared simultaneously. To illustrate features and performances, a PTS computation exercise is demonstrated. The desired target was defined as “CminSS>5 ng/mL”, based on a preclinical test; a 1 compartment PK model with 1^{st} order input was used (mean±SD values in humans for clearance, volume and absorption rate constant were 12±3.6 L/h, 150±45 L, 0.5±0.4 hr^{-1}, respectively, based on allometric scaling). The range of doses considered was 0-20 mg (every 24 hr). With the selected choices, PTS reaches 50% when dose level is between 3 and 4 mg, and exceeds 90% for doses>8 mg.

Conclusions: An R-Shiny application for PTS computation was developed and illustrated through a case study. This tool provides a quantitative assessment of PTS that informs dose selection for a prospective FIH trial to facilitate team discussions and early decision making.

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I-52: *Sebastian Polak* Physiologically based pharmacokinetic model (PBPK) for the halofantrine cardiac effect prediction – proof of concept study towards the system for the antimalarial drugs cardiac safety assessment.

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Objectives: Antimalarial drugs help to cure the disease yet carry serious safety problems at least some of them are connected with cardiac arrhythmias, possibly fatal, in both adults and children. The aim of the study was to establish a model based cardiac safety assessment algorithm. Halofantrine, effective yet potentially cardiotoxic drugs, was chosen as an example.

Methods: Clinical data describing halofantrine (HAL) and its active metabolite N-desbutylhalofantrine (DB-HAL) plasma concentration change in time after single oral dose of 500 mg was derived from the Charbit et al. article [1]. They were used as an input for the simple empirical two-compartmental model to simulate individual concentrations for 12 virtual individuals to mimic the clinical trial. After correction by the protein binding (fu=0.004 for both moieties), the simulated individual plasma exposure was directly used as an input (concentration in the Hill equation). Information about the concentration dependent main ion currents inhibition triggered by the two entities, in a form of IC50 (micromoles) values were derived from the literature (HAL – IKr, ICa, INa; DB-HAL - IKr) or predicted with use of QSAR models (DB-HAL – ICa, INa) [2,3,4]. The IC50 values for HAL/DB-HAL for IKr, ICa, and INa currents were: 0.0216/0.0717, 1.9/6.55, 331.2/6.71 respectively. The Cardiac Safety Simulator v2.1 was used to simulate the drug-triggered ECG modification [5]. The predicted results expressed as the QT (corrected with the use of Fridericia correction formula) change relative to baseline were compared against the observed values of the same character.

Results: Comparison between observed and predicted QTc values at time 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 168 hours after dosing was performed. The observed/predicted values, expressed as described above (% of change against baseline) for the times points listed is as follows: 0.0/0.0, -0.8/0.7, 0.1/1.4, 0.5/1.3, 1.6/1.5, 1.6/1.6, 1.0/2.0, 1.9/1.6, 2.2/2.1, 2.6/2.4, 1.2/1.3, 0.1/0.9, 0.5/1.4, -1.0 /0.6.

Conclusions: The middle-out approach (in vitro currents inhibition data combined with clinical exposure information) was applied to predict cardiac effect of the halofantrine and its active metabolite. The results prove that mechanistic modelling and simulation can be utilized for the safety assessment. For the tested concentrations halofantrine did not prolong the QT above 5% as compared against the baseline yet the prolongation effect was concentration-dependent.

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I-53: *Manuel Prado-Velasco* PBPK versus PK modeling of Tacrolimus drug in patients with renal transplant as knowledge engines for personalized posology software: PhysPK® development and preliminary results

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Objectives: To develop of a customized posology software for defining doses and administration times of Tacrolimus drug in kidney transplanted children and adolescents. A PK model for Tacrolimus is compared with a PBPK model. Both models are built and optimized through a clinical data study, and used subsequently as knowledge engines of a posology software for clinical environment.

Methods: PK and PBPK models were developed starting from previous published Tacrolimus models [1, 2] and optimized by standard methodologies with data from a clinical study. An external validation based on subsequent measurements of the same population was also performed. The models were built using the PhysPK® M&S software system [3], which is an object-oriented cutting edge platform for PK/PD/PBPK advanced modelling. It provides built-in modules for population estimation, optimization and validation of models, and a three-layer architecture that implements the mechanisms (first layer), the pharmacokinetic and physiological elements (second layer), and non-mechanistic computing components for metrics and signal processing (third layer).
The posology software was generated through a pre-built template of the optimization posology module of PhysPK®.

Results: A two compartment model with elimination, and absorption process based on transit compartment kinetics structure was selected as PK model. The PBPK model was made by 13 flow limited tissues for portal vein zone, lung, liver, fat tissue, kidney, brain, heart, skin, muscle, tendon and others, with several relationships among clearance, and plasmatic unbound fraction of Tacrolimus, with genotype and DDI. As expected, the PBPK model delivered a better predictive capacity and behaviour than the PK model, although the parameters' setting was more complex.
Two customized posology software systems were generated, using PK and PBPK, respectively. The software was executed from MS Excel, and includes the initial register of the patient associated with an automatic fitting of their customized parameters, subsequent adjustments, and support for posology definition. Clinicians can execute what-if scenarios before take a posology decision.

Conclusions: The study has shown the reliability of PK and PBPK models to be used as knowledge engines in a customized posology software, built automatically through PhysPK® modelling and simulation software. The software will be tested in a university hospital to validate the accuracy and reliability.

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I-54: *Tim Preijers* Population pharmacokinetic analysis of perioperative factor IX dosing in hemophilia B

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Objectives: To construct a population PK model using retrospective clotting factor IX plasma levels (FIX:C) from hemophilia B patients undergoing a surgical procedure.

Methods: Retrospective data of 118 hemophilia B patients, with a median (range) age of 40.1 years (0.15–90.45) and a body weight of 81.5 kg (5.3-132), undergoing 255 surgical procedures, was available from ten hemophilia treatment centers in the Netherlands (n=25 patients) and the United Kingdom (n=93 patients). From this population, 79% of the patients administered recombinant FIX products, 31% received regular prophylactic treatment, 5% was known to have a history with anti-drug antibodies, 72% was diagnosed with severe hemophilia (<0.01IU/mL endogenous FIX:C) and 36 patients were below 18 years. Non-linear mixed effect modeling was performed using FOCE+I in NONMEM v7.3 [1]. A compartment initialization method was used in case pre-dose measurements of FIX:C were available. For patients with an endogenous baseline level, this measurement was subtracted from each observation. Covariate relationships, such as patient characteristics and clinical features, were evaluated to explain inter-patient variability (IIV). Model diagnosis was performed using GOF plots in Xpose v4.5.3 [2] and VPCs.

Results: FIX:C versus time profiles, comprising 1417 FIX:C observations, were adequately described using a three-compartment model. PK parameters were allometrically scaled using the ¾ power-model for CL and 1 for V. Population PK parameter estimates and IIV (%) were: CL: 293 mL/h/70kg (21.1%), V1: 5010 mL/70kg (16.8%), Q2:102 mL/h/70kg, V2: 4780 mL/70kg, Q3: 1310 mL/h/70kg, V3: 2080 mL/70kg. With rising age, CL and V1 decreased 0.8% and 1.2% per year, respectively, until the age of 32 years. Compared to the United Kingdom, V1 was 14.5% higher for patients treated in the Netherlands. Furthermore, an increase of 16.4% and 22.1% for CL and V1, respectively, was associated to the use a recombinant product. A complication, such as an infection or bleeding, during the surgical procedure resulted in 16.4% increase of CL.

Conclusions: Measured peri-operative FIX:C were described adequately by the established population PK model. Estimated population PK parameters were different from those reported for prophylactic treatment. This model will be used in a prospective clinical trial to perform PK-guided dosing of hemophilia B patients undergoing a surgical procedure.

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I-55: *Angelica Quartino* Crenezumab exposure-response across Alzheimer's Disease endpoints supports a higher dose for Phase 3

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Objectives: Crenezumab is an antibody to treat Alzheimer's Disease (AD). Two Phase 2 studies in mild-to-moderate AD patients evaluated a high 15 mg/kg IV Q4W dose and a low 300 Q2W SC dose.In both Phase 2 studies, crenezumab was well-tolerated with only one case of ARIA-E across both studies. The aim of this analysis was to characterize the exposure-response of Crenezumab to support the Phase 3 dose

Methods: A disease progression model for mild to moderate AD was established that described the longitudinal changes of the clinical endpoints ADAS-Cog and CDR sum-of-boxes (CDR-SB) simultaneously for patients in the Phase 2 studies. The model was extended to describe the effect of covariates on disease progression, and the effect of crenezumab on each endpoint. Clinical trial simulations (CTS) of the Phase 3 study across a range of doses were done, to compute the likelihood of achieving a percent relative reduction of disease progression in treated patients compared to placebo for ADAS-Cog and CDR-SB.

Results: Model validation demonstrated that the model replicated the Phase 2 longitudinal data accurately and is fit for purpose for simulation. The analysis showed faster disease progression in patients with moderate AD disease (lower baseline MMSE), ApoE4 positive genotype, female gender, and younger age. A relationship was seen between crenezumab exposure and treatment effect, which appeared to asymptote at the higher end of the range of exposures measured in Phase 2. Crenezumab treatment effect was associated with high baseline MMSE and ApoE4 positive genotype supporting better treatment effect in patients with mild AD. Compared to 15 mg/kg Q4W dose, a 4-fold increase to 60 mg/kg Q4W dose in Phase 3 is predicted to achieve a 41% greater relative reduction on ADAS-Cog, and 44% on the CDR-SB in the mild AD population.

Conclusions: A 60 mg/kg Q4W dose was selected for Phase 3 (NCT02353598), supported by a drug-disease model for mild to moderate AD. The model adequately summarized longitudinal progression in ADAS-Cog and CDR items, preserving correlation between the endpoints. CTS suggest substantially increased efficacy at higher exposures in patients with mild AD. As the model was trained on Phase 2 dosing, uncertainty in the predicted efficacy increases with increasing exposure where exposure falls outside that observed in Phase 2.

I-56: *Christian Hove Rasmussen* PharmTeX: a LaTeX-based open-source platform for automated reporting workflow

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Objectives: The creation of a submission-ready scientific report can be a tedious task of manually copying and pasting figures into word processors, transcribing numbers into table cells, etc. Moreover, should the report require updates due to reviewer's comments or if the analysis needs to be rerun (e.g. due to a data update), the entire procedure needs to be redone and the resulting report subject to further quality control (QC).

Methods: We present a community effort to make reporting simple, reproducible, and user-friendly using a customized setup based on the document processing system LaTeX. The latter is already the golden standard for scientific journals and in academia, but it has not yet been widely adopted in the pharmaceutical industry.

Results: The LaTeX setup allows the user to create a publishable PDF document directly from figure image files and tables from CSV text files. A predefined template has all submission-ready standards built into it and is therefore fully compliant with regulatory expectations. Numbering of and references to sections, figures, tables, citations, etc. are automatically updated as the document is written. The time required to create and QC the report is reduced from weeks to days, and updating it to a matter of minutes or hours. No prior knowledge of LaTeX and only a few hours of training is required for anyone to get started. The basis for this platform was originally developed by Global Pharmacometrics at Pfizer and is being implemented to improve reproducible research and increase efficiency in reporting. It is currently being converted into a more flexible platform named PharmTex that allows customization to fit specific reporting needs, e.g. modeling reports, study reports, protocols, etc. It will support plugins, e.g. written in perl, to allow integration with any Windows and Linux-based systems. The platform will reside on Github for anyone to access.

Conclusions: Using a LaTeX-based system for reporting substantially reduces the overhead in creating submission-ready reports and in turn can improve the report quality and reproducibility. PharmTeX will make the utilization of LaTeX much simpler and more easily accessible to the pharmaceutical industry and academia. An open-source platform ensures continuous community-based maintenance.

I-57: *Theo Reijmers* 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 reduce the risk of HIV infection through sexual intercourse for women. These rings are placed in the upper third of the vagina resulting in a sustained release of dapivirine for more than a month. A population PK model was built to describe concentrations of dapivirine in vaginal fluids and plasma. The objective was to provide a robust aggregate for exposure from vaginal rings across Phase 1 and Phase 3 trials and to report change in exposure under different conditions or special populations.

Methods: Non-linear mixed effects PK modeling using NONMEM was performed based on vaginal fluid and plasma dapivirine concentrations. Two models were developed, a model specific for the fluid data, and a model describing the fluid and plasma data together. The impact of covariates on the fluid model was tested using the stepwise covariate modeling (SCM) method.

Results: A one-compartmental model with first-order absorption, parameterized in elimination rate and volume of distribution (V), was found to describe all fluid data optimally. After performing SCM and screening for clinical significance, only the relationships of pH of vaginal fluids and site ID with V were retained. The parameters of the fluid model were well estimated with standard errors (<25%) close to the bootstrap results. Simulation properties as assessed using a VPC were considered adequate with most predictions matching the observations at medians and the extremes of the distribution. The fluid-plasma link model was developed by assuming a steady-state concentration ratio between plasma and fluid. Uncertainty of parameter estimates of the model (<33%) were similar to those obtained with a bootstrap. The performance in the VPC of the fluid-plasma link model was not completely adequate (underprediction of median and overprediction of 95^{th} percentile plasma concentrations).

Conclusions: The final fluid model was adequate in terms of parameter estimates, bootstrap performance and simulation properties. The pH of vaginal fluid was included as a covariate and resulted in a 22% reduction in exposure at the 90^{th} percentile of the population. Reduced exposure at 2 South-African study sites (29% and 66%) might be explained by different adherence patterns of ring use that may vary according to local culture.

I-58: *Didier Renard* Label extension for canakinumab in Adult Onset Still's Disease (AOSD) – Extrapolation from pediatrics to adults

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Objectives: Canakinumab (ACZ885) is a high-affinity fully human monoclonal anti-human interleukin-1β (IL-1β) antibody. IL-1β is recognized as one of the principal proinflammatory cytokines, in a variety of inflammatory conditions [1], [2]. As a potent neutralizer of IL-1β, it is expected to treat the underlying structural features of arthritis (inflammation, bone and cartilage degradation). Extensive literature review with biomarkers and gene expression profiling analyses showed superimposable systemic clinical features in systemic juvenile idiopathic arthritis (SJIA) and Adult Onset Still's Disease (AOSD). They suggested that both clinical phenotypes represent a disease continuum ranging from pediatric (SJIA) to older, adult-onset (AOSD) patients [3]. Unfortunately, patients who experience onset of disease in adulthood, i.e. AOSD, cannot benefit from the canakinumab treatment option since it is only approved in the pediatric SJIA population. The objective of the PK/PD analysis was to extend the current label from SJIA to adult patients in the absence of adult data.

Methods: Population PK/PD modeling was performed on pooled canakinumab data across disease to evaluate the pharmacokinetics and exposure-response relationships by age groups to support extrapolation of the efficacy of canakinumab in SJIA to the adult population of AOSD patients.

Results: The distributions of canakinumab exposures predicted from a PK-IL1β model were overall comparable across age groups, including young adult SJIA patients and a simulated population of "SJIA-like" adult patients. Efficacy responses (DAS28 and CRP) to treatment with canakinumab, and corresponding exposure-response relationships, were comparable across age groups.

Conclusions: The population PK analyses and PKPD analyses supported the extrapolation of the efficacy and safety of canakinumab in SJIA to the adult population of AOSD patients. This main contribution helped in the EMA approval of extending the scope of SJIA indication of canakinumab to the treatment of AOSD disease.

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I-59: *Christer Rimmler* Development of a PBPK model to predict the pharmacokinetics of cefuroxime during surgery

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Objectives: The goal of this study is to predict the plasma and tissue concentrations of the cephalosporine antibiotic cefuroxime during surgery. In order to develop an adequate dose recommendation for the perioperative antibiotic prophylaxes, we included relevant changes in physiology during surgery, which may affect the pharmacokinetics of administered drugs. For this purpose, we developed and evaluated a physiologically-based pharmacokinetic (PBPK) model, using PK-Sim®/MoBi® [1].

Methods: Plasma and lung tissue concentrations were obtained from 25 patients (18 to 77 years) receiving i.v. 1.5 g Cefuroxime before start of the surgery and every 2.5 h thereafter. Based on literature data from healthy volunteers, a basic model was established. In order to consider the low albumin concentrations, the individual unbound fraction for each patient was corrected. As main parameters influencing the pharmacokinetics (Pk), the blood loss, administered fluid volume, protein shift from plasma to interstitial and the effect of anesthetic drugs, were included. These modifications were included as a linear function, calculated for each organ and subcompartment. The decrease in the mean arterial blood pressure induced by the administration of anesthetic drugs, results in a reduction of clearance processes of about 10%. Corrections of the partition coefficient and the endothelial permeability especially for the lung tissue of about 50% were necessary. In population evaluations we simulated a scale-up from the fitted tissue concentrations to interstitial concentrations.

Results: The first correction of the fraction unbound in the basic model improved the mean prediction error (MPE) from 8.1 to 4.5 %. The adjustment of the PK, triggered by the surgery, improved the model performance (MPE = 1.4% and MAPE = 29.0%), 84.5% of all predicted plasma concentration being within 50% of the observed. The lung tissue concentration could be also described adequately (MPE = 0.4% MAPE = 34.5%).

Conclusions: We were able to predict the changes of the Pk triggered by a surgery as well as the lung tissue concentration. There was no significant change of the PK triggered by a surgery, because two major effects antagonizing each other. The given dosing regimen lead to adequate interstitial and plasma concentrations for most populations. Higher deviations in the group of small individuals with a high creatinine clearance were observed.

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I-60: *Christelle Rodrigues* Population pharmacokinetics of the sustained-release granule formulation of valproic acid in epileptic children

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Objectives: Valproic acid (VPA) is an antiepileptic drug widely used in pediatric population. A prolonged-release granule formulation facilitating drug intake by children is available at a recommended mean daily dose between 20 and 30 mg/kg [1,2]. The objective of this work was to develop a population pharmacokinetic model for this formulation in epileptic children and to use this model to determine the doses providing a VPA trough concentration (C_{trough}) within the target range (50-100 mg/L) [3].

Methods: 98 children (1 - 17.6 years) were included in the study providing 325 plasma samples. The model was built with NONMEM 7.3. The probability to obtain C_{trough} between 50-100 mg/L was determined by Monte Carlo simulations for doses of 20, 30 and 40 mg/kg/day and body weights between 10 and 70 kg.

Results: VPA data were best described by a one compartment model with first-order absorption and elimination and flip-flop parametrization. Typical values for VPA clearance and volume of distribution were 0.672 L/h/70kg and 13.2 L/70kg respectively. Both parameters were related to body weight via allometric models. Total daily dose also influenced VPA clearance, representing the saturable plasma protein binding of VPA [4]. A 40 mg/kg daily dose was needed for 10 kg children to obtain a C_{trough} within the target range, whereas daily doses of 30 mg/kg and 20 mg/kg were found appropriate for 20 kg and > 20 kg children respectively.

Conclusions: Here was developed the first population pharmacokinetic model for VPA when given as a prolonged-release granule formulation. Current dosing recommendations were found appropriate except for small children (10kg) who could need higher doses than those currently recommended.

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I-61: *Amin Rostami* Predicting diclofenac systemic and synovial fluid concentrations after dermal application using the Multi-Phase Multi-Layer MechDermA PBPK model

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Objectives: To assess the prediction performance of the MPML MechDermA model. The ultimate goal is to develop a flexible simulation framework for the topically applied drugs. Diclofenac in various gel formulations was used as a model compound.

Methods: The physiologically based pharmacokinetics (PBPK) model is a dynamic, Multi-Phase and Multi-Layer (MPML) Mechanistic Dermal Absorption (MechDermA) model, where the stratum corneum (SC) is modelled as a brick-and-mortar structure [1]. The model determines the number of corneocytes that can be accommodated in the skin surface area where the formulation is applied, accounting for the tight packing mosaic arrangement of cells with intercellular lipid thickness. This structure allows simulation of complex diffusion through the SC for drugs with different physicochemical properties as well as different formulations: gels, emulsions, patches, suspensions, and pastes [2]. The tortuosity parameter was taken from the experimentally reported value for in vivo human skin [3]. Blood flow to the dermis was modeled as a function of body cardiac output, body weight and body surface area as per Simcyp Simulator (V16). The Simcyp default diclofenac compound file was used and the skin disposition parameters (partition, diffusion, and binding coefficients) were calculated using the built-in QSAR models. The Single Adjusting Compartment (SAC) was used to mimic the synovial fluid tissue. Clinical data from 6 different studies, 2 different formulations, namely emulsion gel and solution gel of diclofenac, 4 different locations (back, thigh, arm, and knee), a range of application areas (100-1200 cm^2), multiple dosing scenarios (2-4 times a day), single and multiple dosing in various populations for different genders and age distribution were used [4-9]. Plasma and, whenever available, synovial fluid concentration were the endpoints of choice.

Results:

Results expressed in ng/ml are presented either as mean or median (*) values.

PLASMA

Clinical study	**OBSERVED**	**SD or range**	**PREDICTED**	**SD or range**
[4]	4.9*	3.8	8.37	4.3
[5] (knee)	9.7	5.3	9.35	3.5
[5] (knee+hand)	33.6	19.9	32.5	10.5
[6]	8.5	3.6	12.0	3.3
[7]	12.9	8.1	15.1	7.6
[8]	41.0	15.8	23.4	9.0
[9] b.i.d.	3.9*	1.3-302.2	4.5	3.1-8.8
[9] t.i.d.	4.1*	1.1-23.0	11.5	6.4-18.2

SYNOVIAL FLUID

Clinical study	OBSERVED	SD or range	PREDICTED	SD or range
[8]	23.7	8.9	15.2	6.5
[9] b.i.d.	2.6	0.4-408.5	5.0	3.0-8.4
[9] t.i.d.	2.8	0.2-47.1	12.1	6.1-17.5

Conclusions: The MPML-MechDermA model of the skin absorption accounts for the drug, formulation, physiology and environmental parameters with applications in drug development and regulatory assessment.

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I-62: *Hauke Ruehs* Exposure-response analysis of vilaprisan describing uterine fibroid size by population PK/PD modelling

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Objectives: Vilaprisan is a new highly potent and selective progesterone-receptor-modulator (SPRM) in clinical development. The objective of the analysis was to assess the exposure–response relationship of vilaprisan on uterine fibroids in a Phase 2b dose finding study.

Methods: Data from a Phase 2b study, investigating efficacy and safety of different doses (0.5, 1, 2 and 4 mg) of vilaprisan over a treatment period of 3 months in women with symptomatic uterine fibroids, were analyzed by means of nonlinear mixed-effects modeling using the program NONMEM, version 7.3.0 (Icon Development Solutions, Ellicott City, Maryland USA) [1]. A PK model based on healthy subject data from two Phase 1 studies was applied to the data of the Phase 2b study in order to estimate the Empirical Bayes estimates.
With regard to the dose-exposure-response analysis of fibroid volume, the change in the largest fibroid volume - measured by transvaginal ultrasound - over time was analyzed. First, a model for the change in fibroid volume over time without vilaprisan treatment was developed. Based on this, the drug effect on the change in fibroid volume over time was investigated by testing different effect models, including Emax models.

Results: A total of 267 subjects were available for PK/PD analysis, with 217 subjects on active vilaprisan treatment and further 50 subjects who had received placebo treatment. The fibroid volume without vilaprisan treatment could be described as a constant volume, whereas the fibroid volume under treatment decreased exponentially. In the final model, the first-order rate constant for fibroid volume shrinkage depends on the vilaprisan AUC(0-24)ss and this relationship was best described by an Emax model with a shape factor of 1. At the highest dose this corresponds to a shrinkage in fibroid volume relative to baseline of 53.0% after 3 months of treatment.All model parameters were estimated sufficiently well.

Conclusions: An exposure-response relationship for vilaprisan could be established by population PK/PD modelling, showing a high exposure driven effect of vilaprisan on uterine fibroid size. At the highest dose a shrinkage in fibroid volume relative to baseline of 53.0% was determined after 3 months of treatment.

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I-63: *Leire Ruiz Cerdá* Modeling of Interferon effector pathway after viral infection

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Objectives and backgroud: To develop a semi-mechanistic model describing the Interferon (IFN) type I signaling pathway after the administration of a Newcastle Disease Virus (NDV) encoding green fluorescent protein (GFP) in L929 mouse fibroblasts. NDV is an oncolytic vector widely used in cancer immunotherapy [1] but it is a potent inductor of IFNs, limiting the replication of the vector and thus reducing therapy efficacy. Scavenger receptor class B member 1 (SRB1) is a critical modulator of IFN bioactivity, the use of block lipid transport 1 (BLT1), an SRB1 antagonist, have an impact on virus replication [2], and allows to get insights on the regulation pathways of the system.

Methods: Data were obtained from in-vitro experiments performed in L929 mouse fibroblast model and include: (i) GFP expression by infected cells (as indication of virus proliferation), (ii) expression fold change of Interferon b (IFN b) and (iii) fold change expression of 25OAS (2',5'-Oligoadenylate synthetase), an Interferon-stimulated gene (ISG), at 6, 12, 24, 48 hours (h) [1]. Moreover, the interferon- a/ b receptor (IFNAR) expression was measured at (i) a serial of halving doses of BLT1 from 100 to 0 µM, and (ii) different time points (0, 0.5, 1, 2, 3, 4, 5 h), using 25 µM of BLT1. Data were analyzed with NONMEM 7.2 [3].

Results: The following mechanisms were described using turn-over based models: (i) virus replication, (ii) increased intracellular expression of IFN b triggered by viral replication, (iii) binding of IFN b to IFNAR promoting ISGs expression through intracellular signaling pathways, and (iv) IFNAR recycling inhibition and its overexpression as a consequence of exposure to BLT1.

The virus first order rate constant of proliferation ($0.067h^{-1}$) was raised to 0.123 h^{-1} when INFa,b pathway activity was decreased by BLT1. Consequently the synthesis rate of 25OAS ($3.8E\text{-}3h^{-1}$) diminished a 30% in presence of BLT1. After a BLT1 treatment IFNAR expression was up-regulated. The model predicts a 15% IFNAR overexpression at 24h.

Conclusion: A quantitative model has been developed for the type I IFN signaling pathway using *in vitro* data. This model provides mechanistic insights in cancer immunotherapy with oncolytic viruses and paves the way to better understand the clinical implications of the modulation of the type I IFN receptor.

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I-64: *Alberto Russu* Dose-conversion factors for risperidone and paliperidone formulations based on steady-state PK similarity

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Objectives: Several risperidone and paliperidone oral and long-acting injectable (LAI) formulations, each characterized by a unique pharmacokinetic (PK) profile, are available for schizophrenia treatment. In clinical practice, it is important to know how to switch patients from one formulation to another. This work aims to assess the dose strengths of oral risperidone and risperidone LAI (RLAI) resulting in similar steady-state (SS) exposures to dose strengths of paliperidone palmitate 1-month (PP1M) LAI and oral paliperidone extended-release (ER), and to provide prescribers with a practical guidance on transition between formulations.

Methods: Population PK simulations of SS PK were performed using the PK models of oral risperidone [1], RLAI [2], PP1M [3], and oral paliperidone ER [2]. For the two risperidone formulations, active-moiety (ie. risperidone plus paliperidone) concentrations were compared to paliperidone concentrations from PP1M and oral paliperidone ER administration. Similarity was assessed via graphical evaluation of median and 90% prediction intervals of SS PK profiles over 28 days.

Results: Oral risperidone doses of 1, 2, 3, 4, and 6 mg/day are expected to result in similar PK to PP1M doses of 25, 50, 75, 100, and 150 mg eq., respectively (i.e. 25-fold PP1M-to-oral risperidone conversion factor). RLAI doses of 12.5, 25, 37.5, and 50 mg every 2 weeks provide similar PK to PP1M doses of 25, 50, 75, and 100 mg eq., respectively (i.e. 2-fold PP1M-to-RisConsta factor). PP1M 150 mg eq. does not have a marketed RLAI dose resulting in PK similarity (50 mg is the highest marketed RLAI dose strength). Oral risperidone doses of 2, 3, 4, and 6 mg/day result in similar PK to oral paliperidone ER 3, 6, 9, and 12 mg, respectively.

Conclusions: This work established dose-conversion factors for risperidone and paliperidone formulations based on SS PK similarity. Dosing at the time of switching should be in accordance to the respective approved product information (PI). Actual oral risperidone or RLAI doses should take into account concomitant medication with CYP2D6 inhibitors or CYP3A4 inducers [4,5]. In addition to PK considerations, clinical symptoms should always be considered when switching medications. Patients undergoing a switch should be monitored closely before and after the switch. This work provides the clinician with a practical guidance to establish an adequate maintenance dose level when transitioning patients from one formulation to another.

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I-65: *Sunae Ryu* Population pharmacokinetic model of propranolol and its metabolite reflecting the first-pass effect in patients with hepatic impairment

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Objectives: Propranolol, a beta adrenergic receptor blocker, is routinely used for primary prophylaxis of variceal haemorrage in cirrhotic patients [1-2]. Since propranolol is highly hepatic extracted drug and subject to undergo alteration of first-pass effect according to hepatic function status, this study aimed to develop population pharmacokinetic models that described the first-pass effect of propranolol and simulate the optimal dosing regimen for patient with hepatic impairment in different degree of severity [3-4].

Methods: We developed a joint population pharmacokinetic model of propranolol and its active metabolite, 4-hydroxy propranolol, from phase I clinical study with 54 mild to moderate hepatic impaired patients and 24 healthy volunteers. Population PK analysis were performed via nonlinear mixed effects modeling using the software program NONMEM 7 (Version 7.3, ICON, LLC, Maryland, USA) using PREDPP Subroutine ADVAN6 and the first-order conditional estimation with interaction (FOCE-I) algorithms.

Results: The joint model with two central compartments for each compound and direct absorption of the metabolite into the systemic circulation reflecting hepatic first-pass effect described the data adequately. Platelet count and body weight were added in the model as significant covariates. In hepatic impaired patients, the increased systemic exposure of propranolol resulted in the decrease of volume of distribution (Vc) and clearance (CL) of propranolol, whereas clearance of metabolite (CLm) and metabolic rate constant (Km) were increased in association with decreased platelet count. Simulation in varying degree of severity of hepatic impairment revealed that the pharmacokinetic profiles of propranolol were affected by the hepatic impairment but not significant change was found according to the severity of the disease. Also the dosing simulation showed that 25 or 30mg twice a day of propranolol in hepatic impaired patients would give comparable systemic exposure to 40mg twice a day in patients with normal hepatic function.

Conclusions: The population pharmacokinetic model with hepatic first-pass effect adequately described the data for both propranolol and 4-hydroxy propranolol with a two central compartment model for each compound. The dosing simulation suggest a dose reduction in hepatic impaired patients to give similar exposure compared to healthy subjects but further study would be necessary to determine the clinical significance.

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I-66: *Muhammad Waqas Sadiq* A model-based comparison of absorption pharmacokinetics for a selective glucocorticoid receptor modulator administered with different inhalation devices

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Objectives: AZD7594 is non-steroidal selective inhaled glucocorticoid receptor modulator (iSGRM) currently in development for the treatment of asthma. This work presents population pharmacokinetic (PK) modelling performed to quantify the absorption PK after inhaled administration of AZD7594 with different devices.

Methods: PK data from a phase 1 clinical study, in healthy subjects, evaluating inhalation of single doses of AZD7594 via two dry powder inhaler devices (DPI), called the Monodose and SD2FL device, and an intravenous (IV) reference dose was used for model development. A second study in Japanese healthy subjects evaluating single and multiple doses administered via the SD2FL device was used for model validation.

A population modelling approach was used to build a PK model, using NONMEM version 7.3 with first order conditional estimation. The IV model was evaluated first. The IV parameters were subsequently fixed, and the pulmonary absorption model of AZD7594 was developed to compare the absorption pharmacokinetics with different devices.

Results: The IV model was determined to be a three-compartment distribution model with systemic clearance estimate of 72.4 L/h. The absorption of AZD7594 after oral inhalation was best described with three first order (slow, medium, fast) and one zero order rate of absorption. The parameter estimates for the two DPIs were similar, except that the fast absorption rate was unidentifiable for the SD2FL device. For the Monodose device estimates of the fast, medium and slow absorption half-life were 0.1, 1.1 and 71 (h). For the SD2FL, the medium and slow absorption half-lives were 1.4 and 80 (h). The duration of the zero order absorption was estimated to 32 and 24 (h) for the Monodose and SD2FL devices, respectively. The absolute bioavailability after inhalation was estimated to 46% relative to the IV reference dose. The model for the SD2FL device (based on data from healthy non-Asian subjects) successfully describes the trends, but is slightly over-predicting, the concentrations after repeated dosing in healthy Japanese subjects suggesting a lower bioavailability, after inhalation in the Japanese study population.

Conclusions: The developed population PK model successfully describes the trends and variability in the observed data from different inhalation devices. The absorption kinetics of AZD7594 were very similar for the two DPI devices.

I-68: *Mark Sale* Application of global search methods for parameter estimation in models with poorly defined objective function surfaces

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Objectives: Assess performance of global search methods for parameter estimation in nonlinear mixed effect modeling.

Methods: Re-analysis of existing clinical data.

Most nonlinear mixed effect modeling uses quasi-Newton, gradient based methods for parameter estimation. These methods are efficient, finding a solution with few evaluations of the objective function. They are, however, not robust with at least two conditions that result in failure to find the global minimum: an initial estimate whose gradients lead to local (rather than global) minima and the failure to estimate a useful gradient in complex highly nonlinear models.

Alternatives to gradient based methods are global search methods. These methods, including genetic algorithm, simulated annealing and particle swarm optimization, do not require a gradient and can be robust to local minima. We investigated the use of Genetic Algorithm/Nelder-Mead minimization for parameter estimation in a model were problems with local minima occurred using quasi-Newton methods.

We reanalyzed 17-dimethylaminoethylamino-17-demethoxygeldanamycin (DMAG) data [1], from 67 patients. These data and model were known to have irregular objective function surface, and location of global minima by quasi-Newton methods require evaluation at multiple initial parameter estimates. We compare the results from NONMEM with multiple initial parameter estimates with the results from Genetic Algorithm/Nelder Mead [2] using multiple initial seed values.

Results: A model for DMAG was previously established (Aregbe, 2012). Objective function value (OBJ) from different initial estimates using NONMEM are given below.

OBJ
9794.9
10367.9
9923.6
9799.1
9799.1

The same model and data set were used to estimate parameters using the GA package in R. Options for the minimization included population size of 1000, 1000 generations and 32 bits of precision. The search space for GA included the range of the initial estimates for NONMEM +/- 0.5 logs, except for exponential covariate relationships for which the search space was -4 to +4. The resulting objective function from 4 different seeds are given below:

OBJ
9795.4

9798.5
9795.6
9795.8

Conclusions: Genetic Algorithm-Nelder/Mead is an alternative parameter estimation method. As expected, this method is much less efficient than quasi-Newton, but appears to be robust to at least some problems associated with gradient based methods. Also as expected, Genetic algorithm has difficulty finding the optimal value in a search space, but is robust in finding “near optimal” solutions.

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I-69: *Franziska Schädeli Stark* Assessing the adequacy of a minimal PK sampling schedule for individual dose adjustment decisions in a proof of mechanism (PoM) study in a special population

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Objectives: Drug A was previously tested in healthy subjects and patients and is now being investigated in a proof of mechanism (PoM) study for a new indication in a special population with potentially different PK characteristics. Individual dose increases may be required to reach the minimum efficacious exposure (AUCss) for the PoM. The objectives of this work are (i) to propose a minimal PK sampling schedule for making an early individual dose increase decision and (ii) to demonstrate how adequate the decisions will be if CL is up to two-fold different in the special population.

Methods: The PoM study design includes a 3-step dose-escalation phase over 6 weeks to reach the minimum efficacious steady-state exposure that will be maintained from weeks 7 to 17. AUCss prediction and subsequent dose decision (at week 7) will be based on PK samples collected during the dose escalation phase. Prior PK information on drug A in healthy subjects and patients demonstrated linearity over the PoM dose range and was described by a two-compartment model. An optimized and robust PK sampling schedule for empirical Bayes estimates (EBEs) of individual PK parameters was derived from evaluations with PFIM 4.0 [1,2]. Simulations were performed using NONMEM to assess how much this sampling schedule could be further reduced without compromising the decision on a dose increase.

Results: A total of 10 samples per individual up to day 29 yielded PFIM estimates for RSE that were 6% for CL and less than 30% on all other PK parameters; shrinkage was 3%, 10% and 29% on CL, V2 and V3, respectively. Simulations demonstrated accurate dose increase decisions with PK sampling up to day 15, even though EBEs for CL (and AUCss) were less precise and possibly less accurate (especially in the upper range of exposure). With 5 PK samples (day 1: 2 and 12h; day 2: pre-dose; day 15: pre-dose and 3h) the risk of missing a true underexposure was less than 5% in all scenarios.

Conclusions: A minimal PK sampling schedule was shown to facilitate adequate and timely dose decisions to ensure sufficient individual exposure in the PoM study even if the true CL in the new population was two-fold different from the prior value. The additional samples recommended by PFIM for precise and accurate PK characterization may be collected later in the study.

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I-70: *Stein Schalkwijk* Placental Transfer of Darunavir and Simulation of Fetal Exposure

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Objectives: Fetal antiretroviral exposure is usually derived from the cord-to-maternal (ctm) concentration ratio. This static parameter does not provide information on the pharmacokinetics *in utero*, limiting the assessment of a fetal exposure-effect relationship. Pregnancy physiologically-based pharmacokinetic (p-PBPK) modeling could provide a solution, although incorporation of placental antiretroviral transfer remains challenging. Here, we aimed to incorporate placental transfer into a p-PBPK model to simulate fetal darunavir exposure at term.

Methods: An existing and validated p-PBPK model of maternal darunavir/ritonavir [1] exposure was coded in Berkeley Madonna to allow expansion with a feto-placental unit and include bidirectional placental transport of darunavir, at term. In order to parameterize the model, we determined maternal-to-fetal (mtf) and fetal-to-maternal (ftm) darunavir/ritonavir placental clearance with an *ex vivo* human cotyledon perfusion model. Simulated maternal PK profiles were compared with observed clinical data to verify the validity of the maternal model aspect. Next, population fetal PK profiles were simulated for different darunavir/ritonavir dosing regimens. These profiles were compared with available cord blood concentrations *in vivo.*

Results: An average (±SD) mtf cotyledon clearance of 0.91±0.11 mL/min and ftm of 1.6±0.3 mL/min was determined (n=6 perfusions). Scaled placental transfer was included into a feto-placental unit and integrated in the p-PBPK model. For darunavir 600/100mg twice a day, the simulated fetal plasma C_{max}, C_{trough}, T_{max} and $T_{1/2}$ were; 1.1 mg/L, 0.57 mg/L, 3 hours, and 21 hours, respectively. This indicates that the fetal population C_{trough} is higher than the protein-adjusted EC90 for wild type virus (0.20 mg/L) and around the EC90 for resistant virus (0.55 mg/L). The simulated ftm plasma concentration ratio (range) over a dosing interval was 0.30 (0.16 - 0.37), compared to a median (range) ratio for observed darunavir ctm plasma ratio of 0.18 (0 - 0.82).

Conclusions: A p-PBPK model for maternal darunavir exposure was extended with a feto-placental unit. The results indicate that fetal exposure after oral maternal darunavir dosing is therapuetic and this may provide benefits to the prevention of mother-to-child transmission of HIV. Moreover, this model provides a valuable tool to assess fetal exposure with new maternal darunavir dosing regimens and, hence, to optimize therapeutic benefit for the unborn.

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II-01: *Nina Scherer* A population pharmacokinetic (PK) model of metformin regarding immediate and extended release formulations under fasted and fed conditions

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Objectives: Metformin is a widely used biguanide glucose lowering agent and used as the first-line treatment for type 2 diabetes mellitus [1]. The available PK data of metformin indicates a high interindividual and intraindividual variability. We aimed to develop a mathematical model describing the PK of metformin after single and multiple dose of different formulations, and to determine the effect of covariates.

Methods: Metformin plasma concentration-time profiles and corresponding urinary data were used from four clinical phase I trials in healthy adults performed by Boehringer Ingelheim. Volunteers received immediate (IR) or extended release (ER) formulations between 850 mg and 1500 mg as single or multiple dose administration under fasted or fed conditions. The PK model was developed stepwise: first, the structural and the stochastic model were developed. Secondly, a covariate analysis was performed. Parameter estimation and simulations were performed using non-linear-mixed-effects methods implemented in the software NONMEM (version 7.3.0).

Results: The dataset included 5644 plasma and 316 urinary concentrations of metformin from 175 healthy subjects. 32 volunteers received multiple doses of IR and 143 of ER formulation. The PK profile of metformin in healthy volunteers was best described by a two-compartment disposition model following flip-flop kinetics, which is already described in literature [2] (first-order absorption rate constant 0.30 h^{-1}; first-order elimination rate constant 1.07 h^{-1}). To describe the PK of the ER formulation, a zero-order infusion into the absorption compartment was implemented with a duration of 2.34 h in fasted volunteers and increased under fed conditions to 4.00 h. The bioavailability was estimated as 27.7% using the total amount recovered in the urine. As metformin is not metabolized and fully cleared by the kidneys [3] this amount reflects the fraction absorbed and therewith the absolute bioavailability. The ER formulation has a 1.15-fold higher bioavailability compared to the IR formulation. Fed state increases the bioavailability by a factor of 1.67. The volumes of distribution were 30.0 l for central and 196 l for the peripheral compartment.

Conclusions: Metformin blood concentrations as well as urinary concentrations were accurately quantified by a two-compartment model. Food-intake, different formulations and administration regimen were implemented as covariates.

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II-02: *Emilie Schindler* The minimal continuous-time Markov pharmacometric model

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Objectives: To present the minimal continuous-time Markov model (mCTMM) as an alternative to discrete-time Markov model (DTMM) or standard CTMM for analyzing ordered categorical data with Markov properties.

Methods: In the mCTMM, the probability of each score is defined by an ordinary differential equation and the transition rate between two consecutive states is assumed to be independent on the state. The steady-state probabilities are described by a proportional odds (PO) model. The Markov property is accounted for by a single parameter, the mean equilibration time (MET). Covariate effects can be implemented on parameters related to steady-state probabilities or on the MET. The performance of the mCTMM was evaluated and compared to the PO model, which ignores Markov features, and to published models with Markov properties using three examples: the 4-state fatigue data and hand-foot syndrome (HFS) data in cancer patients, initially described by DTMMs [1], and the 11-state Likert pain score data in diabetic patients previously analysed with a count model including Markovian transition probability inflation [2]. The PO models and mCTMM reproduced as closely as possible the random effect structure and covariate effects on the score probabilities as in the published models.

Results: In all three examples, mCTMM adequately predicted the average number of transitions per patient and the maximum achieved score per patient, which were not well described by PO models. As expected, the mCTMM could not describe the data as well as more flexible DTMM but required fewer estimated parameters (7 *vs* 20 for fatigue and 7 *vs* 19 for HFS). The mCTMM better fitted Likert data than the count model while being more parsimonious (18 *vs* 23 parameters). The estimated covariate effects in the mCTMM were consistent with previously published DTMM and count models.

Conclusions: The mCTMM allows the exploration of potential covariate effects on ordered categorical data while accounting for Markov features, in cases where DTMM is not applicable (non-uniform time intervals between observations) and/or CTMM not conveniently implemented (large number of states).

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II-03: *Rik Schoemaker* nlmixr: an open-source package for pharmacometric modelling in R

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Introduction: nlmixr is an open-source R package under development and freely available on GitHub[1]. It builds on RxODE[2], an R package for simulation of nonlinear mixed effect models using ordinary differential equations (ODEs), providing an efficient and versatile way to specify pharmacometric models and dosing scenarios, with rapid execution due to compilation in C. By combining the RxODE core with population-type estimation routines, a versatile pharmacometric ecosystem entirely contained within R becomes feasible. Currently, estimation routines comprise the nlme[3] package in R, a Stochastic Approximation Expectation Maximization (SAEM) algorithm [4], and a proof-of-concept First-Order Conditional Estimation with Interaction (FOCE-I) implementation [5], as well as adaptive Gaussian quadrature for odd-type data. Both closed-form and ODE model definitions are included in nlmixr.

Methods: Richly sampled profiles were simulated for 4 different dose levels (10, 30, 60 and 120 mg) of 30 subjects each as single dose (over 72h), multiple dose (4 daily doses), single and multiple dose combined, and steady state dosing, for a range of test models: 1- and 2-compartment disposition, with and without 1st order absorption, with either linear or Michaelis-Menten (MM) clearance (MM without steady state dosing). This provided a total of 42 test cases. All inter-individual variabilities (IIVs) were set at 30%, residual error at 20% and overlapping PK parameters were the same for all models. A similar set of models was previously used to compare NONMEM and Monolix[6]. Additionally, a sparse data estimation situation was investigated where 500 datasets of 600 subjects each (150 per dose) were generated consisting of 4 random time point samples in 24 hours per subject, using a first-order absorption, 1-compartment disposition, linear elimination model. NONMEM®[5] with FOCE-I was used as a comparator to test the various nlmixr estimation routines.

Results: Theta parameter estimates were comparable across estimation methods. In comparison to NONMEM, nlmixr using nlme was always faster for ODEs (MM-models) and comparable for closed form models, but IIV estimates were regularly estimated close to 0% in nlmixr, whereas NONMEM provided estimates closer to the original simulation values. In contrast, both the SAEM and the FOCE-I estimation routines provided good IIV estimates at higher computational cost.

Conclusion: These findings provide further evidence that ***nlmixr*** may provide a viable open-source parameter estimation alternative for fitting nonlinear mixed effects pharmacometric models within the R environment.

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II-04: *Johannes Schropp* Target-mediated drug disposition model for a bispecific antibody: development of full model and quasi-equilibrium like approximation

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Objectives: Bispecific monoclonal antibodies (BsMAb) are created from two different MAbs that bind simultaneously to two different types of targets. First, we construct a full BsMAb target-mediated drug disposition (TMDD) model based on binding kinetics presented in [1]. Second, a quasi-equilibrium (QE) like method is applied to construct an approximation of the full model with a reduced the number of the parameters and less ordinary differential equations (ODE).

Methods: Model from [1] was extended (i) by typical TMDD properties such as synthesis and degradation behaviour of the two receptors [2], and (ii) inclusion of a first-order elimination process for the BsMAb concentration. This model consists of 6 ordinary ODEs, one for the free BsMAb concentration C, one for each receptor RA and RB, and one for each binary RCA, RCB and ternary RCAB complex. First, a QE like approximation method was applied to reduce the number of parameters by substituting the eight kon and koff binding parameters with its ratio the dissociation constant. Additionally, we use an affinity ratio parameter [2] between C and RCB for receptor RA, and C and RCA for receptor RB so that number of binding related parameters can be reduced from eight to three. Second the approximation is formulated in free BsMAb C and free receptor RA and RB concentration by three ODEs. Further reductions of parameters can be achieved in case of constant total target concentrations.

Results: Similar to single [3] or competitive TMDD [4] a QE like method can be used to reduce the number of parameters in the full BsMAb model by a QE like approximation written in free variables. The reduced QE model could reasonably well approximate the free BsMAb concentration from the full model.

Conclusions: A general full BsMAb TMDD model was developed and the QE like method could be applied to develop a useful approximation. This shows the way to design approximations with less parameter and equations being better suited for data fitting.

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II-05: *Pascal Schulthess* Frequency-domain response analysis for quantitative systems pharmacology models

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Objectives: It was recently demonstrated that key biological control systems (such as the MAPK pathway) are highly sensitive to the frequency of external stimuli in a non-intuitive manner which cannot be predicted by conventional pharmacometrics approaches [1]. This suggests that quantitative systems pharmacology (QSP) can provide novel insights into optimal dosing regimens which could add a new dimension to the design of novel treatments. However, methods for such an approach are currently lacking. We therefore apply frequency-domain response analysis (FdRA), a method widely used in electrical and control engineering and already employed for systems biology models in *S. cerivisae* [1-3], to optimise drug treatment regimen of drug tolerance QSP models.

Methods: FdRA informs on the response of a QSP model to a wide range of perturbations as used in repetitive drug treatment regimen and enables the identification of treatment frequencies that amplify or attenuate the drug response. Here FdRA is analytically and exemplarily applied to four distinct classes of QSP models: indirect response, autoregulation, pool-precursor and moderator-mediated feedback [4]. Additionally, we explore the potential of FdRA for QSP models by combining the pharmacodynamic models with short and long half-life pharmacokinetic profiles.

Results: We show that the pool-precursor model as well as the moderator-mediated feedback model with two transit compartments attenuate slow perturbation drug treatment regimen while all other models amplify such a regimen. Rapid drug treatment regimen on the other hand are only amplified by the autoregulation model. Additionally, the moderator-mediated feedback model with two transit compartments possesses only one drug dosing frequency at 0.45 h^{-1} that results in an amplification of the drug response, i.e. only twice per hour drug treatments get amplified by the model while all others are attenuated.

Conclusions: As a novel analytical method in systems pharmacology FdRA facilitates not only the characterisation of QSP model dynamics with respect to the presence and magnitude of time-delays, model stability and performance but also aids the understanding of the pharmacological system and the optimisation of drug treatment regimen.

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II-06: *Bernard Sebastien* Pharmacokinetic/Pharmacodynamic Modelling of Recurrent Adverse Events as Function of Drug Concentration and Time

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Objectives: To develop a PK/PD model for recurrent adverse events (AE) and perform simulations to predict the incidence of AE for a new design of an upcoming study.

Methods: : PK and AE data were obtained from two Phase 1 studies. A PK model was used to fit the plasma drug concentrations and to predict individual daily Cmax concentrations, using non-linear mixed-effects modelling implemented in Monolix (version 2016R1) [1]. The number of AE per day and per patient was modelled using non-linear mixed-effects modelling, using SAEM algorithm, exploring the relations between AE emergence and drug concentration, drug-dependent or independent time effect and demographic data. Then, the model performance was evaluated by comparing observed and predicted statistics of interest using clinical trial simulation, and the PK/PD model was used to simulate new study designs.

Results: The number of AE per day and per patient was best modeled using a Poisson regression, using a log-linear drug effect consisting of a constant drug effect and an attenuated exponential drug effect describing the improvement of drug tolerability with time. This corresponds to a reduction of the temporary drug effect by 1/3 after 5 days of treatment. Inter-individual-variability on the basal risk was used to reflect the variability of risk between patients, and no demographic covariate was identified as clearly significant. Model evaluation showed that the predicted number of events was in good agreement with the observations, despite a slight tendency to over-prediction. The simulation of new study designs predicted a 3 times higher number of AE for the high dose compared to the low dose.

Conclusions: PK/PD modelling and simulation of recurrent AE could be implemented to support dose and design selection for a new clinical study. The model described the observations well and will be updated with new data to improve its robustness.

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II-07: *Malte Selch Larsen* Using repeated-time-to-event modelling and simulation of spontaneous bleeding events in the F8 KO rat model for informed decision making of study design

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Objectives: The spontaneously bleeding coagulation factor VIII-gene knock-out (F8 KO) rat model presents a unique opportunity to investigate the exposure-response relationship in close agreement with the clinical setting. However, preclinical studies are often limited by small study populations and short study durations which may impede identification of a significant treatment effect. In the current study, it was investigated whether disease progression in terms of bleeding risk in the F8 KO rat model could be described using repeated-time-to-event (RTTE) modelling. Secondly, applying stochastic simulation and estimation (SSE), three different study designs were evaluated on the basis of the power to identify a significant treatment effect.

Methods: The occurrence of spontaneous bleeding events in 89 untreated F8 KO rats, examined daily for bleedings for a period of 52 weeks (1), was described by a RTTE model in NONMEM 7.3 (Laplacian estimation method). SSEs (1000 samples) with and without recombinant FVIII treatment were made using the developed RTTE model, a hypothetical one-compartmental intravenous pharmacokinetic model (V_d=30 mL/kg and CL=4.1 mL/h·kg) and a literature derived exposure-response relationship (2). For all simulations study duration was set to 16 weeks (week 4 to 20). Different conditions were investigated, including three dosing regimens (50 IU/kg every second day, 50 IU/kg daily and 100 IU/kg daily) and sample sizes ranging from 20 to 100 rats. The power to identify a significant treatment effect was evaluated at a significance level of 0.05 for each study condition, aiming for at least 80% power.

Results: The initial increase and subsequent decline in the hazard was best described by a surge function (3). The highest bleeding risk was observed at week 10 (5 bleeds per year) showing a 6-fold increase relative to baseline. A sample size of approximately 30 rats was required to detect a significant reduction in the bleeding risk with a power of at least 80% using a dose regimen of 100 IU/kg daily. The equivalent sample size at a dose regimen of 50 IU/kg daily and 50 IU/kg every second day was 45 and more than 100, respectively.

Conclusions: The occurrence of bleeding events in the F8 KO rat model was well described using RTTE modelling with a surge function. The current study, demonstrates the need for frequent dosing and/or high dose treatment to compensate for small group sizes in F8 KO rat efficacy studies.

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II-08: *Marina Senek* Population pharmacokinetic model for levodopa/carbidopa microtablets in Parkinson's disease patients and healthy subjects

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Objectives: Low dose, dispersible, levodopa/carbidopa microtablets with an automatic dose dispenser, have been developed as a therapy to facilitate individualized levodopa treatment for Parkinson's disease patients [1]. The microtablets were approved in 2014 in Sweden and recently approved (2016) by the EMA in 13 European countries following the mutual recognition procedure. The aim of this study was to characterize the pharmacokinetics (PK) of levodopa after microtablet administration, and evaluate potential differences in PK between patients and young healthy subjects.

Methods: The population PK analysis involved data from 18 healthy subjects [2] and 19 patients included in two single-dose, open-label studies [3]. The healthy subjects received 100/25 mg of the levodopa/carbidopa microtablets while the patients received an individualized dose (110/27.5-410/102.5 mg). Blood samples were collected before dose administration and up to 24 hours post dose for the healthy subjects, and in patients up to a maximum of six hours post dose, depending on how long the patient could remain un-medicated. The analysis was carried out using NONMEM 7.3. The potential influence of age, disease status and sex were investigated using a stepwise covariate modelling procedure (SCM) as implemented in PsN.

Results: The disposition of levodopa was best described by a two-compartment model. Double-peak profiles were observed in some subjects, both patients and healthy, and were here described with two parallel absorption compartments with different estimated lag times. The double peaks were only evident in some individuals and a mixture model was used to account for this variability. Bodyweight was included in all disposition parameters as the primary covariate and was scaled according to the allometric power model. In the SCM, age was found to have a significant influence on levodopa clearance, with a decrease of 0.64 L/h/years of age for a person of 70 kg. Further, patients were found to have a delayed absorption and a higher absorption rate in comparison with healthy subjects.

Conclusions: The presented model adequately described the PK of levodopa, in both young healthy subjects and older patients. The covariate effects found warrant additional investigation in order to further optimize and individualize the levodopa treatment for Parkinson's disease patients. The microtablets offer advantages in the form of shorter time to therapeutic concentration as well as flexibility in dosing.

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II-09: *Jennifer Sheng* Joint modeling of time-varying exposure data and progression-free survival in elotuzumab-treated patients with relapsed/refractory multiple myeloma

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Objectives: Exposure-efficacy (E-R) analyses with Cox proportional hazard (CPH) assume a constant hazard throughout treatment and often use a static value without capturing longitudinal data until the time-to-event [1,2]. A time-varying CPH model incorporates longitudinal data but due to large random errors, may lead to highly biased and inefficient estimates [1]. Here, we explore a joint model (JM) simultaneously integrating longitudinal data and time-to-event data, thereby improving assessment of longitudinal exposure of elotuzumab (plus lenalidomide/dexamethasone [ELd]) on PFS for the treatment of relapsed/refractory multiple myeloma.

Methods: Joint modeling of longitudinal exposure data and PFS was performed using R JM package [3], with evaluable elotuzumab exposure from ELd-treated patients (N = 310) from ELOQUENT-2 (NCT01239797). Elotuzumab was administered at 10 mg/kg once weekly for the first 2 cycles and then twice weekly onwards, resulting in exposure changes over time. The E-R analysis of elotuzumab applied $C_{ave,ss}$ and baseline covariates to the CPH model, predicting clinical outcomes [4]. The final JM used the piecewise proportional hazard model with Gauss-Hermite integration method, and was selected based on Bayesian information criteria using the clinically observed C_{min} time profile. Sensitivity analysis was performed with C_{min1} using the CPH model and time-varying C_{min} in the JM. Additional sensitivity analyses used the clinically observed evaluable C_{min} profile and population pharmacokinetic (PPK) simulated C_{min} profile [4]. Survival dynamic probabilities of individuals were predicted using the final JM.

Results: The JM suggested a weaker dependence of survival outcome (PFS) on longitudinal elotuzumab exposure, and stronger association for other covariates, such as lactate dehydrogenase vs the CPH model. JM results were comparable between clinically observed C_{min} and PPK-simulated C_{min}, with overlapping mean plus one standard error. Individual dynamic predictions provide dynamic assessment of survival as additional longitudinal clinical data become available.

Conclusions: Joint modeling of longitudinal data and PFS provides a new approach to predict clinical benefits using dynamic data. Ultimately, the goal of joint modeling is to utilize earlier clinical data (including progressive disease biomarkers) to predict individual clinical benefit and to reveal the continuous interplay between PK, PD and efficacy to support clinical decisions.

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II-10: *Satoshi Shoji* Slow drug-target complex kinetics and first dose overestimation of free target suppression in target-mediated drug disposition (TMDD) approximation models: An evaluation for tanezumab a NGF antibody for treatment of pain

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Objectives: TMDD model approximations are useful in allowing estimation of alternative hybrid parameters when the full TMDD modelling is over parameterized [1-4]. For the NGF antibody tanezumab, the QSS TMDD approximation model was developed [5]. The free target (NGF) prediction suggested the approximation would overestimate the initial first dose free target suppression. Objectives of this study were to characterize the overestimation and to quantify the impact when varying the target binding parameter values.

Methods: Quasi-steady-state (QSS), Michaelis-Menten (MM), and indirect response (IR) approximation models were evaluated to confirm whether early overestimation existed. Parameters available from the previous model [5] and in-vitro Kd [6] value were used for this investigation. Impact of the overestimation was evaluated based on sensitivity analysis over the first 28 days following the first subcutaneous tanezumab administration. Metrics for the overestimation were root mean squared error (RMSE) reflecting absolute difference (pM) from full TMDD, relative %RMSE and %AUC ratio to full TMDD.

