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## **I-10 Christian Bartels Population PK Model for Pooled Data of Different Oral Diclofenac Formulations**

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**Objectives:** Diclofenac is available in different oral formulations, which are known to have considerable interindividual and intraindividual variation in their plasma PK profiles. To provide a common framework for the description of existing oral formulations and their variability, a population PK model is developed based on data from multiple studies in healthy subjects.

**Methods:** The population PK analysis was performed using the non-linear mixed effects modeling software NONMEM(R) version VI 2.0. The data set was pooled from PK studies of six formulations, including two immediate release formulations with a total of 114 individuals, a mixed release formulation with 21 individuals, a slow release formulation with 12 individuals and an enteric coated form with 21 individuals. A total of 3399 plasma samples were used. The data includes single and multiple dose data. The absorption profiles for some of the formulations had characteristic delays and inter-occasion variability.

**Results:** A two compartment model is used. The absorption is modeled with two first order absorption compartments using lag times, coupled with two sequential first order processes. The two absorption compartments are characterized by a fast and slow absorption rate, respectively. Differences between formulations are described with covariates on absorption rates, relative bioavailabilities, residual errors, fraction that is rapidly or slowly absorbed, and lag times. Inter-individual variability is included on the clearance; inter-occasion variability is included on lag time and absorption rates.

**Conclusions:** Significant differences of the formulations, pronounced inter-individual and inter-occasion variability of some of the formulations pose challenges. The comparatively simple model provides a good description of the different formulations. The formulations are characterized by absorption rates ranging from 5 h<sup>-1</sup> to 0.06 h<sup>-1</sup>; lag times range between 8 min and about 1 h. Possible improvements of the model are discussed.

### **I-35 Vicente G. Casabo Bioequivalence trials simulation to select the best analyte for acetylsalicylic acid**

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**Introduction:** The analyte (parent drug or metabolite) to be evaluated in bioequivalence trials is still today a controversial issue, with different solutions in EMA and FDA guidance:

- FDA: Measurement of a metabolite may be preferred when parent drug levels are too low to allow reliable analytical measurement. Measurement of metabolite(s) is required in addition to the parent drug when metabolite(s) contributes meaningfully to safety and/or efficacy and is(are) formed as a result of pre-systemic metabolism [1].
- EMA: When an inactive pro-drug have low plasma concentrations and is quickly eliminated, it is acceptable to demonstrate bioequivalence for the main active metabolite instead of parent compound. The use of a metabolite as a surrogate for an active parent compound can only be considered if it is not possible to reliably measure the parent compound, and if the metabolite formation is not saturated at therapeutic doses [2].

The EMA and FDA guidelines generally recommended measuring the parent drug bioequivalence, but the situations in which are recommended the measurement of metabolite are different. The objective is to evaluate which analyte (parent drug or metabolites) is more sensitive to detect changes in the quality of the problem medicinal product.

**Materials and methods:** The pharmacokinetic model used represents the LADME process of ASA administered orally in a solid dosage form for immediate release. Different scenarios depending on the in vivo dissolution constant of the problem formulation and dose have been considered. A semi-physiological model was used including pre-systemic intestinal and hepatic metabolism and Michaelis-Menten elimination with two metabolites (first and second-generation metabolites of ASA) [3]. The studies were simulated using NONMEM VI.

**Results:** The plasma concentration-time population fit the experimental curves of the literature [4], so the model is considered validated. The analyte sensitive to decline in quality is the ASA, and the decrease of ratios of AUC and C<sub>max</sub> is more noticeable with increasing dose. The percentages of bioequivalence when drugs are not bioequivalent is lower for the parent drug, and this percentage decreases with increasing dose.

**Conclusions:** The ASA is more sensitive than its metabolites to detect the decrease in pharmaceutical quality. The measurement of metabolites of first and second generation does not provide any additional information to the parent drug.

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## **I-62 Kristin Dickschen Pharmacogenomics of Tamoxifen In Female Patients: A PBPK Model-based Investigation Including The Three Main Metabolites**

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**Objectives:** This work establishes a coupled physiologically-based pharmacokinetics (PBPK) model for tamoxifen, N-desmethyltamoxifen, 4-hydroxytamoxifen and endoxifen that is able to describe their pharmacokinetics (PK) in female patients of different cytochrome P450 (CYP) 2D6 phenotypes [1].

**Methods:** As no human plasma concentration-time data following intravenous (i.v.) administration was available, a tamoxifen PBPK model was developed for i.v. administration of tamoxifen to rats in order to describe the disposition behavior of tamoxifen. The rat model was extrapolated accounting for human physiology. This human tamoxifen PBPK model served as a template for PBPK-models of N-desmethyltamoxifen, 4-hydroxytamoxifen and endoxifen [2]. The coupled model was used to extrapolate PK profiles for the four substances following tamoxifen single and multiple oral dose administrations to female patients with different CYP2D6 phenotypes [3,4].

**Results:** The rat PBPK model of tamoxifen is able to describe the disposition kinetics of tamoxifen after a single i.v. dose. Compared to experimental data, the coupled human PBPK model describes the plasma concentrations of tamoxifen, N-desmethyltamoxifen, 4-hydroxytamoxifen and endoxifen after single and multiple oral dosing of tamoxifen. The integration of known phenotype specific CYP2D6 enzyme activities into the coupled tamoxifen-endoxifen PBPK model leads to the formation of differing endoxifen plasma concentrations as reported in the literature.

**Conclusions:** The established PBPK model is able to describe the PK of tamoxifen and its three main metabolites in virtual female patients. Furthermore, the model can describe the influence of CYP2D6 phenotypes on plasma concentrations of endoxifen. The coupled PBPK model will be used to further investigate physiological variability in populations, especially the influence of characteristic CYP2D6 phenotype distributions in different geographical regions. Also, the model will allow the investigation of CYP2D6 inhibition and CYP3A4/5 inhibition or induction and the subsequent impact on plasma and tissue concentrations of parent drug and active metabolites. Finally, the PBPK model can be extended in order to simulate tumor response with respect to tamoxifen and endoxifen plasma and tissue concentrations influenced by CYP2D6 activity in different virtual patient populations as outlined in [5].

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## **II-20 Ludivine Fronton Monoclonal Antibody Disposition beyond Target Binding: Impact of FcRn on Clearance and Derivation of Mechanistic Compartment Models**

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**Objectives:** Despite the detailed knowledge of the molecular processes involved in the disposition of monoclonal antibodies (mAbs), the development of compartment models to describe mAbs pharmacokinetic data is largely empirical. There is no established strategy to translate the mechanistic understanding into design criteria that guarantee consistency of the structural model with the current knowledge. The objective of this work is to transpose the mechanisms involved in mAbs disposition, when the target is not expressed, from a detailed physiologically-based pharmacokinetic (PBPK) model into a low-dimensional compartment model while retaining a mechanistic interpretation of the pharmacokinetic parameters. The mechanistic nature of the PBPK model allows oneself to assess the relation between the saturation level of the neonatal Fc Receptor (FcRn) and endogenous immunoglobulins type G (IgGendo) and its impact on mAbs disposition.

**Methods:** The experimental venous plasma data of the mAb (7E3), administered intravenously at 8 mg/Kg, were extracted from [1] for FcRn-knockout and wild-type mice using the software DigitizeIt, version 1.5.8a. The steady-state plasma concentration of total IgGendo was reported in [2]. MATLAB R2009a was used for modelling and simulations (ode15s solver with default options). To reduce the dimensionality of the PBPK model we extended the lumping approach presented in [3].

**Results:** The lumping of the PBPK model resulted in a 2-compartment model. The central compartment comprised the plasma and the interstitial spaces of all tissues/organs of the PBPK model, while the peripheral compartment included all the endosomal spaces where the non-linear FcRn-mediated salvage of IgGendo and mAb occurs. We observed that the steady-state (SS) level of IgGendo was not perturbed by the administration of the mAb. Consequently, the SS-IgGendo concentration solely determined the level of saturation of FcRn so that the mAb clearance in the endosomal space appeared to be linear.

**Conclusions:** Based on the extension of the lumping approach presented in [3], we reduced the 35-compartment PBPK model to a mechanistic 2-compartment model which successfully described the experimental plasma concentration-time profiles of the mAb 7E3 in mice. The therapeutic mAb exhibited a linear clearance from the endosomal compartment, even if the FcRn system is not fully saturated.

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## **II-40 Emilie Hénin Meta-analysis of Magnetic Marker Monitoring data to characterize tablet movement through the gastrointestinal tract**

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**Objectives:** The aim of this work was to develop a model predicting tablet movement through the Gastro-Intestinal (GI) tract, based on Magnetic Marker Monitoring data.

**Data & Methods:** Magnetic Marker Monitoring (MMM) is a novel technique to measure in real-time the location of a magnetically labeled formulation in the GI tract. In this work, 5 studies including in total 30 individuals in 94 occasions were considered. The mean residence time (MRT) of the tablet and associated uncertainty in proximal and distal stomach, small intestine, ascending, transverse and descending colon were estimated using a Markov model for probabilities of movement implemented in NONMEM 7 [1,2]. The effect of food intake and other covariates was also investigated on MRT for each GI region. The predictive performance of the model was evaluated based on simulations.

**Results:** Under fasting conditions, the typical MRT of the tablet was estimated to be 10.1 minutes in proximal stomach, 10.8 minutes in distal stomach, 228 minutes in small intestine (SI), 545 minutes in ascending colon, 135 minutes in transverse colon, and 285 minutes in descending colon.

A meal taken simultaneous to tablet intake was found to prolong tablet MRT 8.7 times in proximal stomach, and 20.1 times in distal stomach. A time-dependent function was added on the probability of gastric emptying, increasing the probability of tablet movement to SI of 73% each hour from 2.25 hours after meal.

The effect of a gastro-ileocecal reflex caused by a later meal (4 to 6 hours after tablet intake), described in the literature [3], could not be retrieved in the present data. Others covariates, such as time to censoring and study effect did not have a significant effect on the GI transit parameters.

**Conclusion:** This meta-model of MMM data represents an integration of information for tablet movement through GI tract under various food conditions. This model-based knowledge can be used as prior information in semi-mechanistic model for drug absorption, involving tablet position [4-5].

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### III-09 Donghwan Lee Development of a population model to describe diurnal and chronokinetic variation in cilostazol pharmacokinetics

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**Objectives:** Diurnal variation, characterized by higher  $C_{max}$  and shorter  $T_{max}$  after the morning dose in oral bid treatment, has been reported in many lipophilic drugs, which is known to occur due to higher GI perfusion rates and faster gastric emptying times in the morning. [1-3] The purpose of this study is to investigate such variation in cilostazol pharmacokinetics (PK), and assess seasonal or chronokinetic variation of the drug also.

**Methods:** A total of 1,889 cilostazol plasma concentrations were obtained from 2 PK studies recently conducted in healthy Korean subjects, Study 1 conducted in 26 subjects in February, and Study 2 conducted in 37 subjects in August. A population model was developed using NONMEM 7. To model diurnal variation, the circadian rhythm consisting of cosign functions with various periods were incorporated into the absorption rate constant (KA). Study effect was described as a covariate influencing the typical value of PK parameters. The developed model was then validated using visual predictive check (VPC) using 1000 simulated datasets.

**Results:** A two compartment model with first order absorption was selected for fixed effect, and proportional models for inter and intra-individual errors, allowing for a lag time. The final estimated values (CV%) of KA, oral clearance (CL/F), central volume (Vc/F), inter-compartment clearance(Q/F), peripheral volume (Vp/F) and lag time (LAG) were 0.236 hr<sup>-1</sup> (30%), 13.8 L·hr<sup>-1</sup> (29%), 31.1 L, 14.3 L·hr<sup>-1</sup> (20%), 85.4 L (55%), and 0.236 hr<sup>-1</sup> (%), respectively. The circadian rhythm was best described by the combination of periods of 24 and 12hrs, yielding estimated values (CV%) of amplitude and acrophase for 24 hour rhythm being 0.195 (70%) and 0.668, and those for 12 hour rhythm being 0.314 (30%) and 7.27, which decreased OFV by 336.20. Study difference was found significant in CL/F (p<0.001), yielding 9.4 L·hr<sup>-1</sup> in Study 1 versus 13.8 L·hr<sup>-1</sup> in Study 2. VPC showed the good performance of the model.

**Conclusions:** These results show that cilostazol PK in Korean population are influenced not only by diurnal variation but also by seasonable variation, indicating the importance of considering such variations in optimal drug therapy of this drug. To validate our results, further study with more patients will be necessary.

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### **III-26 *Eugeniy Metelkin* A Systems Pharmacology Model of Anandamide Dynamics After FAAH Inhibitor Administration**

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**Objectives:** Fatty acid amide hydrolase (FAAH) is an integral membrane enzyme hydrolyzing the anandamide and related amidated lipids. Previously it was shown preclinically that the inactivation of FAAH produces analgesic, anti-inflammatory, anxiolytic, and antidepressant effects indicating that FAAH may be a promising therapeutic target. This work describes a detailed mathematical model of anandamide and other ethanolamides kinetics that have been used for analysis of clinical data of PF-04457845 (Pfizer), a highly selective inhibitor of FAAH.

**Methods:** The developed model includes the synthesis and hydrolysis of five major ethanolamides (AEA, OEA, PEA, LEA, SEA) in different tissues and organs as well as the processes of ethanolamides distribution. The detailed kinetic mechanism of each process was included into the model. The partial and global models were verified on the basis of published data on enzyme kinetics and clinical trial data of Pfizer.

**Results:** The developed model is able to simulate anandamide dynamics in man over a wide range of different conditions, including inhibition of different steps of whole pathway, different inhibitors and doses. It also can predict the optimal administration regime as well as combinations of different drugs.

**Conclusions:** The current analysis was consistent with the presence of a second enzyme that hydrolyses ethanolamides that is not inhibited by PF-04457845, but can limit the maximal levels of ethanolamides at high inhibition of FAAH. We suggest a possible candidate is NAAA enzyme that is able to hydrolyse ethanolamides with high activity. The implications of this for end points such as occupancy at the cannabinoid receptor will be discussed.

**III-35 Christoph Niederalt Development of a detailed physiologically based computational kidney model to describe the renal excretion of hydrophilic agents in rats**

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**Objectives:** The aim of the study is to develop a detailed physiologically based computational kidney model in order to simulate the renal excretion process of drugs within whole body physiologically based pharmacokinetic (PBPK) models. As a start, a model of the rat kidney particularly for hydrophilic substances is developed. This model mechanistically describes the concentrating process of the drug within the tubular fluids along the nephrons.

**Methods:** A computational model of the kidney is established representing the tubular fluid within different tubular segments, interstitial space and vascular space including vasa recta. Urine concentration and fluid reabsorption is triggered by osmolality gradients established by NaCl, urea and the drug. Na<sup>+</sup> transport and facilitated urea diffusion is taken into account. Physiologic parameters like blood flows and tissue composition are taken from literature if available [1,2]. Missing parameters are fitted to the osmolality gradient along the cortico-medullary axis in the physiological steady state. The model is evaluated using experimental data from mannitol. [3,4]

**Results:** The model is able to describe the physiological steady state concentrations of NaCl and urea along the cortico-medullary axis. After application of hydrophilic drugs such as mannitol, the model is able to describe the concentrating process within the tubular fluid and the time resolved diuretic effects caused by this agent.

**Conclusions:** An initial physiologically based kidney model to be used within whole body PBPK models is available. The model will be extended to other species and to lipophilic drugs which may also undergo active secretion and reabsorption.

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### **III-40 Kayode Ogunbenro A semi-mechanistic gastric emptying pharmacokinetic model for $^{13}\text{C}$ -octanoic acid: an evaluation using simulation**

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**Objectives:** The  $^{13}\text{C}$ -octanoic acid breath test is widely used for indirect assessment of the rate of gastric emptying and it is yet to achieve universal acceptance due to inconsistencies when the results are compared with simultaneous and direct measurements using scintigraphy. The main objective of this work was to propose a new semi-mechanistic model for analysing  $^{13}\text{C}$ -octanoic acid breath test data and to assess the performance of the new model using simulation studies.

**Methods:** The new semi-mechanistic model has five separate compartments; stomach, intestine, central and peripheral body and breath. A simulation study was performed based on two experiments i.e. two  $^{13}\text{C}$ -octanoic acid breath tests in each individual. The first test is the baseline study and the second test is after treatment with a drug that increases the rate constant of gastric emptying by 50%. Stomach and breath profiles were simulated for 50 individuals under four conditions: (1) variability on all parameters; (2) no variability on the rate constant of gastric emptying and the rate constant of absorption; (3) variability on the rate constant of gastric emptying and the rate constant of absorption only; and (4) no variability on all parameters. A mono-exponential model was fitted to the stomach profile and the new semi-mechanistic model and three other widely used methods (Modified exponential model [1], Ghooos method [1], and Wagner-Nelson method [2]) were fitted to the breath profiles.

**Results:** The gastric emptying half times from stomach profiles correlate better ( $R^2=1,1,1,1$  for the four conditions) with the half emptying times from the new semi-mechanistic model compared with half emptying times from the modified exponential model ( $R^2=0.72,0.53,0.88,1$ ), Ghooos method ( $R^2=0.72,0.54,0.88,1$ ) and Wagner-Nelson method ( $R^2=0.79,0.68,0.89,1$ ) for the four simulation studies.

**Conclusions:** The new semi-mechanistic model is very effective for the assessment of gastric emptying using the  $^{13}\text{C}$ -octanoic acid breath test and could be applied in the development of drugs that influence gastric emptying. This semi-mechanistic model allows direct estimation of the rate of GE while modelling the rate of elimination of  $^{13}\text{CO}_2$  from the ingested  $^{13}\text{C}$ -octanoic acid meal, taking into account the absorption, distribution and elimination by other routes.

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### **III-54 Anna Pieper Development of a PBPK model of doxorubicin**

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**Objectives:** The anthracycline antibiotic doxorubicin (DOX) is one of the most potent cytostatic agents and is used in both solid tumors and leukemia. Although DOX was developed in the 1960's its mechanism of action and its metabolism are not known in detail. The only partially active metabolite results from enzymatic degradation via an Aldo-keto reductase (AKR) and a Carbonylreductase. In addition, inactive 7-deoxy-aglyca are formed via biotransformation by a glycosidase (G). The aim of this work is to assess if the pharmacokinetics of DOX in children can be predicted from a PBPK model developed using data from adults. First of all, a PBPK model for adults has to be developed and it has to be transferred to children in the next step.

**Methods:** By entering several parameters of DOX pharmacokinetics such as  $K_m$  or  $V_{max}$  for drug transporters into PK-Sim<sup>®</sup>, simulations were computed and compared to data from a study from Callies et al. [1]. Our model implicates an AKR, a G and biliary transport in liver, an AKR, a G and active secretion in kidney, a G in heart, gut transport in small intestine and solute like carriers for liver, gonads, bone, and kidney [2, 3, 4]. The known rapid distribution into blood cells is also considered in the model. Data from 29 individuals could be used. Individual body surface area, but only the mean weight, height and age were available. Therefore, we estimated weight and height by using a nomogram.

**Results:** The simulation in PK-Sim<sup>®</sup> showed a mean doxorubicin clearance of 86.1 l/h (SD  $\pm$  12.7 l/h) for a female population vs.  $62.3 \pm 20.5$  % in the study from Callies et al.. Thus, doxorubicin clearance is 19 % higher than the clearance reported in the study. In 25 patients, clearance resulting from PK-Sim<sup>®</sup> was higher than those calculated by Callies et al..

**Conclusions:** To evaluate the influence of age and gender further investigations will be necessary and the comparison with data from other studies is essential. Furthermore it is important to show if a less complex model could come to the same results. The transferability of this model to the younger population has to be proved in future studies as well.

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## **IV-08 Alexander Solms Modelling Inter-Individual Variability in PBPK Models and Deriving Mechanistic Covariate Models for PopPK**

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**Objectives:** Covariate modeling in population pharmacokinetic (Pop PK) is mostly empirical and does rarely profit from the physiologically-based pharmacokinetic (PBPK) modeling framework where anthropometric data or other descriptors can be integrated in a mechanistic way. The objectives are to (i) model inter-individual variability in PBPK models based on body height (BH), body weight (BW), body surface area (BSA) and lean body weight (LBW) with a special emphasize on adipose tissue due to its importance for PK; and to (ii) derive mechanistic covariate models from PBPK models by exploiting the link to empirical models (EM) via lumping.

**Methods:**Physiological parameters for different age classes were reported in [2]. Partition coefficients were calculated using the methods published in [4,5]. Two approaches -a BH and LBW- were evaluated against data measured in an autopsy study published in [1]. Scaling of physiological parameters was subsequently translated from the PBPK parameters to parameters of the EM based on the lumping [3]. The results were illustrated for Lidocaine and compared to data published in [6]. Possible uncertainties for predicting partition coefficients as reported in [4,5] were considered by Monte Carlo simulations.

**Results:** The LBW-scaling generated more variability than the BH-scaling in comparison to experimental data [1]. Compared to the impact of variability in anthropometric data, we found the impact of uncertainty in determining partition coefficients to be much more pronounced on the variability in the concentration-time profiles. We derived a new mechanistic covariate model that specifically addressed the importance of adipose tissue for PK by simultaneously integrating BW and LBW as descriptors. Our predictions were in good agreement with experimental data of Lidocaine. However, not all patient data could be captured based on the variability generated by anthropometric data, which might be due to uncertainty in the partition coefficients. For several compounds and children-age classes, we compared PBPK-based- to the commonly used allometric-scaling applied to adult parameters. The results are in good agreement and theoretically underpin the allometric scaling.

**Conclusions:** Our mechanistic approach gives a general strategy to integrate anthropometric or other descriptors into EM. We find and theoretically understand that the impact of uncertainty in partition coefficients can be more pronounced than the impact of variations in BH, LBW etc within a population.

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## **IV-21 Sonya Tate The Importance of Enterohepatic Recirculation in the Disposition of Pravastatin and Rosuvastatin: A Physiologically-Based Pharmacokinetic Modelling Approach**

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**Objectives:** The majority of the substrates for hepatic uptake transporters are excreted into the bile to some extent. In the case of non-metabolised substrates pravastatin and rosuvastatin, 63-85% of the dose is excreted into the bile in rat [1], and of this amount 40-50% undergoes enterohepatic recirculation [2, 3]. The current study assesses the inclusion of enterohepatic recirculation in the physiologically-based model and its impact on the prediction of pravastatin and rosuvastatin PK in rat.

**Methods:** The whole body physiologically-based pharmacokinetic (WBPBPK) model comprised 13 tissues connected in a closed-loop format by arterial and venous blood flow. All non-hepatic tissues assumed perfusion-limited kinetics; hepatic transporter process were incorporated by assuming permeability-limited kinetics for the liver [4-6]. In house in vitro uptake data obtained in rat hepatocytes were used to evaluate hepatic uptake and passive diffusion; biliary clearance was obtained from sandwich cultured hepatocytes [7]. Oral absorption was incorporated into the model using an advanced compartmental transit model [8]; permeability was incorporated using data from the RRCK cell line. Drug eliminated into the bile was considered either to be (a) removed from the body (no recirculation) or (b) to empty into the duodenum and undergo subsequent reabsorption.

**Results:** The WBPBPK model without recirculation resulted in predicted pravastatin and rosuvastatin i.v. clearances within 1.5-fold of observed data in bile duct-cannulated rats; accumulation in the bile observed was in good agreement with the reported values. The rosuvastatin oral blood AUC tended to be over-predicted in contrast to an under-prediction for pravastatin, in accordance with the over/under-prediction of the i.v. clearances. The model assuming continuous recirculation recovered 55 and 51% of the oral liver AUC for pravastatin and rosuvastatin respectively, compared to the model with no recirculation which provided poorer estimates, with recoveries of 21 and 7%.

**Conclusions:** The in vitro uptake data provided good estimates of uptake and efflux upon comparison to blood and bile concentrations in bile duct-cannulated rats without the need for empirical scaling factors commonly used in PBPK modelling of uptake substrates in human. The inclusion of enterohepatic recirculation into the WBPBPK model provided more accurate predictions of oral blood and liver profiles than a model assuming no recirculation.

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#### **IV-47 Thomas Wendl Development of a physiologically-based pharmacokinetic (PBPK) model for Moxifloxacin and its metabolites in healthy adults**

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**Objectives:** The objective of this study was to establish a PBPK model for Moxifloxacin and its two main metabolites in healthy adults after intravenous (IV) and per oral (PO) administration with and without charcoal co-administration in order to get a detailed understanding of the metabolic processes and parent-metabolite interrelationships.

**Methods:** Starting from an established Moxifloxacin PBPK model [1], a coupled whole-body PBPK model for Moxifloxacin and its two major metabolites, i.e. the sulfated metabolite 1 (M1 Sulfate) and the glucuronidated metabolite 2 (M2 Glucuronide), after IV and PO administration with and without co-administration of charcoal was built using the software tools PK-Sim®, MoBi® and the MoBi® toolbox for Matlab® [2]. A new physiologically-based compartmental absorption model allowing for the mechanistic description of gut wall metabolism, enterohepatic recycling, and binding to charcoal according clinical studies was included into the whole-body PBPK model [3]. Physicochemical data, demographic data, mass balance information and plasma concentration time profiles obtained in clinical studies [4, 5] were used for model establishment and model validation.

**Results:** The established PBPK model describes the PK of Moxifloxacin, M1, and M2 in a very accurate manner, after both, Moxifloxacin IV and PO administration and with and without charcoal co-administration as evidenced by a visual predictive check. The model provides a detailed understanding of the interrelationship of Moxifloxacin and its metabolites with respect to metabolism in the gastro-intestinal tract and the liver. Furthermore, metabolic processes like glucuronidation and deglucuronidation in the gut which are difficult to measure in-vivo were successfully tested in the model.

**Conclusions:** The model was successfully established and validated and, hence, can be used to simulate the pharmacokinetics of Moxifloxacin, M1, and M2 in different scenarios or under modified conditions. In particular, the model is suitable for scaling to pediatric populations and planning of clinical studies.

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## **IV-65 Kirill Zhudenkov Pharmacokinetics of PEG-IFN Alpha in HCV Infected Patients**

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**Objectives:** To investigate PK of PEG-IFN Alpha in HCV infected patients using population modeling and to compare two software packages - NONMEM 7 and Monolix 3.2. Previously the PK of PEG-IFN was studied in [1] without using a population modeling approach. However, data available from [1] suggested application of such methods with the aim of getting more details on the PK of PEG-IFN.

**Methods:** We modeled the plasma concentrations of PEG-IFN collected in 24 patients on two occasions (after 0'th and 7'th day of treatment). Also a variety of covariate data for each patient (race, level of inflammation, level of CD4+ cells, level of alanine aminotransferase (ALT), level of response - sustained virological responders (SVRs) and nonresponders (NRs)) [1] was available. All ODE models built were tested with NONMEM 7 running FOCE with INTERACTION algorithm and with Monolix 3.2 running SAEM algorithm.

The first step of building a model was to choose a basic structural model - estimate number of compartments, model of absorption, check for saturation in absorption and elimination. Further model building implied estimation of inter-individual variability (IIV) for structure model parameters. After IIV estimation we selected the best error model. Further model verification included covariate analysis - building transformations of parameters with IIV for continuous covariates or analysis of different groups of parameters using categorical covariates or even analysis of categorical variability of parameters with IIV using categorical covariates.

**Results:** The model selection was similar using either NONMEM or MONOLIX. The final PK structural model contained one compartment with first order absorption and linear elimination. IIV analysis showed the necessity of application of IIV to volume V and absorption Ka. Analysis using categorical and continuous covariates showed no significant correlations (all correlation coefficients showed to be between -0.5 and 0.5) between means of parameters with IIV and covariates. In contrast, categorical variabilities for V from level of response and for Ka from race were apparent. Further analysis showed that such variabilities did not lead to significant lowering of OFV in NONMEM and -2xLL in Monolix.

**Conclusions:** Final structural model gave the values for V, Ka and Ke parameters (1.08 L/kg, 1.32 1/day and 0.41 1/day respectively) close to values obtained by Andrew H. Talal et al [1]. IIV for V and Ka parameters (0.298 and 0.89 respectively) allowed the data to be more accurately described. No difference between pharmacokinetic parameters for Responders and Non-responders was revealed by population analysis.

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### **III-41 Oliver Ackaert Population modelling of blood pressure: assessing clinically important factors for cardiovascular diseases**

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**Objectives:** Blood pressure exhibits diurnal variation with a chronobiological (circadian) rhythm with an increase in the morning and a decrease during the night. Circadian processes are often analyzed with a Fourier approach, resulting in a sum of cosine functions. However these models fail to relate directly the obtained parameters (e.g. amplitude, acrophase) with important features of the chronobiological rythm. These features, such as nocturnal dip, morning surge and nocturnal blood pressure, are believed to be predictive for cardiovascular diseases [1]. The objective of this research is to describe the chronobiological rhythm in systolic blood pressure (SBP) and diastolic blood pressure (DBP) using a model with clinically relevant parameters, which are predictive for cardiovascular events.

**Methods:** Baseline SBP and DBP were recorded at regular time points during 24h from 192 potentially mildly hypertensive patients, that were screened for inclusion into the ROTATE study [2]. A Fourier analysis for the circadian (24h) and the ultradian harmonic (12, 8, 6,...) cosine rythms was performed using NONMEM v7. The model was reparameterized to describe the BP, using parameters, directly related to the dynamic diurnal variations.

**Results:** A combination of two cosine functions adequately described the circadian variation in both the SBP and DBP. Reparameterization resulted in a model, in which the 2 amplitudes, describing the circadian and ultradian (12h) harmonic rhythm were replaced by the population parameter “morning surge”, representing the change between night and morning BP and by the parameter “nocturnal blood pressure”, defined as the lowest point of BP during a 24h cycle. The model allows estimating clinically relevant parameters using the full 24h profile, whereas previous methods to calculate these dynamic diurnal variations in BP were based on averaged observations in 2-4h time intervals.

**Conclusions:** The reparameterized baseline model can be used in clinical practice to assess the morning surge and nocturnal blood pressure, both associated with cardiovascular events, based on a 24h baseline measurement. Moreover this baseline model can form the basis for the development of a PK-PD model to evaluate the drug effect of anti-hypertensive drugs. In addition, with the proposed model as baseline model it could be evaluated if anti-hypertensive drugs besides a decrease in BP also reduce other risk factors for cardiovascular diseases or events.

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### **I-14 Francesco Bellanti Relevance of QT-RR correlations in the assessment of QTc-interval prolongation in clinical trial simulations**

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**Objectives:** Correction for changes in heart rate is a fundamental step to the evaluation of QTc-interval prolongation. Yet, clinical trial simulations for thorough QT (TQT) studies often rely on approximations to evaluate design factors such as group size. The aim of the investigation was to develop a model-based approach to describe the correlation between QT and RR intervals in healthy volunteers.

**Methods:** A large pool (339 males and 437 females) of healthy volunteer ECG data has been used for the analysis. Data was split into two subsets to allow for the external validation of the final model. The analysis was performed using a non-linear mixed effects approach using NONMEM VI. Model building selection was based on changes in the objective function (OFV) and goodness of fit plots (GOF). Model validation has been carried out internally (simulations and NPDE) and externally (GOF and NPDE).

**Results:** Among the different functions used in the evaluation of the QT-RR correlation [1], a power function allowed the best model performance. Age and gender were the only available covariates; gender has been found to be significant both on slope [181(13.5) females and 166(12.8) males] and exponent [0.85(0.13) females; 0.74(0.13) males]. Inter-occasion variability on slope and exponent was also identified as a significant random effect. Distributions of simulated and real QT values were comparable. Goodness of fit plots clearly showed the ability of the model to predict data from a different subset of studies. Parameter estimates were subsequently used as part of a thorough QT study simulation.

**Conclusions:** The final model allows a reliable and realistic simulation of QT-interval profiles starting from a physiological set of RR values. In the context of clinical trial simulations, the availability of such a model represents a concrete improvement in the evaluation of drug-induced QTc-interval prolongation.

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## **I-28 Christine Brandquist PK/PD Modeling of the Effect of Intravenous Doses of Anzemet® (dolasetron mesylate) and Its Metabolite (hydrodolasetron) on the QT Interval in Healthy Subjects**

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**Objectives:** As part of a post-marketing study performed to clarify the potential activity of dolasetron on ventricular repolarization, a secondary objective was to explore whether there was a correlation between plasma concentrations and QT interval prolongation. The PK profile of dolasetron and its metabolite hydrodolasetron following dolasetron mesylate IV administrations (100 mg and 300 mg) was determined along with the QT interval in healthy normal volunteers. The aim of this project was to develop a PK/PD model to quantify the observed effects on QT interval.

**Methods:** Dolasetron and hydrodolasetron plasma concentrations and ECG data from 78 subjects who received 100 mg (therapeutic dose) and 300 mg (supratherapeutic dose) dolasetron were used in the analysis. Modeling was performed using mixed effect modeling as implemented in NONMEM version VI [1].

**Results:** Administration of the 100 mg dose resulted in a moderate and transient, but statistically significant, increase in placebo-corrected QTcF change from baseline ( $\Delta$ QTcF). Administration of the 300 mg dose resulted in a larger, more sustained, and statistically significant increase in the  $\Delta$ QTcF. Following 15-minute IV infusion, the PK relationship between dolasetron and hydrodolasetron was best described by a combined structural PK model, with 1-compartment for dolasetron and 2-compartments for hydrodolasetron, with an additive residual error model following an IV bolus administration. The relationship between the QTcF and hydrodolasetron concentrations was best described by a direct response sigmoid  $E_{\max}$  model. The prediction estimates for the PD parameters were:  $E_0 = 398$  ms,  $E_{\max} = 65.3$  ms,  $EC_{50} = 878$  ng/mL, and a Hill coefficient of 1.2.

**Conclusions:** This PK/PD model suggests that the relationship between QTcF and hydrodolasetron is one where there is an increase from baseline QTcF ( $E_0$ ) as a function of the plasma hydrodolasetron concentrations,  $E_{\max}$ , and  $EC_{50}$ . A QTc change from baseline  $> 20$  ms may have a substantially increased likelihood of being proarrhythmic [2]. Based on the model, as plasma hydrodolasetron concentrations increase, the QTcF value increases to a maximum change of 65.3 ms, and concentrations of 878 ng/mL will result in a 50% of maximal change in QTcF of approximately 33 ms. The model indicates plasma hydrodolasetron concentrations above 159 ng/mL will result in increases in QTcF of 10 ms or greater.

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## **I-37 Anne Chain Can First-Time-In-Human Trials Replace Thorough QT Studies?**

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*GlaxoSmithKline, London, United Kingdom*

**Objectives:** The aim of the present study was to investigate if the first-time-in-human (FTIH) trials can be modified and optimised to achieve the same information from thorough QT (TQT) studies.

**Methods:** Four different FTIH trial designs were simulated and analyzed using hypothetical drugs that have negative and positive QT/QTc prolongation. First is the traditional dose escalation study simulated and analyzed according to a standard protocol used a control. Second is the same standard study, however, prior information of a positive control compound were used on the parameter estimates during analysis. Third is the traditional study with the addition dose of moxifloxacin where only PD measurements are sampled and historical PK information is used. The last scenario is also with the additional dose of moxifloxacin; however both PK and PD observations are simulated.

Simulations of the FTIH trials are entirely performed in R2.12 for cohorts of 12 and 18 subjects using traditional sampling scheme. The QT-interval prolongation effects of the hypothetical compound were simulated to be 2, 5, or 10 ms. Information on moxifloxacin is derived from a meta-analysis of four different clinical studies where it was used as a positive control. Modeling and simulation efforts were done in NONMEM VI. The analysis of all the simulated trials was performed in WinBUGS v 1.4.3 where the probabilities of a QT/QTc interval prolongation compared [1].

**Results:** All four scenarios performed were able to adequately capture the drug-induced QT-interval prolongation with the probabilities correctly indicating the likelihood of a prolongation greater than 10 ms. Scenarios with moxifloxacin as positive control further supported the simulated analyses by providing the sensitivity of the studies.

**Conclusions:** Thorough QT studies are expensive trials that are required early during clinical drug development. Before true efficacy can be established, it is advantageous to find out the propensity the compound's ability to induce unwanted QT interval prolongation before embarking on further costly studies. By modifying the traditional FTIH studies, we are able to gain valuable safety information early in development which can aid with decision making.

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### **I-63 Jeroen Diepstraten Pharmacodynamics of nadroparin using anti-Xa levels in morbidly obese patients upon subcutaneous administration of 5700 IU**

Jeroen Diepstraten, Esther J.H. Janssen, Christian M. Hackeng, Simone van Kralingen, Mariska Y.M. Peeters, Eric P.A. van Dongen, René J. Wiezer, Bert van Ramshorst, Catherijne A.J. Knibbe

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**Objectives:** Morbidly obese patients (body mass index (BMI) > 40 kg/m<sup>2</sup>) are at increased risk for thromboembolism, especially after surgery. In clinical practice a double dose of nadroparin for thrombosis prophylaxis is often used in (morbidly) obese patients, without proper pharmacodynamic studies. The aim of this study was to develop a population pharmacodynamic (PD) model of nadroparin used for thrombotic prophylaxis in morbidly obese patients, using anti Xa-levels as a PD endpoint.

**Methods:** Twenty morbidly obese patients were included with a median body weight of 144 kg (range 112 - 260 kg), a median BMI of 51 kg/m<sup>2</sup> (range 38-79 kg/m<sup>2</sup>) and median lean body weight of 66 kg (range 54 – 100 kg). At induction of anaesthesia for bariatric surgery, 5700 IU (= 0.6 ml) nadroparin was administered subcutaneously. Chromogenic anti-Xa levels were measured just before and 10, 30, 60, 90, 120, 180, 240, 300 and 420 minutes after nadroparin injection and the next morning within 24 hours after administration. Population PD modelling was performed using NONMEM VI. A step-wise covariate analysis was performed for body weight, lean body weight, ideal body weight, BMI, age, sex, creatinine and bilirubin.

**Results:** In a two-compartment pharmacodynamic disposition model, the pharmacodynamic effect of nadroparin was found to be delayed and could be best described using a single transit compartment with parameters  $k_{tr}$  and  $k_a$ . Body weight (BW) proved to be the most predictive covariate for clearance ( $CL = 47.6 \text{ mL/min} * (BW/144)^{1.5}$ ) while lean body weight (LBW) was the most predictive covariate for volume of distribution ( $V_{ss} = 12.6 \text{ L} * (LBW/66)^{1.5}$ ).

**Conclusions:** We developed a pharmacodynamic model for nadroparin using anti-Xa levels in morbidly obese patients with delayed effect, in which body weight and lean body weight proved to be the major determinant for clearance and volume of distribution, respectively.

## II-01 Vincent Dubois Interspecies differences in moxifloxacin-induced QTc-interval prolongation

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**Objectives:** Assessment of the propensity of non-antiarrhythmic drugs in prolonging QT/QTc-interval is critical for the progression of compounds into clinical development. Different animal models are used in pre clinical assays to assess QTc-interval prolongation liability. However, it's unclear how the QTc-interval changes in dogs and primates can be translated into accurate risk of QTc-interval prolongation in humans, as proposed by the ICH E-14 guidelines, i.e., >10 msec. The aim of this investigation is to characterise interspecies differences in QTc-interval prolongation following administration of moxifloxacin to dogs, cynomolgus monkeys and healthy subjects.

**Methods:** ECG and pharmacokinetic data from experiments in conscious beagle dogs, cynomolgus monkeys and clinical trials in healthy volunteers were evaluated. First, pharmacokinetic models were developed to obtain drug concentrations at the time of each QT-interval measurement. Data analysis was performed using a model-based approach which takes into account the concentration-effect relationship, translating drug effects in terms of the probability of QTc-interval prolongation. NONMEM VII and WinNONLIN 4.1 were used for pharmacokinetic data analysis, whilst PKPD modelling was performed in WinBUGS v1.4.3.

**Results:** Thanks to model parameterisation, drug-specific and systemic specific parameters could be estimated separately and the overall probability associated with QTc-interval prolongation >10msec compared across species. Measurement noise and feeding procedures are important sources of variability and as such affect parameter estimates in dogs and monkeys.

**Conclusions:** The magnitude of the QTc-prolonging effect of moxifloxacin at peak concentrations seems to reflect species differences in sensitivity to hERG inhibition. The differences in the slope of the concentration-effect relationship across species suggest that monkeys are slightly more sensitive than dogs to drug effects.

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## II-11 *Farkad Ezzet* Meta-Analysis of Antiplatelets in Patients with Atrial Fibrillation: A survival Model

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**Objectives:** Warfarin reduces the risk of stroke in patients with atrial fibrillation; however, due to multiple interactions, coagulation monitoring and dose adjustment are necessary. We report analysis and comparisons between treatments from 3 trials of new thrombin inhibitors using meta-analysis and exploiting properties of survival models.

**Methods:** Efficacy was measured by events of stroke or systemic embolism for apixaban vs. aspirin (N=5600) [1], dabigatran vs. warfarin (N=18000) [2] and ximelagatran vs. warfarin (N=3400) [3]. We digitized figures of cumulative hazard Rates (CHR) and obtained rate and time (month) variables. Combined data were modeled to determine linearity or nonlinearity of the hazard rate (HR). The same approach was used for events of major bleeding using data from [1]. The estimated rates were used to 1) compare between treatments, 2) simulate events and compare with observed, 3) design non-inferiority studies and 4) optimize clinical trial design. Under linear hazard, time to event was simulated using an exponential distribution. Virtual clinical trials were obtained and comparisons were made by fitting Cox regression models. The estimated HR was used to explore design of non-inferiority studies

**Results:** CHR for stroke and system embolism was estimated to be linear. Because of similar inc/exc criteria and baseline characteristics, study effect (fixed or random) was small, although improved the fit. Estimated rates were .30, .14, .11, .13, .09 and .13 (%event/month) for aspirin, warfarin, ximelagatran 36 mg bid, dabigatran 110 mg bid, dabigatran 150 mg bid and apixaban 5 mg bid, respectively. SE was < .003. Warfarin event rate was 1.68% or 151 events/year, in agreement with observed [2]. Using data up to 12 months [1], major bleeding was also linear. Estimated rates were .1 and .125 (SE = .002), for aspirin and apixaban. Using warfarin (rate=.14) as a reference and assuming similar efficacy of a comparator, simulations suggested 3000 patients/arm (no dropouts) would be sufficient to establish non-inferiority using a hazard ratio margin of 1.46. Using dabigatran 150 mg bid as a reference (rate=.09), sample size needs to increase to > 4000/arm.

**Conclusions:** 1) Cumulative hazard rates extracted from public literature provide adequate information to characterize drug attributes. 2) Survival analysis allows comparisons between treatments and provides a practical tool for designing and optimizing clinical trials

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## **II-44 Eleanor Howgate PKPD Modelling Of Cardiovascular Safety Pharmacology Data**

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**Objectives:** Modelling and simulation (M&S) techniques are now commonly used to analyse clinical pharmacokinetic (PK) and pharmacodynamic (PD) data as part of a model-based drug development framework. However, their use in the pre-clinical stages is limited and within the safety sciences is virtually non-existent. Application of such techniques to pre-clinical safety pharmacology data may help to improve the predictability of adverse effects compared to conventional methods<sup>[1]</sup>. The aim of this project is to develop PKPD models using cardiovascular (CV) safety pharmacology data, which could eventually be used to predict CV effects in man.