Results: Overestimation of the free target suppression existed and, as expected, was similar across QSS, MM, and IR models in our simulation settings. Higher complex production rate and/or elimination rates relative to drug-target complex rate (*dRC/dt*) were needed to reduce the overestimation. Sensitivity analysis showed increasing koff or kint ~ 6- to 7-fold or increasing both by ~ 4 fold relative to the tanezumab estimates reduced the overestimation to insignificant levels of %AUC (~ 20%). Increasing kon 2- to 20-fold progressively improved RMSE but did not improve %RMSE or %AUC indicating that with production rate already above the drug-target complex rate for tanezumab, a greater production rate due to a higher Kon value would further suppress NGF but have no impact on reducing the initial discrepancy between the full and TMDD approximation models.

Conclusions: Overestimation of free target suppression during the initial “fast phase” in TMDD approximation models is already known. This work illustrates approaches to determine the extent and duration of this difference, which could be important when predicting acute effects, such as the onset of analgesia, for drugs displaying TMDD.

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II-11: *Mahendra Shukla* Population Pharmacokinetic-Pharmacodynamic modeling of furosemide for anti-hypertensive effect

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Objectives: Despite its long term use as an established diuretic, the anti-hypertensive effect of furosemide has not been well characterized. The previous PK-PD studies of furosemide mainly modeled its diuretic effect [1]. The reports pertaining to the use of furosemide in treating different forms of hypertension are limited. Also the multiple dose studies for the anti-hypertensive effect of furosemide are lacking. Therefore, the present study aims at bridging this void by providing a comparative PK-PD analysis for the blood pressure lowering effect of furosemide after multiple dosing in spontaneously hypertensive rats (SHR) and deoxycorticosterone acetate-salt-induced hypertensive rats (DOCA-salt rats), the commonly employed animal models for human primary and secondary hypertension respectively.

Methods: Multiple dose oral (40 and 80 mg/kg dose daily for 3 weeks at 24 h interval) PK-PD study of furosemide was carried out in SHR and DOCA-salt rats. Blood samples were withdrawn up to three weeks post treatment and harvested serum samples were analysed using LC-MS/MS method [2]. For PD study, BP was monitored using noninvasive blood pressure monitoring in conscious rats using tail cuff method at various predefined time points. A simultaneous PK-PD model was developed to allow the estimation of PK as well as PD parameters in a single fit. Analysis was conducted using FOCE I in NONMEM 7.3. Xpose and PsN were used for graphical evaluation and model diagnostics.

Results: A 2-compartment model provided the best fit to the PK data. V1 of furosemide was found to be higher in DOCA-salt rats as compared to SHR at similar dose. A nonlinear behaviour of clearance (2.3-fold increment) was observed in SHR at higher dose owing to the saturable metabolism of furosemide, whereas in DOCA-salt rats, it was found to be dose-independent. The PD parameter estimates from the best fitted E_{max} model with the effect compartment indicated the higher efficacy of furosemide as an anti-hypertensive in DOCA-salt rats as compared to SHR that is shown by the lower EC_{50} values predicted by our finalized PK-PD model. The tolerance was found to be much higher (2-fold) in DOCA-salt model as compared to SHR. Even at the highest dose used in our study, the EC_{50} values were found to be higher as compared to achieved serum concentration.

Conclusions: The final PK-PD model described the data well and provides detailed insights into the use of furosemide as an anti-hypertensive agent.

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II-13: *Sarah Siederer* Model Based Extrapolation Approach Driving a Streamlined Clinical Development Plan for Inhaled Oxytocin

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Objectives: To characterise integrated population (Pop) PK models that describe the disposition of oxytocin (Oxy) following intravenous (IV), intramuscular (IM) and a novel oral inhaled (IH) administration to healthy non-pregnant women (HNPW). These models will be used for the quantitative assessment of systemic comparability to extrapolate clinical safety and efficacy following approved routes (IM/IV) to a novel oral IH route for Oxy. This IH formulation is under development as an an affordable product for low/middle income countries (studies sponsored by GlaxoSmithKline in partnership with Monash University) for the prevention of Postpartum Haemorrhage (PPH).

Methods: A framework for integrated Pop PK models was developed using PK data obtained following IV (n=21), IH (n=15) and IM (n=26) Oxy to HNPW across 2 completed clinical studies (planned post hoc analysis). The IV data were used to estimate the disposition parameters which were then fixed when modelling the IM and IH data. Different absorption models (1^{st}/zero order/Weibull) were tested to adequately characterise the initial time course of drug levels following IM and IH dosing. Model qualification approaches were conducted including the posterior predictive checks. Based on these models, clinical trial simulations will be conducted to identify optimal study designs including sample size, dose selection, decision criteria and population, and to evaluate the probability of reaching the required therapeutic systemic exposure. Modelling was implemented in NONMEM V7.2 or above.

Results: This analysis is first to describe the Pop PK of Oxy after IV, IM and IH dosing in HNPW. A 3-compartment disposition model with 1^{st} order elimination and additive residual error based on log-transformed concentrations adequately described the PK of Oxy (CL_{IV}=37L/h, Vd_{iv}=13L). The multi-phase absorption models were used to characterise the IM (bioavailability (F)~30%) and IH (F<2%) PK. Model diagnostics including goodness of fit, visual and posterior predictive checks indicated the adequacy of the models. An important application of these models will be to support the extrapolation from the IM to IH dosing route by bridging the systemic exposure associated with safety & efficacy.

Conclusions: Model based drug development could be useful to extrapolate to a different route of administration with the potential to make this IH product available in PPH where IV and IM access is limited due to storage and skilled healthcare professional requirements.

II-14: *Giovanni Smania* The role of modelling and simulation in the paediatric investigation plan of a xanthine oxidase inhibitor for tumor lysis syndrome prevention

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Objectives: Febuxostat (FBX) is an oral xanthine oxidase inhibitor which demonstrated its superiority versus allopurinol in controlling serum uric acid levels in adult patients at risk of tumor lysis syndrome (TLS) [1]. Following the recommendations outlined in the EMA reflection paper [2], this work presents the concept and plan for the extrapolation of FBX efficacy and safety data from adults to paediatric patients aged 6-17 years old (target population), emphasising the role of modelling and simulation (M&S) in the paediatric investigation plan (PIP) agreed with the Agency.

Methods: Since FBX elimination pathways are fully mature at 6 years of age [3-6], it is expected that the PK between the target and adult population can be scaled based only upon weight. In addition, considering TLS similarities between the two populations, it is reasonable to assume a comparable response to FBX as well as a similar PK-PD relationship. On this ground, FBX efficacy and safety can be extrapolated from adults and a full clinical development plan could be skipped in favour of a single phase I/II PK-PD study. Dose selection in this study was based on a 2-compartment pop-PK model in adults, which allowed to identify paediatric doses targeting the efficacious and safe exposure range observed in adults. Weight-based allometry was used to scale clearances and volumes [7]. Two age groups were considered: children (6-11 years) and adolescents (12-17 years); the candidate doses were 40 mg, 60 mg, 80 mg and 120 mg QD.

Results: PK simulations revealed that children dosed up to 60 mg would achieve the target AUC and Cmax while remaining below the highest safe exposure observed in adults. With respect to adolescents, doses of 40 mg and 60 mg are not sufficiently high to guarantee the attainment of efficacious exposures. On the contrary, exposures at 80 mg and 120 mg are expected to be within the efficacious and safe exposure range. Should these predictions not be confirmed by actual data, dose recommendations in the target population will be based on PK simulations of alternative dosages and on the data collected in the paediatric study, without the need to run further clinical trials.

Conclusions: M&S played a pivotal role in the definition of the FBX PIP by supporting the selection of safe, efficacious and informative doses to be tested in the paediatric trial and, together with the extrapolation approach, allowed to minimize the number of paediatric patients exposed to clinical investigations.

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II-15: *Konstantina Soulele* Population pharmacokinetic analysis of inhaled budesonide in asthma patients

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Objectives: To apply population pharmacokinetic modeling in order to describe the absorption and distribution kinetics of budesonide in asthma patients after administration of two different dry powder inhalers (DPI).

Methods: Budesonide plasma concentration (C) – time (t) data were obtained from a single dose, 2x2 bioequivalence study comparing two dry powder inhalers in 90 controlled or partly controlled asthma male and female patients under fasting conditions, with co-administration of activated charcoal. Non-linear mixed-effect modeling was applied and a pharmacokinetic model capable of describing the parallel fast and slow lung absorption of budesonide was developed. Several error models were tested, whereas the period and treatment effects, as well as, demographic characteristics were explored as potential covariates. The entire computational work was implemented in Monolix 4.3.3.

Results: A two-compartment disposition model with two parallel first order absorption processes (fast and slow) from the lungs was found to describe successfully the C-t profiles of budesonide. Elimination was considered to take place in the central compartment following first order kinetics. The model was parameterized in terms of the fast (Kaf) and slow (Kas) lung absorption rate constants, the apparent volume of distribution in the central (Vc/F) and peripheral (Vp/F) compartments, the apparent clearance (CL/F), the inter-compartmental clearance (Q/F), the relative fractions of dose absorbed either slowly (Rslow) or fast (Rfast) through the lungs, and the Rfast/Rslow ratio (z). The application of a combined error model led to the optimum performance. The following estimates were found for the pharmacokinetic parameters: Kaf = 19.6 h^{-1}, Kas = 0.11 h^{-1}, Rslow = 0.63, z = 0.27, Vc/F = 271 L, Vp/F = 218 L, Q/F = 305 L/h, and CL/F = 185 L/h. Gender was found a significant covariate on Kas and Vp/F, with men exhibiting higher Kas and lower Vp/F compared to women. No difference in the performances of the two DPIs was observed.

Conclusions: A population pharmacokinetic model, with two parallel lung absorption processes was found to describe successfully the C-t profile of budesonide in asthma patients. Following an initial fast pulmonary absorption, a second slower absorption phase was evident most probably attributed to the lung deposition (central/peripheral) of budesonide and the formation of fatty acid conjugated esters in the airways.

II-17: *Sabine Stuebler* Towards a systems biology model for inflammatory bowel disease

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Objectives: Inflammatory bowel disease (IBD) (major forms: Crohn's disease and Ulcerative colitis) is a chronic disease caused by autoimmunity of T cells against commensal bacteria in the gut. Different treatments, such as immunomodulatory small molecule drugs or monoclonal antibodies (mAbs) targeting TNF-a, are in use, but the therapeutic outcome differs highly between patients. The objective was to mathematically describe the cellular processes of the intestinal immune system to provide a basis for further analysis of drug effects and inter-individual variability.

Methods: Based on the main aspects of a previously published systems biology model of IBD [1] and extensive literature research, we developed an ODE model comprising the dynamics and interactions of different immune cell types (naive, memory, helper and regulatory T cells and dendritic cells in different activation states) in the mesenteric lymph nodes and intestinal lamina propria.

Results: The developed ODE model described activation and antigen uptake by dendritic cells, dendritic cell interaction with naive and memory T cells leading to T cell proliferation and differentiation into effector T cells (helper T cells and induced regulatory T cells, depending on the dendritic cells' activation status), and effector T cell activation by further contact to antigen-presenting dendritic cells. Inhibition of dendritic cell and T cell activation by induced and natural regulatory T cells formed a negative feedback loop. To calculate the cytokine-dependent apoptosis rate of helper and regulatory T cells, induced by re-stimulation with antigen or cytokine deprivation, interleukin-2 was included into the model. Experimentally known healthy steady state levels from the literature (dendritic cells in LP, natural regulatory T cells in MLN and LP, induced regulatory T cells in MLN and LP and memory T cells in MLN and LP) are well described by the model. Further requirements to describe the pathological mechanisms of IBD and to simulate treatment include integration of macrophages and neutrophils, representing the innate immune system, and bacteria, which elicit the immune response.

Conclusions: This is a first step towards a systems biology model to describe the cellular dynamics in IBD.

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II-19: *Waroonrat Sukarnjanaset* Performance of FOCEI vs SAEM in simple population pharmacokinetic analysis of rich, medium and sparse data.

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Objectives: To evaluate the performance (accuracy, precision, completion rates, and runtimes) of FOCEI and SAEM estimation methods in population pharmacokinetic (PK) analysis using NONMEM® when implemented with a one compartment model across rich, medium and sparse sampling data.

Methods: Three types of data (rich, medium and sparse) were explored. For each scenario, 100 datasets were simulated for 100 patients using a one compartment model from previously published results.[1] The simulated data below the limit of quantification of 0.5 mg/L were removed from the datasets. Every dataset was separately estimated with FOCEI and SAEM methods using the same initial estimates. The simulation and estimation were conducted using NONMEM® 7.3 under Windows 7 Enterprise 64-bit operating system. The percentage of relative estimation error (RER) and root mean square error (RMSE) were calculated to assess the accuracy and precision of parameter estimates. The completion rates and runtimes were also compared.

Results: Across the three scenarios, FOCEI and SAEM provided the same completion rate of 100% and both methods accurately and precisely estimated all PK parameters. RERs and RMSEs were comparable. Median RERs were within ±5% and ±10% for fixed and random effect parameters, respectively. For all scenarios, both methods had RMSE < 1.5 and 0.03 for fixed and random effect parameters, respectively. However, the run times were shorter with FOCEI (ranged from 9 to 25 seconds) compared to SAEM (ranged from 215 to 811 seconds).

Conclusions: In simple population PK analysis, FOCEI could provide accurate and precise PK parameter estimates across rich, medium and sparse data similar to SAEM but with shorter run times.

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II-20: *Monika Sundqvist* Preclinical pharmacokinetic-pharmacodynamic modelling to guide first-time-in-human studies with the anti-miR-103/107, RG-125 (AZD4076)

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Objectives: To develop a pharmacokinetic-pharmacodynamic model to describe preclinical data with AZD4076, a novel anti-miR-103/107 GalNAc-conjugated oligonucleotide and predict human dose and time-course of response.

Methods: AZD4076 was administered s.c. once weekly at multiple dose levels to mice (50–450 mg/kg) and non-human primates (NHP; 5–150 mg/kg) in combined pharmacokinetic and toxicology studies. A non-linear pharmacokinetic model was developed describing both plasma and liver exposure for parent drug and its metabolites in mice and NHPs. In a separate series of studies, AZD4076 was dosed once weekly s.c. in DIO mice (1.7–45 mg/kg) and plasma glucose and insulin were measured over time to assess potency and efficacy. The homeostatic model assessment of insulin resistance (HOMA-IR) response in DIO mice was calculated from glucose and insulin, and fit to a turnover model, taking the animal disease progression into account. All data were modelled using non-linear mixed effects modelling with extended least squares estimation (FOCE-ELS) method as implemented in Phoenix 6.4 NMLE 1.3.

Results: A pharmacokinetic model including saturated uptake into liver, predicted observed plasma and liver concentrations of the combined AZD4076 active metabolites in the evaluated animal species well, justifying an allometric approach to predict human pharmacokinetic parameters. The pharmacodynamic model liver IC_{80} parameter estimate was 10 µM (95% confidence interval: 8-14 µM) in DIO mice and assumed applicable to humans. Allometric scaling was further implemented on the pharmacodynamic model to predict human response over time. The observed time to achieve 50% maximal inhibitory response in AZD4076 treated DIO mice (~5 days) was extrapolated to humans (~30 days), based on reported glucose turnover half-life values in mouse (~3 days) and human (~19 days) studies with thiazolidinediones.

Conclusions: The robust insulin sensitization in DIO mice makes AZD4076 an attractive candidate for investigation of insulin sensitization effects in man. The human PKPD model, albeit assumption-rich, could be further used to guide the design of safety studies as well as early clinical trials, impacting both duration and dosing regimen.

II-21: *Ajit Suri* Population Pharmacokinetic Modeling of Brentuximab Vedotin, a CD30-Directed Antibody-Drug Conjugate, and its cytotoxic payload (MMAE) in Patients With Various Hematological Malignancies

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Objectives: To develop population pharmacokinetic models of Brentuximab Vedotin (BV), an antibody-drug conjugate (ADC) and its cytotoxic payload (MMAE) following a 30-minute intravenous infusion of BV administered at 1.8 mg/kg given every 3 weeks.

Methods: The population pharmacokinetics were evaluated (using NONMEM versions 7.2 and 7.3) from several studies including data from 380 patients with various hematological malignancies such as relapsed or refractory (r/r) Hodgkin lymphoma, r/r systemic anaplastic large-cell lymphoma or cutaneous T-Cell Lymphoma.

Results: The model for ADC PK was a linear three-compartment model with zero-order input and first-order elimination. ADC clearance (CL) fell with increasing albumin (ALB); CL and central volume of distribution (Vc) increased with increased body surface area (BSA). The final ADC model included pcALCL tumor type and anti-therapeutic antibody (ATA) status. ATA positivity resulted in increased ADC CL, but overall impact on AUC was minimal (9-12% lower). Higher ADC exposure (approx 35%) in pcALCL patients was observed, but considered relatively modest. The model for MMAE included a link to ADC elimination using the individual parameter estimates from the ADC model to predict the ADC concentrations in the MMAE model. The PK of MMAE was described by a two-compartment model with first-order elimination and formation of MMAE both directly from ADC and through binding of ADC to a hypothetical target. Several patient-specific factors were investigated for their influence on ADC and MMAE PK and the impact of all significant covariates was relatively small. Influence of age, gender and race was not significant in ADC or MMAE models. The final POP PK model was evaluated by Visual Predictive Check method. The simulated concentrations appeared reasonably consistent with the observed concentrations, with no systematic bias. Simulations showed that there is little accumulation of ADC and MMAE exposure with this regimen.

Conclusions: Overall the POP PK models for ADC and MMAE characterized the data well. These analyses provided important support for the proposed dose of BV in the planned sBLA/ MAA filings for CTCL indication.

II-22: *Elin Svensson* Linking rifampicin exposure to treatment response over 6 months in patients with pulmonary tuberculosis

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Objectives: Rifampicin (RIF) is the most important component of first-line anti-tuberculosis (TB) therapy, but the optimal dosing of this pivotal drug is uncertain. The potential for TB treatment shortening with higher doses of RIF has been studied recently[1]. Our aim was to characterize the relationship between RIF plasma exposure and treatment response measured over 6 months as time to stable culture conversion (TSCC, i.e. 2 sequential negative cultures) in this trial.

Methods: The trial included 4 experimental arms with 4 months of treatment and one control arm with standard 6 months of treatment using RIF 10 mg/kg combined with standard TB drugs. The experimental arms used RIF 20 or 35 mg/kg, and/or substitution of ethambutol with moxifloxacin or SQ109. Response was monitored with liquid cultures from sequential sputum samples and TSCC was derived. The dataset included 336 patients (97 with full plasma PK curves, day 28). A sequential PK-PD analysis using multiple imputation (MI) methodology for patients lacking PK data was performed in NONMEM 7.3 [2]. Parameter values from the MI procedure were averaged to final estimates.

Results: RIF PK was described with a simplified version of a previously presented model [3]. The model's prediction of AUC was evaluated [4] and found adequate (median observed values within predicted 95%CI for each dose group). TSCC was modeled with a time-to-event model; a three-parameter surge function defined the hazard. In the MI procedure 100 sets of AUCs were simulated for each patient missing PK observations, and each tested in the PD model. A linear effect of RIF AUC was significant (α=0.05) in 99/100 cases, and a (sigmoid) Emax-model did not improve the fit. Lower bacterial load at baseline, lower proportion of missing sputum samples and substitution with moxifloxacin were found to significantly shorten TSCC, while substitution with SQ109 increased TSCC. Simulations assuming standard regimen components, median baseline bacterial load and no missing sputum samples showed that the proportion of patients with TSCC<8 weeks is expected to increase from 39% to 54% when RIF dose is increased from 10 to 35 mg/kg.

Conclusions: Higher RIF exposure generally leads to faster treatment response. No target exposure indicating maximal effect could be derived, probably due to limited range of exposures. RIF doses of 35 mg/kg, and higher if safe and tolerable, should be further studied for its potential to shorten TB treatment duration.

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II-23: *Lénaïg Tanneau* Bedaquiline's exposure-response relationship evaluated with data from the observational study C209

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Objectives: To confirm a previously characterized relationship between bedaquiline (BDQ) exposure and the decline of mycobacterial load (MBL) during treatment of tuberculosis (TB) [1], and to further explore any study-dependent characteristics such as the duration of the individualized background regimen (BR).

Methods: Data were obtained from the TMC207-C209 phase IIb study (single-arm, open-label) enrolling 233 newly diagnosed or treatment-experienced multi-drug resistant (MDR-TB) subjects. The patients received 24 weeks of BDQ on top of an individualized BR. The trial was conducted in accordance with Good Clinical Practice standards and received ethical approval from appropriate local authorities. The applied model was first developed with data from the TMC207-C208 study enrolling exclusively newly diagnosed MDR-TB patients and receiving BDQ on top of an optimized BR initiated at the same time. The model consists of 3 parts: a longitudinal representation of MBL in patients, the probability of bacterial presence in sputum and a time-to-event model for time to positivity in mycobacterial growth tube. Evaluation of the previously developed model's performance was tested with a set of 500 bootstrapped datasets of individual profiles, stratified by the TB status. It has been carried out by using fixed population parameters from the C208 study, with inclusion of a BDQ effect either by a treatment effect or by an exposure effect described by an Emax function. Analysis of covariate effects was conducted on parameters of the MBL model and the impact of the TB status, the presence and the duration of the previous BR was explored.

Results: The model with the BDQ exposure effect has shown to described the new data better than the model with solely a BDQ treatment effect, with a difference in OFV of -17.1 points (bootstrapped 95%PI = -45 to 10). The evaluation of patient related characteristics revealed that patients with extensively drug-resistant (XDR) TB and pre-XDR TB clear the bacteria slower than patients with MDR TB, resulting in 127% (RSE 36%) and 44% (RSE 21%) longer MBL half-life, respectively. A significant impact of the presence and duration of previous BR was not detected.

Conclusions: The previously developed model including a relationship between BDQ exposure and decrease in MBL describes the data from the C209 study better than a model with only a treatment effect. This supports the use of the model for exploration of potential BDQ dose optimization.

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II-24: *Joel Tarning* Population pharmacokinetic properties of piperaquine in falciparum malaria: An individual participant data meta-analysis

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Objectives: Dihydroartemisinin-piperaquine is one of the five first-line therapies currently recommended by the World Health Organization for malaria. Previous studies [1,2] suggest that young children (< 5 year) with malaria are under-dosed. This study [3] utilised pooled individual level data and a population-based pharmacokinetic approach to optimise the antimalarial treatment regimen for piperaquine.

Methods: Published pharmacokinetic studies were identified through a systematic review of articles published between 1960 and 2013. Individual plasma piperaquine concentration-time data from 11 clinical studies (8,776 samples from 728 individuals) were collated and standardised by the WorldWide Antimalarial Resistance Network. Data were pooled and analysed using nonlinear mixed-effects modelling (NONMEM v.7).

Results: Piperaquine pharmacokinetics were described successfully by a three-compartment disposition model with flexible absorption. Body weight was incorporated as an allometric function, resulting in lower exposures in small children (< 25 kg) compared to larger children and adults (> 25 kg) after administration of the manufacturers' currently recommended dose regimens. The final model identified a mean (95% CI) increase of 23.7% (15.8%±32.5%) in piperaquine bioavailability between each dose occasion. The model also described an enzyme maturation function in very young children, resulting in 50% maturation at 0.575 (0.413±0.711) year of age. Simulations were used to construct an evidence-based optimised dose regimen that would provide piperaquine exposures across all ages comparable to the exposure currently seen in a

typical adult with standard treatment, without exceeding the maximum concentration observed with the manufacturers' recommended regimen.

Conclusions: The derived population pharmacokinetic model was used to develop a revised dose regimen of dihydroartemisinin-piperaquine that is expected to provide equivalent piperaquine exposures safely in all patients, including in small children with malaria. Use of this dose regimen is expected to prolong the useful therapeutic life of dihydroartemisinin-piperaquine by increasing cure rates and thereby slowing resistance development. This work was part of the evidence that informed the World Health Organization technical guidelines development group in the development of the recently published treatment guidelines (2015).

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II-25: *Adrien Tessier* Investigating the PK/PD relationship of a new pro-apoptotic drug through tumor growth inhibition modelling in NUDE rats

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Objectives: Apoptosis is the process of programmed cell death that tumor cells escape. Drug S is a pro-apoptotic compound in preclinical development. Using data from a tumor growth inhibition study in rats, the relationship between drug concentrations and efficacy was estimated through PK/PD modelling in order to determine active concentrations.

Methods: Drug S was administered once to 18 RS4;11 xenografted NUDE rats at doses 30 or 75 mg/kg in 1h intravenous (IV) infusion or 30 mg/kg in IV bolus (6 rats per group + 6 rats in the control group). Two PK samples were performed per rat to measure total plasma concentrations. Tumor volumes were measured for all individuals until 52 days after administration.

A population PK/PD modelling analysis was performed using MONOLIX 4.3.3 and SAEM algorithm to estimate active drug S concentrations to reduce the tumor volume.

Results: A one-compartment model with Michaelis-Menten elimination best described the drug plasma concentrations. The tumor growth was described through the Simeoni model [1] with a sigmoid relationship between drug plasma concentrations and apoptosis triggering. The drug effect was interpreted as the transformation rate (in time-1) of tumor cells from a proliferating to a non-proliferating state. The typical maximum transformation rate (Emax) and plasma concentration leading to 90% of the maximum rate (EC90) were estimated. Emax was estimated at 0.87 h-1, indicating quick triggering of apoptosis. The drug effect showed a high sigmoidicity with a Hill coefficient estimated at 7.09.

Using the same approach as proposed by Simeoni [1] the threshold concentration (leading to tumor stasis) was computed and was approximately 2.5 fold lower than EC90, corresponding to a low activity on the concentrations - drug effect relationship (approximately 1.3% of the maximal effect).

Conclusions: Drug S showed an activity to inhibit tumor growth in rats with a strong tumor regression at the highest dose. A PK/PD modelling approach has allowed to described the steep relationship between drug concentrations and tumor regression and to estimate a concentration EC90 corresponding to a high drug activity. The threshold concentration usually estimated through modelling in such analyses corresponds to the lowest active concentrations. For translation to human, it is more relevant to predict the active dose using the estimated EC90, instead of the much lower threshold concentration.

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II-26: *Donato Teutonico* Development of a PBPK model to describe late colonic absorption after oral administration

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Objectives: The compound S is a drug under development at Servier. It has poor water solubility and its PK profile in blood shows a second peak at about 15-24 h after fasted oral administration in human. Since such late absorption is not likely related to enterohepatic circulation (EHC), it is believed that this second peak could be explained by a colonic absorption of this compound, mainly driven by the solubility. A PBPK model in human was developed in order to test this hypothesis.

Methods: The PBPK model was built in PK-Sim 6.3. Since the colon in the gastrointestinal (GI) model implemented in this software is divided in 6 sub-compartments [1], it is well suited to test the hypothesis of a late colonic absorption. The distribution model as well as the clearance and drug lipophilicity were estimated from PK in 2 intravenous (IV) microdose studies. Intestinal permeability was estimated from PK data with 50 µg oral solution. Drug dissolution, solubility and parameters defining colonic absorption (solubility and permeability) were estimated from PK data after single oral administration of immediate release tablet with doses ranging from 5 to 800 mg.

Results: The PK-Sim standard distribution model and an unspecified total liver clearance were used to describe the drug disposition and metabolism. Weibull dissolution functions were used to describe the drug release from the dosage forms. The late portion of the colon in the PBPK model, sigmoid colon, was identified as the compartment able to explain the late phase absorption. In order to describe the second peak of the PK profile, drug solubility in the sigmoid colon had to be adjusted.

Conclusions: The PBPK model developed was able to describe the concentrations in blood of compound S after IV and oral administration for the tested dose range, in particular with respect to the hypothesis of a late phase absorption. The late portion of the colon, the sigmoid colon, was identified as the segment likely responsible for such late absorption.

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II-27: *Tjokosela Tikiso* Population Pharmacokinetics of Abacavir in HIV-infected African children

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Objectives: Abacavir is a potent nucleoside reverse transcriptase inhibitor (NRTI), recommended by WHO as a component of 1st line antiretroviral treatment (ART) for infants and children

Methods: Data from the studies ARROW [2] and CHAPAS-3 [3] have been collected for a pooled modelling analysis. Both studies recruited HIV-infected African children, who were dosed either once or twice daily based on weight bands as recommended by WHO[4], [5]. Samples were collected immediately before administration and at 1, 2, 3, 4, 6, 8 and 12 hours after dosing (and 24 hours for the once daily regimen), at steady state. Allometric scaling was used to account for the effect of body size [6]. Data below the limit of quantification (LLOQ) was included as LLOQ/2. NONMEM 7.3 was used to analyse PK data.

Results: Abacavir Pharmacokinetics was best described by a two-compartment model with first-order absorption with lag time and first-order elimination. The typical value of clearance was 23.1 L/h for a 20 kg child. No maturation processes were observed in this population group. There was no difference in PK parameters between once and twice daily dosing.

Conclusions: The PK estimates are consistent with literature [7]. The disposition of abacavir in children within the age range from 4 to 12 years appears to be affected only by differences in size, and not age. This model is the first step for a pooled analysis including datasets from younger children and infants < 3 months, and on different ART regimens.

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II-28: *Valentina Topic Vucenovic* Nonlinear mixed effects modelling approach for investigation of 131I kinetics in patients with benign thyroid disease

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Objectives: Radioiodine therapy is a common approach in the treatment of benign thyroid diseases. The aim of the study was to investigate factors that influence intrathyroidal kinetics of ^{131}I in patients with benign thyroid disease and to develop population kinetic model using routine clinical data on radioiodine uptake measurement following administration of the tracer activity.

Methods: Demographic and clinical characteristics of patients with benign thyroid disease were retrospectively collected from patients' medical records. Uptake of radioiodine in thyroid (RIU(t)) was measured 4, 24, 48 h, and in some patients 168 h following oral administration of a capsule with nominal test activity of 1.85 MBq of ^{131}I. Population analysis was performed using NONMEM® software (v7.3) and PsN® (v4.6.0). Following covariates were tested: gender, age, diagnosis, functional thyroid volume, presence of cardiovascular disease, thyroid-stimulating hormone (TSH), free thyroxine (fT_4), previous therapy with anti-thyroid drugs (ATDs) and therapy discontinuation time before administration of the test activity.

Results: In total 366 adult patients, and 899 uptake measurements were included in the analysis. The two-compartment model of ^{131}I biokinetics was used as the structural model [1]. The interindividual variability (IIV) of the rate constant of the uptake of radioiodine in the thyroid (k_{tu}) was described by an exponential model, while the residual error was best described by a proportional model. Results of the study indicate that k_{tu} in patients with benign thyroid disease is significantly influenced by diagnosis, age, functional thyroid volume, fT_4 in plasma, use of ATDs and time of discontinuation of therapy. According to the final model, effective half-life of ^{131}I in typical patient is 6.56 days, and for each additional year it increases on average by 3.95%. Inclusion of the covariates in the base model resulted in decrease of the IIV for k_{tu} from 89.8% (7.6%) to 55.6% (4.5%) with shrinkage of 3.9%. Acceptable performances of the final model were confirmed by nonparametric bootstrap analysis and predictive checks.

Conclusion: The developed population kinetic model of ^{131}I explained significant portion of interindividual variability in ^{131}I intrathyroidal kinetics and can be used for estimation of individual time-integrated activity coefficient of ^{131}I needed for patient specific calculation of therapeutic activity for radioiodine therapy of benign thyroid diseases.

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II-29: *Elena Tosca* A PK/PD model for tumor-in-host growth kinetics following administration of an antiangiogenic agent given alone or in combination regimens

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Objectives: PK/PD models predicting the action of antiangiogenic drugs in tumor xenograft neglect tumor and host interactions[1,2]. Conversely, current tumor-in-host models[3,4], based on cell kill hypothesis, are inadequate to describe the effect of antiangiogenic compounds that act on tumor vascularization. For this reason, a PK/PD tumor-in-host model able to describe tumor growth inhibition (TGI) following cytostatic therapy, as opposed to a cytotoxic treatment, is here proposed.

Methods: *Experiments:* The experimental setting is the typical in vivo study performed on xenograft mice using different human carcinoma cell lines. Mice were treated with vehicle or Bevacizumab, either alone or in combination with cytotoxic compounds. Average data of tumor and mice net body weight were considered for control and treated groups. PK were derived from separated studies. *Model:* Untreated tumor growth was described by a tumor-in-host DEB-based model[3,4]. Assuming a reduction of the nutrient supply to the tumor, antiangiogenic action was implemented as an inhibitory effect on the energy fraction appropriated by the tumor from the host, while no direct drug effect on the mice weight was included. A combination model was also developed under a 'no-interaction' assumption[5] to assess the effect of the combination of Bevacizumab with cytotoxic agents: tumor-in-host kinetics can be described by a joint model incorporating boh the antiangiogenic and cytotoxic DEB-TGI model. Monolix 2016R1 was used for model identification.

Results: The single agent antiangiogenic model was successfully identified on tumor and mice net body weight data from animals treated with vehicle and different Bevacizumab dosing regimens. In the combination setting, the tumor-related and drug-related parameters were obtained by fitting data coming from single-agent arms of the combination experiments. Then, using these parameter values, tumor and mice body weight curves were simulated under 'no-interaction' assumption. Possible drug-drug interactions can be visually assessed by overlapping observed and predicted curves.

Conclusions: The antiagiogenic tumor-in-host model well describing tumor and mice body weight data following Bevacizumab treatment. Furthermore the 'no interaction' model can provide quantitative indications about possible interaction between cytostatic and cytotoxic drugs, resulting a useful tool to investigate the best combination treatments during preclinical experiments.

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II-30: *Mirjam Trame* Translational in-vitro in-vivo model to correlate HIPS derived cardiomyocyte contractility assay and in-vivo dog telemetry based dPdtmax measurements

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Objectives: Cardiovascular safety is one of the most frequent causes of safety related attrition both pre-clinically and clinically. Limited progress has been made in the development of *in-vitro in-vivo* translation of drug induced cardiac contractility changes. The objective was to explore the translation of *in-vitro* cardiac contractility assay results obtained from human induced pluripotent stem cell derived cardiomyocytes (HIPS-CM) to drug induced changes in $dPdt_{max}$ observed *in-vivo*, within dog telemetry studies.

Methods: Pharmacological *in-vitro* alteration of calcium transients in HIPS-CM from compounds at various stages during drug discovery/development within AstraZeneca were available. Additionally, *in-vivo* cardiac contractility biomarker data, $dPdt_{max}$, from in-house AstraZeneca pre-clinical dog telemetry studies were utilized. Plasma drug concentration measurements or predictions from a developed dog PK model were used as exposure data. Drug induced changes in $dPdt_{max}$ were calculated by correcting for baseline/placebo effects and for day-to-day variations in baseline [1]. A 26% change in $dPdt_{max}$, currently used as the effect size to appropriately power dog telemetry studies in AstraZeneca, was considered as a significant pharmacodynamic threshold to identify potent *in-vivo* drug concentrations using LOESS approximation. Geometric mean of concentrations across different compounds was used as the average drug concentration threshold at which *in-vivo* effects of $dPdt_{max}$ leading to safety risks can be expected.

Results: Data from n=6 compounds out of all data provided from in-house AstraZeneca studies were identified to have PK, $dPdt_{max}$ and EC_{50} information and used during this analysis. Unbound plasma concentration ($C_{unbound}$) normalized by the potency (EC_{50}) was used as the appropriate PK parameter. Potency normalized concentrations of 0.10 [95%CI 0.0014-7.65] mM/mM was determined as the potent exposure that would result in a 26% drug induced change in $dPdt_{max}$. Potency normalized plasma concentration was found to be sensitive to the threshold for $dPdt_{max}$ change across all 6 compounds.

Conclusions: A translational *in vitro in vivo* approach was successfully developed and adequate correlation was observed between drug induced changes in $dPdt_{max}$ in dogs and the corresponding *in-vitro* potency normalized unbound plasma levels. This was used to determine the potent exposure at which significant changes in *in-vivo* $dPdt_{max}$, a key cardiac safety concern, can be observed.

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II-31: *Alexios Tsiligiannis* Optimization of a paediatric FDC tablet and dosing regimen for the first line treatment of tuberculosis.

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Objectives: This study was designed to optimize the strengths of a paediatric fixed dose combination (FDC) mini-tablet of isoniazid, rifampicin and pyrazinamide for the first -line treatment of tuberculosis, as well as the corresponding weight based dosing chart in the age range 0.5 to 8 years, using Modeling and Simulation.

Methods: Based on published population pharmacokinetic models (1) (2) (3), we simulated the exposures of Rifampicin, Isoniazid and Pyrazinamide in virtual adult South African patients, which are considered therapeutic. Doses were considered based on both, Rifater® SPC (a well-known and widely used adult anti tuberculosis product) and WHO guidelines for tuberculosis treatment. 970,200 scenarios of virtual paediatric Fixed Dose Combination tablets of first line anti tb drugs and weight bands were tested in silico on paediatric population, using Monte Carlo simulations carried out based on published PopPK models for children (4). The simulations were conducted in Matlab®R2016b. The dosing regimen which produced similar, according to a prespecified criterion, to adult exposures for all weight bands was chosen as the optimal one.

Results: Simulations showed that the optimal dosing regimen includes a new FDC tablet with 90 mg of Rifampicin, 200mg of Pyrazinamide and 75mg of Isoniazid, administered as follows: 1 tablet for children with body weight ≥4 kg and <8kg, 2 tablets for children with body weight ≥8kg and <12 kg, 3 tablets for children with body weight ≥12kg and <18 kg and 4 tablets for children with body weight ≥18 kg and <28 kg. Children with body weight ≥ 28 kg will be treated with adult dosages.

Conclusions: We optimized an anti-tuberculosis FDC tablet not based on predefined mg/kg doses but directly on therapeutic exposures similar to those of adults. This was done by a global optimization of the 3 strengths of the drugs and the weight cut-off points of the groups. A global optimization is needed because, although no synergy is considered between the drugs, all optimized parameters are correlated by the constraint that a single mini-tablet needs to be defined that its multiples scale well for the different age groups, such that the therapy is efficacious for all groups.

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II-32: *Periklis Tsiros* Bayesian Whole Body Population Physiologically Based Pharmacokinetic Approach for Characterization of Interindividual Variability of Diazepam

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Objectives: To develop a Bayesian population approach for an existing whole-body physiologically based pharmacokinetic (WBPBPK) model of Diazepam in order to identify the main sources of variability, through integration of prior knowledge of selected physiological parameters.

Methods: Plasma concentrations-time data from 12 healthy male and female volunteers in [1] were analysed using a well-structured, fourteen-compartment WBPBPK model [2]. A Bayesian hierarchical model, implemented in Stan V.2.14.0 [3], is employed considering the data at an individual level and identifying the variability in physiological parameters at a population level. The parameters of the model were of primarily physiological nature, namely blood flows and tissue volumes. Parameters were selected by combining two sensitivity analysis methodologies, i.e. pertubation analysis of the compartmental matrix and Sobol's sensitivity indices. The physiological parameters that were found to be insignificant, as well as the drug-specific parameters, were given fixed values. The values of the latter ones were retrieved from the posterior analysis of a previous study [2]. Additionally, population covariates were considered as part of the 3-stage hierarchical model developed.

Results: We have found that the presented model adequately describes the experimental plasma concentration-time profiles. Furthermore, the suggested approach identifies the variability in the underlying physiological as well as drug-dependent parameters.

Conclusions: This Bayesian approach showed the potential of uncertainty reduction when predicting diazepam concentrations via integration of the patient's characteristics and can be extended to predict the pharmacokinetic behaviour of new drugs in different populations.

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II-33: *Eirini Tsotsou* Population pharmacokinetics of gentamycin in hospitalized ICU patients

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Objectives: To develop a PopPK model of gentamycin in ICU patients with either obesity, sepsis or acute respiratory distress syndrome, while some undergoing hemofiltration. Gentamycin is a well studied hydrophilic antibiotic, thus in these special situations the pharmacokinetic profile of the drug may be altered, therefore a different dosing regimen could be required.

Methods: PK data of gentamycin were obtained from 82 hospitalized ICU patients. Dosing regimen was 7 mg/kg as a 1 hour infusion. Samples were collected before the administration, at the end of infusion and 8-16 hours after the administration. Fluorometry with TDX analyzer was used for the quantification of gentamycin concentrations. Using the software NONMEM (ver 7.3) with FOCEI method, first a basic model was determined by trying out different compartmental structural models and error models. Then statistically significant covariates were screened. The final PK model was validated using nonparametric bootstrapping and visual predictive check (VPC).

Results: The final model was a one compartment model with combined error, parametrized as clearance (CL) and volume of distribution (V). The covariate model on CL was $CL = \theta1*(WT/84)^{\theta3} *[1-\theta5*(AGE-40)]$ L/h and on $V = \theta2*(WT/84)^{\theta4}$ L. Parameter estimates took the following values (SE in parentheses) θ1=3.81 L/h (10.3%) , θ2=51.4 L (2.9%) , θ3=0.811 (26.8%) , θ4=0.552 (19.2%) and θ5=0.007 1/year (37.1%) . Interindividual variability on CL and V was found to be 34.2% (27,4%) and 17.3% (31,7%) respectively, and residual error parameters were found σ1=19.7% and σ2=1.43 mg/L. Bootstrap ran successfully in 908 out of 1000 bootstraps, with mean θ1=3.86 (11.1%) L/h, θ2=51.4 (2.7%) L, θ3=0.907 (40.5%), θ4=0.554 (25.8%), θ5=0.00687 (39.0%), ω1=0.321 (31.6%), ω2=0.133 (66.8%) , σ1 =0.192 (29.2%) and σ2=1.27 mg/L (47.6%). The VPC plot demonstrated that the 5^{th}, 50^{th} and 95^{th} percentiles of the data fell within the 95% CIs of the respective prediction intervals of the model, except a few points of the upper percentile.

Conclusion: A population pharmacokinetic model for gentamycin in ICU patients was developed which includes the effect of age and weight and can be used to determine dosing regimens in these patients by calculating AUC/MIC target attainment probability through Monte Carlo simulations and considering appropriate AUC/MIC targets from literature.

II-34: *Denise Tuerk* Physiologically-Based Pharmacokinetic (PBPK) Modeling of the CYP2C8 Substrate Pioglitazone

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Objectives: Pioglitazone, a thiazolidinedione, is indicated to treat type II diabetes mellitus. It is an agonist of the nuclear transcription factor peroxisome-proliferator-activated receptor γ and modifies gene-expression, resulting in an insulin sensitizing effect [1]. Pioglitazone is predominantly metabolized by CYP2C8 [2] and it is recommended by the U.S. Food and Drug Administration as a moderate sensitive CYP2C8 substrate [3]. Co-administration of pioglitazone with the strong CYP2C8 inhibitor gemfibrozil leads to a 3.4-fold increase in the area under the curve (AUC) of pioglitazone [4]. Our objective was to establish a PBPK model of the victim drug pioglitazone.

Methods: A PBPK model of pioglitazone was built in PK-Sim® (Version 6.3.2) [5]. Drug-dependent parameters (e.g. acid dissociation constant, solubility) and concentration-time profiles of 11 clinical studies (oral dosing from 15 to 45 mg daily, single- and multiple-dosing) were obtained from literature. Parameters for which no information was found were optimized to describe an internal data set (5 studies) of observed concentration-time profiles. The PBPK model was evaluated by prediction of an external data set (6 studies).

Results: The final pioglitazone model includes metabolism by CYP2C8, CYP3A4 [2] and glomerular filtration. Furthermore, the model is able to describe the effects of a CYP2C8 polymorphism on pioglitazone plasma concentrations. The CYP2C8*3/*3 genotype is related to an increase in pioglitazone metabolism compared to wild-type (CYP2C8*1/*1) and leads to a decrease in the AUC by 34% [6]. The external data set is well predicted. The quality of the model can be characterized by AUC ratios (AUC predicted /AUC observed), which show a very low geometric mean fold absolute deviation of 1.09 (range 1.00-1.28, n=11).

Conclusions: We successfully established a PBPK model of pioglitazone as a CYP2C8 victim drug. The model can be applied to predict drug-gene interactions and to evaluate the drug-drug interaction potential of drugs which are CYP2C8 inhibitors or inducers, to help with clinical study design, drug approval and labeling questions.

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II-35: *Zofia Tylutki* Simulation of pharmacokinetics of amitriptyline and nortriptyline and their common effect on human cardiac electrophysiology in healthy population

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Objectives: In assessing drug triggered cardiac effect the parent drug and its metabolites' exposure in cardiac tissue seems to be of particular interest, although drug level in plasma is the most commonly used as the effective concentration surrogate. The aim of the study was to simulate drug influence on the electrophysiology of human cardiomyocytes in the population, taking into account individual PBPK model-predicted drug and its metabolite concentrations both, in heart and plasma. Amitriptyline and nortriptyline were used as the model substances.

Methods: Amitriptyline time-concentrations profiles in plasma and heart tissue were simulated in a whole-physiologically-based pharmacokinetic (PBPK) model with four-compartment heart model nested in[1]. The model has been extended with the minimum-PBPK model for the metabolite[2] consisted of 4 compartments (plasma, heart, liver, and rest of the body) of physiological volumes and blood flows. 3 parameters were fitted to the clinical data, and the simulation scenario followed study methodology[3]. The models were written in R v.3.3.2. After defining the dose amount (single oral dose of 75 mg), number of individuals (8), number of females (0), and age range (20 – 28) the sex- and age- dependent physiological model parameters were randomized. Predicted individual free concentrations of amitriptyline and nortriptyline both, in plasma and heart, were combined with patient-specific parameters and in vitro ion channel inhibition to simulate pseudoECG traces in Cardiac Safety Simulator (CSS)[4], and ΔQTcB was an ultimate endpoint.

Results: After 10 iterations of the simulation the mean difference between the length of QTcB after drug administration and at baseline (ΔQTcB) simulated for free plasma and free heart tissue were in the range from -3.29 ms 1 h postdose to 4.38 ms 6 h postdose.

Conclusions: Simulated ΔQTcB value did not exceed 5 ms (value of regulatory concern) in neither of the assessed time points. The simulated study was negative regarding a threshold pharmacologic effect on myocardial repolarization which was in accordance with in vivo observations[3]. The results of this study support the predictive abilities of in silico simulations as well as PBPK modeling.

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II-36: *Sebastian Ueckert* Solving linear ODEs using Krylov subspace projection methods

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Objectives: Within the field of pharmacometrics, linear ordinary differential equations (ODE) are used for pharmacokinetic models as well as for modeling of continuous time Markov-Models. The solution of these linear ODEs generally involves the numerical calculation of the matrix exponential. The objective of this work was to evaluate the performance of Krylov subspace projection methods for calculating the matrix exponential and compare it to existing methods.

Methods: A new solver for pharmacometric linear ODE models was implemented by combining a method for the calculation of derivatives of the matrix exponential [1] with a Krylov subspace solver from the EXPOKIT package [2] and linking it to NONMEM 7.3 [3]. The solver was evaluated by comparing the FOCE likelihood evaluation time for a three compartment model with linear absorption, 100 subjects and 15 observations per subject, with the evaluations times from the ADVAN5 and ADVAN6 solvers.

Results: For the evaluated example, the Krylov subspace-based solver was 3.6 times faster than the standard solver for linear ODE ADVAN5 (1.2 vs. 4.3 sec). Compared to the general ODE solver ADVAN6, the novel solver performed 12 times faster (1.2 vs. 12 sec).

Conclusions: Krylov subspace projection methods constitute a promising approach to significantly reduce the runtime of models implemented as linear ODE.

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II-37: *Sami Ullah* Population pharmacokinetic analysis of intravenous telavancin in healthy subjects undergoing plasma and tissue microdialysis

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Objectives: Telavancin is a novel lipoglycoprotein used to treat complicated skin and soft tissue infections and hospital acquired pneumonia with MRSA. Non-compartmental analysis of systemic total telavancin concentrations in a microdialysis study gave an average calculated target index ($AUC_{0–24}$/MIC) slightly below the proposed value [1].

The aim of this additional evaluation of [1] was the development of a compartmental population pharmacokinetic model and its application to evaluate the current standard dosing of 10mg/kg once daily.

Methods: Data was available for eight male healthy subjects (median age and body weight of 27.0 [range 23-35] years and 76.5 [67.0-83.4] kg). A single intravenous infusion of telavancin (10mg/kg within 1 hour) was given to all subjects. Plasma samples and microdialysis samples, representing unbound telavancin concentrations in plasma, muscle and subcutaneous tissue, were taken [1]. Population pharmacokinetic modeling and Monte Carlo simulations were performed using NONMEM VII and Monolix suite 2016R1.

Results: Plasma concentrations of telavancin were best described by a two compartment model with saturable protein binding (B_{max} = 81.0 mg/L [25.7%], K_d = 9.36 mg/L [26.7%]). Elimination clearance from the central compartment and inter-compartmental clearance estimates were 1.44 L/h [4.50%] and 2.59 L/h [16.8%]. Central and peripheral volumes of distribution were 6.52 L [10.8%] and 6.08 L [10.0%], respectively. Clearances and volumes were scaled allometrically. Two additional compartments each (interstitial and peripheral) described the distribution into muscle and subcutaneous tissue. For a 10 mg/kg dose, simulations on total plasma concentrations indicated an $AUC_{0–24}$/MIC of 3497 [range 3140-4008] for a MIC of 0.125 mg/L [2]. The probability of target attainment (PTA) was only 11.6% for the first dose but is expected to approach 100 % at steady state. As simulated $AUC_{0–24}$/MIC values had low variability and were close to the proposed target $AUC_{0–24}$/MIC of 3650 [2], PTA may change dramatically with both small changes in exposure and in MIC.

Conclusions: The empirical model was able to describe the data and to provide a new hypothesis on telavancin plasma protein binding *in vivo*. Further studies are needed to assess whether a slight increase in initial dose (e.g. 12mg/kg instead of 10mg/kg body weight) would result in earlier target achievement and to assess tissue AUC/MIC at steady state.

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II-38: *Moreno Ursino* dfpk: an R package for a practical implementation of PK measurements in dose-finding studies

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Objectives: Dose-finding, aiming at finding the maximum tolerated dose (MTD), and pharmacokinetics (PK) studies are the first in human studies in the development process of a new treatment. In the literature, to date only few attempts have been made to combine PK and dose-finding and no software implementation is available. Our objective was to implement the five PK-based dose-finding methods developed in [1] in an R package, called *dfpk* [2].

Methods: By default, AUC is used as PK measure of exposure, but it can be replaced with other PK measures such as Cmax. AUC is treated as a covariate for the probability of toxicity for PKCOV method, as dependent variable in linear regression versus dose for PKLIM method, and in both ways, in two separated regression models, for PKLOGIT, PKTOX and PKPOP methods. All methods were developed in a sequential Bayesian setting: Bayesian parameter estimation is carried out using the *rstan* package. All available data are used to suggest the dose of the next cohort with a constraint regarding the probability of toxicity. The *ggplot2* package is used to create summary plots of toxicities or concentration curves.

Results: *dfpk* provides, for each method, a function (*nextDose*) to suggest the dose to give to the next cohort, and a function to run trial simulations (*nsim*). *nextDose* requires the method name, the binary toxicity outcomes and the PK measurements for each patient, the panel of doses, the toxicity threshold and the parameter for the prior distributions. The output includes the recommended dose and the estimated probability of toxicity at each dose. *nsim* requires also the cohort size, the sample size for trial, the number of trials and simulated datasets. The *scenario* function generates at each dose the toxicity value related to AUC with an underlying one PK compartimental model with linear absorption. It is included as an example. Similar dataframes can be generated directly by the user and passed to *nsim*.
The online help provides an example of using dfpk for the case-study described in [1].

Conclusions: The developed user-friendly R package *dfpk* supports the design of innovative dose-finding studies using PK information. It can be downloaded freely from the CRAN repository.

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II-39: *Pavan Vaddady* A Comprehensive Model-Based Meta-Analysis (MBMA) of Diabetes Studies in Type 2 Diabetes Mellitus Patients to Quantify the Relationship between HbA1c and Fasting Plasma Glucose

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Objectives: Describe the relationship between fasting plasma glucose (FPG) and HbA1c to predict long term efficacy from early clinical outcome by linking their MBMA based dose-time-response, to identify clinically meaningful covariates, and to evaluate the consistency of FPG-HbA1c relationship within and across mechanisms of anti-diabetic drugs studied.

Methods: A comprehensive Type 2 Diabetes Mellitus clinical outcomes database was developed to document clinical safety and efficacy information from trials investigating sulfonylureas, metformin, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonists, thiazolidinedione, sodium–glucose cotransporter-2 inhibitors, glucagon receptor antagonists and glucokinase activators. For HbA1c and FPG, longitudinal MBMAs were developed using a non-parametric placebo response with Emax dose-response models incorporating covariate effects.

Results: These two MBMAs resulted in robust models from clinical trial data for HbA1c (464 trials) and FPG (477 trials). For HbA1c, dose and time dependencies were successfully characterized for most drugs and HbA1c reduction was greater in patients with higher baseline HbA1c, patients on a background of diet only compared to insulin or oral anti-diabetic drugs supporting less-than-additive efficacy commonly seen with combination treatments [1], patients with higher estimated glomerular filtration rate (for SGLT2s only), and in Japanese patients. The model developed for FPG was structurally similar to the HbA1c model. The covariates identified were identical and in the same direction of impact as in the HbA1c model. For the link between HbA1c and FPG, the drug effects for each of the endpoints at the primary time point were highly correlated. The correlation, however, changed over time until becoming stable after approximately 12 weeks allowing for predicting long term glycemic control based on early glycemic markers. The ratio of HbA1c (%)/FPG (10 mg/dl) followed similar trends over time for all drug classes, but the magnitudes were different.

Conclusion: This analysis provided a quantitative framework for comparison of treatment effects of existing diabetes drugs and linking the short term effects (FPG) to long term outcomes (HbA1c). It also enabled projections of HbA1c for specific subset of covariates which can be helpful in designing clinical trials and assessment of differentiation for novel treatments in the discovery and development pipeline.

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II-40: *Elodie Valade* Population Pharmacokinetic Modeling of Simeprevir – Odalasvir Interaction in Healthy Volunteers

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Objectives: To develop a joint population (pop) pharmacokinetic (PK) model describing the PK interaction between simeprevir (SMV) and odalasvir (ODV), two direct-acting antiviral agents (DAAs) for the treatment of patients with chronic hepatitis C (CHC) infection.

Methods: The data used in the analysis were obtained from a phase 1, open-label, two group, fixed-sequence study in healthy volunteers (HV) [1]. A total of 997 SMV (344 in monotherapy, 653 in combination with ODV) and 1215 ODV (403 in monotherapy, 812 in combination with SMV) plasma concentrations were used. The data were analyzed by a non-linear mixed effects modelling approach, using NONMEM software [2]. Previous models describing the PK of SMV [3] and ODV (data on file) in monotherapy were used to quantify the PK of SMV and ODV in the absence of interaction. Based on available information, the effect of SMV on ODV apparent clearance (*CL/F*) and relative bioavailability was evaluated. Similarly, the effect of ODV on SMV mean transit time, relative bioavailability (F_{rel}), and the parameters quantifying the SMV Michaelis-Menten elimination (V_{max} and K_m) was investigated. The effect of a compound on the other one was tested as a categorical covariate or as being dependent on the other compound's predicted concentration at each time point, according to different mechanism of PK interaction (*i.e.* competitive or non-competitive inhibition).

Results: The effect of SMV on ODV was best described by an inhibition of CL/F with an I_{max} model depending on SMV predicted concentrations. I_{max} and IC_{50} were estimated to 46.7% and 257 ng/mL, respectively. The effect of ODV on SMV was best described by a combination of a categorical effect on SMV F_{rel} and a competitive inhibition on SMV elimination. In presence of ODV, SMV F_{rel} increased by 26% whereas SMV K_m doubled at ODV concentrations of 1610 ng/mL.

Conclusions: A popPK model describing the dual ODV-SMV PK interaction has been developed in HV and was able to capture the increase of SMV and ODV exposures when administered together. This model can be used to investigate the impact of these PK interactions in patients with CHC infection receiving different dosing regimens of ODV and SMV in combination with other DAAs.

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II-41: *Tamara van Donge* Impact of rise in anti-drug antibodies on the pharmacokinetics of the monoclonal antibody adalimumab

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Objectives: To quantitate the high variability in pharmacokinetics (PK) of the monoclonal antibody adalimumab, with specific focus on the role of anti-drug antibodies on elimination process. **Methods:** PK and immunogenic data were obtained from a double blind, 3-parallel groups, single-center biosimilarity trial (n=198) of adalimumab, in which healthy volunteers received, single subcutaneous dose of 40mg of test (ONS-3010) or reference (Humira® EU or Humira® US) product[1]. Population PK modelling was performed using FOCEI in NONMEM 7.3[2]. Structural models with one, two or three compartments including combinations of linear and non-linear absorption and clearance were fitted to the data to determine best structural model. Between-subject variability was assumed log-normal distributed and residual error structures were tested (proportional, additive and combined). Data on body weight, LBW, BSA, BMI, height, age, dosing formulation and neutralizing capacity of anti-drug antibodies was used for covariate analysis. Potential covariate correlations were visually and statistically identified (Pearson's r^2>0.3) before these covariates were formally tested based on improvement in model performance. **Results:** A one-compartmental model with linear absorption and Michaelis-Menten elimination best described the individual plasma concentration over time profiles. Interindividual variability was identified on absorption rate constant (Ka), central volume of distribution (V) and Michaelis-Menten constant (Km) with coefficients of variation of 65.9%, 20.1% and 110%, respectively. Residual variability was best described by a proportional error structure. Allometric scaling on V significantly improved the fit and was incorporated in the model. A direct effect of anti-drug antibodies on the maximum rate of elimination improved the model fit (decrease in OFV of 440 points). Dosing formulations did not contain significant correlations with any of the PK parameters. All PK parameters were estimated with high precision (RSE<30%). Condition number was 10.3, demonstrating no model instability. All parameter estimated lie well within the 95% confidence interval of the bootstrap analysis (98.3% successful runs). The development of neutralizing anti-drug antibodies resulted in reduced exposure of 41.63% in the lower (2.5%-percentile) bound of the AUC. **Conclusions:** PK model suggests that a rise in anti-drug antibodies significantly increases the elimination of adalimumab and therefore reduces exposure, which may partly explain the difference in treatment responses between patients.

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II-42: *Michiel Van Esdonk* Quantifying the growth hormone lowering effect of BIM23B065 after a GH stimulation test

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Objectives: To establish the pharmacokinetic-pharmacodynamic relationship of a novel somatostatin-dopamine chimeric compound (BIM23B065) on a growth hormone (GH) stimulation test.

Methods: A phase I, double-blind, randomized, placebo-controlled study was conducted in 63 healthy male volunteers. The study was performed in two parts; a single ascending dose with 5 cohorts and a 13 day multiple ascending dose with 3 cohorts (1.2 mg q.d., 0.8 mg b.i.d. and 1.0 mg b.i.d. administered subcutaneously). A 6 day up-titration period was included for the 3 cohorts of the multiple ascending dose study to counteract the dopaminergic effect of BIM23B065. Each cohort consisted of 8 planned subjects of which 2 received placebo. GH stimulation tests using growth hormone releasing hormone (GHRH) (1µg/kg bolus injection) were conducted on two occasions during the multiple ascending dose study (24 subjects in total).

Results: Population PK/PD analysis was performed on a total of 276 plasma GH concentrations using NONMEM 7.3 [1]. The structural model contained three key elements: 1) a previously developed PK model of BIM23B065, 2) the PK model of GHRH and 3) the GH release model. As GHRH PK was not obtained, GHRH concentrations over time were simulated using literature data [2]. The GH release model consisted of a turnover compartment (k_{in}= 43.3 mU/L/h, k_{out}= 0.279/h) from which GH was released in the central compartment. A zero-order release from the turnover compartment to the central compartment mimics the endogenous baseline secretion of GH. Stimulation of GH release was modeled as a first-order release from the turnover compartment following an E_{max} relationship (E_{max} = 1/h, EC50= 0.055 µg), driven by the amount of GHRH in the GHRH compartment.

Treatment with BIM23B065 was added as a covariate on the EC50 of GHRH to decrease the release of GH during the GH stimulation test. The addition of treatment with BIM23B065 as a covariate resulted in a significant increase (3000 fold) in the EC50 and drop in OFV. No changes in drug effect between the three different dosing regimens could be identified.

Conclusions: BIM23B065 significantly reduced the release of GH during a GH stimulation test which warrant investigation of the compound in patients with excessive growth hormone production.

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II-43: *Eline van Maanen* A systems pharmacology approach unravels the dynamics of the APP pathway and unfolds Aß oligomer modulation

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Objectives: In Alzheimer's Disease, amyloid-β (Aβ) levels are increased early forming toxic soluble Aβ oligomers (AβO) and plaques. Drug effects on the individual attributes of the amyloid precursor protein (APP) pathway are difficult to predict, because it involves a biological network. The objectives were: (1) To further develop an existing APP systems pharmacology model [3], describing drug effects on individual attributes and their interrelationships; (2) To elucidate the relationship between the AβOs and monomeric Aβ.

Methods: In a 4-way crossover study in monkeys [1] the effects of a BACE1 (MBi-5; 30, 125 mg/kg) and a GS (L675; 240 mg/kg) inhibitor on the CSF concentrations of sAPPβ, Aβ40, Aβ42, Aβ38, AβO and sAPPα were determined. An existing APP systems model [3], was extended in two steps: (1) Aβ38 and AβO response were included and the relationship between monomeric Aβ species and AβO was investigated. (2) The model was extended to GS inhibitor response data and the resilience of the APP pathway was investigated.

Results: The APP systems model quantified the effects on all six biomarkers adequately. The BACE1 effect was described by inhibition of formation of C99 and sAPPβ out of APP. The GS effect was described by inhibition of Aβ formation out of C99. The increase in C99 after GS inhibition stimulated α-secretase processing of APP indicating a homeostatic feedback loop. The ratio Aβ42:Aβ40:Aβ38 following BACE1 *vs.* GS inhibition was found different and was explained by stepwise successive cleavage of C99 by GS, where part of Aβ38 is formed from Aβ42. The APP systems model integrated information from an AβO assay [2] with the PK and APP metabolites concentration measurements in response to both treatments. Interestingly, it was found that: (i) Aβ oligomerization was a higher order process; (ii) Both inhibition of BACE1 and GS resulted in similar reduction profiles for AβOs; (iii) Aβ42 was the only contributor to the oligomer pool.

Conclusions: BACE1 and GS inhibition reduce the putatively neurotoxic oligomer pool. A large change from baseline for AβO compared to monomeric Aβ species is obtained following BACE1 or GS inhibition because oligomerization is a higher order process, The model suggested that GS inhibition enhances the non-amyloidogenic processing of APP by homeostatic feedback via C99. The APP systems pharmacology model can bring us closer to optimizing the therapeutic intervention to reduce AβO burden.

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II-44: *Erno van Schaick* CHF5993 a triple combination therapy for COPD patients: population PK modelling of formoterol following pMDI inhalation

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Objectives: CHF 5993 pMDI is a new extrafine fixed dose combination of beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium bromide (GB), being developed for chronic obstructive pulmonary disease (COPD) and asthma treatment. Data collected in phase II/III studies were used to evaluate the population pharmacokinetics of FF and to investigate the influence of selected covariates on FF pharmacokinetic parameters and their potential clinical impact.

Methods: FF plasma concentrations after oral inhalation in COPD patients were obtained from 2 studies: Triple 6 (ph III) and CARSAF (ph II). Both studies were double-blind, randomized, active-controlled. In Triple 6, patients inhaled two puffs twice daily of CHF 5993 pMDI (BDP/FF/GB 100/6/12.5 µg). In CARSAF, patients inhaled two puffs twice daily of Foster® pMDI (BDP/FF 100/6 µg) plus either 25 or 50 µg GB pMDI. FF plasma concentrations were modelled with non-linear mixed-effects approaches using NONMEM V7.3.0. The explored covariates were age, smoking status, sex, body weight (WT), body mass index, concomitant medications, study effect, use of spacer, forced expiratory volume in 1 second (FEV1), concomitant diseases and glomerular filtration rate (GFR).

Results: The final population model to describe the PK of FF was a two-compartment disposition model with a combined first-order and zero-order absorption process, with inter-occasion variability on relative bioavailability. The residual error model was an additive model for the log-transformed data. BQL concentrations (13% of the data) were handled with the M3-method. WT, study effect, use of spacer and GFR were found to affect FF PK parameters. Simulations were performed to visualize the impact of these covariates on the PK of FF, at steady-state, using a FF dose of 12 µg BID. For sub-populations with extreme values of WT and GFR (i.e. low WT (40 kg) and low GFR (27 mL/min/1.73 m^2)), FF exposure increases by a factor ≈2.5 compared to the reference patients. This higher exposure is of no clinical concern because individual therapeutic doses of up to 2-fold the FF doses used in CHF5993 formulation are currently available on the market and thus this doubling in exposure can be considered safe.

Conclusions: The PK model built on data from COPD patients described the FF exposure well and was able to explain part of the variability in exposure on the basis of some covariates. Based on simulated profiles, no dose adjustments were deemed necessary.

II-45: *Rob van Wijk* A parent-metabolite pharmacokinetic model of paracetamol in zebrafish

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Objectives: The zebrafish larva is a promising vertebrate model organism in drug discovery and development. The pharmacokinetics (PK) of the drugs or their metabolites are however often disregarded[1]. Quantifying internal drug and metabolite exposure is important as they drive the observed pharmacological (side)effects. Additionally, quantification of elimination rates for different pathways increases our understanding of the PK translation potential of the zebrafish larvae towards higher vertebrates[2]. We developed a non-linear mixed effects (NLME) model to quantify glucuronidation, sulphation and unchanged excretion of paracetamol (acetaminophen) in zebrafish larvae, extending our concept for paracetamol PK in zebrafish larvae[3,4].

Methods: Zebrafish larvae of 5 days post fertilization (dpf) were exposed to 1 mM paracetamol either continuously for 10-180 minutes, or for 60 minutes after which they were transferred to clean medium for 60-240 minutes. Paracetamol, paracetamol-sulphate, and paracetamol-glucuronide were quantified by UPLC-QTRAP (ABSciex) in 3 replicates of 5 lysed larvae or in their incubation medium.

A NLME model was developed in NONMEM 7.3, simultaneously modelling internal and excreted amount of parent and metabolites. Destructive sampling imposed fixing the total volume of distribution to total larval volume of 307 nL which was determined by 3D volume modelling[6], and prevented estimation of inter-individual variability. Paracetamol absorption was estimated as zero order process. Metabolism was tested using first order and Michaelis-Menten kinetics. Excretion of parent and metabolite was estimated as first order process.

Results: A one compartment model best described the time course of internal paracetamol and metabolite amounts. Paracetamol absorption rate was 1.86 pmol/min. Sulphation and glucuronidation clearance was 9.2 nL/min and 1.6 nL/min, respectively. Excretion of the sulphate and glucuronide metabolites were a factor 2000 and 3000 lower than their metabolic clearance, respectively. The unchanged excretion was a factor 1000 lower than sulphation clearance.

Conclusions: The observed elimination profile of paracetamol in zebrafish larvae suggests an immature metabolic capacity, with more prominent sulphation than glucuronidation, a distinguishing trait of human neonates[5]. This metabolite model can be used to scale metabolic routes, of interest when considering compounds with active or toxic metabolites, like paracetamol.

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II-46: *Marc Vandemeulebroecke* Multi-state modeling and simulation of patient trajectories after allogeneic hematopoietic stem cell transplantation (allo-HSCT) to inform drug development

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Objectives: To characterize patient trajectories through states of disease after allo-HSCT, quantifying the transition rates into various event states and identifying patient characteristics associated with differential transition rates. This modeling and simulation activity was conducted to investigate drug development scenarios for the prevention of Graft-versus-Host-Disease (GvHD) after allo-HSCT.

Methods: Multi-state models were built on data from the Center for International Blood and Marrow Transplant Research (CIBMTR [4]), a prime data source on stem cell transplantation in the US. Events of interest included acute GvHD (aGvHD), chronic GvHD (cGvHD), relapse of the underlying disease, and death. Six time-continuous, finite-state Markovian models of increasing complexity were built on a sub-set of patients matching the specific target indication. The transition probability matrix was estimated using the Aalen-Johansen estimator [1]. Ten candidate baseline covariates were considered (age, sex, donor type, etc.). Selection of a final model was based on stepwise covariate selection, goodness-of-fit diagnostics, and clinical relevance. In a second step, trial scenarios were simulated based on the final model and assuming various putative drug effects on top of the background transition hazards to quantify 4 composite endpoints of interest. Computations were conducted using the R language [2,3,5-7].

Results: A final 5-state, 10-transition model was selected, and it included 5 baseline covariates affecting 5 transition rates. State probabilities were estimated for target patients, e.g., at 12 months, acute myeloid leukemia recipients of matched related donor allo-HSCT are estimated to have transition probabilities 0.024, 0.039, 0.100 and 0.227, from the initial state to aGvHD, cGvHD, relapse and death, respectively. Simulations from this model allowed us to compare the operating characteristics of a future clinical trial, assuming that the investigational drug reduces selected transition rates to a specified extent, and to compare the trial's power among 4 composite endpoints with various sample sizes.

Conclusion: Multi-state models provide a rich framework for exploring complex progressive conditions such as the patient journey after allo-HSCT. They can help characterize a background disease pattern, and drug development strategies can then be informed by simulations in which this background pattern is varied.

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II-47: *Swantje Völler* Normalisation weight in a covariate function affects the relative standard error of clearance: an example with paediatric data

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Objectives: While in population models most covariates are normalized to the median value, bodyweight (BW) normalization to 70 or 1 kg is often applied. Using a phenobarbital dataset in neonates we investigated the impact of normalization weight on the relative standard error (RSE) and bootstrap values of clearance (CL) estimates. In addition, bootstrap confidence intervals (95%CIs) of typical CL predictions between 1 to 100 kg were generated. Finally, using simulations we studied this impact for different weight distributions.

Methods: For this analysis, a pharmacokinetic model for phenobarbital in 53 (pre)term neonates (0.45 - 4.4 kg) in which BW was incorporated as covariate on CL using a power function with estimated exponent was used. Normalization weight was set to 1 kg, 2.7 kg (median BW) and 70 kg to perform model estimation and bootstraps (1000 runs) using NONMEM. In addition, for all three normalizations, 1000 CL functions were calculated over a weight range of 1-100 kg using the bootstrap estimates of CL and exponent. 95% CI of these functions were compared across normalizations. Additionally, simulations with different median BW and BW ranges were performed.

Results: The RSE of the estimated normalized CL value was the lowest with a normalization to median BW (8.1%), compared to the 1 kg (10.5%) and 70 kg (48.8%), and was comparable for the bootstrap and the NONMEM covariance matrix. The exponent and the RSE of the exponent remained unchanged for all runs. The bootstrap 95%CI of CL over a weight range of 1-100 kg was independent of the normalization weight used, implying that a normalization weight further away from the median of the data does not impact the precision of the CL estimation in the weight range of the studied population. Simulation studies showed that the increase in RSE with 70 kg normalization was highest for paediatric studies with a narrow weight range and with a median BW away from 70 kg.

Conclusions: Using a normalization weight outside the observed covariate range can result in a high RSE of the corresponding population estimate, as the obtained RSE corresponds to the RSE for an extrapolated population parameter value. As this RSE might not be informative about the precision of the CL estimate in the studied BW range, normalizing BW on 70 kg in the paediatric population should be applied with caution as this might lead to wrong decision making in model building.

II-48: *Veronika Voronova* Evaluation of immediate release exenatide effects on gastric motility and intestinal glucose absorption using a systems pharmacology model

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Objectives: Glucagon-like peptide (GLP)-1 and other GLP-1 receptor agonists such as exenatide have been shown to decrease gastric motility [1,2]. This class effect may slow exogenous glucose absorption rate from the gastro-intestinal tract (exGluRa) and consequently modulate postprandial plasma glucose dynamics. The objective of the current modeling study was to evaluate immediate release (IR) exenatide effects on the gastric emptying rate (GER) and exGluRa after administration of liquid or a mixed carbohydrate-containing meal.

Methods: The model is described as a system of ordinary differential equations and can be divided into: (1) a food sub-model, to describe food retention in the stomach during placebo or GLP-1 infusion; (2) an acetaminophen absorption rate sub-model, to capture the effects of exenatide on GER; and (3) a glucose sub-model, to describe glucose transition from the stomach to the intestine and subsequent absorption into the systemic circulation. A published popPK model was used to reproduce experimental plasma exenatide kinetics [3]. Plasma GLP-1 concentrations in the model were set according to experimental conditions. Modeling was performed in Matlab using IQM Tools (http://www.intiquan.com/).

Results: Both GLP-1 and exenatide effects on gastric motility were adequately reproduced by the model; so were rates of exGluRa after administration of different food types. The model was then used to predict exGluRa in response to twice-daily 5- or 10-ug exenatide subcutaneous injections and three time daily liquid or mixed-food intake

Exenatide was shown to cause a split in the exGluRa peak, with a pronounced reduction in the maximal absorption rate of 40-60% after liquid food ingestion. In contrast, after intake of a mixed meal, exenatide treatment caused a significant delay of glucose absorption and delayed Tmax by 2.7 hours, yet, had a mild effect on the peak magnitude (5% reduction). Treatment effect was less pronounced with lunch meals, *vs*. morning and evening meals, the latter being combined with drug administration (hence higher target occupancy).

Conclusion: A mechanistic systems model describing GLP-1 and exenatide effects on gastric motility was developed. It was shown that inhibition of gastric emptying does affect intestinal glucose absorption, a mechanism whereby GLP-1 analogues may modulate postprandial plasma glucose dynamics. The proposed model also supports the recommended exenatide administration regimen and the model may be used for the optimization of other GLP-1 agonist-based therapies.

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II-49: *Janet Wade* Population PK analysis of Sym004 and the influence of variations in base model structure on covariate model building

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Objectives: Sym004 is a mixture of two synergistic full-length anti-EGFR antibodies (futuximab & modotuximab) that bind to 2 separate non-overlapping epitopes and inhibit the sustained growth of cancer cells.
1. Develop a population (pop) PK model for Sym004 and evaluate the potential for covariates to explain the inter-individual variability (IIV) in the model.
2. Evaluate if the Sym004 covariate model depended on the presence/absence of correlations between the IIV parameters.
3. Evaluate if the Sym004 pop PK model could also describe the PK of the 2 constituent antibodies.

Methods: PK data were from 136 patients from 2 trials in advanced solid tumours, SCCHN and mCRC (Sym004-01 and -02). Sym004 (0.4-18 mg/kg) was dosed by IV infusion weekly or every 2nd week or as a 9 mg/kg loading dose followed by 6 mg/kg weekly. Modelling was done in NONMEM v7.3 (FOCEI). Covariate model building was performed by evaluating each covariate one by one and then building a full final model with all covariates whose point estimates were outside the arbitrary range of 0.8 to 1.25 and whose 90% confidence intervals did not overlap the null value [1]. Finally the structure of the base and final Sym004 Pop PK BLOCK(3) models were applied to each Sym004 constituent antibody.

Results: A 2-compartment model with linear and non-linear elimination and a priori inclusion of body weight on CL, VMAX, V1 and V2 was used. IIV was on CL, VMAX and V1. Correlations between the 3 IIV parameters were -0.277, 0.334 and 0.396. Residual variability comprised an additive plus proportional error model.
Covariate model building was performed with diagonal and BLOCK(3) omega structures. Covariates were tested on CL, VMAX, V1 and V2. Final Sym004 BLOCK(3) and diagonal models included 6 and 9 covariates, respectively, above the influence of weight.
Application of the base and final Sym004 pop PK BLOCK(3) models to Sym004 constituent antibodies found only minor differences in parameter values.

Conclusions: The final Sym004 pop PK covariate model structure depended upon the underlying statistical model structure despite low correlations between the IIV parameters [2]. Effort should be made to define when a covariate effect is clinically meaningless (no effect), clinically irrelevant (small effect) and clinically important (larger effect) during the planning of analyses.
The minor differences in the parameter estimates for the two Sym004 constituent antibodies for both base and final pop PK models supports analysing the combination, Sym004.

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II-50: *Thanaporn Wattanakul* Population pharmacokinetics and cardiovascular safety of piperaquine in African patients with uncomplicated malaria

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Objectives: Develop a PK/PD model to describe the relationship between piperaquine exposure and QT-prolongation in order to evaluate the cardiovascular safety in patients with uncomplicated malaria.

Methods: PK samples and electrocardiogram (ECG) measurements were obtained from a total of 1,000 patients, enrolled in a multi-centre safety trial in Burkina Faso, Mozambique, Ghana, and Tanzania [1-3]. All patients had uncomplicated *P. falciparum* malaria and received a standard 3-day treatment of dihydroartemisinin-piperaquine. Nonlinear mixed-effects modelling (NONMEM v.7) was used to evaluate PK-PD properties of piperaquine. Both QTc-prolongation (?QTc) and absolute QTc-intervals (QTc) were evaluated with separate modelling approaches. Direct exposure-response models with linear and Emax relationships were investigated to describe effect of piperaquine on ?QTc/QTc intervals. A cosine function was implemented to account for the circadian rhythm of the cardiovascular system. A stepwise covariate search was used to evaluate the relationship between PK-PD parameters and patient characteristics.

Results: A three-compartment disposition model with three-transit absorption compartments described the piperaquine concentration-time profile well. Body weight was added using an allometric function on all clearance and volume parameters (?OFV = -381). No additional significant covariates were found during the stepwise covariate approach. The effect of piperaquine on ?QTc was described by a linear relationship, resulting in a 6.14 msec QTc-prolongation per 100 ng/mL increase in population piperaquine concentration. The absolute QTc-interval showed a clear circadian rhythm and the effect of piperaquine was best described by an Emax model. The QTc-interval oscillated with a peak amplitude of 5 msec due to the circadian rhythm, and the maximum population increase in QTc-interval, due to drug effect, was 44.8 msec.

Conclusions: The developed PK-PD model described the relationship between piperaquine concentrations and ?QTc/QTc intervals effectively. The model demonstrated that an increased piperaquine concentration was directly related to a prolongation of the QTc interval. However, the prolongation estimated from the model was considered to have an acceptable safety profile in the clinical setting of life-saving malaria treatment.

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II-51: *Sebastian Weber* Bayesian Pharmacokinetic Extrapolation from Dense Adult to Sparse Pediatric Data

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Objectives: To characterize the pharmacokinetics (PK) of pediatric patients has recently gained much in importance due to regulatory requirements. Often we find ourselves in the situation of extensive data on adults while data on pediatric patients are very sparse due to: (i) adult centric drug development, (ii) a changing metabolism due to aging and (iii) ethical and practical difficulties in sample collection.
In this work we explore how a Bayesian approach can bridge the two populations. The objective is to establish an approach suitable to extrapolate between adult and pediatric PK models.

Methods: The pooled study data on adult patients compromises about 600 patients. 25% of the PK samples were collected in the absorption and distribution phase, 50% around the Ctrough at 12h and 25% in the elimination and washout phase. The population PK model adequately describing the data was a 2cmt model with a time-changing clearance. The pediatric data included only 22 patients in a wide age range. The PK samples were timed around 12h after dosing while few measurements were taken in the absorption phase and almost no measurements in the elimination or washout phase.
The base adult model was fit using NONMEM and has been converted into a Bayesian model using Stan [2]. In the analysis we compare the frequentist NONMEM result to the Bayesian Stan posterior estimate. The key step is to use the adult posterior as prior in the pediatric analysis with discounting.

Results: A reparametrized 2cmt PK model with standard allometric 3/4 power-scaling [1] using weight combined with weakly-informative priors was able to robustly fit and describe the adult data set. The derived posterior has been discounted by assuming that weight standardized estimates may at most deviate by 100% from the adult parameter for the pediatric analysis.
The pediatric data slightly updates the adult estimates insofar that the clearance is increased. The respective frequentist result on the pediatric data set revealed that the 2cmt model was not identifiable due to lack of data.

Conclusions: The pediatric data set was well compatible with the adult model. The analysis revealed that the clearance for the pediatric population is likely increased which leads to a decreased steady-state concentration.

In summary, the Bayesian approach warranted model identifiability of a complex PK model despite a very sparse data situation. This was possible by using the discounted adult posterior as prior in the pediatric analysis.

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II-52: *Janak Wedagedera* Statistical Power Analysis to Detect Drug-Drug Interaction between Lorezapam and Probenecid in Healthy and Renal-impaired Populations Using PBPK Modelling and the Simcyp R Package

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Objectives: A tool is already available within the Simcyp Simultaor to calculate the power of studies to correctly detect the difference between PK parameters in two populations. We aim to extend this feature using the Simcyp V16 R package to calculate power in drug-drug interaction (DDI) studies using model compounds Lorezapam and Probenecid.

Methods: We have developed an R library package where the Simcyp Simulator is called from R and facilitates various scenarios [1] such as constrained sensitivity analysis or parameter estimation, and parameter estimation using multiple substrates or populations. The new R package was used to calculate the power of correctly detecting difference in the AUC value after a single dose of Lorezapam between a healthy volunteer and a renal impaired (GFR<30) population, given a set of sample sizes and significance level. These values were then compared with the Simcyp power calculation tool results. It is of interest to extend such power analysis to DDI studies which is not currently available in the Simulator but can be performed using the Simcyp R package. The physiologically-based PK (PBPK) model fora DDI between Lorezapam and Probenecid has previously been verified [2]. The power to correctly detect the difference in AUCs after taking Lorezapam alone and in combination with Probenecid was then determined using the Simcyp R package for the sample sizes 4, 6, 8, 10 and12, assuming a significance level of 0.05.

Results: Using the R package, a sample size of 50 achieved a power of 85.54% to correctly distinguish between the healthy volunteer and renal impaired (GFR<30) AUC after a single Lorezapam dose which is the same as derived using the Simcyp power calculation tool. In the healthy volunteer population the sample sizes 4, 6, 8, 10 and 12 gave a power of 55.18%, 67.21%, 76.16%, 82.78% and 87.64% respectively to correctly detect the difference in AUCs after taking Lorezapam alone and in combination with Probenecid. Using the renal impaired (GFR<30) population a smaller sample size is required to achieve the equivalent power as the healthy volunteer population. A sample size of 4 gives a power of 61.58% and a sample size of 8 gives a power of 82.90%.

Conclusions: An R library package for Simcyp has been developed that enables running virtual clinical trials from within R. This work shows that Simcyp's power calculation tool can be extended to calculating power to correctly identify a DDI using the Simcyp V16 R package.

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II-53: *Gustaf Wellhagen* Impact of genotype assumption in a semi-mechanistic PK model of metformin

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Objectives: Develop a semi-mechanistic model of metformin PK and investigate the impact of different ways of handling missing genetic variants in transporters on metformin pharmacokinetics.

Methods: A semi-mechanistic PK model of metformin was developed using data from three studies; one single- and two steady-state studies. Plasma concentration and urine samples were collected in 87 healthy volunteers. Subjects were genotyped for SNPs previously associated with metformin PK (*MATE1* variants-rs2289669, rs2252281; *MATE2-K* variant-rs12943590; *OCT1* variants-rs622342, reduced function variants (rs12208357, rs34130495, rs72552763 and rs34059508, O1R); *OCT2* variant-rs11212617; *ATM*-rs11212617) [1]. Information on two SNPs (*MATE2-K* and *ATM*) were missing in 49% of the individuals (84% of individuals in single-dose study) and missing genotypes were handled by (i) excluding incomplete cases, (ii) assigning to wildtype (wt), (iii) heterozygote variant (wt/v), (iv) homozygote variant (v/v) or (v) model-based estimation of genotype [2]. For *MATE2-K* , the background frequencies of variants were 55%, 35% and 10% of wt, wt/v and v/v, respectively and for *ATM*, the corresponding frequencies were 26.5%, 54% and 19.5%, which were used in approach (v).

Results: A 2-compartment model including renal clearance with saturable reabsorption, filtration proportional to GFR and active secretion (CL) best fitted the data. No covariates influenced absorption constant (KA), but CL increased by 0.7% per kg. Estimated bioavailability (F) was 49% for subjects with wildtype of O1R and 43% for subjects with the SNP. *MATE1* variant-rs2289669, *OCT1* variant-rs622342 and AGE was found to affect CL, however not when excluding incomplete cases. These covariates mainly improve the fit of single dose-PK. Depending on approach, different genotypes affected inter-compartmental clearance (Q): *OCT2* variant when missing assumed to be wt, *MATE2-K* variant when missing assumed to be wt/v, *ATM* variant when missing assumed to be v/v or inferred by the model.

Conclusions: As expected, how the missing genotypes were handled influenced covariate inclusion. However, approach (i) also affected inclusion of other covariates as there was a correlation between missingness and study design. In this particular case, exclusion of incomplete cases removed data from the single-dose study which is less interesting for treatment of a chronic disease and the results from excluding incomplete cases was the most robust method.

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II-54: *Thomas Wendl* The Open Systems Pharmacology Suite (PK-Sim® & MoBi®): An open source solution for whole-body physiologically based pharmacokinetics and -dynamics

Thomas Wendl on behalf of Open Systems Pharmacology
www.open-systems-pharmacology.org (Author's affiliation: Bayer AG)

Objectives: To present the Open Systems Pharmacology Suite (OSPS), an open source systems pharmacology project making formerly commercial software tools PK-Sim® and MoBi® [1-3] available under GPLv2.

Methods: For details and to follow the community's activities, please see GitHub [3].

Results: The OSPS contains different software tools and has been designed using a modular concept to allow efficient, flexible, and transparent multi-scale modeling and simulation. The overall platform with its various software tools is implemented in a modular way. The central software tools PK-Sim® and MoBi® make use of building blocks and are compatible to each other. While PK-Sim® is based on a whole-body concept, the focus of its counterpart, MoBi®, is at the molecular level.

PK-Sim® is a well-established PBPK tool widely used for more than a decade. It offers different structural models together with relevant physiological and molecular database information for physiologically based pharmacokinetic modeling (PBPK) of small and large molecules in different animal species and human populations. It includes efficient methods for parameter identification and sensitivity analysis as well as easy-to-use features for cross-species extrapolation, pediatric scaling, or the study of drug-drug interactions among others.

MoBi® can directly use PBPK models created in PK-Sim® but is especially designed for the de novo construction, import, or extension of systems biology and pharmacology models in an (extendible) ordinary differential equation framework. Together with interfaces to general computing environments Matlab® (The MathWorks, Inc., Natick, USA) and R, it provides a flexible solution for modeling and simulation. For further details on the software and the open source project see [3].

Conclusions: The Open Systems Pharmacology Suite makes powerful and flexible tools for PBPK and systems pharmacology modeling available open source under GPLv2. We invite everyone in the field of Systems Pharmacology, be it in academia, industry or regulatory bodies, to use the platform. Active participation of computer and modeling & simulation scientists in the further development of the modeling & simulation platform, the incorporated systems models, processes for their qualification and application etc. is encouraged and highly welcome. Please follow the community's activities in this GitHub project [3].

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II-55: *Sebastian Wicha* The purpose determines the predictive performance: Comparison of four population pharmacokinetic models of methotrexate.

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Objectives: High-dose methotrexate (HD-MTX) is a highly effective anticancer treatment in cancer patients. In order to support therapeutic drug monitoring of MTX by model-based techniques, we aimed to compare the predictive performance of four published MTX models [1–4] on a clinical dataset on patients with lymphoid malignancies.

Methods: The clinical dataset comprised 12 patients with lymphoid malignancy, contributing 397 MTX samples over up to 8 dosing occasions. Different prediction settings were explored in NONMEM (version 7.3): (i) population prediction using solely the patient covariates, (ii) individual prediction using all available data, (iii) prediction of the remaining dosing occasion using the first sample, (iv) prediction of the second occasion from the first occasion, (v) prediction of the third occasion and (vi) the fourth from the previous two or three occasions. Graphical measures as well as relative bias (rBias) and relative root mean squared error (rRMSE) were used to judge the predictive performance.

Results: In scenarios (i) and (ii), model [2] provided lowest rBias (+23%, -7%) and rRMSE (103%, 43%). For the within-occasion prediction scenario (iii), model [1] was superior (rBias: -51%, rRMSE: 260%) over the other models (abs. rBias: 140%-1714%, rRMSE: 425%-3648%). For the across-occasion prediction scenarios (iv), model [4] provided the least biased prediction of the subsequent occasion (rBias: +2.5%, rRMSE: 149%) compared with the other models (abs. rBias: 16%-31%, rRMSE: 90%-121%). Qualitatively similar results were observed in scenario (v). When the fourth occasion was predicted form the previous data (vi), model [1] was superior (rBias: -66%, rRMSE: 98%) over the other models (abs. rBias: 75%-197%, rRMSE: 113-287%).

Conclusion: The present study highlights the fact that a models predictive performance depends on the use of the model. Good predictive performance in conventionally evaluated scenarios (i) and (ii) may not translate to the same predictive quality if the models are used in the setting of therapeutic drug monitoring, when prediction of future observations or subsequent occasions is warranted.

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II-56: *Mélanie Wilbaux* Effects of Formula Milk on Weight Changes in Healthy Term and Preterm Neonates

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Objectives: A model has been developed to describe the physiological weight changes during the first week of life in neonates and has been implemented in an online tool to forecast individual weight change as soon as possible after birth [1]. But the current version is limited to healthy, exclusively breastfed term neonates. Objectives of the current work were to expand the existing model by (i) characterizing effects of formula milk on weight changes during the first week of life in term and preterm neonates; (ii) identifying and quantifying maternal and neonatal factors influencing weight changes in newborns; (iii) enhancing the decision support tool to allow neonatologists to optimize and individualize monitoring and management of neonates.

Methods: Longitudinal weight data from a total of 3638 healthy term and preterm neonates were available up to 7 days of life. Two thirds of neonates (n=2425) were randomly selected to update the semi-mechanistic model characterizing weight changes as a function of the balance between time-dependent rates of weight gain and weight loss. Two additional weight gain rates were described as linear dose-effects of formula and pumped breast milk. Population analysis was implemented using NONMEM7.3. Model selection and evaluation were based on statistical criteria, goodness-of-fit plots and simulations. Advanced evaluation was performed on the remaining third of neonates (n=1213).

Results: Key individual characteristics (median, full range) were as follows: gestational age 39.8 weeks (34.7-42.4), birth weight 3394 g (1980–5230), girls 51%, mother age 32 years (15-47). According to goodness-of-fit plots, weight changes were properly fitted by the model. Advanced evaluation demonstrated a good predictive performance of the expanded model (bias=-0.01%, precision=0.5%). The model was able to accurately forecast individual weight with 3 initial weight measurements during the first 48 hours of life and predict effects of formula milk feeding on weight changes up to 1 week (bias=0.4%, precision=1.6%).

Conclusion: We present the first pharmacometric model that describes physiological weight changes and effects of formula milk feeding on weight changes during the first week of life in term and preterm neonates. A user-friendly online tool will allow caregivers to forecast individual weight changes and formula milk effects, optimize and personalize care, monitoring and feeding of neonates.

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II-57: *Francis Williams Ojara* Examining the relationship between paclitaxel exposure and peripheral neuropathy in non-small cell lung cancer

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Objectives: Peripheral neuropathy (PN) is a dose-limiting, cumulative adverse event of paclitaxel (PTX) reported by more than 20% of patients on PTX therapy. High PTX doses and exposure (time above a threshold plasma concentration of 0.05 µM, $T_{C>0.05\mu M}$) are associated with increased risk of PN from standard statistical tests [1,2]. In the CEPAC-TDM study [3], PK-guided dosing of PTX significantly lowered clinically important PN (i.e. grades 2 or 3). This work examined the impact of consistent PTX dose levels and exposure, at an individual level, on PN in advanced non-small-cell lung cancer patients with the goal of dose adaptation to reduce the burden of PN.

Methods: Patients (n = 249) who received consistent PTX doses (not varying more than 50 mg across cycles) every 3 weeks until the first incidence of clinically important PN or across all treatment cycles were considered from a dose adaptation study: CEPAC-TDM [3]. Cisplatin or carboplatin were concomitantly administered. PN was classified using the common terminology criteria, version 4.0 [4]. Exposure (dose, $T_{C>0.05\mu M}$ and AUC_{∞}) at the cycle of incidence and exposure in the first treatment cycle were considered as predictors of clinically important PN and clinically non-important PN (i.e. grades 0 or 1), respectively. The risk of clinically important PN with PTX exposure at the cycle of incidence was examined using binary logistic regression (LR) models considering a linear drug effect. The dataset was formatted in R and modelling was performed using NONMEM 7.4.

Results: 88 of the 249 patients reported clinically important PN. Absolute dose was identified as a statistically significant predictor of PN using the likelihood ratio test at α=0.05 (1 degree of freedom). The odds of clinically important PN increased 5% for every 10 mg increase in absolute dose, OR (95% CI): 1.05 (1.002-1.106). Relative dose (based on body surface area), $T_{C>0.05\mu M}$ and AUC_{∞} were not statistically significant predictors of clinically important PN.

Conclusions: Using the LR model we successfully quantified the relationship between PTX dose and clinically important PN. In the subsequent steps, we will employ Markov chain models to examine transition rates between different PN grades and undertake time-to-event analysis to additionally account for censored observations, with the goal of determining the impact of PTX exposure on transitions between different PN grades.

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II-58: *Jan-Georg Wojtyniak* Physiologically-based Pharmacokinetic (PBPK) Modeling of Simvastatin Drug-Drug Interactions with Rifampin, Clarithromycin and Drug-Gene Interaction with ABCG2

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Objectives: To build and evaluate a PBPK model for simvastatin lactone (SL) for the prediction of drug-drug interactions (DDIs) with CYP3A4 inducers or inhibitors like rifampin or clarithromycin. Additionally, drug-gene interaction (DGI) due to the ABCG2 c.421C>A polymorphism was included.

Methods: PBPK models were built in PK-Sim® modeling software (Version 6.3.2) [1].
For model development physicochemical parameters as well as mean plasma and intestinal concentration-time profiles of SL after oral single dose (SD) and multiple dose (MD) (range 10 to 80 mg) were obtained from literature. For ABCG2 c.421C>A polymorphisms mean hetero- and homozygote profiles were available. Data were separated into internal and external datasets for model development and evaluation, respectively. After model establishment the simvastatin model was coupled to previously developed rifampin and clarithromycin models to predict DDIs [3, 4].

Results: The final model accurately describes the plasma concentration-time profiles of all SL internal and external dataset profiles. Based on homozygote ABCG2 c.421C>A data the heterozygote profile could be successfully predicted with an AUC ratio predicted vs. observed of 0.99. Based on literature ABCG2 c.421C>A increases AUC by 60% and ABCG2 c.421A>A by 111% compared to ABCG2 c.421C>C wild type. Model predicted AUC increase were 37.5% and 105.4% for ABCG2 c.421C>A and ABCG2 c.421A>A, respectively. Furthermore, the DDI with rifampin and clarithromycin were adequately predicted. Co-treatment with rifampin showed significant decreases in AUC of 89.1% for SL. Model predicted rifampin effect on AUC was 91.0%. On the other hand, clarithromycin increases the AUC of SL by 885%. Here the model predicted AUC increases of 801% for SL.

Conclusions: A SL PBPK model including CYP3A4 metabolism as well as ABCG2 transport was successfully developed. The model predicts the effects of genetic polymorphism as well as DDIs due to concomitant use of CYP3A4 inducers or inhibitors. Overall, this model can help to reduce the risk of adverse drug events by improving dosing schemes in personalized medicine.

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II-60: *Gudrun Wuerthwein* Population Pharmacokinetics to model the time-varying clearance of the PEGylated asparaginase Oncaspar® in children with ALL

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Objectives: The pharmacokinetics of the polyethylene glycol (PEG)-conjugated asparaginase Oncaspar® is characterized by an increase in elimination over time. The focus of our analysis was the better understanding of this time-dependency.

Methods: In paediatric acute lymphoblastic leukemia therapy (AIEOP-BFM ALL 2009), two administrations of Oncaspar® (2500 U/m^2 intravenously) in induction phase (14 day interval) and one single administration in reinduction were followed by weekly monitoring of asparaginase activity. Non-linear mixed-effects modeling techniques (NONMEM) were used. Samples indicating immunological inactivation were excluded to describe the pharmacokinetics under standard conditions. Models with time-constant or time-varying clearance (CL) as well as transit compartment models with an increase in CL over a chain of compartments were investigated.

Results: Models with time-constant elimination could not adequately describe 6107 asparaginase activities from 1342 patients. Implementing a time-varying CL improved the fit. Modelling an increase of CL over time after dose (E_{max}- and Weibull-functions) were superior to models with an increase of CL over time after the first administration. However, an empirical transit compartment model came out to be the best structural model.

Conclusions: The increase in elimination of PEGylated asparaginase appears to be driven by physicochemical processes that are drug-related. The observed hydrolytically in vitro instability of the drug leads to the hypothesis that this might be due to in vivo hydrolysis of the instable ester bond between PEG and the enzyme combined with an increased elimination of the partly de-PEGylated enzyme. (Trial registered at www.clinicaltrials.gov, NCT0111744).

II-61: *Rujia Xie* Population pharmacokinetics of PF-04447943 in healthy volunteers (HV), adult patients with Alzheimer's disease (AD) and patients with Sickle Cell Disease (SCD)

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Objectives: PF-04447943 is a selective inhibitor of the cyclic guanosine monophosphate (cGMP)-specific PDE9A enzyme, being developed for the prophylactic treatment of SCD. The purposes of our analyses were to characterize PF-04447943 pharmacokinetics (PK) in HV and adult patients with AD or SCD and to identify factors that may differentiate the populations treated and impact the PK relationship of PF-04447943.

Methods: A total of 10 studies (7 in HV, 2 in AD and 1 in SCD patients) were included in the analyses. Subjects received single or multiple doses (BID) of PF-04447943 ranging from 1 mg to 150 mg. Plasma concentrations over time were analyzed using a nonlinear mixed effects modeling approach (NONMEM). The first order conditional estimation with interaction method was used throughout. Potential covariates (body weight (BWT), age, gender, disease state, race, food, formulation and creatinine clearance) were evaluated using stepwise inclusion/deletion as implemented in the Stepwise Covariate Model (SCM)[1] building procedure. Prediction-corrected visual predictive checks were used to assess model performance.

Results: A total of 261 subjects (163 male and 98 female); including 142 White, 64 Black, 31 Asian and 24 other race, with 3467 concentration records were analyzed. The PK of PF-04447943 was best characterized by a two-compartment model with 1st order absorption (Ka) with lag time (tlag) and 1st order elimination. BWT was incorporated as a structural covariate on clearance (CL/F), central (V_1/F) and peripheral (V_2/F) volume and distributional clearance (Q/F). The other covariates identified were age on CL/F; race on V_2/F; race, sex and population on Q/F and age and food on Ka. The parameter estimates for a typical healthy white male (70kg and 40years) under fasted conditions were 13.9 L/h, 87.3 L, 7.61 L, 0.546 L/h, 4.7 h^{-1} and 0.196 h for CL/F, V_1/F, V_2/F, Q/F, Ka and tlag, respectively. Feeding reduced Ka by 89.9%. Black subjects showed a 11-fold higher V_2/F and a 3.5 fold higher Q/F than White subjects. However, predicted C_{max} and $AUC_{0-¥}$ values at clinically relevant doses were similar across races.

Conclusions: The proposed population PK model adequately describes the available data on PF-04447943. Although a few statistically significant covariates were identified they are not expected to result in clinically relevant differences in exposure. Understanding of the PK of PF-04447943 across a range of populations will assist future drug development.

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II-62: *Joao Paulo Ximenez* Population pharmacokinetic modelling of tamoxifen in breast cancer patients

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Objectives: Tamoxifen is considered a pro-drug of its active metabolite endoxifen. The major metabolic enzymes involved in endoxifen formation are CYP2D6 and CYP3A, whose activity variability influences endoxifen exposure and may influence clinical outcome [1]. In this context, the aim of this study was to develop a population pharmacokinetic model for tamoxifen and its metabolites, and subsequently use it to explore opportunities for treatment personalization.

Methods: 40 breast cancer patients were recruited into the clinical study. Tamoxifen, endoxifen, 4-OH-tamoxifen and N-desmethyl-tamoxifen plasma concentrations were sampled at steady-state, during a 24h interval. PK modelling was performed using NONMEM 7.3. One and two-compartment models with first-order absorption and elimination were evaluated based on previous publications. Additional compartments were appended to the model to allow characterization of the different metabolites. Covariates factors included in the analysis were: age, body weight, hormonal stage, CYP activity *in vivo* activity and genotype. Selection of the best hierarchical model was based on standard model diagnostic criteria[2]. The inter-individual variability in PK parameters was estimated using an exponential model and the residual variability was described by a proportional model. The selection of covariates was performed through a forward selection and backward elimination method. Final model performance was assessed by bootstrapping, visual predictive checks (VPC) and posterior predictive checks (PPC).

Results: The PK of tamoxifen and its metabolites was best described by a five compartment model. Genotype was identified as a covariate factor with moderate effect, along with body weight. CYP3A5*3 AG genotype carriers showed a median increase of 12% in AUC compared to AA (wild type), whereas GG genotype carriers showed a 20% increase relative to AA. CYP3A4*22 mutations showed usually smaller differences relative to the wild type. Likewise, CYP3A4*1b AG genotype carrier showed a 12% increase AUC of tamoxifen relative to AA (wild type).

Conclusions: Although previous models have been developed for tamoxifen, our study is the first to describe tamoxifen metabolism *in vivo*, including information about CYP2D6 and CYP3A genotypes and phenotypes. The proposed parameterization allows the possibility to discriminate the contribution of different moieties and explore dosing algorithms taking into account covariate factors.

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II-63: *Christine Xu* Population pharmacokinetics of sarilumab in patients with rheumatoid arthritis

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Objectives: To develop and characterize a population-pharmacokinetic (PK) model of sarilumab, a human mAb blocking the IL-6Rα currently in development for the treatment of rheumatoid arthritis (RA), and to describe the pharmacokinetics and assess the sources of PK variability in patients with RA.

Methods: A population-PK model was developed from data pooled across seven phase 1, one phase 2, and four phase 3 studies of sarilumab in 1770 adult patients with RA. Covariates evaluated in the analysis included demographic characteristics (eg, age, sex, race, and weight), laboratory tests of renal and liver function, drug product, antidrug antibody (ADA), C-reactive protein (CRP) levels, disease activity score (DAS28-CRP), and concomitant medication. Potential covariates were identified using a stepwise forward-addition and backward-deletion strategy, and the final population-PK model was evaluated by visual predictive check and bootstrap.

Results: The pharmacokinetics of sarilumab were adequately described by a 2-compartment, target-mediated drug disposition model with parallel linear and nonlinear Michaelis-Menten elimination, and first-order absorption. At steady state, $AUC_{0\text{-}14\ days}$ increased 2-fold with an increase in dose from 150 to 200 mg subcutaneously (SC) every 2 weeks (q2w). The main source of intrinsic PK variability was body weight, with lower body weight associated with higher PK exposure. As compared with a typical 71-kg (median) patient, $AUC_{0\text{-}14\ days}$ for an 83-kg patient was 23% and 20% lower and $AUC_{0\text{-}14\ days}$ for a 62-kg patient was 25% and 20% higher for sarilumab 150 and 200 mg q2w, respectively, indicating limited clinical relevance. Other statistically significant covariates, the magnitude of which were of limited clinical importance, included sex, albumin, creatinine clearance, baseline CRP, ADA status, and drug product. Age, race, and concomitant methotrexate were not identified as significant covariates. The variability of sarilumab pharmacokinetics was not associated with baseline DAS28-CRP or prior use of biologics, based on the post hoc analyses.

Conclusions: The population-PK model described the pharmacokinetics of sarilumab SC in patients with RA and allowed for prediction of individual patient exposure. The main source of intrinsic PK variability was body weight. No dose adjustment is required.

II-64: *Dong-Seok Yim* Discrepancy between in vitro potency and in vivo efficacy in human - Implications in PK-PD modeling

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Objectives: Reliability of a PK-PD model is dependent on its assumptions on which the model was build up as well as the robustness in the model building process. The *in vitro* potency parameters such as IC50 have been routinely used to predict human efficacious exposures (AUC, Cmin etc) in PK-PD modeling. However, its fundamental assumption that the *in vitro* potency is well correlated with the *in vivo* efficacy has never been verified extensively. Thus, we tried to look into this assumption by comparing a wide range of published PK and PD data.

Methods: If the *in vitro* potency and *in vivo* effects are well correlated, patients' exposure to unbound drugs at steady state (Cu-ssavg= $fu \cdot F \cdot Dose/(CL \cdot \tau) = fu \cdot AUCss/\tau$) by approved dosage regimens should be higher than or, at least, comparable to the *in vitro* potency parameters such as IC50. We reviewed the ratios of Cu-ssavg / potency for drugs of major therapeutic categories using the dosage, PK and *in vitro* potency information published to journals. As for potency, only those of at least two moieties in a class reported in a single original research article by a single laboratory were included so that inter-laboratory or inter-method variation may be avoided.

Results: A total of 49 drug moieties (13 categories) were reviewed. The ratios were extremely varied (about 100 to 100,000 fold differences in the same category drugs) despite trends by categories. Average ratios (unbound) of statins and CCBs were lower than 0.1. In the 49 moieties, the Cu-ssavg / potency ratios were <1 in 32 (65%) and <0.1 in 15 (31%) moieties. Even in the case of Ctot-ssavg (total concentration), the ratios of 15 (31%) moieties were <1. When the ratios were plotted against fu (unbound fraction), the 'ratio<1' phenomena were more prevalent at drugs with higher protein binding (88% of drugs with fu ≤ 0.05: 22 out of 25). This finding implies that there still remains room for improvement in protein binding assays, especially at the higher extreme.

Conclusions: Efficacious unbound exposure levels (Cu-ssavg) were lower than *in vitro* potency values in 65% of drugs. Our results raise a question on the widely-used assumption of *in vitro-in vivo* correlation. Thus, PK-PD modeling approaches using *in vitro* potency values without *in vivo* PD data does not seem to be appropriate.

II-65: *Anyue Yin* Population pharmacokinetics analysis of olanzapine for Chinese psychotic patients based on clinical therapeutic drug monitoring data with assistance of meta-analysis

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Objectives: The aim of this study was to build an eligible population pharmacokinetic (PK) model for olanzapine in Chinese psychotic patients based on therapeutic drug monitoring (TDM) data, with assistance of model-based meta-analysis [1], to facilitate individualized therapy.

Methods: Population PK analysis for olanzapine was performed using NONMEM software (version 7.3.0). TDM data were collected from Guangzhou Brain Hospital (China). Because of the limitations of TDM data, model-based meta-analysis was performed to construct a structural model to assist the modeling of TDM data as prior estimates. After analyzing related covariates in a stepwise manner [2], a simulation was performed to predict concentrations for different types of patients under common dose regimens.

Results: A two-compartment model with first-order absorption and elimination was developed for olanzapine oral tablets, based on 23 articles with 390 data points, and was well applied on the TDM data. The apparent systematic clearance (CL/F) and apparent volume of distribution for the central compartment (V2/F) were found be correlated and the correlation was as high as 98.2 %. Predictability and stability of the model were confirmed to be acceptable. Gender and smoking habits influenced the clearance of olanzapine significantly. To achieve a blood concentration of 20 ng/mL (the lower boundary of the recommended therapeutic range) [3], simulation results indicated that the dose regimen of olanzapine should be 5 mg BID (twice a day), ≥ 5 mg QD (every day) plus 10 mg QN (every night), or >10 mg BID for female nonsmokers, male nonsmokers and male smokers, respectively.

Conclusions: The population PK model, built using meta-analysis, could facilitate the modeling of TDM data collected from Chinese psychotic patients. The factors that significantly influence olanzapine disposition were determined and the final model could be utilized for individualized treatment.

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II-66: *Gunnar Yngman* Practical considerations for using the full random effects modeling (FREM) approach to covariate modeling

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Objectives: The FREM approach to covariate modeling has been suggested to avoid issues with standard covariate model building approaches, e.g. selection bias [1][2]. FREM is implemented in PsN [3] and is similar to the full fixed effects modeling (FFEM) approach in that all parameter-covariate relationships are estimated simultaneously but has advantages over FFEM, e.g. with correlated covariates [4]. After estimation FREM also allows conditional interpretation of the results, i.e. only a subset of covariates (even a single covariate) without having to re-fit the final model. A disadvantage with FREM, though, is an unusual implementation of the covariate model. The aim of this work is to investigate practical usage considerations of FREM including the estimation method(s), specification of different parameterizations of the parameter-covariate relationships and the sensitivity to the additional distributional assumptions required by FREM.

Methods: A simulation study (n = 150) in NONMEM was performed, based on real data and the final parameters of a docetaxel model for neutrophil counts [5]. All 18 covariate-parameter relationships were re-estimated with FFEM and FREM using IMPMAP and FOCE. Bias, precision, termination and run-time were evaluated. Implementation details of parameterizations of covariate-parameter relations in FREM were investigated. Both transformation of covariate observations and the FREM model were tested.

Results: IMPMAP was found more stable than FOCE (FREM successful minimization: 100%, 62%). Bias and precision of the re-estimated covariate parameters were similar, as were mean run-times (FOCE 16 cores: 14 min, 30 min; IMPMAP 8 cores: 40 min, 90 min). As opposed to FFEM, FREM allowed both uni- and multivariate interpretation of the covariates and when the same relations as FFEM were selected the results were in close agreement (RMSE FFEM, FREM: 0.0272, 0.0271). While modeling covariates as random effects, FREM provided accurate covariate coefficients also for non-normal covariate distributions. Parameterization corresponding to different parameter-covariate relationships could be implemented as either data or model transformations with the same result.

Conclusions: The investigation gives information to implementation of FREM with respect to practical aspects such as estimation method, parameterizations, expected performance and robustness towards covariate distribution. Further, it supports FREM for unbiased covariate confirmatory analyses.

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II-67: *Zakaria Zaril* A Mechanistic Pharmacokinetic Approach to the Development of Predictive Models in HIV-malaria co-infection.

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Objectives: To develop a physiologically-based pharmacokinetic (PBPK) model describing PK relationships between efavirenz and antimalarial.

Methods: In the current project, a stepwise platform was applied to developing a PBPK model to assess the impact of efavirenz on antimalarial PK [1]. Firstly, assessment and optimization of CYP3A4-mediated induction by efavirenz were conducted using kinetic data to drive the model. The model was also populated with relevant pharmacogenetic data. Second, the PBPK model were established for a range of antimalarial compounds, forming a drug-drug interaction (DDI) test-data set. Finally, the developed model was validated and qualified by comparing model-predicted plasma profile with published literature PK data. Simcyp were used to model the data.

Results: Once developed and qualified, our model successfully predicted human plasma drug concentrations of efavirenz and DDI from a limited set of routinely available pre-clinical and in vitro drug-specific parameters. Model also suggested optimal therapeutic doses for treatment with efavirenz in HIV-malaria co-infection patients.

Conclusions: This approach has significant implications for assessing DDI between efavirenz and antimalarial as well as provides an opportunity for exploring the relationship between efavirenz and HIV-malaria co-infection.

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II-68: *Chiara Zecchin* Quantitative modelling to assess target engagement and pharmacology in early clinical development of an anti-OSM humanised mAb

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Objectives: GSK2330811 is a humanized IgG1κ monoclonal antibody (mAb) that functionally blocks human oncostatin M (OSM) from binding to the gp130 receptor. It is being developed for the treatment of systemic sclerosis and other immune-mediated diseases. The aim of this analysis is 1) to develop a PKPD model to describe target engagement (TE) with GSK2330811, 2) to simulate TE with repeat dosing and 3) to optimise the design of the Proof-of-Mechanism (PoM) study.

Methods: Data collected during the Phase I single ascending dose study 201246 were available. Doses of 0.1, 0.3, 1, 3 and 6 mg/kg were given subcutaneously to healthy volunteers. Serial PK and OSM samples were taken for all cohorts. This information was used to develop PKPD models [1] to describe total drug and target concentration values in plasma and in blister fluid.

Simulations of TE during repeat dosing based on parameters uncertainty were performed to support dose selection, dosing schedule and sample size to enhance probability of success in the planned PoM study.

Results: The mPBPK model [1] with target mediated drug disposition (TMDD) in plasma and in leaky tissues best described drug and OSM concentration in plasma and blister fluid. The median estimated in vivo mAb/OSM affinity equilibrium constant was 630 pM and the estimated degradation rate of mAb+OSM complex was 0.0478 hr-1 in plasma and 0.0864 hr-1 in leaky tissue. The quasi-steady-state (QSS) [2] approximation was used to describe TE. PKPD model parameters were estimated simultaneously with the IMP estimation method in NONMEM 7.3 [3].

Virtual trials were simulated using parameter estimated values and their uncertainty to assess the probability of success based on TE criteria. Different study designs (sample size, dose and frequency) were tested. Success was defined as the lower bound of the 95% CI of TE above 85% at steady state (day 56). The optimal dose for the PoM trial was 300 mg every other week.

Conclusions: Mechanistic PKPD modelling and simulation was used to predict TE in human for repeat dosing of GSK2330811 based on data observed in a FTIH study.

These predictions helped to select optimal doses, dosing interval and sample size in the PoM study.

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II-69: *Meng Zhaoling* Exposure/Response modeling for sarilumab dose regimens benefit/risk assessment

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Objectives: Sarilumab, a human mAb blocking the IL-6Rα, is being developed for the treatment of rheumatoid arthritis (RA). Exposure/Response (E/R) analyses of selected efficacy (ACR responses) and safety endpoints (absolute neutrophil count [ANC]) were conducted to better understand sarilumab E/R relationships and to support the benefit/risk assessment of the dose regimens used in phase 3 studies (sarilumab 150 mg every 2 weeks [q2w] and 200 mg q2w).

Methods: Treatment effects of different dose regimens were predicted and evaluated through the empirical E/R models established for efficacy endpoints, including proportions of ACR20, ACR50, and ACR70 responders at selected time points, and safety endpoints, including percent changes in ANC at selected time points and time to first grade 3/4 neutropenia event. In addition, potential impact of baseline covariates on the E/R relationships were explored with the purpose of identifying patient profiles with enhanced benefit and improved safety. For each endpoint, empirical linear, log-linear, and Emax PK/PD relationships were evaluated to select the model that best fitted the data, based on the distribution of the corresponding endpoint. For the time-to-event safety endpoint, either parametric log-normal or Weibull survival model for the event time was selected based on the event time distribution.

Results: Overall, the established log-linear E/R relationships indicated that higher exposure resulted in better efficacy and suggested a consistent trend toward a greater therapeutic benefit for the 200 mg q2w regimen compared with the 150 mg q2w regimen. The E/R relationships indicated that the 150 mg q2w regimen had a lower effect compared with the 200 mg q2w regimen for ANC percent reduction and neutropenia. The effect for ANC percent reduction reached a plateau as exposure increased. For time to first grade 3/4 neutropenia event, the risk of having an event decreased from week 12 to week 24 for both doses. Model-predicted treatment effects of 150 mg q2w and 200 mg q2w were consistent with clinical observed effects of ACR responses and ANC percent reduction and neutropenia. Of the covariates tested, body weight was not significant.

Conclusions: The established E/R relationships for ACR responses and ANC, in addition to observed clinical efficacy and safety findings, provided evidence to support a starting dose of 200 mg q2w with a decrease to 150 mg q2w in the event of laboratory abnormalities.

II-70: *Jochen Zisowsky* Simulation Study on a Method for PK-QT Analyses When Several Active Compounds or Metabolites Are Present

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Objectives: To develop a statistically sound approach for PK-QT analysis when jointly modeling the impact of two active compounds, and to understand its operating characteristics via simulations. The approach should control the type I error for an appropriately defined hypothesis test.