**Methods:** PKPD relationships for the CV effects of N<sup>G</sup>-nitro-L-arginine methyl ester (L-NAME) were analysed using non-linear mixed effects modelling. Data were available for various pre-clinical species and analysis was performed using the MONOLIX software in a sequential manner. Various compartmental PK models, including ones modified to describe the conversion of L-NAME to its active metabolite N<sup>G</sup>-nitro-L-arginine (L-NOARG) were analysed. Indirect effect models with stimulation/inhibition of production of response were used to describe the effects of L-NAME on the haemodynamic parameters. Since haemodynamic parameters display circadian rhythms, various models were assessed to describe baseline data.

**Results:** The PK model that provided the best fit to the data was a 2-compartment, 1<sup>st</sup> order absorption model modified to describe the conversion of L-NAME to L-NOARG. This confirmed previous work that has shown the disposition of L-NOARG is best described by a 2-compartment model<sup>[2]</sup>. Modelling of baseline haemodynamic data was best described by a simple cosine model. A model specifically produced to describe the circadian rhythm of CV parameters<sup>[3]</sup> appeared too complex for this data set. Modelling of the haemodynamic response to L-NAME was adequately described by the indirect response model.

**Conclusions:** The work achieved to date has shown that PKPD models can be developed using typical CV safety pharmacology data and that non-linear mixed effect modelling is an appropriate method for such analysis.

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## **II-55 Helene Karcher Probabilistic risk assessment for QT prolongation and heart rate increase**

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**Objectives:** Oral drug A is in clinical development for several indications between Proof-of-Concept and Phase II. The objective of the modeling work was to quantify the risk of QT prolongation or heart rate increase in a population of patients taking drug A, and thereby characterizing the safety profile of drug A at an early stage.

**Methods:** Assessment of the probability of a patient experiencing QT prolongation or heart rate increase at a certain dose and regimen was performed including inter-individual variability in pharmacokinetics and inter-individual variability in heart rate or QT prolongation at given plasma concentrations. Namely, the following steps were taken:

1. A mixed-effects PK analysis was performed, and the model used to simulate a population of patients treated at different doses and regimens. To obtain the best possible prediction on PK profiles for patients, all available data from disease and healthy volunteer Phase I trials that did not study drug-drug interaction were included to build the mixed-effects PK model.
2. A mixed-effects analysis of the QT (or heart rate) – concentration relationship was conducted on controlled data from a thorough QT study with time-matched electrocardiograms and PK samples.
3. At each considered dose and regimen, the two mixed-effects models above (pharmacokinetic and concentration-QT (or heart rate)) were used sequentially to simulate 1000 patients' steady-state C<sub>max</sub> and corresponding QT prolongation or heart rate increase. The distribution of QT prolongation or heart rate increase in a 1000-patient population was obtained, and used to define the percentage of patients likely to experience a QT prolongation or heart rate increase at a range of threshold values (defined by the clinicians, e.g., 5 ms, 10ms, 20 ms, 30 ms for QT, 2 bpm, 5bpm, 10bpm for heart rate).

**Results:** Distribution of predicted C<sub>max</sub> at steady-state for several doses and regimens highlighted the large variability in patient's pharmacokinetics for drug A. Prediction of the corresponding percentage of patients likely to experience a QT prolongation or heart rate increase at a range of threshold values could be interpreted as either quantification of the risk associated with each dose in a large disease population, or the individual risk for a given patient to experience a QT prolongation or a heart rate increase at that dose. The way the safety profile changed when using once-daily regimen vs. twice-daily regimen was reconciled with other factors (efficacy, market access) to inform the decision on a final regimen.

**Conclusions:** The probability of a patient experiencing QT prolongation or heart rate increase over certain defined thresholds enabled the clinical team to assess and communicate the risk of administering compound A at several doses and regimens to a larger patient population.

**IV-06 Nelleke Snelder Quantitative understanding of drug effects on the interrelationship between mean arterial blood pressure, cardiac output and total peripheral resistance**

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**Objectives:** Since persistent hypertension is a risk factor for heart failure and is a leading cause of cardiovascular disease, evaluating mechanisms that underlie blood pressure (BP) changes is crucial in drug development. BP is maintained constant by the cardiovascular system (CVS) through adapting cardiac output (CO) and/or total peripheral resistance (TPR). Gaining insight into the pharmacology of drugs with desired or undesired effects on the CVS is pivotal in drug development and can be obtained efficiently using a translational modeling approach, in which early insights on efficacy and safety are carried forward to later development stages. This research describes the development of a mechanism-based pharmacodynamic (PD) model using preclinical data to understand drug induced disturbance of BP homeostasis.

**Methods:** A mechanism-based (PK)-PD modeling approach was applied to describe the dynamics of blood pressure regulation by the CVS, with the aim of developing a drug independent model by distinguishing drug- and system-specific parameters. The model was identified by comparing the preclinical effects on BP, CO and TPR, of different marketed antihypertensive drugs with different mechanisms of action.

**Results:** The dynamics of blood pressure regulation by the CVS, including feedback between BP, CO and TPR, could be adequately described by the PD model. Drug- and system-specific parameters were not correlated and could be estimated independently with good precision.

**Conclusions:** It is concluded that establishment of a translational PD model to describe drug induced disturbance of BP homeostasis enables conversion of data into knowledge about the mechanism of action. Ultimately, this approach allows for anticipation of clinical response based on preclinical data and prediction of the system behavior under conditions not previously evaluated, which will contribute to an optimization of the selection and development of new compounds early in development.

**IV-36 Piet van der Graaf Towards a Thorough Preclinical QT (“TpQT”) study paradigm: Pharmacokinetic-Pharmacodynamic (PKPD) Modelling of QT<sub>c</sub> Effects of Moxifloxacin in Cynomolgus Monkeys**

Piet H. van der Graaf, Kenny J. Watson, William P. Gorczyca, John Umland, Ying Zhang, Xian Chen, Sunny Z. Sun, Bernard Fermini, Mark Holbrook  
*Pfizer*

**Objectives:** Delayed ventricular repolarisation is manifested electrocardiographically in a prolongation of the QT interval. Such prolongation can lead to potentially fatal Torsades de Pointes. Moxifloxacin is a fluoroquinolone antibiotic which has been associated with QT prolongation and, as a result, is recommended by the regulatory authorities as a positive control in thorough QT studies performed to evaluate the potential of new chemical entities to induce QT prolongation in humans. The sensitivity of the cynomolgus monkey as a quantitative preclinical predictor of the PK-QT<sub>c</sub> relationship is discussed.

**Methods:** Cardiovascular monitoring was performed in the telemetered cynomolgus monkey for 22 hours following oral administration of Moxifloxacin (10, 30 and 90mg/kg) or placebo. QT<sub>c</sub> was derived using an individual animal correction factor (ICAF) :  $RR-I = QT-I - (RR-550) * (ICAF)$ . A PKPD analysis was performed to quantify the increase in placebo-adjusted QT<sub>c</sub> elicited by administration of Moxifloxacin. In addition, the rate of onset of hERG channel blockade of Moxifloxacin was compared to Dofetilide by whole cell patch clamp technique in HEK-293 cells stably expressing the hERG channels.

**Results:** Moxifloxacin induced a dose dependent increase in QT<sub>c</sub>. A maximum increase of 28msec was observed following administration of 90mg/kg Moxifloxacin. The corresponding maximum free systemic exposure was 18µM. Interrogation of the PK-QT<sub>c</sub> relationship indicated a direct relationship between the systemic exposure of Moxifloxacin and increased QT<sub>c</sub>. A linear PKPD model was found to describe this relationship whereby a 1.5msec increase in QT<sub>c</sub> was observed for every 1µM increase in free systemic exposure.

**Conclusions:** The exposure dependent increases in QT<sub>c</sub> observed following oral administration of Moxifloxacin to the cynomolgus monkey are in close agreement with those previously reported in human subjects. A direct effect linear relationship was found to be conserved in both species. As a result of the quantitative agreement in both species, the utility of the telemetered cynomolgus monkey as a preclinical predictor of QT<sub>c</sub> prolongation is exemplified. Furthermore, the rate of onset of hERG channel blockade observed in patch clamp offers a mechanistic insight into the relative rates of channel blockade observed *in vivo* with both Moxifloxacin and Dofetilide. This work builds on that of Jonker et al. [1] and adds to the growing body of evidence that thorough preclinical PKPD evaluation could provide an effective and efficient quantitative decision framework for derisking of QT liability in man.

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## **I-22 Irina Bondareva Sequential Interacting Multiple Model (IMM) Bayesian Analysis of Carbamazepine and Valproate Repeated Therapeutic Drug Monitoring (TDM) Data from Epileptic Patients**

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**Objectives:** The objective of the study is to examine whether the new Interacting Multiple Model (IMM) sequential Bayesian method and the earlier developed nonparametric population models for carbamazepine (CBZ) and valproate (VPA) monotherapy can track and quantify the pharmacokinetic (PK) behaviour of these antiepileptic drugs (AEDs) in adult epileptic patients during their long-term therapy.

**Methods:** The population PK analysis was performed using the USC\*PACK software based on the earlier developed linear one-compartment models for CBZ and VPA PK and repeated TDM data (peak – trough sampling strategy). This study included 42 adult epileptic patients for whom at least three pairs of serum levels measured on different occasions during different time periods of epileptic therapy were available. These data were not included in the developed population PK models of these AEDs.

**Results:** Epilepsy is a chronic disease, and its treatment in most patients involves long-term mono- or polytherapy. During long-term AED therapy individual PK parameter values appears to vary due to physiological reasons, concomitant medical conditions, etc. These changes can lead to significant interoccasional variability in serum AED concentrations. The traditional Bayesian algorithms are based on conventional assumption that the estimated parameter distributions are fixed and unchanged throughout the observational period, they can not describe possible PK parameter changes. When interoccasional variability is relatively high, information on serum levels measured on only one occasion is useless for future serum level predictions using conventional methods. In contrast, the IMM sequential Bayesian algorithm permits PK parameter values to jump from one support point to another, as new data are available. It was shown that the IMM can capture changes due to physiological reasons, pregnancy, adding another AED, switching to another dosage form, etc in individual PK parameter values of epileptic patients who received CBZ or VPA monotherapy chronically. Magnitude of these changes, when PK data of the individual patient measured on different occasions were analysed separately by the traditional methods, varied from 5 up to 58%.

**Conclusions:** The study demonstrated that the IMM algorithm described and tracked repeated TDM concentration data of AEDs well in epileptic patients with changing PK parameter values during their long-term epileptic therapy.

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## **I-32 Jacob Brogren Separate vs. simultaneous analysis of co-primary endpoints in Alzheimer's disease clinical trials**

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**Objectives:** In clinical trials of drugs intended for treatment of Alzheimer's Disease (AD), cognitive and functional measures may be used as co-primary endpoints. These variables are commonly evaluated in separate statistical tests. In theory, two endpoints measured simultaneously will have a joint distribution with respect to random effects. The power of detecting a treatment effect one or both of the endpoints may differ depending on if simultaneous or separate analyses are performed. The objective of this investigation was to calculate the power of finding a treatment effect on disease progression in a clinical AD trial comparing separate and simultaneous analysis of endpoints.

**Methods:** The ADNI database [1] was used for modeling. A dataset including ADAS-Cog 70 point total score and Functional Assessment Questionnaire (FAQ) was prepared. A mixed effects model was fitted to the data. A treatment effect influencing the disease progression was simulated using the final model. Further power calculations were performed using the MCMP method [2]. A dataset with a large number of individuals was simulated from the model to be used in the MCMP calculation. Target values of 80% and 5% respectively were assumed for power and type-I error rate.

**Results:** The linear mixed effects model for ADAS-Cog and FAQ total scores fitted the data reasonably well. The required sample size for 80% power of detecting a treatment effect differed depending on whether simultaneous or separate analyses were performed.

**Conclusions:** Recognizing the random effects covariance of co-primary endpoints in AD studies may influence power of detecting a treatment effect in clinical studies.

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### **I-56 Elizabeth de Lange Mechanism-based PK-PD model of remoxipride with rat-to-human extrapolation: characterizing remoxipride target site PK and systems homeostatic feedback**

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**Objectives:** In animals, measurement of biomarkers at the target site of dopaminergic drugs can be easier obtained when compared to man. Pop PKPD approaches allows distinction between drug and system-specific properties that determine time course of effect to ultimately predict human PKPD relationships. In this study the time course of prolactin (PRL) concentrations in plasma (PD) in rats was characterized as a function of the PK of remoxipride (REM) in plasma and brain<sub>ECF</sub>. This PKPD relationship was extrapolated to and compared to actual plasma PKPD data in human.

**Methods:** In male rats, plasma and brain<sub>ECF</sub> PK profiles of REM together with PRL concs (PD) in plasma, were obtained after 30-min IV infusion of 4/8/16 mg/kg REM [1,2]. Also, plasma PRL concs were obtained after two subsequent 30 min IV infusions (3.8 mg/kg REM). PK and PD were investigated by NLME (NONMEM VI.2, ADVAN 9). A bootstrap procedure was used to derive the uncertainty in the parameter estimates of the final model, followed by a visual predictive check (VPC). The VPCs were performed by simulating 1000 replications of the PKPD model and a simulation dataset. Clinical REM data on plasma REM and PRL concs (8 healthy male subjects, two consecutive IV doses (data from M. Hammarlund-Udenaes) [3]. A 2-comp PK model was developed and, by applying the compartmental PK ratio of the rat model, translated into a 3-comp model to predict brain<sub>ECF</sub> concs in human. For the PKPD model in human, allometric scaling and independent information on the values of drug- and system specific parameters were used as prior knowledge .

**Results:** In rats, AUC's in plasma and brain<sub>ECF</sub> showed linear REM PK. A 4-comp PK model, consisting of a central (plasma) compartment, a peripheral compartment, a brain<sub>ECF</sub> and an absorption compartment, best described the PK data. Inclusion of brain elimination significantly improved the model. A precursor-pool model with REM brain<sub>ECF</sub> conc-relationship (E<sub>max</sub>) on PRL release, and a positive feedback of plasma PRL concs on the rate of prolactin synthesis in brain lactotrophs (E<sub>max</sub>), best described the PD. In humans, the translated 3-comp model accurately predicted the clinical REM plasma PK data, as well as all PRL plasma profiles.

**Conclusions:** The structure of the preclinical derived MB PKPD model is adequate in describing PRL release in rats and human. Positive feedback on PRL synthesis could be a new feature in describing complex homeostatic feedback mechanisms.

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## **II-26 *Martin Gnanamuthu Johnson* Pharmacokinetic-Pharmacodynamic Modeling of Dopamine D2 Receptor Occupancy in humans using Bayesian modeling tools**

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**Objectives:** Blockade of dopamine-2 receptors is the key pharmacological component to the antipsychotic efficacy of both the typical and atypical antipsychotics (1). A pharmacokinetic-pharmacodynamic (PK-PD) modeling approach was used to describe the relationship between the plasma concentration of antipsychotics (AP) and their D<sub>2</sub> receptor occupancy (D<sub>2</sub>RO) in humans. Bayesian tools were utilized to estimate the PK-PD parameters from the limited data available in the literature.

**Methods:** Plasma levels and D<sub>2</sub>RO of four antipsychotics (risperidone, paliperidone, olanzapine, haloperidol) from 82 schizophrenic patients and 34 healthy volunteers were collected from literature(2). D<sub>2</sub>RO was measured using a PET or a SPECT scan at one or two time points per individual. PK-PD parameters were estimated using nonlinear mixed effect modeling by the Bayesian method with interaction option as implemented in NONMEM VII. Priors and uncertainty on priors were taken from in-house model estimates, when available, or non-informative priors were used. Moreover, the influence of ligand selection on the dissociation constant (K<sub>d</sub>) estimates of paliperidone was checked.

**Results:** A one-compartment pharmacokinetic (PK) model explained the plasma PK profile for olanzapine and paliperidone, whereas a two-compartment PK model was used for risperidone and haloperidol. An Emax model linked with an effect compartment described the relationship between drug exposure and D<sub>2</sub>RO. Ke<sub>0</sub> (equilibration rate to the effect compartment) was allometrically scaled from preclinical literature information and used as prior in this analysis. The estimated K<sub>d</sub> was close to the values in the literature (reported as EC<sub>50</sub>) for risperidone, paliperidone, olanzapine and haloperidol (3). No significant influence of ligand selection was observed in the K<sub>d</sub> estimates of paliperidone.

**Conclusions:** An Emax model linked with an effect compartment adequately described the relationship between the drug exposure and D<sub>2</sub>RO, using a Bayesian method to estimate PK-PD parameters from limited information. The model-estimated K<sub>d</sub> values were close to the values reported in the literature for risperidone, paliperidone, olanzapine and haloperidol.

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## II-25 *Martin Gnanamuthu Johnson* Predicting Dopamine D<sub>2</sub> Receptor Occupancy in humans using a physiology-based approach

Martin Johnson\* (1), Magdalena Kozielska (1), Venkatesh Pilla Reddy (1), An Vermeulen (2), Hugh A. Barton (3), Sarah Grimwood (3), Rik de Greef (4), Geny M.M. Groothuis (1), Meindert Danhof (5), & Johannes H. Proost (1)

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**Objectives:** A hybrid physiology-based pharmacokinetic and pharmacodynamic model (PBPKPD) was used to predict the time course of dopamine receptor occupancy (D<sub>2</sub>RO) in human striatum following the administration of antipsychotic (AP) drugs, using *in vitro* and *in silico* information.

**Methods:** A hybrid PBPKPD model to predict the D<sub>2</sub>RO in human was developed using plasma, brain exposure and D<sub>2</sub>RO information from rats. This PBPKPD model consisted of classical plasma compartments and four physiology-based brain compartments: brain-vascular, brain-extravascular, striatum free drug, and striatum bound drug. The drug distribution from the plasma compartment to the brain-vascular compartment was assumed to be determined by cerebral blood flow. The unbound drug in this vascular compartment crosses the blood-brain barrier into the brain-extravascular compartment, then to striatum where it can reversibly bind to the dopamine receptor complex. This rat brain physiology-based model structure was integrated with available population pharmacokinetic parameters, *in vitro*, *in silico* and human physiological information to predict the human D<sub>2</sub>RO of haloperidol, risperidone and paliperidone at clinically relevant doses. Permeability surface area product (PS) was obtained using *in silico* calculations and used to predict the transport of drug across the human blood brain barrier(1). Active efflux clearance in brain was scaled from the model estimates obtained from the rat PBPKPD model. Berkeley Madonna was used to make these predictions. The predictive power of this physiology-based approach was determined by comparing the simulations with the observed human D<sub>2</sub>RO(2;3).

**Results:** The model-predicted human D<sub>2</sub>RO are in close agreement with the clinically observed D<sub>2</sub>RO at relevant doses for risperidone and paliperidone. However, it was underpredicted for haloperidol.

**Conclusion:** The rat hybrid PBPKPD model structure as integrated with *in silico*, *in vitro* and humanphysiological information was able to predict the time course of D<sub>2</sub>RO in human for risperidone and paliperidone well and less so for haloperidol.

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## II-34 Zheng Guan Population pharmacokinetic and pharmacodynamic analysis of cortisol in serum and saliva in healthy male volunteers after an acute 5-hydroxytryptophan (5-HTP) challenge test

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**Objectives:** Serum cortisol is a frequently used neuroendocrine endpoint of the 5-HTP challenge test, which quantifies central serotonergic neurotransmission. Sampling cortisol from saliva is increasingly used as an alternative for serum cortisol measurement. This non-invasive method avoids blood sampling stress, and salivary cortisol represents the amount of free and thus biologically active cortisol [1, 2]. The current study aims at developing a population PK/PD model for the effect of the 5-HTP challenge test on acute serum cortisol increases, and explores the relationships between salivary and serum cortisol.

**Methods:** Three randomized, double-blind, placebo-controlled, cross-over studies were carried out at CHDR. 5-HTP with carbidopa co-treatment and granisetron were orally administered [3, 4, 5]. The population approach was applied to analyze both PK and PD data. A compartmental model was used to fit the PK profile of 5-HTP. A baseline model of serum cortisol was built to assess the circadian rhythm [6] before a sigmoid model was selected to model the drug effect of the 5-HTP challenge on cortisol. Finally, linear and power function relationships were used to predict the salivary cortisol based on serum cortisol, which was presented by total or free serum cortisol.

**Results:** The PK of 5-HTP could be described with a one compartment model with first-order elimination. A transit absorption compartment was introduced to improve the description of the concentration upswing after oral drug administration. The typical value for clearance showed inter-study variability ( $23.9 \text{ L}\cdot\text{h}^{-1}$  or  $10.5 \text{ L}\cdot\text{h}^{-1}$ ). A cosine function with a trend was chosen to describe the circadian rhythm of serum cortisol. The challenge test involved only one level of 5-HTP, which prevented estimating both the  $E_{max}$  and  $EC_{50}$  in the sigmoid model. Instead, an approximation with the linear model was applied in absence of a plateau in the drug effect (slope =  $0.0406 \text{ ng/ml per ng/ml}$ ). A power function provided a better description than a linear function to relate the salivary and serum cortisol.

**Conclusions:** The PK/PD model could describe and predict total serum cortisol concentration for the proposed dose level in the challenge test, but limitations exist when extrapolating to higher dose levels that were not tested in these experiments. The results provide a rationale to sample cortisol from saliva instead of serum, even after acute stimulation of the hypothalamic-pituitary-adrenal axis.

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## **II-42 Eef Hoeben Population pharmacokinetic analysis of JNJ-37822681, a specific and fast-dissociating D2 antagonist for the treatment of schizophrenia**

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**Objectives:** A population PK model of JNJ-37822681 was developed with the aim to describe the PK of JNJ-37822681 in healthy volunteers and in patients with schizophrenia. Objectives were to obtain estimates for PK parameters and associated variability, to evaluate the effects of covariates and to provide exposure parameter estimates derived from sparse samples of subjects participating in a Phase 2b study. Exposure parameters were used to simulate D2 occupancy and to guide dose selection for subsequent studies.

**Methods:** Data were obtained from 378 subjects enrolled in 3 Phase 1 and 2 Phase 2 trials. Nonlinear mixed effects modeling of pooled data was conducted using NONMEM® (<sup>1,2</sup>). Between-subject variability for PK parameters was evaluated using an exponential error model and the residual error was described using an additive model in the log domain. The FOCE method was applied throughout the analysis. Screening for covariate relationships was based on a graphical analysis of individual posterior estimates of random effects vs. covariates. The model was validated on a subset of data that were not used to build the model and was subsequently used to predict steady-state exposure for each subject in the Phase 2b study. D2 occupancy in striatum was simulated using predicted exposure combined with the PD parameters from a sigmoid  $E_{max}$  model established on former <sup>11</sup>C-raclopride PET data.

**Results:** A two-compartment disposition model with zero-order input in a depot compartment followed by first-order absorption into and first-order elimination from the central compartment combined with a transit compartment provided the best fit to the data. Sex was a significant covariate on oral clearance and food a significant covariate on the absorption rate constant and oral bioavailability. The exposure was somewhat higher in females compared to males. The model passed external validation and allowed determination of individual exposure parameters which were similar to those calculated in a Phase 2a study. PK/PD evaluation demonstrated that simulated D2 occupancy was in the 65-80% range or partially above the 80% threshold at doses of 10, 20 and 30 mg bid. This 65-80% range has been shown to be linked to efficacy (<sup>3</sup>).

**Conclusions:** The developed population PK model successfully described the PK of JNJ-37822681 and allowed the determination of individual exposure parameters in a Phase 2b study. Simulated D2 occupancy based on predicted exposure and former PET-study data guided dose selection for subsequent studies.

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**II-48 Masoud Jamei A physiologically-based pharmacokinetic (PBPK) brain model and its application in simulating drug disposition in brain**

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**Objectives:** The aim of this study is to develop a PBPK brain model to explore the effects of transporters present within the blood-brain/cerebrospinal fluid barriers (BBB/BCSFB) on the drug disposition in brain.

**Methods:** For this purpose, literature was reviewed to collate brain physiological and anatomical attributes as well as any information on transporter abundance and activities on the BBB/BCSFB. A novel 4-compartmental diffusion-limited brain model was developed and implemented in Matlab Simulink®. This model was combined with a whole-body PBPK model. Physiological, anatomical and drug dependent parameters were incorporated into the model to simulate/predict drug disposition into the brain due to intracranial CSF flows and transporter effects.

**Results:** Depending on the drug properties, (1) the concentrations in the spinal CSF can be very different from that of the cranial CSF; (2) the latter may or may not reflect the drug concentrations in brain mass; and (3) the drug concentration in the intracranial blood may not represent that of the brain mass.

**Conclusions:** Consistent with reported clinical studies, the model was able to show disparities in drug concentration-time profiles in the intracranial blood, brain mass, cranial and spinal CSF. Such disparities were related to drug properties, particularly the affinities to transporters.

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## II-65 Huub Jan kleijn Development and Application of a Semi-Mechanistic Model for Modulation of Amyloid-beta in Cerebrospinal Fluid after Inhibition of $\gamma$ -secretase.

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**Objectives:** Establish the relation between drug exposure and amyloid-beta modulation in cerebrospinal fluid (CSF) to enable optimization of drug development strategies and benchmarking across drugs targeted for Alzheimer's disease.

**Methods:** Data on amyloid-beta concentrations in CSF (sampled from the lumbar region) in healthy volunteers (n=47) upon single dose treatment with placebo or the  $\gamma$ -secretase inhibitor MK-0752 were available [1]. The relation between plasma PK and CSF PK was explored. MK-0752 brain concentration profiles, derived from individual plasma kinetics scaled by the individual CNS/plasma partitioning constant from the CSF PK model, were used as the driver for amyloid-beta modulation. Direct and indirect effect models were explored to describe amyloid-beta modulation, and transit compartments were included to address the delay between brain and lumbar CSF amyloid-beta. Linear and non-linear models were explored to account for the substantial baseline drift in CSF amyloid-beta. Data were fitted using the FOCE method in NONMEM VII.

**Results:** CSF exposure was best described with an extended link model connecting a CSF compartment via a transit compartment to the central plasma compartment. Amyloid-beta CSF concentrations could not be fitted with an indirect effect model; amyloid-beta turn-over and CSF flow were indistinguishable. A direct effect model combined with a set of transit compartments best described the amyloid-beta modulation. Population parameter estimates for Emax and IC50 for inhibition of  $\gamma$ -secretase were 0.86 and 14.1  $\mu$ M, respectively. The delay between brain amyloid-beta and lumbar CSF amyloid-beta was addressed by five consecutive transit compartments and a transit rate constant of 0.48 h<sup>-1</sup>. A Hill function with time accounted for baseline drift effects.

**Conclusions:** A model structure and approach for model-based interpretation of CSF amyloid-beta data was developed. The time-courses for amyloid-beta in CSF following placebo and MK-0752 treatment were well characterized. Description of the baseline drift with an empirical time-varying model facilitated a more precise estimation of Emax and IC50 as well as treatment effect size.

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International Conference on Alzheimer's Disease and Related Disorders (July 16-20, 2006, Madrid, Spain).

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### **III-16 Arianna Madrid Modelling the sleep effects of Zolpidem in rats using non-homogeneous Markov chain models**

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**Objectives:** To describe the effects of the hypnotic drug Zolpidem in rats using a semi-mechanistic pharmacokinetic-pharmacodynamic (PK/PD) Markov-chain model

**Methods:** Experimental. Data were obtained from healthy male Wistar rats in which the electroencephalogram (EEG) was continuously recorded for at least two days of alternating dark/light cycles of 12 h. For each 10 second interval, EEG data were scored into awake, REM or NREM stages. The study consisted of a baseline 24 h period (time -24 to 0). At 6 h clock time (CT) during the second dark cycle, methylcellulose (n=16), zolpidem 10 mg/kg (n=16), 20 mg/kg (n=20), or 30 mg/kg (n=11) were administered orally. PK data were not collected during this study. Data analysis. The time course of the 9 possible transition probabilities between the three sleep stages was described using a non-homogeneous Markov chain model based on piecewise multinomial logistic functions[1]. The PK model used to generate plasma concentrations of zolpidem over time was taken from the literature[2,3]. Analyses were performed under the population approach using the LAPLACIAN estimation method implemented in NONMEM VI. Model evaluation was done by constructing visual predictive checks (VPCs) for the 9 transition probabilities, and other data descriptors.

**Results:** Baseline model. Location of breakpoints at every hour and incorporating inter-animal differences at some of the breakpoints provided a good description of the baseline data and precise parameter estimates. Methylcellulose (saline) model. The effects of saline administration were reflected mainly as a decrease in the transition probability from NREM to awake and were described with the use of the Bateman function. Drug effect model. Exploration of the time course of raw transition probabilities revealed that zolpidem elicited an initial time dependent decrease in the transition probability from NREM to awake indicating the animals were sleeping more, and at later times an increase which is interpreted as a rebound effect. Drug effects including the rebound phenomena were described with a turnover feedback model. [4] Data were very well described for the three dose levels and parameter estimates were precise.

**Conclusions:** The model presented here represents an integrated model including baseline, saline, and drug effect models. This type of approach supports the identification and the quantitative description of feedback mechanisms, and represents a promising approach to describe the PD characteristics of different classes of sleep drugs.

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### **III-25 François Mercier A Bayesian meta-analysis of longitudinal lesion count data in multiple sclerosis patients**

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**Objectives:** Multiple sclerosis (MS) is a demyelinating disease of the central nervous system, and the most common neurological disorder diagnosed in young adults. Nowadays, a number of safe and effective medicinal drugs are available for a chronic and symptomatic treatment of this disease; in addition, at least 6 new compounds (NC) are currently in clinical development for this indication. Number of lesions counted on MRI scans have become a widely used outcome measure for monitoring disease activity in clinical trials, in particular in phase 2 trials.

With access to literature data and using meta-analysis methodology, it now becomes possible to inform decision-making to proceed to phase 3 based on phase 2 data, not only by looking at the patient level in-house trial data, but also by comparing the performances of the study drug to the ones of competitors using group-level data (e.g. means).

The aim of this analysis is to characterize the time dynamic of lesion counts observed in MS patients treated with either one of the 6 following compounds: placebo, IFN-beta -1a, glatiramer acetate, natalizumab, fingolimod and teriflunomide, and to compare the time to reach full effect, amplitude of maximum effect and probability of reaching a given level of clinical effect.

**Methods:** Group-level data for mean lesion count were compiled into a comprehensive literature database, corresponding to a total of over 800 patients. A Bayesian model was fitted to these summary data. Various structural models were tested, and the performance of the models were also compared with and without introduction of time-independent covariate like the (mean) number of gadolinium-enhanced lesions at baseline.

**Results:** The model fitted the data well and provided estimates of effect size in line with expectations. The analysis also highlighted a large between trial variability for the placebo treated patients. Introducing the number of gadolinium-enhanced lesion at baseline as covariate significantly improved the goodness-of-fit.

**Conclusions:** Using literature data, it was possible to compare indirectly the effect size and overall trend of reduction of MRI lesion counts over time, in patients treated with various medicinal drugs either marketed or in development. Such type of comparison can be used to support decision-making at end of phase 2, as it provides insight in the potential added-value of a new compound as compared to the marketed drugs or those more advanced on the clinical development path.

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### III-56 Venkatesh Pilla Reddy Exposure-Response Relationship of Typical and Atypical Antipsychotics Assessed by the Positive and Negative Syndrome Scale (PANSS) and its Subscales

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**Objectives:** It has been suggested that atypical antipsychotics (ATAPs), are more effective towards negative symptoms than typical antipsychotics (TAPs) in schizophrenic patients.[1,2] To quantify the above statement, we aimed i) to develop a PK-PD model that characterizes the time course of PANSS score- total and its subscales in patients treated with TAPs and ATAPs; ii) to compare the effect of ATAPs vs. TAPs across the different symptom domains of schizophrenia.

**Methods:** Data from clinical studies with the ATAPs olanzapine (10&15mg/day), risperidone (1-16mg/day), paliperidone (3-15mg/day) and ziprasidone (40-200mg/day) and the TAP haloperidol (10-20mg/day) were used. 3 approaches were used in the analysis of drug effect, on top of the placebo effect (PE): i) overall efficacy (OE), ii) dose-response (DR), and iii) concentration-response (CR). The first two approaches utilized simultaneous analysis of all drugs together, while the CR analysis was performed separately. Sparse PK data & the time course of PANSS were available from the patients of olanzapine, risperidone, paliperidone and ziprasidone treated groups, while only PANSS data were available for haloperidol. A PK model for haloperidol was developed using data extracted from the literature. The predicted concentration was used as an input for the Emax model. The Weibull model was used to account for the PE. The delay in the drug effect was also modeled.

**Results:** Based on OE analysis, all ATAPs except ziprasidone were more effective against the negative symptoms of schizophrenia than haloperidol. The DR analysis posed numerical difficulties, due to the small dose ranges. A one-compartment model described the olanzapine & paliperidone PK adequately, while a two-compartment model was adequate for risperidone & haloperidol. The estimated EC50 values for each of antipsychotic were in line with those reported in literature.[3,4] Based on CR analysis, the effect size was highest for risperidone followed by olanzapine, paliperidone, haloperidol & ziprasidone. The development of a common concentration-response model including all drugs is under progress.

**Conclusions:** Olanzapine, risperidone and paliperidone were more efficacious than ziprasidone & haloperidol in the main domains of the PANSS, i.e positive & negative symptoms of

schizophrenia. Ziprasidone was found to be as efficacious as haloperidol in terms of negative symptoms.

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### III-58 *Bart Ploeger* Confirmation of symptomatic and disease modifying effects of levodopa using the ELLDOPA study

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**Objectives:** The symptomatic relief of levodopa in Parkinson's disease has been well established, but controversy exists about possible disease modifying effects. In this study, we analyzed the ELLDOPA study using a disease progression model that describes the time course of the disease, placebo and drug effects.

**Methods:** In the ELLDOPA trial [1] 361 patients with early PD received a carbidopa-levodopa combination 3 times daily at a final daily dose of 150 mg (n=92), 300 mg (n=88), 600 mg (n=91) or a matching placebo (n=90) for a period of 40 weeks followed by withdrawal of treatment for 2 or 4 weeks.

Data were analysed using a (mixed-effects) linear disease progression model [2]. The probability of dropout was described using a hazard function. For the inactive treatment effects a mixture model was applied to distinguish patients who improved (placebo) or worsened (nocebo) and the onset and offset of these effects were described using a Bateman function. A delayed symptomatic effect, resulting in a transient change in the offset of the disease progression curve was combined with an immediate onset disease modifying effect (i.e. persistent change in the slope of the disease progression curve). Both types of drug effect were investigated using either a linear,  $E_{max}$  or dose-insensitive effect. Visual and numerical predictive checks were used for model evaluation.

**Results:** The analysis confirmed the combined symptomatic and disease modifying effects of levodopa ( $\pm 50\%$  reduction in the offset and slope respectively), as described previously using the DATATOP cohort [2]. Approximately 25% of the patients showed a nocebo effect (transient worsening) while the rest had a placebo effect (transient improvement), which is similar to the results of Ma et al. [3] after analyzing inactive treatment effects in 3 clinical studies (DATATOP, ELLDOPA and TEMPO). The disease progression rate was higher in the population that dropped out. This is consistent with the hypothesis that patients drop out due to relatively high disease progression and was confirmed by the dropout hazard model, showing a reduction in the hazard ratio associated with slowing of disease progression.

**Conclusions:** We believe that a model based analysis, in which assumptions are made explicit and tested when possible, allows more powerful inferences to be made about the type of treatment effect compared to change from baseline methods. This analysis confirms that levodopa has disease modifying effects.

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## **IV-15 Ahmed Suleiman A Mixed-Effects Markov Model for Characterizing the Time Course of the Transitions between Different Extrapyramidal Side Effects Severity Levels**

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**Objectives:** Extrapyramidal side effects (EPS) associated with antipsychotic drug administration are often spontaneously reported by patients and graded by clinicians into different severity levels in clinical trials. Our aim was to build a mixed-effects model capable of characterizing the time course of transition probabilities between the different states of EPS after administration of placebo and the antipsychotic drug paliperidone.

**Methods:** Data were obtained from three phase-III, 7-weeks long, randomized, placebo controlled studies testing paliperidone taken at doses of 3-15 mg once daily, in patients suffering from schizophrenia (placebo: n=320; paliperidone: n=867). An approach using a model with a Markov property where the probability of the different grades of EPS was modeled as compartments was applied [1,2]. Three compartments were used in this model after lumping both moderate and severe events into one compartment owing to the sparse data available for both (1=no EPS, 2=mild EPS, 3=moderate or severe EPS). The rate constants of movement between the compartments which determine the transition probabilities between the EPS states were estimated. This allows predicting all possible transitions at any time instead of estimating the probability of a transition over a fixed period of time. The analysis was performed by estimating the likelihood using the Laplacian estimation method in NONMEM 7. Various functions of increasing complexity (linear, exponential, Weibull, asymptotic, polynomial, Emax) were tested to characterize the different relationships for both the placebo and drug effects.

**Results:** The rate of transitioning between different probability states of EPS was shown to decrease exponentially with respect to time in the placebo group. The effect of the administration of paliperidone was added proportionally on top of the placebo effect. It was found that the rate of worsening of an EPS manifestation while taking paliperidone increases linearly with the model predicted area under the concentration-time curve. Simulations of EPS events indicated that the predicted incidence rates were similar to the observed ones.

**Conclusions:** The Markov property was successfully implemented in a mixed-effects compartmental model in NONMEM and was capable of characterizing the transition of the patients between different severity levels of EPS. This approach can also be used for analyzing other categorical side effect data.

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### **IV-19 Stina Syvänen Quinidine Microdialysis Reveals Altered P-glycoprotein Function in Epileptic Rats in the Brain Parenchyma Rather than at the Blood-Brain Barrier**

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**Objectives:** Increased functionality of efflux transporters at the blood-brain barrier (BBB) may contribute to decreased drug concentrations at the target site in CNS diseases like epilepsy. In the rat, pharmacoresistant epilepsy can be mimicked by inducing status epilepticus by intraperitoneal injections of kainate. The aim of the present study was to characterise kainate induced changes in P-glycoprotein (P-gp) functionality both at the level of the blood brain barrier and brain parenchyma, using population modelling.

**Methods:** Quinidine, a P-gp substrate, was i.v. infused during 30 min or 4 h. Brain extra cellular fluid (free brain) concentrations were measured with microdialysis during 7 hours after start of infusion. Blood samples were obtained in parallel and brain tissue was isolated at the end of the experiment for quinidine concentration determination in plasma and brain tissue, respectively. To investigate the effect of P-gp on quinidine brain distribution, kainate and saline (control) treated rats were studied without or with pre-administration of the P-gp inhibitor tariquidar. A full pharmacokinetic model for quinidine pharmacokinetics in plasma and brain was developed using mixed effects modelling (NONMEM VI). Systematic covariate analysis was performed to identify covariates significant for changes in quinidine pharmacokinetics.

**Results:** Quinidine PK was best described with a 2-comp plasma and 2-comp brain model. Kainate treatment had no effect on quinidine transport across the BBB, but produced a 1.7-fold decrease of the volume of distribution in the brain. Tariquidar pre-treatment was found to be a significant covariate, for quinidine transport across the BBB, producing a 2.7-fold increase in transport into the brain and a 2.6-fold decrease in transport out from the brain. Tariquidar also increased the distribution from the free brain compartment to the deeper brain compartment 5.6-fold. The effect of tariquidar was similar in kainate and control rats.

**Conclusions:** This study did not confirm the hypothesis that P-gp functionality at the BBB is altered in epilepsy, but rather indicated that the P-gp function might be changed at the parenchymal level. Quinidine distribution into the free brain compartment was increased more than 7-fold after tariquidar treatment. Interestingly, tariquidar also increased the distribution from the free to the deeper brain compartment, again, indicating that the P-gp function beyond the BBB should be further investigated.

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### IV-30 Karin Tunblad A pharmacokinetic/pharmacodynamic analysis of central and peripheral effects of GSK3 inhibitors

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**Objective:** The aim was to perform a pharmacokinetic-pharmacodynamic analysis of the central and peripheral effects of Glycogen Synthase Kinase 3 (GSK3) inhibitors in rat pups, and to correlate these effects to *in vitro* pharmacology measures. The influence of plasma protein binding and distribution to the brain was also investigated.

**Methods:** PKPD data for several GSK3 inhibitors at several dose levels was collected. Tau-phosphorylation in the hippocampus (central biomarker) was measured at two epitopes (AT8 and AT180), and the phosphorylation of glycogen synthase (P-GS) in muscle was measured as a peripheral biomarker. Exposure in plasma and in hippocampus and central effects and the peripheral effect were measured at one time-point in each individual. For the model building a mixed approach was used where "individual data" were created by grouping data per study and per compound. All compounds were simultaneously fitted in one model, where drug specific and system specific parameters were estimated. The variability between different study/drug combinations was also evaluated.

**Results:** The plasma concentrations were used to drive the response. The central effects were best described by indirect response models, while a direct effect model described the peripheral effect. The average half-life for the delay in the central effect was 2.7 h for AT180 and 4.1 h for AT8. IC<sub>50</sub>'s were estimated for all effect measures and the rank order of these values was similar for the three effect measures. In the indirect response models the system specific parameters (Kin, Kout and hill slope) were estimated. In the direct effect model the baseline and hill slope were estimated. In both models I<sub>max</sub> was fixed to 100%. There was a good correlation between *in vitro* data and *in vivo* parameter estimates. Also, the IC<sub>50</sub> for peripheral and central effects showed a good correlation. Correcting for plasma protein binding and distribution to the brain did not improve the correlations.

**Conclusion:** The results indicate that the response on P-GS seems to be a good predictor of compound potency for central effect, although not for the time-course of this effect. This provides a translational opportunity to human by characterizing P-GS as a peripheral biomarker also in humans. Additionally the good *in vitro-in vivo* correlation can be used to benchmark new candidate drugs aimed for inhibition of GSK3 *in vitro*, thereby reducing the need for *in vivo* screening experiments.

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**I-45 Steve Choy Application of an integrated glucose-insulin model to investigate the effects of glibenclamide and its active metabolites on postprandial glucose and insulin concentrations in healthy volunteers**

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**Objectives:** The sulphonylurea drug glibenclamide (Gb) is an insulin secretagogue used in the treatment of type 2 diabetes. Previous PKPD modeling showed that both Gb and its active metabolites (M1 and M2) decrease postprandial glucose in man [1]. We applied an existing semi-mechanistic, integrated glucose-insulin (IGI) model [2] to clinical trial data to investigate the pathways predicted to be affected by Gb and its active metabolites.

**Methods:** Rich glucose and insulin concentration-time data from 8 healthy volunteers enrolled in a placebo-controlled, randomized, single-blind crossover study were analyzed using NONMEM7. Standardized meals were consumed 0.5h after a single-dose of Gb, M1 & M2 intravenously; Gb oral tablet; and placebo intravenously 3 months apart [3,4]. The IGI model consists of glucose-insulin compartments, and control mechanisms which were effect compartments. These system specific parameters were fixed throughout the study. Flexible input stepwise absorption function parameters [5] were re-estimated using placebo arm data and fixed in the baseline model before adding data from drug arms. Using the three active intravenous arms of the study, drug effects for Gb, M1 and M2 parameterized for competitive agonist interactions between parent and metabolites using an Emax function were simultaneously estimated on either glucose production, insulin-dependent glucose elimination, insulin production, or insulin elimination. The models derived from these steps were used, without re-estimation, to prospectively model the data from the oral Gb drug arm (external validation).

**Results:** Stimulation of insulin secretion after glucose absorption as a mechanism of action showed by far the largest drop in objective function value ( $\Delta$ OFV) compared to the baseline model in the active intravenous arms of the study. Similarly, when predicting into the oral Gb arm (external validation), stimulation of insulin secretion after glucose absorption provided the largest improvement. The Emax indicate an approximate 6-fold increase in insulin production, and the EC50s for glibenclamide and its metabolites were all similar at about 240 ng/mL.