Methods: We consider exposure(PK)-response(QT) analyses when there are several compounds or active metabolites. We used a joint model including all active compounds, which was linear in all compounds (without/with interaction), included a fixed effect parameter for the diurnal effect, and a random patient effect. This model can be viewed as an extension of the model proposed by Hosmane et al.[1] for a single agent to the situation with two active drugs. On the basis of this model we developed a criterion to understand whether the expected effect in the critical exposure region would be ≥10 msec. We used bootstrap to test the corresponding null hypothesis. The null hypothesis was rejected if the proportion of bootstrap copies with an estimated effect >10 msec was <0.05. The bootstrap procedure consisted in randomly drawing entire patient data from the observed pool of patients. We then conducted a simulation study based on real data to understand the operating characteristics of the procedure, and we applied the method to real examples. The simulations were done using R version 3.0.2.

Results: The simulation study demonstrated that the type I error is adequately controlled, and that the procedure is slightly conservative in some situations. When applying the approach to our main example, the PK-QT analysis revealed competing effects of two compounds on QT. The estimated effect in the critical region was <10 msec and the above mentioned null hypothesis could be rejected. None of the observed concentration pairs were above the 10 msec line and none of the 95% ellipsoids representing the joint two-dimensional distribution of the pairs of maximum concentrations crossed the 10 msec line.

Conclusions: The developed approach to analyze PK-QT data when several active compounds are present worked well. Type I error is adequately controlled, which is important for regulatory purposes. In our data example, the reduction of QT interval by the parent compound and the increase of QT interval by the second compound were nicely reflected in our parameter estimates. This contradicting effect would have shown as hysteresis in a separate PK-QT analysis for each compound, leading to biased and not interpretable results. Our two-dimensional approach nicely overcomes this issue.

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III-01: *Boger Elin* Drug targeting in pulmonary sub-epithelial compartments predicted through systems pharmacology modelling

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Objectives: Although a higher plasma exposure is observed after oral than inhaled dosing of salbutamol (2 mg and 400 µg, respectively), a higher pharmacological effect is obtained after inhalation [1-3]. This analysis aimed to evaluate if a newly developed inhalation PBPK-model could rationalize why inhaled salbutamol produces a higher pharmacological effect.

Methods: A whole-body inhalation PBPK-model, which places emphasis on mechanistically describing important processes for inhaled drug disposition was developed and implemented in MATLAB. Intratracheal (IT) and IV-administration of salbutamol to rats were simulated using drug-specific input parameters from AstraZeneca's internal data-base. A single parameter, the membrane permeability *P*, was adjusted to fit the observed lung concentration profile after IT-delivery. The PK was subsequently translated from animal to man by: 1) switching from rodent to human physiological parameters, 2) using human PK-parameters [1, 4], and 3) considering inter-species differences in the regional deposition pattern.

Results: The developed model could describe the plasma PK after inhaled (400 µg) and oral administration (2 mg) of salbutamol in man, demonstrating that a higher plasma exposure is expected after the oral route. The model predicted a spatial heterogeneity in the free target site concentrations (sub-epithelium) of salbutamol after inhaled drug delivery with higher free levels in the lung as compared to the plasma. On the contrary, the free drug concentrations were predicted to be similar throughout the lung as well as in the plasma after oral administration.

Conclusions: The model could reproduce a lung-selective drug exposure of salbutamol, which has been indicated by results in clinical trials. The predicted free concentrations in the sub-epithelium (the effect site) after inhaled and oral treatment were in line with reported FEV1 measurements [2-3]. Interestingly, the model predicts a spatial heterogeneity of free drug concentrations in the lung. This has important implications for drug discovery programmes targeting the lung as it suggests that the lung should be treated as a heterogeneous organ during PK/PD-analyses.

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III-02: *Esther Encinas* Application of modelling and simulation (M&S) methods within the context of a paediatric-use marketing authorisation (PUMA) application

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Objectives: To develop a pharmacokinetic (PK) model for a dedicated new oral paediatric formulation (active substance so far used off-label), based on a comparative bioavailability (BA) study performed in adults against a comparator product registered outside Europe (reference), and to apply it for bridging to the public domain clinical efficacy and safety data available for the later in children, in support of a PUMA application.

Methods: PK data were obtained from a single dose, two-way crossover comparative BA study in 65 fasted adult volunteers. Plasma levels for each product were separately fitted to a compartmental PK model using non-linear mixed-effects modelling implemented in NONMEM [1] (FOCE method). Final PK models were subsequently scaled to children aged 3 years and above by using simple allometric expressions on clearance and volume of distribution [2]. Assuming the same variability as observed in adults, paediatric models were then applied, via simulation, to guide the selection of the dose titration regimen as well as to give response to a list of questions raised by the European Medicines Agency (EMA).

Results: A one-compartment model with sequential two first-order absorption rates and additive residual error was found to best describe the drug PK for both oral formulations in adults. None of the studied covariates (e.g., age, body weight, sex and race) was statistically significant. PK modelling revealed that lower BA observed for the new formulation could be attributed to minor dissimilarities between products at the absorption level, whereas systemic processes (i.e., distribution and elimination) were mostly formulation-independent. Simulation of steady-state drug plasma levels in paediatrics allowed to adjust the dose titration schedule for the new formulation by targeting a comparable exposure to that achieved with the foreign comparator. Model-based simulations also served as a guiding tool to recommend a 30% reduction in posology in renal impairment paediatric patients [3], to demonstrate similar food effect between formulations and to ensure the cardiovascular safety of the proposed regimen.

Conclusions: Application of M&S methods within the context of a PUMA application for a dedicated new paediatric formulation allowed to satisfactorily establish a link to the public domain knowledge on the drug efficacy and safety profile while avoiding unnecessary studies in the paediatric population.

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III-03: *Elvira Erhardt* Comparison of pharmacokinetic parameters estimated by the experimental R package 'nlmixr' and MONOLIX

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Objectives: To develop a compartment model for infusion data and to compare its parameter estimates produced by two functions of the newly developed R-package 'nlmixr' and by MONOLIX.

Methods: The parameters of the compartmental model were first estimated with non-linear least-squares estimation. These results served as initial values in the following step, the extension of the model to a non-linear mixed effects model [1]. The mixed model estimations were conducted in a frequentist way with 'nlmixr' [2]. More precisely, the analytical as well as the ordinal differential equations (ODE's) model was fitted using the software package mentioned above. In MONOLIX [3], the frequentist maximum-likelihood estimation (MLE) was calculated and the parameter estimates together with the model fit of all three models were compared.

Results: It was shown that a three-compartment model with linear elimination is describing the plasma concentration data of the population adequately. The two different approaches of the 'nlmixr'-package delivered very similar estimates. However, these parameter estimates differed compared to MONOLIX.

Conclusions: The two functions tested included in the recently developed 'nlmixr' package for R offer a fast and satisfactory estimation of pharmacokinetic population data with results similar to those obtained with MONOLIX.

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III-04: *Ruben Faelens* Clinical trial optimization of efficacy studies in slowly progressive diseases

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Objectives: Treatments in slowly progressive diseases, such as Parkinson's or Alzheimer's disease, fall into two categories. Symptomatic treatment will treat the symptoms, while disease-modifying treatment can slow down or even reverse the disease.

Proving the disease-modifying action of a drug is difficult [1]. There is a high variability in disease progression, requiring a high number of patients to detect the effect. The study should also last long enough. This may increase dropout rates. Novel trial designs have been proposed (delayed start, wash-out) [2] [3], but are difficult to implement.

Clinical trial simulation can be a powerful tool to evaluate and improve various study designs, in light of these difficult criteria.

Methods: A literature model [3] was implemented in Simulo clinical trial simulator [4]. Study design parameters (number of patients, study length, observation frequency) were explored, as well as sensitivity to model parameter values (treatment effect, time delay to maximum effect, dropout rate, natural disease progression rate). Three possible analysis methods were evaluated: t-test on endpoint, mixed-effect model repeated measurements (MMRM) and model-based analysis (MBA).

Results: Increasing the number of patients and study length increased the probability to detect a disease modifying effect (probability of success, PoS) for all analysis methods. Measuring the disease progression more frequently than every 3 months improved the PoS when using the MBA but not with the t-test or MMRM methods. A lower treatment effect resulted in a lower PoS. In case of slow onset of treatment effect, the model-based analysis cannot distinguish between a symptomatic and disease-modifying compound. Dropout rate influenced the PoS, but only lightly affected the MBA method. Finally, lower natural disease progression rates did not influence PoS, although this did require an adaptation of the analysis methods.

Overall, MBA performed significantly better than the t-test and MMRM analysis.

Conclusions: Clinical trial simulation is an essential tool to optimize expensive, long-running studies in slowly progressive diseases. These studies may also benefit from a more widespread use of model-based analysis techniques of results.

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III-05: *Kevin Feng* Study and application of nonparametric and parametric population modeling for automatic subpopulation classification to CYP2D6 phenotype compounds and pediatric age groups

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Objectives: Subpopulation classification is an important way to improve the decision making in drug development [1]. Existing population pharmacokinetic methods for subpopulation identification predominantly rely on heterogeneous expression or mixture modeling. If sub-populations distributions overlap, the identification of individual subpopulation based on existing methods becomes difficult and tricky. Taking CYP2D6 phenotype as examples, Dextromethorphan, Bufuralol or Imipramine has many metabolic pathways via other enzymes while Metoprolol or Desipramine or Tolterodine has less metabolic pathways [2]. Finding dosage for pediatric age sub-groups via this polymorphism is tricky. We propose to use nonparametric and parametric population methods combined for automatic subpopulation classification to overcome the problems suffered from current methods [1, 3].

Methods: A selected proportion of CYP2D6 phonotype subpopulation is virtually sampled using physiologically based pharmacokinetic (PBPK) modeling, i.e. to create combinations of heterogeneous virtual patients. CYP2D6 metabolic compounds as above are used to generate the drug exposure with subpopulations distributions overlap. A simplified population PK model is built using parametric method for identifying the initial population distribution. Nonparametric method [4] is added on top of parametric method which reduce the number of support points and automatically determine the number of components of the mixture models to capture the subpopulation. Simulation such as visual predictive check (VPC) is used to confirm the subpopulation.

Results: PBPK modeling successfully creates the overlay mixture distribution samples. The nonparametric support points automatically reduce from a few hundred points to a few points which avoids the current fixed number of components in mixture modeling problems [3]. The converted mixture models then use for simulation nicely in VPC and the subpopulations classification matched the predefined PBPK subpopulation.

Conclusions: The nonparametric methods successfully find differences in exposure in genetic subpopulations and pediatric age/weight groups. The method can be expanded to manage the dose-titration or individual treatment in all patients based on safety and/or efficacy markers, or on Therapeutic Drug Monitoring (TDM), or gene based dosing.

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III-06: *Cecilia Fosser* Model based predictions of the PTG-100 pharmacodynamic responses in ulcerative colitis patients

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Objectives: To develop exposure (dose)-response (DR) models of healthy and colitis mice, and Phase I healthy volunteers (HV) for α4β7 **receptor occupancy** (RO) and **receptor expression** (RE) in the peripheral blood, and then to leverage all three models together to predict colitis patient response to PTG-100. PTG-100 is an oral peptide antagonist that binds specifically to α4β7 integrin on CD4+ memory T cells and alters their trafficking to gut tissues. It is currently in clinical development for ulcerative colitis.

Methods: PK and PD data were obtained from pre-clinical healthy (N=30) and diseased (N=55) mice studies and from a Phase 1, double-blind placebo-controlled single-ascending (N=30) and multiple-ascending (N=30) dose study in HV. Semi-mechanistic, nonlinear, mixed effects models were used to characterize the PD response observed in healthy and colitis mouse studies, and in the Phase I HV study and implemented in Phoenix NLME software [1]. Colitis mouse RO response modeling consisted of the introduction of a non-symmetry parameter, psi, in the emax modeling structure [2]. Key parameters were linked between healthy and colitis mouse models, and these links were used to predict patient PD responses from the HV PD responses.

Results: RO and RE DR relationships were well characterized with a sigmoidal emax model, and a sigmoidal inhibition model, respectively, in healthy and colitis mice, and in HVs. The colitis mouse model was structurally connected with the healthy mouse model by estimating colitis mouse multipliers applied to typical values of key healthy mouse parameter estimates, and this was used to extend the HV models to predict colitis patient responses.

Conclusions: The modeling was able to characterize and leverage the differences and similarities between healthy and colitis mouse DR relationships to extrapolate the HV DR relationship enabling predictions of the colitis patient DR relationship.

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III-07: *Jose Francis* Influence of nevirapine and ritonavir/lopinavir based antiretroviral therapy on Lumefantrine exposure in HIV-1 infected patients.

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Objectives: Artemether-lumefantrine is the most widely recommended first-line treatment for uncomplicated falciparum malaria globally. Considering the substantial geographic overlap of HIV and malaria disease burdens, it is important to understand any potential drug interactions. Lumefantrine and many of the antiretroviral agents are metabolized by CYP3A4 isoenzyme. Nevirapine may be an inducer (and occasionally an inhibitor) whereas ritonavir is a potent inhibitor of CYP3A4, which can lead to potential drug interactions. The aim of the present study was to characterize the population pharmacokinetics of lumefantrine and to explore the impact of nevirapine- and lopinavir/ritonavir- based antiretroviral therapy (ART) on lumefantrine exposure.

Methods: The study was conducted in malaria negative but HIV positive adults in three different arms. The first arm consists of subjects on Artemether-Lumefantrine (AL) alone, the second arm consists of AL+ Nevirapine-based ART patients and the third arm comprises of patients on AL+lopinavir/ritonavir-based ART. A total of 55 patient's data were available for analysis with 1908 lumefantrine concentration observations. The median weight and age in all arms was 59 kg and 32.3 years respectively. The pharmacokinetic data was analysed by NONMEM 7.3 with FOCE-I.

Results: A three compartment model with transit absorption described the data well. The final estimates for clearance and Vd were 11.4 l/hr and 169 litres respectively. The allometric scaling for body size was better described by fat free mass rather than total body weight. The clearance was 19.7% and 51.7% lower in patients treated with nevirapine-based ART (arm 2) and lopinavir/ritonavir-based ART (arm 3) compared to the ARV naïve group (arm 1). The bioavailability of lumefantrine was increased by 36% and 181% in Arm 2 & 3 respectively. Additionally, there was a significant difference in the bioavailability of lumefantrine with respect to morning and evening doses.

Conclusions: The concomitant administration of nevirapine and lopinavir/ritonavir based ARV's increases lumefantrine exposure significantly. The drug interaction with lopinavir/ritonavir was as expected more pronounced than with nevirapine-based ART. Further consideration is required to understand the clinical consequences of this drug-drug interactions and subsequent dose modifications in malaria patients.

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III-08: *Aline Fuchs* Minimization of a utility function for optimizing the dosing frequency of amoxicillin administration in neonates according to a fixed PK/PD index

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Objective: To optimize *a priori* amoxicillin dosing individualization in neonates according to demographic characteristic (covariate) cut-offs by achieving antibiotic exposure to concentrations above the minimum inhibitory concentration (MIC) during the entire dosing interval (100%T>MIC), while avoiding drug administered in excess or prolonged time below the MIC.

Methods: The approach uses a data-derived model and minimization of a utility function to identify optimal dosing strategies. The utility function implemented in NONMEM allows quantification of (i) the risk associated with the deviation from the treatment target (100%T>MIC) i.e. aiming to achieve drug concentrations for 100%T>MIC (efficacy), and to minimize the time neonates are exposed to concentrations below the MIC (risk of regrowth), and (ii) the amount administered in excess (risk of adverse events)[1]. The non-species related breakpoint for amoxicillin resistance of 8 mg/L was used for the MIC[2]. Single administered dose was fixed, dosing interval and covariate cut-off were the parameters to be optimized

Results: For a fixed dose of 50 mg/kg, up to 3 dosing categories were investigated, optimum weight cut-offs were 3 kg for 2 categories, and 1.5 and 3 kg for 3 categories. However, the difference in estimated dosing interval per weight subgroup was small: for 2 dosing categories, the dosing intervals were 16.4h (<3kg) and 15.3h (> 3kg); for 3 dosing categories, they were 18.5h (1.5 and <3kg) and 15.8h (>3 kg) for first dose of treatment, respectively. This suggests that amoxicillin exposure might be optimal without neonatal dosing categories based on weight cut-offs when using 50 mg/kg as a fixed dose. For clinicians and driven by efficacy endpoints, a 12h interval appears to be the most convenient. In terms of efficacy, 50 mg/kg every 12h leads to 93% of patients being above 100%T>MIC and 1.5% being > 4h below the MIC after the first dose.

Conclusions: The method illustrates a weighted-quantitative drug dosing decision based on a combined utility function. This is particularly valuable in the dynamic neonatal population which exhibits highly correlated weight and age values. Further investigations are required with regards to the choice of the most appropriate demographic factor(s) readily implementable during routine clinical care that can be used for a priori dosing individualization in this fragile population. *The unpublished population PK model used here requires validation.*

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III-09: *Saskia Fuhrmann* Model-based comparison of mAb clearance in pediatric populations*

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**This work was conducted during a PharMetrX-Internship (I2) at Roche.*

Objectives: Health authorities demand the early use of predictive models to support pediatric drug development. So far, few models to predict monoclonal antibody (mAb) pharmacokinetics (PK) in children have been used. However, no comparison of the model-based predictions across age exists. The objective of this study was to quantitatively compare age-dependency of clearance (mean and spread) using the available models.

Methods: We reviewed literature on POP-PK models involving pediatric populations (including individuals < 12 years of age). Linear clearance (CL) was compared using these models by linking the reported covariates (typically body weight) to age, e.g., using CDC/WHO growth charts [1]. In addition, we included simulations of the age-dependency of CL using commercial PBPK software. Mean and variability of predicted CL vs. age profiles were compared.

Results: Current POP-PK models mainly include purely body weight-based scaling methods. Only for Palivizumab, an explicit age-based 'maturation' function was used [2]. Pronounced differences in the trend of CL across age are visible between the investigated mAbs, in particular, a difference in predicted CL between 'maturation' and body weight-based methods for infants. The Simcyp® PBPK model incorporates age-related changes in system parameters and ontogeny of endogenous IgG. However, maturation processes, e.g., FcRn ontogeny, is lacking (Simcyp®Simulator v16). As a consequence, Simcyp® predicts a different trend of CL across age especially during the first years of age. Ontogeny of FcRn expression and of endogenous IgG concentration is not included in the currently available version of GASTROPLUS® 9.0.

Conclusions: Investigating the impact of empirically-based and PBPK models on predictions helps to gain confidence in predicting the PK of mAbs in children. It remains to be elucidated within further research whether differences in age dependency of CL between mAbs are related to a bias in assessment due to usually sparse data below 6 years of age (except Palivizumab) or due to the effects of disease and study population.

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III-10: *María García-Cremades* Mechanistic multi-scale systems pharmacokinetics model applied for the anticancer drug gemcitabine in pancreatic cancer

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Objectives: Build a mechanistic multi scale model for gemcitabine based on its molecular metabolic pathway, integrating in vitro- in vivo data, to anticipate the different rate of responses to treatment in pancreatic cancer depending on the accumulation and retention of the gemcitabine active metabolite (dFdCTP).

Methods: A mechanistic network of gemcitabine metabolism pathway was developed using in vitro literature data[1] and was coupled with a physiological pharmacokinetic (PBPK) model. Once the model was built, simulations of different concentration profiles of the active metabolites of gemcitabine in pancreas were generated based on known genetic polymorphisms affecting the enzymes´ expression responsible of gemcitabine metabolism pathway[2]. Analyses were done with Matlab R2016b.

Results: The network is able to describe the time course of extracellular and intracellular metabolites of gemcitabine for two different pancreatic cancer cell lines (normal-PK9 and resistant to gemcitabine-RPK9) using the same set of parameters and including the ratio of protein concentration of the target metabolic enzymes (CDA (1.64), dCK(<0.02)) and transporters (hENT1(1.35))as covariates of the model. Once the system model was integrated with the PBPK model, it was possible to generate plasma concentrations of gemcitabine (AUC $4.43x10^{-2}$ mmolxh/L; C_{max} $4.07x10^{-2}$ mmol/L) and of dFdCTP in pancreas (AUC $2.21x10^{-5}$ mmolxh/mL; C_{max} $1.05x10^{-6}$ mmol/mL) of the range of those reported in literature[3] given the standard dose used for pancreatic cancer patients (3.34 mmol/m^2 iv infusion (0.5h)).

Conclusions: A multi scale system pharmacokinetics model characterizing the metabolic pathway of gemcitabine, and predicting the pharmacokinetics of its active metabolite has been developed. The model is able to generate different concentrations of dFdCTP depending on individual's enzyme levels, which would explain the different rate of responses to gemcitabine treatment observed in patients with pancreatic cancer[4,5,6]. The developed platform has the potential of being used together with PKPD models[7] providing different predictions of clinical response to gemcitabine associated to individual genetic factors affecting, among other processes, the gemcitabine metabolism pathway.

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III-11: *Iain Gardner* A Whole body Physiologically based Pharmacokinetic Model for Antibody drug conjugates - model development and validation in rat

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Objectives: To develop and qualify a whole body physiologically-based Pharmacokinetic model for simulating Antibody Drug Conjugates (ADCs) disposition in tissues.

Methods: The whole body PBPK approach adapted here combines features of a previously published minimal PBPK model for mAbs [1] and a compartmental model for ADCs [2]. The base model incorporates new tissue-specific data related to IgG transport via both convection/diffusion and an FcRn-mediated pathway, including tissue-dependent FcRn expression (derived from data in transgenic mice [3]), an estimate of tissue endosomal volume, published tissue lymphatic flows, predicted vascular reflection coefficients [4], and tissue-dependent recycling rates [5]. This base model is applied to all ADC DAR (Drug Antibody Ratio) species, which are subject to deconjugation, catabolism, and any other additional clearance, resulting in release of the payload. The released fluxes of payload are directly fed into a full PBPK model describing the disposition of the small molecule drug which is treated as a metabolite of the ADC. Target binding models to account for target mediated disposition (TMDD) can be applied to any possible combination of multiple target binding in plasma and the interstitial space of any tissue. The ADC model parameterised with DAR-dependency allows simulation studies on various factors which influence ADC disposition to be conducted. Model verification was performed using *in vivo* rat data to qualify the model in three steps: (1) matching IgG plasma and tissue profiles in rat, (2) matching the plasma profile of naked monoclonal antibody (mAb) for a vc-MMAE ADC, (3) matching plasma and tissue profiles of the vc-MMAE ADC.

Results: The base model adequately describes IgG kinetics in rat, and the plasma profile of naked mAb for vc-MMAE ADC is matched well when the *in vitro* binding affinity of human IgG to rat FcRn is accounted for [6]. The profiles of conjugated payload and released payload in both plasma and individual tissues can be matched well by specifying DAR-dependent plasma clearances and delayed release of payload from the ADC.

Conclusions: The developed full PBPK model for ADCs provides a useful platform to study the integrated effect of different processes on ADC disposition. The model was successful in predicting the *in vivo* ADC disposition in rat using available physiological and *in vitro* data together with a fundamental understanding of the mechanisms of ADC disposition.

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III-13: *Silke Gastine* Population Pharmacokinetics of Micafungin in critically ill patients - evaluation of a fixed dose regimen

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Objectives: For the treatment of invasive fungal infections (IFIs) micafungin is usually applied with a fixed dose of 100 mg for all adult patients. In this study, we investigated the influence of different cofactors on the pharmacokinetics of micafungin in critically ill patients. Particular attention was given to time-varying covariates describing the critical state of the patient and the status of renal replacement therapy (RRT).

Methods: Plasma sample collection was conducted at the intensive care unit of the University Hospital of Münster, Germany. Micafungin was applied as short-time infusion once daily with a fixed 100 mg dose.

Non-linear mixed effects modelling (NONMEM 7.3) was used to develop the pharmacokinetic model. For model evaluation, model diagnostic plots were performed using R in combination with the Xpose package. Covariate testing was performed using the SCM module in PSN 4.6.0.

In addition to the demographics of the patients, a retrospective chart review was conducted for covariates such as: Sequential organ failure assessment-score (SOFA-score), simplified acute physiology-score (SAPS II-score), bilirubin, transaminases, pseudocholinesterase (PCHE), status on extra corporal membrane oxygenation (ECMO), albumin, protein and creatinine clearance. Renal replacement therapy (RRT) was documented with following categories: no RRT, slow extended daily dialysis (SLEDD), continuous veno-venous dialysis (CVVHD). All covariates were collected as time varying covariates.

Results: A two compartment model with linear elimination was found to most adequately describe the obtained data.

The SOFA score representing the patients' critical status was found as significant covariate on both clearance and central volume of distribution, respectively. Clearance decreased linearly by a factor of 0.024 with the SOFA score. Patients in highly critical condition, represented by a SOFA above 10 showed 30.8% lower V_1 than the less critically ill patients. For patients with hepatic insufficiency with bilirubin levels above 4 mg/dl, clearance decreases by 21.1%.

The different status in RRT did neither influence micafungin clearance nor the volumes of distribution, but was correlated with the SOFA score.

Conclusions: Micafungin pharmacokinetics appear not to be influenced by the status of RRT. Highly critical patients are more likely to have higher peak concentrations for micafungin and micafungin clearance decreases for patients with elevated bilirubin levels.

III-14: *Francois Gaudreault* Circadian quantitative system pharmacology model to inform clinical study design and translation to human

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Objectives: A system pharmacology model of the circadian clock based on data from rodents has been developed [1] to enable predictions of the effects of light and pharmacological manipulation (dose and dosing time) on circadian rhythms using clock gene expression as a biomarker. Here, we compare prospective projections from the model with observed human clinical data to illustrate the application of system modelling as a translational tool informing early clinical trial design and pharmacology of a compound with a novel mechanism of action.

Methods: Clock gene data were obtained from a Phase 1, double blind, placebo and active comparator controlled multiple ascending dose safety study involving approximately 96 healthy volunteers dosed either in the morning (AM) or evening (PM). Daily variations (Days 0, 7, 14) in peripheral blood mRNA levels [0, 4, 8 (AM), 12, 16, 20 (PM) and 24 h] of periodic genes were fitted to a 24-h cosinor model using non-linear mixed-effects modelling implemented in R V3.0.1 [2]. Periodicity was assessed using a Lomb-Scargle analysis [3] using a p-value

Results: The 24-h cosinor model with treatment effects on both phase and amplitude was shown to adequately describe the human data. Among the periodic genes (*CLOCK, CRY1/2, NR1D1 and PER3), PER3* showed the largest drug effect at steady-state (by Day 7), with dose-responsive phase delays of approximately 7.45 +/ 0.86 h (AM) and 15.37 +/- 1.21 h (PM) at the top dose. These results are consistent with the system model predictions [1], suggesting that the compound pharmacologically induced phase delay, with a more robust response when administered in the evening.

Conclusions: Quantitative system pharmacology is a valuable approach to comprehensively elucidate, validate and test new pharmacological concepts for the development of novel drugs. This case study illustrates how integrated knowledge of both pre-clinical and clinical data informed optimal trial design while improving confidence in the targeted pharmacology.

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III-15: *Parviz Ghahramani* Antimicrobial Drug Development Common Practices in PK-PD Model Selection and Common Misconceptions

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Introduction: For antimicrobial drug development, relationship between efficacy and indices of exposure (e.g. AUC, C_{max} ,%Time above MIC) are often examined to select the most relevant driver of efficacy. Coefficient of determination (R^2) is often used for evaluation of target attainment and determination of PK driver of antimicrobial efficacy [1]. This abstract presents current extent of application and limitations of the approach.

Objectives: To assess the extent to which R^2 is used as a model selection criterion in the development of antimicrobial agents, and to provide recommendations for alternative methods when selecting PK drivers of antimicrobial efficacy.

Methods: Published literature between 2006-2016 was searched using a range of terms associated with R^2 and PK indices in the Journal of Antimicrobial Agents and Chemotherapy and the Journal of Antimicrobial Chemotherapy. Each publication was scrutinized for methodology used to evaluate the PK-PD relationship. Simulations were also conducted to compare performance of R^2 vs. Residual Standard Error (RSE) statistics and to examine the effect of: 1) non-linearity, 2) variability.

Results: There were a total of 15313 published articles (2006-2016) in the two journals. Of these, 63 met the search criteria of which, 26 publications were not relevant for the objectives of this work, the remaining 37 publications all used R^2 as the statistics to choose among non-linear models and select the best PK parameter as the predictor of antimicrobial efficacy. In addition, none of the articles attempted combination of PK parameters as a predictor of antimicrobial efficacy. With increasing non-linearity for a given variability, R^2 may provide incorrect parameter selection (>25% of cases), whereas RSE statistics is not affected by non-linearity.

Conclusions: R^2 is widely used in selection of PK parameters driving efficacy of antimicrobial agents regardless of the nature of the relationship [1]. Majority of articles apply R^2 to non-linear models which is associated with major inadequacies and may result in erroneous model/parameter selection. Other statistics such as RSE provide more robust method in the context of antimicrobial PK-PD. In addition, current practices assess mainly one PK index as predictor of efficacy and no attempt is made to examine predictive value of the combined parameters. An example of application of appropriate alternative methodology using RSE and combination of parameters is presented.

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III-16: *Anais Glatard* Varenicline exposure is associated with abstinence from smoking in a cohort of smokers from the general population

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Objectives: The overall abstinence rate after varenicline treatment at the effective dose is reported to be less than 35%. High interindividual variability in plasma concentrations of varenicline may lead to suboptimal drug concentration. This study aimed to characterize the genetic and non-genetic sources of variability of varenicline pharmacokinetics and to relate them to drug effectiveness.

Methods: 82 smokers (121 varenicline concentrations) were genotyped for common polymorphisms in Uridine glucuronosyltransferase (UGT) 2B7, Organic Cation Transporter (OCT) 2 and some nuclear factors genes. Varenicline pharmacokinetics was analyzed using non-linear mixed effect modeling in NONMEM. For each concentration, the area under the concentration-time curve over 24 hours, AUC0-24, was computed in NONMEM analytically based on the dose history and the pharmacokinetic parameters. Correlations between AUC0-24 and withdrawal symptoms or carbon monoxide and cotinine levels were assessed by the Pearson correlation coefficient and linear mixed modeling, respectively.

Results: A one-compartment model with first order absorption and elimination appropriately described the 121 varenicline concentrations. Varenicline systemic clearance was 8.51 L/h (CV 25.7%), the volume of distribution was 228 L and the absorption rate was fixed to 0.98 h-1. Varenicline clearance increased by 68% with body weight doubling and was found to be 21% higher in UGT2B7 rs7439366 CC genotype carriers compared with CT and TT carriers. These covariates explained 14% and 9% of the interindividual variability in varenicline clearance, respectively. No correlation between the AUC0-24 and scores of appetite/weight gain (p=0.5) or nicotine craving (p=0.2) was found. With an AUC0-24 increase of 1 ng-1.h-1.mL, carbon monoxide and cotinine levels were significantly decreased by 0.06 ppm (95%CI= -0.07 ; -0.04) and by 0.63 ng/mL (95%CI= -0.92 ; -0.38), respectively.

Conclusions: Body weight and genetic polymorphisms of UGT2B7 play a significant role in varenicline exposure variability. Significant association was identified between varenicline AUC0-24 and two biomarkers of abstinence from smoking, therefore dosage titration based on carbon monoxide or cotinine might increase the treatment success. Although the limited amount of pharmacokinetic data would require further analysis, the originality of this work relies in the analysis of the influence of genetic factors on varenicline clearance.

III-17: *Ignacio Gonzalez* Comparison of FO – FOCE population parameter estimation methods in PhysPK 2.0 against NONMEM 7.3

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Objectives: To develop a population pharmacokinetic model and compare the estimates using FO and FOCE in NONMEM 7.3 against PhysPK 2.0 by studying population parameters, interindividual and residual variability, weighted residuals and shrinkages, and sensitivity of solutions to perturbations and initial conditions, using real data obtained from different clinical trials.

Methods: The PK model was developed in NONMEM 7.3 [1] in order to speed up the development process and to focus the goal of this work. The final model was built and analysed also in PhysPK [2] and the results were compared with those of NONMEM using standard metrics. The sensitivity of NONMEM and PhysPK methods to changes in initial conditions or even in fixed population parameters used in covariates equations was quantified. PK data was taken from several clinical trials sponsored by Pharma Mar were the drug under development was given as single agent at different doses and different schemes.

Results: A three compartment model with linear disposition and elimination, with BSA effect on clearance and disposition, displayed the most accurate predictions. No major differences in parameters estimation were obtained by both software's systems, but the sensitivity and robustness to initial conditions and parameter perturbations were different. A formal analysis of these ones and their implications in the development of PK models is presented.

Conclusions: PhysPK 2.0 is a new software for modelling and simulation of PK/PD/PBPK systems that can also be used for population parameter estimation. This work shows a preliminary study that compares FO and FOCE linear methods of PhysPK against the current gold standard FO and FOCE methods of NONMEM 7.3, with successful results. However, there are differences in the methods' sensitivity to initial conditions and other parameter perturbations. A first analysis of them is presented for a better knowledge of their influence in FO and FOCE limitations.

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III-18: *Sungwoo Goo* Population pharmacokinetics(PK)/Pharmacodynamics(PD) modeling and simulation of vancomycin in pediatric infectious patients

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Objectives:
The aim of this study is to develop population PK/PD model of vancomycin in pediatric infectious patients for dose optimization of vancomycin.
Pediatric patient's ADME is different to general adult patient's. therefore, pediatric modeling should be considered about allometric scaling and maturation function.
Drug Plasma Concentration/MIC is used as antibiotics' PD marker frequently. But time to get MIC value takes about a week commonly. Therefore, MIC is difficult to use clinically in early stage of infection. However, plasma levels of CRP may rise rapidly and markedly, as much as 1000-fold or more, after an acute inflammatory stimulus.[1] therefore, CRP is able to be used to PD markers at early stage of infection.

Methods: 81 pediatric patients' PK and clinical laboratory data as PD data were obtained from Electronic Medical Record (EMR) at Chungnam National University Hospital. 81[HY1] demographics of patient were tested by PK covariates (postnatal age(PNA), postconceptional age(PCA), genital age(GA), weight, etc). C-Reactive protein(CRP) was selected as PD because this parameter is representative to infectious factor. Plasma concentrations were fitted with one-compartment and indirect response model(IDR) was selected to connecting between PK and PD model. Kin was defined CRP synthesis rate. Kout was defined CRP degradation rate.

Results: PK base model was described by 1-compartment model. And PK final model was explained by Allometric scaling and maturation function. Allometric scaling was applied to Vd and CL. And maturation function was applied to CL. Maturation function's parameters that were TM50 and Hill were not estimated but gotten from reference.[2]
For Inhibitory Emax model, IC50 value was 10.7 mg/L that was in through therapeutic range(10-20 mg/L). PD model was described by IDR model. Kin and Kout were estimated 0.0207/hr and 0.0129/hr. Kin's and Kout's individual variation were 123 CV% and 26 CV%.

Conclusions: Pediatric PK model had lower individual error when allometric scaling and maturation function were considered. Allometric scaling was applicable for all pediatric groups. The maturation function was applicable to infants.
PD model had higher individual error than PK model. PD model was not considered about covariate since PK model was considered about it and valid covariate is not defined during EDA. And PD model was not considered about time. So predicted CRP value had higher error after stopping dose than during dosing.

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III-19: *Verena Gotta* Conceptual evaluation of urea rebound in pediatric hemodialysis patients by a physiology-based pharmacokinetic simulation study

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Objectives: Pediatric hemodialysis (HD) dosing and monitoring strategies are mainly derived from adult studies, based on pre- and post-HD urea plasma concentration sampling. Accuracy of such HD evaluation approach depends on extent and duration of post-HD urea rebound, which occurs due to redistribution of urea from slowly perfused (peripheral) to quickly perfused (central) body compartments. The goal of this urea kinetic simulation study was to evaluate expected urea rebound in paediatric HD patients.

Methods: Realistic pediatric HD prescription parameters and demographics were calculated over body weight (BW)-bands of 5 kg from a large registry database (DaVita) with ≥20 patients and >130 HD sessions per BW-band. Typical urea concentration-time profiles during and after HD sessions were simulated applying published urea kinetic data[1,2] and implementing expected physiologically-based kinetic changes in pediatrics (age-, body weight, and gender-dependency of total body water[3,4], cardiac output[5], and fraction of skeletal muscle mass[6] as indicator of slowly equilibrating somatic tissue mass). Time to regaining equilibrium after HD sessions between central and peripheral urea concentration (TTE) was calculated (i.e. at least 97% of complete equilibrium).

Results: In children up to 25 kg (10 years) predicted TTE was ≤5 min, in adolescents up to 35 kg (17 years) ≤10 min. In young adults (19-21 years, 40-120 kg) TTE was up to 25 min (longest in boys weighing >80 kg), while almost 90% of complete equilibrium was predicted to be achieved 5 min post-HD.

Conclusions: Results from urea kinetic simulations that take HD prescription parameters and physiologic changes in pediatrics into account indicate that time to equilibrium is shorter in pediatric than in adult HD patients, with urea rebound occurring within 5-10 min after HD sessions. This finding can be utilized to design optimal sampling strategies in urea kinetic studies in pediatric HD patients.

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III-20: *Sebastiaan Goulooze* Kernel-based visual hazard comparison (kbVHC): a simulation-free diagnostic for parametric repeated time-to-event models

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Objectives: Repeated time-to-event models are the preferred method to characterize the repeated occurrence of clinical events [1]. Commonly used diagnostics for parametric repeated time-to-event models (e.g. Kaplan-Meier VPC) require simulations, which may be difficult to generate in situations with dose titration or informative dropout [2]. Here, we present a novel simulation-free diagnostic tool for parametric hazard models, the kernel-based visual hazard comparison (kbVHC). The kbVHC relies on the visual comparison of the predicted mean hazard rate of a parametric model with a non-parametric kernel estimator of the hazard rate [3,4] with a mismatch between the two suggesting misspecification of the parametric model.

Methods: The degree of smoothing of the kernel estimator is determined by its bandwidth. Here, the local kernel bandwidth is set to the lowest value that results in a bootstrap coefficient of variation of the hazard rate that is equal to or lower than a user-defined CV_{target}. Bootstrapping was used to determine the 95% confidence interval of the kernel estimator. The predicted mean hazard of the parametric model was calculated from the individual post-hoc estimates. The kbVHC was evaluated by simulating various scenarios with different number of subjects (50-500), hazard rates, CV_{target} values, and hazard models (Weibull, Gompertz, and circadian-varying hazard). The kbVHC was compared with the Kaplan-Meier VPC in terms of its sensitivity to detect hazard model misspecification [5].

Results: The kbVHC was able to distinguish between Weibull and Gompertz hazard models, even when the hazard rate was relatively low (< 2 events per subject), performing comparable to the Kaplan-Meier VPC. Additionally, it was more sensitive than the Kaplan-Meier VPC to detect circadian variation of the hazard rate. Interpretation of the kbVHC depends on the degree of smoothing of the kernel hazard rate. Ranges for appropriate CV_{target} values are provided, based on the number of events in the dataset.

Conclusions: The kbVHC has a good sensitivity for model misspecification, even outperforming the existing Kaplan-Meier VPC for circadian-varying hazard models. Because the kbVHC does not require simulations, it can also be used in situations where appropriate simulations are difficult to generate. An additional useful feature of the kernel estimator, is that it can already be generated prior to model development to explore the shape of the hazard rate function.

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III-21: *Silvia Grandoni* Evaluation of a minimal WB-PBPK platform supporting different routes of administration

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Objectives: Assessing in different species a minimal whole-body (WB) PBPK platform, implemented in Matlab from literature information, able to predict, from physiological literature parameters and drug *in vitro* data, concentration-time profiles of drugs administered following two different routes of administration: intravenous (IV) and oral (PO).

Methods: The WB-PBPK model was built considering twelve tissue compartments plus the ACAT model to describe the PO administration. No enzymatic reactions were explicitly modelled. The information required to simulate a new experiment are: the species (to upload the related physiological parameters derived from the literature [1,2]), some *in vitro* characteristics of the drug (e.g. acidic/basic/neutral or zwitterionic character, pKa, intrinsic solubility, logP, blood-plasma ratio), the route of administration, the type of input (bolus or infusion), the dose (or the rate, for the infusion). Two different strategies to calculate the partition coefficients were considered and are available: one based on the work of Poulin et. al [3] and the other based on Rodgers et al. [4,5]. The value of the Caco2 permeability must be specified to allow the calculation of the absorption parameters of the ACAT model. A function to compute the hepatic extraction ratio using the intrinsic microsomal clearance as input value is also considered.

Results: The platform was assessed on different drugs given IV and PO to rats, dogs and humans, by using in-house data and several clinical studies available in the literature [6-10]. The selected literature studies report both *in vivo* measurements and *in silico* profiles, some of them obtained with the Gastroplus software. The plasmatic concentration-time profiles of the new WB-PBPK platform reasonably describe the data and the computed pharmacokinetic parameters (i.e., AUC, Cmax, Tmax, CL and V) are, for almost all the considered studies, within two-fold range. Moreover, interestingly, the predictions of the implemented platform are similar to those obtained by GastroPlus and by the model in [6].

Conclusions: The implemented WB-PBPK platform, while requiring few basic *in vitro* information for simulating a new experiment, is able to reasonably describe both the in-house data and those reported in the selected literature studies. Moreover, for all the considered experiments, its performances are comparable to those of a more sophisticated PBPK model and modelling tool, such as GastroPlus.

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III-22: *Ana-Marija Grisic* Towards understanding the loss of response to infliximab in patients with inflammatory bowel disease: A population PK modelling approach

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Objectives: Infliximab (IFX) is an anti-tumour necrosis factor α monoclonal antibody (mAb) used in the treatment of inflammatory bowel disease (IBD). The biggest challenge with IFX therapy is loss of response over time observed in up to 60% of patients. The loss of response has been related to low IFX plasma concentrations [1]. The aim of the current study was to investigate the impact of patient and disease characteristics on IFX exposure in order to identify the subpopulations at risk of therapy failure.

Methods: A pharmacometric analysis was performed on data ($n_{patients}$ = 122) collected as a part of an investigator initiated trial at the outpatient clinic of the Medical University of Vienna. The IBD patients received 2-h IFX infusions of absolute doses between 100 and 1300 mg during induction and/or maintenance phase. The samples ($n_{PK\ observations}$ = 388) were collected mainly at minimum concentrations and approximately at the middle of dosing interval (0.6-12.4 weeks after last dose). The analysis was conducted using R (version 3.2.4), NONMEM (7.3.0), PsN and Pirana. Impact of covariates on interindividual variability (IIV) of CL was investigated.

Results: The data is best described by a 2-compartment model with linear elimination. Due to the sparse nature of the data, the model had to be reinforced with a previously published model by using the PRIOR functionality of NONMEM. All estimated parameters (CL, V1, V2, Q) were in the range of previously reported IFX values [2-7]. Estimated CL was comparable to values reported for non-specific mAb CL [8], indicating that target-mediated CL was negligible. An exponential IIV model revealed ~40 %CV in CL and residual variability (combined additive and proportional) was ~30 % ± ~0.3 µg/mL. As expected from data availability, shrinkage in IIV of both volumes of distribution was high (> 50%) and low for IIV of CL. Identified covariates with significant influence on CL were anti-IFX antibody status, disease activity, concomitant therapy with immunomodulators and body size. The model exhibited a good performance.

Conclusions: A population PK model on ambulatory data was successfully developed, identifying covariates influencing CL of IFX and contributing to identification of subpopulations at risk. The developed model will be used for PKPD modelling, with the final goal to explain and reduce the occurrence of the loss of response in patients with IBD.

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III-23: *Benjamin Guiastrennec* Model-based prediction of plasma concentration and enterohepatic circulation of total bile acids in human

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Objectives: To predict the enterohepatic circulation of total bile acids (BA) from their plasma concentrations in relation to fat intake.

Methods: Data were obtained from a previously published study [1] involving 30 subjects who were administered 4 test drinks (350 mL) with 0, 2.5, 10 and 40 g fat, respectively, in a cross-over design**.** Gallbladder volume and total plasma BA concentration were measured repeatedly from 15 min before and up to 240 min after test drink intake. A published mechanism-based gastric emptying model [2], including a gallbladder compartment, was modified in order to predict the enterohepatic circulation of BA. Structural model development and the effect of test drink fat content were based on prior knowledge of BA physiology.

Results: The model featured a gallbladder compartment emptying into the small intestine, implemented as a chain of transit compartments. The bile volume emptied from the gallbladder was a function of the test drink fat content. Upon absorption in the distal end of the small intestine, BA could either be extracted by the liver back to the gallbladder compartment or spill over to the systemic plasma compartment. Hepatic extraction was implemented using a well-stirred model with constant intrinsic clearance (CL_{int} = 285 L/min). Literature values were used for hepatic volume (0.0143 L/kg) and blood flow (3.5 L/h/kg$^{3/4}$) [3], mean small intestinal transit time (200 min) [4], BA concentration in gallbladder (100 mM) [5] and the fraction of unbound BA in plasma (6.9%) [6]. The model appropriately described the gallbladder volume time-course for all test drinks and the total plasma BA time-course with the exception of the 40-g fat content test drink where concentrations were systematically underpredicted.

Conclusions: The developed enterohepatic circulation model accurately predicted the gallbladder volume and total plasma BA concentrations time-course following the 0, 2.5 or 10-g fat content test drinks. However, the total plasma BA concentrations were systematically underpredicted for the 40-g fat content test drink, indicating a possible threshold effect of fat on BA absorption or hepatic extraction. In the future, the proposed model could be used to predict intestinal BA concentrations from their plasma concentration and their influence on the absorption of lipophilic compounds.

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III-24: *Monia Guidi* Adequacy of open-loop Target Controlled Infusion devices during anesthesia

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Objectives: Open-loop Target Controlled Infusion (TCI) devices are largely used in clinical practice to aid optimization of propofol dosage for induction and maintenance of anesthesia. Propofol infusion rates are adjusted aiming to a defined target, based on model-predicted plasma or brain concentrations. Pharmacokinetic models used in TCI pumps were developed on small groups of healthy volunteers [1]. However, clinical conditions may markedly alter propofol pharmacokinetics and actual propofol levels could significantly differ from predicted ones, leading to important under- or over-exposure. The aim of our analysis was to assess the adequacy of TCI-predicted propofol dosage in virtual individuals simulated using a comprehensive population model developed on a large population of patients [2].

Methods: A virtual male patient (70 kg, 170 cm, 36 y) with changing propofol target brain concentration of 6 à 4 à 5 mg/L during a 15 min surgical operation was chosen. TCI dosage scheme, *i.e.* propofol infusion doses and durations required to achieve these targets, was retrieved applying the model of Schnider *et al.* [1] as implemented in the BasePrimea pump (Fresenius Kabi, Germany). The equilibration time between target brain and plasma concentrations was extracted. The comprehensive population model with between-subject variability developed in 660 patients by Eleveld *et al.* [2] was then used to simulate plasma propofol concentrations in 1000 individuals with the same characteristics as the index patient. Median plasma concentrations with 90% prediction interval ($PI_{90\%}$) were calculated and compared to the target brain concentrations at equilibrium according to TCI prediction. The percentage of virtual patients reaching propofol levels above 15 mg/L (maximum allowed in TCI) was also estimated.

Results: Median ($PI_{90\%}$) plasma concentrations of 5.6 (3.7–8.1), 3.7 (2.6–5.3) and 4.6 (3.3–6.5) mg/L were calculated when the target levels of 6, 4 and 5 mg/L, respectively, were reached according to TCI predictions. Furthermore, 12% of virtual patients were found with concentrations exceeding 15 mg/L within the first minute of propofol infusion.

Conclusions: Due to between-patient variability, current TCI pumps might deliver inadequate propofol dosages to patients with possible clinical consequences. Our simulations show a potential for a closed-loop control of drug administration based on real-time propofol measurement to improve automated anesthesia delivery.

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III-25: *Anubha Gupta* Power calculation methods to detect covariates effect when combining observed and simulated data.

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Objectives: Monte Carlo Mapped Power (MCMP) has been developed as an alternative rapid method [1] with respect to stochastic simulation and re-estimation (SSE) method for power calculation using non-linear mixed effect models based on likelihood ratio test. The aim of this work is to compare MCMP and SSE methods to identify covariates effect when combining existing data with simulated data. A specific example based on population PK model for a monoclonal antibody is presented.

Methods: Routine to implement MCMP [1] and SSE methods are available in PsN [2] for power calculation of a planned study. We borrowed the same principle to calculate the power to detect a covariate effect when combining existing rich PK data from healthy volunteers and simulated sparse PK data from a patient population.

A 2-compartment PK model for monoclonal antibody with first-order absorption and elimination was previously developed using a rich dataset in healthy volunteers (n=62). Sparse data (4 samples from each of 100 subjects) in patient population (n=1000) was simulated assuming significant effect of covariate on bioavailability and was combined with observed data. Higher between–subject variability in clearance was also considered for the patient population. The combined dataset was re-estimated in NONMEM® 7.3 using reduced and full PK model.

To avoid differences in the individual objective function (iOFV) for the real subjects all the parameters values, other than effect of covariate and residual error, were fixed to that estimated from observed data. An R script was developed to calculate the power for a given sample size N based on the change in iOFV between full and reduced model [1]. The results were compared with SSE method still using a combined dataset with existing and simulated data.

Results: The number of subjects required to detect a 27% difference in bioavailability with 90% power were 8 when assuming the same between-subject variability in clearance (26%). A higher (50%) between subject variability in the patient population, increased required sample size to 15. These results were comparable between the extended MCMP method developed in R and SSE method.

Conclusions: The method was successfully implemented to estimate the minimum number of subjects required to detect the difference in bioavailability for a monoclonal antibody using observed PK data and sparse PK study design in the population of interest.

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III-26: *Serge Guzy* Population Pharmacokinetic of L-DOPA and its main metabolites: Use of the Phoenix based QRPEM algorithm

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Objectives: To obtain population PK characteristics of L-DOPA and its metabolites in plasma and urine using the parametric, non-linear mixed effect modelling with Phoenix NLME. To show the advantage of QRPEM algorithm compared to standard FOCE-ELS. To present a new parallelization technique using large grid computing resources to solve complex problems without time consuming runs.

Methods: Blood and urine concentration over 24 hours were determined after administration of 37.5 mg carbidopa (tablets) and 150 mg L-DOPA (oral solution) 30 min after carbidopa to 11 healthy subjects. Time profiles of L-DOPA, dopamine, DOPAC, HVA and 3-OMD in plasma and cumulative amounts in urine were modeled simultaneously including double peak, and extravascular formation of dopamine.

Optimization was achieved with a new accurate parametric EM method QRPEM in Phoenix NLME that uses low discrepancy Sobol sequences, as opposed to the stochastic Monte Carlo sampling technique.

Locally initiated model runs were sent to remote computing platforms for execution and results returned to the local application using parallelization techniques in Phoenix 8 and a 300 core SGE grid hosted on Amazon Web Services by means of CFN grid software.

Results: The model estimated 23 fixed and 23 random effects. Only QRPEM had enough driving force for optimal minimization. FOCE-ELS locked multiple times into local minimums with bad diagnostics. Optimization was performed sequentially, starting with the fit of L-DOPA and dopamine data. The corresponding clearance terms split across the different paths. This resulted in satisfactory goodness-of-fit, good concordance between observed and simulated visual predictive checks and very good individual Bayesian fits for all responses. The new technique shortened run times significantly. Precision of parameters could not be assessed because the number of fixed effect parameter estimates was larger than individuals.

Conclusions: A complex model has been developed and fit to the data using a combination of optimization, adjustment and Bayesian algorithm to achieve reasonable model fits and population predictions (VPC). This predictive model can be used for extrapolation to any dosage regimen.

The QRPEM algorithm coupled with the parallel computing capabilities of Phoenix 8 permitted efficient modeling of a complicated dataset in reasonable time. The tools will increase productivity of individual modelers and expand the number and type of models to support drug developments.

III-27: *Bengt Hamrén* Pharmacokinetic and exposure-response analyses supporting ticagrelor dosing recommendation in patients with prior myocardial infarction (PEGASUS-TIMI 54)

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Objectives: To characterise the pharmacokinetics (PK) of ticagrelor and its active metabolite and further, to describe the exposure-response relationships between drug exposure and the composite risk of cardiovascular (CV) death, myocardial infarction (MI) and stroke as well as the risk of TIMI (the Thrombolysis In Myocardial Infarction) major bleeding during long-term treatment with ticagrelor in patients with prior MI.

Methods: Population PK (n=4426) and time-to-event exposure-response analyses (n=20942) were performed in patients with prior MI during long-term treatment with either placebo, 60 or 90 mg of ticagrelor (the PEGASUS-TIMI 54 study).

Results: The PK of ticagrelor and its active metabolite was stable over time. Multiple statistically significant covariates were identified, however only body weight was found to affect the apparent ticagrelor clearance (CL/F) greater than 20%. The exposure-response analyses supported the primary reported efficacy results and showed clear separation between placebo and active treatment. In addition, the exposure-response analyses provided insight into the contribution of individual exposure levels, rather than dose, as a predictor of events and accounted for differences in the baseline risk between patients. The predicted risks of CV death/MI/stroke were similar despite an increase in the median predicted ticagrelor average steady-state concentration from 606 nmol/L with ticagrelor 60 mg to 998 nmol/L with ticagrelor 90 mg (hazard ratios vs placebo of 0.83 and 0.81, respectively). The corresponding predicted risk of TIMI major bleeding slightly increased (hazard ratios vs placebo of 2.4 and 2.6, respectively). Apart from Japanese patients, showing a lower risk of CV death/MI/stroke, the response to ticagrelor was consistent across the study population.

Conclusions: The ticagrelor exposure-response relationships were relatively flat and consistent across the study population. These analyses supported the selection of the 60 mg dose for all demographic subgroups of patients studied.

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III-28: *Nina Hanke* Physiologically-based pharmacokinetic (PBPK) modeling of alfentanil as a CYP3A4 victim drug

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Objectives: PBPK modeling is a powerful tool to explore and quantitatively predict the magnitude of drug-drug interactions (DDIs) and may even offer an alternative to dedicated clinical studies. Alfentanil is a sensitive CYP3A4 substrate (≥ 10-fold increase of AUC with strong inhibitors) and recommended by the FDA for the assessment of the DDI potential of investigational new drugs [1]. Our objective was to establish a full body PBPK model of alfentanil and to demonstrate its ability to predict the rifampicin-alfentanil DDI.

Methods: PBPK models of alfentanil and rifampicin were built in PK-Sim® modeling software (Version 6.3.2) as part of the Open Systems Pharmacology Suite [2, 3]. Alfentanil drug-dependent parameters as well as plasma and urine concentration-time profiles of various clinical studies (dosing range 15-50 µg/kg as intravenous and 60-75 µg/kg as oral application) were obtained from literature and used to establish a model accurately describing and predicting observed clinical data. The alfentanil model was then coupled to a previously established rifampicin model [4], clinical DDI studies were predicted and the results were compared to published observed data.

Results: Model development was accomplished with data of 3 clinical studies as an internal dataset; model evaluation was performed with an external dataset of 4 different trials. The newly developed alfentanil model applies metabolism by CYP3A4. The passive glomerular filtration rate was reduced to a fraction of 0.06 to recover the low urinary excretion of approximately 0.3% as unchanged drug [5]. Although in clinical use alfentanil is administered solely in intravenous form, some DDI studies published plasma concentrations of alfentanil after oral application. Colonic absorption was disabled in our model, as late absorption was not consistent with the reported concentration time-profiles after oral administration. Simulation of 12 different DDI scenarios with the coupled models generates alfentanil plasma concentration-time profiles during rifampicin treatment that are in very good agreement with observed data. Predicted AUC ratios (AUC with rifampicin /AUC without) show a low fold bias of 1.19 (geometric mean fold absolute deviation, range 1.01-1.84, n=12).

Conclusions: We provide a full body PBPK model of alfentanil as a tool for the drug development process for dynamic evaluation of the DDI potential of investigational drugs that are CYP3A4 inducers or inhibitors.

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III-29: *Niklas Hartung* Quantifying adaptive resistance in bacteria using well-designed dynamic time-kill curve experiments

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Objectives: In vitro time-kill curve (TKC) experiments allow to study the dose-effect relationship of antimicrobial treatments, either in a static (constant drug concentrations) or a dynamic setting (time-varying drug concentrations, usually to mimic PK in vivo). Mathematical models contribute to this understanding by offering the possibility to simulate microbial growth under clinically relevant conditions and under combination therapy. However, some dynamic processes such as adaptive resistance and persister formation (dormant state), both stress-triggered phenotypic changes, are difficult to quantify reliably from these experiments [1]. Here, we explore the use of a mathematical model for bacterial growth parametrized from static TKC data to design dynamic TKC experiments aiming not at mimicking typical PK, but at differentiating adaptive resistance and persister formation processes.

Methods: We used a previously developed cell-level bacterial population growth model under meropenem treatment [2]. Reflecting cell-level processes, adaptive resistance and persister formation are incorporated into this model. While persister formation could be parametrized from static TKCs on methicillin susceptible Staphylococcus aureus with a meropenem minimal inhibitory concentration (MIC) of 0.13 mg/L [3], assumptions had to be made on adaptive resistance parameters. We explored intermittent exposure designs (static exposure, then fast decrease to low concentrations, then again static exposure at a different concentration) to determine the unknown maximum adaptive resistance (MaxAR) and loss rate of adaptive resistance (LossAR). Within this class of designs, DS-optimal designs were determined [4]. All simulations were carried out in R software.

Results: Initial exposure at 10*MIC for 3 h, followed by a 7 h rest and subsequent low exposure close to MIC leads to good identifiability of LossAR for a range of assumed true parameters. In contrast, MaxAR was difficult to quantify reliably with any design even if bacterial load was very sensitive to the parameter, which is probably due to correlations with other model parameters such as persister formation.

Conclusions: Mathematical models parametrized from static TKC data can be leveraged for the design of dynamic TKC experiments. Model-based experimental design allow for a better characterization of bacterial resistance. As the next step, further scenarios for MaxAR quantification will be considered.

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III-30: *Paul Healy* Impact of metabolic polymorphism on the exposure to tramadol and its active metabolite in children

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Objectives: It is estimated the M1 metabolite has 6 times greater analgesic potency than tramadol [1]. Patients with 'ultra-rapid', metabolising function of the CYP2D6 enzyme are more susceptible to adverse effects, notably respiratory depression [2], as the concentration of M1 metabolite increases rapidly. The objective of the current investigation is to demonstrate the relevance of clinical trial simulations as a tool for the evaluation of the systemic exposure to tramadol and its metabolite in paediatric populations and explore the potential clinical implications of CYP2D6 phenotype variants, focusing on UR-metabolisers [2].