**Conclusions:** The IGI model could be successfully applied to meal test data. The effect of glibenclamide and its active metabolites on the effect on insulin production provided the best description and prediction of the glucose and insulin data in healthy volunteers. This adds to previous experience with identifying drug mechanisms using the IGI model [6].

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## **II-07 Petra Ekerot Mechanism-based Pharmacokinetic-Pharmacodynamic Feedback Model of Thyroid Hormones after Inhibition of Thyroperoxidase in the Dog. Cross-species Prediction of Thyroid Hormone Profiles in Rats and Humans.**

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**Objectives:** Thyroperoxidase (TPO) is an enzyme involved in the synthesis of T<sub>4</sub> and T<sub>3</sub> in the follicular cells of the thyroid gland. Inhibition of TPO will result in decreased plasma T<sub>4</sub> and T<sub>3</sub> and elevated TSH (thyroid-stimulating hormone) levels. The aim was to develop a mechanism-based pharmacokinetic-pharmacodynamic feedback model to describe the impact of TPO inhibition on thyroid hormone homeostasis in the dog and to predict thyroid hormone profiles in rats and humans based upon inter-species differences in hormone degradation rates and *in vitro* IC<sub>50</sub> values for TPO inhibition.

**Methods:** The PK/PD model was developed based on a simultaneous analysis of concentration-time data of T<sub>4</sub>, T<sub>3</sub> & TSH at multiple dose levels in the dogs following once daily oral dosing of a TPO inhibitor (Cmpd I) for up to 6 months. The model consists of linked turnover compartments for T<sub>4</sub>, T<sub>3</sub> & TSH. First-order degradation rate constants for T<sub>4</sub> & T<sub>3</sub> ( $K_{T4}$  &  $K_{T3}$ ) were fixed at known physiological values. The fraction (*Fr*) of T<sub>4</sub> peripherally converted to T<sub>3</sub> was estimated. Homeostatic feedback mechanisms were included to explain the negative feedback from T<sub>4</sub> on TSH levels. Cmpd I was assumed to inhibit the synthesis rate of T<sub>4</sub> using an  $I_{max}$  function. Model development and fitting was performed using NONMEM VII. Berkeley Madonna was used to predict rat and human thyroid hormone profiles.

**Results:** The PK/PD model could well describe the concentration-time profiles of T<sub>4</sub>, T<sub>3</sub> and TSH in the dog after repeated administration of Cmpd I. The validity of the model was confirmed by successfully predicting T<sub>4</sub>, T<sub>3</sub> & TSH levels for Cmpd II in the dog on basis of *in vitro* IC<sub>50</sub> for TPO inhibition. By altering  $K_{T4}$  and  $K_{T3}$  to reflect interspecies differences in hormone  $t_{1/2}$ , adjusting *in vivo* IC<sub>50</sub> (to maintain a constant *in vitro* IC<sub>50</sub>/*in vivo* IC<sub>50</sub> ratio cross-species) and adjusting fraction of T<sub>3</sub> converted from T<sub>4</sub>, the model successfully predicted the observed T<sub>4</sub> & TSH profiles in rat and human for Cmpd I.

**Conclusions:** The proposed mechanism-based PK/PD feedback model provides a scientific basis for the prediction of TPO inhibition mediated effects on plasma thyroid hormones levels in humans based on results obtained in animals studies.

### III-06 Anna Largajolli Meal Tolerance Test (MTT): Nonlinear Mixed-Effects Modeling of Insulin Secretion

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**Objectives:** The C-peptide oral minimal model (COMM) allows to quantitatively assess the  $\beta$ -cell function (1). Up to now, the COMM has been identified at individual level (IND). This study aims at comparing the performance of the NLMEM to both the full and reduced MTT protocol (2). We also investigate the performance of the NLMEM techniques by randomly discarding the C-peptide data of the reduced meal protocol, firstly, by removing 25% and, then, by removing 50% of the original samples.

**Methods:** The analysis was performed on a dataset of 204 nondiabetic subjects that received a mixed meal (2) considering the full (21 samples in 7 hours) and the reduced (7 samples in 2 hours) protocol. Once COMM parameters are estimated, three  $\beta$ -cell responsivity indices can be derived: static ( $\Phi_s$ ,  $10^{-9} \text{ min}^{-1}$ ), dynamic ( $\Phi_d$ ,  $10^{-9}$ ) and total sensitivity ( $\Phi_t$ ,  $10^{-9} \text{ min}^{-1}$ ). COMM was implemented and identified in NONMEM VI by using FOCE with interaction. The population parameter distributions were assumed lognormal, BSV was modeled with a full covariance matrix and the C-peptide (C) measurement error was modeled as  $\text{Var}(C)=2000+0.001 \cdot (C)^2$ .

**Results:** The population description obtained from FOCE using the full MTT dataset in terms of fixed effects and BSV is comparable with the first and second-order moment obtained with IND. We detect an overestimation of the BSV with IND as reported in (3-4). The linear regression analysis between FOCE vs IND estimates results having a highest correlation of  $r=0.96$  and a lowest correlation of  $r=0.66$ . The mean  $\beta$ -cell indexes obtained with the full MTT are the following (FOCE vs IND):  $\Phi_s$  is  $32.55 \pm 10.92$  vs  $33.9 \pm 13.85$ ,  $\Phi_d$  is  $418.57 \pm 207.63$  vs  $374.32 \pm 290.21$  and  $\Phi_t$  is  $143.58 \pm 104.44$  vs  $140.84 \pm 126.51$ . Regarding FOCE,  $\beta$ -cell values do not change with the reduced or the two discarded reduced protocols and the correlation values are: a) full vs reduced protocol:  $r_s=0.87$ ,  $r_d=0.96$ ,  $r_t=0.98$  b) full vs randomly 25% reduced protocol:  $r_s=0.86$ ,  $r_d=0.94$ ,  $r_t=0.97$  c) full vs randomly 50% reduced protocol:  $r_s=0.81$ ,  $r_d=0.88$ ,  $r_t=0.95$ .

**Conclusions:** NLMEM can be successfully used to estimate the COMM parameters. The population description is comparable to that obtainable considering the IND approach. COMM parameter estimates with FOCE are not significantly different in a data poor context. This paves the way to other studies that aim to further narrow down the reduced protocol in order to better deal with the typical data poor epidemiological study condition.

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### III-29 Jonas Bech Møller Model-based Analysis of the GLP-1 Response Following an Oral Glucose Tolerance Test (OGTT)

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**Objectives:** GLP-1 is an insulinotropic hormone giving rise to an increased insulin response in synergy with glucose [1]. In order to investigate how the secretion of this hormone is affected by demographic factors and by the progression of diabetes, a mechanistic model was built for characterising the secretion of GLP-1 following an oral glucose tolerance test (OGTT). Indices based on such a model can in subsequent studies provide further pathophysiological insight compared to a standard non-compartmental approach (NCA).

**Methods:** Single 75 g dose of glucose was administered orally to subjects ranging from healthy volunteers to patients with type 2 diabetes. Glucose, insulin, and total GLP-1 concentrations were measured sequentially [2]. Prior population data analysis of glucose and insulin were performed in order to estimate the glucose absorption rate. The values of absorption rates were used in the model for GLP-1 secretion. Estimation of parameters was performed using the FOCE method with interaction implemented in NONMEM VI.

**Results:** The final indirect-response model for GLP-1 production following an OGTT included two components on the stimulation of the zero-order production rate of GLP-1 [3]. One component related to the ingestion of glucose (fast), and a component related to the absorption rate of the glucose (slow). The identification of the fast component (with a peak prior to the glucose absorption peak) could indicate the presence of a proximal-distal loop for fast secretion from L-cells. This component was estimated to peak around 25 min. after glucose ingestion, whereas the slower component peaked around 100 min after ingestion. Elimination of total GLP-1 was characterised by first-order elimination. The individual parameter values of the early phase GLP-1 secretion were correlated ( $r \sim 0.64$ ) with the AUC (0-60 min.) for GLP-1.

**Conclusions:** A mechanistic population model was successfully developed to describe total GLP-1 concentrations over time observed in an OGTT. The model indicates two different mechanisms for stimulating GLP-1 secretion and may serve as a tool for studying the influence of factors (demographics etc.), on these components.

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### III-46 Joanna Peng A Mechanistic Model for the Effects of A Novel Drug on Glucose, Glucagon and Insulin Applied to Adaptive Phase II Design

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**Objectives:** Drug A was developed for the treatment of Type 2 diabetes (T2D). A mechanistic model was developed to describe Drug A pharmacokinetics and glucagon, insulin and glucose profiles in healthy subjects during a glucagon challenge. The model was adapted for the T2D patient population to assess the need for dose adjustment at the interim analysis of a Phase IIa study.

**Methods:** Single oral doses of Drug A (0-900 mg) were given to 36 healthy subjects in a Phase I study. Starting from 3, 12 or 24 hr post dose, glucagon, sandostatin and basal insulin were infused for 2 hrs (glucagon challenge). A published model was expanded incorporating drug, glucagon and sandostatin.[1] The model was then modified using steady-state analysis for patients accounting for differences in the PD parameters between healthy subjects and T2D patients. Clinical trial simulations (CTS) were subsequently performed to extrapolate drug effects to T2D patients in a Phase IIa study setting where no glucagon challenge was given. NONMEM and R were used for modeling and NONMEM and SAS were used for CTS.

**Results:** The model assumed that the glucose production rate (GPROD) was modulated by glucose and glucagon independently. The drug effect was modeled by using an inhibitory  $E_{\max}$  model ( $I_{\max}=0.96$  and  $IC_{50}=13.7$  nM) on the ability of glucagon to increase GPROD. In addition, an  $E_{\max}$  model ( $E_{\max}=0.79$  and  $EC_{50}=575$  nM) to increase glucagon secretion by the drug was used to account for the increased glucagon concentrations pre-challenge (*via* compensatory feedback). The model adequately captured the observed profiles of glucose, glucagon and insulin pre- and post-challenge. For CTS (1000 trials), the parameter estimates were adapted using baseline covariate data for the ongoing Phase IIa study in T2D patients and prior knowledge from a lead compound in the same class. Because the model PD output was fasting plasma glucose (FPG), but weighted mean glucose (WMG) was the PD endpoint for the Phase IIa study, a linear model between FPG and WMG was developed using the data from the Diabetes Control and Complications Trial.[2] The CTS results suggest that the dose selection for the Phase IIa study was adequate and that there was no need for a dose adjustment.

**Conclusion:** A PK/PD model was developed to capture the interplay between glucose, glucagon and insulin. A linear model to correlate FPG to WMG was developed and provided robust predictions to assist with the dose adjustment for the interim analysis.

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[2] The Diabetes Control and Complications Trial (DCCT) was a clinical study conducted from 1983 to 1993 funded by the National Institute of Diabetes and Digestive and Kidney Diseases with 1441 Type 1 diabetic patients treated with insulin.

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### **III-49 Kirill Peskov A Quantitative Systems Pharmacology Model Provides Insights into Phosphate Homeostasis through Multiple Interacting Pathways**

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**Objectives:** Phosphate is an important mineral required for numerous cellular functions such as DNA and membrane lipid synthesis, generation of high energy phosphate esters, and intracellular signalling. However, an integrated understanding of phosphate regulation, the various control mechanisms, and interactions between the mechanisms is not available yet. We describe here the first attempt, to our knowledge, to develop an integrated quantitative understanding of the factors responsible for endogenous phosphate regulation.

**Methods:** Based on Bergwitz (2010), a minimal model consisting of bone, serum, parathyroids, intestine, and kidney tissues and fibroblast growth factor (FGF) 23, parathyroid hormone (PTH), VitaminD, and phosphate entities was developed. The known dependencies (Ben-Gov 2007) were hypothesised based on literature and quantitatively characterised based on available data. The individual submodels were integrated to provide a unified model of phosphate homeostasis. Model predictions were verified with available literature data on therapies known to impact phosphate levels (e.g. FGF23, and FGFR modulators) and from human genetic disorders. We then used the model to simulate single and multiple dose phosphate changes for different FGFR modulators that can potentially alter endogenous phosphate levels.

**Results:** All individual submodels provided adequate descriptions of isolated interactions. The magnitude, but not time course of Vit D changes after FGFR modulation was predicted correctly. The integrated model provided good descriptions of literature-reported changes in phosphate, and Vit D levels after FGFR therapy. FGFR-subtype specific modulators had generally different VitD and phosphate effects. The contribution of PTH to overall phosphate homeostasis was found to be not significant compared to that of bone (through FGF23).

**Conclusions:** A minimal quantitative system pharmacology model of phosphate homeostasis was developed. The model can be used to evaluate the potential effect of various therapeutic options affecting the phosphate homeostasis pathway.

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### **IV-37 Piet van der Graaf Application of a Multiscale Physiologically-Based Bone and Calcium Systems Model to Guide the Development of GnRH receptor modulators for the Management of Endometriosis**

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**Objectives:** To provide model-based decision support toward the selection of doses, endpoints and study durations for gonadotropin releasing hormone (GnRH) antagonist clinical programs intended for the management of endometriosis (EM).

**Methods:** A previously reported, multiscale physiologically-based calcium homeostasis and bone remodeling model has recently been adopted to describe the effects of estrogen loss during menopause transition [1]. Longitudinal effects of varying estradiol (E2) reductions caused by GnRH suppression on biomarkers of bone turnover (BM) and bone mineral density (BMD) changes were simulated from this model. The relative percent decreases in E2 affected by varying degrees of GnRH inhibition were used to fit a differential equation linking bone marker changes with BMD effects to publicly available elagolix, leuprolide and triptorelin data using Berkeley Madonna. A larger literature-based database (1988-2006) that included clinical study-level summary data from various GnRH agonist treatments was used to provide an external evaluation of the 6-month BMD predictions from the multiscale model. Additionally, a logistic regression model describing the relationship of estrogen and total endometrial symptom severity score (ESSS) was fit to patient-level data from three clinical studies using WinBUGS 1.4

**Results:** Suppression of E2 through GnRH-mediated effects (either agonism or antagonism) occurs within the first month of treatment. Bone markers showed an increase at 6 months in bone specific alkaline phosphatase (BSAP) and serum c-telopeptide (CTX) of 39% and 88%, respectively. BM and BMD model predictions were consistent with these observed data. The model results indicated that bone marker changes are delayed compared to the E2 decrease. In addition, within the range of acceptable 6-month BMD, there was minimal early differentiation of BM across doses. An extension of the model adequately predicted the broader literature database, indicating that E2 was a reliable predictor of 6-month BMD. Logistic regression indicated that P(ESSS=0) increased to 26% and 29% at E2 values of 40 and 20 pg/mL, respectively.

**Conclusions:** E2 was shown to be a reliable early predictor of 6-month BMD change, whereas bone markers, as affected through GnRH inhibition, were projected to change too slowly to provide reliable early dose differentiation. Doses within a GnRH antagonist development program that target E2 in the range of >20 to 40 pg/mL are expected to provide efficacious EM pain response while minimizing BMD effects.

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#### **IV-59 Stefan Zajic Semi-mechanistic PK/PD Model of the Effect of Odanacatib, a Cathepsin K Inhibitor, on Bone Turnover to Characterize Lumbar Spine and Distal Forearm Bone Mineral Density in A Phase IIb Study of Postmenopausal Women**

Stefan Zajic, Julie A. Stone, David Jaworowicz, Albert Leung, Le Thi Duong, Julie Passarell, Jill Fiedler-Kelly, Dosinda Cohn, Nadia Verbruggen, and S. Aubrey Stoch  
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**Objectives:** Odanacatib (ODN, MK-0822), a potent oral inhibitor of cathepsin K, is being developed to treat osteoporosis. A semi-mechanistic model of bone turnover was developed to account for responses in cortical and trabecular bone, as described by creatinine adjusted urinary aminoterminal crosslinked telopeptides of Type I collagen (uNTx), a bone resorption biomarker, and lumbar spine and distal forearm bone mineral density (lsBMD, dfBMD) data from a Phase IIb study.

**Methods:** Data from 391 postmenopausal women (PMW) receiving placebo or 3 to 50 mg weekly ODN for up to 2 years were used. Patients who completed 2 years of treatment were re-randomized to placebo or 50 mg weekly ODN and followed for an additional year. ODN concentration, biomarker, and BMD data were collected. A population PK model was used to estimate individual exposures and an indirect response model to characterize the timecourses of lsBMD and dfBMD as functions of bone formation and resorption rates. The PK/PD model describes the action of ODN through an inhibitory sigmoid Emax function applied to the bone resorption rate and the release rate of uNTx, which is a function of resorption. Transient elevation of bone resorption biomarkers after cessation of treatment is described by incorporating active and inactive osteoclasts as system variables and including an inhibitory sigmoid Emax function describing ODN inhibition of osteoclast apoptosis rate to reflect an increase in osteoclast numbers during therapy. Effects on bone formation from treatment with placebo or ODN were included using an empirical, time-dependent term to better account for the BMD response profile.

**Results:** The population PK/PD model was simultaneously fit to uNTx, lsBMD and dfBMD data from all treatments. Goodness of fit diagnostics and visual predictive checks indicate that the model well characterizes the uNTx, lsBMD and dfBMD data. Only underlying bone formation and resorption rate parameters need to be adjusted between bone sites with primarily cortical (dfBMD) versus trabecular (lsBMD) bone.

**Conclusions:** The model supports that a combination of drug effects on bone resorption and osteoclast cycling can generate the behaviors observed in the Phase II data, including a non-monotonic dose-response relationship and enhanced bone resorption post-cessation of therapy in both cortical and trabecular bone.

## **I-29 Karl Brendel A comparison of MONOLIX, NONMEM 6 and NONMEM 7 based on a simulated PK example**

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**Introduction:** From decades, NONMEM is the gold standard software for NLME modelling. However, several alternative software, like MONOLIX (using SAEM algorithm), become more and more appealing. Regarding the algorithms, NONMEM 7 includes now new methods, like ITS, IMP and SAEM. Moreover the existing estimation methods in previous NONMEM versions, like the FOCE method, were improved in NONMEM 7 by decreasing abnormal termination of estimation.

A comparison between MONOLIX 3.1, NONMEM 7.1 and NONMEM 6.2 was performed on a simulated population PK example.

**Methodology:** A joint population PK model for the parent drug and its metabolite was previously built using NONMEM 6 (FOCEI) on simulated plasma concentration-time data[1]. The reference model, called NM6\_FOCEI, was implemented in NONMEM 7 and in MONOLIX, and parameters were estimated with both FOCEI and SAEM methods in NONMEM 7 (called NM7\_FOCEI and NM7\_SAEM) and with SAEM in MONOLIX (called MX\_SAEM). At last, simulations were performed for each different software/method, and 90% prediction interval (PI) and the median were plotted. Parameter estimates were compared to the reference model NM6\_FOCEI using Wald tests ( $p < 0.05$ ). Moreover, run time duration was compared and a graphical comparison was performed for simulations in superposing 90% PI and median profiles.

**Results:** No differences were observed between parameter estimates obtained with NM7\_FOCEI, NM7\_SAEM and NM6\_FOCEI. However statistical significant differences were found with MX\_SAEM compared to NM6\_FOCEI for several parameters. The range of run time duration was very large: 2h for MX\_SAEM, 4h30 for NM7\_FOCEI, 7h for NM6\_FOCEI and 4 days with NM7\_SAEM (1 day for SAEM only and 3 days for the IMP step). Regarding simulations performed with the different models, no differences were observed in term of simulation as P5, median and P95 were all superimposed to the ones obtained with the reference model NM6\_FOCEI.

**Conclusion:** One of the major improvements of NONMEM 7 is the implementation of new algorithms like SAEM. However the run time seems to be very time long compared to MONOLIX. With NONMEM 7, parameters estimation seems to be very sensitive to the initial parameter values contrary to MONOLIX. The FOCE method seems to be more efficient regarding run time consumption in NONMEM 7 compared to NONMEM 6. This comparison will be further extended to other types of models.

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## **I-40 Ng Chee Novel GPU-based Parallelized Qausi-random Parametric Expectation-Maximization (QRPEM) Estimation Method for Population Data Analysis**

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**Objectives:** GPU is a graphic processing unit with hundreds of processor cores on a single chip and can be programmed to perform many numerical operations simultaneously for complex data analysis. Parallel code exploiting GPU hardware may yield results equivalent to many traditional CPUs at a fraction of the cost and consume much less energy. At the present time, three of the top five supercomputers of the world are based on GPU-computing technology [1]. Monte-Carlo parametric expectation-maximization method (MCPEM in NONMEM 7 and S-ADAPT) is an exact likelihood estimation method that is well-suited for parallel computing because the most computational intensive Expectation (E)-step of the algorithm can be analyzed independently [2]. Recently, a quasi-random (QR) sampling technique has been shown to be more efficient than a traditional sampling method in evaluating multidimensional integrals during the E-step of the PEM method [3]. In this study, first and novel GPU-based QRPEM method (GPU-QRPEM) was developed for population data analysis.

**Methods:** A GPU-QRPEM was developed in a single laptop computer equipped with an INTEL Core i7-920 processor and a NVIDIA Quadro FX3800M video graphic card that contained 128 stream processors. The QR samples were generated using Sobol sequences with Owen scrambling technique [4]. A one-compartment IV bolus PK model was used to simulate population data in assessing the performance of GPU-QPREM and QRPEM method developed for a single CPU (CPU-QRPEM).

**Results:** The GPU-QRPEM consistently achieved model convergence faster than the CPU-QRPEM and has a better scaling relationship between converging times and number of random samples ( $Nmc$ ) used to compute the E-step of the algorithm. By increasing the  $Nmc$  from 1000 to 20000, the mean converging times increased from 2.87 to 38.1 min for CPU-QRPEM, but only from 0.539 to 1.93 min for GPU-QRPEM. GPU-QRPEM was about 20-folds faster in achieving model convergence when  $Nmc$  of 20000 was used. The precision and bias of the final model parameters were comparable for both methods.

**Conclusions:** To my best knowledge, this is the first GPU-based parallelized QRPEM estimation algorithm developed for population data analysis. Innovative, GPU-oriented approaches to modify existing estimation algorithms can lead to vast speed-up, and critically, enable data analysis and model development that presently cannot be performed due to limitations in traditional computational environment.

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## **I-44 Jason Chittenden Evaluation of the Lindstrom-Bates FOCE Algorithm with Simulated Pharmacokinetic Datasets**

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**Objective:** Accuracy, run time, and robustness are primary concerns when selecting a method for estimation of a population pharmacokinetic model. Historically, the most popular methods have been the First Order Conditional Estimation (FOCE) methods provided by NONMEM®, which generally provide acceptable accuracy in parameter estimates and likelihood evaluation. An alternative FOCE algorithm was proposed by Lindstrom and Bates [1] that allows a significant simplification to the optimization of the likelihood and should result in faster runtimes. To our knowledge, an extensive investigation of the accuracy, speed, and robustness of the Lindstrom-Bates FOCE (FOCE-LB) algorithm with respect to pharmacokinetic data has not been conducted. This work compares the FOCE-LB algorithm implemented in Phoenix® NLME 1.1 with NONMEM VII FOCE (FOCE-ELS) results.

**Methods:** For this evaluation we use a large set of test data and models that were previously generated by Laveille et al [2] for an evaluation of the SAEM algorithm implemented in MONOLIX. The models were transcribed to Pharsight Modeling Language (PML) for use with Phoenix NLME and both Phoenix NLME and NONMEM model sets were automated in the same environment with equivalent settings and initial estimates. We compare run time of the main algorithm (excludes covariance estimate), ELS log-likelihood to ascertain quality of convergence, convergence code or message, and parameter estimates. We compare cases where FOCE-ELS and FOCE-LB both converge and highlight cases where convergence is different.

### **Results:**

1. The FOCE-LB algorithm obtains comparable accuracy in over 95% of the mutually successful runs.
2. The FOCE-LB algorithm was faster in over 95% of the cases where it converged. On average it was 4 times faster than FOCE-ELS and it was 10 times faster over all the converged problems.
3. The FOCE-LB algorithm converged in over 95% of the cases in which FOCE-ELS also converged. Of these, 25% were significantly worse and 23% were significantly better than FOCE-ELS results.

**Conclusions:** The FOCE-LB algorithm as implemented Phoenix NLME is a fast, accurate, and reliable method for estimating population pharmacokinetic models.

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## I-50 *Emmanuelle Comets* SAEMIX, an R version of the SAEM algorithm

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**Objectives:** The Stochastic Approximation Expectation Maximization (SAEM) algorithm has proven very efficient, quickly converging to the maximum likelihood estimators [1] and performing better than linearisation-based algorithms [2]. It has been implemented in the Monolix software [3] which has enjoyed increasingly widespread use over the last few years, more recently in the Statistics toolbox of Matlab (`nlmefitsa.m`), and is also available in NONMEM version 7 [4]. The objective of the present package was to implement SAEM in the R statistical software [5].

**Methods:** The SAEM algorithm is used to obtain maximum likelihood estimates of the parameters of nonlinear mixed effects models without any linearisation of the model. The log-likelihood for nonlinear mixed effect models is analytically intractable since it requires integration over the unknown individual parameters. The SAEM algorithm uses an EM algorithm [6], where the unknown individual parameters are treated as missing data, and replaces the usual E-step with a stochastic approximation step [7,8]. The missing parameters are simulated at each iteration via a MCMC procedure, which can be used after the algorithm has converged to obtain the conditional modes, the conditional means and the conditional standard deviations of the individual parameters.

We implemented the SAEM algorithm in R, in the package SAEMIX. It provides estimates of the population parameters and their standard errors for nonlinear mixed effect models expressed in analytical form.

**Results:** The algorithm was applied to several example datasets and models, and showed good performance. The package provides summaries of the results, individual parameter estimates, standard errors (obtained using a linearised computation of the Fisher information matrix) Wald tests for fixed effects, and a number of diagnostic plots, including VPC plots and npde [9]. The log-likelihood can be computed by three methods: a linearisation of the model, an importance sampling procedure, or a Gaussian quadrature. The diagnostic graphs can be tailored to the user's individual preferences by setting a number of options, and are easily exported to a file.

**Conclusion:** The SAEMIX package provides the SAEM algorithm for R users, as an alternative to linearisation-based algorithms, implemented in `nlme` [10], or quadrature methods, implemented in `glmmML` or `lme4` [11,12]. The current version handles models in analytical form, with continuous or binary covariates.

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## **I-54 Alexander Danis Set-valued methods for estimation of parameters in population models**

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**Objectives:** The estimation of parameters with statistical methods, well-known in the pharmacometric community, often rely on assumptions about parameter distributions. Less well-known are the deterministic methods based on set-valued computations [2] which originate from the work of Moore in the 1960's. Here we present a new method that combine two complementary set operations, expansion and contraction. We apply it to estimate parameters in mixed effects models under simulated noisy time series data and compare the results with those obtained by the well-known NONMEM software package.

**Methods:** In set-valued methods, the values that a variable can assume is enclosed by a real interval, and all computations are performed with interval arithmetic, ensuring rigorous results. Intervals of possible values of parameters are split into subintervals and the consistency of each such subinterval with the data is examined. Contraction of the parameter and data intervals is obtained by constraint propagation [1] and expansion of data intervals occurs when the whole parameter search space is inconsistent. This procedure continues until there is a set of values in parameter and data space that are consistent. The sets resulting from the estimation procedure can be transformed into point clouds from which statistical properties such as means and covariances can be retrieved.

**Results:** The performance of the presented methods were tested on three population models, each containing one individual parameter and two population parameters. One of the models was constructed to be non-identifiable. Cases with poor and rich data, with varying type and amount of noise, and, various population sizes, were considered. For normally distributed noises, the results were compared with those obtained by NONMEM. For all three models, the set valued estimator performed well. NONMEM produced results with comparable accuracy on the identifiable problems, but, could not produce adequate estimates for the non-identifiable model. The consistency approach has the advantage that it does not need distributional information to work properly.

**Conclusions:** Solution strategies based on set-valued computations can be a complement to traditional estimation methods. They apply directly to raw data and do not require a priori information about parameter distributions. Being set based, they naturally solve non-identifiable estimation problems. Their scope of application include model selection and experimental design [3].

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## **II-29 Helen Graham Development of a novel method for updating the predicted partition coefficient values generated by an existing in silico prediction method**

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**Objective:** The use of PBPK modelling is becoming an increasingly important step in the drug development process as it aims to reduce the amount of in vivo and in vitro work needed during the early stages. Partition coefficients (Kps) are a vital input parameter for these models, as they help to describe the distribution of a drug within the body, and can be used to predict volume of distribution. Many in silico methods exist in the literature for the prediction of these Kp values, with varying degrees of accuracy. Six of these methods have been compared in previous work, with the Rodgers & Rowland method [1,2] found to be the most accurate across all drug classes and in all tissues. Therefore this method has been chosen as the basis for a novel Kp predictor which takes the predictions made by the Rodgers & Rowland method and updates them, taking into account experimental data gathered during the early stages of drug development. These updated Kp predictions can then be used to generate predictions for other pharmacokinetic parameters, such as concentration-time profiles, V<sub>ss</sub>, and t<sub>1/2</sub> in both rat and human.

**Methods:** A covariance matrix was generated from prior knowledge of the error of the Rodgers & Rowland Kp predictions when compared to experimental values. A Monte Carlo simulation was performed to produce randomly generated sets of Kp predictions (using the Rodgers & Rowlands predictions as the mean), and these values were then used within a PBPK model to produce a set of predicted concentration-time profiles. Using a conditional log likelihood function, information taken from the Monte Carlo simulations was used along with prior knowledge from the experimentally derived concentration-time profile to produce a set of updated Kp values. This work was performed using the modelling tool AcslX®.

**Results:** The updated Kp values for certain tissues (such as muscle and adipose) were shown to be an improvement upon the Kp predictions generated by the Rodgers & Rowland method when compared to experimental values, and they were shown to produce improved predictions for V<sub>ss</sub>, in addition to predicted concentration-time profiles that mimic more closely the experimental data.

**Conclusion:** A novel method has been described that can generate updated Kp values that are an update of the predictions generated by the Rodgers & Rowland method, using information about the error of the method and experimentally-derived iv profiles as prior knowledge.

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### **III-08 Robert Leary Exact Reproducibility of Population PK/PD NLME Numerical Results across Different Computational Environments**

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**Objectives:** NLME PK/PD software implementations such as NONMEM®, Phoenix® NLME™, and MONOLIX share a basic structural similarity in that models are expressed in a high level modeling or scripting language (NMTRAN, Pharsight Modeling Language, MLXTRAN) which is then translated into a standard programming language (Fortran, C, C++). The result is then compiled and linked to a precompiled NLME estimation engine. Due to a variety of software and hardware factors, this structure may not produce consistent numerical results across different computational environments [1]. Here we investigate whether Phoenix NLME can be configured to give exactly reproducible numerical results over a wide range of modern processors and Windows operating systems.

**Methods:** A suite of five test problems was assembled to be run across a range of recent Intel processors and Windows operating systems (Windows 2000 through Windows 7, Intel Pentium IV through Intel Core i3/i5/i7) using the March, 2011 1.2 release version of Phoenix NLME.

Additional runs were made with different compiler settings than the release version in order to gain insights into factors influencing numerical variability. Double precision (64-bit) values of all parameter estimates (THETA, OMEGA, SIGMA) and POSTHOC ETA values were written to a binary file to enable bit level comparisons.

**Results:** All Windows operating systems produced bit-for-bit identical numerical results on all Intel processors tested. Runs made with changes to compiler settings usually produced slightly different numerical results. However, in general, all results within any cohort of runs made with a fixed set of compiler settings were exactly consistent. Factors influencing inter-cohort variation were identified, with many traceable to precision differences in the 80-bit x87 Floating Point Unit used in all the Intel processors and the standard IEEE 64-bit double precision representation in memory.

**Conclusions:** Exact bit-for-bit reproducibility of numerical Phoenix NLME results across all recent Windows operating systems (Windows 2000 through Windows 7) and Intel processors (Pentium IV through Core i3/i5/i7) has been demonstrated. The key enabling factor is the selection of an appropriate compiler and application of standardized compiler settings.

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### **III-42 Erik Olofsen Population Analysis of Kalman-Filtered Permutation Entropy of the Electroencephalogram**

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**Objectives:** General anesthetics produce dose-dependent effects on the electroencephalogram (EEG).[1] A novel EEG parameter is the permutation entropy (PE).[2] An important advantage is its robustness under eye blinks. EEG data fits often show correlated residuals, which might lead to false statistical conclusions. The main objective was to construct a pharmacokinetic-pharmacodynamic (PK-PD) model with a Kalman filter.[3] Another objective was to assess whether covariate sex is a significant one.

**Methods:** Fourteen EEG data sets (7 male and 7 females) were analyzed, using a population PK-PD model. Two versions of the Kalman filter were constructed. Version A assumes that colored noise is present at the PD model output; version B assumes that noise is present at the level of anesthetic concentration. The best model was used to generate artificial data, which were analyzed by the same model, and the model without Kalman filter.

**Results:** Analysis of the PE data with Kalman filter A displayed a large value of the steepness parameter of the PD model. In contrast, analysis with Kalman filter B showed a relatively low value, so that the model output responds smoothly to changes in concentration. Gender was not statistically significant covariate. Estimated parameter values from simulated data were similar if the Kalman filter was present or absent, except for the inter-individual variabilities. Without the Kalman filter, these were overestimated with a factor of 10-30.

**Conclusions:** While the PE is insensitive to eye blinks, it is sensitive to high frequency components present in the EEG just before loss of consciousness. Analysis of EEG data with a Kalman filter accentuated or filtered out this phenomenon, depending on the postulated location of process noise. The model parameter values were not dependent on the gender of the patients. The simulation study showed that, if Kalman filtering is not applied, inter-individual variability may be overestimated; variability that is actually intra-individual process noise.

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### III-43 *Itziar Oteo* Differences among six prevalent creatinine clearance calculation methods by covariate modeling of CL for Netilmicin using NONMEM for inference

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**Objectives:** To evaluate the ability of 6 different methods in estimating creatinine clearance (CrCL) as predictor of clearance (CL) within a pharmacokinetic (PK) model for netilmicin, a potentially nephrotoxic aminoglycoside drug. .

**Methods:** Plasma levels (n= 310) and serum creatinine levels, from 62 adult patients treated with netilmicin (a single dose of 100 mg) for short-term prophylaxis after minor urological surgery as previously analyzed in Jauregizar et al (2003)<sup>2</sup> were used. Patients were in good general health, and had normal renal function (serum creatinine  $\leq$  1.9 mg/dL). Here, CrCL was estimated by Cockroft & Gault (1976)<sup>3</sup>; Mawer et al. (1972)<sup>4</sup>; MDRD formulae<sup>5</sup>; DAF method (2010)<sup>6</sup>; Jelliffe et al. (1973)<sup>1</sup> in addition to the method used in Jauregizar et al (2003)<sup>2</sup> (Mawer method corrected by ideal weight, calculated from Peck's formula<sup>7</sup> (MM)). The NONMEM<sup>®</sup> objective function (OFV) was then used to compare the predictive ability (for the CL of Netilmicin in this population) of the 6 methods of CrCL calculation using the same model ( $CL=q_{slope} * CrCL$ ). The OFV is approximately chi-square distributed and a change of 3.8 is significant at  $p < 0.05$ . A third order GAM was also applied in covariate fits for all methods with CrCL as the sole variable.

**Results:** Preliminary ANOVA analysis showed that CrCL estimation using MM method resulted statistically different when compared with DAF and MDRD methods. In the same way, Jelliffe was different compared with Mawer, DAF and MDRD methods. The MDRD had OFV= 173.342 (vs. 141.858 for MM) with other methods lying in between but also significantly less predictive than MM. Similarly, the interindividual variability was higher for MDRD compared with MM 38.60% vs 29.22% respectively). The parameter  $q_{slope}$  varied from 0.051 - 0.066 among methods, this fact could affect variably to netilmicin clearance.

**Conclusions:** The use of alternative methods for CrCL calculation for a specific drug and patient population is not justified without model specific development.

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#### **IV-41 Georgios Vlasakakis The impact of modified-release formulations on bridging of pharmacokinetic data from adults to children**

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**Objectives:** Besides the known effects of age and weight on drug disposition, formulation-specific differences create additional complexities in terms of data fitting and extrapolation from adults to children. Of particular interest in paediatric development is the role of transit time and gastric emptying on lag time, rate and extent of the absorption processes. Yet, such processes may be mathematically intractable by conventional estimation procedures. The aim of this study was therefore to assess the suitability of Bayesian methods in NONMEM and WinBUGS to deal with data sparseness and problematic absorption using small datasets. Diclofenac was selected as a paradigm compound.

**Methods:** Pharmacokinetic data from enteric-coated diclofenac tablets (30 adults) derived from a previously analysed large population (141 adults and children) was used in this evaluation. The original dataset consisted of different formulations, but the enteric coated data was discarded due to long lag time observed in the trial [1]. Experimental data was modelled using a 1-compartment model with first-order absorption (WinBUGS) and a 1-compartment model with 2 sites of first-order absorption (NONMEM7) using Bayesian methods. Goodness-of-fit, statistical and graphical diagnostic measures were used to assess model performance. Model parameters were subsequently used for extrapolation purposes.

**Results:** WinBUGS was required to characterise the lag time, whereas absorption rate and drug disposition parameters were estimated in NONMEM7. Different model parameterisations based on algebraic and analytical solutions were explored, but our results show that the description of the lag phase cannot be obtained by conventional methods.

**Conclusion:** The use of pharmacokinetic bridging is highly desirable in paediatric drug development. However, whilst data sparseness has been the focus of modelling methodologies, pharmaceutical factors have important effects on drug disposition, which cannot be overlooked and may not easily addressed by maximum likelihood methods. The incorporation of priors ensures stabilisation of parameter estimation, preventing bias and deterioration of precision.

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## **I-02 Mona Alameddine Population Pharmacokinetic Analysis and Effects of Raltegravir In HIV positive and Healthy Individuals**

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**Background:** Raltegravir (RAL) pharmacokinetics (PK) exhibit large inter and intra-individual variability. The aims of the study were to (1) quantify the variability affecting RAL PK parameters (2) identify demographic factors that influence RAL concentration (3) explore the correlations between exposure and markers of efficacy and toxicity (4) simulate different dosage regimens for predicting and comparing drug levels at trough.

**Methods:** 544 RAL plasma concentrations were collected in 145 HIV+ participants from the Swiss HIV cohort study and 19 healthy volunteers. One and 2 compartments with various absorption models were tested using NONMEM. A relative bioavailability ( $F_{\text{HIV}+}$ ) was introduced to capture a scale shift in the PK parameters observed in HIV+ patients compared to healthy individuals. Distinct absorption rate constants ( $k_a$ ) were also allowed. Demographic factors and co-medications were evaluated. Posterior Bayesian individual estimates of  $C_{\text{min}}$  and  $\text{AUC}_{0-24}$  were correlated with  $\text{CD4}+$  count, viral load, total bilirubin, AST and ALT levels using linear regression analyses.

**Results:** A 2 compartment model with first order absorption adequately described the data.  $F_{\text{HIV}+}$  amounted to 80% of RAL bioavailability in healthy subjects ( $\text{CV}=86.4\%$ ). Average apparent clearance was  $98.7 \text{ Lh}^{-1}$ , volumes of distribution 393 L for the central compartment ( $\text{CV}=76.8\%$ ), and 182 L for the peripheral compartment,  $k_a$   $0.2 \text{ h}^{-1}$  and  $0.8 \text{ h}^{-1}$  ( $\text{CV}=100\%$ ) in HIV+ and healthy individuals, respectively. Atazanavir, female gender and hyperbilirubinemia (stage 1 or higher) affected  $F_{\text{HIV}+}$ , yielding an increase of 40%, 60% and 400% in RAL bioavailability, respectively. No correlations were detected between RAL exposure and  $\text{CD4}+$  and HIV RNA count or AST/ALT and total bilirubin. Model-based simulations predicted average trough concentrations of 124 ng/ml (95% prediction interval 9.7 - 1381) for the 400 mg b.i.d regimen and of 52.2 ng/ml (4.2 - 817) for the 800 mg q.d regimen.

**Conclusion:** RAL PK confirmed a large interpatient variability, of which only 6% was explained by atazanavir intake, female gender and by the association with high total bilirubin levels. The smaller relative bioavailability in HIV+ patients could result from HIV related pathophysiological differences, compliance or food. 800 mg once daily yielded average trough predictions 50% lower than 400 mg twice daily, which might impact treatment efficacy. No clear

correlation between RAL exposure and efficacy or toxicity markers could nevertheless be detected.

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### **I-03 Sarah Alghanem Development of a Tobramycin Dosage Adjustment Nomogram for Patients with Cystic Fibrosis**

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**Objectives:** A tobramycin dose of 10 mg/kg every 24 hours is recommended for patients with cystic fibrosis. However, there is no nomogram currently available to help clinicians interpret measured concentrations and determine dosage adjustments. This study used data collected during routine therapeutic drug monitoring over 16 years to determine within-subject variability (WSV) and the influence of covariates on aminoglycoside pharmacokinetic parameters in patients with cystic fibrosis. The population model was then used to develop a dose adjustment nomogram for this patient group.

**Methods:** The study involved a retrospective analysis of the aminoglycoside database for patients with cystic fibrosis and covered the period 1993 to 2009. The data were analysed by NONMEM (version 7) (1). One and two compartment models were compared and the influence of covariates, including a range of methods for estimating renal function, was examined. WSV was investigated with the assumption that one course of therapy represented one occasion. Internal validation was conducted with 1000 bootstrap samples and a prediction-corrected VPC. Typical concentration-time profiles were used to generate the nomogram.

**Results:** Aminoglycoside concentrations (n = 2238) were available from 166 patients aged 14 to 66 years (median 23 years). Peak concentrations measured within the first 2 hours after the infusion ranged from 2.6 to 18 mg/L (median 9.3 mg/L). Trough concentrations ranged from 0.1 to 3.5 mg/L (median 0.48 mg/L). The number of occasions available ranged from 1 to 28 with a median of 5. Data were fitted with a two compartment model and the inclusion of WSV on CL produced a further improvement in fit. The final covariate model for CL included creatinine clearance estimated by the Cockcroft and Gault equation (2), with the minimum serum creatinine concentration fixed to 60  $\mu\text{mol/L}$ . Between-subject variability (BSV) in CL was 18.5% and WSV was 11%. V1 was best described using height, which reduced BSV from 16% to 12%. BSV could not be estimated for V2 and Q. Internal methods supported the validity of the final model. A nomogram was developed to aid in the interpretation of tobramycin concentrations with extended interval dosing.

**Conclusions:** Since unexplained WSV in the handling of aminoglycoside antibiotics in patients with cystic fibrosis is low, patients can be started on a previous individualised dosage regimen if a new course of therapy is required. A tobramycin dosage adjustment nomogram may help in the interpretation of measured tobramycin concentrations.

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## I-16 Julie Bertrand Extensive Population Pharmacokinetic-Pharmacogenetic Study of Nevirapine in HIV-Infected Cambodian Patients

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**Objectives:** Focused genotyping of *CYP2B6* 516G/T in HIV-infected Cambodians in the ANRS12154 study showed its association with steady-state NVP clearance (Cl/F) using nonlinear mixed effect models (NLMEM) to analyse the concentrations data [1]. The present study more thoroughly investigated *CYP2B6* and other genes to better understand the genetics of NVP Cl/F.