Methods: A population pharmacokinetic model by Bressole et al [3] was adapted for the purpose of our analysis. This model was developed using data from children (1–8 years), who were given tramadol by continuous infusion. Given the use of intravenous route, estimates were obtained for absolute clearance (14.7 L/hr) and volume of distribution (8.01 L). The model was combined with estimates of the absorption rate constant observed after administration of an oral formulation using data from Payne et al [5]. When simulating the effect of metabolic polymorphism in clearance, the dataset was expanded to patients with ages from 3 months to 18 years. In addition to the time course of drug levels in plasma, Cmax, AUC, Css as well the ratio between parent drug and metabolite were derived as parameters of interest.

Results: A two-compartment model with absorption rate constant of 0.83 min^{-1} best described the PK of tramadol and M1. The clearance values differed substantially between extensive (0.361 L/hr) and UR-metabolisers (0.843 L/hr). Simulated profiles showed that Cmax depends on the dosage form, and the exposure (AUC) varies with age and weight. Whereas variability in drug exposure is driven primarily by the effect of body weight, clearance in fast metabolisers leads to significantly higher levels of the metabolite in this subgroup of the population.

Conclusions: The clinical implications of CYP2D6 ultra-rapid phenotype in paediatric patients taking tramadol ultimately depends on the dose and formulation used at the onset of treatment. The proposed simulation scenarios suggest that titration procedures are essential in clinical practice when no prior knowledge is available about the metabolic phenotype of individual patients.

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III-31: *Lee Heechan* A population parmacokinetic analysis of fimasartan, a novel angiotensin-receptor antagonist, in healthy subjects and patients with hypertension

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Objectives: Fimasartan is a newly developed antihypertensive agent that selectively blocks the type 1 angiotensin II receptor. The objectives of this study were to develop a population pharmacokinetic (PPK) model of fimasartan and to identify significant covariates that may affect the PPK parameters in healthy subjects and patients with hypertension.

Methods: A total of 4,692 fimasartan plasma concentrations were obtained from 269 subjects enrolled in 11 clinical trials including a first-in-human study, drug-interaction studies, and a proof-of-concept dose-response study. A PPK model was developed using nonlinear mixed-effects modeling analysis methods implemented in NONMEM (ver. 7.30). The iterative-two stage, Stochastic Approximation Expectation-Maximization and Monte-Carlo Importance Sampling assisted by mode a posteriori estimation with mu-referencing were implemented, which was followed by model qualification using bootstrapping and visual predictive checks (VPCs).

Results: A two-compartment linear model with mixed zero- and lagged first-order absorption and first-order elimination adequately described plasma fimasartan concentration. A proportional error models were used to account for remained intra-subject variability. The typical values of population PK parameters (inter-individual variability, CV%) of apparent clearance, apparent central volume of distribution, and fraction absorbed via first-order process was 185 L/h (54%), 344 L (89.5%), and 0.459 (107.5%). Covariates such as body weight and age were included in the model. Model evaluation by goodness of fit plots, bootstrapping and VPCs suggested that the proposed model was adequate and robust with good precision.

Conclusions: The final population PK model adequately described the observed plasma concentration of fimasartan in various population groups. Body weight and age were the most significant covariate for the PK parameters of fimasartan.

III-32: *Eleanor Howgate* Sensitivity analysis of P-glycoprotein Ki values in dynamic DDI predictions

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Objectives: The advantages of using PBPK models for prediction of transporter-mediated DDIs have been recognised [1]; although at present the observed degree of interaction is often under-predicted. One of the potential issues is the large variability in measured IC_{50} values [2]. The importance of using sensitivity analysis for key experimentally determined parameters has been highlighted in recent draft guidance for PBPK modelling [3,4]. The objective of this work was to investigate the fold range of intestinal P-gp Ki values required to recover digoxin DDIs with known inhibitors.

Methods: Published clinical studies involving inhibition of intestinal P-gp, using oral digoxin as the victim compound, were identified using the University of Washington drug interaction database [5]. *In vitro* P-gp inhibition data (IC_{50}) for perpetrator compounds, measured in Caco-2 cells with digoxin as the probe substrate, were collated from the literature. IC_{50} values determined using the efflux ratio (ER) of digoxin were favoured; if only net secretory flux (NSF) or unidirectional flux (UF) approaches had been used the data was corrected to representative ER values (ER values are on average 3-fold lower than NSF or UF [2]). DDI simulations were performed (Simcyp Simulator V15.1) using the clinical study designs and Ki values calculated using the Cheng-Prusoff equation [6]. Sensitivity analyses for Ki were used to determine the values required to recover the observed *in vivo* C_{max} ratios.

Results: Healthy volunteer DDI studies with orally administered digoxin as the victim compound were identified for Clarithromycin, Itraconazole, Ritonavir and Verapamil. A range of IC_{50} values were identified for each compound, typically using the ER or NSF methods. Simulations using Ki values calculated from the lowest IC_{50} (ER method) were unable to recover the *in vivo* C_{max} ratios. The results of the sensitivity analyses revealed that Ki values of <0.1 µM were required for all four compounds. The difference between the 'fitted' and *in vitro* Ki values (ER method) ranged from 4.1-fold to 654-fold, with a mean of 94-fold.

Conclusions: *In vitro* P-gp inhibition data required an average fold decrease of 94-fold to recover the *in vivo* interactions with digoxin. Potential reasons may relate to the (pre-)incubation conditions, inhibitor binding in the assay and inhibitory metabolites.

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III-33: *Gailing Li* Mechanism-Based Modeling In Chronic Heptatis B

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Objectives: Chronic hepatitis B virus (HBV) infection contributes to a severe disease burden all around the world. In order to gain a better quantitative understanding of HBV disease progression, a mechanism-based model was built through mathematically integrating data/information from disease natural history, therapeutic experiences of anti-HBV drugs as well as knowledge on molecular virology or immunology of HBV.

Methods: Literature search was through PubMed from 1995 to 2015. The database is composed of clinical data of 12 drugs from 2 classes (immune therapy, and nucleoside analogue i.e. NUC). A modified viral kinetic (VK) model was built using clinical data following NUC treatment only in previously untreated HBV patients (45 studies, 746 observations), including intra- and extra-cellular components such as intrahepatic cccDNA and serum HBsAg.

Results: The typical VK model (Nowak et al. 1996) was modified to account for several intracellular and extracellular components such as serum HBV DNA, serum HBsAg, and intracellular cccDNA. This modified model covers the whole life cycle of a virus. Parameters were either referenced from published in vitro/in vivo/clinical research or estimated by fitting to observed data. A serial sensitivity analysis was performed to identify critical steps/parameters that substantially influence the model outputs. Simulated profiles of viral endpoints were compared with observed data from literature. It showed that HBsAg elimination was estimated at much slower rate than in vitro measurements. Furthermore, some parameter estimates from classic VK model using HBV DNA data only were suggested new values when in our modified VK model using multiple endpoints data. In addition, simulation was performed by interfering in the different steps/pathways in the viral life cycle. It showed inducing immune-mediated elimination of infected cells might be the most effective effort to lead to disease cure. Overlaid with clinical data, simulated virus rebound following cessation of treatment also suggested that immune response might play an important role in sustained virus suppression.

Conclusion: This mechanism-based model incorporated multiple viral endpoints (HBV DNA, cccDNA, and HBsAg) within the context of virus life cycle. The effort in establishing a quantitative framework for HBV disease progression would not only improve our understanding of the disease, but facilitate the advance of discovery and development of new anti-HBV therapies.

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III-34: *Moustafa Ibrahim* Model-based diagnostics post-processing for fast automated model building; show-cased with residual error models and CWRES.

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Background and Objectives: Graphical diagnostics often provide useful indication of model misspecification. Here we investigate if model-based post-processing of common diagnostics, can provide additional advantages. We have selected to show-case this principle with CWRES [1], and residual error (RUV) models, where the new diagnostic tool is used to scan seven extended RUV models [2-4]: between-variable-(L2)-correlation, interindividual variability (IIV) on RUV, power model, time varying error magnitude, autocorrelated errors, t-distributed errors, and dynamic transform both sides (dTBS).

Methods: CWRES outputted from the original model, expected to be distributed N(0,1) for a correct model, were treated as dependent variable DV and modelled by a base model: y=Θ+?+?. The base model was then extended with the different RUV models, and used to model CWRES, e.g. IIV on RUV: y= Θ+?1+?*exp (?2). ΔOFV was calculated for each extended RUV model as the difference between base model objective function value OFV and extended RUV model OFV. The agreement, in ΔOFV between implementing these extended RUV models on the original model (conventional analysis) and just doing it on the CWRES, was evaluated in both real (n=15) and simulated (n=7) data examples.

Results: The agreement in improvement in fit (dOFV) between the original and CWRES models was high for all 7 RUV extensions (r across all models = 0.88 with an average ratio of ΔOFVs of 0.92) and the typical improvement was substantial (average (median) dOFV across all models = -220 (-70)). Also the parameters governing the extended RUV showed good concordance between the estimates obtained in the CWRES and original models. The simulated examples further supported a good agreement between the true misspecification in error model and what was identified by modelling of CWRES.

Conclusions: CWRES modelling is a promising, fast and easily automated diagnostic tool for model development process. It provides guidance for the nature and magnitude of potential model misspecification/improvements. It can be easily implemented in analysis software and is already implemented as resmod tool in PsN.

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III-35: *Ibrahim Ince* Extension of a pregnancy physiologically-based pharmacokinetic model for renally cleared drugs to the postpartum period

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Objectives: The objective of this study is to extend a pregnancy physiologically-based pharmacokinetic (PBPK) model to the postpartum period and verify it for the prediction of pharmacokinetics (PK) of renally cleared drugs.

Methods: A systematic literature search was carried out to collect study data on anatomical and physiological changes in the postpartum period. Collected data were quality appraised and compiled in a database if they met predefined inclusion criteria. Using a previously described approach [1], mathematical functions were fitted to the collected data to describe anatomical and physiological dynamics observed in the postpartum period. These functions were combined with previously reported functions for pregnancy-dependant changes [1,2] and implemented in PK-Sim and MoBi as part of the Open Systems Pharmacology Suite [3,4]. Finally, a PBPK model was developed to predict the disposition of a predominantly renally cleared drug, amoxicillin, in late pregnancy and in early postpartum period on the first day after delivery. PK predictions were verified using in vivo data from the literature.

Results: The literature search yielded 105 studies with 1096 anatomical and physiological data on 3742 women in the postpartum period. The PBPK model for amoxicillin successfully predicted the altered disposition of amoxicillin during pregnancy and in the postpartum period. PK parameters were also adequately predicted by the PBPK model showing a significantly higher clearance in pregnancy and a somewhat lower, albeit still elevated, clearance on the first day after delivery compared to the non-pregnant level.

Conclusions: A set of mathematical functions describing anatomical and physiological changes during the postpartum period was developed and coupled to a previously presented pregnancy PBPK model. This allows the longitudinal description of anatomical and physiological changes observed between the onset of pregnancy and eventual restoration of pre-pregnant levels in the late postpartum period. A subsequently developed PBPK model successfully predicted observed amoxicillin disposition in late pregnancy and early postpartum period. Ultimately, such a model could be applied to investigate in silico the PK of drugs in the postpartum period including potential drug transfer to the neonate via breast-feeding.

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III-36: *Itziar Irurzun-Arana* Population PD modelling of circulating biomarkers in patients with melanoma treated with interferon alpha2b

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Objectives: To stablish a semi-mechanistic model describing the time course of several circulating biomarkers (LDH, S-100B, and MIA) in advanced melanoma patients treated with adjuvant high-dose interferon-α2b.

Methods: Data related to different biomarker levels in plasma were obtained from 48 melanoma patients (stage IIB/IIC, IIIB/IIIC and IV according to the criteria of the AJCC) treated with adjuvant high-dose interferon-α2b (IFN-α2b) at the University Clinic of Navarra (Pamplona, Spain). The high-dose regimen followed the Kirkwood scheme: $20x10^6$ U/m^2/day intravenous in the induction phase (20 doses: 5 days/week during 4 weeks) and $10x10^6$ U/m^2/day subcutaneous administration in the maintenance phase (3 days/week during 48 weeks) [2,3]. In total, 17 patients (35%) had at least one dose reduction and 25 patients (52%) had dose delays during the induction or maintenance phase due to toxicity.

LDH, S-100 and MIA concentrations measured in plasma were analyzed simultaneously using the population approach with NONMEM 7.3. Due to the lack of pharmacokinetic data of IFN-α2b, the K-PD approach was used [1].

Results: The structural model developed combines indirect response-based models representing synthesis and degradation processes of tumor biomarkers driven by an underlying latent variable [Tumoral activity (TA)] corresponding to the (unobserved) tumor progression dynamics. Drug effects were incorporated in the model as an irreversible lost (cytotoxic effect) of TA. Two different patterns were seen in the biomarkers profiles: (i) relapse after treatment was stopped, and (ii) disease control over the full period of evaluation. The latter described assuming the presence of long-lasting immune response induced by IFN-α2b.

The proliferation rate of TA in the absence of treatment was $2.3x10^{-3}$ weeks^{-1}. Maximal response to treatment appeared after 80 weeks of starting the treatment according to a mean signal transduction time value of 18 weeks. The estimate of the first order rate constant of synthesis of long-lasting immune response was 0.006 weeks^{-1} for the individuals responding to the treatment, resulting negligible otherwise.

Conclusions: A model for the dynamics of circulating biomarkers has been established and evaluated in patients with melanoma during treatment with IFN-α2b, open the possibility to study the prognosis capability of those biomarkers on disease progression of overall survival using parametric survival analysis.

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III-37: *Masoud Jamei* Virtual Bioequivalence Assessment of Two Tramadol Formulations using the Advanced Dissolution Absorption and Metabolism (ADAM) model via Simcyp R Package

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Objectives: A qualified PBPK model of tramadol has previously been used to simulate virtual bioequivalence (BE) trials using a random error approach [1]. We aim to expand this approach using the Simcyp16 R package to assess the impact of inter-occasion variability on the bioequivalence (BE) of two tramadol formulations.

Methods: Mechanistic absorption models such as the Advanced Dissolution Absorption and Metabolism (ADAM) model implemented within population based Physiology-Based Pharmacokinetic (PBPK) models are useful tools in integrating various physiological parameters and formulation specifications affecting drug products. An important feature of PBPK modelling is accounting for within- and between- subject variability, when reference and test formulations are compared from a BE perspective.

Previously, PBPK models of tramadol for different formulations were developed and qualified. Then random residuals were added to their PK parameters to simulate virtual BE of the two formulations. In this work, the models are used to assess the formulations BE when inter-occasion variability are incorporated within parameters affecting the GI tract motility. In order to add inter-occasion variability the Simcyp Simulator parameters were modified using the Simcyp16 R package where variability is added to each individual gastric emptying time, small intestine transit time, and colon transit time. This process is repeated for each formulation for a specified number of times. Then the Bioequivalence between the test and reference formulations was assessed using the AUC, Cmax and Tmax values.

Results: Using the Simcyp16 R package the previously qualified PBPK model of tramadol was used for various formulations for 16 virtual subjects using a healthy volunteer population. Each subject was simulated 10 times where their gastric emptying time, small intestine transit time, and colon transit time were changed using a normal distribution by the assigned mean and a 10% CV. Then to assess the BE of these formulations the PK parameters, namely AUC, Cmax and Tmax were compared and the acceptable ranges based on the upper and lower bound of dissolution profiles were determined.

Conclusions: Mechanistic absorption models incorporated within population-based PBPK model can be used to run virtual BE studies and evaluate reference and test formulations. Such approach allows incorporation of inter-occasion variability in parameters that affect the formulations performance. These simulations may inform the optimal design of BE studies.

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III-38: *Candice Jamois* Quantification of Anti-Drug-Antibodies (ADA) Impact on Drug Exposure Using a Population PK modeling Approach

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Objectives: New engineered monoclonal antibodies (mAbs) represent effective therapeutic agents with high specificity for their targets-binding and efficient effector functions. However, the production of anti-drug Abs (ADAs) has become an important challenge during drug development as it may significantly influence the pharmacokinetics (PK), efficacy, and/or safety profiles of the mAbs [1]. The aim of this analysis is to quantify the impact of ADAs on clearance and exposure of Drug X using a population modeling approach, and to determine if a "dosing through" strategy [2] by increasing the dose is likely to succeed.

Methods: 1007 Drug X serum concentrations in 42 Phase 1 subjects receiving weekly IV doses (12.5 to 1500 mg) of drug X were analyzed using NONMEM. A 2-compartment PK models with time-dependent clearance (CL) and/or a time-dependent relative bioavailability (BIO) were tested to describe the Drug X PK in ADA- and ADA+ subjects. After validation by diagnostic plots and predictive check procedures, the model was used to quantify the impact of ADAs on exposure.

Results: 31% subjects receiving doses ≥ 150 mg developed ADAs leading to faster elimination of the drug. While sophisticated models (TMDD-like) [3] could describe the ADA-mediated clearance, simpler models with a time effect on parameters prove useful with better numerical properties. The final model is a 2 compartment PK model. The time dependent CL and BIO describe the effect of ADA on the PK of Drug X. Overall the parameters were adequately estimated except the time-effect on BIO for which RSE was >50%. Despite some (not yet resolved) misspecification of the model, it is nevertheless able to describe the observed PK profiles, and can be used to derive individual cumulative exposure (AUC). The ratio of AUC in ADA+ over AUC in ADA- subjects was computed after the 4^{th} infusion. The ratio varies from 17% to 71% [150-1000 mg]. A trend towards a reduction of the impact of ADA on exposure is observed for doses ≥ 340 mg, suggesting that a "dosing through strategy" could work, assuming acceptable benefit/risk ratio of Drug X at higher doses.

Conclusions: A population PK model describing the PK profiles of Drug X in the presence or absence of ADAs was developed. Although some unresolved misspecification are present, the model is still useful to quantify the impact of ADAs on exposure and assess the efficiency of dosing through strategy during the conduct of a Phase I trial to evaluate.

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III-39: *Julie Janssen* Clinical trial simulations to optimize dose finding studies in paediatric oncology

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Objectives: Paediatric dose finding studies are challenging to perform due to ethical reasons, the limited number of available patients and the restricted number of blood samples. In certain cases, the adult exposure can be used as target for dose finding in paediatrics. A paediatric phase I dose finding clinical trial, targeting the observed adult area under the plasma concentration-time curve at steady-state ($AUC_{24,SS}$), has been designed for the anticancer drug bosutinib (study ITCC054). In this ITCC trial, the approved adult dose scaled based on body surface area is to be given to a small number of children to show similar pharmacokinetic (PK) exposure and safety. The aim of this study was to investigate the power of this design to show similar PK exposure as observed in adults.

Methods: Paediatric PK parameters were extrapolated from adult values by allometric scaling [1, 2]. Based on the scaled parameters, individual simulated body weights and doses, individual paediatric PK curves were simulated. Subsequently, a clinical trial simulation was performed to determine the power of the proposed trial design, consisting of 6 paediatric patients and 6 sample time points (pre-dose and 1, 3, 6, 8, 24 hours post-dose). Power was defined as the fraction of 1000 trials with a geometric mean $AUC_{24,SS}$ within the target range (±20% of the adult geometric mean $AUC_{24,SS}$, i.e. 3640 h*ng/mL). Different sampling schedules were compared in additional simulations to optimize the trial design.

Results: At the starting dose of 300 mg/m^2 (equivalent to the approved 500 mg dose in adults), the power of the trial design was 66.9%. The exposure on this dose level was 3442 h*ng/mL. Power did not improve by increasing the dose to 350 mg/m^2, the next higher predefined dose level (65.3%). Addition of one sample resulted in similar results as the original sample schedule (67.5% and 67.7% versus 66.9%). Removal of one sample in the absorption and elimination phase of the curve did not substantially decrease the power (64.8% and 57.9% versus 66.9%). Increasing the number of patients to 10 patients per trial resulted in an increased power of 78.9%. Increasing the sample size to 10 patients is currently being considered.

Conclusions: The power of PK analysis in paediatric clinical trials can be predicted and optimized through PK simulations. This enables clinical trials in paediatrics to be performed as efficient as possible while protecting the child from unnecessary harm.

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III-40: *Jihyun Jeon* Pharmacokinetic modeling of Donepezil after transdermal administration in rat

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Purpose: Donepezil (DPZ) is a widely used for treatment of Alzheimer's disease. But, most of patients were suffered from gastrointestinal symptoms such as nausea, vomiting, and diarrhea at a high start dose. Thus, transdermal administration is proposed to provide continuous drug delivery, leading to reducing side effects. The aim of this study was to develop a population pharmacokinetic (PK) model of transdermal DPZ patch in hairless rats.

Methods: The plasma concentration data was collected from the hairless rats during 0 to 168 hour, after administering transdermal patch at 6 dose-groups. Population PK analysis was performed using non-linear mixed effect modeling (NONMEM) software ver. 7.3 One- or two-compartment PK models were compared as structural model. A combination of zero- or first-order absorption with or without lag time was tested to consider the drug disposition from skin to blood. The inter-individual variability was estimated using additive, proportional, and exponential model. The residual error model was evaluated to be additive, proportional, or combined. All NONMEM analyses were carried out using the first-order conditional estimation method with the interaction option (FOCE + I). Final model was selected considering the goodness-of-fit and evaluated with visual predictive check (VPC, n=1,000) method.

Results: From 332 plasma concentrations (n=34), the final model was developed using one-compartment model with sequential zero- and first-order absorption. The estimated population mean values of clearance (*CL*) and volume of distribution (*V*) were 2.41 L/h and 17.3 L, respectively. The first order absorption rate constant (K_a) was 0.0213 h^{-1} (11 %) and duration of zero order absorption (D1) was 12.2 h (22 %). These estimated parameters of absorption phase were reasonable to reflect the physiologic feature of transdermal administration.

Conclusion: A transdermal absorption PK model was successfully developed using donepezil data and acceptable parameters were estimated. With our final model, absorption of donepezil amount through skin can be predicted and the basal form of our final model with zero-order absorption from skin compartment, can be extrapolated to other transdermal patch drug.

III-41: *Jin Jin* Crenezumab exposure-response across Alzheimer's Disease endpoints supports a higher dose for Phase 3

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Objectives: Crenezumab is an antibody to treat Alzheimer's Disease (AD). Two Phase 2 studies in mild-to-moderate AD patients evaluated a high 15 mg/kg IV Q4W dose and a low 300 Q2W SC dose.In both Phase 2 studies, crenezumab was well-tolerated with only one case of ARIA-E across both studies. The aim of this analysis was to characterize the exposure-response of Crenezumab to support the Phase 3 dose.

Methods: A disease progression model for mild to moderate AD was established that described the longitudinal changes of the clinical endpoints ADAS-Cog and CDR sum-of-boxes (CDR-SB) simultaneously for patients in the Phase 2 studies. The model was extended to describe the effect of covariates on disease progression, and the effect of crenezumab on each endpoint. Clinical trial simulations (CTS) of the Phase 3 study across a range of doses were done, to compute the likelihood of achieving a percent relative reduction of disease progression in treated patients compared to placebo for ADAS-Cog and CDR-SB.

Results: Model validation demonstrated that the model replicated the Phase 2 longitudinal data accurately and is fit for purpose for simulation. The analysis showed faster disease progression in patients with moderate AD disease (lower baseline MMSE), ApoE4 positive genotype, female gender, and younger age. A relationship was seen between crenezumab exposure and treatment effect, which appeared to asymptote at the higher end of the range of exposures measured in Phase 2. Crenezumab treatment effect was associated with high baseline MMSE and ApoE4 positive genotype supporting better treatment effect in patients with mild AD. Compared to 15 mg/kg Q4W dose, a 4-fold increase to 60 mg/kg Q4W dose in Phase 3 is predicted to achieve a 41% greater relative reduction on ADAS-Cog, and 44% on the CDR-SB in the mild AD population.

Conclusions: A 60 mg/kg Q4W dose was selected for Phase 3 (NCT02353598), supported by a drug-disease model for mild to moderate AD. The model adequately summarized longitudinal progression in ADAS-Cog and CDR items, preserving correlation between the endpoints. CTS suggest substantially increased efficacy at higher exposures in patients with mild AD. As the model was trained on Phase 2 dosing, uncertainty in the predicted efficacy increases with increasing exposure where exposure falls outside that observed in Phase 2.

III-42: *Martin Johnson* Exposure response relationship for interstitial lung disease (ILD) events following osimertinib treatment

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Objectives: Osimertinib is indicated for the treatment of patients with T790M mutation positive advanced non-small cell lung cancer (NSCLC) who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy [1]. In general, ILD incidence with TKIs is variously reported to be approximately 1.6 – 4.3%in Japanese populations and 0.3–1.0% in non-Japanese populations [2]. In this analysis, a potential relationship between systemic exposure of osimertinib and the incidence of ILD events was evaluated.

Methods: ILD event information from patients with advanced NSCLC from Phase I, Phase II, and Phase III studies (n = 1088) was used in this analysis as a categorical variable. Thirty-seven (3.40%) patients had ILD events. Occurrence of ILD was higher in the Japanese population (8.42%) than in the non-Japanese population (2.30%). A penalised logistic regression was applied to account for the separation problem due to the low number of ILD events. Ethnicity, exposure of osimertinib and other relevant covariates were used in the covariate analysis.

Results: A linear logistic regression model described the relationship between exposure and ILD events adequately (slope for change in logAUCss: 0.80 [0.308, 1.28], Intercept -10.9 [-15.7,-6.21]). Parameter estimates and predicted probabilities were represented as Median [95% confidence intervals]. Model predicted probability of a patient experiencing ILD increases with increasing osimertinib exposure as 0.0191 [0.0111 – 0.0328] for lowest quartile (steady state AUC 6361 nM*h) vs 0.0542 [0.0375 – 0.0777] for highest quartile (AUC 24460 nM*h). At the recommended 80 mg/day dose, Japanese patients are predicted to have higher (0.079 [0.042 – 0.13]) probability of experiencing ILD events compared to other ethnic populations (0.032 [0.015 – 0.052]). Estimated ILD incidence rate for non-osimertinib or placebo treatment was lower (0.0046%) than the ILD incidence rate reported in literature for placebo or chemotherapy treatment (0.9 to 2%) in NSCLC patients. When including information about ILD incidence rates for non-osimertinib or placebo treated NSCLC patients, the estimated exposure dependency of ILD events under osimertinib treatment was lower.

Conclusions: Our model-based exposure-response analysis accounted for low number of events and suggested a relationship between osimertinib exposure and ILD incidence. At 80 mg dose, Japanese population predicted to have higher probability compare to other population.

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III-43: *Koen Jolling* CHF5993 a triple combination therapy for COPD patients: population pharmacokinetic modelling of beclometasone-17-monopropionate (B17MP) following pMDI inhalation.

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Objectives: CHF 5993 pMDI is a new extrafine fixed dose combination of beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium bromide (GB), being developed for chronic obstructive pulmonary disease (COPD) and asthma treatment. Data from phase II/III studies were used to evaluate the population pharmacokinetics of B17MP (main BDP metabolite) and to investigate the influence of selected covariates on B17MP PK parameters and their potential clinical impact.

Methods: B17MP plasma concentrations after oral inhalation in COPD patients were obtained from 2 studies: Triple 6 (ph III) and CARSAF (ph II). Both studies were double-blind, randomized, active-controlled. In Triple 6, patients inhaled two puffs twice daily of CHF 5993 pMDI (BDP/FF/GB 100/6/12.5 µg). In CARSAF, patients inhaled two puffs twice daily of Foster® pMDI (BDP/FF 100/6 µg) plus either 25 or 50 µg GB pMDI. B17MP concentrations were modelled with non-linear mixed-effects approaches using NONMEM V7.3.0. The explored covariates were age, smoking status, sex, body weight (WT), body mass index, concomitant medications, study effect, use of spacer, forced expiratory volume in 1 second (FEV1), concomitant diseases and glomerular filtration rate (GFR).

Results: The final model describing B17MP PK was a three-compartment disposition model with first-order formation process and first-order elimination with inter-occasion variability on relative bioavailability. The residual error model was a combination of a proportional and an additive component for the log transformed data. GFR, WT, smoking, study effect and repeated administrations were found to affect B17MP PK parameters. Simulations were performed to visualize the impact of the different covariates on the PK of B17MP, at steady-state, using a BDP dose of 200 µg BID. For a sub-population with extreme values of WT and GFR (i.e. low WT (40 kg) and low GFR (27 mL/min/1.73 m^2)), B17MP exposure increases by a factor of 1.8 compared to reference patients. This higher exposure is of no clinical concern because BDP therapeutic doses up to 2-fold the doses used in the CHF5993 formulation are currently available on the market and this doubling in exposure can thus be considered safe.

Conclusions: The PK model built on data from COPD patients described the B17MP data well and was able to explain part of the variability in exposure on the basis of some covariates. Based on simulated profiles, no clinical dose adjustments were deemed necessary.

III-44: *Siv Jonsson* Placebo and drug response assessment on Unified Parkinson's Disease Rating Scale using longitudinal Item Response Modelling

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Objectives: To employ an Item Response Model (IRM) to describe the time course and drug effect in advanced Parkinson's disease (PD) subjects based on longitudinal Unified Parkinson's Disease Rating Scale (UPDRS) data.

Methods: An IRM with 4 latent variables [1] has been used to describe baseline 44-item UPDRS data from 2 clinical trials in early [2] and advanced [3] PD. This IRM was applied to the extended data with longitudinal UPDRS recordings collected in the randomized advanced PD study [3], comparing ropinirole to placebo as adjunct therapy to L-dopa over 24 weeks at individually titrated doses between 6 and 24 mg/day. For placebo, a linear model assessed the disease progression (Slope), or an exponential model the extent (Shift) and onset rate (Onset) of symptom relief over time. Exposure independent disease modifying (DM) and symptomatic (SY) drug effects were assessed as follows: Linear: Baseline+(Slope+DM)·time; Exponential: Baseline+(Shift+SY)·(1-exp[-Onset*time]). Modelling was performed using NONMEM7.3.

Results: The data comprised of 72,167 (552 patients) UPDRS recordings, whereof placebo and ropinirole data from [3] accounted for 31,212 (190 patients) and 33,951 (201 patients) records. The exponential model resulted in statistically significantly better description of the longitudinal data than the linear model. The placebo time course parameters were estimated for each latent variable, defining the observed small improvement in disease over time (Shift ranging from -0.30 to -0.058) corresponding to an approximate decrease in total UPDRS of 3 points in the placebo group. Drug effects could not be differentiated statistically among latent variables and one common drug effect was estimated disclosing additional improvement (SY -0.54) corresponding to an approximate decrease in total UPDRS of 11 points in the ropinirole group.

Conclusions: The longitudinal IRM model adequately described the data, reflecting a gradual onset of symptom relief from baseline by the drug, in addition to the placebo effect. The progression of the symptoms during placebo treatment or the drug effect on this progression could not be reliably assessed, due to the insufficient trial duration. The use of multiple latent variables revealed the differentiated nature of symptom relief by placebo among various aspects of the clinical endpoint. This model can be further extended to allow simulations for drugs with differentiated pharmacological profiles.

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III-45: *Matts Kågedal* Herceptin in HER2-positive Gastric Cancer: Evaluation of Exposure-Response with Two Dose Levels.

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1. Genentech INC 2. Certara

Objectives: Previous exposure response analyses of Herceptin treatment in patients (pts) with HER2+ metastatic gastric/GEJ Cancer (TOGA study), suggested an association between Herceptin exposure and overall survival (OS), where pts with low drug exposure had shorter OS. It was unclear whether the observed association represented a true causal relationship or if it resulted from confounding factors influencing both drug clearance (CL) and OS[1,2]. A new study (HELOISE) in HER2+ metastatic gastric/GEJ cancer has subsequently been performed including two treatment arms with different dose levels[3]. The objective of this exploratory analysis was to assess the exposure-response relationship for OS and the potential confounding effect of clinical factors based on results from the HELOISE phase III study.

Methods: HELOISE randomized pts with HER2-positive metastatic gastric cancer with poorer clinical factors to receive one of two Herceptin regimens. After an initial Herceptin dose of 8mg/kg in both arms, pts received either 6mg/kg (SoC) or 10 mg/kg (High) Herceptin every three weeks in combination with chemotherapy. Plasma clearance (CL) as well as AUC, Cmax and Cmin after the first dose (cycle 1) and at steady state were derived. Graphical exploration and multivariate Cox regression were performed to identify predictors of survival and any exposure-response relationship.

Results: Although higher Herceptin maintenance dosing is associated with higher concentrations in HELOISE, we observed no increased efficacy (OS)[3]. This finding was consistent across cycle 1 exposure levels, suggesting that increasing the dose/exposure did not improve survival even in the pts with the lowest exposure. Multivariate Cox regression across both arms including the covariates; number of metastatic sites, Albumin, Cmin,ss and CL suggested that CL was a predictor of OS (p=0.009), and that Cmin,ss may also contribute (p=0.02).

Conclusions: No improvement in efficacy was seen by increasing dose over SoC, irrespective of exposure level. The apparent exposure OS relationship based on the single dose TOGA study appears to be a confounding effect of CL along with poorer clinical factors, rather than a causal exposure-response relationship. Tumor growth inhibition metrics may be used to further address the confounding in exposure-response (OS)[4].

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III-46: *Vangelis Karalis* On the population pharmacokinetics and the enterohepatic recirculation of inhaled formoterol in asthma patients

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Objectives: To develop a population pharmacokinetic (PK) model for describing the absorption kinetics and enterohepatic recirculation (EHC) of formoterol (FOR) following inhaled administration.

Methods: Plasma concentration (C) – time (t) data of FOR were obtained from a single dose, 2x2 bioequivalence study comparing two dry powder inhalers (DPIs). The study included a number of ninety, controlled or partly controlled, male and female patients under fasting conditions, with activated charcoal administration. Non-linear mixed-effect modeling was applied and a PK model able to describe the kinetics of FOR was developed. Different methodologies were tested, including multi-compartment models with an enterohepatic loop using first or zero order transfer rate constants, sine function models for gallbladder control, gallbladder emptying time, presence or absence of bile elimination. Several error models were tested, whereas the period and treatment effects, as well as, demographic characteristics were explored as potential covariates. The entire computational work was implemented in Monolix 4.3.3.

Results: The FOR C-t profiles were best described by a two-compartment disposition model linked to bile and gastrointestinal (GI) compartments. Elimination from the central and bile compartments was considered to follow first order kinetics. The final model included an EHC loop with the introduction of two additional compartments (i.e., bile and GI) linked by first order kinetics and a gallbladder emptying time interval. The model was finally parameterized in terms of the lung absorption rate constant (K_L =15.8 h^{-1}), the apparent volume of distribution in the central (Vc/F=873 L) and peripheral (Vp/F=1,460 L) compartment, the apparent clearance from the central compartment (CL/F=110 L/h), the inter-compartmental clearance (Q/F =2,850 L/h), the transfer rate constant to bile (Kb=0.36 h^{-1}), the excretion rate constant from bile to the intestine (Kg=0.57 h^{-1}), the GI absorption (Ka=0.28 h^{-1}) and fecal elimination (Kfec=0.02h^{-1}) rate constants. The application of a combined error model led to the optimum performance. No significant covariate was found and no difference in the performances of the two DPIs was observed.

Conclusions: A population PK model with an EHC component was found to fit suitably the plasma C-t data of inhaled FOR. Several EHC scenarios were developed and their performance was evaluated in terms of physiological soundness and goodness-of-fit criteria.

III-47: *Johannes Kast* Antibiotic Efficacy during Spaceflight: Impact of Simulated Microgravity on Killing of S. pneumoniae by Ciprofloxacin

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Objectives: To explore the effects of the microgravity environment observed during spaceflight on the killing of *S. pneumoniae* by ciprofloxacin by developing a PK/PD model to compare the efficacy of dosing regimens in simulated microgravity and Earth's gravity.

Methods: Free interstitial tissue concentration-time profiles of ciprofloxacin in simulated microgravity (0G) and Earth's gravity (1G) were simulated for different dosing regimens in R v.3.3.2. The model was obtained from the literature [1]. Pharmacokinetic profiles were simulated for 36 hours after oral administration of ciprofloxacin with a dose of 250, 500 and 750 mg every 12 hours (BID). To describe the killing of *S. pneumoniae* by ciprofloxacin, *in vitro* time kill curve experiments were performed at 0.25 to 16XMIC in simulated microgravity and Earth's gravity. The bacterial killing was modelled using a one bacterial population model where the ciprofloxacin effect was described as a sigmoidal E_{max} model in NONMEM v.7.3. Finally, bacterial response for each dosing regimen was predicted using the developed pharmacodynamic model.

Results: Free interstitial tissue ciprofloxacin concentrations were lower in 0G as compared to 1G for all simulated dosing regimens. Ciprofloxacin concentrations after 36 hours were 35.13, 70.27, 105.40 ng/ml in 0G and 40.23, 80.45, 120.68 ng/ml in 1G for 250, 500 and 750 mg ciprofloxacin BID, respectively. The *in vitro* time kill curves of ciprofloxacin against *S. pneumoniae* were successfully described with the developed model (for 0G: EC_{50} 0.60 mg/l ciprofloxacin, Hill factor 1.34, maximal kill rate constant 3.81 h^{-1}, for 1G: EC_{50} 0.67 mg/l ciprofloxacin, Hill factor 1.18, maximal kill rate constant 4.26 h^{-1}). Bacterial concentrations after 36h were higher in 0G as compared to 1G. Bacterial loads in log(CFU/ml) after 36h were 8.72, 8.67, 8.42 in 0G and 8.70, 8.63, 8.10 in 1G for 250, 500, 750 mg ciprofloxacin BID, respectively.

Conclusion: Based on the simulated kill-curve profiles of different ciprofloxacin dosing regimens against *S. pneumoniae,* none of the simulated dosing regimens are adequate to treat infections of *S. pneumoniae* with ciprofloxacin on Earth or in microgravity since adequate killing of bacteria is not achieved in either scenario after 36h. More research, especially inflight studies, is needed to further investigate the impact of the spaceflight environment on the pharmacokinetics and pharmacodynamics of antibiotics to ensure adequate pharmacotherapy during space missions.

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III-48: *Tatiana Khariton* Human Population PK Model, Dose Selection and Target Attainment Simulations for CF-301 - a Novel Antibacterial Lysin

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Introduction: CF-301, a novel bacteriophage-derived lysin that has completed the first Phase 1 trial in the US, is being developed for treatment of *S. aureus* bacteremia, exhibits rapid *S. aureus*-specific bacteriolysis, anti-biofilm activity, has low propensity for resistance and pronounced synergy with antibiotics.

Objectives: To develop a population PK model for CF-301 in humans and to perform target attainment simulations to determine optimal clinical doses for Phase 2 study in patients.

Methods: Data from 13 healthy subjects (receiving single doses of CF-301, 0.04-0.4 mg/kg 2-hr infusion) were used to develop the population PK model. The clinical relevance of statistically significant covariates was assessed based on the magnitude of effect on the PK profiles. The final PK model was used to perform target attainment simulations for various IV dosing regimens to select optimal dose for the first study in patients.

Results: 200 CF-301 plasma concentrations were available for the analysis. Two-compartment model with proportional residual error described the data best. PK parameters were well estimated, CL=7 L/h (RSE=5.4%) and Vc=6.5 L (RSE=6.5%). Influence of weight, gender, age, race and dose was assessed on clearance and volume of distribution. Sex and weight were determined to be statistically significant covariates for CL. Based on these detectable covariate effects, females are expected to have ≤15% lower AUC or C_{max} than males; impact of weight on AUC and C_{max} was ≤25%. Dose was a statistically significant covariate on CL and Vc. The relationship between dose and AUC or C_{max} was determined to be linear, but less than dose proportional with a slope of ~0.75. Target attainment simulations determined that doses 0.12-0.4 mg/kg (2-hr infusions) maintain AUC and C_{max} above clinically relevant exposures.

Conclusions: The population model described the PK of CF-301 adequately. Weight and sex, although statistically significant covariates, were not clinically relevant (≤25% effect). PK of CF-301 was linear, but not dose-proportional with a 2-fold increase in dose resulting in a 1.75-fold increase in C_{max} and AUC. Target attainment simulations predicted doses of 0.12-0.4 mg/kg (2-hr infusion) to be efficacious with almost all patients expected to achieve targets (AUC/MIC≥0.5), that are expected to be efficacious.

III-49: *Yu Kyong Kim* Population Pharmacokinetic Model Development for Long-Acting Intramuscular Injection of Drug X in Healthy Subjects

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Objectives: Drug X, a new long-acting intramuscular (IM) injection formulation for the chronic disease, is currently under development in hope to improve patient compliance by extending the dosing frequency compared to that of the currently available once daily oral formulation. Population pharmacokinetic (PK) analysis was carried out for characterisation of drug X after IM injection in healthy subjects.

Methods: A nonlinear mixed effect modelling for population PK analysis was performed with 608 concentrations from 20 healthy subjects, who received 35, 70 or 140 mg of single IM injection of drug X. The first-order conditional estimation with interaction estimation method implemented in NONMEM (version 7.3.0) [1] was used, followed by standard goodness-of-fit diagnostics and visual predictive check for qualification evaluation of the model predictions.

Results: One-compartment with two independent first-order absorptions with lag time and combined error model best described the PK of drug X. The typical population estimates (intrasubject variabilities shown as coefficient of variation, CV%) of the apparent clearance (CL/F), volume of distribution (Vd/F), the primary (Ka1) and secondary (Ka2) absorption rate constants, and the lag time of secondary absorption were 9.01 L/h (21.8%), 1270 L (27.2%), 0.0023 h^{-1}(17.0%), 0.0113 h^{-1} (47.6%) and 352 h (fixed to 0.0%), respectively.

Conclusions: A population PK model of drug X was developed and such model predictions may contribute towards selection of dose for the phase II clinical study.

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III-50: *Yun Kim* A population pharmacokinetic analysis of voriconazole according to CYP2C19 phenotype in healthy subjects

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Objectives: Voriconazole is a broad-spectrum antifungal agent for the treatment of invasive aspergillosis. The aims of this study were to develop a population pharmacokinetic model of voriconazole, and to evaluate the demographic and genomic determinants of plasma voriconazole levels.

Methods: A population pharmacokinetic analysis was performed using 1408 voriconazole concentrations in 82 healthy male subjects who received intravenous (IV) and/or oral voriconazole. The First-Order Conditional Estimation with Interaction estimation method was used with NONMEM (version 7.3). The effects of age, weight, height, and CYP2C19 phenotype on the pharmacokinetics of voriconazole were evaluated.

Results: A two-compartment model with first-order absorption and nonlinear (Michaelis-Menten) elimination with proportional residual error adequately described the time-concentration profiles of voriconazole. The typical values (inter-individual variability in CV%) of the maximum elimination rate (V_{max}), Michaelis-Menten constant (K_m), central volume of distribution (V_2), peripheral volume of distribution (V_3), inter-compartmental clearance (Q), and first-order absorption rate constant (k_a) were 15.1 mg/h (24.7%), 0.115 mg/L (48.1%), 51.0 L (36.5%), 232 L (25.1%), 38.4 L/h (15.1%), and 1.09 /h (57.2%), respectively. Weight was found to be a significant covariate for the Q and V_3 of voriconazole, while CYP2C19 phenotype had a significant effect on the K_m. The K_m estimates in CYP2C19 intermediate and poor metabolizers increased 1.4 and 5.46 fold over that in extensive metabolizers.

Conclusions: The pharmacokinetic parameters of IV and oral voriconazole were well described by the developed population model. The contribution of CYP2C19 to the pharmacokinetic variability of voriconazole in the patient population should be further investigated in the context of individualized optimal dosing to improve clinical outcome.

III-51: *Lena Klopp-Schulze* Exploring and explaining variability in tamoxifen and endoxifen pharmacokinetics in breast cancer patients: A pooled analysis

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Objectives: To improve tamoxifen treatment, it is crucial to better understand the complex pharmacokinetics (PK) of tamoxifen and its major metabolites, which is influenced by many internal (e.g. CYP polymorphisms) and external factors (e.g. drug-drug interactions). By combining data from different clinical studies we enriched the single database for analysis, i.e. increased the power to detect covariate relationships. This study aimed to explore and explain different levels of variability in tamoxifen and endoxifen PK.

Methods: Plasma concentration data of tamoxifen and metabolites from 468 breast cancer patients were pooled from six clinical studies: two large studies ($N_{patients}$=375) with sparse sampling (≤4 occasions, 1 sample/occasion) [1,2] and four smaller studies ($N_{patients}$=93) with rich sampling (≤3 occasions, ≤9 samples/occasion) [3–6]. A patient's CYP2D6 phenotype was predicted from genotype according to CPIC guidelines [7]. A joint parent-metabolite model including key covariate relationships (based on prior knowledge) was developed. To account for different levels of variability (study, individual, occasion), several variability models were tested. Modelling activities were performed using NONMEM (v. 7.3).

Results: Large parts of the interindividual (IIV), inter-occasional variability (IOV) and inter-study variability (ISV) were explained by the investigated covariates: Drug-drug interactions (DDI) with the potent CYP3A4 inducer rifampicin (CL_{TAM} increased by >500%) and the strong CYP2D6 inhibitors fluoxetine and paroxetine ($CL_{TAM\text{-}ENDX}$ reduced by >60%) had a tremendous impact on tamoxifen and endoxifen PK. For CYP2D6 poor, intermediate and ultra-rapid metabolisers (reference group: normal metabolisers), a change in $CL_{TAM\text{-}ENDX}$ of -65%, -45% and +75% was identified. However, unexplained variability remained in IIV and ISV (>25% CV).

Conclusions: By combining data from six studies influential factors on PK were identified and quantified, thereby substantially reducing ISV and IIV. However, unexpectedly high differences between the pooled studies were found, which could not be explained by the investigated covariates. Study design, bioanalytical methods or factors that had not been reported, such as adherence or tamoxifen formulation, might cause these differences [8]. To avoid subtherapeutic concentrations we need to identify and control these factors which will improve dose individualisation strategies such as model-based therapeutic drug monitoring.

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III-52: *Frank Kloprogge* Pharmacodynamics of vancomycin in children

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Objectives: The European Medicines Agency is currently updating product information of vancomycin, including investigating its appropriate dosing and monitoring in children [1]. Vancomycin is used to treat serious Gram-positive infections resistant to other antibiotics. It is a narrow therapeutic index drug requiring therapeutic drug monitoring after intravenous administration. Initial paediatric dosing schedules are based on extrapolations from adults which might result in sub-optimal exposures (AUC's). The aim of this study was to determine the pharmacodynamic target for vancomycin in a paediatric population and to simulate an initial dosing regimen which maximises the antibacterial effect.

Methods: Using a nonlinear mixed-effects model vancomycin plasma concentration-time profiles from a large retrospective database were analysed. The vancomycin exposure threshold (Vancomycin AUC/MIC at day one and day two) associated with an increased chance of treatment failure was identified using Classification And Regression Tree (CART) analysis, which was a similar procedure as previously performed in an adult population [2]. Monte-Carlo simulations were performed to select initial doses mitigating the risk of antibacterial failure across the paediatric population.

Results: The pharmacokinetic model was developed using data from 902 patients (age range: 0.03-255 weeks body-weight range: 0.742-95.0 kg) and adequately described Vancomycin exposure. For 71 of the patients (age range: 0.32-205 weeks body-weight range: 0.742 - 76 kg) also clinical MIC's of invasive blood stream isolates were available from a variety of Gram-positive bacteria. The CART analysis indicated that age at 1.7 years was an important cut-off with patients younger then this requiring an AUC/MIC at day one of 133 versus 58 for those older. Corresponding doses to reach target attainment within the paediatric population were identified.

Conclusions: The presented research has identified the paediatric pharmacodynamic endpoint for vancomycin and provided an initial paediatric dosing schedule ensuring target attainment and maximum clinical efficacy through Monte-Carlo simulations. Less than 10 percent had a blood isolate highlighting the difficulty of running clinical pharmacokinetic-pharmacodynamic trials in children.

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III-53: *Ben Kluender* Pharmacokinetic and Exposure-Response Analyses for Extrapolation of Efficacy of Adalimumab in Adolescent Patients with Hidradenitis Suppurativa

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Objectives: As a clinical trial in adolescents with hidradenitis suppurativa (HS) was not feasible due to the rarity of HS in this population, pharmacokinetic (PK) and exposure-response (E-R) analyses were performed to allow extrapolation of adalimumab (ADA) efficacy and support dosing recommendation in adolescent HS patients (pts) using PK and efficacy data from adult HS pts and PK data from other pediatric populations.

Methods: A population PK model was developed based on ADA PK data (524 pts aged 2-17 years) in other pediatric indications (pediatric psoriasis, crohn's disease, polyarticular juvenile idiopathic arthritis, and enthesitis-related arthritis). PK simulations were performed to predict a dosing regimen for adolescent HS pts that would achieve concentrations similar to those observed in adult HS pts. ADA serum concentrations and HS Clinical Response (HiSCR) rates from adult HS Phase 3 studies were used to develop an E-R model for ADA in adult HS pts. Assuming a similar E-R relationship between adult and adolescent HS pts, the model was used to predict clinical outcomes in adolescent HS pts.

Results: Disease indication was not found to be a significant factor affecting ADA PK, suggesting that ADA PK in adolescent HS pts can be extrapolated from other pediatric populations. Simulation results showed that predicted ADA steady state concentrations (mean±SD) in adolescent HS pts (8.4 ± 5.2 μg/mL) were similar to those observed in adult HS pts (8.8 ± 6.3 μg/mL) at a dosing regimen of 80 mg(Week 0), then 40 mg every other week (eow) (from Week 1). Results of the simulations based on the developed E-R model showed that the predicted HiSCR rates in adolescents were 55% and 28% after 12 weeks of ADA treatment (80 mg, then 40 mg eow) and placebo, respectively. These rates were similar to the overall response rates observed for adults in the Phase 3 HS studies (51% and 27% after 40 mg every week and placebo dosing, respectively).

Conclusions: Population PK and E-R modeling and simulation analyses enabled extrapolation of ADA efficacy from adults to adolescent HS pts in the absence of clinical trial data in the adolescent HS population. Based on the predicted ADA concentration and efficacy in adolescent HS pts, a dosing regimen of 80 mg at Week 0 and 40 mg eow is expected to provide similar ADA exposure and efficacy in adolescent HS pts to those observed in adult HS pts.

III-54: *Franziska Isabelle Kluwe* Population pharmacokinetics of unbound voriconazole following two different routes of administration during sequence therapy

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Objectives: Voriconazole (VRC), a broad-spectrum antifungal drug used to treat invasive fungal infections, shows complex pharmacokinetics and is primarily metabolised by CYP isoenzyme 2C19 [1]. The aim of the current work was to investigate the pharmacokinetics of VRC after standard sequence dosing in healthy volunteers in plasma.

Methods: A prospective, open-labelled, uncontrolled study was conducted in collaboration with the Medical University of Vienna. 10 healthy male individuals (age: 21-46 years, weight: 65-83 kg) received the standard dosing regimen for VRC of initially short-term i.v. infusions and subsequently p.o. administrations every 12 hours (2x6 mg/kg i.v., 2x4 mg/kg i.v., 3x200 mg p.o.). Intensive plasma sampling was carried out over 4 days and the unbound VRC concentrations were determined by high-performance liquid chromatography [2]. Data analysis and modelling activities were performed using R (3.3.2) and NONMEM (7.3.0) with first-order conditional estimation method and interaction option. To assess the model performance, graphical model evaluation techniques, such as goodness-of-fit plots were used.

Results: High variability in the VRC concentrations was shown and increased with the number of VRC doses administered. A two-compartment model with zero-order input (i.v) and first-order absorption (p.o) was suitable to describe the pharmacokinetics of unbound VRC in healthy volunteers. Oral bioavailability was fixed to a published value [3]. VRC clearance (CL) was estimated to be 14.4 L/h, central volume of distribution (V_c) 161.0 L, intercompartmental clearance (Q) 71.9 L/h, peripheral volume of distribution (V_p) 603.0 L and absorption rate constant (k_a) 2.21 h^{-1}. Interindividual variability implemented on CL, V_c, V_p, Q and k_a and using an exponential model was highest for CL (84.4 CV%).

Conclusions: The developed model adequately described the pharmacokinetics of unbound VRC in plasma and despite standard dosing in healthy volunteers identified substantial interindividual variability in clearance. The model performance was better for the initial i.v. phase of the sequence therapy, i.e. time- and/or concentration- and/or formulation-dependent pharmacokinetics will be further investigated. Next, a covariate analysis will be performed to identify factors (e.g. *CYP2C19* genotype) explaining the high pharmacokinetic variability.

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III-55: *Jane Knöchel* A novel measure of importance of state variables for model reduction: results for the blood coagulation network

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Objectives: An increasing understanding of complex processes in biology and pharmacology has led to large-scale mechanistic models. These models, however, are not suitable for the analysis of sparse clinical data due to parameter identifiability issues. A potential solution is to reduce the complexity of the system using model reduction techniques. While many purely computational approaches exist, a quantity that supports the model reduction process by ranking the state variables according to their importance for the systems dynamics is still lacking. The objective was to derive a novel measure of importance for the state variables with a focus on nonlinear dynamical systems.

Methods: By considering the drug or some other stimulus as a model input and the drug effect or some surrogate as the output, we rephrased the problem into a control-theoretical input-output setting. The derivation of the new measure exploited a characterisation of the system based on controllability ('How does the input affect a states?') and observability ('How does a state impact the output?'). The measure is explicitly defined with respect to a reference solution of the system and thereby dependent on the initial state. We used the blood coagulation network model [1] to illustrate our approach.

Results: Based on a generalisation of so-called empirical gramians, we derived a novel index that measures the importance of a state variable for the given input-output relationship as a function of time. A first automated model reduction technique was developed that 'removes' the time-dependence of unimportant state variables by considering them as constant (rather than lumping them). Applied to the prothrombin time (PT) test using the blood coagulation model with tissue factor (TF) concentration as input, we identified different reduced models depending on the TF concentration (high versus low). This confirmed findings from literature that based on the magnitude of the TF concentration different pathways of blood coagulation network become relevant (factor IX and VIII deficiencies cannot be diagnosed with high TF concentrations).

Conclusions: The novel measure of importance is a powerful tool for model reduction of nonlinear models that provides insight into the system dynamics.

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III-56: *Gilbert Koch* Characterization of heart rate and sleeping patterns in pre-term neonates

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Objectives: As a result of post-natal maturation sleeping patterns (SL) and circadian changes of heart rate (HR) are different in new-borns than in older children and adults. The goal of this model-based analysis was to characterize and compare SL and circadian changes of HR in pre-term neonates during their first 5 days of life.

Methods: SL and HR measurements were available from almost 100 pre-term neonates (GA < 32 weeks, birth weight < 1500 g) in their first 5 days of life. SL and HR were monitored daily during a continuous 3 hour interval. HR measurements were obtained by electromyography and sleeping behaviour was scored every 10 seconds as awake, active sleep or quiet sleep based on video recordings. For data analysis the average value from each minute interval was used. As dynamics of HR and SL followed oscillating patterns cosine functions with period length and amplitude as key parameters were applied. Non-linear mixed effect modelling was utilized to estimate individual and population behaviour.

Results: Individual SL and HR oscillations could be well described by the applied cosine functions. SL and circadian oscillations of HR in pre-term neonates had different population period lengths: 1.5 hrs and 2.5 hrs, respectively. Interestingly, HR showed a second, even faster oscillation with a period length of 15 mins, indicating that this endpoint has at least two overlying ultradian rhythms.

Conclusions: As a result of an immature "internal clock", pre-term neonates show SL and HR oscillations that are not yet completely synchronized and have shorter period lengths than those observed in older children and adults.

III-57: *Yuri Kosinsky* Radiation and anti-PD-L1 treatment combinations: Immune cell responses and dose scheduling optimization using a joint experimental and systems modeling approach

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Objectives: Investigations into the interactions between radiotherapy(RT) and the host immune system have uncovered new mechanisms that can potentially be exploited to improve the efficacy of RT [1]. RT not only exerts direct cytotoxic effects on tumor cells, but may also modulate the tumor microenvironment to facilitate a significant anti-tumor immune response. Combination therapies of radiation and mAb blockade of the immuno-suppressive programmed death-ligand 1 (PD-L1) have indeed shown synergy in a number of preclinical studies [2, 3].

Methods: Based on data from [2], we developed and independently validated a semi-mechanistic population model of anti-tumor T cell immune response development linked to CT26 tumor size dynamics in mice, under control, mono- and combination settings of RT and anti-PD-L1 treatments. Variability in individual tumor size dynamics was taken into account using a mixed effects model at the level of tumor infiltrating T effector cell influx.

Results: Upon validation, the proposed model was used successfully to reproduce anti-tumor efficacy in a broad range of therapeutically-realistic RT and anti-PD-L1 mono- and combination dosing schedules. Also the model is able to reproduce the tumor size dynamics under CD8+ cell depletion conditions, highlighting a pivotal role of T effector cells in RT-induced tumor growth inhibition.

Using such a validated QSP model, we gained a detailed quantitative understanding of the synergistic effects underlying immune cell interactions as linked to tumor size modulation, under RT and anti-PD-L1 treatments. We further show the potential in using this model as an in-silico evaluation tool to explore, prospectively, different combination dosing regimens and sequencing, in order to achieve optimal anti-tumor responses. Particularly, a single-dose RT 10 Gy scenario with concurrent anti-PD-L1 (0.2 mg 3qw) was found to be optimal for CT26 tumor bearing mice.

Conclusions: This modeling study provided quantitative mechanistic explanations of the links between RT and anti-tumor immune responses, and described how appropriate combinations and schedules of immuno-modulation and radiation may tip the immune balance in favor of host, robustly enough to lead to tumor shrinkage or rejection.

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III-58: *Pavel Kovalenko* Pharmacodynamic (PD) model of neutrophil margination to describe transient effect of sarilumab on absolute neutrophil count (ANC) in patients with rheumatoid arthritis (RA) after single-dose administration

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Objectives: To present a PD model that explains the time course of the decrease and recovery of ANC, describes potential margination of neutrophils from vascular circulation, and accounts for the rapid development of ANC-specific tolerance, after a single dose of sarilumab, a human mAb blocking the IL-6Rα that is being developed for the treatment of rheumatoid arthritis.

Methods: In a phase 1 PK/PD study, 56 patients received a dose of sarilumab 150 or 200 mg SC. Sarilumab concentration and ANC were measured until 42 days postdose. Data were analyzed using stochastic approximation expectation-maximization and importance sampling methods.

Results: The PD model for ANC value and time course that described the observed nadir and return to baseline was a margination model (MM) that also accounted for tolerance. Margination of ANC, where neutrophils are excluded from the circulation in blood (central compartment), is a plausible mechanism to describe the transient effect of IL-6 inhibitors on neutrophils without affecting their function. Tolerance accounts for an attenuation of sarilumab effect on ANC over time [1]. The tolerance is specific to ANC. The MM was represented by ANC circulating between central blood and margination compartments. A link function was imposed on the rate from the central to margination compartment. Estimated parameters included tolerance rate, 0.169 d^{-1}; EC_{50}, 6.59 mg/L; E_{max}, 4.02; and baseline rate between central and margination compartments, 6.45 d^{-1}. Observed tolerance was manifested by a nadir in ANC that precedes the maximal drug concentrations and counterclockwise hysteresis or by absence of plateau in nadir when ANC response was saturated. Accounting for tolerance led to a substantial decrease of 143.60 in objective function value. The MM is the biologically plausible model, considering the margination of neutrophils to be the underlying mechanism for the decrease in ANC observed with IL-6 inhibitors. The margination and tolerance are consistent with the absence of both impairment in neutrophil activity [2] and lack of association of decrease in ANC with increased risk of infection [3, 4].

Conclusions: A PD model that implements neutrophil margination with ANC-specific tolerance and describes the mechanism of transient decreases in ANC observed with IL-6 inhibitors was constructed. The MM describes the data well and is consistent with known neutrophil dynamics.

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III-59: *Anu Shilpa Krishnatry* Population pharmacokinetics and pharmacodynamics of GSK525762 in patients with solid tumors

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Objectives: To develop a population PK/PD model describing the PK and platelet time profile following oral dosing of a potent pan-BET inhibitor, GSK525762, in patients with solid tumors, including NUT midline carcinoma (NMC) and to use the model to predict platelet changes for other conditions.

Methods: PK and platelet data from oncology patients (N=86) receiving daily administration of GSK525762 at doses of 2 to 100 mg from a first time in patient study were included in the analysis. The data also included PK from 10 subjects who participated in a single dose cross over pilot bioavailability study followed by repeated administration. Plasma concentrations were fitted to a PK model using non-linear mixed-effects modelling implemented in NONMEM V7.2 [1]. Different models to describe the autoinduction of clearance (CL) were tested. Patient demographics, hepatic/renal function labs and cancer related covariates were tested on the PK parameters. Platelet data was modeled using a semi-mechanistic PKPD model [2].

Results: A two compartment model with first-order absorption (ka) with lag; between-subject variability on CL, central (Vc) and peripheral (Vp) volume of distribution, and Ka; inter-occasion variability on Ka and CL and proportional residual error model adequately described GSK525762 pharmacokinetics. The autoinduction effect on CL was described by an empirical model including induced / pre-induced CL, induction lag time and turnover rate of the induced enzyme (Kout) [3]. A more mechanistic enzyme model was not supported by the data. The PK parameters were Ka= 3.0 h^{-1}, lag= 0.15 h, Vc= 61.3 L, CL = 12.9 L/h, Vp = 19.0 L , Kout= 0.125 day^{-1} and Q= 1.51 L/h. Body weight was the only covariate identified and impacted Vc. GSK525762 effect on the platelet was best described with an Emax model and covariates could not be identified.

Conclusion: The PK and PD model adequately described the time-course of concentration and platelet count, including following dose adjustment, and was used to simulate alternate or reduced dosing schedules. GSK funded study.

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III-60: *Anders Kristoffersson* A Novel Mechanism-Based Pharmacokinetic-Pharmacodynamic Model Describing Ceftazidime-Avibactam (CAZ-AVI) Efficacy Against β-lactamase-Producing Klebsiella pneumoniae and Pseudomonas aeruginosa Isolates

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Objectives: To develop a mechanism based PKPD model describing the interaction between the diazabicyclootance (DBO) β-lactamase inhibitor Avibactam (AVI) and ceftazidime (CAZ) in order to enable comparative evaluation with other β-lactamase inhibitors in clinical development.

Methods: Static *in vitro* time-kill data was generated for the KPC-3 producing *Klebsiella pneumoniae* strain NCTC13438 over 24h, testing CAZ alone, AVI alone, CAZ-AVI (CAZ + 4mg/L AVI), and growth control. The CFU counts and the drug concentrations were measured over the course of the experiment. The model structure was externally evaluated using extensive literature data of three *Pseudomonas aeruginosa* strains [1]. The modelling was performed in NONMEM7.3 [2], guided by visual predictive checks (VPC) and a p-value of 0.001 for parameter inclusion. Parameter uncertainty was determined by SIR [3], as implemented in PsN [4]. Inter strain variability (ISV) for *P. aeruginosa* were added on relevant parameters and MIC values investigated as covariates.

Results: The AVI and CAZ dynamics were modelled for NCTC13438: the CFU count influenced CAZ degradation by an Emax-function, and AVI inhibition of β-lactamase activity was modelled by an Imax-function with IC50 fixed to a measured value. For *P. aeruginosa* no IC50 was available, and instead the reported half-lives of CAZ were used [1]. The bacterial dynamics were modelled with a two-state two-subpopulation model [5]. The CAZ effect was described by a sigmoidal Emax-function with the EC50 scaled by the CAZ MIC, and regrowth explained by a higher EC50 for the second subpopulation. For NCTC13438 a direct antibacterial effect of AVI was evident, and modelled by a slope function affecting the main subpopulation, and fast regrowth explained by the lack of AVI effect on the second subpopulation. In addition, as described for aztreonam [6], a potentiation of CAZ by AVI was observed and modelled by an Emax-function. For *P. aeruginosa* no direct antibacterial effect of AVI was found, however ISV on the AVI EC50 of the potentiation effect was required to fit the data adequately.

Conclusions: A novel PKPD model for the DBO- β-lactam combination CAZ-AVI was successfully developed to describe the longitudinal effect on *K. pneumonia* and *P. aeruginosa.* The model enables comparison of the effect of AVI with other DBO- β-lactam inhibitors in simulation, and may be an aid in translating PKPD results from *in vitro* to animal and human.

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III-61: *Fabiola La Gamba* A Bayesian PK/PD model for synergy; a case study

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Introduction: The co-administration of two or more treatments can alter underlying body exposure (pharmacokinetic, or PK, interaction) and/or effects (pharmacodynamics, or PD, interaction) of the individual compounds. Studies on drug-drug interactions are usually performed in an in-vitro setting [1].

Objectives: In this work, the co-administration of a novel molecule with a marketed treatment is studied through an in-vivo study, where a continuous safety biomarker under study is assessed at 4 different time points after oral administration of the two drugs.

Methods: The change over time of the biomarker is expressed through an indirect response model [2], where a virtual PK profile of the marketed treatment is assumed to drive the effect [3]. Since previous studies showed no drug-drug interaction at the PK, a pharmacodynamic interaction was assumed by expressing EC50 as a function of both treatments' doses.
Several studies at different dose level combinations were performed sequentially. A traditional analysis consists of a pooled modeling of all the data simultaneously in a frequentist fashion. Besides the frequentist model, a Bayesian framework is used in order to sequentially pool data collected in different studies. As such, modeling results from one study serves as prior distribution for the analysis of the next study.

Results and Conclusion: Both frequentist and Bayesian models showed a significant pharmacodynamic interaction. Future work will focus on improving the efficiency of the Bayesian nonlinear mixed models performance.

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III-62: *Christian Laveille* Population pharmacokinetics of Rimeporide: a sodium-hydrogen exchanger (NHE-1) inhibitor for patients with Duchenne Muscular Dystrophy (DMD)

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Objectives: To build a population model for Rimeporide based on healthy adult data in order to simulate Rimeporide concentrations in young boys suffering from DMD (6 to 14 years old). To check the adequacy of the model developed in adults with the concentrations obtained in patients in an ongoing phase Ib clinical trial.

Methods: Rimeporide plasma concentrations, after intravenous and oral administrations in adult healthy volunteers, were obtained from 6 clinical studies. After IV administration, the dose range was 25 to 350 mg while for oral administration the range was 25 to 600 mg after single dose and 50 to 200 mg tid after multiple doses. Plasma concentrations were modelled with non-linear mixed-effects approaches using NONMEM V7.3.0. Available covariates were Age, ALT, AST, Bilirubin, BMI, Body Weight, Creatinine clearance, Dose, Food, Lean Body Weight and Serum creatinine. A pilot phase Ib, open-label, ascending oral doses, trial is currently ongoing in young boys suffering from DMD. There are 4 dose levels, with 5 boys dosed by cohort: patients with body weight ≤ 30kg receive 50, 100, 150 or 200mg tid and patients with body weight > 30 kg received 75, 150, 200 or 300 mg tid.

Results: The final population model to describe Rimeporide PK in adults (156 HV for 3302 observations) was a three-compartment disposition model with a complex absorption process described by a transit compartment model and first-order elimination. The residual error model was an additive model for the log transformed data. Body weight and renal function were found to affect Rimeporide PK parameters. Pred-corr VPC were performed in order to confirm the predictive performance of the adult model. Preliminary results on the first cohorts of the paediatric trial, confirm that the exposure after body weight correction is similar to what was observed in healthy adult volunteers.

Conclusion: The PK model built on adult data from healthy volunteers described the Rimeporide data well and was successfully used to analyse the preliminary data obtained in an ongoing paediatric study. After the completion of the phase Ib study in children, the Rimeporide PK model will be refined and potential relationships between muscle damage biomarkers and PK will be investigated.

III-63: *Silvia Maria Lavezzi* Modelling of rituximab clearance reduction due to ibrutinib co-administration

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Objectives: Ibrutinib is an oral covalent inhibitor of Bruton's tyrosine kinase indicated for the treatment of patients with B cell malignancies such as chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) [1]. In a recent phase III study (HELIOS), the combination of ibrutinib with bendamustine + rituximab (BR-I) in patients with previously treated CLL or SLL resulted in significant improvements in disease outcomes compared to BR + placebo (BR) [2]. The systemic exposure of rituximab, assessed only at selected sites, was higher in the BR-I arm than in the BR arm [3]. The aim of this work was to explore this difference in rituximab exposure using a modelling approach.

Methods: Rituximab serum concentrations (1174 observations, obtained at day 1 and 15 of cycle 1, predose on day 1 of cycles 2-6 and day 1 of cycles 7-9, in the washout phase) and tumour burden (857 observations, measured as sum of the products of the largest diameters, SPD) were evaluated in 147 patients, given either ibrutinib (n=77, 612 rituximab plasma observations) or placebo (n=70, 562 observations), together with BR. Rituximab pharmacokinetics were assessed using a nonlinear mixed-effects compartmental approach. A model previously reported in the literature [4], which includes a clearance term decreasing exponentially with time, was refined through the evaluation of treatment and SPD as meaningful covariates. Model estimation and simulation were performed with NONMEM version 7.1.0, while model diagnostics and plots were obtained via R version 3.2.4.

Results: The inclusion of both the treatment arm as a categorical covariate on the decay of the time-dependent clearance term, and SPD as a continuous time-varying covariate on overall rituximab clearance (expressed as a power model normalized for baseline) significantly improved the fitting of the data.

Conclusions: A model for describing the interaction between ibrutinib and rituximab in patients enrolled in the HELIOS study was developed, including both treatment arm as a discriminating factor and a clearance term which is dependent on tumour burden. These data suggest that rituximab disposition is, at least in part, target mediated. This finding is in agreement with what was reported in a recent paper [5], in which rituximab clearance was related to CD20 antigen count at baseline. Further modelling work may be needed to have a fully mechanistic representation that further elucidates rituximab disposition.

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III-64: *Jacob Leander* Pharmacodynamic modeling of uric acid turnover and the effect of Verinurad (RDEA3170), a novel selective uric acid reabsorption inhibitor for the treatment of gout and asymptomatic hyperuricemia

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Objectives: Verinurad (RDEA3170) inhibits the uric acid transporter URAT1 that is responsible for most of the reabsorption of uric acid from the renal tubule. A pharmacokinetic-pharmacodynamic model was developed and qualified to predict dose-response of verinurad for lowering of serum uric acid both alone and in combination with the xanthine oxidase inhibitor febuxostat.

Methods: Measurements of plasma drug concentrations and uric acid concentrations in serum and urine were obtained in 513 subjects from 11 clinical studies. The clinical data included both single and multiple dose data in healthy volunteers and hyperuricemic gout patients.

An indirect response model was developed that incorporated the relevant aspects of uric acid turnover, including intestinal and renal elimination and reabsorption of uric acid [1]. The verinurad effect on renal reabsorption of uric acid and febuxostat effect on production of uric acid was described by inhibitory expressions dependent on the respective plasma drug concentrations.

The model was developed in NONMEM 7.3.0 [2], to allow estimation of individual variability in parameters of uric acid turnover and drug effects.

Results: The uric acid model describes the data well and clinically relevant serum uric acid lowering was seen for the lowest studied dose of verinurad. Moreover, the model describes the difference in uric acid turnover between healthy volunteers and patients. In patients, the estimated production rate was higher (51.5 mg/h versus 36.2 mg/h) and the estimated fractional excretion of uric acid was lower (0.049 versus 0.056).

Dose-response simulations show that for verinurad doses in the range 2.5-10 mg serum uric acid levels are reduced by 20-45% on top of febuxostat mono therapy.

Model simulations for patients with varying renal function showed that impaired renal function was associated with higher serum uric acid level and lower renal excretion rate before treatment. Moreover, simulations show that the relative decrease in serum uric acid concentration following verinurad treatment is decreased in patients with impaired renal function, which is consistent with verinurad's renal based mechanism of uric acid lowering.

Conclusions: The uric acid model enables a quantitative approach for assessing dose-response for the effect of verinurad alone and in combination with febuxostat on serum uric acid and urinary uric acid excretion rate that can support dose selection in clinical trials of verinurad.

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III-65: *Jong Bong Lee* In silico modelling of chylomicron association to predict lymphatic absorption of small molecules

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Objectives: Association of drugs with chylomicrons (CM) in the enterocytes is a key process involved in intestinal lymphatic transport of drugs. The association can be measured by means of previously established *ex vivo* assay for the prediction of lymphatic transport potentials. The aim of this study was to generate an *in silico* model for prediction of association of drugs with CM based on physicochemical properties of molecules.

Methods: *Ex vivo* data for CM association has been obtained from published articles (1-3) or obtained in our laboratory employing methods established in the literature. The modelling was performed using R software version 3.3.2 (4) with packages caret (5) and Random Forest (6). Three data sets have been compared: whole data set (55 compounds), cannabinoids and bexarotene (BEX) prodrugs, and BEX prodrugs only. For each data set, a test set of approximately 20% of compounds of the corresponding set has been defined to assess the accuracy of the models by means of 5-fold cross-validation and calculating root-mean square errors (RMSE). Influence of the descriptors was assessed by means of recursive feature elimination (RFE), which selected the features to be used by RF model, or by the Random Forest's built-in feature ranking function.

Results: Comparison of most influencing descriptors and test set RMSE for models made using RF alone or using RFE prior to RF algorithm showed that both methods perform equally well. Two new descriptors of distribution coefficient per heavy atoms count ($LogD_{7.4}$/HA) and polar surface area per molecular volume (PSA/MV) were found to be important for the models. The most influential descriptors were $LogD_{7.4}$, $LogD_{7.4}$/HA, PSA/MV, LogP-$LogD_{7.4}$ and formal charge. After excluding descriptors with little physical value, a final model was established using RF alone and using whole data set. The simulation gave 12% RMSE and r^2=0.84, for which the RMSE decreased to 10% after normalisation using the regression line.

Conclusions: A predictive model was developed ensuring high confidence in the values obtained. The model performed well for compounds representing different scaffolds. The accuracy of the model is limited by the size of the data set, the chemical space it covers and the physicochemical properties employed here. Nevertheless, our analysis highlights the importance of lipophilicity and polar interactions for the association of compounds with CM, a process that has not been described in detail yet.

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III-66: *Donghwan Lee* Population pharmacokinetic analysis of meropenem in Korean patients with acute infections

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Objectives: The aim of this study is to investigate the population pharmacokinetic (PK) profiles of meropenem in Korean patients with acute infections.

Methods: Four consecutive 500-mg or 1000-mg doses of meropenem were intravenously infused over 1 hour every 8 hour for patients with creatinine clearance of ≤ 50 ml/min or > 50 ml/min, respectively. Blood samples from 37 patients at steady-state were taken pre-dose and at 0 min, 30 min and 4-6 hours after the 4^{th} infusion. The population PK analysis was conducted using a nonlinear mixed effect modeling software, NONMEM. Covariate screening was conducted applying general additive models for PK parameters. Likelihood ratio test was used to select significant covariates, with the significance levels of $p < 0.05$ for selection and $p < 0.01$ for elimination. The final model was evaluated by the visual predictive check. The probability of patients with T>MIC (the percentage of a dosing interval during which the concentration of drug exceeds the minimal inhibitory concentration) of ≥40% was obtained applying Monte-Carlo simulation with various dose, infusion time, infusion interval and creatinine clearance.

Results: The meropenem PK was well described by a one-compartment model. The typical values (relative standard error) were 0.2657 L/h/kg (12.29%) and 0.4886 L/kg (11.01%) for weight normalized clearance and volume of distribution, respectively. The coefficient of variations of the inter-individual variability (relative standard error) for these parameters were 66.84% (14.37%) and 55.10% (15.06%). Residual variability was best explained by a poisson error model. Doripenem CL was significantly influenced by serum creatinine level (SCR), which explained 11% of the interindividual variability of clearance. The proposed equations to estimate meropenem CL in Korean patients were $CL/WT\ (L/h/kg) = 0.2657 \times WT \times [SCR / 0.74]^{-1.017}$. Most of the observed data were within the 90% prediction interval in the visual predictive check. The simulation shows that the current dosing regimen is less likely to treat patients infected with normal or augmented renal function.

Conclusions: The PK profiles of meropenem at steady-state in Korean patients with acute infections were well described by a one-compartment model. Meropenem clearance was significantly influenced by the serum creatinine level. The dose of meropenem should be adjusted according to MIC.

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III-67: *Jennifer Leohr* A Semi-Physiologic Model of Postprandial Triglyceride Response following Anti-Obesity Therapy

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Objectives: Obesity is a disorder of chronic positive energy balance, whereby excess of energy intake beyond energy utilization leads to an increase in adipose tissue. The ability of an anti-obesity agent to induce weight loss requires transport of fat from storage depots to sites of utilization. Therefore, a model of triglyceride (TG) transport would further increase understanding of the dynamics of these lipids and improve determination of drug efficacy, the selection of the appropriate dose level for future studies, as well as patient identification. The aim of this study was to quantify the postprandial TG response of chylomicrons (CHO) and large very low-density lipoprotein V6 particles (VLDL-V6) following a high fat meal, as biomarkers of drug pharmacology using a mechanistic PKPD modeling approach. LY was found to cause weight loss by reducing food intake and increasing the oxidation of TG in rodents.

Methods: Data was collected from a single-center, double-blind, randomized, placebo-controlled study evaluating the safety and tolerability of single, escalating, 7 oral doses of LY (5–130mg) in a total of 17 healthy obese subjects (BMI:27.6-37.8 kg/m). The drug exposure data and TG response following the test meal was used to develop the model. Nonlinear mixed-effect modeling was used to analyze the TG in CHO and large VLDL-V6, using NONMEM® and Perl-speaks-NONMEM as the modeling environment.

Results: The LY data was best described by a two-compartment model with first-order elimination. The values of population parameter estimates for CL, V1, Q and V2 were 73.4 L/h, 676 L, 79.6 L/h and 585 L respectively. A model describing the TG data consisted of four compartments: two transit compartments for the lag between meal consumption and appearance of TG in the blood and turn-over models for the CHO and large VLDL-V6, respectively. The rate constants for the absorption of TG (0.62 h^{-1}) and elimination of large VLDL-V6 (1.4 h^{-1}) along with the conversion rate of CHO to large VLDL-V6 (9.3 h^{-1}) were well determined. HOMA-IR was found to be a significant covariate on the conversion rate of CHO to large VLDL-V6. The drug effect of LY was found to decrease the conversion from CHO to VLDL-V6.

Conclusions: This is the first PKPD model that describes the absorption of TG from dietary fats into the blood and identifies the anti-obesity pharmacology on the dynamics of TG in CHO and large VLDL-V6 in obese subjects.

III-68: *Sarah Lezzar* Population pharmacokinetics and pharmacodynamics analysis of hydroxyurea, in adult patients with sickle cell anemia (SCA), and evaluation of disease markers

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Background. Hydroxyurea (hydroxycarbamide) (HU) is an antineoplastic agent, it was approved for indication of sickle cell anemia (SCA), and it acts in reducing the frequency of painful crises. The efficacy of HU in the treatment of SCA is generally attributed to its ability to boost the levels of fetal hemoglobin (HbF). This increasing of HbF% is followed by a decrease of rate of abnormal hemoglobin (HbS) who is responsible of the transformation of the red blood cells from a round shape to a sickle shape and to become rigid and sticky.

Objective. The aim of this study was to characterize the exposure-efficacy relationships between HU and the two disease markers: HbF% and mean corpuscular volume (MCV).

Methods. First, a population pharmacokinetic (popPK) model for HU was established in 120 patients receiving an oral dose (500 – 2000) mg of Hydrea®, once daily for 7 months. Then, the selected popPK model was used in PK-PD modelling, consisting on two independent PK-PD models respectively for HbF% and VCM. Indirect pharmacokinetic-pharmacodynamic (PK-PD) models were tested for both relations since drug impact on each marker was observed after few weeks of treatment.

Results. The popPK model was a 2-compartment parameterized in terms of CL/F, V2/F, Q, V3/F and Ka. For a 70 kg patient, CL/F was 9.87 L/h with a 32% inter- patient CV and the volume of the central compartment was 31.7 L with 80% inter-patient CV. Inter-compartment clearance (Q) was 2.29 L/h, the volume of the peripheral compartment was 73.4 L and constant of absorption Ka was 5.54 h^{-1}.

PK-PD model for HbF% was a model of stimulation of the production of the response parameterized with E_{max}, EC_{50}, k_{in} and k_{out}. E_{max} was 17.3%, EC_{50} was 22.1 mg/L, k_{in} was 0.002 HbF%/day with a 60% inter- patient CV and k_{out} was 0.00047 day^{-1}.

For MCV, the PK-PD model was described by a model of inhibition of the elimination of the response parameterized with IC_{50}, k_{in} and k_{out}. IC_{50} was 16.8 mg/L with a 71% inter- patient CV, k_{in} was 0.112 MCV (fL)/day with a 10% inter- patient CV and k_{out} 0.0013 day^{-1}.

Conclusion. The observed delay between the blood concentrations and the effect was due to the mechanism of action of hydroxyurea, which acts indirectly on the response. MCV increased more quickly than HbF% and reached a plateau after 3 months while HbF% increase was maintained even after 6 months of treatments. HbF% seems to be a better biomarker than MCV.

IV-01: *Khaled Abduljalil* Application of Physiologically-Based Pharmacokinetic model To Predict Tramadol Concentration in human Milk

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Objectives: To use a Physiologically-Based Pharmacokinetic (PBPK) model for prediction of Tramadol milk concentration in mothers with different CYP2D6 Phenotypes.

Methods: A predictive PBPK model was developed based on physiological and drug specific parameters (Fleishakeret al 1987) to predict tramadol concentration in 100 extensive metabolizers (EM CYP2D6) lactating mothers after twice daily administration of 333umol (100 mg). The compound model was developed in the Simcyp Simulator V16 and the lactation model coded using the Simcyp Lua scripting functionality. Predictions of milk concentration in other CYP2D6 phenotypes were performed and compared to EM mothers. The relative infant daily dose (RID) is calculated form the predicted milk concentration in different phenotypes.

Results: The model replicated the clinical observation adequately in EM mothers during lactation at steady state. Predicted milk-to-plasma (M/P) ratio was 1.87±0.06 (vs observed 1.9 (Salman et al., 2011)). The calculated AUC12h for tramadol in milk at steady state were 43882, 28190, and 21196 nmol/L*hr for PM, EM and UM respectively. The predicted RID (%) was 5.18±1.47, 3.98±1.19, and 3.31±1.08 for PM, EM and UM, respectively.

Conclusions: PBPK models can be used to predict M/P ratio and its inter-subject variability using the drug physicochemical properties and system (mother and lactation) parameters. While, the predicted RID for tramadol was below 10% of maternal dose, it may pose potential risk if mothers are poor metabolizers or for a given phenotype take higher doses. The PBPK model can be used to explore additional scenarios, such as DDIs, dose modification and/or incorporating metabolites data.

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IV-02: *João Abrantes* Alternative approaches to handle inter-occasion variability in therapeutic drug monitoring

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Objectives: The potential of dose individualization using therapeutic drug monitoring (TDM) is known to be challenged by high magnitudes of inter-occasion variability (IOV) [1]. This analysis aims at comparing different approaches to handle IOV in a TDM context, using a population PK model for coagulation factor VIII (FVIII) [2].

Methods: Using the data for which the original IOV model was developed, an alternative model was derived without IOV (IIV model). The IOV model was used to simulate PK parameters and steady-state FVIII activity for 1000 severe haemophilia A patients at 4, 24 and 48 h following FVIII administration (30 IU/kg) on 4 occasions (OCCs). Empirical Bayes parameter estimates (EBEs) were obtained based on the simulated data using the 2 models, varying the amount of data included (only OCC 1, OCC 1+2, etc.). From the EBEs the individual doses resulting in the FVIII activity target (0.01 IU/mL at 48 h) were calculated and used to predict the FVIII activity for the subsequent OCC using the simulated (true) parameters, thus evaluating and mimicking a real-world TDM setting. For the IOV model the individual doses were obtained based on PK parameters including IIV (IOV1) or IIV+IOV (IOV2) etas. The performance was quantified as the 2.5^{th}, 50^{th} and 97.5^{th} percentiles of the predicted 48 h FVIII activity, reflecting accuracy and precision. Estimations and simulations were conducted using NONMEM 7.3.

Results: The individual predicted doses resulted in low bias in predicted FVIII activity (median FVIII predictions for the subsequent OCC 2 to 4 were ~0.010 IU/mL). Overall, the IOV1 and IIV approaches resulted in similar and the most precise predictions. Further, the IIV and IOV1 showed improved precision with increasing amount of data available (2.5^{th} and 97.5^{th} percentiles of FVIII predictions based on 1 OCC were 0.0025-0.030 IU/mL; based on 3 OCCs 0.0028-0.024 IU/mL, respectively). In contrast, precision tended to be constant regardless of the amount of data used for the IOV2 approach (1 OCC 0.0024-0.037; 3 OCCs 0.0024-0.032 IU/mL).

Conclusions: Ignoring IOV when performing dose individualisation resulted in a less variable achievement of the FVIII activity target. However, the absolute error in achieving the target FVIII is relatively large and further methods for handling IOV in the TDM setting need exploration, for example using dynamic IOV and stochastic differential equations [3].

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IV-03: *Malidi Ahamadi* Operating Characteristics of Stepwise Covariate Selection in Pharmacometric Modeling

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Objectives: Stepwise covariate modeling (SCM) is a widely used tool in pharmacometric analyses to identify covariates that explain source of variability and improve model predictive performance. However, potential weaknesses of this approach include over-estimated covariate effect [1] and incorrect selection of covariates due to collinearity [2]. In this work we have investigated the operating characteristics of SCM in a controlled simulated setting.

Methods: Using a two-compartment model with first-order absorption, 16 scenarios were simulated based on the permutations of 4 covariates (body weight (BW) and creatinine clearance (CrCL) on apparent clearance, BW and SEX on volume of distribution). The simplest case was no covariate relationship and the most complex case was all 4 covariate relationships. For each scenario, 250 datasets were simulated with a sample size of 300 subjects and 6 observations per subject. In total 5 covariates (BW, BMI, CrCL, SEX, RACE), with high collinearity between BMI and BW, were bootstrapped from the NHANES dataset [3]. The scenarios were first assessed by re-estimating the simulated data with the respective true model and RMRSE was evaluated together with the model stability information (convergence, covariance step, etc.). Subsequently, each dataset was analysed by a full SCM procedure, as implemented in PsN and the power to select the true covariate model and RMRSE were derived.

Results: All re-estimated parameters had RMRSEs below 50% in all scenarios, confirming that the simulation design was appropriate. The SCM analysis showed a decrease in the power to detect the true covariates from 96% in the simplest scenario (no true covariates) to 25% in the most complex scenario (4 true covariates). Furthermore, BMI was frequently selected in place of BW in replicates where the true model was not recovered. The RMRSEs were below 50% for all fixed effects parameters, increased with model complexity and were slightly higher than the RMRSE obtained with a simple re-estimation as already observed in [1]. RMRSE on BSV increased with model complexity with the correlation term reaching a RMRSE of 150% in the most complex scenario.

Conclusion: Model complexity can have a great impact on the power to identify the true covariate model and on the accuracy and precision of the parameter estimates. Future research will investigate the effect of different sample sizes and observation schedules on the operating characteristics of SCM.

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IV-04: *Pascal André* Population pharmacokinetics of vancomycin delivered from active calcium sulfate bone graft substitute.

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Objectives: Resorbable bone graft substitutes such as calcium sulfate ($CaSO_4$) can be used as carrier material for local antimicrobial therapy in orthopedic surgery [1]. Vancomycin (VA) is an antibiotic of choice to treat bone infections caused by Gram-positive bacteria and offers many advantages for this type of administration. However, VA is known to induce nephrotoxicity when high blood levels (>25 mg/L) are maintained over a prolonged period (>10 days) [2]. On the other hand, subinhibitory VA plasma levels (0.4-4 mg/L) may induce the emergence of VA-resistant bacterial strains [3]. The aim of our analysis was to develop a population pharmacokinetic model of VA release in blood from active $CaSO_4$, to predict ensuing systemic VA exposure and to infer about the risks for patients to develop nephrotoxicity or carriage of VA-resistant bacteria.

Methods: A total of 651 VA plasma levels collected from 86 patients treated for bone and joint infections of various sites were available for this pharmacokinetic analysis (NONMEM®). Patients received 2 (23%), 4 (21%) or 6 g (38%) of VA added into variable quantities of $CaSO_4$ pellets. Age, body weight, sex, creatinine clearance estimated by the Cockcroft-Gault formula (CLCG) and number of days after intervention were tested as covariates. 1000 patients with various CLCG (15 to 120 mL/min) receiving 2-6 g were simulated using the final pharmacokinetic model to assess the percentage of patients at risk of nephrotoxicity and how long patients would exhibit VA concentrations in the critical interval for VA-resistant bacteria induction.

Results: A one-compartment model with first-order absorption best described VA pharmacokinetics. Average clearance (CL) was 8 L/h, volume of distribution (V) 61 L and absorption rate constant (Ka) 0.0025 h^{-1}. CLCG on CL and number of days after intervention on Ka were retained as covariates. Only 0.2% of the simulated patients maintained blood levels above 25 mg/L during 10 days under the worst conditions (6 g with CLCG of 15 mL/min). The persistence of VA plasma concentrations in the subinhibitory range was observed for an overall mean of 29 days, which reduced to 13 days in the best conditions (2 g with CLCG of 120 mL/min).

Conclusions: Clinical and microbiological follow up studies should be conducted to confirm the low nephrotoxicity risk and to evaluate the consequences on patient's bacterial flora before recommending the widespread use of VA-loaded $CaSO_4$ pellets in orthopedic surgery.

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IV-05: *Louise Andrews* New population pharmacokinetic model that predicts the individual starting dose of tacrolimus following pediatric renal transplantation

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Objectives: Multiple clinical, demographic and genetic factors affect the pharmacokinetics (PK) of tacrolimus (Tac) in children, yet in daily practice the starting dose is based solely on bodyweight. TDM limits the time a patient is exposed to concentrations outside the target range, but it can take two weeks to reach the target Tac concentration. The aim of this study was to improve the starting dose of tacrolimus after pediatric renal transplantation.

Methods: Clinical, demographic, PK and genetic data were collected for the first six weeks after renal transplantation. All children were treated with basiliximab, Tac, mycophenolic acid and glucocorticoids. Every child had at least one Tac PK profile performed over 4 h. A population PK analysis was conducted using NONMEM (version 7.2, FOCE+I). Demographic, clinical and genetic parameters were evaluated as covariates for all PK parameters containing interpatient variability (IIV). The final model was internally and externally validated using visual predictive checks. Simulations were performed to determine the ideal starting dose.

Results: 46 children with a median age of 9.1 years (range 2.4-17.9) were included. Population PK was best described by a two compartment model. The mean absorption rate was 0.56 h^{-1} (188% IIV), clearance (CL) was 50.5 L/h (25% IIV), central volume of distribution (V_d) was 206 L (69% IIV) and the peripheral V_d 1520 L (62% IIV). Inter-occasion variability was added to CL (18%) and the peripheral V_d (35%). Allometric scaling was used to adjust for differences in bodyweight. Smaller children had a higher Tac CL. CYP3A5 expressers had a 2 times higher CL. An increase in eGFR from 30 to 90 ml/min resulted in a 19% higher CL, whereas a decrease in hematocrit levels from 0.3 to 0.25 L/L corresponded with a 20% higher Tac CL. Transplantation with a kidney from a deceased donor was associated with a higher Tac CL than living donor. In total, these covariates explained 41% of the variability in CL. No co-medications or time after transplantation were associated with Tac PK. The model was externally validated using an independent dataset of 23 patients.

Conclusions: The tacrolimus weight-normalized starting dose should be higher in patients with a lower bodyweight, who express CYP3A5 and those who receive a kidney from a deceased donor. Using these parameters an individualized dosing regimen has been developed for the initial dosage.

IV-06: *Usman Arshad* Population pharmacokinetic model of mitotane enzyme autoinduction in adrenocortical carcinoma patients

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Objectives: Mitotane is the first choice drug for the treatment of adrenocortical carcinoma (ACC). It has a remarkable inter-patient variability, a narrow therapeutic range and is subject to CYP3A4 auto-induction. Although therapeutic drug monitoring (TDM) is commonly used, it remains unclear which loading dose and TDM schedule would be optimal. The objective of this study is to develop a population pharmacokinetic model of mitotane and to investigate model-based optimizations of dosing regimens and TDM schedules.

Methods: Plasma concentrations from TDM of 45 ACC patients (29 females, mean (SD) age 47 (14) years, body weight 75 (14.4) kg) receiving 0.5-10g mitotane per day were analyzed using NONMEM. A hypothetical enzyme compartment with enzyme synthesis depending on mitotane plasma concentrations was introduced to model autoinduction and a covariate model was developed to identify sources of variability. Simulations of different combinations of loading and maintenance doses were performed to identify the optimum dosing regimen.

Results: The suitable base model to describe the data was a one-compartment model with first order absorption (absorption rate constant: 2.08 h^{-1}; volume of distribution (V): 3740L; baseline clearance ($CL_{baseline}$): 0.0296 L/h). High interindividual variability (IIV) was associated with both V (105%) and the baseline clearance (88%). An indirect response model with the change in enzyme linearly related to mitotane plasma concentrations described autoinduction appropriately. A 72-fold increase in enzyme synthesis rate was estimated for the median mitotane plasma concentration of 14.6mg/L. Individual body mass index and sex were identified as statistically significant covariates and reduced the IIV for V by 34%. Similarly, 25% of IIV for $CL_{baseline}$ was explained by individual triglyceride, γ-glutamyltransferase and creatinine plasma concentrations. Preliminary simulation results suggest a high loading dose of 6g daily followed by a first TDM at day 7 to safeguard a high probability of target attainment and an appropriate adjustment of maintenance doses.

Conclusions: Our results support the clinical practice to use a high mitotane loading dose. The model facilitates the optimization of TDM and is a useful tool to establish individualized maintenance doses by forecasting individual plasma concentrations.

IV-07: *Muhammad Waqar Ashraf* A semi-mechanistic model to characterize the pharmacokinetics of orally administered S-Ketamine in healthy human subjects

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Objectives: *S*-Ketamine is a potent analgesic which can be effectively used in pain management as an adjuvant to enhance analgesia and reduce the need for opioids. The objective of this study was to develop a semi-mechanistic model to characterize the pharmacokinetics of orally administered *S*-Ketamine.

Methods: *S*-Ketamine concentration-time data was gathered from five placebo-controlled, blinded, randomized, crossover studies [1-5]. Nonlinear mixed effects modeling was performed with NONMEM software (version 7.3.0). A semi-mechanistic structural model was developed with differential equations for gut-wall, portal vein, and liver, alongside a three compartment model for describing the pharmacokinetics of *S*-Ketamine. Gut-wall clearance was modeled using Michaelis-Menten kinetics considering a limited amount of metabolizing enzymes, and hepatic clearance was specified through a well-stirred clearance model.

Results: Our results suggest that gut-wall does not play a significant role in the first pass metabolism of *S*-Ketamine contrary to the liver, which metabolizes *S*-Ketamine extensively during the first pass. The final structural model was constituted by applying only hepatic first-pass extraction. The use of an additive plus proportional residual variability model significantly reduced OFV value (?OFV=-195). Parameter estimates obtained with our final model were: Ka=8.94 hr-1, CL1=12.6 L/hr, V1=205 L, CL2=33 L/hr, V2=119 L, CL3=112 L/hr, V3=388 L (calculated as output compartment i.e. Vperiph2*Vperiph1). Our final model adequately captured the data leading to plausible values of parameter estimates, predicted concentrations and goodness of fit plots. The model was further evaluated with prediction-corrected visual predictive checks and Sampling Importance Resampling procedure [6], both of which proved the appropriateness of the final model.

Conclusions: The semi-mechanistic approach developed in the study adequately describes *S*-Ketamine pharmacokinetic data and inter-individual variability in healthy human volunteers. Our final model will be used for the optimization of *S*-Ketamine dosage regimen in acute postoperative pain management.

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IV-08: *Eduardo Asín-Prieto* An Immune quantitative network aimed for viral hepatitis B

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Background: The liver is a well-known immunotolerogenic environment characterized by absence of exacerbated immune responses, thus providing the adequate setting for liver infectious pathogens persistence such as the hepatitis B virus (HBV). A good understanding of viral dynamics and its interaction with the immune system is essential to identify key biomarkers, potential therapeutic target and predict responses to current or future therapeutic approaches. Different efforts have been undertaken to model individual aspects of the immune response and its interplay with the virus[1–3]. However, little has been done to integrate this information into multiscale QSP models. The FIRM represents an integrative effort of different sub-models in lung immunology[4]. The objective of this work is to provide a comprehensive overview and topological representation of a model able to characterize the full immune response against HBV.

Methods: A comprehensive bibliographic review in different public databases and repositories has been performed, with special focus on original studies performed in humans, to identify and characterise the main components (nodes) involved in the immune response to HBV and its viral dynamics. A topological representation of the interplay between the different identified elements has been created to describe the extracted information.

Results: An annotated repository with over 200 publications has been created. The full model has been divided into four interconnected sub-models characterising the viral dynamics, innate response and humoral and cellular responses. A total of 60 nodes, including viral components, immune cells, receptors and cytokines, in 3 different physiologic spaces (blood, lymph tissue and liver) have been identified together with their role in the system and implemented in a QSP model.

Conclusion: An immune platform beyond the FIRM[4] has been developed, which, once it has undergone model reduction, will be able to help understand, simulate and predict the response of and to different therapeutic agents against HBV. The resulting immune model can be used to (i) understand the mechanism of action of different agents and their effects (in terms of efficacy and safety), (ii) identify predictive biomarkers and/or (iii) optimise dose and dosing regimens and experimental designs of both in vitro and in vivo studies and clinical trials. Finally, the developed model has the potential to be extrapolated to other immune diseases.

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IV-09: *Geraldine Ayral* Target-mediated drug-disposition (TMDD) model comparison using the MonolixSuite

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Objectives: The increase of biologic drugs in development leads to a rise of the use of target-mediated drug disposition (TMDD) models to describe their kinetics. As the original full TMDD [1] model is often overparametrized, a number of approximations have been proposed (see [2] for a review). The workload of implementing the differential equations representing these approximations hampers the testing of a large range of approximations to find the best one. We here propose an extensive comparison and explanation of the hierarchy of TMDD model approximations, as well as guidelines to choose an appropriate model.

Methods: For the comparison, we have developed a library of TMDD models that contains 608 model files, corresponding to the combination of the following options:

- Model/approximation: full, QSS, QE, irreversible binding, constant Rtot, Wagner, MM
- Administration type: bolus, infusion, first-order absorption, zero-order absorption
- Number of compartments: 1 or 2
- Parametrization: using elimination rates or clearances
- Presence of a lag time for the absorption: yes or no
- Output considered: free ligand, free+bound ligand or custom output

A comparison in terms of response w.r.t. time of these models is proposed along with the impact of each parameter of the concentration-time curves.

Results: Using the Mlxplore application from the MonolixSuite, we explore the behavior of each model/approximation using a sensitivity analysis approach. This permits to derive a summary scheme of the behavior and limitations of each approximation compared to the full original model, thereby greatly helping in the choice of an appropriate model depending on prior knowledge and the data characteristics. Guidelines to choose a first model and improve it based on diagnostic graphics are given.

Conclusions: The availability of a large number of ready-to-use TMDD models, together with an extensive comparison of concentration-time curves, will help modelers to find the best model for their data with no implementation work, thus contributing to efficient and reliable modeling results.

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IV-10: *Hyun-moon Back* Development of a Semi-mechanistic absorption model for explaining effect of food on itraconazole

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Objectives: Oral administration of drugs has several advantages over other administration routes including lack of pain, easy to administer, portability and so on [1]. However, it has certain limitations that can potentially be affected by many factors in gastrointestinal system. Consumption of food is one of the major factors that can affect GI system and consequently absorption of drug [2]. The aim of this study was to develop a mechanistic absorption model for explaining effect of food on itraconazole by food type and volume.

Methods: Itraconazole PK data was pooled from 4 clinical studies and used for model development. The studies included in total 144 healthy Koreans and had three different food conditions (Fasting condition, Korean meal type, Western meal type). Phoenix WinNonlin (ver.7.0, Pharsight) was used for noncompartmental analysis and NONMEM (ver.7.3, ICON) was used for developing mechanistic model. Model diagnostics was assessed by goodness of fit plot and model evaluation was done using visual predictive check.

Results: Multi-compartment model with two physiological & one systemic compartments for itraconazole and four physiological compartments for food consumption (Food calorie, Food volume) was successfully developed. Bioavailability of itraconazole was increased depending on amount of drinking water (150mL, 200mL) when taking drug and also changed by food type. Gastric emptying rate of itraconazole was decreased almost 58% after food consumption. Goodness of fit and visual predictive check plot of final model was adequate and acceptable.

Conclusions: A semi-mechanistic absorption model for explaining effect of food on itraconazole was successfully developed and acceptable parameters were obtained. With this final model, quantification of food effect by food volume and type on itraconazole is possible and can extrapolate to other drug as a basis of mechanistic absorption model.

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IV-11: *Suruchi Bakshi* Systems pharmacology modelling of alternative pathway of complement activation

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Objectives: The complement system can be activated by three pathways, namely classical, alternative and lectin. The Alternative pathway (AP) of complement activation is responsible for rapid amplification of signals from all three pathways. Its dysregulation leads to autoimmune diseases such as haemolytic uremic syndrome and age-related macular degeneration [1]. AP activation involves formation of several intermediate complexes (ICs). We aim to construct a systems model of AP activation to identify suitable ICs as drug targets and to study the amplification behaviour.

Methods: We have constructed differential equation-based models of AP, which are smaller in size in contrast to previous modelling efforts [2,3], thus allowing mathematical analysis. These models are analysed using techniques from dynamical systems and sensitivity analysis combined with fitting in vitro data. We are working with experimental biologists at GSK, with the results of mathematical analysis feeding into the experimental designs and vice versa.

Results: In a minimal model of AP, we selected potential drug targets from AP ICs with hypothetical drugs. We found that target suitability strongly depends upon certain reaction rates.
Steady-state analysis of the model predicted the equilibrium levels of ICs, which disagree with experimental data, suggesting hitherto unaccounted losses in the experimental system. Further experiments are underway to detect such losses.
Quasi-steady state analysis of the minimal model has provided insights into the timescales involved in the pathway. We extended this model by adding regulators of AP and re-evaluated target-suitability. Through sensitivity analysis and data fitting we have discovered crucial parameters.

Conclusions: Systems models of AP activation have allowed us to explore drug target-suitability of AP ICs and their dependence upon crucial parameters. Modelling and steady state analysis have been vital in uncovering and quantifying discrepancies with experimental data. In the future, we expect to gain further insight into the timescales and thresholds of amplification behaviour through mathematical analysis.

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IV-12: *Pavel Balazki* Physiologically-based Pharmacokinetics/Pharmacodynamics model of Dapagliflozin, an oral SGLT2 inhibitor

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Objectives: Physiologically-based (PB) systems pharmacology models of glucose homeostasis allow insight into diseases such as type 2 diabetes mellitus (T2DM). Combined with PB pharmacokinetics (PBPK) models of anti-diabetic drugs, they allow hypothesis testing, treatment personalization, or disease-progression studies. Our objectives are: 1) to develop a PBPK model of dapagliflozin, first approved inhibitor of SGTL2 glucose transporter and 2) to couple the PBPK model with a model of glucose homeostasis based on [1] to predict the observed pharmacodynamic (PD) effects.

Methods: PK and physico-chemical parameters of dapagliflozin as well as mean concentration-time profiles were extracted from literature for model development and validation. The data include concentration profiles gathered in a 80 µg intravenous (*iv*) micro-tracer [2], oral single ascending dose (SAD) (range 2.5 – 500 mg) [3, 4], or multiple ascending dose (MAD) (14 days once daily, range 2.5 – 100 mg) [3] studies.

The PBPK model was developed with PK-Sim® and MoBi® as part of the Open Systems Pharmacology Suite (OSPS), version 7.0 [5], and coupled with a glucose-insulin homeostasis model based on [1]. The PD effect on urinary glucose excretion was evaluated by simulating the stepped hyperglycemic clamp with a single 10 mg dapagliflozin dose reported in [6].

Results: Model development and parameter identification were performed with the *iv* and 2.5, 5, and 50 mg SAD datasets. The final model includes metabolization of dapagliflozin by the enzymes CYP3A4 and UGT1A9. The drug is filtrated in the glomeruli and reabsorbed in the proximal tubuli of the kidney. Distribution in tissues is calculated by the OSPS software including P-gp transport as an active process. Along with the four datasets used for development, the model is able to reproduce observed dapagliflozin data from the 12 remaining datasets with maximal 20% AUC deviation.

Inhibition of SGLT2 is modeled as reversible binding of dapagliflozin to the transporter. With *in vitro* values for K_d = 6 nM and k_off = 0.12 1/min [6], the model successfully predicted increased urinary glucose excretion observed over a wide range of plasma glucose concentrations (5.5-30.5 mM).

Conclusions: The developed model incorporates all relevant processes involved in PK of dapagliflozin. Its mechanistic coupling with the glucose homeostasis model extends the area of application of the latter towards personalized treatment or treatment combination exploration.

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IV-13: *Violeta Balbás Martínez* Validation of a Network Systems Pharmacology model for Inflammatory Bowel

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Objectives: To validate a robust Systems Pharmacology (SP) model for Inflammatory Bowel Disease (IBD) characterizing qualitatively the main IBD components and their dynamics.

Methods: A Boolean Network model[1] for IBD, comprised mostly of immune components, was implemented in the SP package SPIDDOR[2]. Simulations of the immune response were performed assuming chronic response to three different types of gut-bacterial antigens and impairment in antigen elimination. Relative expression of nodes was calculated by obtaining the activation probability of each node after the network reached the attractor state. The network was validated as follows: (i) comparing the simulation results with the reported alterations for IBD patients for each node, and (ii) comparing simulation vs reported outcomes from clinical trials for four investigated molecules: anti-TNFα, a monoclonal antibody (mAb) approved for IBD disease, and the failed treatments anti-IFNγ, anti-IL17, or human recombinant IL10(rhuIL-10). In addition a new promising therapy, Granulocyte and Monocyte Apheresis (GMA), was tested. Reported CDAI (Crohn Disease Activity Index) was compared with the average expression of the Metalloproteinases (MMPs), our output response-related node, in the attractor state. MMPs was selected as output node because this group of proteins are directly associated to intestinal fibrosis and tissue damage in IBD and have been recently proposed as a relevant biomarker[3]. Before model validation a network perturbation analysis was performed to know the model robustness.

Results: The network perturbation analysis indicates that our SP model for IBD is robust. SP model has satisfactorily been validated with data from the literature. Additionally, the SP model for IBD replicates the outcome of the current approved anti-TNFα therapy and the promising therapy GMA with a substantial decrease in MMPs (close to 30%). For the failed treatments (anti-IL17, rhuIL-10 and anti-IFNγ) only a slight decrease (6% for anti-IL17 and 3% for rhuIL-10) and an increase (15% for anti-IFNγ) of MMPs simulated expression was obtained, which is in line with CDAI score in clinical trials.

Conclusions: The proposed SP model represents a robust modelling tool for target and therapy identification, as well as an in silico platform to test a variety of therapy combinations. The model can be used to better understand and interpret, from a most molecular point of view, clinical trials results.

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IV-14: *Guillaume Baneyx* Population pharmacokinetic modeling of pazopanib in healthy volunteers and patients with advanced renal cell carcinoma.

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Objectives: Pazopanib, a tyrosine kinase inhibitor [1], has been approved as monotherapy for patients with advanced renal cell carcinoma and advanced soft tissue sarcoma. The objective of this analysis was to update the pazopanib population PK (popPK) model by considering all available historical PK data.

Methods: A pazopanib popPK model was previously developed with a subset of historical PK data and 3 aspects had to be refined: i) dose effect on oral bioavailability was only characterized for 400 and 800 mg oral doses limiting its utility; ii) oral bioavailability was predicted higher when co-administered with acid reducing agents which is in disagreement with prior knowledge; iii) one compartment disposition model was not adequate given the bi-exponential elimination observed after intravenous infusion. The structural model, parameter estimates and covariate effects were updated by analyzing all available historical PK data including 451 subjects (healthy volunteers and cancer patients) and 4011 PK observations (rich/sparse sampling) collected after a single intravenous infusion of 5 mg (7 subjects) and daily oral doses ranging from 50 to 2000 mg. Model parameters were estimated by a nonlinear mixed effect modeling approach using Monolix 4.3.2 [2].

Results: Updated structure was a two-compartment disposition model with delayed first order absorption and first-order elimination including an oral bioavailability decreasing with dose and time. After single administration of 800 mg, absolute oral bioavailability was estimated at 30% with a clearance of 0.19 L/h and a total volume of distribution of 12.9 L. Absolute oral bioavailability was 40 % higher at 400 mg than 800 mg and 30 % lower at steady state than after single administration. After single administration of 800 mg, the food intake increased oral bioavailability and absorption rate by 2.9 fold and 62%, respectively. Co-administration with acid reducing agents decreased oral bioavailability by 12% which is compatible with prior knowledge but this effect was not retained in the final model.

Conclusions: Integration of all available PK data improved the understanding and the characterization of the non-linear pazopanib exposure explained by an oral bioavailability decreasing with dose and time. Implementation of a continuous dose effect on oral bioavailability will extend the ability of the model to simulate pazopanib exposure at any dose levels.

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IV-15: *Catalina Barceló* Modelling body mass index trajectory in HIV-infected individuals

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Objectives: Weight gain is common following antiretroviral therapy (ART) initiation, especially during the first years, and might be associated with an increased risk of diabetes and cardiovascular disease[1,2]. The aims of this study were to develop a population model characterizing body mass index (BMI) evolution before and after ART initiation, and to quantify the relative contribution of demographic and clinical factors.

Methods: We included 1303 participants of the Swiss HIV Cohort Study who initiated ART after 2005. A piecewise-linear mixed-effects model was developed based on longitudinal BMI data covering a median of 10 (range 5 to 31) years of follow-up (NONMEM 7.3). The impact of different individual characteristics (age, gender, ethnicity, CD4 nadir, smoking and physical activity habits, educational degree and diabetes and HCV diagnostic) was tested using the linearized stepwise covariate model building combined with cross-validation (PsN 4.2).

Results: Baseline BMI (BMI_0) with between-subject variability (BSV %CV) was 23.6 kg/m^2 (13.7%). The final model included a pre-ART slope (SL_0) of 0.1 kg/m^{2}year (275%), a first post-ART slope for the first 2.5 years (SL_1) of 0.2 kg/m^{2}year (316%), and a second post-ART slope (SL_2) of 0.1 kg/m^{2}year (304%). A proportional error model with autocorrelation was used to describe residual variability. BMI_0 was higher by 6% in Africans and 16% in diabetics, increasing by 0.03 kg/m^2 per 10 additional years, while Asians had 9% lower BMI_0. CD4 nadir <100 cells/µL decreased SL_0, resulting in weight loss or stability, while a nadir <200 cells/µL increased SL_1 by 1-fold. SL_1 was zero in Hispanics and 84% higher in Africans compared to other ethnicities. HCV co-infection decreased SL_2 by 74%.

Conclusions: Individual factors such as CD4 nadir and ethnicity have an important effect on weight gain following ART initiation. After a relatively steep slope during the first 2.5 years of ART, weight gain returns to an average level comparable with the general population, being lessened by HCV co-infection[3]. Such a model, further refined according to genetic markers and type of ART regimens, might inform metabolic risk factor management in the HIV-infected population.

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IV-16: *Carla Bastida Fernández* Population pharmacokinetic model for intravenous tocilizumab in rheumatoid arthritis

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Objectives: To develop a population pharmacokinetic (PK) model to describe the PK characteristics of intravenous (iv) tocilizumab (TCZ), estimate interindividual variability (IIV) and assess the influence of different covariates.

Methods: PK and clinical data were obtained from a prospective, observational, single-center study involving 35 subjects with rheumatoid arthritis (RA) treated with iv TCZ at a dose range from 8 to 4 mg/kg every 28 days. Samples were collected before TCZ administration and, when possible, once a week until the next administration. A PK model was developed using non-linear mixed-effects modeling implemented in NONMEM v7.3. Internal evaluation was assessed by visual predictive checks (VPC) and bootstrap resampling technique (with replacement).

Results: A total of 109 TCZ serum concentrations were adequately described by a one-compartment disposition model with parallel first-order (linear) and Michaelis-Menten (nonlinear) elimination kinetics. IIV was incorporated on clearance (CL) and volume of distribution (V) parameters. Residual variability was characterized by a combined error model with an additive part of 0.165 µg/mL (SD) and a proportional part of 24.2% (CV). Weight and C-reactive protein (CRP) levels (inflammatory biomarker) significantly affected CL. An increase in weight from 40 to 110 kg led to a 34% increase in CL and an increase of CRP levels from 0.01 to 20 mg/dL led to a 122% increase in CL. The VPC indicated adequate goodness-of-fit and the bootstrap 95% CIs demonstrated satisfactory precision.

Conclusions: A population PK model was developed to describe the PK of iv TCZ in RA patients. Drug disposition was significantly affected by weight and an inflammatory biomarker.

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IV-17: *Brendan Bender* A Mechanism-Based Model of Tumor Quiescence and Resistance in HER2-Negative Metastatic Breast Cancer in Patients Receiving Docetaxel or Paclitaxel

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Objectives: In patients receiving docetaxel or paclitaxel, patient tumor responses exhibited variable patterns of shrinkage and quiescence, followed by drug–resistant tumor regrowth. A pharmacometric analysis was used to characterize these tumor response patterns and evaluate patient characteristics and tumor model metrics as predictors for overall survival (OS).

Methods: Tumor responses were evaluated from HER2–negative metastatic breast cancer patients receiving either docetaxel (N=185) or paclitaxel (N=242). A population kinetic/pharmacodynamic (K/PD) model was fit to tumor sum of longest diameter (SLD)–time course data. The baseline tumor size (TBSL) was parameterized as composed of a drug resistant (FNR) and drug sensitive (1-FNR) fraction. The development of drug–resistant tumor was modeled using transit compartments, and a mixture model implementation on the transit rate parameter (k_{delay}) was used to capture the rapid or delayed tumor resistance. Two tumor growth rates ($k_{Grow,Sens}$ and $k_{Grow,Resist}$) described tumor growth rates for the drug–sensitive and drug–resistant tumor compartments, respectively. Patient baseline characteristics (Age, ECOG, TBSL), model parameters, and tumor metrics (tumor size ratio (TSR) at week 6; time to tumor growth (TTG)) were evaluated as predictors for OS in a parametric time–to–event (TTE) analysis. NONMEM 7.3.0 software was used for model development.

Results: The model well–described the variable patterns of longitudinal tumor data, and model fits indicated superior results when compared to the tumor growth inhibition (TGI) model (1). The typical docetaxel patient had a TBSL equal to 70mm, consisting of ~35mm drug–sensitive and ~35mm of drug–resistant tumor SLD. The k_{Delay} parameter was bimodal, and patients had a 37% probability to develop resistance during the treatment period. For these patients, the drug–resistant tumor doubling time was calculated to be 5.8 weeks. Model results for patients receiving paclitaxel were similar. TTG and TBSL were significant predictors of survival for both docetaxel and paclitaxel treatment.

Conclusions: This tumor K/PD model successfully integrates tumor kill, tumor quiescence, and tumor drug–resistance as linked to taxane drug exposure, providing an additional modeling approach to characterize tumor response data. An increased tumor baseline–reflective of higher tumor burden, and a shorter TTG–reflective of treatment efficacy, was associated with poorer survival prognosis. In cases of tumor quiescence followed by resistance, the model provided better fits than the TGI model.

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IV-18: *Sophie Berends* A Target-Mediated Drug Disposition model for infliximab in patients with Ulcerative Colitis

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Objectives: Ulcerative Colitis (UC) is an inflammatory bowel disease (IBD) affecting the colon and rectum of the gastrointestinal tract. Infliximab (IFX) is an intravenously administered monoclonal antibody (mAb) directed against the pro-inflammatory cytokine tumor necrosis factor (TNF). The mechanism of clearance of mAbs is not exactly known, but the primary route is via proteolytic catabolism after receptor-mediated endocytosis in the cells of the reticuloendothelial system[1–3]. Target-mediated drug disposition (TMDD) is reported for mAbs meaning that the pharmacokinetics of mAbs are affected because of their high target affinity[4,5]. The objective of this study is to characterize the pharmacokinetics of IFX in patients with UC.