**Methods:** Analyses included patients from the Phnom Penh Esther cohort who consented for genetic testing. All received standard dose NVP plus two nucleoside analogs and NVP trough plasma concentrations were measured 18 and 36 months after the treatment onset along with complete pharmacokinetic profiles (5 samples) in 10 patients.

A one compartment model with first-order absorption and elimination was used accounting for between and within subject variability on Cl/F. Empirical Bayes estimates of NVP Cl/F were derived from the model and the average over the occasions was used as phenotype in the analyses.

Linear regressions on minor allele dosage were performed on all single nucleotide polymorphisms (SNP) genotyped and their haplotypes with a FDR correction to account for tests multiplicity. Analyses were performed in PLINK [2], and haplotype blocks defined with the D' confidence intervals method in Haploview [3].

**Results:** Genotypes were obtained in 129 patients. The population Cl/F estimate was 2.67 L/h with between and within subject variability of 28 and 17%, respectively. The derived average individual NVP Cl/F estimates over the occasions were ranging from 1.06 to 7.81 L/h with a mean at 2.72 L/h.

Of the 196 SNPs assayed in *CYP2B6*, *CYP3A4*, *CYP3A5*, *NR1I2* (*PXR*) and *ABCB1*, 126 were polymorphic in this population. Minor allele frequencies of *CYP2B6* 516G/T and *CYP3A5* 6986A/G (loss-of-function variant) were 0.34 and 0.37, respectively.

In univariate analyses, 17 SNPs in *CYP2B6* and 1 in *CYP3A4* as well as 6 haplotypes in *CYP2B6* were associated with Cl/F. In multivariate analyses conditioned on 516G/T, no other SNP was independently associated to Cl/F. *CYP2B6* 516TT homozygosity predicted a 36% reduction in Cl/F.

**Conclusions:** NLMEM enabled the quantification of between and within subject variability of NVP Cl/F in this HIV-infected Cambodian population and investigate the influence of several genetic polymorphisms. The strong association between *CYP2B6* 516G/T and decreased steady-

state NVP Cl/F may represent the effect of an extended *CYP2B6* haplotype block that encompasses promoter regions and multiple exons.

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**I-30 Margreke Brill Cefazolin pharmacokinetics in morbidly obese patients following a prophylactic dose during weight reducing surgery.**

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**Objectives:** In this study we aimed to investigate the pharmacokinetics of cefazolin in morbidly obese patients undergoing weight reducing surgery.

**Methods:** At induction of anesthesia, morbidly obese patients received a dose of cefazolin 2 gram for the prevention of surgical site infections. Blood samples were drawn at T=0, 5, 10, 30, 60, 120, 180 and 240 min. after dosing and were analyzed using HPLC-UV. Cefazolin plasma concentrations were modelled using NONMEM VI and S-PLUS. A step-wise covariate analysis was performed to identify the influence of total body weight, lean body weight, ideal body weight, body mass index, age, sex, creatinine and bilirubin on the pharmacokinetics of cefazolin.

**Results:** Twenty morbidly obese patients with a median body weight of 144 kg (range 112 - 260 kg), a median age of 48 (range 22-59) and a median BMI of 51 kg/m<sup>2</sup> (range 38-79 kg/m<sup>2</sup>) were included in the study. Cefazolin plasma concentrations were best described by a two-compartment model. Parameter estimates for clearance and central volume of distribution were 66.1 ml/min and 6.9 L, respectively. Total bodyweight proved the most predictive covariate for central volume of distribution (linearly centred) with inter-individual variability decreasing from 27.8% to 16.5% ( $p < 0.001$ ). Age as a covariate for clearance implemented in an exponential manner further improved the model and reduced inter-individual variability for clearance from 42.1% to 34.9% ( $p < 0.05$ ).

**Conclusions:** We developed a two-compartment pharmacokinetic model for cefazolin in morbidly obese patients in which total body weight and age proved to be the major determinants for respectively central volume of distribution and clearance of cefazolin. Plasma concentrations profiles in lean patients are awaited to confirm the currently observed covariate functions of clearance and central volume of distribution.

**I-39 Georgia Charkoftaki Pharmacokinetics of doripenem in cerebrospinal fluid**

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**Objectives:** To characterise the pharmacokinetics of the antibiotic doripenem (DRP) in cerebrospinal fluid (CSF).

**Methods:** 44 neurological patients received a single 500 mg prophylactic dose of DRP at various times before surgery for implantation of a pump for intrathecal administration of baclofen or after lumbar puncture for the trial intrathecal infusion of baclofen. Patients had neither active neurological disease nor infection of the CNS. One and in some cases two samples of CSF per patient were collected, as well as one blood sample. Samples were analysed using an HPLC method [1] and DRP concentrations were quantified. A NONMEM pharmacokinetic analysis was carried out in two stages. The first stage used the plasma samples and literature population priors for a two-compartment model [2] to estimate the Empirical Bayesian Estimates (EBE) of the PK parameters of each patient for DRP in plasma. The EBE of the PK parameters were used as covariates to estimate the PK parameters of a third distribution compartment corresponding to CSF [3]. The structural parameters included in the model were the rate constant,  $k_{CSF}$ , and the partition coefficient PC.

**Results:** The VPC of the literature PK model for the plasma together with the plasma data showed that the model describes the data reasonably. In the second stage a model was developed for the CSF data, using EBE estimates for the PK parameters from the plasma model as covariates. The final model estimated the mean values of  $k_{CSF}$  and PC and the interindividual variability for PC, while the residual variability was fixed to the corresponding plasma value. The model was validated internally using VPC and bootstrap. The estimates for the mean of the parameters were  $k_{CSF}=0.11 \text{ h}^{-1}$ ,  $PC=0.05$  while IIV for PC was 56%. These values correspond to a mean steady state CSF concentration of 0.22 mg/L, for 1500 mg daily dose and a mean half-life time to equilibrium of 6.3 hours. Comparing MIC concentrations for different bacteria to this CSF value, is promising for the potential use of DRP for CNS infections, taking into account that in case of meningitis drug penetration through BBB will be significantly more extensive. More clinical trials in patients are needed with richer samples, to characterise the kinetics of DRP in the CSF more accurately.

**Conclusion:** The present NONMEM analysis of DRP CSF data shows that DRP crosses BBB significantly even in healthy non-inflammating meninges and therefore may be appropriate to treat certain CNS infections.

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## **I-60 Paolo Denti Population PK of Isoniazid in South African Adults.**

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**Objectives:** Isoniazid, together with rifampicin, forms the backbone of 1st line antitubercular treatment. The rate of isoniazid metabolism is highly dependent on genetic polymorphisms of N-acetyltransferase 2 [1]. The objective of this study was to develop a population PK model of isoniazid.

**Methods:** A cohort of 62 South African HIV infected subjects with pulmonary TB was treated with a fixed dose combination of rifampicin, isoniazid, pyrazinamide, and ethambutol, according to the WHO weight-based dosing recommendations [2]. Intensive PK sampling was performed on 4 occasions, on the 1st, 8th, 15th and 29th day of antituberculosis treatment. A population PK model was built in NONMEM VII. Several absorption and disposition models were tested, and variability between subjects (BSV) and occasions (BOV) in the PK parameters was quantified. Samples below the limit of quantification (LOQ) were handled with the M6 method from [3], and a dedicated additive error structure was used. Since no genotyping or metabolite information was available, a mixture model was used to explore the presence of subpopulations with respect to acetylator phenotype.

**Results:** Isoniazid PK was described by a two compartment disposition model with absorption through a series of transit compartments [4] and first-order elimination. A large variability was observed in absorption and bioavailability and mainly at BOV, rather than BSV level. The clearance, instead, was found to be strongly subject-specific and did not vary much between occasions. The large BSV in CL (initially more than 50%) was explained with the introduction of a mixture model, which estimated a CL of 26 L/h for about 45% of subjects, and a value more than doubled for the rest. After the implementation of this mixture, BSV in CL dropped to 20%. The subpopulation with fast clearance was also found to have lower bioavailability (about 70%).

**Conclusions:** Although no direct acetylator status information was available for the subjects in this study, and thus no verification was possible, the improvement in fit obtained with the introduction of the mixture modeling indicated the presence of at least 2 subpopulations, likely corresponding to slow and fast acetylators. In fast metabolizers, a reduction in bioavailability was also detected, possibly due to a larger extent of first-pass metabolism.

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## II-17 *Monika Frank* Integrated Population Pharmacokinetic Model Development of Nevirapine for Mothers and Newborns including Healthy Male Volunteer Data

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**Objectives:** A population pharmacokinetic (PK) model of nevirapine (NVP) was developed to describe the population PK of NVP after single dose administration during prevention of mother-to-child (PMTCT) HIV transmission. [1]. Autoinduction of CYP3A and CYP2B6 pathways limits the use of NVP models developed from steady-state data in PMTCT [2]. Sparse data in pregnant women/mothers and newborns were supplemented with rich single dose data in healthy male volunteers.

**Methods:** In Uganda NVP-based prophylaxis consisted of 200 mg NVP tablets for women and 2 mg/kg NVP syrup for newborns. Healthy males received 200 mg NVP. The PK analysis was supported by 113 plasma data of mothers (N=62) and newborns (N=62) and 95 breast milk samples. In a first step an integrated PK model for mothers/newborns was developed using the NLME approach implemented in NONMEM VI (ADVAN6). Subsequently, 390 plasma samples of 26 healthy males were added to the analysis. Data were analysed with NONMEM VI (all FOCE INTER). Model fit and performance were guided by various diagnostic tools.

**Results:** Based on a previously published integrated PK model [3], further model development focused on mother and newborn plasma data only [4]. In a subsequent step, milk data was included to incorporate breastfeeding. Due to sparse data the absorption rate constant ( $K_A=1.34$  1/h) was fixed (interindividual variability (IIV): 170% CV). The volume of distribution and clearance estimates for mothers were  $V/F=101$  L (IIV: 31% CV),  $CL/F=1.4$  L/h (IIV: 31% CV) and for newborns  $V/F=14.8$  L and  $CL/F=0.2$  L/h (IIV: 13% CV), respectively. NVP plasma/placental transfer was estimated to be 89 L/h and the partition coefficient was estimated to be 1.24. The precision of estimates was <35%, except IIV of newborn CL (53%). In the final step healthy male plasma data were added to support the integrated PK model.  $K_A$  was estimated to be 0.9 1/h (IIV: 128% CV) for mothers and healthy males. All other parameter estimates revealed similar values and good precision (RSE<29%), except IIV newborn CL (48%). Both integrated models presented adequate model fit and predictive performance.

**Conclusions:** A population PK model integrating single dose NVP data from pregnant women, newborns and healthy volunteers was developed to guide dosing regimens for newborns to assist MTCT strategies.

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## II-22 *Maria Garrido* Population Pharmacokinetics/Pharmacodynamics of Ganciclovir after Intravenous Ganciclovir and Oral Valganciclovir Administration in SOT Patients Infected with CMV

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**Objectives:** Cytomegalovirus (CMV) infection is the most common opportunistic infection following solid organ transplantation (SOT) that may facilitate the acute or chronic rejection. Ganciclovir (GCV) or its prodrug Valganciclovir (VGC), are widely used to control virions replication<sup>1</sup>. The aim of this study was to establish the population pharmacokinetics/pharmacodynamics (PK/PD) of GCV after iv GCV followed by oral VGC, in SOT recipients infected with CMV.

**Methods:** 20 SOT patients enrolled in the study received one hour iv infusion of 5 mg/kg/12 h of GCV for 5 days followed by oral doses of VGC (900 mg/12 h) for 16 days. Doses were adjusted by estimated of creatinine clearance (CRCL). Blood samples for PK were collected on days 5 and 15 of treatment. Viral load quantified as PCR, was determined at baseline and on days 5, 15, 21 during treatment, and on days 30, 60, 90, and 180 post-treatment. The analysis was done sequentially, first the population PK model was developed and with the individual Bayes estimates, the exposure-response model was developed (PD). All analyses were performed with NONMEM VI using the FOCE interaction method.

**Results:** The PK of GCV was described by a bi-compartmental model with 1<sup>st</sup> order absorption. Interindividual variability (IIV) was associated to total plasma clearance CL (33%), central distribution volume  $V_1$  (48%), absorption rate constant  $K_A$  (68%) and bioavailability  $F$  (22%). CRCL covariate in CL described part of its IIV. An absorption lag time of 0.38 h was found significant. Internal model validation was done by a bootstrap analysis.

The CMV dynamic model was represented by two compartments, Infected cells ( $I$ ) and free virions ( $V$ ), where new virions produced from infected cells at a rate,  $P$  can either death at a rate,  $c$ , or infect new cells<sup>2</sup>. GCV acts by blocking  $P$ . This effect was modelled by an inhibitory  $E_{MAX}$  model. The  $IC_{50}$ , drug concentration that induced the 50% of maximal inhibitory effect ( $0.85 \pm 0.2$ ), was  $7.2 \pm 11.4$  mg/L. This model could describe the individual decrease of viral load in most of the patients, failing in those CMV seronegative [donor (+)/ recipient (-)]. In some of them, a new viral replication peak is observed at 30-40 days post-treatment. In order to explore this effect, mechanisms corresponding to immuno status are being investigated<sup>3</sup>.

**Conclusions:** A population PK/PD model for GCV in SOT patients infected with CMV is being developed to describe data from CMV sero-positive and negative, simultaneously.

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## **II-27 Sylvain Goutelle Comparison of Four Renal Function Estimator-Based Models for the Prediction of Gentamicin Concentrations in Geriatric Patients by Use of Nonparametric Population Approach**

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**Objectives:** Most aminoglycoside pharmacokinetic models include an index of renal function, such as creatinine clearance to describe elimination [1]. However, the best clinical descriptor of renal function for PK modeling of aminoglycosides has not been established. The objective of this study was to compare four gentamicin (GENT) PK models based on the Cockcroft-Gault (CG), Jelliffe (JEL), MDRD, and modified MDRD (MDRDm, adjusted to individual body surface area) formulae.

**Methods:** This analysis was based on 427 gentamicin concentrations from 92 geriatric patients who received intravenous GENT for various infectious diseases. Monitoring of gentamicin concentrations was part of routine patient care. Four bicompartamental models were fitted to GENT concentrations in a learning set of 64 patients using the NPAG algorithm [2]. Each model included an index of renal function (CG, JEL, MDRD, or MDRDm) as a covariate influencing GENT serum clearance. The Akaike information criterion (AIC) was used to assess the goodness-of-fit of candidate models. Mean prediction error and mean squared prediction error were used to evaluate bias and precision, respectively. In a validation set of 28 patients, population and individual predictions were made from each of the four model nonparametric population PK parameter joint densities. Bias and precision of the four models were compared with the Kruskal-Wallis test in both the learning and validation sets.

**Results:** In the learning set, the CG-based model best fitted the data (lowest AIC value), followed by JEL, MDRD, and MDRDm-based models. Bias and precision of population predictions were significantly different ( $p < 0.001$  and  $p = 0.027$ , respectively). In the validation set, bias and precision of population predictions were not significantly different between the models. However, individual predictions from the four models showed marginally different bias ( $p = 0.04$ ). Overall, the CG-based model provided the best fit and predictive performance.

**Conclusions:** PK models of GENT based on various estimators of renal function may provide significantly different results. In this study, the model based on the CG equation predicted GENT concentrations slightly better than the JEL, MDRD, and MDRDm equations in geriatric patients. In clinical practice, one should continue to use the CG equation for model-based adaptive control of GENT dosage regimens.

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## II-35 *Monia Guidi* Population Pharmacokinetics of Nevirapine in HIV-positive Patients

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**Objectives:** The aim of this observational study was to determine the population pharmacokinetic parameters of nevirapine, their variability, and to identify factors which might explain variations in drug levels in HIV+ patients. Simulations were performed to predict the concentrations at trough associated with the 400 mg once-daily (q.d) and the 200 mg twice-daily (b.i.d) dosage regimens and to compare their probability to stay over the suggested minimum target level of 3000 ng/mL.

**Methods:** The analysis was performed on plasma samples of HIV infected patients of the Swiss HIV cohort study receiving nevirapine as part of their anti-retroviral therapy. A one compartment model with first order absorption and elimination was used to fit the data using NONMEM. Co-administered drugs and demographic, clinical variables and genetic polymorphisms of CYP2B6 and CYP3A4 were tested as covariates.

**Results:** 734 plasma concentrations from 370 patients were included in the analysis. Average oral clearance was 3.1 L/hr (CV 31%), volume of distribution 97 L (CV 56%) and the absorption rate constant 0.98 h<sup>-1</sup>. Among all the evaluated covariates, body weight, concomitant administration of atazanavir/ritonavir (n = 62), elevated ASAT (n = 39), inducers of CYP3A4 (n = 10) and the *CYP2B6\*6* and *CYP3A4\*1B* alleles significantly affected nevirapine clearance, however explaining only 4% of interpatient variability altogether. Simulated average concentrations at trough after 400 mg q.d or 200 mg b.i.d were 3964 ng/ml (95% prediction interval 1476-7746 ng/ml) and 4990 ng/ml (95% prediction interval 2162-9302 ng/ml), respectively. Taking into account variability, 64% and 82% of the simulated individual concentrations at trough would reach the therapeutic target of 3000 ng/ml in naïve patients, after 400 mg q.d and 200 mg b.i.d, respectively.

**Conclusion:** The covariates identified as significant on NVP clearance had a limited impact on explaining interpatient variability. Concentration exposure appears less frequently maintained over the target trough level with the 400 mg q.d. regimen than with the currently recommended 200 mg b.i.d regimen, which could counterbalance the potential advantages of q.d. prescription regarding adherence.

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## II-43 Richard Höglund Population modelling of the pharmacokinetics of a mefloquine-artesunate treatment at the Thai-Myanmar border

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**Background:** Malaria is an important health problem in tropical regions of the world. Artesunate-mefloquine is a standard treatment against *Plasmodium falciparum* malaria in Thailand, but there might be a developing drug resistance against both of the combination partner drugs.

**Objectives:** The objective of this study was to describe the pharmacokinetic properties of mefloquine, artesunate and dihydroartemisinin, which at a later stage will be used in the development of PK-PD models for different molecular markers and their impact on the outcome and efficacy of the treatment, as well as possible resistance development.

**Methods:** One hundred thirty Burmese patients with uncomplicated *P. falciparum* malaria were given a three-day oral dose regimen of artesunate and mefloquine. Details on the study have previously been published [1]. Venous blood samples were drawn from each patient resulting in either a full or sparse concentration-time profile. Whole blood or plasma concentrations of mefloquine, artesunate and dihydroartemisinin were quantified using LC-UV and LC-MS/MS [2,3]. Drug concentrations were analysed with nonlinear mixed-effects modelling in NONMEM VI. Multi-compartment distribution models with different absorption models were evaluated. It was explored whether covariates such as parasite clearance time, weight, age or parasitemia could explain the variability between patients. Baseline measurements of drug concentrations, due to self-medication before the initiation of the study, were modelled as a baseline in the PK model.

**Results:** A total of 677 plasma samples were analysed. 11.4 % of the patients had baseline concentrations of mefloquine. None had artesunate or dihydroartemisinin concentrations at enrolment to the study. The concentrations were adequately described by the used modelling approach taking into account the baseline concentrations. For mefloquine a regular two compartment disposition model were used and artesunate-dihydroartemisinin were described by a metabolite model.

**Conclusions:** The developed model could adequately describe the PK for this mefloquine-artesunate combination treatment.

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## II-46 Arantxa Isla Population Pharmacokinetics of Cefoxitin as a Prophylactic Antimicrobial Agent

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**Objectives:** The aim of this study was to develop a population pharmacokinetic (PPK) model of cefoxitin (FOX) as a prophylactic agent in patients undergoing elective rectal or colon surgery in order to quantify the degree of inter-patient variability and identify the patient characteristics responsible for such variability.

**Methods:** Plasma concentration-time data were obtained from 56 patients who received 2 g FOX q2h during surgery. The PPK model was developed using NONMEM VII and the FOCE estimation method with INTERACTION. Selection between models was based on the value of the objective function, the precision of parameter estimates and the goodness of fit plots. Once a base model was selected, patient characteristics including demographic, clinical, laboratory and surgical data were explored for influence on PK parameters. For model evaluation, parameter precision was evaluated computing the 2.5<sup>th</sup>, 50<sup>th</sup>, and 97.5<sup>th</sup> percentiles obtained from the analysis of 1000 bootstrap datasets [1]. Visual and numerical predictive checks were used to explore model performance of the selected model [2]. In both procedures 1000 datasets with the same study design characteristics as the original dataset were simulated.

**Results:** A one-compartment model best fitted the data. Creatinine clearance ( $CL_{CR}$ ) was found to have a significant correlation with the total clearance of the drug. The population clearance was expressed as  $11.5 \times (CL_{CR}/77)^{0.52}$  and the apparent volume of distribution was 12 L. The percentage of  $\eta$ -, and  $\epsilon$ -shrinkage [3] was greater than 25%, and therefore the use of goodness-of-fit based on the normalized prediction distribution errors (npde) [4] was justified. The selected model was capable to capture the mean tendency and dispersion of the data during the first two administrations involving 90% of the observations available. The percentiles for  $C_{max}$  and  $AUC_{last}$  obtained from the simulated dataset during the performance of the numerical predictive check were in agreement with raw data, with median values of 159 mg/L, and 201 mgxh/L, respectively.

**Conclusions:** This study has quantified the influence of  $CL_{CR}$  on the PK of FOX in patients undergoing colorectal surgery. Considering that the main objective of antimicrobial prophylaxis is to maintain free-drug plasma levels above the MIC for common contaminating pathogens during the surgery, the developed PPK model will be helpful to redefine dose regimens of FOX for surgical prophylaxis in patients with high  $CL_{CR}$ .

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## II-60 Dalia Khachman Optimising ciprofloxacin dosing in intensive care patients based on pharmacodynamic target attainment

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**Objectives:** The objective was to explore different dosage regimens of ciprofloxacin for the treatment of Intensive Care Unit (ICU) patients against the main Gram-negative pathogens of interest, in order to maximise clinical efficacy while minimising the risk of bacterial resistance.

**Methods:** A number of ciprofloxacin dosage regimens were investigated for each pathogen within the limit of 2400 mg/day. Targets to achieve were: free  $AUC_{24h}/MIC \geq 90h$  as a predictor of clinical outcome [1] and  $T_{MSW} \leq 20\%$  as a predictor of selecting resistance [2], where MIC is the minimum inhibitory concentration and  $T_{MSW}$  the time spent within the mutant selection window over 24 h. Ciprofloxacin AUC and  $T_{MSW}$  were simulated for 10,000 patients using a previous population pharmacokinetic model for ciprofloxacin developed in 102 ICU patients from the University Hospital of Toulouse-Rangueil, France, and including creatinine clearance as a covariate [3]. Here, creatinine clearance was assumed to follow a uniform distribution over [30;120] mL/min and the unbound fraction of ciprofloxacin to follow a uniform distribution over [0.6;0.8] [4]. Two simulation trials were conducted: Trial 1 took into account the whole MIC distribution for each causative pathogen in line with empirical antibiotherapy; Trial 2 used the MIC breakpoints established by the French antibiogram committee in order to treat the "worst-case" scenario. In both trials, mutant prevention concentrations (MPC) were simulated assuming a uniform distribution of the MPC/MIC ratio over [4;16] [5-7].

**Results:** Trial 1 showed that for *P. aeruginosa* and *A. baumannii*, the common dosage regimens of 400 mg q12h and 400 mg q8h did not achieve the desired target attainment rates (TAR) with respect to  $T_{MSW}$ , while suboptimal TAR were found for  $AUC_{24h}/MIC$ . Increasing the daily dose did not allow a major improvement of TAR. Trial 2 showed that  $\leq 18\%$  of patients reached the target of  $T_{MSW} \leq 20\%$  for MIC breakpoints of 0.5 and 1 mg/L, regardless of the administered dose.

**Conclusions:** Based on the mutant selection window concept, our simulations question the use of ciprofloxacin for the treatment of *A. baumannii* and *P. aeruginosa* infections in ICU patients due to the potential for developing resistance. They also suggest that the breakpoints of antibiograms should be used with caution and should probably be revised.

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## II-61 *David Khan* PKPD-modeling of time-kill curves from *E. coli* mutants exposed to ciprofloxacin

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**Background:** There is a need to better understand how antibiotics should be dosed to overcome and minimize development of resistance and much information can be gained from modeling and simulations based on *in vitro* experiments of bacteria kill. A semi-mechanistic model describing *in vitro* antibiotic effects has been proposed based on a strain of *Streptococcus pyogenes* [1]. The model includes two subpopulations of bacteria, one drug-susceptible population and one resting insusceptible population. The semi-mechanistic model structure allows for application on other types of bacteria with parameter estimates dependent on the degree of bacterial resistance and fitness. The aim of this work was to develop a PKPD-model describing the time-kill curves of wild-type and three well-characterized mutants of *E. coli* exposed to different concentrations of ciprofloxacin.

**Methods:** Time-kill curve data from 24h static *in vitro* experiments with *E. coli* MG1655 and three mutants thereof were used for model development. Ciprofloxacin concentrations were constant during the experiment and ranged from 0.06 to 8 x MIC for each bacterial strain. Modeling was performed in NONMEM 7. The drug effect on the susceptible bacteria was described by an Emax-model. Differences in the parameters for the wild-type and resistant bacteria were searched for. Regrowth in the wild-type bacteria experiments were described as pre-existing resistance for some bacteria in the starting inocula.

**Results:** Time-kill curves for all investigated strains and concentrations were well predicted by the model. Growth rates were 10% lower for the three mutants compared to wild type. EC50 was higher for the mutants and different for all strains. Emax was the same for the wild type and two of the mutants while one mutant had a 30-fold higher Emax. Allowing for pre-existing resistant bacteria in the wild-type starting inocula resulted in a decrease in OFV of 75 units with an estimate of 8 bacteria per 10<sup>6</sup> bacteria.

**Conclusions:** The model successfully described the time-kill curves following ciprofloxacin exposure for all investigated mutants and explained the regrowth occurring in the wild type bacteria experiments. The model can be used to predict the time-course of bacterial kill following different dosing regimens and in the presence of mixtures of wild-type and mutant bacteria, and may thereby be a valuable tool in the search for dosing regimens that minimize the growth of resistant mutants.

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### III-05 *Ryuji Kubota* A Novel Framework of Long-term Prediction of integrase inhibitors for treatment naïve patients

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**Objectives:** Dolutegravir (DTG, S/GSK1349572) is an unboosted, once daily integrase inhibitor currently under development for the treatment of HIV infection. A mathematical representation of long-term viral responses for integrase inhibitors remains challenging because it must include phenomenon that are difficult to model such as resistance, background therapy and adherence. The objective was to develop a framework that describes complicated interactions in long-term treatment with integrase inhibitors, and that predicts efficacy at 96 weeks in Phase 3 clinical trials.

**Methods:** A simple PK/PD model for virologic response, which was developed previously [1], was used to predict HIV-1 RNA time courses in treatment naïve patients. The model was modified for incorporating resistance, adherence, subject dropout and the effect of background therapy (dual nucleoside reverse transcriptase inhibitors). Viral load influenced the probability of resistance-associated mutations. The basic model parameters were based on the estimates from Phase 2a 10-day monotherapy studies. Some of model parameters were adjusted so that the model described the observed data for up to 24 weeks in SPRING-1 [2] and STARTMRK [3, 4]. The model was used for predicting long-term viral responses for up to 96 weeks to simulate the results for a treatment-naïve Phase 3 study.

**Results:** Predicted proportion (90% simulation interval) of patients with <50 copies/mL HIV-1 RNA at 24 weeks were simulated as 90.0% (83.9%-96.0%), 96.0% (90.0%-100.0%), and 96.0% (92.0%-100.0%) at 10, 25 and 50 mg QD of DTG, respectively, and 92.0% (85.9%-96.0%) at 400 mg BID of raltegravir (RAL). These predictions were reasonably consistent with the data in SPRING-1 and STARTMRK. DTG was predicted to suppress viral loads to less than 50 copies/mL over a long duration: 82.0% (73.9%-90.0%) at 10 mg QD, 90.0% (84.0%-96.0%) in the 25 mg QD, and 92.0% (86.0%-96.1%) at 50 mg QD at 96 weeks, while 84.0% (76.0%-92.0%) at 400 mg BID of RAL.

**Conclusions:** We propose a novel framework for long-term prediction of efficacy with integrase inhibitors. The simulation shows durable efficacy of DTG for treatment naïve patients and supports the dose selection of 50 mg QD in Phase 3 studies.

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### III-36 *Elisabet Nielsen* PK/PD Indices of Antibiotics Predicted by Mechanism-Based PKPD Models

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**Objectives:** Currently used dosing regimens of antibiotics are generally based on summary endpoints. One of three PK/PD indices ( $C_{\max}/\text{MIC}$ ,  $\text{AUC}/\text{MIC}$ , or  $T_{>\text{MIC}}$ ) is selected for each drug and the magnitude of the index required for efficacy is assessed and assumed to be consistent across patient populations. Mechanism-based PKPD models, considering the time-course of efficacy, may provide for a better characterization of the exposure-response relationship. The aim was to evaluate the capability of PKPD models developed based on in vitro data (1, 2) in identifying the currently used PK/PD indices and their magnitudes reported for efficacy. A secondary aim was to challenge the methodology used in the establishment of the PK/PD indices, and thereby their consistency across study conditions.

**Methods:** Six drugs (benzylpenicillin, cefuroxime, erythromycin, gentamicin, moxifloxacin, and vancomycin) representing a broad selection of PK and PD characteristics were investigated. For each drug, a dose fractionation study was simulated, using a wide range of total daily doses given as intermittent doses or as constant drug exposure. The time-course of the drug concentration (PK) and the bacterial response to drug exposure (PKPD) were predicted. Non-linear least squares regression analyses determined the PK/PD index being most predictive of the effect.

**Results:** In accordance to previous findings,  $T_{>\text{MIC}}$  was the PK/PD index best correlated to the PD endpoint for benzylpenicillin and cefuroxime, while  $\text{AUC}/\text{MIC}$  was the best predictor of the effect for the remaining four antibacterial drugs. The estimated magnitudes of the PK/PD index required for efficacy corresponded well with those earlier observed clinically. However, the choice and magnitude of the PK/PD index were both shown to be sensitive to study design, the PK profile of the drug and the uncertainty in MICs.

**Conclusions:** The currently used PK/PD indices were successfully selected based on predictions from mechanism-based PKPD models for all six drugs investigated. This supports that PKPD models based on in vitro time-kill curve studies can be predictive of antibacterial effects observed in vivo. As the selection and magnitude of the PK/PD indices were sensitive to study design and not always consistent between patient subpopulations with different PK, the PK/PD indices can extrapolate poorly across patient sub-populations and mechanism-based models may be of more predictive value in development of dosing regimens.

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### III-63 *Dinko Rekić* Bilirubin - a biomarker of atazanavir exposure in HIV/AIDS patients

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**Objectives:** The protease inhibitor (PI) atazanavir is currently recommended for the first line treatment of HIV-1 infected patients. Although elevated bilirubin levels are commonly observed in patients on a atazanavir treatment it is an uncommon cause of treatment discontinuation. Several studies have shown a concentration dependent increase in bilirubin levels (1). This study aimed to quantify the relationship between bilirubin and atazanavir through the use of modelling and investigate the possible uses of bilirubin as a biomarker of atazanavir exposure.

**Methods:** The population pharmacokinetic/pharmacodynamic analysis was performed using NONMEM VI based on atazanavir (n=200) and bilirubin (n=361) plasma concentrations of the atazanavir arm (n=82) in the NORTHIV trial (2). A one compartment model with fixed first order absorption and lag-time was fitted to atazanavir concentrations. Individually predicted plasma concentrations were used to drive the bilirubin time course in each individual. An indirect response model adequately described the atazanavir-bilirubin relationship. Simulations of the typical individual were performed to assess the influence of non-adherence and suboptimal exposure on bilirubin levels.

**Results:** Oral clearance and volume of distribution were estimated at 6.47 L/h and 93.6 L, respectively. The between subject variability was estimated at 53% for clearance and at 43.8% for volume of distribution. Bilirubin baseline was estimated to 7.69  $\mu\text{mol/L}$  while the fractional turnover rate ( $K_{out}$ ) was estimated to 0.423  $\text{h}^{-1}$ . Atazanavir was estimated to inhibit bilirubin elimination with an  $I_{max}$  of 0.91 and an  $IC_{50}$  concentration of 0.303  $\mu\text{mol/L}$ . The between subject variability of the baseline was estimated to 32%. The half-life of uninhibited bilirubin was estimated to 1.64 h, in fair agreement with a literature beta-phase value of 1.16 h (3). Atazanavir inhibition resulted in a seven-fold increase in bilirubin half-life.

**Conclusions:** The atazanavir-bilirubin relationship was well described by the proposed model. PK parameter were in agreement with previously reported values (4). Based on simulations, bilirubin was a good indicator of non-adherence and suboptimal exposure in patients.

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#### **IV-04 Andre Schäftlein Comparison of elimination and absorption pharmacokinetics of linezolid in cystic fibrosis patients by three nonlinear models**

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**Objectives:** Linezolid, an oxazolidinone antibiotic used for the treatment of serious Gram-positive infections in cystic fibrosis patients (CFP), displays nonlinear pharmacokinetics (PK) by decreasing clearance over time. The PK of oral linezolid may be affected by gut absorption impairment, particularly in CFP. The objective of this analysis was to develop a population PK model adequately reflecting the elimination and absorption of this special population and to compare its predictive performance with other suggested nonlinear PK models for linezolid.

**Methods:** A concentration-time-dependent clearance inhibition (CTDCI) model [1], a Michaelis-Menten-type elimination model [2] and a linear/nonlinear elimination mixture model [3] were compared on their ability to describe and predict the elimination process of multiple dose linezolid in 8 CFP. All CFP received oral and intravenous linezolid 600 mg twice daily for 9 doses, separated by a 9 day washout [4]. Visual inspection of the PK data revealed a delay in absorption after oral dosing in selected patient, which was investigated by implementing a lag time or absorption process via transit compartments (TCA) [5] in the final selected model. All data analyses were performed using the nonlinear mixed-effect modelling approach (NONMEMTM, Version VI). Model comparison was guided by the Akaike information criterion (AIC), goodness of fit (GOF) plots, and visual predictive checks (VPC).

**Results:** The data were best described by the CTDCI model resulting in the lowest AIC value (779) compared with the other elimination models (819-1080). GOF plots showed that the Michaelis-Menten and the mixture model were less capable of describing the data compared with the CTDCI model. The VPC of the CTDCI model best reflected the general trend of the time course and the variability observed in this population. The model with TCA was inferior to the one with lag time; the observed mean transit time was incorporated as prior knowledge for the lag time in the final model.

**Conclusions:** Among nonlinear models, the concentration-time-dependent inhibition model appeared to be most suitable to describe and predict linezolid elimination PK in CFP. The absorption process was well represented by the incorporation of the lag time model.

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**IV-09 Ivy Song Applications of Population Pharmacokinetic Modeling during Phase 2B to Support the Clinical Development of Dolutegravir (DTG, S/GSK1349572)**

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**Objectives:** Population pharmacokinetic (PK) analysis performed in early and late stages of clinical development generally serves different purposes. Population PK analysis is routinely performed when data from Phase 3 become available with the purpose of evaluating the effects of various patient characteristics on the PK of the drug of interest, while analysis conducted in the early phases (Phase 1-2) often have different utilities. DTG is a new integrase inhibitor currently in Phase 3 clinical development for the treatment of HIV infection. This abstract presents several applications of a population PK model of DTG developed during Phase 2B.

**Methods:** DTG plasma concentration-time data from two dose-ranging Phase 2 studies in HIV-infected subjects (n=164) were used to fit various base PK models using a mixed-effects modeling approach with the first-order conditional method (FOCE) of NONMEM. Covariates including age, weight, gender, race, liver functions, smoking status, and use of certain concurrent medications were evaluated.

**Results:** PK of DTG were best described by a 2-compartment linear model with first order absorption. The resulting population PK model was used to: (1) guide the design of optimal sparse PK sampling scheme in Phase 3 trials; (2) model the relationship between DTG PK exposure and changes in serum creatinine levels from baseline in response to a clinical finding in Phase 2b and to support the safety monitoring plan in Phase 3; (3) support sample size selected for a proposed pediatric study with PK evaluation as the primary objective; (4) to simulate DTG exposure with consideration of variability in comparison to target exposure(s) support dose selection for the proposed pediatric study.

**Conclusions:** Population PK analysis performed early in clinical development (prior to Phase 3) has broad applications. This approach in the development of DTG supported decision making for Phase 3, allowed for evaluation of exposure response relationships for safety, and informed study design for pediatric trials.

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## IV-12 Joe Standing Methods for Optimising Neonatal Antimicrobial Use: Time- and Concentration-Dependent Agents

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**Objectives:** Pharmacokinetic studies in neonates are increasingly common; it is important their results are used rationally. This study arose from two questions on treating sepsis in neonates. Firstly (time-dependent): what infusion length maximises time above MIC ( $T > MIC$ ) for meropenem? Secondly (concentration-dependent): what is the optimum dose of gentamicin? We aimed to answer the above questions and in doing so develop methods for finding optimal treatments.

**Methods:** A meropenem pharmacokinetic model was derived from premature neonates receiving infusions of 0.5 or 4h [1], and a gentamicin model from a freely available dataset [2]. For meropenem utility the aim was 100%  $T > MIC$ , and penalties for increasing infusion length were explored. For gentamicin utility, a model for clinical response was fitted to literature data [3] and target set to 100%; the penalty function was a model for uptake kinetics into renal cortical cells [4] and set to 0%. Uncertainty on benefit and risk functions was incorporated. For meropenem a fixed dose was used, and infusion length optimised; for gentamicin dose was optimised. EUCAST MIC distributions [5] for *E. coli* were used to assign values to simulated subjects. Optimal infusion length/dose was derived for a range of fixed MIC values.

**Results:** For meropenem pharmacokinetics a 1-compartment model provided best fit and optimal infusion length for a 20mg/kg dose with randomly assigned MIC was 0.99h, although this was sensitive to individuals with outlying MIC values. At fixed MIC values below 0.08mg/L optimal infusion time was 5min, rising steeply to 6.07 and 6.98h for the sensitivity and resistance breakpoints of 2 and 8mg/L. For gentamicin a 2-compartment model was chosen, and the optimal dose for randomly assigned MIC was 2.25mg/kg. Optimal doses for sensitivity and resistance breakpoints of 2 and 4mg/L were 4.54 and 6.74mg/kg respectively.

**Conclusions:** Optimising utility functions provides a more efficient method than exploring dose recommendations by simulation. Details of the approach used will be discussed to show how these methods can be applied.

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#### **IV-16 Elin Svensson Mega-model of nevirapine population pharmacokinetics**

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**Objectives:** To develop a mega-model, i.e. a model driven by raw data from multiple sources, of nevirapine (NVP) pharmacokinetics (PK) in a diverse population of HIV-infected South African adults on anti-retroviral therapy (ART).

**Methods:** Data of NVP plasma concentrations from four different South African clinical studies including 116 patients, some intensively and some sparsely sampled were available. All patients were HIV-infected and on ART regimens including 200 mg NVP BID. Sampling was conducted at steady state in all the studies, but sampling schedule and conditions varied. A population model was developed in NONMEM7, using a stepwise approach, starting with the rich data and subsequently adding the sparse data. Inclusion of significant covariates was explored. Model development was guided by goodness of fit and VPCs.

**Results:** NVP PK was described by a one compartment disposition model with absorption through two transit compartments and first-order elimination. The model included a mixture of two sub-populations with different typical values of clearance (CL): 3.14 L/h/60 kg and 1.39 L/h/60 kg, respectively. The proportion of the lower CL sub-population was estimated, although with poor precision, to 14% (RSE 47%). Volume of distribution (V) was 91.4 L/60kg, while the mean transit time (MTT) was 2.41 h if the drug was ingested with food, and 0.59 h when taken in fasting conditions. Concomitant antitubercular-treatment including rifampicin decreased bioavailability (F) by almost 40%, and between-subject variability (BSV) was supported in F for patients on such antitubercular-treatment. BSV in CL (19%) and between-occasion variability (BOV) in MTT (61%) and F (24%) were also significant. The residual error (proportional) was estimated to 7.8% with BOV of 20%. The model included allometric scaling with body weight of CL and V.

**Conclusions:** This is the first population model including a mixture on clearance to describe individuals with extremely high concentrations, potentially due to genetic polymorphisms. The model identified effects of antitubercular-treatment and food with precise and stable estimates of the typical values and variability of the model parameters. This model may serve as a starting point for development of a larger mega-model, possibly including data from other countries.

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## IV-18 *Ami Fazlin Syed Mohamed Pharmacokinetic-Pharmacodynamic Modelling of Pre-existing and Emerging Resistance of Pseudomonas aeruginosa to Colistin*

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**Objectives:** In recent years, colistin has gained popularity as a last resort antibiotic in the battle against resistant bacteria. *Pseudomonas aeruginosa* is well known to develop resistance against multiple antibiotics and thus, there is a need to ensure proper dosing of colistin either as a monotherapy or in combination with other antibiotics. As colistin is administered as CMS, a prodrug, there is a delay before efficient concentrations are obtained and a loading dose may be warranted. The aim of this study was to develop a pharmacokinetic-pharmacodynamic (PKPD) model that describes the time course of the bactericidal activity of colistin against wild-type and resistant *P.aeruginosa in vitro*, and to investigate the bacterial kill after different dosing schedules based on PK in patients and the developed model.

**Methods:** *In-vitro* time kill curve experiments were conducted for 24 hours on two strains of *Pseudomonas aeruginosa*, wild-type (ATCC 27853) and a clinically isolated resistant-type (PL0603761). Colistin exposure was at constant concentration ranging between 0.25-16 times the MIC. Actual colistin concentrations were measured at 0, 8 and 24 hours by LCMS-MS (1) as colistin is binding to material and is degrading during the experiments. Semi-mechanistic PKPD models with compartments for susceptible and resting bacteria (2) were fitted to the observed bacterial counts in NONMEM. Prediction of bacterial kill in patients was based on PK in a previous study (3).

**Results:** As expected, the growth rate was significantly lower and  $EC_{50}$  higher for the resistant strain compared to the wild-type bacteria. The application of actual colistin concentrations in the modeling was important in the characterization of the concentration-effect relationship. The emergence of resistance in the experiments was best described by a binding function (4). VPCs showed the adequacy of the model for both wild-type and resistant bacteria. For the wild-type bacteria, it was predicted that administration of a loading dose of 6MU CMS results in a bacteria count below the limit of detection at 5 h compared to 10 h for a dose of 3MU. None of the dose levels was sufficient to reduce the resistant bacterial counts.

**Conclusions:** The PKPD model for colistin described both wild-type and resistant mutants and will be evaluable in the exploration of potential dosing regimens. For the resistant bacteria, a combination of colistin with other antibiotics is indicated.

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### **IV-34 Marta Valle Effect of Ritonavir Concentrations on Atazanavir Pharmacokinetics: Population Pharmacokinetic Analysis**

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**Objectives:** Atazanavir (ATV) is a protease inhibitor indicated for the treatment of HIV infection, with approved doses of unboosted 400mg (2 capsules, approved in the USA) or 300mg boosted with 100mg of ritonavir (2 capsules, approved in the EU and USA), both qd. The aim of this study was to develop a population pharmacokinetic (pk) model for atazanavir and ritonavir in a population of HIV-infected adults. The model sought was to detect possible pk differences in ATV when administered unboosted or boosted with ritonavir (RTV), and to incorporate patient characteristics influencing variability in ATV and/or RTV concentrations.