Methods: Twenty anti-TNF naive patients with UC were included in this prospective cohort study and received IFX at a dose of 5 mg/kg at week 0, followed by infusions (5 mg/kg) at week 2 and 6, according to standard guidelines. IFX, antibodies-to-IFX (ATIs) and TNF serum concentrations were measured at day 0 (1hr after the end of the first infusion), 1, 4, 7, 11,14, 18, 21, 28 and 42. Data were analysed with the use of NONMEM using First-Order Conditional Estimation with Interaction (FOCE+I). Concentration-time profiles of TNF were first described using a binding model. Next, a TMDD was developed to describe the target-dependent pharmacokinetics of IFX.

Results: A two-compartment model best described the concentration-time profiles of IFX in this study population. Mean values (plus interindividual variability) for CL, Q and Vc, Vp were 0.396 L/day (29.6%), 0.344 L/day and 3.2 L (21.4%) and 1.81 L (59.7%), respectively. As a binary covariate the formation of ATIs increased clearance 2.3-fold. Patients with low albumin serum concentrations exhibited higher clearance. The binding model described the concentration-time profiles of TNF. Estimates for BMAX and KD were 3.89 pg/ml and 18.2, respectively. Estimated TMDD parameters of the preliminary TMDD model were within the expected range.

Conclusions: The formation of ATIs and low serum albumin levels increased clearance. With the binding model, the concentration-time profile of TNF could be described. A preliminary TMDD model was developed to describe the target-dependent pharmacokinetics of IFX.

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IV-19: *Aliénor Bergès* Dose-exposure-response model between an ATR inhibitor and peripheral monocytes

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Introduction: AZD6738 is a potent, selective inhibitor of the ATR protein kinase, currently being tested in patients with solid malignancies. Thrombocytopenia is one of the main dose-limiting toxicity [1]. In order to support dose and schedule selection, we utilised emerging phase I data and modelled the relationship between dose, plasma exposure and peripheral blood cell counts.

Methods: We assessed blood cell counts (neutrophils, platelets, erythrocytes monocytes or lymphocytes) from patients of AZD6738 dosed alone (continuous doses from 40 to 480mg), or in combination with the PARP-1 inhibitor, olaparib 300mg bd, or the PD-L1 inhibitor, durvalumab 1500mg Q4W (intermittent doses up to 320mg). Individual time profiles were plotted to show any trend during AZD6738 treatment and exposure-PD correlation plots were generated using specific PK parameters and change from baseline in cell counts. The correlation plots were compared across blood cells and the differential effect of AZD6738 between two cells of interest was modelled.

Results: Monocytes were found to be the most sensitive cells, with a decrease up to 80% from the 160mg dose. This decrease was not observed with either single agent olaparib or durvalumab. Upon cessation of dosing, monocyte levels return to baseline values within 14 days. A decrease in the other blood cells counts was noticed at 480mg and to a lesser extent. These results were consistent across studies.
An E_{max} model characterised well the correlation between the decreases of monocyte over platelets as a function of AZD6738 C_{max} values, and predicted a response plateau at 13ug/mL. Beyond this value (reached between 320-480mg), the gain of monocyte decrease (considered as target exposure), versus safety was considered minimal.

Conclusion: This analyses allowed predicting AZD6738 dose with the maximum cell type-specific differential effects during the study. This modelling and process is expected to be refined on a regular basis, with the integration of further trial data.

Reference:
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IV-20: *Julie Bertrand* Joint pharmacogenetic model of tenofovir and emtricitabine and their active intracellular metabolites in HIV Patients

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Context: According to the 2016 NIH guidelines, tenofovir (TFV) and emtricitabine (FTC) are part of the recommended antiretroviral therapy (ART) regimen for naïve HIV patients and since 2012, the WHO recommends offering oral PrEP containing TFV. Several pharmacokinetic (PK) and some PK/pharmacodynamic models have been proposed for both molecules leading to identification of target concentrations for their active intracellular metabolites (TFV-DP and FTC-TP, respectively) [1, 2]. However the large inter-individual variability in TFV, TFV-DP, FTC and FTC-TP PK parameters is so far unexplained.

Objectives: To perform a joint population pharmacogenetic analysis of TFV, TFV-DP, FTC and FTC-TP concentrations and genetic variants collected in the ANRS 134 COPHAR3 trial.

Methods: The trial included 35 HIV naïve patients on an atazanavir/ritonavir/TFV/FTC treatment in MEMS-capped bottles. Plasma TFV and FTC concentrations were measured at W4 (pre and 1, 2, 3, 4, and 8 h after the dose) and at W24 (trough) with trough intracellular TFV-DP and FTC-DP on both occasions. In addition to classic demographic and biologic covariates, three genetic polymorphisms were studied: MRP2 (rs717620), MRP4 (rs1751034), and MDR1 (rs1045642).

Results: A six compartments joint model was selected to describe the PK of the four compounds with common absorption mean transit time (M_{TT}) and scale factor capturing correlations between apparent clearances and volumes. Plasma TFV and FTC diffuse each in two compartments and enter linearly into cell compartments to become TFV-DP and FTC-TP.
The final model fitted the data satisfactorily and contained an effect of age, MRP2 and MDR1 on M_{TT}, creatinine clearance on both compounds clearances (CL_{TFV}/F and CL_{FTC}/F) and MRP2 on CL_{TFV}.
TFDV and FTC $t_{1/2}$ estimates were within the range of published values [1] but TFV-DP and FTC-TP estimates were twice as long. Consequently predicted average concentration for TFV-DP and FTC-TP at W4 were $C_{av,TFV\text{-}DP}$=137 fmol/10^6 cells and $C_{av,FTC\text{-}TP}$=8.4 pmol/10^6 cells, both consistent with literature values [1], but below their respective EC_{50} for competition with the HIV reverse transcriptase natural substrates [1]. $C_{av,TFV\text{-}DP}$ was however above the EC_{50} for preventing cell infection [2].

Conclusions: Covariates on M_{TT} had little impact, but patients with the lowest creatinine clearance and heterozygotes for MRP2 rs717620 had 86% and 39% higher $C_{av,TFV\text{-}DP}$ and $C_{av,FTC\text{-}TP}$, respectively.

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IV-21: *Souvik Bhattacharya* Longitudinal Parkinson's Disease Progression Model using Item-Response-Theory Utilized to Predict Treatment Effect of Levodopa

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Objectives: To evaluate and understand the natural history of early and long-term disease progression in Parkinson's Disease (PD) and to predict the effect of Levodopa treatment of the longitudinal change of item-level data from the Unified Parkinson Disease Rating Scale (UPDRS) using Item-Response-Theory (IRT).

Methods: Item-level UPDRS data from 1990 subjects, from five different National Institute of Neurological Disorders and Stroke (NINDS) trials, early and advanced stages of PD, was used to develop a Bayesian longitudinal IRT model with uninformative prior. The model was developed in R 3.2.3 to predict the patient specific latent traits of 44 individual subscores of the UPDRS at each study visit and estimate the change and severity of each subscore over time for placebo and treatment (levodopa) effect. An initial Bootstrap clustering was implemented on the UPDRS subscores in order to obtain a hierarchical structure identifying the most sensitive subscore and to determine the pattern of linkage between the UPDRS subscores. Prediction of subscores were implemented using a logistic regression algorithm ("nnet" package) in R. A time-varying function (including inter-individual variability) was developed to study the longitudinal trajectory for the placebo and treatment effects ("brms" package in R) based on the latent score of the most sensitive subscore. External model evaluation using data from two NINDS trials was performed over continuous (Visual Predictive Check) and at discrete (Boxplot) times.

Results: Bootstrap clustering identified "Rapid/Alter Movements (RAM)" and "Hand Movements (HM)" to be the most influential and predictive subscores within the UPDRS, hence the estimated combined population mean latent score of RAM & HM (LS=0.5792+random|ID) were used to predict subscores higher in hierarchy over time. Including an additional dose dependent function into the combined IRT logistic regression placebo model describing the treatment effect allowed for adequate predictions of the change and severity for each subscore within the UPDRS over time. External model evaluation showed good agreement with the observed subscores for both continuous and discrete times.

Conclusions: A Bayesian longitudinal IRT regression model was successfully developed to predict the overall disease progression and the levodopa treatment effect in PD based on early disease progression information. The developed longitudinal IRT model is embedded in a Shiny application.

IV-22: *Bruno Bieth* Use of population PK/PD modeling to support the regulatory approval of canakinumab as first biologic treatment in patients with periodic fever syndromes

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Objectives: Periodic Fever Syndromes is a group of rare orphan diseases classified together under a single term and classically consists of 4 separate conditions: Cryopyrin Associated Periodic Syndrome (CAPS), colchicine resistant Familial Mediterranean Fever (crFMF), Hyper-immunoglobulin D (hyper-IgD) Syndrome/ Mevalonate Kinase Deficiency (HIDS/MKD) and TNF receptor Associated Periodic Syndrome (TRAPS).

Canakinumab (ACZ885) is a high-affinity fully human monoclonal anti-human interleukin-1β (IL-1β) antibody. IL-1β is recognized as one of the principal proinflammatory cytokines, in a variety of inflammatory conditions [1], [2]. As a potent neutralizer of IL-1β, it is expected to treat the underlying structural features of arthritis (inflammation, bone and cartilage degradation). Canakinumab was previously approved in CAPS, and had been shown to be effective in isolated case reports and preliminary studies regarding the other Periodic Fevers Syndromes.

The objective of the PK/PD analysis was to support the recommended dosing regimen in the 3 remaining PFS conditions.

Methods: PK and efficacy/safety data were obtained from a phase III double-blind, placebo controlled umbrella study in PFS patients with subcutaneous administration of canakinumab every 4 weeks (up-titration in case of lack or incomplete response to the initial dosing regimen). PK data from another proof-of-concept study and from other phase III studies in CAPS were also included.

Population PK/PD modeling including one-compartment PK model and PK/PD model for the probability of flare (primary efficacy endpoint) were developed to explore the exposure response relationship for selected efficacy and safety outcomes.

Results: The pharmacokinetics of canakinumab in PFS was consistent with other indications (e.g. CAPS). The treatment was associated with decreased levels of acute phase proteins (CRP and SAA) and improved Physician Global Assessment, which are key components of flare (primary efficacy endpoint). The exposure-response modeling for the probability of flare suggested a difference in drug sensitivity across disease conditions. HIDS/MKD and TRAPS patients tended to have higher IL-1β levels and require higher doses to prevent flares.

Conclusions: The population PK knowledge from previous indications could be leveraged in the new PFS disease conditions. Analyses supported the up-titration dosing scheme in case of new flare, especially in patients with HIDS/MKD and TRAPS. This work supported the simultaneous approval of canakinumab in 3 PFS conditions.

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IV-23: *Roberto Bizzotto* A model of insulin kinetics describing tests with various insulin secretion and infusion patterns by means of a consistent mechanism

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Objectives: Insulin kinetics is an essential component of glucose homeostasis. Due to system complexity and limited data availability, models of this process have typically been linear, in contrast to physiological evidence [1]. In this work, we overcome this limitation developing a nonlinear model that describes a variety of tests with a wide insulin span produced by glucose-stimulated insulin secretion (IS) and insulin infusion.

Methods: Data included: A) tests stimulating IS by different patterns and levels of glucose infusion (6 different studies [2-7], N=204); B) one- or two-step hyperinsulinemic euglycemic clamps with different insulin infusions (4 protocols in 3 studies [8-10], N=150). Subjects had normal, impaired or diabetic glucose tolerance. A circulatory model [11] of insulin kinetics was developed including heart and lungs, gut, liver, and extra-hepatic organs. Insulin clearance (IC) in the liver was described using a saturable function. In studies A, IS was separately computed by deconvolution of plasma C-peptide; in studies B, IS was estimated by simultaneously fitting plasma C-peptide concentrations, using Van Cauter's model of C-peptide clearance [12]. Parameters were estimated by mixed-effect modeling using Monolix 4.3.2.

Results: In all studies, the model predicted insulin concentration adequately; the parameters were homogeneous across the studies. The typical endogenous IC computed at IS of 100 and 400 pmol/min/m^2 (representing basal and glucose-stimulated IS) was 1.46 and 1.16 L/min/m^2, respectively. The 4-fold increase in IS produced a 5-fold increase in insulin concentration; the deviation compared to linear kinetics would be 70 pmol/L. For endogenous IC at standardized IS of 100 and 400 pmol/min/m^2, significant relationships were found with body mass index (inverse) and insulin sensitivity (direct).

Conclusions: We have developed a unifying mechanistic model describing insulin kinetics in a variety of tests in which a wide range of insulin levels were produced by glucose-stimulated IS and insulin infusion. Using the model, we could calculate IC at standardized insulin secretion levels and determine that the relationships of IC with adiposity and insulin sensitivity were primary and not consequent to an indirect effect of hypersecretion-induced IC saturation. Prediction of the effects of drugs enhancing IS or of subcutaneous insulin infusion may benefit from the use of this new model in the glucose homeostasis representation.

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IV-24: *Agnieszka Borsuk-De Moor* Tigecycline population pharmacokinetics in patients with severe sepsis or septic shock resulting from abdominal surgery

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Objectives: Tigecycline is the first glycylcycline antimicrobial drug approved in Europe for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections at 100 mg initial dose followed by 50 mg every 12 h [1]. However, it has been reported that higher dose regimens of tigecycline may be more effective than recommended dosing [2]. In this study a higher dose of tigecycline was administered to adult patients with severe sepsis or septic shock resulting from abdominal surgery. The objectives of the study were to develop a tigecycline population pharmacokinetic model and assess the relationship between patient covariates and individual PK parameters.

Methods: The analyzed population included 37 patients aged 25-79 years old treated in Intensive Care Unit. Each patient received initial dose of 200 mg of tigecycline in a short 30 min infusion, followed by multiple doses of 100 mg in 30 min infusion every 12 h. The covariates recorded for each patient included time-independent covariates: age, weight, height, death, sex, the use of extracorporeal membrane oxygenation, the use of continuous renal replacement therapy and the time-dependent covariates: dialysis volume, ultrafiltration speed, extravascular lung water index, cardiac output, sequential organ failure assessment score and procalcitonin concentration. Population nonlinear mixed effects modeling was conducted using NONMEM software.

Results: Tygecycline pharmacokinetics was described by a two-compartment disposition model. The population model included inter-individual variability in CL, V1 and V terms and inter-occasion variability in individual CL and V2 parameter values. The typical values of elimination and inter-compartmental clearance were 22.1 L/h and 69.4 L/h; the typical values of volume of central and peripheral compartment were 162 L and 87.9 L. The inter-individual variability was intermediate for CL (17.3%) and V1 (19.2%) and higher for V2 (38.7%). The inter-occasion variability for CL and VT was 14.4% and 20.8%, respectively.

Conclusions: The population PK model was successfully developed to describe the time course of tigecycline concentrations in the analyzed population. None of the available covariates was found to explain part of the inter-individual or inter-occasion variability in the pharmacokinetic parameters. The model can be useful for further analysis of tigecycline exposure-response relationships.

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IV-25: *Thomas Bouillon* Efficient identification of the optimal dosing regimen with a nonparametric method

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Objectives: To propose a method for efficient identification of a covariate adjusted dosing regimen in "open loop" situations using a nonparametric algorithm.

Methods: Data from 70 adult patients (CYP3A5.0: n=55; CYP3A5.1: n=15) receiving tacrolimus at steady state was used for demonstration. All patients underwent therapeutic drug monitoring (TDM). 1. Standard PK parameter estimation was done with Pmetrics (NPAG)[1]. 2. Probability weighted support points from this analysis were implemented as covariates in a new dataset, “actual” covariates (age, weight, CYP3A5, day after transplantation, hct), a unit dose and a PK target (Cmin,ss 8mcg/L (median in the study population)) were added for every patient. 3. Using bioavailability as "surrogate parameter", the best dose for target attainment (TA) was estimated. 4. Bayesian estimates (EBE) of the individual doses were used for covariate identification. 5. Selected covariates were implemented into the model and the difference in -2log likelihood evaluated. 6. Candidate dosing regimens and their TAs were displayed as empirical cumulative distribution functions (ecdf’s).

Results: A 2 compartment model with first order input adequately described the PK of tacrolimus. Although this type of model can be solved analytically for the optimal dose, the "dose estimation" approach was favored in order to demonstrate applicability to more complex systems. As expected, the ecdf of the EBEs of dose was virtually identical to that of the support points, justifying the use of nonparametric EBEs vs. covariate plots. CYP3A5 expression was the only covariate identified and decreased -2LL by 50. Weight based dosing was deliberately added to demonstrate the (lack of) effect of a naively complex dosing regimen. Rounded Dose(s) were 2-13 mg/d (Q5-Q95) for TDM based, 5 and 9 mg/d (95% CI: 4.3-6.1; 8.0-11.2 mg/d) for CYP3A5 based, 3.5-11 mg/d (Q5-Q95) for CYP3A5+weight based and 5 mg/d (95% CI: 4.7-6.8 mg/d) for unique dose. TDM based dosing achieved Cmin,ss concentrations between 5-11 mcg/L in 95% of the investigated patient population. The respective values for CYP3A5 based, CYP3A5+weight based and unique dose are 65%, 65% and 50%. CYP3A5 is relevant for TA of tacrolimus, but not sufficient to replace TDM adjusted dosing.

Conclusions: The proposed method correctly represents dose as a parameter to be optimized. Covariates are implemented directly on the relevant dose and their effect(s) regarding target attainment assessed.

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IV-26: *Ari Brekkan Viggosson* Parameter Estimation in Bivariate Mixed Hidden Markov Models

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Objectives: Observable stochastic processes may depend on underlying hidden processes that can be modelled with mixed hidden Markov models (MHMMSs), allowing for inferences about the hidden state of individuals at any time-point given a set of observations (1), and can be implements in NONMEM (NM), as described by Plan et al. (2). Here we aim to i) extend the work in (2) by developing a bivariate MHMM (BV-MHMM) and ii) explore parameter estimation in a BV-MHMM in terms of accurat and precision.

Methods: A novel 2-state BV-MHMM with simultaneous calculation of the likelihood for 2 variables was developed based on (2). Of the potentially correlated continuous variables (through parameter ρ), one was more variable than the other and subject to time decay. An IIV term (ω12) and a drug effect (DE) were introduced on 1 of the 2 transition probability parameters. A simulation study with ρ set to either 0 or 0.33 and different combinations of ω12 and DE was set up, generating data for 500 individuals, each with 60 observations per variable. Stochastic simulations and estimations (n=100) were used to determine the bias and imprecision of parameters. Estimation was done in NM with SAEM/IMP and mu-parameterization.

Results: : Data simulated with correlation (ρ=0.33) and fitted without (ρ fixed to 0) yielded imprecise and biased estimates for all parameters (average absolute bias [AB] and average root mean squared error [RMSE] increased by 2881% and 16%, respectively, compared to when ρ is estimated), including DE (AB and RMSE increase of 138% and 12%, respectively) and ω 12 (largely unaffected). Further, the objective function value (OFV) increased by an average of 3197 points. Simulating without correlation (ρ=0) but estimating it resulted in estimates of ρ that were close to 0, but OFV increased by an average of 66 points, but fell within the 90% confidence interval of the OFV from runs with ρ fixed to 0. This was not translated into a meaningful increase in average AB (14% decrease) or average RMSE (1% increase) of all parameters.

Conclusions: A BV-MHMM capable of describing the relationship between 2 hidden states and 2 observed continuous variables was developed. The model was able to estimate correlations between the variables. When the correlation was not considered although it was present, parameter estimation was biased and imprecise and goodness-of-fit markedly impacted.

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IV-27: *Jantine Brussee* Distinguishing between first-pass and systemic CYP3A-mediated metabolism of midazolam in preterm neonates using physiologically-based pharmacokinetic modelling

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Objectives: Most pharmacokinetic (PK) models do not discriminate between presystemic (intestinal and first-pass hepatic) and systemic (hepatic) CYP3A-mediated metabolism of midazolam, and can therefore not describe the presystemic formation of the primary metabolite 1-OH-midazolam. Our aim is to describe first-pass and systemic clearance of midazolam in preterm neonates using a physiologically-based PK modelling approach.

Methods: Plasma concentrations of midazolam and 1-OH-midazolam from 37 preterm neonates (postnatal age 3-46 days, body weight 0.77-2.0 kg), enrolled in a cross-over PK study, were used in this analysis [1,2]. The neonates were randomized to receive midazolam orally (n=13) or via a half-hour infusion (n=24), and an additional dose via the alternate route after >72 hours, if they still met the inclusion criteria (n=6 and n=7, respectively). A physiologically-based PK model [3,4,5] using NONMEM 7.3 was applied to describe the data, in which intrinsic clearances and distribution volumes were estimated. This model includes physiological compartments representing the gut wall, the portal vein and the liver. Tissue volumes and hepatic blood flow in preterm neonates were allometrically scaled from literature values of a term neonate [6]. The well-stirred model described hepatic clearance and the 'Q_{gut}' model [7] was used to describe intestinal clearance. To describe the observed multiple peaks after a single oral or IV administration, several physiological and empirical redistribution mechanisms were tested. The model was evaluated using bootstrap and VPC.

Results: The physiologically-based PK model described midazolam and 1-OH-midazolam concentrations both and intravenous and oral doses well, except for the redistribution peaks. Intrinsic hepatic blood clearance (CL_h) values were >80 times larger than intestinal blood clearance (CL_g) values (4.9 L/h and 0.058 L/h respectively). Total plasma clearance was 0.195 L/h (with an estimated inter-individual variability (IIV) of 69.7%) and volume of distribution was 1.55 L (IIV 94.0%).

Conclusions: The physiological PK model could distinguish between first-pass and systemic metabolism of midazolam in preterm neonates allowing to provide additional insight in (different) maturation profiles of intestinal and hepatic CYP3A-mediated metabolism in children. The multiple peaks after a single oral or IV dose could not be described accurately by any of the evaluated redistribution models and need further research.

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IV-28: *Núria Buil Bruna* Predicting myelosuppression from phase I data: Which model should we use?

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Objectives: Ever since the semi-mechanistic model to describe drug-induced myelosuppression was published by Friberg et al. [1] (M1), several generalisations have been developed. For example, Mangas-Sanjuan et al. [2], incorporated cell cycle dynamics to improve the model's ability to predict toxicity under alternative schedules (M2), Bender et al. [3], incorporated an additional cell kill effect to describe the downward drift in cell-count profiles seen in some patients (M3), and Quartino et al. [4], improved the model's ability to accurately describe nadir cell counts (M4). Here we aim to assess these models for their ability to predict tolerable dose and schedules based on early phase I data.

Methods: A simulation and estimation procedure was performed. PK data was generated for a hypothetical small molecule. For each extended model scenario, potency parameters were scaled to ensure the 4th dose escalation predicted 33% grade 3/4 (G3/4) events. Each model was used to simulate 300 small datasets mimicking cycle 1 (21 days) of a phase I dose escalation study (weekly schedule: 3 days on/4 days off). Datasets were reestimated with all four models which were then used to simulate long-term toxicity (up to 8 cycles, 189 days) of a large population receiving different drug schedules (continuous and a variety of intermittent schedules). Bias (mean error, ME) was obtained by comparing incidence of G3/4 events to the true simulation model.

Results: All models successfully converged when reestimating their training datasets. M3 had more difficulties in numerical estimation across all scenarios (average successful rate 78.5% compared to 100% of other models). This is probably due to cycle 1 data being insufficient to estimate cumulative toxicity.

Assuming M4's scenario represents realistic nadirs, all models performed broadly similarly on estimating cycle 1 nadirs. The greatest bias was seen in M1 (ME M1= -8.7%, M2=-5.4%, M3=+1.8% points), which underpredicted %G3/4.

Assuming M2's scenario represent a realistic depiction of the impact of different schedules on toxicity, all models performed similarly with an average ME between 5% and 7% points.

Assuming M3's scenario represents a realistic long-term cumulative toxicity scenario, all models underpredicted %G3/4 after 8 cycles (M1 ME=-18.7%, M2 ME = -12.7%, M3 ME = -8.9% points).

Conclusions: All three extended models have advantages over the original Friberg model. Choice of extended model in a phase I setting depends primarily on whether cumulative toxicity is observed/expected.

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IV-29: *Charles Burdet* Joint modeling of moxifloxacin pharmacokinetics and fecal microbiota disruption in healthy volunteers

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Objectives: Metagenomic analysis provides a detailed picture of the intestinal microbiota. Among the various factors that shape the microbiota, antibiotic administration has a major impact in disrupting its composition [1]. Animal data suggest that the impact of antimicrobials can be predicted from fecal antibiotic exposure [2]. We developed a joint model of plasma and fecal pharmacokinetics (PK) of moxifloxacin (MOX), a fluoroquinolone antibiotic, after oral administration in humans, and of MOX effect on bacterial richness observed within the intestinal microbiota.

Methods: Twenty two healthy volunteers were included in a randomized clinical trial (sponsor Da Volterra) among which 14 received MOX (400 mg orally OAD) from D1 to D5. MOX plasma concentrations were assayed at D1 and D5. Fecal samples were obtained before treatment and up to D37 for measurements of free MOX concentrations and microbiota analysis by 16S rRNA gene profiling. Bacterial richness was evaluated using the number of operational taxonomic units (OTUs). Nonlinear mixed-effects modeling was used to analyze the plasma PK of MOX and its fecal excretion, and to evaluate the effect of fecal concentration on bacterial richness. Analysis was performed using the SAEM algorithm in the Monolix software (Lixoft, France) [3]. Model selection was performed by visual inspection of goodness of fit plots and the Bayesian Information Criteria.

Results: MOX plasma concentrations were best described by a 2-compartments model with transit compartments for absorption and linear elimination. Fecal concentrations were modeled using a transit compartment between plasma and feces, with reabsorption from the fecal compartment to the central compartment. The effect of MOX on the number of OTUs was best described by a turn-over model, with an Emax model where fecal MOX concentration increased the loss rate. Goodness-of-fit of this model was satisfactory.

Conclusions: We developed the first joint model of the co-evolution of individual plasma and fecal exposure to an antibiotic, and of bacterial richness observed in the intestinal microbiota. The analysis of other microbiota metrics such as the α- or β-diversity is necessary to refine MOX effects on the intestinal microbiota.

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IV-30: *Unai Caballero* Pharmacokinetic/pharmacodynamic modeling of anidulafungin time-kill curves against Candida considering antifungal resistance

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Objectives: Echinocandins are first-line agents to treat invasive candidiasis. However, resistance to these drugs is increasing. As pharmacokinetic/pharmacodynamic (PK/PD) modelling of *in vitro* data is an effective tool to describe the activity of antimicrobial drugs, the aim of this study was to develop a PK/PD model that described the activity of anidulafungin against *Candida* considering the emergence of resistant subpopulations.

Methods: *In vitro* static and dynamic time-kill (TK) experiments for anidulafungin against *Candida* were performed in triplicate. Concentrations assayed for the static experiments ranged from 0.0015 to 32 mg/L[1]; for the dynamic experiments, a single concentration of 5.47 mg/L was tested [2]. In both TK experiments, samples for viable counts were taken at 0, 2, 4, 6, 24 and 48 h. Several models explaining the reduced drug sensitivity were tested [3]. Data was modeled using NONMEM V7.3.0 with first order conditional estimation method Goodness of fit plots, change in OFV values and precision of parameter estimates were evaluated to assess model performance.

Results: Anidulafungin TK data were best described using a model that included a sensitive (S) subpopulation and a non-growing drug-resistant (R) fungal subpopulation, with a first- order transfer rate constant from S to R (KSR). A sigmoidal Emax model best described the drug effect, in which anidulafungin effect was included as an increase in the killing rate (Kd) of Candida in the S subpopulation. Both in static and dynamic models, the transfer rate from S to R was faster than the killing rate of anidulafungin (for C.albicans, KSR=0.17 h-1 static, Kd=0.0016 h-1 static, KSR=0.05 h-1 dynamic, Kd=0.0003 h-1 dynamic).

Conclusions: The developed model successfully described the activity of anidulafungin regarding less sensitive subpopulations of *Candida*. This kind of model development might be helpful in the design of dosing regimes that minimize antifungal resistance.

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IV-31: *Sophie Callies* Increase in glucose as pharmacodynamic biomarker following administration of the PI3K/mTOR inhibitor LY3023414: quantitative description using modelling.

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Introduction: The phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway is disregulated in many malignant diseases. LY3023414 (LY) is an oral ATP competitive inhibitor of the class I PI3K isoforms, mTOR and DNA-PK currently investigated in patients with advanced solid tumors. PI3K signalling has a major role in insulin homeostasis, mainly via the activation of the Akt/PKB and the PKCζ cascades [1].

Objectives: To quantitatively describe the possible impact of LY3023414 on glucose homeostasis through modelling.

Methods: LY pharmacokinetics (PK), glucose (GL) and Cpeptide (Cpep) data under fasting condition (predose and post LY administration – up to 4 h) from first in man dose escalation study were analysed using non-linear mixed effect modelling (implemented in NONMEM (version VII)). Data: 1192 LY PK N=89 patients, 718 GL N=87, 503 Cpep on N=43.

Results: A two compartment model with first order absorption rate describes LY PK profile (mean values: Clearance 91.1 L/h, volumes, Vc and Vp, 133 and 81.9 L, distribution clearance 5.46 L/h and absorption rate 0.877 h-1). Graphical evaluation indicates LY leads to dose dependent increase in GL (hysteresis loop). Hence, LY impact on GL is described by an indirect response model with a sigmoidal EMAX relationship linking LY to GL input rate (output rate of GL (KeG) 0.788 h-1, baseline GL 102 mg/dL, baseline input rate in GL (KAG) equal to baseline GL times KeG, EmaxG 0.991, LY50 852 ng/mL, hill coefficient 1.5). A similar model describes the effect of GL on Cpep (output rate (KeC) 16.1 h-1, baseline Cpep 824 pMol, baseline input rate (KAC) equal to baseline Cpep times KeC, EmaxC 2.65, GL50 129 mg/dL, hill coefficient 8.8).

The model predicts the maximum increase in GL, 1.2 fold (1.13-1.25 90% CI) following 200 mg, at approximately 3 h post dose followed by a return to baseline GL value by approximately 8h (dosing interval of 12 h). This effect is lower than the reported maximum increase in GL (approximately 1.5 fold) following standard meal [2].

Conclusions: In line with the mechanism of action of LY of inhibiting the PI3K/mTOR pathway, LY do lead to mild and temporary increase in GL. The model developed will help to bring these data in perspective of the literature historical information of the daily variation in GL due to meal consumption. We plan to further develop this model in perspective of the long term assessment of GL homeostasis, HbA1c.

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IV-32: *Elisa Calvier* Accuracy of plasma clearance scaling from adults to children using pathway-specific covariate models: a systematic investigation using a physiologically-based pharmacokinetic workflow

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Objectives: Pathway-specific covariate models (PSCMs) have been proposed to scale plasma clearance (CLp) in paediatrics [1-2]. This method requires the development of a PSCM describing the maturation of CLp using a model drug. Then, this PSCM is used to predict the maturation of CLp of another drug (test drug) sharing the same elimination pathway. As the accuracy of this method has not been systematically investigated, the aim of this project was to define conditions for which PSCMs lead to accurate CLp scaling from adult to paediatric patients.

Methods: In R, 'true' CLp was simulated using PBPK principles [3] for 7560 hypothetical drugs either binding to human serum albumin (HSA) or alpha-1 acid glycoprotein (AAG) with a wide range of fraction unbound (fu), extraction ratio (ER) and blood to plasma ratio. For each hypothetical drug, metabolism by 1 isoenzyme (A) or 2 isoenzymes (A and B) was investigated for 15 different hepatic isoenzymes A and B in children from 1 day to 15 years, assuming different fractions metabolized by isoenzyme A in adults (fmA-adults). PSCMs were developed and used for scaling CLp by metabolism by isoenzyme A only. Prediction errors (PE) between 'true' CLp and CLp scaled from adults to children with PSCM was computed. Scenarios where PSCM systematically leads to accurate predictions (all PEs within +/-30%) in all investigated ages were defined.

Results: For each of the 15 isoenzymes investigated, the accuracy of CLp scaling across the entire paediatric age range was found to be dependent on the properties of the model drug and test drug. The drug properties best discriminating between accurate and inaccurate CLp predictions in all ages were the type of binding plasma protein, the fmA-adults, the ER of the model drug, and the difference in fu and in ER between the test drug and the model drug. For HSA bound drugs, lower ER of the model drug and test drug yielded more accurate scaling. This accuracy decreased as the ER of the test drug increased compared to the ER of the model drug. For drugs eliminated by two isoenzymes, the accuracy of PSCM decreased with decreasing fmA-adults. For AAG bound drugs, PSCM generally led to inaccurate CLp predictions.

Conclusions: PSCM can be used to accurately scale CLp from adults to children as young as 1 day for HSA bound drugs undergoing hepatic metabolism, but is limited to specific combinations of model drug and test drug properties.

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IV-33: *Letizia Carrara* Which data are necessary to build a WB-PBPK model that accurately predicts exposure in the lung? A case study using Ethambutol for tuberculosis treatment

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Objectives: Characterising exposure profiles in different organs is a key feature of Whole-Body Physiologically–Based Pharmacokinetic (WB-PBPK) models. However, it remains unclear which data are needed to enable accurate predictions. Using a relevant case, ethambutol (EMB) for pulmonary tuberculosis treatment, we investigated this. The aims of this work are: 1) to develop a WB-PBPK model to predict EMB lung concentration; 2) to evaluate the predictive performance of the WB-PBPK framework for prospective evaluation of molecules in *first-in-human* and in *poor data* scenarios.

Methods: The model was built in PK-Sim[1]. Plasma EMB concentration and urinary data[2] collected after intravenous infusion were used to estimate clearance parameters. Absorption parameters were estimated from EMB plasma levels following oral administration[4]. Plasma data were simulated via the SimulX function of the R package mlxR[3], according to the models reported in[2,4]. The observed amount excreted in urine was used. Model-predicted drug profiles in plasma and in the lung at steady state were compared to observed plasma and Alveolar Cells (AC) EMB concentrations[5].
The predictive performance of the PBPK framework was evaluated based on *what-if* scenarios, in which data were added progressively into model development, starting from *in vitro* and animal experiments, up to human clinical trials.

Results: A PBPK model with hepatic clearance and both passive and active renal elimination was built. The model successfully describes plasma and urinary data after the infusion, and plasma EMB profiles after oral administration. Despite the model was parameterized on mean data, the variability of the biometrics included in the PK-Sim internal database well captures the observed inter-individual variability of the population plasma concentration profiles. Steady state drug levels in plasma and AC were well predicted. Simulated scenarios showed that for drug mainly excreted via the kidneys, such as EMB, information on the renal elimination is needed to make reasonably accurate predictions. Thus, both animal and human urinary data should be collected. In addition, since the crucial parameter was found to be the intestinal permeability, in vitro experiments with Caco-2 cell line should be performed as well.

Conclusions: The model showed good descriptive and predictive power of data of different studies, also in a population context. Crucial parameters and data to obtain accurate predictions were identified.

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IV-34: *Massimo Cella* CHF5993 a triple combination therapy for COPD patients: population PK modelling of glycopyrronium bromide (GB) following pMDI inhalation.

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Objectives: CHF 5993 pMDI is a new extrafine fixed dose combination of beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium bromide (GB), being developed for chronic obstructive pulmonary disease (COPD) and asthma treatment. Data collected in phase II/III studies were used to evaluate the population pharmacokinetics of GB and to investigate the influence of selected covariates on GB pharmacokinetic parameters and their potential clinical impact.

Methods: GB plasma concentrations after oral inhalation in COPD patients were obtained from 2 studies: Triple 6 (ph III) and CARSAF (ph II). Both studies were double-blind, randomized, active-controlled. In Triple 6, patients inhaled two puffs twice daily of CHF 5993 pMDI (BDP/FF/GB 100/6/12.5 µg). In CARSAF, patients inhaled two puffs twice daily of Foster® pMDI (BDP/FF 100/6µg) plus either 25 or 50 µg GB pMDI. GB plasma concentrations were modelled with non-linear mixed-effects approaches using NONMEM V7.3.0. The explored covariates were age, smoking status, sex, body weight, body mass index, concomitant medications, study effect, use of spacer, forced expiratory volume in 1 second (FEV1), concomitant diseases and glomerular filtration rate (GFR).

Results: The final population model to describe the PK of GB was a two-compartment disposition model with first-order absorption and first-order elimination, and inter-occasion variability on relative bioavailability. The residual error model was an additive model for the log-transformed data. BQL observations represented 15% of the data and were handled with the M3-method. Bodyweight, study effect and GFR were found to affect GB PK parameters. Simulations were performed in order to visualize the impact of the different covariates on the PK of GB, at steady-state, using a GB dose of 25 or 50 µg BID. For sub-populations with extreme values of body weight and GFR (i.e. low body weight (40 kg) and low GFR (27 mL/min/1.73 m^2)), GB exposure increases by a factor around 2.7 compared to the reference patients. This higher exposure is of no clinical concern because, in clinical studies, GB doses of up to 4-fold the one used in CHF5993 formulation didn't show any safety signal.

Conclusion: The PK model built on data from COPD patients described the GB data well and was able to explain part of the variability in exposure on the basis of some covariates. Based on simulated profiles, no clinical dose adjustments were deemed necessary.

IV-35: *Marc Cerou* Development and performance of npde for the evaluation of time-to-event model

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Objectives: Normalised prediction distribution errors (npde) are used to evaluate graphically and statistically continuous responses in non-linear mixed effect models [1]. Here, our aim was to extend npde for time-to-event (TTE) models and to evaluate their performances.

Methods: Let V denote a dataset with TTE observations. The null hypothesis H_0 is that observations in V can be described by a model M. Prediction discrepancies (pd) are defined as the quantile of the observation within its predictive distribution, which is approximated through Monte-Carlo simulations. pd for unobserved (censored) event times were imputed using a similar method as the one developed to handle data under the Lower Quantification Limits (LOQ) [2]. npde are then obtained using the inverse function of the normal cumulative density function. Under H_0, they follow a normal N(0,1) distribution, which was tested through a combined test [1].

We evaluated the performance of npde for TTE data through a simulation study inspired by the work of Desmée et al. [3]. They characterised the relationship between the biomarker PSA (prostate specific antigen) and survival in 500 metastatic castration-resistant prostate cancer patients via joint modelling. We simulated event times from the joint model, based on the predicted PSA trajectories, for different sample sizes. We evaluated the type I error and power of npde to detect different types of model misspecifications for the TTE component in several scenarios.

Results: Type I error was found to be close to the expected 5% both with true and with censored event times, for all tested sample sizes. npde were able to detect misspecifications in the baseline hazard as well as in the link between the longitudinal variable and survival. The power to detect model misspecifications was more important as the difference of survival was large. As expected, the power also increased as sample size increased. The percentage of rejection was closer to 5% when censored events were considered.

Conclusion: npde can be readily extended to TTE data, and we found that they performed well with an adequate type I error. The next step will be to evaluate the npde for the joint model, also considering the longitudinal measurements and its impact on TTE. We will also extend npde to evaluate repeated TTE models including inter-individual variability on the parameters of the hazard function.

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IV-36: *Anne Chain* An Extrapolation Approach to Aprepitant Pediatric Drug Development

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Objectives: 1- Identify an appropriate 1-day intravenous (IV) dose of fosaprepitant in pediatric subjects that provides exposures similar to those associated with efficacy in adults. 2- Identify a 3-day combined IV/oral fosaprepitant and aprepitant regimen that provides exposures similar to the approved pediatric 3-day oral regimen of aprepitant.

Methods: A population PK model of fosaprepitant and aprepitant was developed using 4 completed studies with different formulations (capsule, powder for suspension, IV) and various dose amounts and regimens (3-day oral, 3-day IV and oral, 1-day IV) in 316 pediatric subjects aged 6 months to 17 years old. Monte-Carlo simulations were performed using the final model to simulate exposure profiles of aprepitant to support 1-day and 3-day dosing regimens of fosaprepitant and aprepitant in pediatric subjects. Model fidelity was assessed using goodness-of-fit plots and VPCs. Individual PK parameters were computed using a non-compartmental analysis approach on simulated rich concentration-time profiles. Simulated 1-day IV exposures were compared with target exposures corresponding to the 1-day IV fosaprepitant regimen approved in adults. The simulated 3-day IV/oral exposures were compared with target exposures corresponding to the approved three-day oral regimens in pediatric population.

Results: The final model was a two-compartment model with first-order absorption, lag-time and bioavailability. Allometric factors were included in all systemic parameters. Age, dose and formulation were identified as covariates in the model. Based on exposure levels observed in adults after a single IV dose of fosaprepitant, a regimen of 5 mg/kg and 4 mg/kg were appropriate for subjects 6 months to <2 years old and 2 to 12 years old, respectively. Regimens of 115 mg on Day 1 and 80 mg on Days 2 and 3 in adolescents as well as 3 mg/kg on Day 1 and 2 mg/kg on Days 2 and 3 in subjects < 12 years old were adequate for a 3-day IV /oral regimen.

Conclusions: Appropriate 1-day IV doses of fosaprepitant were identified for pediatric subjects. These results supported an extrapolation approach in the 1-day IV setting using model-based evaluations to ascertain a dosing recommendation, which facilitated the early termination of a Phase 3 trial. In addition, a successful bridging strategy was also used to find 3-day IV/oral regimen for use in children.

IV-37: *Kaelig Chatel* Tobramycin dose individualization using the MonolixSuite

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Objectives: The concept of personalized medicine has long been promoted to bring more benefits to patients, in particular by adapting the administrated dose to the patient's characteristics. Methodologically and practically, dose individualization is a challenging task. We show how this can be done in an efficient way using the MonolixSuite.

Methods: For the case study, we use the antimicrobial agent Tobramycin, which has a narrow therapeutic index. For efficacy, a sufficiently high serum concentration must be achieved. On the other hand, an excess exposure over a long time period bears the risk of nephrotoxicity and ototoxicity. Using the non-linear mixed-effect model and data published in [1], we performed simulations to determine (i) if the typical treatment is safe and efficient, and (ii) the dose that would be most likely to be safe and efficient.

Results: We first show that the default dosing regimen of 1mg/kg every 8 hours is safe in only 75% of the simulated healthy individuals. This calls for an individualization of the dosing regimen. We thus used the individual covariates to predict via simulations the concentration interval for one specific individual taking into account the residual random effects that remains after consideration for a specific covariate value. We implemented a simple optimization algorithm to determine a priori the dose that has the highest chance of being safe and efficient. For an individual weighting 78kg and with an impaired renal function (creatinine clearance 30mL/min), we propose to adapt the dosing regimen to 1.2mg/kg every 14 hours. If in addition, early drug monitoring permits to measure the drug's concentration at a few time points after the initial dose, these data can be used to obtain the distribution of the individual's parameters (given the covariates and the population parameters), using the Markov Chain Monte-Carlo procedure implemented in the Monolix software. We show that 4 measurements permits to reduce the concentration prediction interval width 5-fold for this individual.

Conclusions: This example shows how a personalized treatment can be realized using population PK modeling and simulation, and how the MonolixSuite software (Monolix for parameter estimation and Simulx for simulations) components facilitate an efficient implementation. The modeling/simulation approach permits to precisely assess the trade-off between the prediction precision and the costs of information acquisition.

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IV-38: *Jonathan Chauvin* Longitudinal Model-Based Meta-Analysis (MBMA) for rheumatoid arthritis with Monolix

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Objectives: Model-based meta-analysis (MBMA) uses published aggregate data from many studies to develop a study-level model and support the decision process. Because in an MBMA approach one considers studies instead of individuals, the formulation of the problem as a mixed effect model differs slightly from the typical PK/PD formulation. Here we present how MBMA models can be implemented, analyzed and used for decision support in Monolix and Simulx. As an example, we focus on longitudinal data of the clinical efficacy of drugs for rheumatoid arthritis (RA), following [1]. The goal is to evaluate the efficacy of Canakinumab in comparison to two drugs already on the market (Adalimumab and Abatacept).

Methods: We first collected literature data, incorporating new studies compared to the work presented in [1]. We focus on the ACR20 as endpoint, i.e the percentage of patients achieving 20% improvement. We then formulate a longitudinal mixed effect model with: (i) an Emax structural model, (ii) between-study variability (BSV), (iii) between treatment arm variability (BTAV), and (iv) a residual error. The variances of the BTAV and residual error terms is weighted by the number of individuals per arm, which requires a careful implementation, that we demonstrate using the Monolix software. The model is then used to simulate the true effect of the three drugs, taking into account the uncertainty of the parameter estimates.

Results: The proposed model satisfactorily describe the longitudinal ACR20 data for the three drugs. After parameter estimation, the model is used to predict the chances of Canakinumab to be a more efficacious drug than Adalimumab and Abatacept. To compare the true efficacy (over a infinitely large population), we perform a large number of simulations for the 3 treatments, drawing the Emax population value from its uncertainty distribution. These simulations can easily be done using Simulx, giving the correlation matrix estimated by Monolix as argument. The results show that there are only 6% chances that Canakinumab is better than Abatacept and 16% chance that it is better than Adalimumab.

Conclusions: We have shown that chances are low that Canakinumab performs better than the two drugs already on the market. As a consequence of study [1], the development of this drug has been stopped, thus saving the high costs of the phase III clinical trials. The MonolixSuite offers a powerful environment for longitudinal MBMA analysis.

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IV-39: *Chao Chen* A clinical trial simulation study to investigate and compare efficacy and toxicity findings in parallel and titration designs

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Background & Objectives: Dose-ranging studies are designed to understand the efficacy and toxicity of an investigational compound, aiming to maximise its benefit-risk ratio. Both parallel and titration designs are commonly used to evaluate population and individual dose-response relationships [1]. In this work, we used computer simulation to investigate treatment success level, as well as efficacy and toxicity profiles, for these two designs.

Methods: Clinical trials with both designs were simulated and analysed using the MSToolkit package in R. The dose-response relationships for efficacy and toxicity were defined as a simple Emax model; the mean doses producing 50% of maximum efficacy (ED50) and 50% of maximum toxicity (TD50) were set at 1 and 8 respectively [2].

Three active doses (0.5, 1 and 2) were given to parallel groups. In the titration study, the dose for each patient increased step-wise until at least 90% of maximum efficacy or at least 20% of maximum toxicity was observed. The placebo effect was not separated from active treatments due to its questionable nature in titration designs [3, 4].

In total 10,000 patients were simulated. Three levels of between-subject variability in ED50 and TD50 (25%, 45% and 75%) and three levels of measurement error (10%, 30% and 60%) were considered. Both low and high correlations between ED50 and TD50 were investigated. A dropout rate of 10% was assumed for each treatment period.

The responder rate and distributions of efficacy, toxicity and efficacy-toxicity ratio (reflecting benefit-risk ratio) among responders were compared between the two designs.

Results: For all evaluated scenarios, the responder rate in the titration trials was consistently higher; it was up to 75% higher than that at the high dose in the parallel trials. The efficacy profile for the titration trials was similar to that at the high dose of the parallel trials. Both toxicity and the efficacy-toxicity ratio profiles in the titration trials were similar to that at the middle dose of the parallel trials.

Conclusion: The current exploration study suggests that titration design is likely to be more effective than parallel design. Compared to the parallel design, it results in higher responder rate with optimal benefit-risk profile. The placebo effect and interaction between dose-response and time for this design remain to be further assessed.

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IV-40: *Dina Chernikova* Inhibition of bile acids synthesis via fibroblast growth factor 19 (FGF19) through intestinal signaling: A population analysis

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Objectives: Regulation of bile acid (BA) synthesis is mediated through the farnesoid X receptor (FXR), which is predominantly expressed in the liver and intestine (1). The role of direct interaction of BAs with hepatic FXR versus the influence of FGF19 which is secreted from the small intestine after BA-mediated FXR activation is still unclear (2, 3). Objective of this population analysis was to estimate the possible role of intestinal signaling via FGF19 in the inhibition of BA synthesis.

Methods: Data for analysis was obtained from 11 healthy volunteers under sequential treatment with cholestyramine (CME) (4g QID), CME preceded by atorvastatin (40 mg daily) and without treatment. Statistical analysis was performed using a sample cross covariance function in R and MATLAB, to investigate time correlations of FGF19/7-alpha-hydroxy-4-cholesten-3-one (C4), FGF19/BA and BA/C4. The model describing the functional relationship between FGF19 and C4 was obtained based on an analytical solution of the corresponding system of differential equations.

Results: The analytically-obtained functional relationship between FGF19 and C4 reproduced the central trend and, partially, variability in the observed data. Values of the population parameter estimates revealed an inverse square root dependence of CYP7A1 activity on FGF19. The sample cross-correlation analysis demonstrated the presence of a time lag (up to 3.5 h) between FGF19 synthesis and C4 response. Positive correlations were observed between FGF19 and glycine-conjugated bile acids, GDCA and GCDCA, but not GCA.

Conclusions: The effect of intestinal signaling via FGF19 on the inhibition of BA synthesis can be approximated by an empirical model with an inverse square root dependence of CYP7A1 activity on FGF19. However, additional data are required to improve quality of predictions and allow for further analysis.

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IV-41: *Manoranjenni Chetty* Prediction of the pharmacokinetics of renally excreted antiretrovirals in older patients, using physiologically based pharmacokinetic (PBPK) modelling.

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Objectives: Despite our knowledge of diminishing renal function with advancing age, information on the impact of aging on the pharmacokinetics (PK) of antiretroviral drugs that are mainly excreted unchanged by the kidney is sparse. The objective of this study was to use PBPK modelling to determine whether changes in the exposure to antiretroviral drugs warrant dosage adjustments in older patients.

Methods: PBPK models for tenofovir, emtricitabine and lamivudine were developed previously [1]. These three drugs were selected on the basis that excretion via the kidney is >70%. The PBPK models for these drugs were verified initially in the Simcyp Simulator (v16) using available clinical data and then used to predict their pharmacokinetic profiles for standard doses in Caucasian population groups aged 20 to 49 years; 50 to 64 years and 65 to 75 years respectively. The Simcyp Geriatric Caucasian population was used for the 65 to 75 year age group. Since drug response has been associated with the area under the plasma concentration versus time curve (AUC) for these drugs, changes in exposure (AUC) were compared between the age groups.

Results: The PBPK models for tenofovir, emtricitabine and lamivudine showed good recovery of the clinical data, indicating the suitability of the models to be used in the prediction of PK. A decrease in CL and an increase in AUC with advancing age was observed for all three drugs. The mean increases in exposure (AUC) between the youngest and oldest age groups were about 40% for emtricitabine, lamivudine and tenofovir.

Conclusions: These results suggest that doses lower than the standard 200mg, 300mg and 300mg daily dose for emtricitabine, tenofovir and lamivudine respectively should be considered in patients aged between 65 and 75 years.

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IV-42: *S. Y. Amy Cheung* Optimising Phase 1 oncology dosing schedule of an ATR inhibitor in real time using a model informed approach to predict myelosuppression

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Introduction: AZD6738 is an ATR kinase inhibitor being tested in patients with solid malignancies as monotherapy and in combination. A quantitative understanding of duration and severity of myelosuppression is vital for dose-regimen optimisation in oncology [1]. As part of a model informed drug development [2], a PK-safety modelling approach was applied by integrating data across phase 1 studies to support dose-regimen selection.

Methods: The PK-safety model [3] was built in NONMEM, using emerging phase 1 PK, absolute platelet count (APC) and absolute neutrophil count (ANC) from 2 phase 1 studies of AZD6738 dosed alone (continuous doses from 40-480mg), or in combination intermittent doses from 80-320mg) with carboplatin and the PARP-1 inhibitor, olaparib. The model describes the baseline circulating count, a linear relationship between drug concentration and reduced proliferation in the bone marrow precursor cell population, a mean transit time (MTT) for the delay before reduction is seen in circulating cell counts and homeostasis increasing precursor proliferation to return cell counts to baseline. It was tested whether the effects of AZD6738, carboplatin and olaparib were additive or synergistic interactions. Simulations of the model in the software R were used to explore dose and schedule options.

Results: Blood counts in patients were well described by the model, following AZD6738 alone (n=32) and in combination with carboplatin AUC 5 every 3 weeks (n=33) and olaparib 300mg twice daily continuous dosing (n=31). AZD6738 was dosed on various intermittent regimen. AZD6738 alone showed a minimal impact on blood cell count compared to carboplatin and no synergy with carboplatin and olaparib could be estimated. The estimated mean MTT was 9 days in comparison to 5 days in the literature [3]. Simulations indicated that a 4 week treatment cycle of carboplatin and AZD6738 would provide time for APC and ANC to recover to 90% baseline. Continued reductions in cell counts are not predicted by the model whereas some patients with grade 2 reductions on cycle 1 experienced grade 4 on repeated cycles: Evaluation of alternative mathematical myelosuppression models [4] is ongoing.

Conclusion: The model simulations supported team decisions on dose and schedule and will minimise dose adjustments in future trials. Understanding single agent and combination safety profiles provided confidence for combination choices and differentiation strategy.

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IV-43: *Maxwell Tawanda Chirehwa* A semi-physiological model for moxifloxacin pharmacokinetics which includes the effect of co-administered drugs and genetic polymorphisms

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Objectives: Moxifloxacin (MOXI) is currently recommended for the treatment of MDR-TB [1]. It could potentially reduce the time to culture conversion in patients with drug-susceptible TB [2]. We describe the pharmacokinetics (PK) of MOXI and identify the effect of selected covariates on PK parameters.

Methods: Blood samples were collected from 58 tuberculosis (TB) patients from South Africa recruited in the PK sub-study of the IMPRESS study. Patients received 400 mg of MOXI for 6 months together with weight-adjusted doses of rifampicin and isoniazid, and pyrazinamide in the first 2 months of treatment. HIV+ patients received ART, mostly efavirenz-based. PK sampling was conducted on 2 visits in the intensive phase and on 1 day in the continuation phase. Additional PK sampling was done after administration of a single dose of MOXI, one month after completion of TB treatment. On a PK sampling day, four serial blood samples were collected prior to dosing and at 2.5, 6 and 24 hours post-dose. Plasma moxifloxacin was quantified using HPLC-MS/MS, and the LLOQ was 0.05 mg/L. Data were analysed using nonlinear mixed effects modelling in NONMEM 7.3 and FOCE-I.

Results: PK of MOXI was best described using a 2-compartment disposition model, and a semi-mechanistic model to capture liver first-pass effect (ΔOFV 24 vs. no first-pass effect). The hepatic volume of distribution and plasma flow (Q_H) were fixed to 1 L and 50 L/h, and MOXI unbound fraction was fixed to 50% [3]. Priors were included on Ka and ALAG to using parameter estimates from Zvada et al. [4]. Allometric scaling using FFM on all clearance and volume parameters was supported by the data. The model identified the effect of rifampicin co-administration, efavirenz co-administration, and genotypes of rs8175347 and rs3755319 on exposure. The liver extraction ratio (E_H) was highest (44%) for patients that were administered rifampicin based anti-TB treatment, efavirenz-based ART, and have AC or AA genotype for rs3755319. Intrinsic clearance after a single dose of MOXI was 29% less compared to steady-state with rifampicin co-administration. However, the model also estimated a 22% reduced pre-hepatic bioavailability after a single dose of MOXI.

Conclusions: A semi-mechanistic model with hepatic extraction describes the data adequately. The clinical significance of the effects found warrants further investigation on the proportion of patients attaining therapeutic exposure using MIC distributions determined and the currently recommended dose of 400 mg.

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IV-44: *Joannellyn Chiu* Pre-clinical Population PK Model of CF-301 - a Novel Antibacterial Lysin

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Background: CF-301 is a lysin with rapid S. aureus-specific bacteriolysis that completed Phase 1 trial [1].

Objectives: To develop a pre-clinical population PK model (PPK) for CF-301 in animal species (rats and dogs) and apply interspecies scaling to predict human exposures over a range of doses.

Methods: Data was pooled from 10 PK studies in rats and dogs with various infusion regimens. 1, 2 and 3-compartmental models with zero-order infusion were evaluated using interspecies scaling on PK parameters. Covariates sex, age, formulation, total daily dose were assessed. The PPK model was validated with bootstrap and VPC. The animal PK model was allometrically scaled to predict human exposures (AUC and C_{max}) over the dose range 0.12 to 1.6 mg/kg 2-hour IV infusion. The predicted human exposures from animal PPK model were compared to predicted exposures from human PPK model [1].

Results: Data included 393 animals (78 dogs, 315 rats), 2083 observations. A 3-compartment linear model with zero-order absorption adequately described the animal PK data. All fixed effect parameters were estimated with good precision (%RSE<11%). Sex was a primary predictor of V2. For a given weight of 0.304 kg, male and female rats were predicted to have comparable C_{max} and AUC_{0-24}. Total daily dose was found to be a predictor of CL and V1. For example, CL and V1 were estimated to be 3% and 4% higher for 2.5 mg dose vs 5 mg dose, respectively. Model validations support that the animal PPK model adequately describes the data. There was no significant effect of age or formulation on PK parameters. When comparing predicted human exposures from the animal PK model to exposures predicted from a human PK model, the difference in AUC_{0-24} and C_{max} were <40% for doses ranging 0.12-0.8 mg/kg in human, which indicates a reasonable agreement between the two models. The predicted exposures from animals for a human dose of 1.6 mg/kg overestimated exposures by approximately 2-fold.

Conclusion: The population PK model parsimoniously described the data for both animal species and was deemed to be suitable for simulations to predict PK profiles in rats and dogs at various doses. Total daily dose was found to be statistically significant on CL and V1, but not clinically meaningful (<%5 effect). No meaningful effect of sex was detected on PK parameters. The allometric scaling of animal PPK model adequately predicted the exposures of CF-301 in humans within the dose range 0.12-0.8 mg/kg 2-h IV infusion.

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IV-45: *Palang Chotsiri* Population pharmacokinetic and time-to-event modelling of the antimalarial drug lumefantrine in young children with severe acute malnutrition

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Objectives: Malaria and severe acute malnutrition (SAM) are a common co-morbidity in Sub-Saharan African children. The pathophysiological properties of SAM might adversely affect the pharmacokinetic properties of administered drugs. This is the first study aimed to investigate the pharmacokinetic properties of the antimalarial drug lumefantrine in children with SAM at two sites in Niger and Mali.