**Methods:** HIV-infected adults on stable therapy with oral atazanavir unboosted (400mg qd) or boosted (400mg/100mg rRTV, qd) in routine clinical practice for at least 4 weeks were included. A concentration-time profile was obtained for each patient, and serial blood samples were collected immediately before and over 24h after a morning-dose or between 12 and 24h after a night-dose. ATV and RTV concentrations in plasma were determined by high performance liquid chromatography. A population pharmacokinetic model was developed for ATV and RTV. Pharmacokinetic parameters, interindividual variability and residual error were estimated, and the influence of different patient characteristics on the pharmacokinetics of ATV and RTV was explored. The final model incorporated the effect of RTV exposure on ATV oral clearance (CL/F). Population analysis was performed using non-linear mixed effects modeling (NONMEM, version VI).

**Results:** A total of 29 Caucasian patients were included in the study. Atazanavir and ritonavir pharmacokinetics were described with one-compartment models with first order absorption and elimination. An absorption lag-time was needed to describe ATV absorption phase. Atazanavir CL/F was inhibited by RTV concentrations following an exponential model. The model predicted a 30% decrease in ATV oral CL/F at a 0.63mg/mL of RTV in plasma. This concentration represents the average observed concentration of RTV in the dosing interval. The final model appropriately predicted plasma concentrations, with no systematic bias and adequate precision.

**Conclusions:** No differences in the pharmacokinetics of atazanavir were found apart from a decrease in plasma clearance when co-administered with ritonavir. Bayesian estimates of the

individual parameters of ritonavir and atazanavir could be useful to predict boosted and unboosted atazanavir exposure in an individual manner.

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### IV-35 Georgia Valsami Assessment of dosage regimens of tigecycline in hospitalised patients

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**Objectives:** To study various dose regimens of the antibiotic tigecycline in a group of hospitalised patients and assess the potential applicability of TDM for this drug.

**Methods:** Blood samples from 11 hospitalised patients were collected, during treatment with tigecycline and the concentrations of the drug were quantified using an HPLC method [1]. Patients were treated for about 2 weeks and were administered either a 100 mg or a 150 mg daily dose, with or without a loading dose of 100 mg. Using literature population priors for the two-compartment pharmacokinetic parameters [2], Empirical Bayes Estimates (EBE) were derived for each of the patients' PK parameters with NONMEM and the corresponding AUC<sub>24</sub>/MIC were calculated. Further, using the population estimate and the intersubject variability of clearance from [2] and clinical targets from literature, Monte Carlo (MC) simulations were performed and the distributions of AUC/MIC were computed to assess the applicability of the different dosing schemes.

**Results:** The MC simulations showed that the high dose of 150 mg is theoretically efficacious for almost all patients while the low dose of 100 mg leaves a significant percentage of more than 20% of the population in undertherapeutic levels. The clinical picture for the efficacy of the drug in the group of real patients partially confirms the result that the low dose may be undertherapeutic for some patients, while the high dose was very often not tolerated by the patients causing GI adverse effects. This mixed picture suggests that dose adjustment with TDM may be applicable for this drug.

**Conclusion:** Monte Carlo simulations show that the low dose of Tigecycline may produce undertherapeutic levels of the drug in a significant portion of the population while in a group of patients the high dose was often not tolerated, suggesting that potential dose adjustment could be useful.

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### **IV-38 Jan-Stefan van der Walt The effect of nevirapine-based antiretroviral therapy on the population pharmacokinetics of artemether and dihydroartemesinin in HIV-infected adults**

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**Objectives:** Artemether-lumefantrine (AL) and nevirapine (NVP) are currently the most widely recommended antimalarials and antiretrovirals in Africa.[1] Artemether (AM) is rapidly demethylated to active dihydroartemesinin (DHA) via CYP3A4/3A5, and may exhibit autoinduction.[2] Co-administration of NVP, an inducer of CYP3A4, may alter the pharmacokinetics of AM and DHA.[3] We investigated the interaction between NVP-based antiretroviral therapy (ART) and AM/DHA in HIV-1 infected adults.[4]

**Methods:** AM and DHA plasma concentration-time profiles from 2 groups of HIV-infected adults (ART-naïve [N=18] and NVP-based ART [N=18]) with CD4+ lymphocyte counts >200 cells/ $\mu$ L who received AL 80mg/480mg twice daily for 3 days were analyzed using NONMEM7 (FOCE INTER). A published semiphysiological autoinduction model [5] was adapted by (1) adding a transit compartment model to describe the highly variable absorption of AM and (2) incorporating the conversion of AM to DHA.

**Results:** NVP-based ART significantly reduced AM and DHA exposure. The autoinduction enzyme kinetics was described by a precursor and an enzyme pool. NVP-based therapy increased both the precursor production rate constant and the slope describing the linear effect of AM liver concentrations on the rate of enzyme precursor production by 66% and 87% respectively. AM absorption was rapid and variable with a typical mean transit time of 0.9 h (IIV 44%, IOV 25%) and 2.6 transit compartments (IIV 133%). In the NVP group the mean transit time was decreased by 38%. This could, in part, be explained by a larger proportion of AM observations below the limit of quantification in the NVP vs the naïve group (36% vs. 13%). Goodness-of-fit plots confirmed adequate model fit for both AM and DHA. Residual variability in AM observations was high (51% CV) but comparable with previous reports. [5]

**Conclusions:** Autoinduction was faster in subjects treated with NVP-based ART compared with ART-naïve subjects. The decreased bioavailability of AM and DHA may be of concern when using AL for treating malaria in patients co-infected with HIV treated with NVP-based ART.

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### **IV-17 Svetlana Vinogradova Applying of population PK-PD methods to analysis of viral dynamics of HIV/HCV-Coinfected Sustained Virological Responders and Nonresponders treated with PEG-IFN**

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**Objectives:** Mathematical models have been widely used for understanding viral dynamics of hepatitis C virus (HCV) [1,2]. An adapted model of viral dynamics developed by Neumann et al. [2] was used to describe the kinetics and interaction of target cells, infected cells and viruses in HIV/HCV-coinfected patients. Previously it was reported that high inter-individual variability (IIV) on many PD parameters is observed, so population approach seems reasonable.

**Methods:** Plasma concentration of PEG-IFN (350 samples) and viral load (HCV RNA, 333 observations) arising from 24 HIV/HCV-coinfected patients were available from [1]. The viral inhibition was driven by the predicted PEG-IFN PK profile based on the population PK parameter estimates including IIV on rate of absorption of PEG-IFN and volume of distribution. The viral load data was fitted using FOCEI method in NONMEM and SAEM method in MONOLIX, assuming that viral load and number of target and infected cells was in steady-state before therapy was initiated, with baseline at V0, T0 and I0. The preferred model was selected based on the precision of parameter estimates, standard error of population parameters, correlation of estimates and log-likelihood. Goodness of fit plots for individuals were also checked.

**Results:** The preferred model is model with IIV on EC50 and infected cell loss rate. Population values of the parameters were close to median values obtained in [1]. We used nonparametric methods to compare parameters of the model for SVR group with those of NR group. The median EC50 didn't differ significantly between SVR and NR groups (0.42 vs 0.59). By contrast, the median infected cell loss rate is significantly faster in SVRs compared with NRs (0.51 vs. 0.12 days<sup>-1</sup>, P=0.029), that is in agreement with the results obtained in [1]. Introducing SVR/NR grouping as covariance parameter results in decreasing of log-likelihood, but not all the IIV parameters are estimated precisely (CV>50%).

**Conclusions:** The current analysis demonstrated that both FOCEI and SAEM algorithms implemented in NONMEM and MONOLIX are useful for fitting complex mechanistic models requiring multiple differential equations allowing good fitting and sufficiently precise parameter estimation.

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## **IV-42 Max von Kleist A Mathematical Modelling Framework to Assess the Impact of Nevirapine-based Prophylaxis on vertical HIV Transmission**

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**Objectives:** Single dose nevirapine (NVP) prophylaxis, administered to HIV-positive mothers before birth and to their newborns shortly after birth, is a widely used intervention in resource-constrained settings to prevent vertical HIV transmission. The objective of this study was to develop a mathematical modelling framework to quantify the impact of different single and multiple dose NVP prophylaxis regimens on the risk of HIV transmission from mother-to-child and on drug resistance development.

**Methods:** We used a population pharmacokinetic (PK) approach to assess and describe the pharmacokinetics of NVP in Ugandan pregnant women and their newborns [1,2]. Subsequently, a stochastic model of HIV-1 dynamics, resistance development and vertical HIV transmission via intrapartum- and breastfeeding was developed. Individual NVP pharmacokinetics were then coupled to the HIV model to predict the cumulative two years postpartum HIV transmission risk after different single and multiple dose NVP prophylaxis regimens and to predict the risk of drug resistance development in the mothers and newborns.

**Results:** The risk of HIV transmission following three different short-course and extended NVP dosing regimens was well predicted. Our combined pharmacokinetic-pharmacodynamic investigation revealed that single dose maternal intrapartum NVP prevents newborn infection by providing protective NVP concentrations via placenta-transfer at delivery, while only insignificantly reducing the number of infectious viruses in the pregnant women coming into contact with the newborn during delivery. The predicted cumulative 2 years postpartum transmission risks, after 6-, 14-, 21-, 26-, 52-, 78- and 102 weeks of extended newborn NVP were  $18.5\% \pm 2.1\%$ ,  $16.1\% \pm 1.9\%$ ,  $14.9\% \pm 1.9\%$ ,  $14.3\% \pm 1.8\%$ ,  $12.5\% \pm 1.6\%$ ,  $8.6\% \pm 1.2\%$  and  $7.0\% \pm 0.9\%$  respectively, when combined with perinatal NVP prophylaxis.

**Conclusions:** The developed mathematical modelling framework successfully combined *in vitro* and *in vivo* pharmacokinetic and pharmacodynamic data to estimate clinically relevant HIV transmission risks. These risks were very well predicted for all clinically investigated single and extended newborn NVP prophylaxis regimens. The presented modelling framework can be adapted to *a priori* assess the potential of other drugs/drug combinations in reducing HIV transmission and could therefore be used as a supportive tool for prospective studies to improve HIV prevention, maximize effectiveness and reduce the risk of resistance selection.

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## **IV-45 Toshihiro Wajima Pharmacokinetic/pharmacodynamic Modeling and Long-term Simulation of Dolutegravir (DTG, S/GSK1349572) in Integrase Resistant Patients with a Simple Viral Dynamic Model**

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**Objective:** DTG is an unboosted, once daily integrase inhibitor (INI) currently under development for the treatment of HIV infection. Effectiveness of DTG is being examined for use across the treatment spectrum including treatment-naïve to INI-resistant patients. [1, 2, 3]. A mathematical representation of viral dynamics for INIs combined with a pharmacokinetic model is useful to assess dose-effect and concentration-effect relationships and thus aid in dose selection. A simple PK/PD model was developed for describing antiviral activity in 10 day monotherapy studies for 3 INIs in INI-naïve patients [4]. The objective was to apply the simple PK/PD model for describing short-term antiviral activity from a clinical study in INI-resistant patients and to simulate long-term efficacy of DTG.

**Methods:** The PD part consists of 1 compartment for describing viral dynamics with first-order viral depletion and viral count-related viral replication, which is inhibited by INIs with an Emax model. The model was applied to the profiles of plasma concentrations and changes in HIV-1 RNA during 10-day monotherapy or functional monotherapy data from 2 clinical studies of DTG in INI-naïve patients [2] and INI-resistant patients [1]. The effects of baseline HIV-1 RNA values, baseline fold-change and PSS (phenotypic susceptibility score) were included into EC50 parameter of the Emax model. Long-term efficacy of DTG for INI-resistant patients was simulated based on the developed PK/PD model. The effect of background therapy, dropout rate, adherence and viral mutation were incorporated into the model for simulating the long-term efficacy [5].

**Results:** The profiles of plasma concentrations and HIV-1 RNA counts in short-term studies of DTG for INI-naïve patients and INI-resistant patients were well described by the simple PK/PD model. Moreover, the profiles of the probability of < 50 copies/mL RNA counts for 24 weeks in INI-resistant patients were well characterized by the model. The long-term simulations suggested that 50 mg BID would provide a higher response rate compared to 50 mg QD or 100 mg QD in INI-resistant patients.

**Conclusions:** The PK/PD model initially used for INI-naïve subjects was modified for describing viral dynamic profiles in INI-resistant patients. Simulations suggest that DTG will have robust long-term efficacy in this population and support 50 mg BID for difficult-to-treat patients with INI-resistance.

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## **IV-54 Hongmei Xu Mechanism-based Modelling of the Antagonism between Polymyxin B and Levofloxacin against *Pseudomonas aeruginosa* using Mono- and Combination Therapy**

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**Objectives:** Polymyxins have become the last line of defence against multidrug resistant *Pseudomonas aeruginosa* and other gram-negative bacteria. Polymyxin B (PB) first displaces  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  from their binding sites on the outer membrane and causes leakage of intracellular components and bacterial killing. Levofloxacin (LEV), a fluoroquinolone targeting DNA gyrase, has different mechanisms of action and of resistance compared to PB. Our objective was to develop a mechanism-based population pharmacodynamic (PD) model for the time course of killing of *P. aeruginosa* by PB and LEV alone or in combination via an Importance Sampling algorithm.

**Methods:** In vitro time kill experiments were performed using eight PB concentrations up to 64 mg/L and LEV from 1 to 16 mg/L against *P. aeruginosa* (strain PAO1) at an initial inoculum of 10<sup>8</sup> colony forming units per mL (CFU/mL). In addition to monotherapy by PB or LEV, bacterial killing was studied by simultaneous and sequential dosing. For sequential dosing, cells were exposed to 4 mg/L PB for 1.5 h, PB was then removed by centrifugation and resuspension in fresh broth containing LEV (or PB). Serial viable counts were determined over 24 to 48 h. All log<sub>10</sub> CFU/mL were simultaneously modelled using the importance sampling Monte Carlo Parametric Expectation Maximization (MC-PEM) algorithm in parallelized S-ADAPT (v. 1.57) and SADAPT-TRAN.

**Results:** The rapid, concentration-dependent killing of *P. aeruginosa* by PB (4 log<sub>10</sub> killing at 2 h for 4 mg/L and 6 log<sub>10</sub> for 8 mg/L PB) was modelled as a second order killing process subject to a competitive inhibition with divalent cations [1]. Levofloxacin was assumed to stimulate the natural death rate constant up to 17-fold with an SC<sub>50</sub> of 2.8 mg/L. The model contained 5 subpopulations with different susceptibility to each antibiotic. A joint resistant population was not required. There was a slight, but noticeable antagonism when PB and LEV were given simultaneously with 1-2 log<sub>10</sub> less killing compared to LEV monotherapy. PB was assumed to increase the SC<sub>50</sub> of LEV.

**Conclusions:** The proposed mechanism-based PD model described the rate and extent of killing by PB and LEV in monotherapy as well as in sequential and simultaneous combination therapy excellently. We suspect that polymyxin B may have up-regulated the efflux of levofloxacin.

### **References:**

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## **I-46 Christine Xu Population Pharmacokinetics (PPK) and Pharmacokinetic-Pharmacodynamic (PK/PD) of Vicriviroc in Treatment Naive HIV**

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**Objectives:** Vicriviroc is a potent CCR5 antagonist for treating HIV-1 infection. This study aimed to (1) assess vicriviroc pharmacokinetic (PK) profile and interpatient versus inpatient variability in HIV positive patients using PPK, and (2) to explore PK/PD association using drug exposure and efficacy.

**Methods:** This global Phase 2 trial explored a class-sparing regimen of vicriviroc, a CCR5 antagonist vs Truvada, each in combination with ritonavir-boosted atazanavir (ATV/r). CCR5 HIV-infected treatment-naïve subjects were randomized 1:1 to open-label treatments with 95 and 123 subjects in Stage 1 and 2, respectively. The PPK analysis was performed using NONMEM based on plasma samples from patients receiving vicriviroc. Two plasma samples were collected pre-dose and approximately 1 hr post-dose on Weeks 4 and 12. Since the sparse PK sampling scheme was utilized in this Phase 2 trial, PK data from Phase I studies were combined and used for the population PK analysis. The influence of demographic and clinical characteristics on clearance and volume of distribution were examined. The drug exposure (AUC, C<sub>min</sub> and C<sub>max</sub>) was estimated for each patient and the exposure-virologic response association was explored.

**Results:** 105 vicriviroc treated patients contributed to 402 vicriviroc concentrations. Two-compartment model with first-order absorption and elimination was chosen as the pharmacokinetic base model. The apparent clearance (CL/F) was 3.39 L/h, apparent volume of distribution of the central compartment (V<sub>c</sub>/F) was 170 L and the absorption rate constant (K<sub>a</sub>) was 0.743 hr<sup>-1</sup>. Of the covariates evaluated, body weight was a significant covariate for CL/F and age was a significant covariate for V<sub>c</sub>/F. A large interpatient variability was found for K<sub>a</sub> (CV 70%), while the inpatient variability was relatively small (CV 19%). The final model was evaluated by the bootstrap technique and the visual predictive check. The correlation between trough drug concentration (C<sub>min</sub>) and viral load change was assessed. Despite 99% patients has vicriviroc C<sub>min</sub> greater than 100 ng/mL, higher response rates were observed in naive subjects with higher vicriviroc C<sub>min</sub>.

**Conclusions:** A two-compartment model adequately described the vicriviroc PK in naïve HIV patients. Body weight and age were significant covariates. The integrated population PK model and PK-PD association can be used to predict antiviral activity and select the optimal dose regimen in naive patients.

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#### **IV-57 James Yates Population PK/PD modelling of AZD9773 in patients with severe sepsis.**

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**Objectives:** AZD9773 is an intravenously infused ovine-derived polyclonal anti-TNF- $\alpha$  Fab fragment currently being developed as a treatment for severe sepsis. The aim of this analysis was to develop a population PK/PD model in patients with severe sepsis. This model was then used to simulate proposed dosing regimens for a phase IIb trial (NCT01145560).

**Methods:** A phase IIa trial in patients with severe sepsis was conducted (NCT00615017). A total of 71 patients were recruited, 47 of whom received study treatment. Serum AZD9773 and TNF- $\alpha$  levels were measured.

A population pharmacokinetic analysis was performed in NONMEM and serum pharmacokinetics of total AZD9773 were described by a two-compartment model. The variation in TNF- $\alpha$  levels between individuals over time and the drug effect were captured using an indirect response model with a variable production rate of TNF- $\alpha$ . Two routes of elimination of TNF- $\alpha$  were accounted for in the model: natural removal of TNF- $\alpha$ ,  $TNF_{out}$ , and a drug dependent process,  $k_{bind}$ .

The apparent appearance of TNF- $\alpha$  in the serum was described by a quadratic function parameterised by: *slope* describing the initial slope; *peak* describing the peak (or trough) rate of appearance; *ttp* (time to peak) describing the time at which this peak (or trough) was achieved.

**Results:** The population PK model had one covariate: creatinine clearance on drug clearance. A mixed effects model with random effects on *peak*, *slope*, *ttp* and  $TNF_{out}$  was used to describe the TNF- $\alpha$  data. The parameter  $k_{bind}$  was kept as a fixed effect only because a random effect on this parameter might have been confounded by  $TNF_{out}$  inter-individual variability. Parameter estimation in NONMEM terminated normally.

A number of different regimens were simulated for 100 patients in each arm. 100 trials were simulated and the effects on TNF- $\alpha$  levels were summarised across these.

**Conclusions:** TNF- $\alpha$  serum levels and the pharmacodynamic effect of AZD9773 on TNF- $\alpha$  were well characterised by the model across the cohorts in the Phase IIa study. The model was used to simulate different dosing options to support design of a now ongoing phase IIb trial.

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## IV-62 Chao Zhang Population Pharmacokinetics of Lopinavir and Ritonavir in Combination with Rifampicin-based Antitubercular Treatment in HIV-infected Adults

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**Objectives:** Lopinavir is an antiretroviral drug administered with ritonavir to enhance its exposure. Rifampicin, a key component of antitubercular treatment, profoundly reduces lopinavir concentrations. Increasing the amount of fixed dose combination of lopinavir/ritonavir (4:1, LPV/r) has been shown to overcome this effect. The aim of this study was to develop an integrated population pharmacokinetic model accounting for all the drug-drug interactions between lopinavir, ritonavir and rifampicin, and to evaluate optimal dose of LPV/r when coadministered with rifampicin.

**Methods:** Steady state pharmacokinetics of lopinavir and ritonavir were evaluated at baseline in a cohort of 21 HIV-infected South African adults virologically suppressed on a LPV/r regimen (400 mg/100 mg 12 hourly). Rifampicin 600mg daily was then introduced. After one week of rifampicin, the LPV/r dose was increased 1.5 times (600 mg/150 mg 12 hourly), and after another week it was doubled (800 mg/200 mg 12 hourly). Intensive pharmacokinetic sampling was performed one week after each dose adjustment following a morning dose, administered on an empty stomach. A population pharmacokinetic analysis was conducted using NONMEM VII.

**Results:** A simultaneous integrated model was built in this study. A one-compartment model with first-order absorption and elimination best described the pharmacokinetics of lopinavir, while a two-compartment model with transit compartments was used for ritonavir. Rifampicin reduced the oral bioavailability of lopinavir and ritonavir by 68.2% and 59.1% respectively, and it increased their clearance by 68.0% and 33.8% respectively. With increasing concentrations of ritonavir, clearance of lopinavir decreased in an  $E_{\max}$  relationship. Exposure to ritonavir increased by 48.2% for every 100 mg increment in its dose. Morning trough concentrations of lopinavir were on average higher than the evening trough concentrations, although the trend was not consistent in all subjects or occasions. Simulation indicated that, keeping the same pharmacokinetic parameters, the dose of LPV/r would need to be increased 2.7 times to account for the difference.

**Conclusions:** The model describes the drug-drug interactions between lopinavir, ritonavir and rifampicin. Doubling the dose of LPV/r seems to counteract the effect of rifampicin in most patients. The difference between morning and evening trough concentrations is unlikely to be entirely explained by increased absorption with the evening meal.

**References:**

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#### **IV-66 Simbarashe Peter Zvada Population Pharmacokinetics of Isoniazid in Children with Pulmonary Tuberculosis**

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**Background and Objectives:** There is limited isoniazid pharmacokinetic information in children, and daily doses (4-6 mg/kg) derived from adult doses have been reported to be inadequate [1]. The World Health Organisation's revised guidelines (2010) recommend a dose of 10 (10-15) mg/kg/day in children across weights [2]. The aim of our study was to develop a model that describes population pharmacokinetics of isoniazid in children with tuberculosis.

**Methods:** Previously published isoniazid concentration-time (530 observations) data from 56 children hospitalized for treatment of tuberculosis were used to describe the population pharmacokinetics of isoniazid [3]. The median age for the children was 3.2 years (interquartile range: 1.6-5.4 years) and the median isoniazid dosage was 5 mg/kg/day (range: 2.9-15.6 mg/kg/day). Twenty-two patients were HIV infected and 18 had kwashiorkor (13 being females). The children were treated with daily doses of rifampicin, isoniazid and pyrazinamide for 2 months before pyrazinamide was stopped. "Pediatric" dispersible fixed dose combination tablets were used. Isoniazid concentrations were measured in plasma samples at 1 month and 4 months after starting treatment and analysed using NONMEM 7. Various models including single and multi compartment models as well as enzyme maturation, linear or nonlinear elimination of isoniazid were tested. Body weight was included through allometric scaling on all clearance and volume parameters. Median body weight of 12.5 kg was used as reference. Acetylator genotype information, known to influence isoniazid PK, was available and included in the model.

**Results:** The pharmacokinetics of isoniazid was best described by a two-compartment model with first-order elimination. Interindividual variability was supported on oral clearance and volume of central compartment, while interoccasional variability was significant on relative oral bioavailability and rate of absorption. Oral clearances in slow, intermediate and fast acetylators were estimated to 5.7, 9.92 and 15.0 L/h, respectively, in a 12.5 kg child. Using these values of CL, if the children were given 10 mg/kg doses in accordance with the new WHO guidelines, we estimate a median  $AUC_{0-\infty}$  of 21.9, 12.6 and 8.3 mg•h/L in slow, intermediate and fast acetylators, respectively. These AUCs are low when compared to the value of 32.5 mg•h/L (interquartile range: 22.5-42.4 mg•h/L) obtained in an ethnically similar but adult population [4].

**Conclusion:** Our model adequately described the pharmacokinetics of isoniazid in children taking doses ranging from 2.9 to 15.6 mg/kg/day, and suggests that, even with the new target

dose (WHO guidelines - 2010); children, especially the fast acetylators, may be under-dosed compared to adults.

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## II-24 Leonid Gibiansky Mechanistic Modeling of the Link between Interleukin 6 Receptor Blockade with Tocilizumab and Its Hematological Effects

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**Objectives:** Tocilizumab (TZ) is a recombinant humanized IL-6 receptor monoclonal antibody that inhibits binding of IL-6 to its soluble (sIL-6R) and membrane-expressed (mIL-6R) receptors. Elevated serum IL-6 levels have been reported in rheumatoid arthritis (RA) patients and have been shown to be associated with disease activity. The aim of this study was to investigate whether the decline in peripheral neutrophil and platelet counts after TZ administration can be directly explained by IL-6R blockade, thus demonstrating its mechanism of action.

**Methods:** Serum concentrations of TZ, total sIL-6R (bound and unbound to TZ), and neutrophil and platelet counts from 4 phase 3 studies in patients with moderate to severe active RA who received 4 or 8 mg/kg TZ infusions every 4 weeks (total of 6 doses) were used. Mechanistic population PK/PD models were developed to describe the relationship between TZ and sIL-6R concentrations and subsequent changes in neutrophil and platelet counts.

**Results:** Following TZ administration, concentrations of total sIL-6R increased, while neutrophil and platelet counts declined. These changes were transient, with counts starting to return to baseline levels after TZ infusion. The nadir of cell counts was similar for 4 and 8 mg/kg dose groups. However, the rate of rebound was dose-dependent, with cell counts returning to baseline approximately 4 weeks later for 8 mg/kg compared to the 4 mg/kg dose. A 2-compartment model with parallel linear and Michaelis-Menten (MM) elimination described the TZ time course. Quasi-steady-state (QSS) approximation of the target-mediated drug disposition model described the relationship between TZ and total sIL-6R, allowing computation of unbound sIL-6R concentrations. Interestingly, MM and QSS constants were found to be similar to the in-vitro values for TZ binding to mIL-6R and sIL-6R, respectively. The observed neutrophil changes were described as a direct function of the unbound sIL-6R concentrations. The observed platelet counts were described by the transit-compartment lifespan model with inhibition of production that depended on the unbound sIL-6R concentrations. Diagnostic plots and predictive check simulations indicated excellent agreement of model predictions with the observed data.

**Conclusions:** The observed changes in sIL-6R, neutrophil and platelet data are consistent with the TZ mechanism of action and can be fully explained by TZ binding to both soluble and membrane-expressed IL-6R.

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### **III-01 Gilbert Koch A multi-response model for rheumatoid arthritis based on delay differential equations in collagen induced arthritic mice treated with an anti-GM-CSF antibody**

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**Objectives:** 22E9 is a monoclonal antibody that binds to the pro-inflammatory cytokine granulocyte macrophage colony-stimulating factor (GM-CSF), thereby neutralizing its biological activity. This cytokine is thought to play a key pathogenic role in rheumatoid arthritis. Our goal was to describe the time course of the unperturbed arthritis development and the effect of the anti-GM-CSF antibody 22E9 in the collagen induced arthritis (CIA) mouse model [1]. The pharmacodynamic readouts consist of the total arthritic score (TAS), an overall estimation of disease severity, and the ankylosis score (AKS), a measure for bone destruction.

**Methods:** Three doses (0.1, 1 and 10 mg/kg) of 22E9 were administered intravenously (i.v.) once a week starting from the day of first signs of arthritis in the mice. PK samples and PD readouts were collected throughout the observation period of 24 days. The PD readouts, TAS (scored by integer values ranging from 0 to 16) and AKS (integer values from 0 to 8) were assessed every second day. Start of visible ankylosis was delayed by about 10 days in comparison to the TAS. The PK as well as PD data of the different dosing groups were modelled simultaneously using MATLAB and ADAPT.

**Results:** We used a semi-mechanistic PKPD model consisting of three meaningful compartments: a hypothetical cytokine compartment at which the drug operates, an inflammation  $I(t)$  compartment, and a bone destruction  $D(t)$  compartment. Primary assumption in the model was that the cytokine drives the inflammation and causes ankylosis, delayed in time. The sum  $I(t)+D(t)$  corresponds to the measured TAS and  $D(t)$  stands for AKS. To account for the large time shift observed in AKS, we used delay differential equations. The nonlinear dose-response of the drug is incorporated into the model by an effect term of exponential type. The concentration data of 22E9 were fitted very well by a 2-comp i.v. PK model. The final PKPD model describes both PD readouts simultaneously over all available doses. This model was equivalently rewritten into ordinary differential equations (ODE) which grants the use of standard solvers.

**Conclusions:** We developed a PKPD model, based on delay differential equations, describing the development of arthritis in the CIA mouse model and its attenuation by a monoclonal antibody. Our mechanistic model fitted adequately the data. Further development into a population PKPD model is planned for the future.

**References:**

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**II-55 Etienne Pigeolet Population PKPD modeling of dose-response and time course of peripheral lymphocytes after single and repeated administration of the S1P1/5 modulator, BAF312, in healthy volunteers.**

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**Objectives:** BAF312 is a next generation S1P receptor modulator, selectively targeting S1P1 and S1P5. The drug reduces the peripheral blood lymphocytes count by retaining cells into the lymph nodes. This poster presents a model based estimation of the dose-response of BAF312 on this efficacy biomarker in a population of more than 200 healthy volunteers.

**Methods:** A sequential population PKPD model was built in NONMEM using data from three healthy volunteer studies. All studies were single center, randomized, double-blind and placebo controlled. The first one was a single ascending dose study with dose levels ranging from 0.1 to 75 mg and the two others were multiple ascending doses studies covering a dose range from 0.25 to 20 mg. A one and two-compartment PK model with different absorption structures were fitted to BAF312 concentration data. An indirect response model with inhibition of lymphocyte input rate in the blood linked to BAF312 concentrations was fitted to the peripheral lymphocyte count data. Time course of drug effect was modeled using a parameterization involving the rate of lymphocyte input ( $K_{in}$ ), baseline lymphocyte count (Base), maximum inhibitory effect of the drug on  $K_{in}$  ( $I_{max}$ ) and the drug concentration that produces 50% of the maximum response ( $EC_{50}$ ). No covariate analysis was performed.

**Results:** PK was adequately described by a 2 compartment model with a combined zero and first order absorption process. The precision of the parameter estimations was very good (less than 6%). The peripheral lymphocyte count time profiles were adequately described by an indirect response model with an inhibiting effect on lymphocyte input rate. The inhibitory effect is non-linear with respect to drug concentration in the plasma and can be described using a sigmoid  $I_{max}$  type model. The precision of the parameter estimations was very good (less than 7%). The inter-individual variability in baseline lymphocyte count is small (19%) and that for  $IC_{50}$  and  $I_{max}$  is moderate (52 and 58% respectively).

**Conclusions:** This model based analysis very well characterized the time course of the drug effect for healthy volunteers receiving a wide range of doses. Simulations from the model can guide the development team to select doses to reach a pre-specified peripheral lymphocyte count. Further work is needed to define the potential translation into clinical efficacy.

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## **IV-61 Miren Zamacona Model based approach to inform early clinical development for a biologic**

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**Objectives:** The knowledge from preclinical in vitro and in vivo preclinical models was integrated in a model-based approach in order to inform the design of early clinical trials for a biologic under development for an inflammatory condition. The objective of this analysis was to determine the therapeutic concentration range and subsequent dose range that was expected to result in clinical efficacy.

**Methods:** The following modeling & simulation steps were followed: a) PK/target turnover model: a population PK model was built from monkey data and human PK parameters were obtained by allometric scaling. In vitro properties of the biologic and relevant physiologic and pathophysiologic data from the literature were combined to build the turnover model. The PK/target turnover model was used to simulate different dose levels, regimens and routes of administration to predict the anticipated target occupancy in plasma and lymph; b) PKPD models were built from data obtained in preclinical models of disease for three pharmacodynamic endpoints. The PK model was used to derive the AUC as the exposure variable to be related to the pharmacodynamic endpoints. c) Translation of PKPD models to humans based on potency and PK and integration with the PK/target turnover model to determine the therapeutic dose regimen. PK/target turnover model simulations were performed with Berkeley Madonna version 8.3.14. and PKPD analysis were performed with NONMEM version 6.

**Results:** The PK/target turnover model simulations showed that sustained target engagement was achieved following an every two weeks administration regimen. The relationship between exposure and the three pharmacodynamic endpoints was best described using an inhibitory Emax model. Based on the potency estimates, the expected human doses resulting on 20 to 90% of maximum response were calculated. These results were combined with the PK/target turnover to estimate what target receptor occupancy was needed in order to observe pharmacological response.

**Conclusions:** The integration of disease and target knowledge, with in vitro and in vivo preclinical disease experiments into a model based approach allowed the prediction of the pharmacologically active concentration/dose level/regimen informing in this way the early clinical development plan.

## **I-51 *Emmanuelle Comets* Prediction discrepancies (pd) for evaluation of models with data under limit of quantification**

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**Objectives:** Prediction discrepancies (pd) for model evaluation were first used to evaluate nonlinear mixed effect models by Mesnil et al. in 1998 [1,2]. Normalised prediction distribution errors (npde) are normalised pd taking into account correlations within subjects [3,4]. In the current version of npde [5], data below limit of quantification (BQL) are removed before computing pd and npde but this approach can introduce fake indications of model misspecification if the amount of BQL data is important [6]. Our objective were : i) to develop a new approach for quantifying pd for BQL observation, ii) to propose additional graphs, iii) to illustrate these new features using real data from a clinical study of HIV viral dynamic response (COPHAR 3-ANRS).

**Methods:** pd are computed as the quantile of the observation in the predictive distribution [3]. To deal with BQL data, we first evaluate for each time point the probability of BQL data (pLOQ) from the predictive distribution. For each BQL observation, pd is then drawn randomly from a uniform distribution on  $[0;pLOQ]$ . This method was applied to evaluate the adequacy of the bi-exponential model describing the virus load decrease of COPHAR 3 trial, in which the percentage of BLQ viral loads is high due to high treatment efficacy (49%). To estimate parameters, we used the SAEM algorithm implemented in MONOLIX 3.2 [7].

**Results:** In accordance with the results of other studies, taking into account the BQL in modelling the full dataset resulted in adequate estimates. However, the residuals graphs, including VPCs and npde, indicated model misspecification and were misleading for model evaluation. The new approach for computing pd on the other hand provided evaluation graphs correctly indicating model adequacy.

**Conclusions:** Presently, goodness-of-fit plots proposed by most software discard BQL observations and/or impute them to LOQ, even when those observations were correctly handled in the estimation process. If the amount of BQL data is important this provides distorted graphs. pd can easily be modified to accommodate left-censored data and these new diagnostic plots offer a better assessment of model adequacy without the need to split the graphs for measured observations and BQL data as in usual VPC. Taking into account correlation within subjects for the new pd is under development. The same idea can be applied for model evaluation for binary or categorical data.

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## **II-33 *Namyi Gu* Population Pharmacokinetics of a new TRPV1 antagonist in healthy volunteers.**

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**Objectives:** The transient receptor potential cation channel subfamily V member 1 (TRPV1) is reported to be involved in the transmission and modulation of pain. Drug X is a TRPV1 antagonist for analgesic treatment currently under clinical investigation. This work aimed to investigate population pharmacokinetics of drug X in healthy volunteers.

**Methods:** Ninety-seven volunteers had been orally administered single or multiple doses of Drug X ranging from 10 mg to 600 mg in two randomized, placebo-controlled, ascending dose studies. The 1908 plasma concentrations-time points were used to analyze the population pharmacokinetics with NONMEM VI. The demographic and laboratory data were screened as covariate of pharmacokinetic parameters.

**Results:** The model was composed of 4 compartments (absorption, central, peripheral and gallbladder) with first-order absorption and enterohepatic recycling. The gallbladder emptying was added twice a day after lunch and dinner[1]. The population typical estimates of clearance and volume of distribution with its relative standard errors were 5.6 L/h (6.4%) and 35 L (10.3%) in the central compartment. The typical intercompartment clearance and peripheral distribution volume were 16 L/h (9.7%) and 122 L (7.4%). Body weight, daily administered dosage and serum albumin level were selected as covariates of pharmacokinetic parameters; body weight for central and intercompartment clearances and peripheral distribution volume, dose in a day for central volume and intercompartment clearance, serum albumin level for central distribution volume.

**Conclusions:** This population pharmacokinetic model may produce beneficial information in designing further clinical trials along the drug development process.

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## **II-49 Masoud Jamei Modelling the Effect of Interleukin-6, an Inflammatory Cytokine, on Time-dependent Reduction of Cyclosporine Clearance: An Application of the Simcyp Population-based Simulator to Suppression of CYP450 by Biologics**

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**Objectives:** Modelling the effect of interleukin-6 (IL-6) on the pharmacokinetics (PK) of cyclosporine in virtual bone marrow transplant patients and comparing predictions with the observed data (Chen *et al.*, 1994) to assess the possibility of *in vitro in vivo* extrapolation (IVIVE).

**Methods:** The serum IL-6 levels from two representative patients were fitted with appropriate PK models. These models were used to simulate the serum profile of IL-6 in virtual patients within Simcyp (Version 10, Service Pack 1). The effect of IL-6 was investigated on the cyclosporine PK following intravenous administration. The study design was consistent with that of reported clinical investigation.

**Results:** A zero order input rate and first order elimination, adequately recovered the clinically reported endogenous IL-6 profiles in patients. The linked model predicted a marked increase in systemic cyclosporine levels in the presence of IL-6, consistent with its suppression of CYPs. The IVIVE-generated pattern in time-varying systemic cyclosporine levels was broadly comparable with the observed data (Chen *et al.*, 1994). The simulated results suggested the possibility of predicting suppression effects on CYPs by biologics/therapeutic proteins acting *via* IL-6 or in similar fashion to that of IL-6 (*i.e.* suppression of CYP3A4 enzyme; Aitken and Morgan, 2007). The observed high inter-individual variability in IL-6 profiles in patients (Chen *et al.*, 1994) as well as possible involvement of other factors such as C-reactive protein and variable levels of  $\alpha$ 1-acid glycoprotein might have an impact on the magnitude of prediction. These factors were not considered in the current model. Nonetheless, these preliminary results are encouraging for further investigation into IVIVE of CYP-mediated effects by therapeutic proteins on reducing the clearance of smaller drug molecules.

**Conclusions:** Application of a novel Simcyp module was successful in demonstrating predictability of the effect of IL-6 on cyclosporine PK in patients with elevated levels of IL-6. The simulations pave the way for extrapolating the *in vitro* information on CYP-mediated drug-drug interactions involving biologics.

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### III-07 *Marc Lavielle* Improved diagnostic plots require improved statistical tools. Implementation in MONOLIX 4.0

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**Objectives:** Model evaluation is a crucial part of model building. The modeler needs numerical and graphical tools for deciding if the proposed model adequately describes the underlying system. Because of the complexity of pharmacometrics models (mixed effects models, non linearities, covariates, residual errors, BLQ data,...), these tools must be used carefully to avoid misinterpretation due to a poor use. Several diagnostic tools (VPC, npde, weighted residuals,...) have been already developed and implemented in different softwares (Xpose, Monolix, ...). Our objective is to improve some of these existing tools and implement them in MONOLIX 4.0.

**Methods:** *Visual Predictive Checks* (VPC) compares the distribution of the observations with the distribution of simulated data by grouping the data into bins. We propose a method that automatically determines the optimal binning. The optimal limits of the bins are obtained by optimizing a modified least-squares criteria using a dynamic programming algorithm. The number of bins is selected using a model selection approach. Because of possible shrinkage, we suggest replacing the *Empirical Bayes Estimates* (EBEs) with predicted individual parameters correctly simulated with their conditional distribution. An MCMC procedure is used for this simulation. In presence of *Below the Limit of Quantification* (BLQ) data, we propose replacing these BLQ data by data correctly simulated with their conditional distribution. An acceptance-reject procedure is used for this simulation.

**Results:** We applied the proposed methodology to several real and simulated PK examples: *i)* when the data presents clusters of different sizes, the proposed binning algorithm perfectly detects the clusters and the resulting VPC is improved, *ii)* we show that inference on the population distribution should not be based on the EBEs but on simulated parameters which are not affected by any possible shrinkage, *iii)* we show that residuals computed by replacing the BLQ data with the LOQ present a positive bias. On the other hand, no bias is introduced when imputing the BLQ data with simulated data.

**Conclusions:** Even if the existing procedures generally used for producing diagnostic plots are satisfactory in standard situations, some improvements appear to be necessary in more difficult situations (sparse data, BLQ data,...). Computational statistics can provide different new valuable tools (simulation procedures, MCMC, optimal segmentation,...) to improve model evaluation.

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### **III-10 Annabelle Lemenuel-Diot External evaluation of a Hepatitis C viral kinetic model which links viral dynamics to sustained virologic response (SVR)**

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**Objectives:** A Hepatitis C viral (HCV) kinetic model has been developed based on a large clinical database (1773 Chronic Hepatitis C (CHC) patients) treated with peginterferon  $\alpha$ -2a  $\pm$  ribavirin for either 24 or 48 weeks<sup>1,2</sup>. This model characterizes the complexity and diversity of clinically observed HCV kinetics and links it to sustained virologic response (SVR, the primary clinical endpoint of HCV treatment defined as an undetectable viral load at 24 weeks after treatment completion). The objective of this analysis was to conduct an external evaluation of this model by simulating the outcomes of clinical trials involving treatment strategies or populations different from those entering into the model.

**Methods:** Two trials have been used to perform this external evaluation. One trial, known as CHARIOT<sup>3</sup>, was designed to examine the benefits of using a fixed-dose induction (360  $\mu$ g) of peginterferon  $\alpha$ -2a in combination with ribavirin for the first 12 weeks of therapy in patients infected with genotype 1 HCV. The second trial, known as PROGRESS<sup>4</sup>, was designed to examine the benefits of using the same fixed-dose induction (360  $\mu$ g) of peginterferon  $\alpha$ -2a for the first 12 weeks of therapy in combination with different doses of ribavirin in difficult-to-cure genotype 1 HCV patients. The viral kinetic model has been implemented into a simulation software (Trial Simulator®). The individual model parameters have been sampled from a subset of the individual post-hoc parameters generated by the final model. This subset was defined based on the main inclusion criteria specific to each trial: treatment-naïve genotype 1 patients for CHARIOT, and treatment-naïve genotype 1 patients with high baseline viral load and high body weight for PROGRESS. Visual and posterior predictive checks were performed by simulating each study design 300 times.

**Results/Conclusions:** The time course of the viral load and the SVR rate from the CHARIOT and PROGRESS studies were adequately predicted by the model, confirming that a 12-week induction period of peginterferon  $\alpha$ -2a does not lead to a further increase in the SVR rate. The successful external evaluation of our viral kinetic model supports the further use of this model to perform simulations investigating new treatment strategies in Hepatitis C patients.

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### **III-51 Klas Petersson Assessment of bias in model parameter estimates of continuous time Markov models for categorical data**

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**Objectives:** Models with Markovian elements where the estimated parameters are rate constants describing the flow of probability over time [1,2] are a fairly new way of modeling categorical data with high correlation between consecutive observations. These models generally require fewer parameters than ordinary Markov models and do not assume equally spaced observations; there is also less need to know the exact time of transition. When modeling ordered categorical or repeated time to event data and the number of observations is few in one category or only a few individuals have multiple events the LAPLACE method in NONMEM has been prone to bias [3]. The objective was therefore to assess bias in continuous time Markov models and later the Type I error

**Methods:** Two models of the continuous time type Markov model for categorical data formed the basis for the evaluation. The first model, which described EPS events of antipsychotic drugs, had only one parameter for inter-individual variability (IIV) [PAGE 2011 ref] while six IIV parameters were included in the second model characterizing ACR response [1]. To assess the influence of sparse data in a category and IIV magnitude on bias six scenarios were tested where data were simulated using; 1) parameters estimated from the original data, 2) parameters resulting in few observations of highest category (

**Results:** The EPS model showed a mean of the parameters' absolute bias of 20% (Range: 8 - 34%) for the non-sparse data and 40% (3.8 – 135%) for the sparse scenario. Bias was highest in IIV estimates and rate constants associated with the most sparse observation type. Bias decreased with the higher IIV magnitude; mean 10% (2.7-19%). For the larger ACR model, with much longer runtimes, preliminary results were pointing in the same direction as the model for the EPS data. Low IIV or omission of IIV in the model would occasionally yield datasets where one or more population parameters were not estimable.

**Conclusions:** Biased parameter estimates were found also for continuous time Markov models and increased when the observed data distributions became more skewed. As expected, increased IIV made the number of transitions increase and the bias decreased.

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## **I-06 Orna Amir Predictive Model for Identification of Responders/Non Responders in Metastatic Breast Cancer Patients Treated with Docetaxel**

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**Objectives:** Breast cancer is a complex disease caused by the progressive accumulation of multiple gene mutations combined with epigenetic dysregulation of critical genes and protein pathways [1]. The majority of women with early-stage breast cancer are advised to receive chemotherapy, yet research has not demonstrated that chemotherapy benefits all of them equally [2,3]. This study aimed to create a predictive personalized tool for metastatic breast cancer patients treated with Docetaxel.

**Methods:** A population pharmacodynamic analysis was performed using MONOLIX, Matlab, and R based on tumor diameter measurements over time from metastatic breast cancer patients receiving tri-weekly Docetaxel. Missing data for covariates from histopathology and patient data were generated using multiple data imputation methods. Using a population pharmacokinetic model for Docetaxel and a mixed effects model for tumor diameter and drug effect, relationships between model parameters and covariates were established. Furthermore, using the covariates, baseline tumor measurements, and the first measurement taken after the beginning of treatment, individual tumor dynamics were estimated using the Markov Chain Monte Carlo simulation.

**Results:** 25 patients contributed to 287 tumor measurements from 64 metastases. The estimated model parameters were tumor growth rate, tumor carrying capacity, effect clearance and accumulation rates. Using the covariate data, the tumor carrying capacity was found to be highly correlated to the initial tumor size, and dependency was found between the effect clearance and accumulation rates. Given these covariate relationships plus the baseline and the measurement taken after the first treatment cycle, we were able to predict the tumor dynamics over the rest of the treatment and follow-up period with a relative error of 21.5% and an accuracy of 84.7% in predicting metastasis elimination.

**Conclusions:** Many failures in drug development and treatment in Oncology result from large patient variability and the lack of tools to identify responders. This presents a growing need for treatment individualization tools. Using Optimata's tumor growth model for Breast cancer treated with Docetaxel, long term response can be estimated after only 1-2 cycles of treatment helping to identify non-responders earlier on.

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**I-15 Brendan Bender A semi-mechanistic population Pharmacokinetic-Pharmacodynamic (PKPD) model of thrombocytopenia characterizing the effect of trastuzumab-DM1 (T-DM1) on platelet counts in patients with HER2-positive metastatic breast cancer**

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**Objectives:** T-DM1 is an antibody-drug conjugate in development for HER2-positive metastatic breast cancer[1]. In clinical trials of single-agent T-DM1, thrombocytopenia (TCP) was the dose-limiting toxicity[2,3]. In some patients, platelet time profiles drifted slowly down after multiple cycles of T-DM1. A population PKPD model was developed to describe the time course of patient platelet response to T-DM1, to support mechanistic hypotheses for platelet response, and to predict patient platelet response in future clinical trials.

**Methods:** A semi-physiologic population PKPD model with transit compartments mimicking platelet development and circulation was fit to the concentration-platelet-time data from a phase I dose escalation study (N=52) and a phase II study of T-DM1 (3.6 mg/kg every 3 weeks (q3w); (N=112). Overall, 4340 platelet counts were used in the analysis, with dose levels from 0.3-4.8 mg/kg q3w and from 1.2-2.9 mg/kg weekly. The rate and extent of platelet drift was modeled as a time and drug concentration effect on the platelet proliferation pool. NONMEM software was used for the modeling analyses, with a mixture model approach used to identify two patient groups with different rates of platelet drifts. Patient baseline characteristics were tested as covariates on the final model parameters. A separate phase II study (3.6 mg/kg q3w; N=110) was used for model evaluation.

**Results:** The PKPD model described the data well and predicted the 9% incidence of grade  $\geq 3$  TCP observed in the evaluation dataset. Two populations of patients were identified by the model, with platelet profiles from 25% of the patients drifting downward more rapidly before stabilizing by 8 treatment cycles (cycle = 3 weeks) to typically 50% of the original baseline platelet count. Patient baseline characteristics were not significant covariates for platelet kinetics.

**Conclusions:** The model accurately predicts clinical observations of platelet counts during T-DM1 treatment and supports T-DM1 3.6 mg/kg q3w as a well-tolerated dose, requiring minimal dose delays/ reductions for TCP. In addition, the model supports partial depletion of the platelet proliferation pool as a mechanism of the downward drift in platelet count. Platelet response to T-DM1 could not be predicted *a priori* from baseline characteristics.

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## **I-21 Michael Block Mechanistic PBPK/PD modeling for prediction of study outcome of cancer therapies: Translating in-vitro information into valid in-vivo predictions**

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**Objectives:** Getting a valid quantitative assessment of clinical endpoints for a planned study based on preclinical observations is one of the most demanding tasks during the pharmaceutical research and development process. In order to obtain high quality predictions of study outcome it is of major importance to integrate as much prior knowledge and information as possible while performing physiological modeling. It was our aim to demonstrate how in the field of cancer research the use of mechanistic multiscale models representing the in-vitro and in-vivo situation can be applied for the estimation of efficiency of different tyrosine kinase inhibitors (e.g. Sunitinib, Imatinib).

**Methods:** We developed whole body physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) models for different tyrosine kinase inhibitors using the software PK-Sim® and MoBi®. Basically, pharmacokinetic (PK) models for the above mentioned chemotherapeutic agents were built to estimate the drug concentrations in the tumor site. These PK models were then coupled to a mechanistic pharmacodynamics tumor growth model, integrating detailed information to cell growth, cell cycle progression and apoptosis. The thus built multiscale tumor growth model was then parameterized using in-vitro data measured in cancer cell lines, in-vivo information derived from xenograft models as well as plasma concentration-time profiles from preclinical studies.

**Results:** The developed whole body PBPK/PD multiscale models for all tyrosine kinase inhibitors provide an excellent description of drug pharmacokinetics in xenograft models and humans and accurately predict the tumor growth under control and inhibition conditions. Using the mechanistic model to predict the outcome of a xenograft study leads to an excellent agreement of the simulated and experimentally determined Kaplan-Meier plots.

**Conclusions:** The multiscale model approach presented here provides a sophisticated mechanistic framework to obtain high quality predictions of study outcome by integrating as much prior information of different cell types (i.e. cancer types) and various compounds as possible. It offers the opportunity to systematically increase our knowledge on tumor growth and cancer therapy efficiency by translating all available in-vitro information into valid in-vivo predictions.

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**I-23 Guillaume Bonnefois A nonlinear mixed effect model to study albumin-mediated drug transport into endothelial cells in vitro.**

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**Objectives:** Albumin penetrates into endothelial cells after binding to albumin, and is recycled to the surface by FcRn [1]. The objective was to study the impact of albumin-mediated drug transport on drug intracellular concentration in vitro. Sorafenib, an antiangiogenic drug with high affinity for albumin, was used as a probe.

**Methods:** Human Pulmonary Artery Endothelial Cells were used for cell culture. Cell cultures were exposed to different concentrations of sorafenib (0, 0.0064, 0.021, 0.064, 0.64  $\mu\text{M}$ ) and albumin (0, 14.5, 43.5, 145, 725  $\mu\text{M}$ ) in triplicate. Sorafenib intracellular concentration was measured by LC-MSMS. A mixed-effect regression model was fitted to the apparent intracellular sorafenib concentrations (NONMEM 7). Two compartments were considered: the medium (A) and the cells (B). Albumin active transport in each direction was assumed to be either nonlinear or linear. In the linear case, the transports were characterized by their clearance in each direction. Sorafenib was assumed to cross the cell membrane by passive diffusion, and by active transport of the albumin-sorafenib complex, with the same rate as albumin. In each compartment, sorafenib was allowed to bind reversibly to albumin. The dissociation constant of this equilibrium was assumed to be the same in both compartments. The unknown factor of dilution of the intracellular content was also estimated. An explicit solution of the steady-state model was derived.

**Results:** Direct evidence of albumin penetration into cells was obtained by FITC-albumin. The full nonlinear and the reduced linear models could be fitted to the data, but there was no evidence of a better fit with the full model ( $p = 0.10$ ). The distribution of NPDEs for the linear model was random and showed no trend with increasing concentrations of either albumin or sorafenib. Removing the active transport from the final model (i.e., fixing  $CL_{AB} = 0$ ) resulted in a significantly worse fit ( $p < 0.0001$ ). The ratio of albumin concentration A/B was equal to 7.

**Conclusions:** Albumin increases sorafenib penetration either by enhancing diffusion or active transport. Simulations show that the intracellular total concentration of sorafenib would be much lower if albumin was not actively transported. In case of rapid drug elimination from the cells, this active transport may enhance intracellular free drug concentration. The model equation may be applied to other drugs, binding proteins and cell types.

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## I-24 Stephan Borghorst Age Dependent Volume of Distribution of Pegylated Asparaginase (Oncaspar™) in children and adults

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**Objectives:** A higher volume of distribution normalized to body surface area (V/BSA) was reported for PEG-asparaginase in adults [1]. A Population pharmacokinetic (PopPK) analysis for PEG-asparaginase in children also identified a trend towards higher V/BSA with increasing age [2]. Therefore, we analysed serum activities from both children and adults to get a better insight into possible age dependent pharmacokinetics of PEG-asparaginase.

**Methods:** 2089 serum activity measurements in 449 patients aged 0.8 to 80.6 years (median age 27.1) from the paediatric ALL/NHL-BFM 95 and ALL/NHL-BFM REZ protocol as well as the adult GMALL 07/03 and GMALL Elderly 1/2003 protocol were analysed using nonlinear mixed effect modelling (NONMEM Vers. VI). Paediatric patients received 500, 750, 1,000 or 2,500 U/m<sup>2</sup> PEG-asparaginase (Oncaspar™) during induction and relapse treatment, adult dosage ranged from 500 to 2,000 U/m<sup>2</sup>.

**Results:** A one-compartment model with BSA as covariate for clearance (Cl) and volume of distribution (V) as well as Cl increasing with time best described the pharmacokinetics of PEG-asparaginase in children and adults. Age was included as covariate on V for individuals younger than 18 years of age according to the formula:  $V = V_i * e^{((AGE - median\ AGE) * 0.107)}$  where  $V_i$  = initial volume of distribution and AGE fixed on 18 for individuals older than 18 years of age. Parameters found were:  $V_i = 2.27\ l\ per\ 1.73m^2$  and  $Cl = 0.009\ l/h \pm 58.1\%$  per  $1.73m^2$  (mean  $\pm$  interindividual variability).

**Conclusions:** Children and adolescents younger than 18 years of age exhibit a significant lower volume of distribution normalized to BSA when compared to adults (1.23 vs 2.62 l/m<sup>2</sup>). The influence of age on dosing and schedule of PEG-asparaginase will be analysed in future studies.

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## II-09 *Fernandez Eric* Using the Virtual Tumour to predict and optimize drug combination regimens

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**Objectives:** Drug combination therapy is widely used to treat cancer because of the limited number of malignancies that can respond to single-agent chemotherapy. But when multiple drugs, combination schedules, sequences and doses are considered, the number of possibilities increases combinatorically, and can not be realistically tested either clinically or in animal models. We have designed a computational model, the Virtual Tumour, to help predict, optimize and allow prioritisation of the most effective drug combinations schedules.

**Methods:** The Virtual Tumour [1] is a computer model of a growing tumour, which integrates the cell division dynamic with the effect of antineoplastic agents. The simulation platform is composed of PK models of the drugs of interest, as well as a pharmacodynamic model of cell cycle progression. Drug effect can be calibrated by using various data sources: in vivo target inhibition (IVTI), xenograft growth timecourses, flow cytometry and public literature data. In order to validate the predictions made with the Virtual Tumour, we set up a validation study with our partner Lilly. The goal was to predict the xenograft course for two different combination regimens – one simultaneous and one sequential – using two drugs. The simulated timecourses were compared with experimental results in a single-blind test.

**Results:** We accurately predicted xenograft growth of two anti-cancer drug combinations using experimental data collected from single drug exposure uniquely. We show how a computational approach helps explain how multiple drug exposure and correct sequence leads to synergy, and how it can be used to subsequently design optimal schedule and combination treatments.

**Conclusions:** We have developed the Virtual Tumour model to aid with the design of optimal drug schedules. The model combines disparate data, at the cell and tumor level, into a consistent picture, and leverages them to make testable predictions about tumor response. Thousands of simulations can be performed if necessary to find the best treatment regime, reduce experimental costs and provide insights on optimizing use of a particular drug.

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## II-14 Gregory Ferl Population analysis of the DCE-MRI response of liver metastases to a single dose of bevacizumab in CRC patients

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**Objectives:** Our objective is to analyze the time course of the Ktrans response to a single dose of bevacizumab (bev) based on Dynamic Contrast Enhanced MRI data from a previously published phase II clinical trial [1], where Ktrans is a measure of vascular permeability to contrast agent, surface area and rate of tissue perfusion. Decrease in Ktrans is observed shortly after dosing, however, the subsequent dynamics of this parameter over a 12 day period are not entirely clear due to inter-patient variability.

**Methods:** 2 baseline (3 and 2 days predose) plus 4 subsequent DCE-MRI scans following a single 10 mg/kg dose of bev (4hr, 2d, 8d and 12d) were obtained from 10 patients, each with between 1-6 colorectal liver metastases (26 lesions total). Two patients had missing data points; the first (4 lesions) missed the 8d scan while the other (3 lesions) missed the 8d and 12d scans. Ktrans values for each scan were estimated [1] using the extended Tofts version of the Kety compartmental model [2]. Ktrans dynamics plus inter-individual (IIV) and inter-lesion (ILV) variability were described using an indirect response model with feedback, implemented in NONMEM. True individual baseline Ktrans was estimated for each lesion by assuming that it varies around the observed average baseline with variance  $(\sigma^2)/2$  [3]. Post-hoc analysis provided parameter estimates for each lesion and simulated Ktrans profiles were produced using the estimated population mean and variance parameters.

**Results:** ILV was not identifiable and was assumed to be zero, except for inter-lesion variability in baseline Ktrans. Inter-patient variability was significant. IIV of model parameters is identifiable and estimated to be larger for parameters in the indirect response equation than for the feedback equation (79% CV vs. 49% CV). The predicted population response describes a rapid decrease of Ktrans to 70% of baseline followed by a slower return to baseline within 12 days after a single dose of bev, with rebound over baseline in some patients.

**Conclusions:** There is a significant amount of inter-patient variability (IIV) in Ktrans response to a single dose of bev; inter-lesion variability (ILV) is not detectable within these data. However, a population trend of fast decrease of Ktrans to 70% of baseline followed by a return to baseline within 12 days is clear from this analysis. Based on data from a previous PK analysis, this does not appear to be driven by a decline in plasma bevacizumab concentration.

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## **II-16 Nicolas Frances Integrating distribution to tumor tissue into a dynamic PK/PD model to evaluate the anti-cancer effect of erlotinib in patient-derived LXFA 677 tumor xenograft mice**

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**Objectives:** Development of a dynamic PK/PD model to describe the anticancer effect of erlotinib in patient-derived LXFA 677 tumor xenograft mice as a function of drug concentration in tumor tissue.

**Methods:** Two independent experiments were designed in female NMRI nu/nu mice implanted with human LXFA677 primary patient tumors. For assessing tumor growth inhibition, a repeated oral dose study with 100, 25, 6.25 mg/kg/d of erlotinib was conducted. Tumor volume was monitored twice weekly during and after drug treatment and a sparse plasma PK sampling scheme (2 observations per mouse) was applied. In a second study aiming to assess the drug distribution to the tumor tissue, a staggered sampling approach was applied. For each mouse, a single sampling time point for drug concentration in plasma and tumor was obtained after oral administration of 100 mg/kg/d for single and repeated dose.

As a first step, the area under the tumor growth curve was described as a function of the cumulative dose. Next we developed a dynamic PK/PD model relating the time course of the tumor volume to the exposure in the tumor. Concentration in the tumor was directly linked to the effect. Population analyses were performed using MONOLIX v3.2 [1] and simulation analyses using Matlab v9b.

**Results:** First, an Emax model related the area under the tumor growth curve to the cumulative dose. The distribution of erlotinib was described by a 'hybrid' PK model consisting of a one compartment model describing the plasma erlotinib concentration profile and a tumor compartment describing the tumor concentration profile. The parameters estimated from this model included clearance (CL), volume of distribution of the central compartment (Vc), absorption rate constant (ka), inter-compartmental Clearance (Q) and volume of distribution in the tumor compartment (Vt). Time course of plasma and tumor concentration were fitted simultaneously to this PK model. The fitting was improved by using the observed tumor volume as a covariate to Vt. Finally, the dynamic model predicted the PK in the tumor and related this to the dynamics of tumor growth.

**Conclusions:** Linking the effect to the exposure at the tumor compartment improved the PKPD modeling first by accounting separately for the delay due to distribution to the biophase and the delay triggered by biological cascade. Second, the anticancer effect can be related to any kind of PK profile in the biophase.

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## **II-28 Iztok Grabnar Bayesian Estimation of Methotrexate Pharmacokinetics in Children with Acute Lymphoblastic Leukaemia and Prediction of Folinic Acid Rescue**

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**Objectives:** Acute lymphoblastic leukaemia is the most common childhood cancer and high dose-methotrexate (MTX) is still the mainstay in the chemotherapy. Due to high variability in pharmacokinetics and well established relationship between treatment toxicity and MTX exposure, TDM and adaptive folinic acid rescue are essential for clinical management of patients. We have previously studied the association of genetic polymorphism in the folate metabolic pathway with MTX pharmacokinetics and toxicity [1]. The aim of the present study was to evaluate Bayesian predictions of MTX concentrations in the elimination phase based on scarce samples.

**Methods:** Routine TDM data from 64 patients were used. Four courses of MTX treatment were infused over 24 hours and blood samples were collected at 24, 36, 42 and 48 hours. Additional samples were obtained, if MTX concentration at 48 hours was above 0.5  $\mu\text{mol/L}$ . Pharmacokinetic parameters of MTX were estimated by NONMEM VI.

Additional data from 37 patients were used for evaluation of prediction performance of the Bayesian method. MTX concentrations at 48 h were predicted from measured concentrations at 24 and 42 h and predictive performance of the model was evaluated by comparison with the actual concentration measurements at 48 h.

**Results:** Pharmacokinetic data from 252 courses and 919 MTX concentration measurements were available for analysis. MTX concentration profiles were fitted with a two compartment model. In a typical patient CL was estimated at 7.12 L/h (IIV 31%), volumes of the central and peripheral compartment were 9.73 (IIV 6%) and 3.61 (IIV 63%) L, respectively and distribution clearance was 0.134 L/h (IIV 65%). IOV in CL was estimated 14.8%. Residual variability was estimated at 0.0642  $\mu\text{mol/L}$  (additive component) and 68.1% (proportional component). In the independent group of patients bias of the predicted concentrations at 48 h was 10% with precision of 77%. Dosage adjustment of folinic acid rescue based on predicted MTX concentration was accurate in 81% of courses.

**Conclusion:** Bayesian estimation is a useful tool for prediction of MTX concentration in the elimination phase and can be used for adjustments of folinic acid dosing.

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gene polymorphism G80A to methotrexate plasma concentration, toxicity, and disease outcome in childhood acute lymphoblastic leukemia. *Leuk Lymphoma*. 2010;51(4):724-6.

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## **II-31 Joachim Grevel A physiology-based model predicts pharmacokinetics, target occupancy in the tumour, and HSP70 biomarker response in serum for the HSP90 inhibitor, 17-AAG**

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**Objectives:** HSP90 inhibitors of various structures (geldamycin analogs, ATP analogs) are currently in clinical evaluation [1]. The front-runner, 17-allylamino-17-demethoxygeldamycin, 17-AAG, was in phase 2 [2] but its development has been stopped. All HSP90 inhibitors lack a reliable biomarker to guide dose selection in the absence of typical cytotoxic effects. This simulation study predicts an increase in HSP70 serum levels in cancer patients.

**Methods:** A LC-MS/MS method determined conc. of both 17-AAG and 17-AAGH2. A two-comp. model [3] was used to simulate plasma 17-AAG level in patients of 80 kg body weight (BSA=1.96m<sup>2</sup>, HCT=0.4) bearing a 500g solid tumour and being treated with six weekly i.v. infusions of 450 mg/m<sup>2</sup>. The uptake of 17-AAG into tumour cells was predicted from the scaled permeability surface-area product (0.26 L/h)[4], from the ratio of tumour plasma (0.02 L) versus peripheral volume (90 L), and from the rate constants between interstitial and cellular space [4]. Tumour tissue conc. of 17-AAG, CT, were calculated. The relationship between CT and % occupancy of HSP90, OCC, was obtained by fitting (LL.3 in R) published data [5]. The relationship between intracellular 17-AAG and levels of HSP70 was obtained by fitting published data [6]. Secreted HSP70 was predicted from intracellular HSP70 [6] and the latter was diluted to arrive at the HSP70 serum level.

**Results:** Plasma conc. of 17-AAG reached 15000 nM at the end of the infusion and were BLQ at 48 h. Interstitial and cellular 17-AAG reached 1800 nM and 4800 nM at 6 h and 24 h after the end of the infusion, respectively. CT reached 2700 nM. There was little accumulation of 17-AAG tumour conc. between the 1st and 6th week. OCC varied between 35% and 10%. High intracellular levels of HSP70 (2500 ng/mL) contrasted with 100 ng/mL in the tumour interstitial space and with only a 6 ng/mL increase from baseline serum HSP70.

**Conclusions:** This simulation shows the possibility to monitor HSP90 inhibitors with increases in serum HSP70 and to simulate OCC from plasma PK. The simulations show that the clinical development of 17-AAG was stopped when the highest doses resulted in only 35% OCC while xenografts (NSCLC) in mice were maximally inhibited at 70% [5].

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## II-36 *Neeraj Gupta* Population PK and PK/PD Analysis of Intravenous Investigational Agent MLN9708 in Solid Tumors and Lymphoma Patients

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**Objectives:** MLN9708 is an investigational potent, reversible and specific 20S proteasome inhibitor in phase-1 and phase-1/2 clinical trials. The objectives of this analysis were to characterize the population pharmacokinetics of intravenous MLN9708 and explore the effect of body size on PK variability. A PK/PD (20S proteasome activity) model was also developed to describe the concentration-effect relationship for target inhibition in humans.

**Methods:** MLN9708 dose was based on body surface area (BSA) for both twice-weekly and weekly dosing schedules in solid tumor and lymphoma patients (N=42). Plasma concentrations and whole blood 20S proteasome activity data available after single and multiple doses for 168 hours were used for the analysis. Population PK and PK/PD data were analyzed using NONMEM VII. Various covariates including BSA, age, sex, and race were tested. Standard goodness-of-fit diagnostics, posterior predictive checks and bootstrap analysis were done to evaluate the adequacy of models.

**Results:** MLN9708 population pharmacokinetics was described by a three-compartment model with first order elimination. Body size descriptors (Body weight and BSA) were found to be a significant covariate only on peripheral volume of distribution ( $p < 0.01$ ). Since both BSA and body weight are correlated, BSA was kept in the final model for ease of clinical translatability of the results since BSA based dosing was used in phase-1 studies. The estimates of pharmacokinetic parameters for a typical individual were 2.15 L/hr for clearance, 5.4 L for central volume of distribution (V1) and 419 L for peripheral volume of distribution (V2). Inter-individual variability (IIV) was approximately 45% for CL, 46% for V1, and 39% for peripheral volume of distribution (V2), with only 20% of IIV in V2 explained by BSA. Based on simulations using the final pop PK model, there were no differences in concentration-time profiles or exposures (AUC or Cmax) between the BSA-based dose ( $1.76 \text{ mg/m}^2$ ) and the flat-fixed dose (3.3 mg). PK/PD relationship was explained by an inhibitory sigmoidal Emax model. IC50 obtained from the model was 21.1 ng/mL (IIV=30%).

**Conclusions:** Population PK analysis showed that BSA did not significantly impact AUC or Cmax, supporting a switch from BSA-based dosing to flat-fixed dosing in clinical development. An inhibitory sigmoid Emax model adequately describes the concentration-20S activity relationship.

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## **II-52 Jin Jin Mechanism-Based Population Pharmacokinetic (PK) Modeling of Hedgehog Pathway Inhibitor Vismodegib (GDC-0449), a Novel Molecule with Unique PK Nonlinearity in Humans**

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**Objectives:** Vismodegib, a small-molecule Hedgehog pathway inhibitor with unique nonlinear pharmacokinetics, has shown encouraging anti-tumor activity in advanced basal cell carcinoma patients. The objectives of this work were to use mechanism-based population PK (popPK) modeling to quantitatively describe the unique PK of vismodegib, and to support the optimization of vismodegib dose and schedule.

**Methods:** Vismodegib was administered orally to patients with refractory solid tumors in a Phase 1 trial. In the dose escalation portion of the study, vismodegib was given as a single dose followed by continuous once-daily (QD) doses starting from Day 8 at 150, 270, or 540 mg. Frequent PK sampling was obtained after the single dose followed by weekly trough collection during continuous dosing. Multiple population PK models were tested using NONMEM to evaluate the mechanistic hypotheses for the observed nonlinear PK. The model fitting was assessed via goodness-of-fit plots and visual predictive check.

**Results:** The mechanism-based popPK model can quantitatively describe the unique nonlinear PK characteristics of vismodegib, namely: (1) dose-proportional increase of drug exposure from 150 to 270 mg, but similar exposure for 270 and 540 mg, as well as a flat PK profile with minimal decline up to 7 days after the single dose; (2) similar steady-state concentration across three dose levels upon continuous daily dosing, as well as a flat PK profile with minimal fluctuation over 24 hr sampling period; (3) strong linear correlation between total vismodegib and Alpha1-Acid Glycoprotein (AAG) across all dose groups; (4) parallel unbound and total vismodegib PK profiles, and (5) higher unbound fraction at steady-state than after single dose. Key hypotheses incorporated in the current mechanism-based popPK model include: (a) nonlinear absorption due to poor solubility, which partly explains the dose- and time-nonlinearity; (b) unique binding to AAG, which explains the tight correlation between total vismodegib and the protein as well as the PK nonlinearity with time; (c) slow elimination, which explains the observed long half-life.

**Conclusions:** Our mechanism-based popPK model quantitatively evaluated the multiple hypotheses for the unusual nonlinear PK behavior of vismodegib in humans. Extensive simulations have provided guidance for hypothesis testing, as well as quantitative support for the recommended vismodegib dose and schedule of 150 mg QD.

### III-04 Steve Kuan Population Pharmacokinetic Modeling of Investigational Agent MLN4924 in Cancer Patients

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**Objectives:** MLN4924 is a novel investigational inhibitor of NEDD8-activating enzyme [1] that is being evaluated in patients with hematologic and non-hematologic cancer. A population model was developed to characterize the pharmacokinetics of MLN4924 administered as a 1-hour intravenous infusion following multiple dosing schedules and to assess the effects of patient covariates and dose.

**Methods:** The population pharmacokinetic model was developed on plasma concentration-time data using NONMEM (version 7.1.2). Two- and three-compartment disposition and zero-order input models were tested with or without logarithmic transformation of concentrations. Following identification of the base model, the effects of demographics (age, sex, body size), clinical laboratory parameters (hepatic transaminases and creatinine clearance) and assigned dose ( $\text{mg}/\text{m}^2$ ) were assessed in stepwise procedures using likelihood ratio testing of nested models. Model goodness-of-fit and performance were evaluated by common diagnostic tools.

**Results:** One hundred and four patients enrolled in four ongoing Phase 1 dose-escalation clinical studies provided 1262 concentrations with a median of 11.5 observations per patient (range 2 to 19). A two-compartment model with log-transformed concentrations most reasonably described the data. The final model estimated systemic clearance (CL), central volume of distribution (V1), inter-compartmental clearance (Q) and peripheral volume of distribution (V2) to be 59.1 L/hr, 136 L, 35.2 L/hr and 187 L, respectively, after centering on the median. The inter-individual variability (IIV as CV) was estimated to be 26.5 % for CL, 43.3 % for V1, 53.7 % for Q and 28 % for V2. Age (29.3-90.8 years) and body surface area (BSA;  $1.48\text{-}2.72\text{ m}^2$ ) were significant covariates on CL reducing the parameter's IIV by 7.3 %. Assigned dose (25-278  $\text{mg}/\text{m}^2$ ) and BSA were significant covariates on V1 reducing the parameter's IIV by 17.7 %. Sex (37 women, 67 men) was a significant covariate on V2 reducing the parameter's IIV by 7.9 %.

**Conclusions:** The effect of BSA was significant on both CL and V1, lending support to MLN4924 administration on the basis of body size. In addition, CL was decreased with increasing age; V1 was decreased with increasing assigned dose; and females had a smaller V2 compared with males. Clinical relevance of these statistically significant covariates will be further evaluated in the context of safety and efficacy.

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### **III-14 *Lars Lindbom* Acknowledging informative dropout by simultaneous model fitting of tumor size and dropout data may improve parameter estimates for tumor growth inhibition models**

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**Objectives:** Tumor growth inhibition (TGI) models are increasingly used to support the development of new cancer drugs. TGI models often consist of three elements: the tumor growth rate without drug, the drug cell kill rate and the rate by which resistance to the drug develop. Data from cancer trials are unbalanced with regard to the information relevant to these elements; patients drop out during the course of a trial for reasons related to the disease or the treatment and more data are therefore available describing the drug-related cell kill rate compared to the development of resistance which is a slower process. The current work has been performed to assess the benefit of simultaneously modeling the TGI model and a partially tumor size driven dropout rate.

**Methods:** Simulated tumor growth data for a phase II clinical trial with 60 patients was replicated 500 times. Patient drop out was simulated using a hazard function consisting of a constant risk plus an added risk dependent on tumor size. Two models were estimated on each simulated data set using NONMEM 7, one describing only the tumor growth and another that simultaneously describes the tumor growth and risk of drop out. Parameter estimates for the tumor growth inhibition parts of the two model types were compared using estimates of bias, precision as well as standard error.

**Results:** The bias and precision of the TGI model was improved by simultaneously estimating a dropout rate, partially dependent on tumor size. In addition, the magnitudes of the standard error estimates were reduced by more than 50% for the combined model.

**Conclusions:** Implementing a combined tumor growth inhibition and dropout model in NONMEM 7 is feasible and provides improved parameter estimates for simulated data compared to a model describing only tumor growth. This approach should be evaluated using real data to confirm its usefulness and assumed links between tumor size and dropout.

### **III-17 Paolo Magni A new population PK/PD model to assess the myelotoxicity of candidate drugs in preclinical and in clinical studies**

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**Objectives:** Bone marrow suppression or myelotoxicity is a serious side effect of chemotherapy and drugs affecting the immune system inducing neutropenia and leucopenia, conditions that can lead to infections and fever. The risk is especially high in cytotoxic chemotherapy for leukemia. A new population PK/PD approach can be adopted during the different phases of drug development to test and select new candidate compounds devoid of myelosuppression effects preserving the therapeutic efficacy.

**Methods:** Myelotoxic adverse effect was evaluated using a recently developed semi-mechanistic PK/PD model, characterized by a dynamical system with non-linear feedback [1]. The aim was to describe leukocytes or neutrophils peripheral concentrations during and after the treatment in order to predict the minimum concentration (nadir), and the time necessary to reach that concentration (time-to-nadir).

**Results:** The proposed model was implemented in NONMEM and successfully applied to analyzed different datasets. Preliminary results indicate that it is able to describe experimental data also in a population context and that it can be used to rank compounds on the basis of their myelotoxicity.

**Conclusions:** PK/PD modeling approaches can impact each different phase of R&D process to characterize drug myelotoxicity for improving drug development plan, enabling critical decision making, and eventually bringing safe and effective medicines to patients. Overall, the results of myelotoxicity testing were consistent allowing to predict human neutropenia grade from animal PK/PD data. The human PK/PD model can be also used for saving resources and time during dose escalation.

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### **III-21 Maria Matoses Osborne Ex Vivo modeling of the apoptotic effects of Vivia009 and its metabolite in patients with Chronic Lymphocytic Leukemia**

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**Objectives:** Vivia009 is a patented new drug indication for B-cell chronic lymphocytic leukaemia (B-CLL), a cancer of white blood cells that originates in bone marrow and develops in lymph nodes. Both, Vivia009 and the metabolite have shown in vitro and ex vivo activity. The aim of this study is to develop a pharmacodynamic model describing the apoptotic effects of the two compounds in combination characterizing the type of interaction (additivity, antagonistic, or synergistic).

**Methods:** Samples were extracted from patients diagnosed with B-CLL. Blood was then diluted with RPMI and 45ul of the suspension is added to each well of a 96-well plate that contains the pharmacological agents. The plate is divided in rows containing Vivia009, its metabolite or the combination of both. Drugs alone are set up in dose-response, starting at 100 uM with a 1 to 3 dilution, and for combinations, a fix amount of Vivia009 is added to a dose-response of the metabolite. The compound plates are then incubated for 6, 12 or 24 hours at 37°C with 5% CO<sub>2</sub>. After incubation, the erythrocytes are lysed and Annexin V-FITC, monoclonal antibodies anti-CD45-APC and anti-CD19-PE, are added to each well. The plates are then transferred to an automated flow cytometry system where the contents of each well is aspirated and analyzed by a CyAn flow cytometer[1]. All data generated were analyzed simultaneously. The relationship between concentration and time of exposure and the percentage of apoptotic cells was described using the population approach with NONMEM VII.

**Results:** Visual inspection of the response vs. concentration profiles revealed that time of drug exposure, in addition to concentration was an important factor in the apoptotic effect, which was taken into account in the model including a delayed compartment for the parent drug and the metabolite. Isobolograms indicated a synergistic interaction which was modeled using an empirical model for synergism[2]. Vivia009 and the metabolite showed similar potencies and mean apoptotic signal transduction times. The interaction parameter alpha was estimated with a value greater than 0 (0.43) indicating synergistic effects between Vivia009 and its main metabolite.

**Conclusions:** The results of this modeling exercise together with an integrated parent drug and metabolite pharmacokinetic model will help to optimize the dose to achieve a desirable active concentration (Vivi009 + metabolite) in patients diagnosed with B-CLL.

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### III-30 *Daniele Morpurgo* Predicting the Gemcitabine efficacy by a stochastic language based model

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**Objectives:** This study is aimed at developing a discrete algorithmic model of biochemical action mechanisms of gemcitabine. The model has two main functions: (i) to predict the gemcitabine efficacy in terms of kinetic parameters governing the dynamics of drug phosphorylation and incorporation into growing DNA, and (ii) to provide a molecular interpretation of the observed tumor shrinkage curves.

**Methods:** BlenX [1] is the stochastic language that we used to specify the model. BlenX enables the specification of parallel and concurrent interactions; it is compositional as it allows the modeler to extend a model incrementally when new experimental data are available. Our model describes the metabolic reactions that gemcitabine undergoes, the competition between gemcitabine and the deoxycytidine triphosphate for the incorporation into the DNA, and the death and survival of the cell as a function of the amount of accumulated damage on the DNA. We calibrated the model on experimental time series data of the concentration of the main gemcitabine metabolites [2,3] with KInfer [4]. KInfer infers the kinetics by maximizing a Gaussian probability model of the observed time changes of the gemcitabine metabolites and substrates concentration.

**Results:** The simulations fit the observed dynamics of the metabolites and the tumor shrinkage curves, as reported in Lecca et al. [5]. The gemcitabine efficacy has been found to be directly proportional to the kinetic rate constants of the following reactions: phosphorylation of the gemcitabine, interaction of the ribonuclease reductase with gemcitabine diphosphate, incorporation of the gemcitabine triphosphate into the DNA. Conversely, the drug efficacy proved to be inversely proportional to the kinetic rates of the dephosphorylation of the gemcitabine monophosphate and of the gemcitabine deamination.

**Conclusions:** The BlenX model reproduces the experiments in [2,3] and predicts the drug efficacy value reported in [6]. Our approach to the pharmacodynamic modeling proposes an unconventional way to estimate the efficacy of the therapy. We built a modular multilevel model of the mechanism of drug action and identified the reactions giving the highest contribution to the toxicity of gemcitabine. In this context, the drug efficacy has an interpretation at molecular level in terms of the contribution of these reactions, whereas usually the drug efficacy is estimated as derivative of the tumor shrinkage with respect to the drug dose.

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### III-34 *Ronald Niebecker* Importance of study design for estimation of $V_{max}$ and $K_m$ characterising nonlinear monoclonal antibody clearance

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**Objectives:** For numerous monoclonal antibodies (mAbs), nonlinear pharmacokinetics (PK) has been reported, and Michaelis-Menten elimination pathways are commonly employed in population PK models [1, 2]. However, characterisation of this nonlinearity – in particular  $V_{max}$  and  $K_m$  – did not always succeed, thus linear models were often regarded as sufficient. As PK analyses depend on the data situation, the number and range of dose groups in the clinical studies together with other aspects of study design influence the reliability – i.e. accuracy and precision – of parameter estimation. The objectives of this analysis were to explore the importance of several dose groups concerning the estimation of  $V_{max}$  and  $K_m$  at the example of a humanised mAb directed at a tissue-bound antigen, and to establish a workflow for more systematic investigations on critical parameters of study design.

**Methods:** The PK of the mAb has been previously described by a 2-compartment model with parallel linear and Michaelis-Menten elimination from the central disposition compartment. Model development was based on data from three multicentre multiple-dose studies. Dosing ranged from 5 mg/m<sup>2</sup> body surface area to a fixed dose of 100 mg. For the current investigations, the total dataset was split in two: A low dose subset (median dose=11 mg) and a high dose subset (median dose=100 mg) were analysed separately. In order to establish a basis for more systematic investigations, analyses with stochastically simulated data were to be performed. The development of an appropriate workflow was based on that reported in a recent simulation study [3]. All analyses were performed with NONMEMTM VI FOCEI.

**Results:** For the total dataset, the estimates for  $V_{max}$  and  $K_m$  were 141 µg/h [95% CI: 74.4; 226] and 1.43 µg/mL [95% CI: 0.646; 2.92], respectively. If estimation was based on the two subsets, considerable differences became apparent: The point estimates for  $V_{max}$  and  $K_m$  were up to 12-fold and 40-fold higher for the high dose subset, compared to the low dose subset. The workflow for systematic simulation studies from [3] could successfully be adapted to the local IT environment and is currently exploited.

**Conclusions:** The investigations confirmed the influence of study design and in particular the administered dosing regimen on parameter estimates. Using the established workflow, further research might contribute to study design enabling better determination of critical model parameters.

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### III-37 Valerie Nock Leukopenia following triple high-dose chemotherapy and stem cell rescue

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**Objectives:** Myelosuppression is one of the most important dose-limiting adverse events in many anticancer regimens. In a clinical study 17 patients received a combination therapy of carboplatin (C), etoposide (E) and thiotepa (T) including a stem cell rescue consisting of peripheral blood stem cell retransfusion (PBSCT) and G-CSF treatment. The current data analysis describes the leukopenic effect of all drugs in this combination regimen following a population PK/PD modelling approach.

**Methods:** Population PK models for 17 patients receiving CET doses up to 1500, 2400 and 750 mg/m<sup>2</sup> body surface area, respectively, were developed. In addition, data on PBSCT on day 7 were available for 17 patients as well as information on granulocyte colony stimulating factor (G-CSF) treatment for 16. Individual PK profiles for all drugs were estimated and integrated into a PD model for myelosuppression [1] assuming an additive effect of the drugs (SLOPE) on the proliferation rate of the cells in the bone marrow. The leukopenic potency of each drug in the triple regimen was investigated. Modelling and simulation activities were performed using NONMEMTM VI (ADVAN 6, FOCE+I), statistical analyses using R 2.10.

**Results:** PK parameter estimates for all drugs were in accordance with previous published ones [2,3,4]. The leucocyte-time course exhibited an initial increase in leukocyte count probably due to dexamethasone administration [5] during the first few days. After the nadir was reached a steep increase in counts followed by a pronounced rebound after G-CSF administration was observed. C was estimated to have the highest influence (SLOPE=0.13 L/ $\mu$ mol, RSE: 35.4%) on the proliferation of progenitor cells, showing a 6.5-fold higher drug effect than E (SLOPE=0.02 L/ $\mu$ mol, RSE: 56.8%). Compared to the other drugs T exhibited negligible toxicity, keeping in mind that its active metabolite tepea was not taken into account.

**Conclusions:** Based on the successful integration of the generated individual PK profiles of the drugs in the PD model for leukopenia discrimination between the drug effect size of C, E, and T was possible. Estimation of the PD parameters was precise. First results suggest an improvement of the model by integration of the stem cell rescue in order to better describe this dose-limiting toxicity and guide future chemotherapy.

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### III-50 Kirill Peskov Systems Modeling of EphB4/ephrinB2 Signaling Pathways

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**Objectives:** It has recently been shown that Eph-ephrin interactions play an essential role not only in tumor angiogenesis but also in tumor progression and/or suppression. The exact mechanism contributing to such a multitude of responses, however, remains unclear. In order to better understand this problem we studied the intricacies of EphB4 biology using a systems modeling approach. The main aims of this study were to: (1) reconstruct the EphB4/ephrinB2 signaling pathways based on information mined from the literature; (2) develop a kinetic model for EphB4/ephrinB2 forward signaling, and (3) analyze the model behavior and prediction to gain deeper insight into EphB4/ephrinB2 forward signaling and its influence on tumor progression and/or suppression mechanisms.

**Methods:** DBSolve Optimum software was used for all model development and analysis steps. Kinetic model verification was performed using data from ephrinB2-Fc induced EphB4 activation, internalization and degradation obtained in a MCF7 breast cancer cell line and other datasets (approx. 30 datasets) published in the literature.

**Results:** The signaling pathways of EphB4-ephrinB2 interactions were successfully reconstructed and a kinetic model of EphB4-ephrinB2 forward signaling was developed. Analysis of the model behavior allowed us to make the following predictions about the system regulation and possible cellular responses at different physiological conditions: (1) the Abl/Rac/Rap branch of EphB4-induced forward signaling was cell specific, (2) one of the main reasons for (1) was an inhibition of Abl function by filament actin. In addition, it followed that cell types with high concentration of filament actin were less sensitive to EphB4 inhibition of migration, (3) cell proliferation potential had low sensitivity against EphB4 activation and (4) EphB4 activation had an important influence on AKT phosphorylation.