Methods: 131 SAM children and 266 non-SAM children with uncomplicated *falciparum* malaria were recruited and administered a standard weight-based treatment of artemether-lumefantrine twice daily for 3 days. Pharmacokinetic and pharmacodynamic properties of lumefantrine were investigated using nonlinear mixed-effects modelling (NONMEM v.7). All malnutrition related covariates were evaluated using a stepwise covariate modelling approach as well as a full covariate modelling approach. Time to malaria re-reinfection was used as a pharmacodynamic endpoint.

Results: Lumefantrine capillary plasma concentrations were adequately described by two transit-absorption compartments followed by three-distribution compartments. Pharmacokinetic parameters were scaled using an allometric function of body weight. Elimination clearance of lumefantrine was also influenced by the level of enzyme maturation in these very young children (6-59 months). Mid-upper arm circumference (MUAC) is a well-established measure of SAM, and it was a significant covariate on the relative bioavailability of lumefantrine in the children studied here, resulting in a 23.8% decreased drug absorption per 1 cm reduction in MUAC. Parasite density at the time of malaria detection was used for interpolation of the likely time interval of malaria acquisition. An interval-censoring time-to-event model with a sigmoid E_{MAX} inhibitory effect of lumefantrine described the recurrent malaria in this vulnerable population successfully.

Conclusions: The pharmacokinetic and pharmacodynamic properties of lumefantrine were successfully described by the developed pharmacometric model. Modelling conducted here suggests that children with SAM are at risk of under-dosing compared to well-nourished children.

IV-46: *Shafi Chowdhury* Using "Big" NONMEM Dataset Generated from Standard SDTM to Review Data and Accelerate Model Building Process

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Objectives: The use of standard SDTM structured data has given us the opportunity to generate one "BIG" NONMEM dataset by merging required SDTM datasets together. This can merge all related data together by using the key identifying variables within those datasets which are always the same. The advantage of doing this is that we are then in a position to easily analyse how all the data relate to each other and see if there are any issues or unexpected trends in the data before finalizing the NONMEM dataset specification.

Methods: Once the "big" NONMEM dataset is created using the standard SDTM datasets, the data is ready for statistical analysis. Statistical analysis can be performed automatically to check associations of all types of data based on age, sex, race, country and all other covariates specified within a project. Associations can be highlighted and potential data quality issues or trends in the data can be explored on an ongoing basis prior to database lock. Graphical tools can be used to see how values are changing over time, and if there are unexpected results then actions can be taken to raise the quality of the data. This will not only lead to cleaner data, but also to an accelerated model determination process.

Results: The statistical methods display association between the different combinations of covariates both in tabular and graphical form. Those with significant results are then summarised and grouped so that they are easy to see by the pharmacometrician. All data outside the reference ranges are also highlighted.

Conclusions: Looking at all associations and summary data of individual covariates makes it easy to see if there are any data issues, and which covariates are more logical for inclusion in the NONMEM dataset specification. This allows a more focussed specification to be created, and as the "BIG" NONMEM dataset was already generated, the reduced dataset is produced with minimum additional time. As associations between covariates are also known, this can therefore aid the modelling process, helping to accelerate the process.

This helps to bring some of the exploration of the data prior to database lock, thus ensuring the Pharacometrician is more familiar with the data by the time they start the modelling process. This can speed up the delivery of the analysis and mean the results will be available in time to influence future decisions.

IV-47: *Pieter Colin* Dexmedetomidine pharmacodynamics in healthy volunteers: Striking a balance between the hypnotic and sedative properties and the haemodynamic side effects.

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Objectives: To develop a PKPD model which allows the description of dexmedetomidine (DMED) induced effects on clinical measures of hypnosis and sedation and haemodynamic side effects. A secondary goal was to investigate the effects of stimulation on the sedative properties of DMED. For this, two methods of stimulation were studied: continuous background auditory stimulation and short, sudden verbal/tactile/painful stimulation.

Methods: DMED plasma concentrations, Bispectral index (BIS), Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S), mean arterial pressure (MAP) and heart rate (HR) were recorded from 18 healthy volunteers on two separate occasions. DMED was dosed using a target-controlled infusion system[1]. Volunteers were isolated from background noise during 1 session and were exposed to looped operating room background noise in another session. In a sequential PKPD modelling approach using NONMEM, we explored the concentration-response relationship between DMED and the different endpoints.

Results: The modelling revealed an increasing delay between plasma concentrations and HR, BIS, MAP and MOAA/S, with half-lives for effect-site equilibration ranging from 1.7 to 14.3 min. Concentration-responses were described by an Emax model (HR), a double Emax model (MAP) and a latent-variable based linear interpolation between two Emax models (BIS). The BIS model adequately described the BIS signal both before and after sudden stimulation. MOAA/S were best described using a proportional odds logistic regression model with different C50s for both sessions. No relevant covariate relationships were detected, apart from those already included in the PK model[2] and the influence of age on the baseline MAP.

Conclusions: Our model provides valuable insight in the phenomenon of DMED mediated arousable sedation and the influence of sudden stimulation on this arousability. Moreover, it shows that by depriving a volunteer from background noise the sensitivity towards the sedative effects decrease. Finally, simulations show that BIS is useful for guiding DMED dosing and that its relationship with the MOAA/S scale is similar to other hypnotics, such as propofol. Also, the haemodynamic side effects and the DMED induced hypnotic and sedative properties go hand in hand, such that the former might serve as a surrogate for the latter when BIS monitoring is not available to guide dosing.

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IV-48: *Camille Couffignal* Population pharmacokinetic modelling of sustained-release lithium in the serum, erythrocytes and urine of patients with bipolar disorder.

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Objectives: Bipolar disorder is a major affective disorder. Sustained-release lithium (srLI) is now the first-line treatment with a narrow therapeutic margin adapted empirically from immediate-release form studies [1]. Indeed, to date, there exist no specific pharmacokinetics (PK) studies for the sustained-release form. Our aim was to propose a population model of the PK of srLI using serum (S), erythrocyte (E) and urinary (U) samples in bipolar patients.

Methods: A prospective study was conducted in French bipolar disorder centers in patients treated with srLI for at least two years. For 15 days srLI was given once per day in the morning at the patient usual dose. Adherence was controlled using a medication event monitoring system [2]. Blood samples were collected at day 15 before drug intake and at H1, H4, and H8, with U samples between H0 and H8. Population PK parameters were estimated using the SAEM algorithm (MONOLIX 4.3.3 software) [3].

Results: Seventeen patients were included from, age median=40 range [27-63] y and srLI dose 1000 [600-1600] mg. The srLI PK was best described with an 8 parameters model with a first order absorption process with bioavailability F and a lag-time Tlag, a S one-compartment with an elimination clearance Cls to the U one-compartment, a E one-compartment with a transfer clearance Clse into the E compartment and a transfer clearance Cles back to the S compartment. A proportional variance model best described the residual errors for the S concentrations. For the E concentrations and U amount the residual errors were best depicted by an additive variance model. The mean and between-subject variability (BSV %, if estimated) were for F= 62% (98%), Tlag=55 minutes and ka=2.22 h^{-1} (72%), Vs=23 L (30%), Cls=1.21 $L.h^{-1}$ (20%) and Clse=3.63 $L.h^{-1}$, Ve=64.7 L, Cles=9.46 $L.h^{-1}$ (27%). The goodness-of-fit plots were satisfactory. The ratio of exposition to LI in E over S (as measured by the ratio of predicted AUC_{ss}) is of 0.38 (20%).

Conclusions: This is the first study in bipolar patients to inform on srLI PK and provide mean and BSV estimates of the ratio of exposition to LI in E over S which is deemed to be a proxy of LI penetration into the brain [4].

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IV-49: *Sinziana Cristea* The impact of renal transporters on paediatric renal clearance

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Objectives: Although transporters hold a key role in drug disposition, their impact on renal clearance (CL_R) has been less studied, particularly in children[1]. Using physiologically-based simulations, we investigate the impact of physiological changes, transporters activity ($CL_{s,int}$) and their ontogeny on CL_R.

Methods: Using R, we generated virtual paediatric individuals to simulate CL_R of hypothetical drugs with low, median and high reference unbound fractions ($f_{u\text{-}HSA}$). CL_R simulations were based on a model that comprises glomerular filtration and active tubular secretion[2]. Ontogeny of $f_{u\text{-}HSA}$[3], renal blood flow[4], kidney size[5], and glomerular filtration[6] was implemented based on literature. The contribution of active tubular secretion to CL_R was assessed for a $CL_{s,int}$ range in adults between 2-250 µL/min, representing one or more transporters. For transporters ontogeny, percentages between 50 and 200% of $CL_{s,int}$ adult values were tested. The impact of ontogeny on CL_R for each age was expressed as a percentage difference compared to 100% $CL_{s,int}$ for that specific age.

Results: Glomerular filtration and active tubular secretion changed proportionally with $f_{u\text{-}HSA}$. The impact of active tubular secretion on CL_R was influenced by age-related physiological changes. For a $CL_{s,int}$ of 50 µL/min, the contribution of active tubular secretion to CL_R varied between 25-39% due to variation in renal blood flow and kidney size. In the studied $CL_{s,int}$ range we showed that a 5-fold increase in $CL_{s,int}$ yielded a 2-fold increase in contribution of active tubular secretion to CL_R. The impact on CL_R of ontogeny in $CL_{s,int}$, expressed as a percentage difference compared to 100% $CL_{s,int}$, decreased with age, i.e., for an enhanced transporter activity of 200%, the percentage difference decreased from 15% in a 1 day old neonate to 9% in adults.

Conclusions: In the present work, we established the variables that impact CL_R in the context of physiological changes and transporter ontogeny in children. Throughout the studied age range, glomerular filtration is the main driver of renal clearance unless multiple transporters contribute to active tubular secretion which could result in a contribution of up to 73%.

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IV-50: *Vincent Croixmarie* DDMoRe private repository linked with an in-house PK database

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Objectives: The Drug Disease Model Resources (DDMoRe) Repository [1] is a powerful online tool for reference models storage [2]. It has been developed to "enable access to community curated models for the benefit of model-informed drug discovery, development (MID3) and usage". From frozen databases, time-concentration profiles are analyzed with population modeling approach and individual secondary pharmacokinetics (PK) parameters are derived. As an internal solution at Servier, a dedicated PK database was design to store such secondary PK parameters as well as the associated final models. This parameter database is built for each compound during drug development. Models developed for the determination of such secondary PK parameters are considered as metadata associated with the parameters and are stored as such in the database. The objective of the project was to define a consistent workflow for model storage with both tools and to integrate DDMoRe metadata capabilities to account for internal needs.

Methods: A working group of PBPK and PK/PD modelers was established to define the appropriate database integration and to define the requirements of metadata annotation needed for the DDMoRe private repository.

Results: A private version of the DDMoRe repository was deployed at Servier. A connection between the DDMoRe internal repository and the PK database was established. Due to their different nature, the DDMoRe repository is integrated to host models as a model library, including final and draft versions, while finalized models and derived PK parameters are stored in the PK database. Consistency of final models across the two platforms will be assured thanks to their connection. Metadata capabilities of the original DDMoRe repository have been enhanced internally in order to allow deeper search across model parameters and features.

Conclusions: A workflow for model storage was showed integrating an internal storage solution for final models and model parameters with the DDMoRe model repository, which will be used as general model library. Such integration allows to profit from the advantage of combining a fully customized internal solution with the current and future functionalities of the DDMoRe model repository.

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IV-51: *Andre Dallmann* Physiologically-based pharmacokinetic modeling of drugs metabolized via several CYP enzymes in populations of pregnant women

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Objectives: The objective of this study is to verify a physiologically-based pharmacokinetic (PBPK) model for the prediction of pharmacokinetics (PK) of drugs metabolized via several CYP enzymes in populations of pregnant women.

Methods: A recently developed and verified pregnancy PBPK model for renally cleared drugs [1,2] was extended to predict the disposition of drugs metabolized via several CYP enzymes, including CYP 2A6, 2E1 and 3A4/5. Therefore, the literature was screened for quantitative information on pregnancy-dependent changes in the activity of relevant CYP enzymes. In case sufficient data were available throughout pregnancy, the observed changes were described by a monotonous function fitted to the data. Otherwise the changes were described in steps of trimesters. If conflicting data or no data on enzyme activity were available, sensitivity analyses were performed based on in vivo concentration-time profiles to identify the apparent changes in enzyme activity. Subsequently, pregnancy PBPK models were built to predict the PK of drugs metabolized by CYP 2A6, 2E1 and/or 3A4/5. PK predictions were evaluated by comparing them with in vivo data taken from the literature. The physiological changes related to pregnancy as well as the substance PBPK models were developed in PK-Sim and Mobi as part of the Open Systems Pharmacology Suite [3,4].

Results: Compared to the non-pregnant state, an average 1.8-fold increase was reported for CYP 2A6 and 2E1 at the end of pregnancy. A somewhat lower increase was obtained on the basis of a sensitivity analysis for CYP 3A4/5. Using these increases in enzyme activity, the PBPK models successfully predicted the PK of all drugs administered to pregnant women. More than 90% of the predicted mean plasma concentrations in pregnant women fell within the 1.5-fold error range. For all drugs, ratios of predicted to observed AUC were within the range of 0.8 – 1.2.

Conclusions: We successfully developed and verified a pregnancy population PBPK model for drugs metabolized via several CYP enzymes. Ultimately, this model can be applied to investigate in silico the PK of drugs undergoing metabolism in pregnancy and help design dosages e.g. for clinical trials in this vulnerable special population.

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IV-52: *Olivier David* CNP520 Phase III dose selection support: Identifying the doses producing a desired reduction in CSF Aß-40

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Objectives: One important pathological feature of Alzheimer disease (AD) is the presence of deposits forming amyloid plaques in the brain cortex of affected individuals. These plaques are constituted of aggregated fibrils of Aβ peptides that derive from the amyloid precursor protein (APP) [1]. There is a growing body of evidence that beta-amyloid peptides are involved in the pathophysiology of AD [2]. CNP520 is an orally-available, centrally active and potent inhibitor of BACE-1, an enzyme involved in the processing of APP. CNP520 by reducing Aβ generation and restoring Aβ equilibrium offers the promise of disease modification in AD. The goal of this population pharmacokinetic/pharmacodynamic (PK/PD) analysis was to characterize the dose-exposure and the exposure-response (CSF concentration of Aβ-40 peptide) of CNP520. This work was used to support the selection of doses providing the desired level of CSF Aβ-40 inhibition for a long term disease prevention study.

Methods: The popPK/PD modeling was performed on clinical data from a first-in-human, single and multiple ascending oral dose study in healthy adult and elderly subjects (n>200). The model was then validated on data from a 3-month study in healthy elderly subjects (n>120). The CNP520 and CSF concentration of the Aβ-40 peptide were fitted to a PK/PD model using non-linear mixed-effects modelling implemented in NONMEM (version 7.3.0) and Monolix 2016R1. The validation on the second study and further simulations were performed with mlxR version 3.1.0.

Results: CNP520 PK is best described with a linear two-compartment model with an absorption lag time, sequential zero and first-order absorption processes and first order elimination. Weight and age were statistically significant predictors of CNP520 PK.

The drug effect was modeled by linking plasma CNP520 concentrations to CSF Aβ-40 concentrations via an indirect response population PK/PD model, in which CNP520 inhibited the Aβ-40 synthesis. This model estimated a maximal CSF Aβ-40 inhibition of approximately 95% with an IC50 of 28.4 ng/mL. Simulations on the external dataset were accurate with an estimation of approximately 60% CSF Aβ-40 inhibition at steady-state for a dose of 10 mg/day.

Conclusions: The PK of CNP520 and its PD effect were modeled and validated. The model was further used to derive CSF Aβ-40 inhibition for many different doses supporting the selection of doses for a long term prevention study of the disease.

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IV-53: *Miné De Kock* Population Pharmacokinetics of Sulfadoxine and Pyrimethamine: A pooled analysis to Inform Optimal Dosing in African Children with Uncomplicated Malaria.

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Objectives: To analyse pooled data from four previously published trials on the pharmacokinetics of sulfadoxine and pyrimethamine in children and adult patients, using nonlinear mixed-effects modelling and to evaluate the current dosing regimen and propose an optimised dosing regimen in children under the age of five.

Methods:

Pharmacokinetic (PK) data was pooled from 4 different studies (1,2,3,4) from the African countries of Mozambique, South Africa, Mali, and Malawi. The data from studies in Mali and Malawi were only from children while the data from studies in Mozambique and South Africa included both children and adults. Seven to ten samples were collect for each patient, with samples collected at pre-dose and day 1, 3 ,7 ,14, 21, and 28 in all patients. Nonlinear mixed-effects modelling was implemented in the software Monolix Suite 2016R1 (Lixoft, France) to analyse the PK data, and parameters were estimated using the Stochastic Approximation Expectation Maximization (SAEM) algorithm. The effect of weight - using allometric scaling (5), age - using maturation (5), weight for age z-score, study site, sex, baseline haemoglobin, mg/kg dose, concomitant medications, baseline parasitemia, and sample blood matrix were tested as predefined covariates. The -2 x log-likelihood value (-2LL), goodness of fit plots, visual predictive checks (n=1000), residual error plots, and Wald's test guided the model development.

Results: Differences in PK properties between adults and children were described with body size, age and weight-for-age z-scores. Underweight-for-age children were found to have 13.3% and 26.7% lower bioavailability of sulfadoxine and pyrimethamine respectively, for each unit of z-score below -2. Under WHO dosing recommendations, with simulation based predictions, patients who weigh 8-9 (-12%), 19-24 (-12%), 46-49 (-7%) and 74-79(-4%) kg have median sulfadoxine C_{day7} lower than the chosen efficacy target: 75% of the median C_{day7} of a typical patient (50kg), and the same for pyrimethamine in the weight-bands 8-9 (-22%), 14-24 (-18%) and 42-49 (-6%) kg.

Conclusion: Suboptimal sulfadoxine/pyrimethamine exposures in some weight bands given the current WHO recommended dose regimens were confirmed in this pooled PK analysis. We found that children who were underweight for age had decreased bioavailability with a greater effect on pyrimethamine. PK modelling and simulation was used to derive an optimised antimalarial dosing regimen.

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IV-54: *Mailys De Sousa Mendes* Predicting human foetal exposure using physiologically based pharmacokinetic models

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Objectives: Pregnant women and their foetuses are exposed to numerous drugs. However, due to obvious ethical reasons *in vivo* foetal risk assessment studies related to maternal drugs exposure remain extremely limited. The aim of this work was to develop a novel approach to quantitatively predict drug foetal exposure.

Methods: Physiologically based pharmacokinetic (PBPK) models were developed for 3 antiretroviral drugs, tenofovir (TFV), emtricitabine (FTC) and nevirapine (NVP) in Simcyp® for non-pregnant population. All known physiological changes that could impact the drugs PK were taken into account (i.e. change in body weight, glomerular filtration rate, enzymatic activity, plasma volume). After model verification against in vivo concentrations the model was further developed in R software to study foetal exposure. Transplacental transfer parameters were estimated from the ex-vivo human placenta perfusion experiments and then were implemented in the PBPK models. A sensitivity analysis was performed on physiological foetal parameters and transplacental transfer parameters to evaluate their impact on foetal and amniotic fluid PK. Model verification was done by comparing observed maternal and cord blood concentrations to predicted concentrations.

Results: PBPK models successfully predicted the disposition of two renally excreted drug (TFV and FTC) and one metabolized drug (NVP) in pregnant women. The maximum clearance increases were approximately 30% (TFV: 33%, FTC: 31%). Because of CYP3A4, 2D6 and 2B6 inductions, we predicted a clearance increase of 21 % and 38 % in late pregnancy after a single dose administration of NVP and at steady state respectively. Parameters obtained from the ex-vivo experiment allow the prediction of TFV, FTC and NVP concentrations that match observed cord blood concentrations. The foetal-to-maternal AUC ratios (0-24 h interval) were 0.63, 0.41, 0.77 for TFV, FTC and NVP respectively. Physiological foetal parameters as exchanges with amniotic fluid had no significant impact on foetal PK. Therefore, uncertainties on these physiological constants were not a major issue.

Conclusions: PBPK models are useful tool to *a priori* quantify drug exposure changes during pregnancy. Moreover, the integration of *ex-vivo* human placental perfusion parameters in these models is a promising new approach for predicting human foetal exposure to xenobiotics in late pregnancy.

IV-55: *Aurelia de Vries Schultink* Modeling of cardiac biomarkers in breast cancer patients treated with anthracycline and trastuzumab regimens.

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Objectives: Trastuzumab is used to treat HER2-receptor positive breast cancer patients. Trastuzumab treatment is associated with cardiotoxicity, manifesting as a decline of the left-ventricular ejection fraction (LVEF) values [1]. Patients treated with trastuzumab are often pretreated with anthracyclines, which are also known to induce cardiotoxicity. Troponine-T (TnT) is a molecular marker suggested to allow earlier detection of drug-induced cardiotoxicity. In this analysis we aim to quantify the kinetics and exposure-response relationship of TnT and LVEF measurements, in patients receiving anthracycline and trastuzumab treatment.

Methods: Repeated measurements for cardiotoxicity biomarkers LVEF and TnT were available from a previously randomized clinical trial investigating protection for trastuzumab induced cardiotoxicity with candesartan [2] (n=206). Individual patient dosing records of anthracycline and trastuzumab were also available. The mean PK of trastuzumab was described using a previously published PK model [3]. A K-PD approach [4] was used for the anthracyclines (doxorubicin and epirubicin). We used a single effect-compartment model to associate drug exposure to the LVEF measurements and a turn-over model to associate anthracycline exposure to TnT concentrations.

Results: Anthracycline-induced cardiotoxicity translated into a peak increase of TnT, with a turnover time of 106 days (relative standard error (RSE) 8%). De linear slope effect of anthracycline on the Kin rate for TnT was significantly affected by the type of anthracycline administered, translating into a decrease in the slope parameter by 0.521 (RSE 17%) for epirubicine compared to doxorubicine. Trastuzumab-induced cardiotoxicity translated into a decrease of LVEF values, which recovered after treatment (recovery half-life of 57 days, RSE 22%). The maximum TnT concentrations during anthracycline treatment were related to the baseline LVEF values before start of trastuzumab.

Conclusions: A PK/PD model was developed, describing the relationship between trastuzumab exposure and LVEF and the relationship between anthracycline exposure and TnT. This analysis demonstrated, as previously reported, that the decline in LVEF recovers after treatment cessation. In addition, the maximum TnT concentrations during anthracycline pretreatment affected the baseline LVEF value before start of trastuzumab-treatment and can therefore possibly identify patients susceptible for cardiotoxicity.

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IV-56: *Neel Deferm* Modeling of telmisartan disposition in sandwich-cultured rat hepatocytes. Does cryopreservation change disposition kinetics?

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Objectives: To develop a physiological model which describes hepatic uptake, metabolism and biliary excretion of the angiotensin II type-1 receptor antagonist telmisartan and its glucuronide in sandwich-cultured rat hepatocytes (SCRH) and to utilize it to quantify differences in estimated kinetic parameters between cryopreserved and freshly-isolated hepatocytes.

Methods: *In vitro* disposition data were obtained by incubating SCRH (freshly-isolated or cryopreserved) with 1,3,10 or 20 µM telmisartan. Incubation buffers containing telmisartan and its glucuronide were collected, followed by cell lysis to determine intracellular levels. Additionally, biliary excretion of telmisartan and its glucuronide were calculated. An ordinary differential equation (ODE) model was fitted to concentration and amount-time profiles using NONMEM v7.3.0 [1]. The model includes compartments representing the buffers, cells, bile and cells+bile with compound distributed among them through both linear and non-linear processes. Cell source (freshly-isolated or cryopreserved) was implemented as a covariate in the dataset and its effect on parameter values was assessed by the difference in objective function values (log likelihood ratio test and Akaike criterion).

Results: A mechanistic eight-compartment model was developed which adequately described the *in vitro* disposition of telmisartan and its glucuronide. Passive diffusion clearance and kinetic parameters for active uptake of telmisartan from the medium compartment to the intracellular compartment were estimated to be 3 (±12%) µL/min ($CL_{u,int,pass}$), 260 (±15%) pmol/min/well ($V_{max,act}$) and 10 (±19%) µM ($K_{m,act}$). The biliary excretion rate constants of telmisartan and its glucuronide were estimated at 3 (±10%) min^{-1} (K_{bile}) and 7 (±6%) min^{-1} ($K_{bile,glu}$), while estimates of metabolism kinetic parameters were 225 (±13%) pmol/min/well ($V_{max,met}$) and 33 (±17%) µM ($K_{m,app,met}$). Covariate analysis showed a significant effect ($p < 0.01$) of cryopreservation on K_{bile} (fresh: 3 (±18%) min^{-1}, cryo: 2 (±10%) min^{-1}), $V_{max,met}$ (fresh: 930 (±10%) pmol/min/10^6 cells, cryo: 1768 (±10%) pmol/min/10^6 cells), $K_{bile,glu}$ (fresh: 7 (±18%) min^{-1}, cryo: 6 (±10%) min^{-1}) and $V_{max,act}$ (fresh: 1545 (±17%) pmol/min/10^6 cells, cryo: 2936 (±17%) pmol/min/10^6 cells).

Conclusions: Modeling of *in vitro* telmisartan disposition suggests that cryopreserving rat hepatocytes affects biliary excretion, metabolism and uptake of telmisartan and its glucuronide in SCRH.

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IV-57: *Douglas J. Eleveld* How many bits of information did my study provide? Examining Kullback-Leibler divergence, standard errors and shrinkage

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Objectives: To explore Kullback-Leibler divergence (information gain) as a measure of information gained by model estimation. A useful information measure should 1) have units of *bits*, a natural unit of information, 2) should increase proportionally with increasing number of individuals 3) increase with the number of observations per individual, 4) increase with decreasing observation error 5) increase with decreasing parameter relative standard-error, and 6) insensitive to non-eta-influential individuals.

Methods: Simulated data sets were constructed using NONMEM V7.3.0[1] using a one-compartment PK model with absorption. The number of simulated individuals, number of observations per individual, and observation error were varied. The directed Kullback-Liebler divergence of the (assumed multivariate normal) individual posthoc estimates (NONMEM eta and phi) from the population estimate were calculated and the sum (or average per individual) evaluated as a measure of the total quantity (or average quality) of information obtained from model estimation from data. Parameter relative standard errors and shrinkage were also calculated for comparison.

Results: For the model and datasets tested, the total individual Kullback-Liebler divergence satisfied all of the expected properties of a measure of information. In contrast, parameter shrinkage does not reflect parameter certainty when individuals vary in informativeness. A close relationship was observed between parameter shrinkage and the average (per individual) single parameter (1-dimensional) Kullback-Leibler divergence.

Conclusions: The sum of the Kullback-Liebler divergences of the individual posthoc estimates from the population estimate may be a useful as a quantification of the amount of information obtained from model estimation. It can be interpreted in a per-experiment, per-parameter, or per-individual context. The approach avoids a number of shortcomings of shrinkage as an information quality (or quantity) measure. The approach allows model diagnostics to summarize the total amount of information gained by model estimation in a natural unit of information, the *bit*.

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IV-58: *Chenhui Deng* Tofacitinib exposure-response modeling of partial Mayo score in ulcerative colitis patients in phase 3 induction studies

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Objectives: Tofacitinib is an oral, small molecule Janus kinase inhibitor that is being investigated for ulcerative colitis (UC). This analysis aimed to characterize the relationship between tofacitinib exposures and partial Mayo score (PMS) over time and identify covariates that may impact exposure-response of tofacitinib as induction therapy.

Methods: Two phase 3 induction studies were analyzed. Categorical PMS (range 0-9) from 1161 patients (pts) receiving either placebo (234pts), 10 (905pts) or 15 mg (22pts) tofacitinib twice daily were analyzed using FOCE with Interaction in NONMEM. A proportional odds model was used to describe the probability of each PMS. The following characteristics were tested as covariates on tofacitinib efficacy using a stepwise covariate modeling approach: race, age, sex, baseline albumin, baseline body mass index, concomitant medication (oral steroid, immunosuppressant or 5-ASA), Mayo score at baseline, prior tumor necrosis factor inhibitor (TNFi) failure and non-failure. Likelihood ratio test and simulation approach such as visual predictive checks (VPC) were applied for model selection and evaluation.

Results: A longitudinal proportional odds model was built to fit the data and steady-state average concentration was used as an exposure metric describing linear drug effect. The time courses of placebo and drug effect were characterized by exponential equations. The final model included baseline albumin on baseline logit value and TNFi failure on placebo effect. The half-life of onset of drug effect, after accounting for onset of placebo response, was estimated to be 1.24 weeks, indicating hysteresis between plasma tofacitinib concentration (half-life = 3h) and drug effect. VPC results indicated the final model described data adequately except for the 15mg group due to the small sample size. Simulations were conducted to illustrate the model-predicted drug efficacy and the influence of covariates. For a reference pt, >95% of maximum effect was achieved at Week 8 (end of the induction treatment period), and 68% of the Week 8 effect was achieved by Week 2. In pts who did not fail TNFi, PMS decrease from baseline was 3.35, compared to a decrease of 2.62 in pts with prior TNFi failure.

Conclusion: The proposed longitudinal proportional odds model adequately describes exposure-response of PMS for the induction studies. Onset of efficacy was achieved within 2 weeks of start of induction therapy, with near-maximal effect by Week 8.

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IV-59: *Menshykau Denis* Computational Modelling of Personalized Hemodynamic Response to Valve Replacement Surgery in Heart Failure Patients

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Objectives: A Cardiovascular (CV) Systems Pharmacology Platform (SPP) is being developed, with the aim to predict whole-body hemodynamic response to pharmacological or other interventions [1]. The capabilities of CV SPP are exemplified here by modelling hemodynamic changes in patients enrolled into a publically funded and currently conducted clinical study (SMART) on heart failure (HF) patients with aortic stenosis (AS). Patients enrolled into SMART study undergo aortic valve (AV) replacement surgery.

Methods: The CV SPP includes a detailed description of the CV physiology and is developed in the Open Systems Pharmacology Suite [1,3,4]. To model HF patients enrolled into the SMART study, the model was modified to account for non-linear resistance in AV [4]. Based on the individual patient data before/after the surgery the CV model was individually fitted to recapitulate pressure gradients across AV as well as other hemodynamic characteristics. Mechanistic modelling of the CV system was complimented with data-driven approaches to identify covariates and significant changes in biomarkers.

Results: Analysis of CV model parameters demonstrates that patients with aortic stenosis – in contrast to healthy individuals - have elevated peripheral resistance, reduced arterial compliance and altered myocardium function. The pressure-volume loops inferred from the patient data demonstrate that AV replacement drastically reduces systolic pressure in the left ventricle. Overall inter-individual variability of parameters describing heart mechanics was larger than those describing vasculature. Statistically significant (Welch's test) and physiologically meaningful reduction in cardiac mass within a few months after the surgery was also observed. We finally discuss approaches to predict outcomes of AV replacement surgery.

Conclusions: Personalized computational models for the CV system of HF patients before and after AV replacement surgery are developed. Analysis of model parameters inferred from the patient data provides additional information about the changes in the CV system induced by the surgery. Using the identified hemodynamic changes in the current patient population, the CV model enables predictions of valve replacement surgery outcome in AV stenosis patients. This, in turn, will facilitate an informed adjustment of the concomitant pharmacologic medication. Data-driven analysis complements modelling for the variables, currently not accessible with mechanistic model.

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IV-60: *Paolo Denti* Lopinavir/Ritonavir Super-boosting Overcomes Interactions In Children Treated With Rifampicin: A Model-Based Approach For Non-Inferiority Trials

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Objectives: The 1st-line HIV treatment for infants includes lopinavir/ritonavir 4:1 (LPV/r). In high-burden settings, rifampicin (RIF) co-treatment for tuberculosis (TB) is common and lowers LPV exposure. Adding ritonavir (RTV) to achieve a 4:4 ratio (super-boosting) is effective, but PK was studied in 15 children only [1].

Methods: A study in South Africa compared the PK of super-boosted LPV whilst on concurrent RIF, with LPV/r alone in children weighing 3-15 kg. The objective was to prove non-inferiority defined as no more than 10% difference (with 95% confidence) in the proportion of children not achieving the therapeutic target of LPV morning Cmin>1 mg/L [2]. Blood was taken before and 1, 2, 4, 6, 10 h after dosing at 3 visits: while on LPV/r super-boosting after 1-2 months of RIF (PK1) or in the last month of RIF (PK2), and while on normal LPV/r 4:1 at 4-6 weeks after stopping RIF (PK3). Data was modelled in NONMEM 7.3. Pre-dose concentrations were modelled with a baseline approach (B2, from [3]) to handle poor information on prior doses. A structural model developed on PK1 was used to fit PK2 and PK3 data for the comparison, after adding flexibility by allowing the inclusion of separate typical values for all parameters at each PK visit and BSV and BOV whenever possible, irrespectively of statistical significance. A nonparametric bootstrap (n=500) assessed parameter uncertainty and the estimates from each iteration were used for simulations of PK profiles (n=10 000) assuming a 30% decrease in clearance overnight to account for the known diurnal variation [4]. The percentage of model-simulated morning Cmin<1 mg/L at PK2 and PK3 was compared to obtain a 95% CI and assess non-inferiority.

Results: Of 96 children enrolled, 80 completed the study. A 1-comp PK model with 1st-order absorption and elimination suitably fitted the data, allometric scaling adjusted for weight, and no effect of age could be identified. The simulated percentage of children below target with super-boosting was 7.6% (95% CI: 0.4%, 16.2%) and on normal dose was 8.8% (0.6%, 19.8%), thus resulting in a difference of -1.1% (-6.9%, 3.2%) and confirming the non-inferiority of LPV exposure during super-boosting compared with standard LPV/r.

Conclusions: LPV super-boosting during RIF treatment is as effective as standard dosing alone to achieve the therapeutic target. We suggested and successfully implemented a model-based approach to evaluate non-inferiority (or other comparisons) of PK exposure.

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IV-61: *Solène Desmée* Mechanistic joint modelling for longitudinal PSA and survival data in advanced metastatic prostate cancer

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Objectives: In phase III clinical trials, treatments for metastatic Castration-Resistant Prostate Cancer (mCRPC) are evaluated on their impact on time-to-death. Prostate-specific antigen (PSA) is frequently monitored as it is assumed to be linked to survival. Using nonlinear joint modelling which consists in the simultaneous analysis of biomarker's evolution and survival [1,2], we aim here to characterize the relationship between PSA kinetics and risk-of-death and identify the impact of covariates on both processes, in mCRPC patients from the phase III study Proselica [3] who were previously non-responders to docetaxel and treated as second-line chemotherapy by Cabazitaxel.

Methods: 9443 PSA measurements from 1174 patients were used. 580 received Cabazitaxel at dose 20 mg/m² and 594 at dose 25 mg/m². The model developed in [4] relying on 3 mechanistic differential equations describing the PSA production by treatment-sensitive (S) and –resistant tumor cells was adapted to the main mechanism of action of Cabazitaxel, the stimulation of the S cells elimination. For joint modelling several links between PSA kinetics and risk-of-death were compared by BIC. After exploration of the impact of covariates on the individual Empirical Bayes Estimates (EBEs) and on Weibull survival model, stepwise elimination from the full joint model was carried out. Estimations were conducted using the SAEM algorithm [5] of Monolix2016R1. Model evaluation was based on individual weighted residuals (IWRES) and on Cox-Snell and Martingale residuals.

Results: The joint model involving current PSA provided the smallest BIC. The treatment increased the stimulation of the S cells elimination with a factor 1.6 and 1.9 for the doses 20 and 25 respectively, in absence of other covariates. Several covariates showed a significant effect on PSA and/or survival. In particular, the presence of liver metastases impacted both PSA kinetics and risk-of-death. Although the decrease of PSA was more pronounced in the 25mg/m² group compared to the 20mg/m² group, the difference appeared too small to significantly impact survival.

Conclusions: This mechanistic joint model developed in advanced prostate cancer allowed to study treatment response in subgroups of patients and identify covariates associated with survival. It could be used in personalized medicine to predict patient's risk-of-death from baseline covariates and longitudinal measurements.

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IV-62: *Cheikh Diack* A model-based meta-marker to characterize the response to ranibizumab in wet AMD patients

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Objectives: To derive a composite parameter (meta-marker) from the baseline characteristics that quantitates the high heterogeneity in response to ranibizumab and in deterioration of vision in wet AMD.

Methods: An empirical drug-disease progression model for visual acuity (VA) was developed on the 24-month patient level data from phase 3 and 4 trials of ranibizumab (MARINA, ANCHOR, PIER and HARBOR). Details of the trial designs and patient characteristics have been reported previously [1,2]. Data from untreated patients (sham) were included. The model (an updated version [3]) describes the change over time in VA of patients receiving ranibizumab or sham injections in three components: baseline of VA, decay of VA over time and drug effect on VA.

The influences of available baseline covariates from fundus fluorescence angiography (FFA) and from optical coherence tomography (OCT) on all model parameters were tested.

Results: Using the final model, a meta-marker that is a function of baseline covariates was derived. The meta-marker is a single value which can be determined at entry into the trial and allows the characterization of individual AMD patients into “poor”, “moderate” and “super” responders to ranibizumab treatment. In addition to this innovative tool for the prediction of response at study entry, we show that “poor” and “super” responders, when assessed by the change from baseline are comparably benefiting from treatment when drug response is assessed as the simulated change from the untreated progressed state.

Conclusions: The proposed model-based meta-marker can prove to be an important factor in explaining the heterogeneity in response to ranibizumab treatment. Based on the model we also suggest that the main difference between “poor” and “super’ responders is that the former would have a much greater deterioration in VA if left untreated than the latter patient population.

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IV-63: *Christian Diedrich* Towards population physiology based pharmacokinetics modelling (popPBPK) in an industrial environment

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Objectives: Establish Bayesian Population Physiology based Pharmacokinetics (popPBPK) workflow

Methods: Over the last decade whole body physiology based pharmacokinetics (PBPK) has become an established tool for rationalising drug absorption distribution metabolism and excretion (ADME) at a mechanistic level (see e.g. [1]). In order for these approaches to be applied in a statistically sound population approach we have established a Bayesian hierarchical modelling framework [2]. In this way, the vast available prior knowledge on physiological parameters can be incorporated into statistical inference of population PBPK (popPBPK) models. Sampling of the high dimensional (several hundred parameters) posterior distribution of the hierarchical model parameters is done using a tailored Markov Chain Monte Carlo algorithm.

Results: A workflow for setting up and performing popPBPK calculations based on physiological prior knowledge from the PK-Sim [3] data base as well as clinical PK data has been established and will be presented. The workflow will be applied to a typical use case. We will demonstrate that PBPK models can be qualified in a statistically rigorous fashion given (clinical) data, a model structure and prior knowledge using established population PK techniques. Additionally methods of information theory can be used in order to quantify differences between prior and posterior distribution. Using this approach full control of the information flow from clinical data into the popPBPK model is achieved. The popPBPK model is then used to break PK population variability as well as uncertainty down to physiological parameters.

Conclusions: A popPBPK workflow for deriving Bayesian hierarchical population models given prior knowledge, PBPK model structure and clinical data using MCMC sampling has been established. We thereby provide a statistically sound methodological framework for qualifying PBPK models against clinical data sets and measuring the flow of information from data into population models. The population models assessed in this way are then used for simulating untested scenarios with controlled Bayesian credible levels.

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IV-64: *Richard Dimelow* Effect of dataset characteristics on estimation method performance: a TMDD model example

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Objectives: Expectation maximisation (EM) algorithms included in NONMEM from version 7.0 have shown increased numerical stability and reduced parameter bias in comparison to the traditional gradient based algorithms, FO and FOCE, in a selection of models [1, 2]. The aim of this work is to compare the performance of the FOCE and importance sampling EM methods in relation to different dataset characteristics. The target mediated drug disposition (TMDD) model [3] was chosen as the data descriptor.

Methods: As a reference, the model application by Ng and colleagues [4] has been selected. Phase 1-like datasets were simulated in different scenarios derived by the combination of low (15%) and high (30%) proportional residual variability, rich and sparse (50% of rich scheme) PK and PD sampling, and dose levels from a partial (2 dose levels) or full (3 dose levels) dose range. The variance of the inter-subject variability of the log-normally distributed parameters was estimated from the data. Argument settings for the importance sampling method were selected according to [2]. The comparison between estimation methods has been based on the following metrics: estimated versus true parameter values, standard error estimates of each parameter, number of iterations to convergence, and run time.

Results: The IMPMAP algorithm (importance sampling algorithm assisted by mode a posterior) was selected over the IMP algorithm for model parameter estimation, due to a more stable route to convergence. Both the FOCE and IMPMAP (with ISAMPLE=1000) algorithms successfully converged, and estimated well the fixed effect and residual model parameters, in all tested datasets. Run times were comparable between the FOCE and IMPMAP methods.

Conclusions: IMPMAP showed superior convergence stability over IMP when fitting a TMDD model to a PK/PD dataset. FOCE and IMPMAP performed equally well in the tested noise levels and sampling schemes.

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IV-65: *Christiane Dings* Mathematical modeling of glucose, insulin and c-peptide during the OGTT in pre-diabetic subjects: A DIRECT study

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Objectives: Development of a mechanistic model of glucose, insulin and c-peptide levels during an oral glucose tolerance test (OGTT) in pre-diabetic subjects with high risk of developing type 2 diabetes mellitus (T2DM).

Methods: Data from the Diabetes Research on Patient Stratification (DIRECT) study was used[1]. The subjects in the study were pre-diabetic, which was defined by the inclusion criteria of HbA1c <6.5% and fasting plasma glucose <10 mM without antidiabetic treatment, and a high risk of developing T2DM according to the DETECT2 risk algorithm[2]. All subjects underwent an OGTT. Glucose, insulin and c-peptide concentrations were measured before and 0, 15, 30, 45, 60, 90 and 120 min after oral glucose intake. Modeling and simulation was performed using non-linear mixed-effects methods implemented in the software NONMEM (version 7.3.0). Stochastic simulations were performed for model evaluation.

Results: The dataset included 2281 subjects and 54562 data points. Glucose, insulin and c-peptide concentrations were described simultaneously using one compartment turn-over models with zero-order synthesis or release rates (0.15 g/(l*h), 48.7 pM/h and 331 pM/h, respectively) and first-order utilization or degradation rates. Baseline levels of glucose, insulin and c-peptide were estimated as 1.01 g/l, 47.6 pM and 759 pM, respectively. Oral glucose uptake was described using a transit model with a first-order absorption rate constant (3.86 h^{-1}) and one transit compartment. The influence of insulin levels on the glucose utilization as well as the effect of glucose levels on the release of insulin and c-peptide were modelled using exponential effect models (effect rate constants of 0.7, 3.4 and 3.2, respectively). Further, the incretin effect was implemented as an additional release of insulin and c-peptide with linear dependency of the amount of glucose in the transit compartment. The precision of parameter estimates was excellent (residual standard error <12%).

Conclusion: An OGTT model simultaneously describing the changes in glucose, insulin and c-peptide levels was successfully developed for pre-diabetic subjects. The inclusion of both c-peptide and insulin release enabled the distinction between changes in beta-cell function and first pass clearance of insulin, which improved the characterization of the individual glycemic condition. In future application this model is planned to be used to observe and predict disease progression of T2DM.

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IV-66: *Mike Dunlavey* Use of distributed delay in PML

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Objectives: ODEs incorporating delay are called Delay Differential Equations (DDEs). They can be thought of as convolving an input function with a probability density function. In the case where the probability density function is a unit delta function at a delayed time, we call it "discrete delay". This is used to distinguish it from "distributed delay"(e.g. see [1]), in which the convolution is not with a delta function, but with a continuous probability density function. This can be used to model such things as absorption delay and delayed drug effect in a realistic manner.

Methods: A compartment-modeling statement was added to the PML language, and a previously existing function was extended, to incorporate distributed delay for the common case of a Gamma distribution. The Gamma distribution is useful in that it has a scale parameter (>0, corresponding to the mean delay time in our parameterization), and a shape parameter (>0). It models absorption and delayed drug effect well, and it has Exponential and Erlang distributions as special cases. If the optional shape parameter is not given, or if it exceeds a threshold, discrete delay is assumed.

Results: Predictions by the delay functions were compared against predictions obtained by superposition, with agreement within four or more decimal digits, over a variety of dosing histories and time scales. Performance appears to be comparable with multi-compartment models of absorption.

Conclusions: Further work will include extension to other distributions such as Weibull and log-normal distributions, and it will include processing to accomplish steady-state.

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IV-67: *Sulav Duwal* Multiscale, mechanistic pipeline to assess the prophylactic efficacy of anti- HIV compounds

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Objectives: While HIV-1 cannot be cured to date, pre-exposure prophylaxis (PrEP) has been suggested to halt the ongoing spread of HIV [1]. It requires that individuals take anti-retrovirals (ARVs) chronically, to avert infection in the case of exposure. Prophylaxis is the only method by which women can circumvent infection, however it can be anticipated that adherence levels are low in a roll-out and that individuals, unknowing of delays in the onset of drug action, may actually take the prophylaxis after exposure (PEP).

We developed a predictive mechanistic model for the efficacy of ARVs in the context of chronic PrEP, 'PrEP on demand' [2] and PEP. By coupling our model with drug-specific pharmacokinetics, we assess the mechanisms of prevention, the pharmacological limitations and opportunities for various prophylactic schedules using approved- and neglected drugs.

Methods: A technical difficulty was to estimate infection probabilities after viral challenge in a time-varying environment. We derived analytical solutions for the probability of virus clearance, depending on a constant, drug-class specific viral inhibition and fixed inoculum size. The latter was used to reduce the relevant state space of our stochastic model, where infection is reversible. We then develop an extrande algorithm, sampling the stochastic dynamics within the eradication polyhedron, considering the time- and dosing dependent efficacy of anti-retrovirals (ARVs). This allows proper PK-PD coupling to predict the stochastic endpoint (infection probability).

Results: We extend an existing framework [3], which allows integrating virus loads in the transmitter, mode of exposure and timing of viral challenge, with this time-dependent component to estimate the infection probability for unprotected sex for any particular ARV-prophylaxis. We observed drug-class specific prophylactic efficacies, with protease inhibitors exhibiting switch-like response profiles. Our simulations indicated that, unlike approved nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and integrase inhibitors may be highly efficient, even when used in 'PrEP on demand' or PEP. Specifically, we study the efficacy of dolutegravir, including inter-individual PK variation [4].

Conclusions: Our findings warrant further clinical assessment, particularly since some NNRTIs are extremely cost-efficient and thus suitable for large-scale rollout in resource-constrained settings.

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Dickinson, Margherita Bracchi, Emilie Elliot, Laura Else, Saye Khoo, David Back, Mark Nelson, Marta Boffito. Poster P094, HIV Drug Therapy, Glasgow 2016

IV-68: *Lisa Ehmann* Is a pooled population pharmacokinetic model predictive of plasma and microdialysate pharmacokinetics of linezolid in obese and non-obese patients?

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Objectives: Linezolid (LZD) is an oxazolidinone antibiotic exhibiting wide activity against gram-positive pathogens. Antibiotic concentrations at the site of infection are crucial for treatment success and can be obtained by the microdialysis technique. This work aims at investigating the applicability of a pooled population pharmacokinetic (PK) model [1] to predict LZD plasma and microdialysis data of a new population of obese and non-obese patients.

Methods: The evaluation dataset originated from 15 obese (BMI_{median}=45 kg/m^2) and 15 non-obese patients (BMI_{median}=24 kg/m^2, ~2/3 cancer patients) treated with 600 mg LZD (30-min i.v.) for infection prophylaxis before abdominal surgery. Rich sampling was performed for 8 h in plasma (n=269) and via microdialysis in the interstitial space fluid of s.c. adipose tissue (n=322). Unbound plasma concentrations were determined by ultrafiltration (n=90). For external model evaluation, concentration-time profiles of obese and non-obese patients were predicted using PK parameters estimated based on an overweight diabetic (BMI_{median}=31 kg/m^2) and a healthy population (BMI_{median}=23 kg/m^2), respectively. The MAXEVAL=0 functionality in NONMEM® 7.3 was used for Bayesian estimation of individual PK parameters. Model adequacy was assessed by goodness-of-fit plots, visual predictive checks and calculation of prediction errors (PE).

Results: The external model evaluation showed that maximum LZD concentrations were less well captured than those measured in the elimination phase: Whereas total and unbound *plasma* concentrations were underpredicted (PE_{median} of C_{total_max} obese/non-obese: -5.6%/-6.9%), an overprediction was observed for initial *microdialysate* concentrations especially in the obese population (PE_{median} of $C_{0\text{-}90min}$ obese/non-obese: 40%/28%), indicating slower tissue distribution in the patients of the evaluation dataset.

Conclusions: Although the overall model structure (2-CMT with nonlinear elimination) seemed adequate, the distribution processes did not seem satisfactorily captured. This might be caused by patient- and disease-specific differences in the populations underlying the original model building and model evaluation (e.g. regarding BMI, diabetes vs. non-diabetes, healthy volunteers vs. cancer patients). Next, the model will be further refined to adequately describe the PK of LZD in plasma and microdialysate and to ultimately assess the need of dose adjustments in the special population of obese patients.

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S-01: *Robert Bauer* DDEXPAND interface for coding delay differential equations based models in NONMEM

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Objectives: Models using delay differential equations (DDEs) can be coded as ordinary differential equations (ODEs) with the method of steps [1]. A drawback of method of steps is the large number of ODEs and delays making the DDE model implementation strenuous to code. DDEXAPND is a program that uses the method of steps to expand the base ODE's to include their time-delayed ODE's, and generate a NONMEM control stream for the DDE model.

Methods: DDEXPAND is a utility program that expands an NM-TRAN-template control stream to form a functional NMTRAN control stream to be run by NONMEM. DDEXAPAND requires for input a template text file (*.dde) with base model equations and a regular NONMEM data file (*.csv). The program outputs a text file (*.ctl) with a NMTRAN control stream and a modified data file (*.csv). DDEs are implemented in the *.dde file using the NMTRAN syntax for ODEs with additional structures accounting for delays (TAUy) on states x (AD_x_y) and their past conditions (state values for negative times) (AP_x_y). Published DDE models of rheumatoid arthritis (RA) development in collagen-induced arthritic mice [2] and influenza A virus (IAV) infection in humans [3] were used to test DDEXPAND functionality. Time courses for model states were simulated using NONMEM 7.3 [4] and compared with time courses generated by DDE solver dde23 in MATLAB (MathWorks, Natick, MA).

Results: The *.dde RA model has 8 base ODEs with one delay TAU1, two delay states AD_1_1 and AD_6_1, and two past condition equations for the delay states, AP_1_1 and AP_6_1. The *.ctl RA model generated by DDEXPAND had 4 additional ODEs that used the original 8 user-defined ODE's as their template. DDEXPAND also modified the *.csv file to include dose records for the additional ODEs. The *.dde IAV model has 5 base ODEs with one delay TAU1, one delay state AD_3_1, and one constant past equation for the delay state, AP_3_1. The *.ctl IAV model generated by DDEXPAND had 35 additional ODEs that used the original 5 user-defined ODE's as their template to cover a simulation time of 8*TAU1. For both models, simulated time courses of the model states were no different from analogous ones obtained by the MATLAB dde23 solver.

Conclusion: DDE based models can be implemented in NONMEM using the method of steps. DDEXPAND provides a convenient tool for propagating and coding DDEs in NONMEM. DDEXPAND solutions of DDE models are equally accurate as solutions obtained by standard DDE solvers.

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S-02: *Svetlana Freiberga* PsN and Xpose

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PsN is a toolbox for population PK/PD model building using NONMEM. It has broad functionality ranging from results extraction from output files to advanced computer-intensive statistical methods. Updates since PAGE 2016 include major extensions to simeval [1], a tool for simulation-evaluation diagnostics for outlier detection, updates to frem [2,3], a tool for full random effects modelling for covariate building, resmod [4], a new tool to evaluate different residual models, the addition of support for rmarkdown when using rplots greatly facilitating the automatic creation of reports, support for NONMEM 7.4 and the migration of the development and public webpages to github for simplified interaction with the community.

Xpose 4 is an open-source population PK/PD model building aid for NONMEM. Xpose attempts to facilitate the use of diagnostics in an efficient manner, providing a toolkit for dataset checkout, exploration and visualization, model diagnostics, candidate covariate identification and model comparison.

Xpose has customized functions for generating plots based on PsN output, and several of them can be automatically run by adding the -rplots option to the PsN command. This gives pdf documents with, for example, visual predictive checks as part of the PsN output, without the need to manually run any R script.

Both PsN and Xpose are freely available at https://uupharmacometrics.github.io/PsN/ and at http://xpose.sourceforge.net

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S-03: *Roger Jelliffe* The Pmetrics Population Modeling and Monte Carlo Simulation, and BestDose Clinical, Software

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The **Pmetrics** population modeling software runs on Windows or Mac machines, and is imbedded in R. The user defines a structural PK/PD model The data files are entered. along with the instructions. Routines for checking data files and viewing results are provided. Likelihoods are exact, behavior is statistically consistent, and parameter estimates are precise [1]. **Rigorous Monte Carlo simulation** is provided which **preserves the unique discrete point mass** nonparametric models. The **Pmetrics** and **BestDose** software is available free by license from Dr. Neely.

The **BestDose** clinical software [2] uses **Pmetrics** population models, currently for a 3 compartment linear system. More complex and capable software to manage multiple nonlinear interacting multidrug systems is in development. **BestDose** computes the dosage regimen to hit desired targets with minimum expected weighted squared error, thus providing **maximal precision in dosage regimen design**, a feature **not seen with any other currently known clinical software**. Models for planning, monitoring, and adjusting therapy with aminoglycosides, vancomycin (including continuous IV vancomycin), digoxin, carbamazepine, and valproate are available.

The interacting multiple model **(IMM)** Bayesian fitting option [3] now allows parameter values to change if needed for analysis of acutely ill unstable patients with high intrapatient variability, and provides the most precise tracking of drugs in over 130 clinically unstable gentamicin and 130 vancomycin patients [4].

Multiple model optimal **(MMopt)** sampling strategies for developing the **most informative TDM protocols** are also available, using a new strategy not based on Fisher information, but rather on **minimizing the Bayes risk** of misclassification of the nonparametric support points which make up the population and each patient's individual models. MMopt outperforms the methods based on Fisher information such as ED, EID, and E log D optimal. MMopt also does not require 1 sample per parameter but can also use only one or two samples as desired [5,6].

In all the software, creatinine clearance is estimated based on one or two either stable or changing serum creatinines, age, gender, height, and weight [7].

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S-04: *Daniel Röshammar* Simulo – a platform for advanced model based simulations using R

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Objectives: Clinical trial simulation is a powerful tool in the optimization of study designs and for making model-based inference. However, including all various aspects of the model, the target population and the experimental design may be complex and time-consuming. Adequate post-processing, integration and visualisation of the simulated data, needed to convince decision-makers, is not always a trivial task. Simulo was developed to offer a clear framework and user-friendly interface with the ability to simulate and visualise the likely outcome of clinical studies or dosing scenarios, using public or custom-developed nonlinear mixed-effects models.

Methods: Simulo is a Java-based application running on an R backend with a graphical user interface. Simulations are performed after automatic translation of a user defined model and study protocol to R code, followed by efficient execution of the code. The model can be described through algebraic, ordinary and/or delayed differential equations. Model parameters can include different levels of uncertainty and variability. Inclusion criteria, treatments (route of administration, dosing schedule), observations (type and sampling schedule) and study designs are easily defined. If and whenever desired, the user may directly modify the R code and include various R-packages as fit for purpose. Moreover, the resulting simulation code may always be executed outside of Simulo in any standard R environment.

Results: Simulo comes in two versions. Simulo Light, a limited version, is offered for free to scientists who wants to illustrate the model based results from a single or few simulation replicates, to familiarize with the strengths of simulation and for training purposes. Simulo Expert is the full version, recommended for intensive simulation projects where models are used to more thoroughly address key questions in project work. Any empirical or advanced PK/PD and disease model may be applied in simulation scenarios of all complexities. Recent applications of Simulo showed how simulations can help in predicting the effect of dose adaptation on clinical endpoints as well in comparing different study designs and data analysis approaches.

Conclusions: Simulo offers a platform for all sorts of model-based simulation activities, both for experienced and non-technical users. Simulo can facilitate both internal and regulatory decision making in a clear and visually attractive way.

S-05: *Tarjinder Sahota* NMproject: Tidy, Reproducible, Script Based NONMEM projects in RStudio. A Step Toward Pharmacometric Industrialisation.

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Objectives: Modern computer systems should allow organisations and individuals to efficiently manage knowledge. Have you ever spent time implementing model code you later found out had already been implemented by someone else? Have you ever had to continue a colleague's work but struggled to figure out what he/she did? Have you ever wasted time rerunning NONMEM and reproducing all post processing steps because of a small change to the dataset? Have you ever had trouble reproducing a plot because an R package may have been updated? We aim to develop an R package to overcome these challenges.

Methods: Two R packages have been created:

TidyProject: Directory and code management with a code repository interface.

NMproject: all functionality of TidyProject with a light interface to NONMEM from R for script based model development (requires installation of NONMEM and Perl speaks NONMEM (PsN)).

Installing NMproject will install both packages. They will soon be released on the Comprehensive R Archive Network (CRAN), but are currently available on GitHub via the following R command:
devtools::install_github("tsahota/NMproject")

Results: AstraZeneca employees have successfully used NMproject to conduct NONMEM model development for over a year. Features include:

Tidy directory structure: Standardised, version controlled, directory structure for all NONMEM users.

Code library: Import NONMEM/R template scripts and functions into your project from a built-in code repository. Functionality to attach your own code repositories (can be simple directories of R scripts or NONMEM control streams). Search the code library using keywords, tags, or raw text search.

Private project library: Store R packages and version information alongside scripts in project directory. Aids in project reproducibility and portability.

Script based model development: Code your model development process using end-to-end R scripts. Switch between interactive and non-interactive mode.

Shiny run monitor: Shiny GUI interface for run management, monitoring and results comparison.

Conclusions: NMproject is a prototype of industrialised knowledge management for NONMEM and R users.