**Conclusions:** It was shown that EphB4-ephrinB2 forward signaling had a negative effect on cell proliferative, survival and migratory potential. However, those effects were cell specific and can be weakened in certain cell types. In these cases, increasing the concentration of filament actin could completely inhibit the Rac/Rap branch of EphB4-ephrinB2 signaling.

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### **IV-03 Franziska Schädeli Stark A semi-mechanistic population pharmacokinetic model for trastuzumab emtansine (T-DM1) antibody-drug conjugate and total antibody in patients with metastatic breast cancer (mBC)**

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**Objectives:** Antibody-drug conjugates (ADC) are a class of targeted drugs with antibodies bearing covalently bound cytotoxic agents designed to target antigen-specific cells to enhance efficacy and reduce the toxicity associated with the cytotoxic agent alone. T-DM1, an ADC conjugating the antimicrotubule agent DM1 with trastuzumab (Tmab), exhibits faster elimination than total trastuzumab (TT, i.e. T-DM1 + unconjugated Tmab). The objective of this study is to characterize the pharmacokinetics (PK) of T-DM1 by integrating prior preclinical knowledge with clinical data.

**Methods:** T-DM1 and TT serum concentrations from a phase I dose escalation study (TDM3569g) in 52 patients [1], and from a phase II study (TDM4258g) in 111 patients [2] with mBC were available for model building. T-DM1 drug-antibody-ratio (DAR), i.e. the number of DM1 molecules per Tmab, ranges from 1 to 8. A semi-mechanistic PK model developed for monkey data, linking 8 measured DAR species with a chain of transit compartments [3], was used as a starting point. T-DM1 elimination kinetics is characterized by the net effect of transitions from higher to lower DAR species with loss of DM1 containing moieties, and proteolytic antibody elimination. Stepwise reduction of the number of compartments was performed to account for the reduced information (T-DM1 is the sum of DAR>0) in the clinical data set. The model was developed in S-ADAPT using Monte Carlo parametric expectation maximization.

**Results:** The transition from T-DM1 to Tmab was described with 5 distinct DAR species (DAR<sub>4</sub> to DAR<sub>0</sub>), and each was characterised by a 2-compartment model with the same central volume (VC: 3.21 L; inter- individual variability: 17.5%), peripheral volume (VP: 1.70 L; 62.3%), inter-compartmental clearance (Q: 0.576 L/day; 63.1%), and Michaelis-Menten elimination (K<sub>m</sub>: 11.1 mg/L; 129% and V<sub>max</sub>/K<sub>m</sub> 0.751 L/day; 75.8 %). A first-order transition rate constant was used to link the different DAR species (K<sub>td</sub>: 0.35 day<sup>-1</sup>; 15.5%) and the fraction of DAR<sub>0</sub> in the administered T-DM1 dose was estimated (fr<sub>0</sub>: 0.045; 63.6%). Both T-DM1 and TT PK data were adequately described by the model.

**Conclusions:** A semi-mechanistic PK model was able to successfully link the different DAR species of T-DM1 and to capture the extended terminal half-life of TT relative to T-DM1. This modeling framework may be useful to further investigate the release kinetics of DM1, and to characterize the PK of other ADCs.

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#### **IV-11 Alexandre Sostelly Characterization of the interaction between irinotecan, SN-38 and MBLI-87, a new BCRP inhibitor, with a multi-scale semi-mechanistic PKPD model**

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**Background:** Breast Cancer Resistance Protein (BCRP) confers resistance to irinotecan (CPT11) and its active metabolite, SN38. MBLI87, a new BCRP inhibitor, has proven its efficacy *in-vitro* and *in-vivo* against BCRP-mediated resistance<sup>1,2</sup>. We aimed at characterizing the 2 levels of interaction, intracellular and pharmacodynamic, between CPT11, SN38 and MBLI87 with a semi-mechanistic PKPD model to find key factors for treatment efficacy.

**Methods:** Plasmatic drugs disposition was evaluated in mice after single administration of CPT11 or MBLI87. Tumor growth data were issued from 2 proof-of-concept studies (POC1, POC2) where xenografted mice received vehicle or CPT11 or CPT11+MBLI87. Tumor size was repetitively measured during 40 days. Treatment intensity and delay between tumors implantation and 1st drug administration were greater in POC2. Plasma drug kinetics was modeled using a compartmental approach. Natural tumor growth was described with Simeoni model<sup>3</sup>. The 1<sup>st</sup> level of interaction was integrated in an intracellular drug disposition model: a mechanistic model was developed on *in-vitro* data to quantify CPT11, SN38 BCRP-affinity constants ( $K_m$ ), MBLI87 BCRP-inhibitory constant ( $K_i$ ) and importance of active efflux<sup>4</sup>. The 2<sup>nd</sup> interaction model consisted in CPT11 and SN38 cooperative interaction on tumor growth characterized by a semi-mechanistic pharmacodynamic model derived from Greco<sup>5</sup>. The 4 submodels were combined and fitted separately on POC1 and POC2 to find key factors for treatment efficacy according to dosing regimens.

**Results:** Based on plasma concentrations, no plasma-PK interaction was found between the 3 compounds. Intracellular-PK interaction between CPT11, SN38 and MBLI87 was better described by a competitive interaction. BCRP-affinity was greater for SN38 than for CPT11, MBLI87 inhibitory constant was estimated at 2.5  $\mu$ M.

*In-vitro*  $K_m$  and  $K_i$  were corrected to take into account plasma protein binding. Active efflux was greater for SN38 and in POC2 study whereas CPT11 and SN38 cytotoxic potencies were in the same range in POC1 and POC2.

Despite greater treatment intensity in POC2, tumor shrinkage was greater in POC1 indicating that tumor access is a key factor for treatment efficacy.

**Conclusions:** This complex model including 2 levels of interaction was successfully applied to proof-of-concept data and allowed to point out key factors for treatment efficacy. MBLI87 is under further development, this model will be useful to guide its next development steps.

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## **IV-27 Mirjam Trame Busulfan Dosing in Children: Body Weight versus Body Surface Area or Allometric Body Weight Dosing**

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**Objectives:** Busulfan is frequently used in high-dose conditioning regimens prior to bone marrow transplantation in children. The aim of the current analysis was to evaluate whether the EMA dosing recommendation in the labelling of IV busulfan [Busilvex®] according to body weight [BW] is adequate for dosing busulfan in children or if more precise dosing recommendations can be suggested. Of particular interest was the comparison of the area under the curve [AUC] of a BW based dosing regimen as recommended in the labelling of Busilvex® with other dosing regimens such as a body surface area [BSA] based dosing regimen.

**Methods:** We retrospectively analysed two different datasets from three different dosing regimens by using NONMEM. The development dataset consisted of plasma samples from 94 children, aged 0.4-18.8 years, receiving either oral or IV busulfan. The external model evaluation dataset included 24 children, aged 0.1-18.9 years, from once-daily IV busulfan dosing regimen. A one-compartment model with first-order absorption using BSA or allometric BW as covariate on clearance [CL] and BW as covariate on volume of distribution [V] described the results sufficiently. Apart from interindividual variability on all pharmacokinetic parameters, interoccasion variability was included for CL and V. On the basis of the two final models, new dosing regimens according to BSA or allometric BW were simulated.

**Results:** CL values did not reflect the shape of the CL versus BW curve reported in previous investigations. By external model evaluation and simulations, using prediction corrected Visual Predictive Checks, we were able to confirm these findings. Further, bioavailability was calculated to be between 93-99% for the development dataset. Based on the final models, we simulated two dosing schemes for dosing IV busulfan according to allometric BW and BSA showing that we estimated to get about 30% more patients into the proposed therapeutic AUC range of 900-1500  $\mu\text{M}\cdot\text{min}$  and could further achieve a decrease in the AUC variability as when dosed according to the labelled EMA dosing recommendation. Furthermore, to explore the maximum theoretical benefit with TDM another simulation was performed assuming that the true CL for each individual could be assessed during the first treatment cycle. Adjusting the dose according to these individual CL values by using the new formulas resulted in 90% of the patients being within the desired AUC range of 900-1500  $\mu\text{M}\cdot\text{min}$ .

**Conclusions:** According to our calculations, the labelling of Busilvex® might be redeveloped for dosing IV busulfan in children in order to optimise the dose intensity. We would recommend using one of the two newly suggested dosing regimens according to each individual's BSA or

allometric BW. These dosing regimens are expected to provide AUCs closer to the therapeutic target for a priori and TDM dose adjustments.

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#### **IV-50 Mélanie Wilbaux Population K-PD modeling of CA125 and tumor size kinetics in relapsed ovarian cancer patients**

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**Objectives:** Ovarian cancer (OC) is the leading cause of death among cases of gynecologic cancer. Indeed, the majority of OC patients presents with advanced stage of disease at diagnosis's time, and most of them relapse. CA 125 (Cancer Antigen) is used as a biomarker for epithelial ovarian cancer, representing 90% of all ovarian cancers' types.

The aim of this work is to characterise CA 125 and tumor size kinetics using a K-PD model with a population nonlinear mixed-effects modeling approach.

**Methods:** *Data:* Data stems from the database of CALYPSO trial: a randomized phase III study, comparing two chemotherapies, the standard's treatment Carboplatin-Paclitaxel (CP) versus Carboplatin-Pegylated Liposomal Doxorubicin (C-PLD), in relapsed ovarian cancer. Medians of 10 CA 125 concentrations values and 4 tumor size observations per subject were assessed for 533 OC patients receiving chemotherapy. Moreover, some covariates were available.

*Model:* Due to absence of PK data, CA 125 concentrations and tumor sizes were described by a Kinetic-Pharmacodynamic model (KPD model). The population analysis was performed using the non-linear mixed effects modeling approach implemented in Monolix 3.2. Criterion used for selection of best model were the likelihood ratio test for nested models, and AIC for non-nested models. Model evaluation was performed using classical Goodness Of Fits plots and simulation-based diagnostics.

**Results:** The PK was described by two virtual compartments: one central compartment, receiving the dose of treatment, and one transit compartment. The PD was an indirect effect model with inhibition of tumor growth, which was linked with to a CA125 compartment. Eight random parameters were estimated, with a low standard error for each random effect. In addition, 2 covariates were found: lesion size and number of cycles. The CA125 half life was 1.16 days. The individual estimation's median of the random parameter Q50, describing treatment potency, was equal to 0.388 for C-P, and 0.456 for C-PLD.

**Conclusion:** A joint model for describing CA 125 and tumor size profiles was built, and some covariates were found, in relapsed ovarian cancer patients receiving chemotherapy. This K-PD model is the first characterizing CA 125 and tumor size variations. It leads to better understanding of CA125 as biomarker and its use for treatment monitoring and evaluation.

## **IV-58 James Yates Characterisation of Xenograft Response to Docetaxel by Nonlinear Mixed Effects Modelling**

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**Objectives:** The human derived Xenograft tumour model is one of the main pre-clinical disease models used in oncology drug R&D. In the xenografted PC3 cell-line a steep and variable dose response to Docetaxel (Taxotere®) has been observed. This can make the design of combination therapy experiments challenging. The aim therefore was to develop a "Population" model of the Pharmacokinetics and Tumour growth inhibition of Taxotere that can be used to simulate the response to untested doses.

**Methods:** All analysis was performed in NONMEM v6 and R v2.9. A two compartment model was fitted to Pharmacokinetic data from mice. Xenografted tumour growth data was also available from two separate studies where doses of 15 and 20mg/kg were tested. There were no pharmacokinetic data from these studies; therefore PK was simulated for these studies using the mean parameter values. A second mixed effects model was developed using the Simeoni model to describe the tumour growth curves.

The identified model was used simulate the response to untested doses. The simulations were then summarised in terms of mean and standard deviation of tumour growth inhibition for each dose across the studies as well as the proportion of studies for which a particular dose had a significant effect against control.

**Results:** The simulated dose response suggested that it would be difficult to recommend a dose that would give a moderate response (~50% growth inhibition) whilst being significant against control. However a dose of 5mg/kg gave a mean response of 51.4 percent growth inhibition with an 80% chance of being significant against control.

As a form of model validation, data resulting from a previously untested dose 7.5mg/kg) was compared to a monte carlo simulation of the model at that dose. There were some disparities noted. However the response was in the range suggested by the simulations

**Conclusions:** Using a mixed effects model approach the xenograft response to a chemotherapeutic was characterised. It is clear from the model validation that inter-study variability should be characterised as well.

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## IV-63 Jianping Zhang Population Pharmacokinetics of Lapatinib in Cancer Patients

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**Objectives:** Lapatinib (Tykerb<sup>TM</sup>) is a potent and selective inhibitor of the EGFR and HER2 tyrosine kinases. It is approved for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2. This analysis was performed to describe the pharmacokinetic (PK) profile of lapatinib and to identify patient characteristics that influence lapatinib pharmacokinetics.

**Methods:** 27 patients from a Phase I study (dense data) and 263 patients from 3 Phase II studies (sparse data) contributed 2025 plasma lapatinib concentrations. Dosing in these studies varied from a single dose (SD) at 1500 mg to multiple doses at either 1500 mg daily (QD) or 500 mg twice daily (BID). For multiple dose studies, lapatinib concentrations were sampled on both Day 1 and Day 28. The population pharmacokinetic analysis was performed using a nonlinear mixed-effects modelling approach with NONMEM VI. Patient demographics, liver function, concomitant medications, and diarrhea scores were evaluated for their influence on lapatinib PK. The full covariate model was subject to backward elimination of insignificant or poorly estimated covariates. Visual predictive check was implemented for final model evaluation.

**Results:** Lapatinib PK was described by a two-compartment linear model with delayed zero-order and a first-order absorption functions. Mean (95% CI) parameter estimates were  $CL/F=40.2$  (36.3, 44.1) L/hr,  $Vc/F=45.0$  (33.7, 56.3) L,  $Q/F=10.9$  (8.5, 13.4) L/hr, and  $Vp/F=338$  (286, 390) L. Inter-individual variability in  $CL/F$  and  $Vc/F$  were 43% and 76%, respectively. Inter-occasion variability for  $CL/F$  between Days 1 and 28 was estimated to be 53%.  $CL/F$  was 42% lower (AUC 72% higher) with BID dosing. Bioavailability was 28% higher in Asian patients.  $Vc/F$  was 61% higher in Hispanic patients. Absorption rate ( $Ka$ ) decreased with age. Drug induced diarrhea was not found to influence the lapatinib PK.

**Conclusions:** The population PK model developed in this analysis adequately characterized the pharmacokinetics of lapatinib which enabled identification and quantification of patient characteristics that influence lapatinib exposure. The model allows further analysis of relationship between lapatinib exposure and tumor response in patients with breast cancer.

## **I-05 Claire Ambery Modelling impact of dropout mechanisms in Chronic Obstructive Pulmonary Disease (COPD)**

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**Objectives:** The objective of this analysis was to investigate the impact of modelling jointly the drug-disease and dropout models to predict observed longitudinal response.

**Methods:** A population kinetic-pharmacodynamic (K-PD) model (Model 1) was developed describing the longitudinal trough FEV1 response in subjects with COPD after inhaled administration of anti-inflammatory and bronchodilator medicines as part of monotherapy and combination therapy including placebo over 24 weeks. One of the combination components included different doses of the anti-inflammatory drug. Model 1 included disease progression and PD parts. The disease progression part was described by a linear decline over time. Consistent with previous reports [Celli, 2008], Model 1 also showed the FEV1 baseline was influenced by gender, smoking status, severity of disease, previous medication, age factoring smoking status and height factoring gender. The slope of the disease progression was influenced by baseline and smoking status. The PD part was described by an indirect response model, which also incorporated a less than additive interaction term for describing the FEV1 response of combination therapy. Dropout was modelled jointly with the drug-disease progression model using a parametric hierarchical model for evaluating various dropout mechanisms namely, completely at random, random, and informative [Hu & Sale, 2003]. Parameters were estimated by maximising the approximate joint likelihood as implemented in the software NONMEM. This work was motivated by the recent EMEA guidance [EMEA, 2010] on missing data in confirmatory clinical trials.

**Results:** Although Model 1 was adequate in describing the longitudinal FEV1 observed data, inclusion of the joint dropout model showed improvement in the model diagnostics and also reflected in the observed versus predicted FEV1 response. The longitudinal FEV1 response profiles over 24 week treatment suggest patient dropout can be explained with the missing at random mechanism or with the informative dropout mechanism. Inclusion of the drop out model did not appear to influence parameters of the disease progression model and provided some insight in the dose response for the combination therapy.

**Conclusions:** Inclusion of a dropout model jointly with the drug-disease progression model in COPD has potential to improve the prediction of longitudinal FEV1 response specially for prospective simulation of future study designs in COPD.

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### **I-09 Jacqueline Anderson Comparative pharmacokinetics of dimethoate poisoning in the minipig and human**

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**Objectives:** Organophosphorus pesticide (OP) poisoning is a major clinical problem in rural Asia. In contrast to other class II OPs, dimethoate is more toxic and most deaths result from refractory hypotension 12-36 hours after exposure. A pig model was developed to explore the pathophysiology of this poisoning. We wished to establish if pharmacokinetic and toxicity profiles in this model are similar to acute human poisonings. For this purpose, a population PK model was developed for pigs to compare with data from humans

**Methods:** Six Gottingen minipigs (Weight: 16-26kg) were dosed with dimethoate at 1g/kg (3 pigs), 0.5g/kg (2), or 0.33g/kg (1). Serial plasma samples were collected hourly for 13 hrs (when they were euthanized) or until death. In addition, acute poisoning data was collected from patients (n=62; female=4; age 15-68; samples 1-11 per patient) where the volume ingested was unrealisable in most cases. Dimethoate, omethoate, RBC-AChE and BuChE were measured at each time point for pigs and humans. PK models for dimethoate in pigs and humans were developed using NONMEM 7.

**Results:** A one compartment PK model with absorption described as a combination of zero (~25%) and first order (~75%) kinetics best described the pig data. There was a large volume of distribution:  $V_d/F = 319$  L, 0.3% CV. Elimination was rapid and non-linear with  $V_{max} = 37$  ng/h, 27% CV;  $K_m = 440$  mM (HIV not significant). The full PK model comparison with human acute poisoning data is in development; however, preliminary findings suggest a dimethoate kinetic profile similar to that in minipigs considering shape and duration. The pig model indicates a plasma half-life of ~6hrs. Calculations from acute poisoning data in humans indicated a plasma half-life ~6-8 hrs (Eyer, unpublished). The large  $V_d/F$  is unexpected given the low lipid solubility of dimethoate ( $\log P_{o/w}=0.7$ ), but indicates widespread tissue binding and/or a low bioavailability. Interestingly, bioavailability appeared to decrease as dose increased.

**Conclusions:** Our preliminary PK findings support the further use of this toxicological minipig model to examine delayed sub-acute clinical outcomes such as respiratory failure and hypotension. The human PK, metabolite and PD models for pigs and humans are in development

### **I-49 Adriaan Cleton Population Pharmacokinetics of a Monoclonal Antibody Tanezumab in Chronic Pelvic Pain Conditions**

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**Objectives:** Tanezumab is a fully human monoclonal antibody targeted to the human nerve growth factor receptor (NGF). A comprehensive population pharmacokinetic model of tanezumab was developed using nonlinear mixed-effects modeling of 303 patients (3239 observations) with Chronic Pelvic Pain Conditions (Institual Cystitis, Chronic Prostatitis and Endometriosis) and osteoarthritis population based on 5 clinical studies using IV administration. The influence of demographics and population (OA versus Chronic Pelvic Pain) on the pharmacokinetics of tanezumab was explored.

**Methods:** Nonlinear mixed effects modeling methodology was implemented in this analysis using NONMEM® (version 6). The first-order conditional estimation (FOCE) method with interaction was used to fit tanezumab plasma concentration data. Stepwise forward selection was used to identify relationships between population PK parameters and selected covariates including baseline body weight, age and gender. Standard goodness-of-fit diagnostics and posterior predictive checks were used to evaluate the adequacy of the PK model fit and predictions.

**Results:** The disposition of tanezumab was best described with a 2-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination pathways. The population pharmacokinetic parameter estimates for this dataset were for the linear clearance (CL), the maximum nonlinear clearance ( $V_{max}/K_m$ ), the central volume of distribution ( $V_1$ ), the peripheral volume of distribution ( $V_2$ ), and the Michaelis-Menten constant ( $K_m$ ) 0.182 L/d, 0.33 L/d, 3.4 L, 2.86 L, and 15.3 ng/mL, respectively. Body weight was found to be the most influential covariate on tanezumab exposure, affecting CL,  $V_1$  and  $V_2$ . The presence of anti-tanezumab antibodies in patients was low and not evaluated as a covariate.

**Conclusions:** The population PK model adequately characterized tanezumab PK in subjects in Chronic Pelvic Pain and Osteoarthritis. Consistent with the expected behaviour of the monoclonal antibodies, no notable difference in the PK between the different patient populations was observed.

## **II-23 Cecile Gerard Factors influencing pharmacokinetics of tacrolimus during the early liver post-transplantation period: a population analysis**

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**Objectives:** Tacrolimus (TAC) is an immunosuppressive agent used for the prevention of acute rejection after liver transplantation. Clearance and bioavailability of TAC are controlled by the activity of P-glycoprotein (P-gp) and CYP3A5 in the gut and the liver. P-gp and CYP3A5 are polymorphic, and the genotype of the donor and the recipient may differ. The objective was to investigate the population pharmacokinetics (PK) of TAC during the first 15 days post-transplantation and identify recipient and donor characteristics that influence PK parameters.

**Methods:** This was a prospective multicentric study (3 sites). 65 adult patients receiving oral TAC after liver transplantation were included. For each patient, at least 3 blood samples were taken at J2, J7 and J14. Patients characteristics collected and tested were: age, body weight, total plasmatic proteins, albumin concentration, coagulation factor V, prothrombin time, total and conjugated bilirubin, alkaline phosphatase (AP), Gamma Glutamyl Transferase, ALAT, ASAT, serum creatinine concentration (SCR), red blood cell count and haematocrit. Genetic factors were also collected for each donor and transplant recipient : CYP3A5 (intron 3) and P-gp (3435C\_T in exon 26) genotypes. PK analysis was carried out by using Monolix V3.1.

**Results:** Mean patient age and body weight were  $52.9 \pm 10.1$  years and  $70.8 \pm 13.4$  kg, respectively. Mean dosage regimen of TAC was  $0.074 \pm 0.059$  mg/kg per day. A one compartment model with first order absorption and elimination adequately described the data. Typical population estimates (relative standard error) of absorption rate constant, apparent distribution volume and apparent clearance (CL) were  $0.91 \text{ h}^{-1}$  (216%), 486 L (21%) and  $11.7 \text{ L/h}$  (14%), respectively. CL of TAC was negatively related to AP, ASAT and SCR. CYP3A5 donor and P-gp recipient genotypes were significant covariates of CL. Mean CL was lower when the donor was CYP3A5\*3/\*3 homozygote rather than carrying at least one CYP3A5\*1 allele :  $12.6 \pm 4.6$  vs  $24.8 \pm 3.1 \text{ L/h}$  ( $p < 0.005$ ). For P-gp, there was a significant difference between the mean CL of the 3 types of patients :  $13.7 \pm 6.1$  for T/T homozygotes ("mutant" alleles) ;  $14.2 \pm 4.6$  for C/T heterozygotes and  $18.5 \pm 5.3$  for C/C homozygotes ( $p < 0.05$ ).

**Conclusions:** During the early post-transplant period, some biological parameters but especially CYP3A5 and P-gp genotypes, should be taken into account because of their effect on the CL and consequently on the initial dosage regimen of TAC.

### III-02 *Julia Korell* Modelling red blood cell survival data

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**Objectives:** The survival time of red blood cells (RBCs) is commonly determined based on labelling experiments and an estimate of the mean RBC lifespan is obtained [1]. However, a better insight into the processes of RBC destruction would be desirable, especially in pathological states such as anaemia of chronic kidney disease (CKD), where the lifespan of RBCs is decreased [2] due to either an increase in random destruction or an accelerated senescence.

A previously developed model for RBC survival that accounts for plausible processes of RBC destruction [3,4] was applied to clinical data, and differences in the RBC lifespan in anaemic CKD patients compared to healthy controls were investigated.

**Methods:** RBC survival data using radioactive chromium as a random labelling method was available from 14 CKD patients receiving haemodialysis and 14 controls. The data were modelled based on two approaches: (1) a two-stage approach in MATLAB using generalized least squares; and (2) a full population approach in MONOLIX.

Two scenarios were considered: (1) estimating the main parameter controlling senescence; and (2) estimating the parameter controlling random destruction. An initial two-stage approach was conducted to assess whether a consistent preference towards one of these scenarios could be found across the individuals within each group. The goodness of fit between the scenarios was compared based on the OFV. Visual predictive checks (VPCs) were plotted for model evaluation.

**Results:** In the two-stage approach, the mean RBC survival was found to be significantly reduced by about 28% in CKD patients compared to healthy controls. Estimating the random destruction component provided a better fit for the majority of individuals (11 out of 14 in both groups).

In the full population approach, a combined error model described the data best. CKD was included as covariate in the full model, reducing between subject variability by 44% to 27% for the full model. The population approach confirmed the preference for estimating random destruction based on OFV in the whole population and that this mechanism was preferred to describe the decreased lifespan in CKD patients. The population mean RBC survival was 69.4 days for controls and 56.2 days which the covariate effect of CKD included, a reduction of approximately 19%.

**Discussion:** RBC survival in CKD patients was found to be decreased by approximately 20-30% compared to healthy individuals. The data support an increase in random destruction as the preferred underlying mechanism. Given the known shortfalls associated with the random labelling technique care should be taken when interpreting absolute values of RBC lifespan.

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### **III-28 Dirk Jan Moes Population pharmacokinetics and pharmacogenetics of everolimus in renal transplant patients on a calcineurin inhibitor free regimen**

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**Objectives:** Everolimus is an immunosuppressant with a small therapeutic window. Its highly variable pharmacokinetics complicates prediction of the individual dose as to assure reaching adequate everolimus exposure in renal transplant patients. The aim of this study was to describe the population pharmacokinetics in renal transplant patients following oral administration of everolimus twice daily in absence of CNI's and to investigate whether demographic factors or polymorphisms in genes coding for *ABCB1*, *CYP3A5*, *CYP2C8*, Pregnane X receptor could explain the observed inter-individual variability.

**Methods:** A total of 779 blood samples obtained from 53 renal transplant patients who had been switched from cyclosporine to a calcineurin inhibitor free regimen of everolimus (3 mg twice daily) and prednisolone were collected over a 1.5 year period. Everolimus blood concentrations were analyzed using liquid chromatography tandem mass spectrometry during routine therapeutic drug monitoring. A population pharmacokinetic model using NONMEM was build and demographic factors and genetic polymorphisms in genes coding for *ABCB1*, *CYP3A5*, *CYP2C8*, *Pregnane X receptor* were included as covariates.

**Results:** The pharmacokinetics of everolimus was best described by an two compartment disposition model with first order absorption and lag-time. Parameter estimates of the final model were:  $K_a$  7.55,  $CL/F$  17.9 L/h,  $V_c/F$  148 L,  $Q/F$  55.7 L/h,  $V_p/F$  498 L. A significant contribution was found for the demographic covariate Ideal Weight on everolimus distribution volume of the central compartment which explained 15.4 % of the inter-individual variability. None of the selected genetic polymorphisms contributed significantly in explaining the variability in everolimus pharmacokinetics. The remaining inter-individual variability in  $CL/F$  was 26.2% and inter-occasion variability of F was 25.9 %.

**Conclusions:** A two compartment pharmacokinetic model with lag-time describing the concentration time profile of oral everolimus in renal transplant patients has been developed. Ideal Body Weight significantly influences the apparent volume of distribution of everolimus, whereas polymorphisms in genes coding for *ABCB1*, *CYP3A5*, *CYP2C8*, *Pregnane X receptor* do not significantly influence everolimus pharmacokinetics.

### **III-47 Mark Penney Using Mechanistic Modelling of Cyclic Neutropenia to Predict the Effects of a COPD Therapeutic on Systemic Neutrophil Levels**

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**Objectives:** AZD002 is being developed for the treatment of Chronic Obstructive Pulmonary Disease (COPD). In healthy volunteers it has been shown to cause a dose-dependent reduction in the blood neutrophil count that reverses on the cessation of dosing. Low blood neutrophil counts which are observed in a condition known as cyclic neutropenia or which can be induced by certain chemotherapies are associated with an increased risk of infection and it is therefore important to determine whether there is potential for a similar risk with AZD002.

**Methods:** As part of this assessment we present a mathematical model based on an existing model of cyclic neutropenia[1], but which has been extended with the addition of a compartment for mature neutrophils, an implementation of the effect of challenging healthy volunteers with the immune response stimulant lipopolysaccharide (LPS) and with the mechanism of action and PK/PD of AZD002.

**Results:** Simulating the effects of both LPS and AZD002 together would produce distinct results depending on whether we assume that the LPS-driven rise in blood neutrophil counts is inhibited by, or occurs independently of, AZD002. Only the scenario where the LPS effect is independent of AZD002 is consistent with clinical observations (observed in a trial with AZD001). Moreover, the model predicts that the response to LPS challenge is sub-normal in cyclic neutropenia patients during their neutropenic phase.

**Conclusions:** Taking both results together predicts a key difference between the mechanisms that cause suppressed blood neutrophil counts in cyclic neutropenia and those induced by AZD002.

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### **III-48 Henry Pertinez Physiologically based, POP-PK modelling of a bone seeking agent in the ovariectomised rat disease model of post menopausal osteoporosis.**

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**Objectives:** Compound X is a bone seeking agent currently prescribed for the treatment of post menopausal osteoporosis. The aim of the work described in this poster was to develop a physiologically based pharmacokinetic (PBPK) model that would be able to describe bone exposure data for Compound X in the ovariectomised (OVX) rat pre-clinical disease model for post menopausal osteoporosis. The PBPK model would then serve as the basis for a human PBPK model for Compound X in future work, through the application of standard scaling methodologies.

**Methods:** For initial PBPK model development a naïve pooled approach was taken with the data and nonlinear regression used for parameter optimization. Once a suitable model was developed, a more appropriate POP-PK approach (given the nature of the OVX rat exposure dataset) could then be taken. The final PBPK model design incorporated elements from literature PBPK models for bone seeking agents [1] allowing for a description of the heterogeneity of bone tissue in the structure of the model (i.e. cortical and trabecular bone compartments and bone surface and bone matrix sub-compartments) and also for a physiologically rationalized description of the processes of bone remodelling. Descriptions of tissues other than bone adopted standard perfusion rate limited tissue compartment models, making use of a separate rat tissue distribution study for Compound X to provide required tissue  $K_p$  values. The model was implemented in both open loop and closed loop configurations. For the former, a forcing function for the blood/plasma compartment was derived from an empirical, 3-compartment, 1st order absorption model, POP-PK fitting to the OVX rat plasma exposure data (in a combined analysis with a satellite IV rat PK study), carried out in a Bayesian paradigm in WinBUGS using non-informative priors. Once adequate performance of the PBPK model had been demonstrated in open and closed loop configurations, treating the data with a naïve pooled approach, the bone exposure data was re-analysed with the PBPK model in an open loop configuration, using a Bayesian POP-PK approach in WinBUGS. In this analysis individual PK parameter estimates from the empirical fit to plasma data were used to provide a subject specific forcing function for each individual in the bone dataset.

**Results and Conclusions:** The PBPK model successfully describes the bone exposure of Compound X in the OVX rat in a physiologically rationalized manner. Parameter estimates and model behaviour are in keeping with known aspects of the distribution and incorporation of Compound X into bone and the model has the potential for future use in modelling the PK-PD of compound X and/or other bone seeking agents and for scaling to model human bone exposures for Compound X.

**References:**

[1]. Stepensky, D., L. Kleinberg, and A. Hoffman, *Bone as an effect compartment : models for uptake and release of drugs*. Clin Pharmacokinet, 2003. **42**(10): p. 863-81.

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## **IV-05 Rik Schoemaker Modelling Ordered Categorical Allergic Rhinitis Scores in an Environmental Exposure Unit Study**

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**Introduction:** An Environmental Exposure Unit (EEU) study was performed in allergic rhinitis patients to determine the effects of placebo (n=90), fexofenadine (n=225) and cetirizine (n=225) on self-assessed rhinoconjunctivitis symptoms. Patients were exposed to ragweed pollen and treated on two consecutive days. Day 1 consisted of seven hours of ragweed pollen exposure where treatment was started two hours after initiating allergen exposure and Day 2 consisted of six hours of ragweed pollen exposure where treatment was started three hours after initiating allergen exposure.

**Methods:** Model development was performed using non-linear mixed effects modelling with a proportional odds model. A new modelling approach was obtained by describing both the increase in score due to allergen exposure and the subsequent decrease in score due to treatment where the treatment profile for both active and placebo treatments was described using K-PD-type methodology[1]. Parameters were estimated using the SAEM algorithm in both Monolix and NONMEM VII. Novel graphics were developed to generate visual predictive checks for time profiles of ordered categorical data.

**Results:** Sensitivity to treatment was quantified using an  $EDF_{50}$ -parameter where cetirizine and fexofenadine were shown to induce a significant decrease in the estimated value relative to placebo. Duration of action over both days of treatment was quantified using a half-life parameter where placebo was shown to be associated with a shorter effect half-life. Various predictive checks illustrated the adequacy of the model both for predicting symptom-score time profiles and for predicting derived statistics, such as average score 2-5 hours post-treatment and time to onset of effect. Monolix seemed less critical in the choice of initial estimates than NONMEM and was therefore used initially.

**Conclusion:** Excellent descriptions were obtained of individual score profiles both for the five scores on the 0-3 point scale and the Total Symptom Severity Complex (TSSC), an aggregated score on the 0-12 point scale. Implementation of a proportional odds model allowed a proper description of the specific ordered categorical nature of the data with model predictions corresponding to the observed data range. The underlying K-PD model allowed both a description of the treatment profile in the absence of concentration measurements and an adequate description of the placebo treatment effect.

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#### **IV-40 Erno van Schaick PK-PD modelling of bone density and turnover effects of denosumab based on a circular model of bone remodelling**

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**Objectives:** To evaluate and update a previously developed bone cycle model (BCM) to describe the long-term effects of denosumab on bone density and bone turnover.

**Methods:** Bone turnover markers and bone mineral density (BMD) changes following treatment with denosumab, a fully human monoclonal antibody to RANK ligand (RANKL), were modelled using the BCM. The data were from a phase 2 trial in postmenopausal women, where denosumab was given every 3 months (Q3M; 6, 14, or 30 mg) or every 6 months (Q6M; 14, 60, 100, or 210 mg) for 24 months followed by either a continued treatment of 60 mg Q6M, off treatment for 24 months, or an off treatment for 12 months followed by re-initiation of 60 mg Q6M denosumab for 12 months [1]. Individual predicted denosumab concentrations obtained from the population pharmacokinetic analysis, serum C-telopeptide (sCTX), bone specific alkaline phosphatase (BSAP) and BMD were jointly modelled using NONMEM.

**Results:** A mechanism based circular multi-compartmental model with distinct compartments representing bone remodelling (bone resorption, collagen matrix formation, and fast and slow mineralization) was used. Disease progression, rebound of sCTX, BSAP and BMD upon termination of denosumab, and inhibitory effect of denosumab on resorption were estimated. Some parameters describing the bone remodelling process were derived from literature or previous analyses. The model satisfactorily described biomarker-time profiles after denosumab long-term treatment, but underestimated the rebound in sCTX and BSAP upon termination of treatment. Predictive checks indicated that the model adequately predicted changes in BMD. External validation of the model is currently ongoing.

**Conclusions:** The adapted bone cycle model adequately described the changes in bone turnover markers and BMD following treatment of denosumab at different doses and dose schedules. Improvement may still be envisaged, but may need a more mechanistic description of denosumab's action on osteoclast activity.

**Acknowledgement:** The initial structural development of the bone cycle model was performed by Exprimio in collaboration with F.Hoffmann-La Roche Ltd.

#### **References:**

[1] Miller et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: A randomized blinded phase 2 clinical trial. 2008 *Bone* 43: 222-229.

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### **IV-51 Christian Woloch Population Pharmacokinetics of Mefloquine and its Major Metabolite in Healthy Volunteers.**

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**Objectives:** Mefloquine has a pivotal position as an important first-line anti-malarial drug and needs to be used to prevent resistance. The aim of the study is to propose a population pharmacokinetic (PK) model for mefloquine and its major metabolite in healthy volunteers during prophylaxis for malaria infections and to investigate the mefloquine prophylactic efficacy achievement [1].

**Methods:** Data came from 118 French soldiers based in Djibouti. Subjects received an oral weekly maintenance dose of 250 mg mefloquine over 4 months. Sparse plasma concentration profiles for both compounds were available (4 per subjects). The sampling protocol included plasma trough concentration before the next drug intake at week 2, 5, 14 and a peak plasma concentration 6 hours after the sixth weekly dose. Kinetics profile of mefloquine and of its metabolite were analysed simultaneously using the population approach implemented in NONMEM VI (FOCE Interaction) and Monolix 3.1.

**Results:** The final model consisted of two compartments. One compartment with first order absorption and elimination rates best described mefloquine concentration; an additional compartment described the PKs of drug metabolite with first order metabolism and elimination rates. Inter-individual variability was described by exponential terms and residual variability by a proportional error model. The population PK parameters describing the model were for mefloquine, absorption rate  $k_a$ , total clearance CL, distribution volume V1 and for mefloquine metabolite, total clearance CL<sub>m</sub>, distribution volume V2 and metabolism ratio R. A sensitivity analysis resulted in introducing the same distribution volume for both compounds ( $V_1=V_2$ ), a fixed mefloquine absorption rate  $k_a$  at 6 d<sup>-1</sup> and a same inter-individual variability for CL<sub>m</sub> and R. Typical values (inter-individual variability expressed in percent) for CL, V1, CL<sub>m</sub> and R were respectively 32.8 L/d (28%), 535 L (41%), 85 L/d and 1.85 (24%). Residual variability for mefloquine and its metabolite were 29% and 36% respectively. No covariates were included in the model. The results are similar for both approaches (NONMEM vs. Monolix) and they are in adequacy with previous report for mefloquine [2].

**Conclusions:** The model adequately described the PK of mefloquine and its major metabolite. It would be used next to investigate mefloquine accumulation and its impact on the relationships between adverse events-compliance-resistance during chemoprophylaxis.

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Harris IE, Reid MP, Edstein MD. Population pharmacokinetics of mefloquine in military personnel for prophylaxis against malaria infection during field deployment. *Eur J Clin Pharmacol* 2007; 63: 271-278.

## **I-41 Marylore Chenel Developing an In Vitro – In Vivo Correlation Model Using a Population Approach in NONMEM**

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**Introduction:** *In vitro* drug dissolution-time profiles can be used to predict *in vivo* plasma drug concentration-time profiles if an appropriate mathematical model can be found to describe the *In vitro - In vivo* Correlation (IVIVC) defined by the FDA [1]. Such models are beneficial in terms of both time and cost savings as *in vitro* dissolution fractions can be used as a surrogate for clinical bioequivalence studies during the initial drug development process as well as with scale-up and post approval changes. Traditional methods are suboptimal under certain conditions [2,3]. A modelling approach based on differential equation system (DES) has been proposed [4,5].

**Objectives:** The aim is to illustrate, using clinical data, the implementation of a population approach to the development of an IVIVC model in NONMEM.

**Methods:** This study used observed plasma concentration profiles of 12 healthy volunteers following cross-over oral administration of immediate release (IR) and modified release forms as well as 6 *in vitro* dissolution profiles of molecule S. Three model-building steps were required. First a function, *f*, describing *in vitro* dissolution was selected. Secondly, a population PK model was fit to the IR data. Lastly, a model correlating the *in vitro* and *in vivo* dissolution-time profiles was developed, taking *f* and individual PK parameters from the IR model into account. Therefore, *in vivo* individual plasma concentration profiles were predicted directly in a one-step process from *in vitro* dissolution data. The percentage prediction errors (%PE) on observed and predicted  $C_{max}$  and AUC were calculated to evaluate the predictability of the model.

**Results:** A Gompertz function was used to describe *in vitro* dissolution. Individual PK parameters were taken from a 2-compartment IR model (with IIV on clearance, central volume, absorption rate constant and lag time). A cubic polynomial was used to describe the relationship between *in vitro* and *in vivo* dissolution. This IVIVC model, with separate *in vitro* and *in vivo* residual error models and variability between tablets and subjects, enabled the prediction of individual *in vivo* plasma concentration profiles. The %PE observed were less than 15%..

**Conclusions:** This work illustrates the application of a compartmental model-based Pop-PK approach to IVIVC model building, and provides a reliable method to help the initial drug development process.

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### **I-47 Jae Yong Chung Modelling of Atorvastatin Pharmacokinetics in relation to SLCO1B1 genotype and Simulations for Bioequivalence Study**

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**Objectives:** The pharmacokinetics of atorvastatin is affected by SLCO1B1 genotype and highly variable. This study aimed to assess atorvastatin pharmacokinetic profile and variability in relation to SLCO1B1 genotype by population pharmacokinetic modelling and to build up a clinical trial simulation approach for optimal bioequivalence (BE) design considering the genotype

**Methods:** The population pharmacokinetic analysis was performed using NONMEM7 based on plasma samples from a single dose PK with genotyping study in 28 healthy subjects. With the use of a two-compartment model with first order absorption, the influence of SLCO1B1 genotype on absorption rate constant and oral bioavailability was examined. The final pharmacokinetic model was used for clinical trial simulation of bioequivalence study. Simulation scenario consists of varying the sample size from 40 to 64 and variant genotype frequencies from 0 to 100%. Each study was simulated 300 times using TrialSimulator2.2.1 and the percent of successful BE results was calculated as a statistical power.

**Results:** The SLCO1B1 genotype showed a significant influence on atorvastatin pharmacokinetics. Oral clearance was 23 L/h, volume of distribution of steady-state was 180.5 L, inter-compartmental clearance was 43 L/h, the absorption rate constant was 1.51 h<sup>-1</sup> for wild-type and 0.82 for variant-type, and bioavailability was 7.2% for wild-type and 10.9% for variant-type. A large intersubject variability was found to affect atorvastatin absorption (CV 54.7%), and the residual variability was large (CV 48%). An inverse correlation between the percentage of SLCO1B1 variant-type and the success rate (power) of average BE were detected by clinical trial simulation. For achieving 80% power, minimum 46 subjects would be necessary and cut off for variant-type frequency in study population was 10%. For the 90% power, minimum subjects and the cut off were 64 and 30%, respectively.

**Conclusions:** The SLCO1B1 genotype frequency in study population may influence the success rate of bioequivalence study. Applying genotyping to subject screening could be a valuable option for a more efficient and successful approach to the BE study design of atorvastatin.

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## **I-57 Willem de Winter Dynamics of a Two-Receptor Binding Model: How Affinities and Capacities Translate into Long- and Short-Term Behaviour and Physiological Corollaries**

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**Objectives:** We show that data described by a two-receptor model may settle relatively quickly (months) at an apparent steady state, only to rise to a significantly higher final steady state over a much longer period over time (years). The objective of this project is to develop an analytical tool for making predictions about the long-term drug concentrations on the basis of short-term measurements, and for designing optimal dosing regimens.

**Methods:** The two-receptor model of Snoeck et al [1], one receptor having high affinity and low capacity, and the other having low affinity but high capacity, was analysed by means of simulations and mathematical analysis. Attention was paid to the relation between drug concentration in plasma and the concentrations at the two receptors. The analysis employed dynamical systems analysis and singular perturbation theory.

**Results:** Analytical expressions for the lower apparent steady state and the higher final steady state concentrations in plasma and at the receptors were derived and formulas for the time to the apparent and the final steady state were constructed. It was shown how the amount of drug in the large capacity receptor could eventually exceed that in plasma by far. Thus a tool was developed which can be used to predict long term concentrations in the different compartments on the basis of short term data about concentrations in plasma.

**Conclusions:** When relatively short term data point to a specific model, it is important to analyse the implications of this model for long term behaviour when chronic administration of the drug is considered. This can be done through simulations, but it is better still when analytic expressions are derived for the steady states and for time to steady state, in order to pinpoint the impact of different parameters on these quantities.

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### **I-59 Ivan Demin Longitudinal model-based meta-analysis in rheumatoid arthritis: an application towards model based drug development**

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**Objectives:** The aim was two-fold, first to quantify the longitudinal behavior of the key clinical measure of signs and symptoms (ACR20) in rheumatoid arthritis (RA), over time and across drug treatment and patient population and second, to apply this knowledge in the decision making process for an internal Novartis compound, canakinumab.

**Methods:** Summary level data was extracted from 39 phase II and III studies including data for all currently approved biologics (nine), in total 105 treatment arms and about 17,000 patients. The longitudinal meta-analysis model describes the full time course of ACR20 of all nine, currently approved biologics, standard of care (methotrexate) as well as true placebo across different patient populations.

**Results:** This provides insight into the clinical efficacy of the different treatment options and allows a quantitative assessment of the efficacy observed in clinical studies of existing biological treatments in RA. This knowledge was used retrospectively to assess a go/no go decision for canakinumab by incorporating the phase IIb results into the meta-analysis framework. The integrated analysis supported the interpretation that canakinumab had an effect on ACR20, however it also showed that the probability to be as good as the current most effective treatments in terms of the magnitude of effect was low, thereby supporting the decision not to progress canakinumab in RA.

**Conclusions:** This integrated approach, can be extended to any other compound targeting RA, supporting internal, and external decision making at all clinical development stages.

## **I-61 Vincenzo Luca Di Iorio Application of Stochastic Differential Equations to Disease Progression in a Neuropathic Pain Model in Rats**

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**Background:** In nonlinear mixed-effects modelling the variability may be decomposed into an inter-individual, an inter-occasion and a residual component. Stochastic Differential Equations (SDE) can be used instead of Ordinary Differential Equations (ODE) to further decompose the residual variability into system and measurement noise. The former may reflect true physiological fluctuations in the biological system, whilst the latter encompasses measurement errors and other unexplained sources of variability.

**Objectives:** The aim of this work was to evaluate the feasibility of using SDEs in a model of Neuropathic Pain in rats, as compared to the use of Ordinary Differential Equation.

**Methods:** Neuropathic Pain was induced in rats by Chronic Constrictive Injury (CCI), i.e. applying loose ligatures around the sciatic nerve. Paw Withdrawal Threshold (PWT), measured in grams, was used as a measure of response. For the current analysis only placebo data were available. PKPD models were built with both SDE and ODE. Subsequently, the models derived were used to perform simulation in order to compare performances of ODE and SDE. Several scenarios were also used to determine the impact of different sampling schedules on the predictive value of the models. Data analysis was performed in NONMEM v7. R was used for data manipulation, statistical and graphical summaries.

**Results:** Despite the increased complexity, the use of SDEs does not seem to capture time dependent changes in CCI-induced allodynia. The results of the simulations suggest that limitations in the sampling scheme may contribute to the limited performance of SDEs.

**Conclusions:** Our findings demonstrate that SDEs are a valuable tool in modelling of disease progression. However, their usefulness in capturing time-dependent oscillations in system-specific parameters is very sensitive to sampling frequency.

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### **II-03 Anne Dubois Clinical trial simulations to design a crossover study assessing the equivalence on the pharmacodynamic surrogate marker between an immediate and a modified release formulations**

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**Objectives:** After the marketing authorisation of a b.i.d. immediate release formulation (IR) of drug X, Servier developed three o.d. modified release formulations (MR) in order to improve patient compliance. A study comparing the pharmacodynamic surrogate marker (SM) between IR and at least one of the three MR has been planned. Modelling & Simulation techniques are playing a key role in designing this study in selecting the MR formulation(s), the equivalent doses of IR and MR, and the measurement times.

**Methods:** Plasma concentrations of the parent drug and its active metabolite, obtained from a crossover trial performed on 14 healthy volunteers (HV) in fasted conditions, were used to jointly model the IR and each MR formulation. The model assumes the same disposition for IR and MR. It takes account of the hepatic first pass effect and the transformation of the parent drug into metabolite. For the pharmacodynamics (PD), an agonist  $E_{max}$  PK/PD model was previously developed in HV to describe the time course of effect of the IR parent drug and its metabolite on SM. For each MR, we used the PK parameter estimates of the joint IR/MR PK model and the PD parameter estimates of the previously developed PK/PD model to simulate crossover trials on 24 HV at steady state. We simulated 100 trials with different doses. For each simulated trial, we performed an equivalence test on the daily mean SM assuming an equivalence interval of  $\pm 2$ , 3 or 5 SM units (SMu). For each MR, each tested dose and each equivalence interval, we computed the percentage of trials where the equivalence is demonstrated ( $P_{eq}$ ). This analysis was first performed assuming no food effect on the IR and MR PK and using a 28-measurement design. As a food effect was found on the IR but not on the MR, we also simulated with a food effect for the IR. At last, the impact of different measurement designs on  $P_{eq}$  was evaluated. We used NONMEM VI and SAS 9.1 for this analysis.

**Results:** Based on both simulations results and clinical relevance, the equivalence interval was fixed to  $\pm 3$  SMu. For this value, when an IR food effect was simulated with the 28-measurement design,  $P_{eq}$  was above 80% for the 3 MR formulations. Results were similar for all tested measurement designs.

**Conclusion:** The present clinical trial simulations were determinant to design the PD equivalence crossover study as its results allowed to choose the equivalence interval, the MR formulation, the equivalence dose and the measurement design.

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## II-02 Anne Dubois Pharmacokinetic bioequivalence analysis of biologics using nonlinear mixed effects modeling

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**Introduction:** Among the required information to assess the similarity between different formulations of biologics, a pharmacokinetic (PK) bioequivalence study is usually performed as for chemical drugs [1,2]. Bioequivalence tests are performed on the area under the curve (AUC) and the maximal concentration ( $C_{\max}$ ) computed by non-compartmental approach (NCA). However, this approach could be inappropriate in some cases such as sparse sampling designs or nonlinear PK which is often exhibited by biologics. Then, nonlinear mixed effects models (NLMEM) can be used to analyse such data [3,4]. In that context, our objective was to illustrate PK NLMEM-based bioequivalence analysis using two examples.

**Methods:** NCA-based tests and NLMEM-based bioequivalence Wald tests were performed on two PK datasets from studies comparing different biosimilars: a three-way crossover trial on somatropin [5] and a multiple dose parallel group trial on epoetin alpha [6]. To perform NLMEM-based bioequivalence Wald test, a statistical model taking account of formulation, period and sequence effects on all PK parameters was used. Between and within subject variability were included for all PK parameters. NLMEM analyses were performed using MONOLIX 3.1R2 [7]. For both examples, bioequivalence tests were performed on *the formulation effect* of AUC and  $C_{\max}$ . From the somatropin dataset, two sparse datasets were produced with twice less sampling times than the original: the optimised (OD) and empirical design (ED) datasets. For somatropin, we estimated the standard error (SE) of the formulation effect of  $C_{\max}$  by the delta method. Because of the nonlinear PK of epoetin alpha, its structural PK model is written with differential equations. So, the formulation effect of AUC and  $C_{\max}$ , and their SE were estimated through simulations of PK profiles using the fixed effect estimates and their Fisher information matrix. Furthermore, we estimated the formulation effect on the proportion of the dose nonlinearly eliminated (PDNE) in our NLMEM-based analysis.

**Results:** Somatropin PK was described by a one-compartment model with delayed first order absorption and first order elimination. For the complete and both sparse datasets, the bioequivalence criteria were met for AUC and  $C_{\max}$  using NLMEM and NCA. For NLMEM estimates, the geometric means of AUC and  $C_{\max}$  were similar for the three datasets. For NCA estimates, they were lower for OD dataset compared to complete and ED datasets. Epoetin alpha PK was described by a two-compartment model with linear and Michaelis-Menten elimination. The bioequivalence of AUC and  $C_{\max}$  was demonstrated using NCA and NLMEM. By NLMEM, the test/reference ratio of PDNE was estimated as 0.95 with a 90% CI of [0.72; 1.24].

**Conclusion:** NLMEM-based equivalence tests were performed on secondary parameters of the models. NLMEM and NCA results were similar thereby demonstrating that NLMEM can be used for equivalence testing.

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## **II-10 Charles Ernest Multinomial Markov-chain model of sleep architecture in Phase-Advanced Subjects (PAS)**

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Phase-advance is used to induce a state qualitatively similar to insomnia. Subjects are asked to begin trying to sleep several hours before their usual bedtime and remain in bed whether asleep or not. The ability of a drug to allow a subject to sleep during what is otherwise a normal wake time may predict efficacy of the drug in insomnia patients (IP). Recently, a mixed-effect Markov-chain model based on transition probabilities (TP) as multinomial logistic functions was developed on polysomnography (PSG) data after placebo dosing in IP [1,2].

**Objectives:** The aims were to examine the sleep architecture in PAS compared to IP over the first 8 hours and incorporate model enhancements to describe current PAS data.

**Methods:** PSG data were collected for 13 hours after placebo dosing to PAS from two studies at different sites. TP between sleep stages were modeled as multinomial logistic functions depending on nighttime (NT) and time elapsed since last change in sleep stage (STE). Modification to the model structure and predictors was investigated to accommodate the current data: 1) number of break points in the piecewise linear logit functions, 2) different likelihood of probability for each study based on relatively infrequent transitions and 3) study effect on individual TP. Model building was guided by log likelihood ratio test and AIC, posterior (PPC) and visual predictive checks (VPC).

**Results:** PAS generally displayed a lower transition frequency from one sleep stage to another, faster onset of sleep and different total time spent in sleep stages compared to IP. The model was fit to study data to describe the sleep architecture in PAS. There were significant differences between studies 1 and 2 for most transitions, excluding from SWS, during both NT and STE. VPCs and PPCs for the final model demonstrated general agreement between the statistics derived from raw and simulated data.

**Conclusions:** The PAS and IP displayed different sleep architecture over the first 8 hours. PAS generally had fewer transitions between sleep stages and generally displayed a higher propensity to stay in the existing sleep stage compared to IP. The multinomial mixed-effect Markov-chain model presented for IP was further developed with the intent of providing a useful tool for analyzing sleep data in PAS. The final model VPCs and PPCs demonstrated that the proposed model is sufficiently robust for describing data characteristics and dynamic behavior of the sleep process in PAS.

## **II-15 *Martin Fink* Diversity: Academia-Industry Collaborations on Modeling and Simulation to enhance Scientific Capability Development – The Novartis Experience**

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**Objectives:** Academic and industry collaboration for the advancement of science has a long history and track record of success. We investigate how the unique but complementary contributions and perspectives of each can create a fruitful synergism.

**Results:** We report on our experience of collaborations between the Novartis Modeling and Simulation Department (M&S) and several academic centres of excellence. These bring people with diverse scientific qualifications (engineering, biology/pharmacology, mathematics/statistics, clinical medicine), thinking and learning styles, and educational and demographic backgrounds from across the world to the same table. Scientists from the global Novartis M&S group are currently involved in academic collaborations in Europe, the USA and Africa. In this paper, we will present the benefits, challenges, and caveats in the conduct of academia-industry collaborations. This includes issues related to intellectual property, potential funding mechanisms, integration and inclusion aspects, and the benefits of obtaining different viewpoints that can leverage key strengths of the diverse partners. Expansion of our M&S academic collaborations to include scientific capability development in emerging countries provides opportunity for creating shared business value with scientific leaders across the full spectrum of geographical locations where the world's healthcare needs are located. The paper will emphasize the added value to both participants, e.g.

- Academia benefits via access to data, relevant research questions to development of new drug treatments, and opportunities for funding.
- Industry benefits via access to research into cutting edge methodologies, linkage to key scientific leaders and to well-trained scientists – who may also be future employees.
- Publications emanating are mutually beneficial - indicating productivity for academia, with increased visibility and credibility for the industry collaborators among the company's stakeholders (e.g. scientific community, Health Authorities, and patients).
- Investment in M&S in emerging countries requires modest investment for Pharma companies compared to the large infra-structure costs of building drug discovery and clinical research laboratories.

**Conclusions:** Our experience shows the value of academic- industry collaboration in modeling and simulation which we are committed to continue and expand in the future.

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## II-21 *Sathej Gopalakrishnan* Population PK/PD evaluation of the effect of dienogest on Hoogland Score in young healthy women

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**Objectives:** Dienogest (DNG) is a 19-nortestosterone derivative that exhibits selective binding to the progesterone receptor and displays neither agonist nor antagonist activity on androgenic, glucocorticoid or mineralocorticoid receptors. It is used for oral contraception and menopause management, as part of a combination treatment, and, as mono-preparation, for the treatment of endometriosis. The aim of our study was to develop a sequential PK/PD Model to characterize the concentration-response relationship with regard to Hoogland Score, a common tool to assess ovarian function.

**Methods:** The data was taken from 86 healthy subjects, who received DNG in daily oral doses of 0.5 mg, 1 mg, 2 mg and 3 mg over 72 days, in a single-center, randomized, double-blinded, dose-controlled study [1]. Individual AUC was selected as a predictor for the PD parameter Hoogland Score (HS), a categorical measure of the extent of follicular development. HS data were grouped into three levels: HS 1 or 2: no or minimal ovarian activity, HS 3 or 4: residual ovarian activity, and HS 5 or 6: ovulation. Subsequent to the development of a Population Pharmacokinetic (popPK) model, an EMAX-based proportional odds model was implemented in NONMEM VI to construct a PK/PD description.

**Results:** The popPK model developed was a linear two compartment model with first order absorption and linear elimination from the central compartment. Moderate interindividual variability (~25%) was estimated for oral clearance (CL/F) and central volume of distribution (V2/F). An EMAX based proportional odds PD model, driven by AUC, of the form  $\text{Effect} = \text{EMAX} \cdot \text{AUC}^G / (\text{AUC}^G + \text{AUC50}^G)$  with  $G=1$ , was used. The model converged successfully with acceptable relative standard errors (<35%) for all parameters. The estimates were  $\text{EMAX} = 10.1$ ,  $\text{AUC50} = 0.3 \text{ mcg} \cdot \text{h/mL}$  (fixed to observed mean AUC for medium effect - i.e. a HS of 4),  $\text{ODDS1}$  (for HS less than or equal (LE) 2) = -6.27 and  $\text{ODDS2}$  (for HS LE 4) = 3.53. Different Hill coefficient possibilities were looked at and  $G=1$  adequately described the data. The predicted probabilities were in excess of 0.5 for a HS LE 2 and in excess of 0.9 for a HS LE 4, even for relatively moderate DNG exposures of  $0.5 \text{ mcg} \cdot \text{h/mL}$ , for the 2 mg dose group.

**Conclusions:** The PK/PD evaluation shows that DNG AUC is a good predictor for PD response in terms of Hoogland Score using a proportional odds model. The model may be further used for the prediction of ovulation inhibition based on DNG exposure.

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## **II-37 Manish Gupta Application of Two-Target Quasi-Steady-State (QSS) Model in Population Pharmacokinetic and Pharmacodynamic (PK-PD) Modeling of MNRP1685A in Cynomolgus Monkeys**

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**Objectives:** MNRP1685A (anti-NRP1) is a fully human IgG1 monoclonal antibody against neuropilin-1 (NRP1), a protein necessary for blood vessel maturation. Anti-NRP1 showed strong nonlinear PK across a wide dose range in preclinical species. It is currently evaluated in Phase I studies as a single agent and in combination with bevacizumab with or without paclitaxel. MNRP1685A binds to both membrane-bound (mNRP1) and circulating (cNRP1) targets. The purpose of the study was to develop a mechanism-based model to simultaneously describe the kinetics of MNRP1685A and total cNRP1 in monkeys; thus to understand the nonlinear PK of MNRP1685A and to support pharmacological dose selection.

**Methods:** MNRP1685A was dosed in monkeys at 0.5, 3, 15, or 50 mg/kg (single dose) or 10, 30, or 100 mg/kg (9 weekly doses). Serum samples for MNRP1685A and total cNRP1 were collected at predose and various time points from 15 minutes up to 56 days post dose. The analysis was performed in NONMEM using FOCE with interactions. The two-target QSS model was applied to describe cNRP1 and mNRP1. Model performance was tested with diagnostic methods including visual predictive check. Free cNRP1 and mNRP1 levels were simulated based on model fitting results.

**Results:** The concentration-time profiles of both MNRP1685A and total cNRP1 after single-dose or multiple-dose administrations in monkeys were well described by the two-target QSS model. Parameters for MNRP1685A, mNRP1, and cNRP1 were estimated with reasonable precision. Nonspecific CL and V1 were estimated to be 3.26 mL/day/kg and 38.2 mL/kg, respectively. Maximum elimination rate through mNRP1 was 98.8 nM/day. For cNRP1, the model-derived rates of degradation, synthesis, and internalization were 1.53 day<sup>-1</sup>, 3.8 nM/day, and 0.260 day<sup>-1</sup>, respectively. QSS constants for mNRP1 and cNRP1 were 6.94 and 2.8 nM, respectively. Simulation results suggest that both mNRP1 and cNRP1 can be blocked by MNRP1685A in a dose and dosing frequency-dependent manner.

**Conclusions:** The two-target QSS model provides mechanistic understanding of the nonlinear PK of MNRP1685A. Modeling results suggest minimal impact of cNRP1 but major impact of mNRP1 on MNRP1685A PK; cNRP1 has higher binding affinity to MNRP1685A than mNRP1. The model was able to provide precise estimates of both soluble and membrane target parameters, which is potentially useful to select clinical dose/regimen that can saturate targets.

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## **II-38 Serge Guzy Optimizing The Entire Drug Development Process Using Pharmacometric Tools: From Preclinical To Marketing**

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**Objectives:** This study concentrates on T2D patients where the main goals were to characterize the PK correlation with a PD biomarker, to propose the optimal trial conditions for the upcoming Phase 2 trial, to estimate using the PK/PD model results the probability of technical success (PTS) for Phase 2 using the target Product Profile criteria and finally modifying the current decision analysis based estimation of the product value (Expected Net Present value, ENPV) using the model based estimation of the Phase 2 PTS.

**Methods:** The Monte Carlo Expectation Maximization algorithm combined with importance sampling [1, 2] was the tool from which we perform all the fitting procedures. The Precision tree software (Precision Tree) was used to build an interactive program of the product market forecast. The risk analysis software (RISK) was combined with Precision Tree to quantify the uncertainty in all the business related parameters of the decision tree program .

**Results:** The Preclinical analysis helped defining the PK model and the dosing conditions for the subsequent Phase 1 trial. The Phase 1 PK/PD model included semi mechanistic as well as engineered based processes that could mimic in particular a special Bell-shape dose response relationship showing that the response increases first with dose but then starts to be inhibited at large doses. The PK/PD model analysis was used to predict the optimal conditions for the Phase 2 trial. The criteria for Phase 3 go/no go (PTS) was defined from which the PK/PD model combined with parametric bootstrap and uncertainty analysis resulted in a distribution assessment for the Phase 2 PTS. Decision tree analysis was finally performed and resulted in an updated ENPV for the product that took into consideration the information retrieved from the data using the PK/PD population modeling approach.

**Conclusions:** PK/PD modeling combined with decision analysis allow changing dramatically the forecast of the Product value from the sponsor's side (part of the pie the sponsor would get in the deal). The modeling of the PK/PD correlation leads to an estimate of the PK/PD parameters as well as their uncertainty. These sets of parameters were used to estimate the PTS distribution for Phase 2 and how it would result in a new estimate of the all the possible ranges of the ENPV for the product. The new average ENPV increased by a almost 80% compared to the original estimate that did not consider the PK/PD modeling output results.

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**2006;79(2):P28**

## **II-50 Candice Jamois Title Pharmacokinetic-Pharmacodynamic Modeling of the Relationship between Aleglitazar Exposure and Lipids Response in Type 2 Diabetes Patients.**

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**Objectives:** To develop population pharmacokinetic-pharmacodynamic (PK-PD) models describing the relationships between selected efficacy parameters, TG, HDL-C and LDL-C and aleglitazar exposure in patients with T2DM.

**Methods:** Data from SYNCHRONY, a 16-week phase 2 dose-ranging study which evaluated 4 doses of aleglitazar (50, 150, 300 and 600 mg), were used to investigate the relationship between aleglitazar exposure at steady state (SS) and the subsequent lipid response. Non linear mixed effect approaches, using NONMEM, were used to characterize the pharmacokinetic (PK) and the exposure-response relationships (PK-PD) of aleglitazar. TG, HDL-C and LDL-C response were analyzed separately and related to aleglitazar exposure at steady-state (AUC). Emax and power models were tested to describe the relationships between aleglitazar exposure and TG, HDL-C and LDL-C. Effect compartments were used to describe the link between PK and lipids parameters. Simulations were performed to evaluate the predictive performance of the PK-PD models and to illustrate in a large population of T2DM patients the expected lipids response at SS.

**Results:** Plasma concentrations of aleglitazar over time were accurately described by a two-compartment disposition PK model with first-order absorption and first-order elimination. Significant Emax relationships were established between the AUC of aleglitazar at SS and the decrease observed in LDL-C and TG in SYNCHRONY, while a power model adequately described the relationship between AUC and HDL-C increase. The effect mean equilibration half-life was 18.7, 4.1, and 8.7 days for HDL-C, LDL-C and TG respectively. The steady-state of the effect was reached in approximately 13, 3 and 6 weeks for HDL-C, LDL-C and TG respectively. At steady-state, the respective TG and LDL-C mean decrease from baseline were estimated to 81 and 49%. The slope parameter was estimated to  $1.9 \cdot 10^{-2} \text{ day}^2$  for HDL-C. Visual predictive checks have confirmed the good predictive qualities of these models. Subsequently, the three exposure-response models were used to explore the response at SS in a large population of 1000 patients.

**Conclusion:** Population PK-PD analyses confirmed the clinical efficacy of aleglitazar on dyslipidemia in T2DM patients. The effects of these population PK-PD parameters will be evaluated in an ongoing prospective cardiovascular outcome study to assess the impact of improvements in lipid parameters on reducing the cardiovascular sequelae of T2DM.

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## **II-51 Hyewon Jeon A Population Pharmacokinetic/pharmacodynamic Approach of Drug X in Healthy Korean**

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**Objectives:** Drug X is a selective arginine vasopressin (AVP) V<sub>2</sub>-receptor antagonist which is used for treatment of acute and chronic hyponatremia. The aim of this study was to develop the population pharmacokinetic (PK) and pharmacodynamic (PD) model of Drug X in healthy male Koreans.

**Methods:** A dose-block randomized, double-blinded, single-dose study was performed to evaluate pharmacokinetics and pharmacodynamics of 15, 30, and 60 mg of Drug X. Blood samples were collected up to 48 hours after drug administration. Free water clearance was estimated from 24-hour urine excretion rate (0-4, 4-8, 8-12, 12-24 hour interval), urine and plasma osmolality. Baseline for pharmacodynamic endpoints was the value of the predose sample. A non linear mixed-effect modeling approach, using NONMEM 7 (version 7.1.2) was implemented in modeling plasma Drug X concentration-time profiles and free water clearance of each timepoint.

**Results:** A total of 473 concentrations from 36 subjects were included in population analysis. Drug X concentrations were best described by a two-compartment model with first-order absorption and elimination. The estimate of pharmacokinetic parameters and inter-individual variability (IIV, % CV) for clearance (CL) was 15.5 L/h (30.3), central volume of distribution (V<sub>2</sub>) was 49.3 L (12.9), inter-compartment clearance (Q) was 15.3 L/h (31.8), absorption rate constant (K<sub>A</sub>) was 0.27 h<sup>-1</sup> and peripheral volume of distribution (V<sub>3</sub>) was 1360 L. Posthoc Bayesian predicted concentrations of effect compartment were used for estimate PD using sigmoid E<sub>max</sub> model. The estimated E<sub>max</sub> and baseline of free water clearance were 7.99 and -0.63 mL/min, respectively. The exposure associated with a 50% increase (EC<sub>50</sub>) (IIV, % CV) was 48.6 µg/L (24.5) and Hill's coefficient was 1.1.

**Conclusions:** A PK/PD model was utilized to characterize the effect of Drug X on the free water clearance. Further studies will be needed to investigate the influence of subject's characteristics and mechanisms related to arginine vasopressin V<sub>2</sub> receptor.

**Acknowledgments:** The clinical study was supported by funds from Korea Otsuka Pharmaceutical Co., Ltd.

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## **II-59 Thomas Kerbusch Phase 2b dose selection for the treatment of autoimmune disorders leveraging comparator data**

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**Objectives:** Selection of dose levels for Phase 2b development resulting in an optimal probability to: (1) establish the plateau of the dose-response curve, (2) demonstrate a dose-response relationship, (3) determine the lowest dose resulting in maximal efficacy.

**Methods:** SCH900XXX Phase 2b doses were selected with a model-based comparative efficacy analysis across 5 comparators (adalimumab, etanercept and infliximab (TNF $\alpha$  antagonists) and ustekinumab and briakinumab (p40 antagonists)) using published mean study-arm level data (> 10,000 patients) and in-house Phase 1b data of SCH 900XXX. Drug potencies were compound-specific, but onset of action and Emax were assumed similar across all comparators and comparator class, respectively. Clinical trial simulations were used to select a dose range bracketing a dose resulting in maximum response and ED50.

**Results:** Despite the availability of very limited Phase 1b data on SCH900XXX, the comparative efficacy analysis resulted in adequate estimation of the model parameters with an acceptable level of uncertainty. The dose-response model was used for comparative landscape evaluation to predict the efficacy of SCH 900XXX relative to its comparators. Establishing dose-response in Phase 2b requires a dose level between placebo and plateau. The probability that doses of 5 and/or 25 mg were (1) less effective than the maximal response and (2) more effective than placebo was demonstrated to be high. Doses of 100 and 200 mg were predicted to be at the plateau of the dose-response relationship. A 40-fold dose-range 5-200 mg brackets a dose resulting in maximum response ( $\geq 50$  mg) and ED50 (8.4 mg, 80% CI 3.0-21.2 mg). The selected SC doses 5, 25, 100 and 200 mg SCH 900XXX were predicted to allow for (1) establishment of the plateau of the dose-response curve, (2) demonstration of a dose-response relationship, (3) model-based determination of the lowest dose resulting in maximal efficacy. The recommended Phase 2 dose levels of SCH 900XXX were 5, 25, 100 and 200 mg.

**Conclusions:** The value proposal of the modeling was that a more informed and robust decision could be made by leveraging comparator data to support the limited internal data. This greatly enhancing the probability of success of establishing dose-response in the Phase 2b study.

### **III-13 Lay Ahyoung Lim Development of a longitudinal model for characterizing adverse events of psychiatric drugs in routine clinical care**

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**Objectives:** In routine clinical care of psychiatric patients, the early treatment is important because adverse events (AEs) in this period often lead to noncompliance to a drug and lowering the therapeutic effect. This study aimed to develop a longitudinal model to describe early-phase AEs in Korean psychiatric patients in an effort to be used as a guide to improve medication compliance and drug efficacy.

**Methods:** Data were collected retrospectively from the medical records of outpatient clinic in Severance hospital, Seoul, Korea, involving 150 patients treated with anxiolytics or antidepressants. Data were censored on day 60 from their first visit. Using NONMEM 7, three different longitudinal models were developed within a mixed-effect model framework to describe the incidence, the time-to-event (TTE), and the count of AEs. The hazard function to describe censored data or dropout was chosen to be a constant for the incidence model and the Weibull function for TTE and count models. For the incidence model, a first order Markov element was also included. To evaluate the model performances, visual predictive check (VPC) was performed using 100 datasets simulated from each model using estimated parameters.

**Results:** The most frequently observed AE was drowsiness. About 30% of the patients reported AE more than once during the observed period. For the incidence model, a Markov element added in the baseline logit adequately described the data. Incorporating an exponential decay function as a time effect further improved the model, dropping OFV by 134.28. VPC showed good the performance of the model. For TTE model, the estimated shape parameter of hazard function was 2.08, indicating the hazard probability increasing with time, and VPC showed the prediction somewhat overestimated. Of several models, the Weibull hazard model dropped the OFV most significantly in both TTE and count models.

**Conclusions:** Our preliminary results show that the incidence model described the data well whereas the TTE model needs to be further developed. To generalize our results, more work will be necessary, including assessing covariate influence on AEs with more patients. Including severity into the model will further improve the applicability of the model if such information is available.

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### **III-22 *Hugh McDevitt* Technology Roadmap to Support Model Based Drug Development**

Hugh McDevitt, Martin Spendiff, Henning Schmidt, David A James, Vincent Buchheit  
*Novartis*

#### **Objectives:**

Modeling and simulation has become firmly established over the last decade in the pharmaceutical development sector of the industry with most organizations establishing modeling and simulation groups. To support these groups highly specialized computing services are required that provide the required computational power but at the same time will stand up to regulatory scrutiny. The purpose of this poster is to solicit feedback and discussion on how best to solve the challenges we all face in order to best support model based drug development into the future.

#### **Methods:**

1. Identify the opportunities
2. Prioritize the different needs
3. Deliver the required infrastructure
4. Review progress

Emerging technology and increasing computing power offer many possibilities to facilitate modeling and simulation activities. However, not all these technologies can be introduced at the same time so priorities have to be set. Delivering quality solutions that create real value is essential. Reviewing and adapting plans based on experience ensures resources are deployed in the best manner possible.

#### **Results:**

Several areas of interest can be identified:

1. Emerging modeling algorithms
2. Industrialization of model based drug development
3. Knowledge Management

NONMEM improvements and monolix are some of the new algorithms we are considering. Integrating the work environment and making the web browser the main entry point improve productivity and compliance. Reusing and extending the previous modeling efficiently is also a key driver to increase productivity.

#### **Conclusions:**

Technology and computing power are essential to the effective application of model based drug development. High performance computing is now well established but there is still work to be done to integrate all the steps for maximum efficiency. With continuing cost pressures and ever

increasing demands for computing power the industry must come together to increase productivity cost effectively and deliver on the promise of model based drug development. How can the industry and academia come together to deliver the best possible technology platform?

### **III-27 Enrica Mezzalana Title: Quantitative Assessment of First Night Effect in a Polysomnographic Insomnia Study through a Multinomial Mixed-Effect Markov-Chain Model**

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**Objectives:** Sleep structure recorded in a laboratory is distorted, particularly during the first night [1]. This phenomenon, called First Night Effect (FNE), is likely due to change in sleeping environment or discomfort caused by electrodes. The FNE may significantly influence the reliability of a single-night study, therefore drug efficacy is usually evaluated on the average of two nights. A multinomial mixed-effect Markov-chain model has been recently validated for describing sleep structure in primary insomnia [2,3]. The aim of this work was to apply this model to assess the impact of FNE on sleep structure.

**Methods:** Data were obtained from the first two nights of a polysomnographic study in insomnia patients treated with placebo. Each individual sequence of sleep stages (awake (AW), stage 1 (ST1), stage 2 (ST2), slow-wave sleep (SWS), and REM sleep) was treated as a Markov-chain and transition probabilities were modeled as piecewise-linear multinomial logistic functions of time [2,3] in NONMEM VI. Transition probabilities among the different stages were separately estimated from night 1 and 2.

**Results:** Most of the probabilities were well characterized in terms of parameters precision (SE<25%). Model predictions showed a small difference between night 1 and 2 in the typical transition probabilities from AW and ST1. During the whole first night the probability of staying awake was slightly higher ( $\Delta=4\%$ ) compared to the second night while the transition probability from AW to ST1 was reduced ( $\Delta=4\%$ ). Moreover in the first two hours of night 1, the transition probabilities from ST1 to AW and from ST1 to REM sleep were 8% higher and lower respectively, resulting in a lower probability of staying in ST1 ( $\Delta=8\%$ ).

**Conclusions:** FNE is characterized by an increased probability of staying awake as a result of a lower probability to go from AW to ST1 and a higher probability of moving from ST1 to AW in the first part of the night. Moreover, transitions from ST1 to REM appeared to be less likely at night 1. These results are consistent with the observed sleep parameters for night 1: reduced total sleep and REM sleep time, increased intermittent wake time and longer latency to REM sleep. Overall FNE appeared more marked in the first part of the night and not sufficiently large to invalidate the one-night PSG assessment. In conclusion, the multinomial mixed-effect Markov-chain model is a valuable quantitative tool to interpret sleep structure differences induced by FNE.

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### **III-31 Flora Musuamba-Tshinanu KPD modelling of trough FEV1 in chronic obstructive pulmonary disease (COPD).**

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**Objectives:** FEV1 (forced expiratory volume in one second) is the most frequently used endpoint in clinical trials in COPD, with change from baseline ( $\Delta$ FEV1) corrected for placebo being the primary measure of efficacy. However, this approach ignores the time course of disease progression, which partly contributes to failure in identifying treatment effects in longitudinal studies in COPD. Recently, a KPD modelling approach was proposed to characterise the time course of treatment effect which overcomes some of the limitations associated with lack of pharmacokinetic data [1].

The aims of this investigation were: (1) to develop and validate a KPD model to describe the time-course of FEV1 in COPD including relevant patient demographics- and disease-related covariates; (2) to explore the influence of these covariates on the outcome of clinical trials.

**Methods:** A KPD model was developed using data from 6 Phase III studies, in which placebo and two different active drugs (salmeterol and tiotropium) were available. Patient demographics and disease related factors were tested as covariates on model parameters. Model diagnostics and performance included bootstrapping, visual predictive check and NPDE. Subsequently, simulations were performed to evaluate treatment effect across different scenarios. Scenarios were based on a typical placebo-controlled parallel group design with 100 and 150 patients per treatment arm. The influence of relevant covariates on the treatment effect size ( $\Delta$ FEV1) was explored by varying drug dose levels and inclusion and exclusion criteria (i.e., reversibility to salbutamol/albuterol, disease severity, gender, body height and previous use of inhaled corticosteroids (PICS)). NONMEM v.7.1.2 and R were used in an integrated manner for data handling and subsequent statistical analysis. Statistical significance of the treatment effect was assessed using mixed effect for repeated measurement modelling.

**Results:** The use of a KPD model permits the characterisation of the time course of FEV1 in the absence of PK data. Severity, gender, PICS and body height were found to affect baseline FEV1, whilst reversibility and severity are covariates on drug-related parameters ( $E_{max}$ ). Our results show that covariates do not only alter the treatment effect size at completion of treatment, but can also influence the onset of response.

**Conclusions:** Demographic and disease-related factors can affect the decline of FEV1 during the course of treatment in COPD patients. Model-based simulations should be used prior to the design of a clinical protocol to assess the implications of patient stratification and other relevant confounders on treatment outcome in COPD trials.

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### **III-44 Zinnia Parra Target Mediated Drug Disposition Model to Describe the Expression and Kinetics of IL12 And IFN $\gamma$ in Gene Therapy**

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**Objectives:** Interleukin-12 (IL12) has shown to have a great therapeutical potential in the treatment of chronic hepatic diseases [1]. Nevertheless its in vivo efficacy is hampered by a negative feedback mediated by the interferon  $\gamma$  (IFN $\gamma$ ) produced in response to this cytokine [2]. A model able to describe the relationship between IL12 and IFN $\gamma$  has already been developed when constant doses of mifepristone (RU, inductor of the gene expression of IL-12) were administered [3]. The aim of the study is to challenge an improved the previously developed model when knock-out mice for the receptor of the IFN $\gamma$  are used or when increasing doses of the mifepristone are administered under different dosing regimens.

**Methods:** Knock-out and wild type mice were infected with gutless adenoviral vectors containing a mifepristone (RU486)-inducible system for liver-specific expression of interleukin-12. Daily induction of constant or increasing doses of RU was performed and levels of IL12 and IFN $\gamma$  were measured. Berkeley-Madonna, R and NONMEM VII softwares were used to develop the model.

**Results:** A target drug mediated disposition (TMDD) model for the IL12 successfully described the wild type mice observations when constant doses of RU were administered. However, simulations of the model, where decreasing elimination rates of IFN $\gamma$  were used to emulate the knock-out mice conditions, were not able to describe the profiles of these mice. The introduction of a second TMDD [4] for the IFN $\gamma$ , and an indirect response model mediated by the bound IFN $\gamma$  instead of the free molecule, allowed a good description of the complete set of experimental data. Finally, an Emax model was introduced to account for those experiments where increasing doses of RU were administered.

**Conclusions:** A kinetic-pharmacodynamic model able to describe jointly the IL12 and IFN $\gamma$  profiles observed both, in wild type and knock-out mice, through diverse experimental conditions has been developed.

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**III-52 Olivier Petricoul From Animal to Human with a new monoclonal antibody: An example of the use of pharmacokinetics only to assist on the choice of first in human dose.**

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**Objectives:** Drug A is a fully human antibody that binds with high affinity to a ligand binding site on Cells C. Drug A is able to induce expansion of Cells C in normal young mice, young and old rats and cynomolgus monkeys. The objective of this analyze was to assist in obtaining a minimally acceptable biological effect level (MABEL) in Human.

**Methods:** The pre-clinical program included four studies in rats (N=2) and cynomolgus monkeys (N=2) that showed clear concentration/response relationship with Target Mediated Drug Disposition (TMDD). However, no ligand concentrations and receptor occupancy data could be obtained and thus a full mechanistic PKPD model could not be identified. Therefore, the PK profile was taken as an auxiliary biomarker that can be used for dose selection in human (assuming similar TMDD in human).

**Results:** The TMDD observed with rat and cynomolgus data is most likely related to a loss of target saturation below a threshold concentration. Moreover, it was shown that the PD effect took place with saturation of receptor only, i.e. in the linear portion of the PK profile. For a rapidly accessible target, saturation of clearance and target are equivalent, and the point of inflection in the exposure profiles indicating TMDD was interpreted as the point of transition between receptor saturation and first-order clearance. In humans, doses of 0.1 to 30 mg/kg were predicted to give receptor saturation rates in the range of 30 to 99.9%.

**Conclusion:** Preliminary results from the First in Human study confirmed the predictions from allometric scaling using PK only.

### **III-57 Gregory Pinault A structured approach to industrialize the data sourcing to support model based drug development**

Pinault Gregory, Ette Georges, McDevitt Hugh, Steimer Jean-Louis, Buchheit Vincent  
*Novartis Pharma AG*

**Objectives:** The Novartis Modeling & Simulation (M&S) programmers recently revisited and harmonized their individual experiences of building modeling ready data files from clinical databases and other sources. The authors would like to highlight the different steps undertaken to industrialize the crucial part of any modeling activity which is the data preparation

**Methods:** As M&S staff increased over the past years [1], the experience and variety of ways to deliver data has also evolved and expanded. Meanwhile, the value of M&S support for key decisions at key stages in the drug development process is now widely recognized and is expected to increase as model based decision making is embedded within the wider organization of Novartis Development. Consequently, any model based analysis is now likely to be reported to health authorities. This implies state of the art preparation and validation [2] of the data. To face the increasing demand in a strict regulatory environment, the authors lead the industrialization of data preparation by revisiting the modeling data file composition, the programming organization, and the data request tracking and management.

**Results:** The number of clinical parameters of interest and the subjectivity of the modeling approach to investigating the available data, lead to inconsistencies between data requests. The regulators expect validation of data prepared for a modeling analysis to be submitted to them, which impacts the department resources. The request specifications have been fine tuned by identifying classes of variables and defining the key common properties to characterize them. This puts the focus of standardization on the methodology rather than the data output. The carry over of programs amongst individuals and projects has been optimized by simplifying the programming framework and workflow. In alignment with the two previous work streams, a request tracker has been designed. Every data request is saved in a database, which can then be used to build activity reports for management and more.

**Conclusions:** Industrialization of M&S activities implies faster and better access to validated data. Enhancing the process of bringing the required data together is laying the foundation for further industrialization [3]. The authors believe it is one step forward in blurring the boundaries between data sourcing and exploratory modeling.

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### **III-65 Martijn Ruppert Population PK/PD Modeling of a Hepatitis C NS3 Inhibitor**

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**Objectives:** ACH-0141625, currently in development for treatment of HCV infection, is a potent inhibitor of HCV NS3 protease suited for once daily oral dosing. The aim of this modeling exercise is to evaluate several candidate dosing regimens on their impact on PK and viral load.

**Methods:** A pharmacokinetic model was built in NONMEM v6 using data from a randomized, double-blind, placebo controlled dose escalating phase 1 study on both healthy volunteers and hepatitis C infected subjects. Absorption was described with a time-dependent first order absorption rate. An increase in bioavailability for subsequent intakes was implemented, as well as a food effect. Subsequently, individual PK curves were linked to anti-viral activity using a viral dynamics model as described by Neumann et al.[1] Due to a prolonged anti-viral effect after the end of treatment, efficacy was related to concentrations in an effect compartment. Simulations were performed to assist in choosing a next dosing level, to evaluate the necessity of a loading dose and to assess the anti-viral effect for several different dosing schemes.

**Results:** A VPC confirmed that the PK model described the data well. Bioavailability for multiple dosing increased 3-fold for fasted intakes and 6-fold for fed intakes. Simulations showed that a loading dose can be used for reaching near steady state after one intake, but that the effect on viral inhibition is negligible. Estimates for EC50 and EC90 were obtained by linking anti-viral efficacy to individual PK curves. The effect-site equilibrium delay rate constant implied that steady state at the site of action will be reached in about 3 days. Simulation showed that all patients receiving 200 mg QD fed, 200 mg QD fed with an accidental fasted intake at steady state or 200 mg QD fasted would reach trough concentrations at the site of action above the EC50. Corresponding fractions of patients reaching trough concentrations above EC90 are 100%, 99.8% and 98.4%, respectively.

**Conclusion:** Viral load was described well using a viral dynamics model as described by Neumann but with the effect linked to an effect compartment. As fluctuations in concentration at the site of action are small, it shows that average plasma concentrations are more relevant than plasma C<sub>0h</sub>.

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#### **IV-02 Tarjinder Sahota Parameterisation of biomarker response in the assessment of long term safety**

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**Objectives:** Despite major regulatory concern regarding long term safety, traditional methods are still applied to the evaluation of the so-called safe drug exposure, often expressed as AUC and CMAX. Given current understanding of PK, PD and disease processes, these parameters are unlikely to be predictive of long term toxicity.

We use naproxen as a paradigm compound to assess the ability of current preclinical experimental protocols to provide necessary information for predicting drug-induced effects in humans using nonlinear mixed effects modelling (NLME). We determine the feasibility of parameterising drug exposure in terms of biomarkers (prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and thromboxane B<sub>2</sub> (TXB<sub>2</sub>)) for prediction of target related toxicity in rodents (ulcer formation). We then show that extrapolations based on these biomarkers can be used to predict treatment effects in humans.

**Methods:** A general toxicity study protocol was conducted in rodents according to standard practice with the exception of biomarker samples being collected at PK sampling times. PKPD modelling was performed in NONMEM VII. Model validation included VPCs, NPCs, and NPDE analysis. Translation to drug effects in humans took account of expected differences in the therapeutic exposure in patients. The accuracy and precision of predictions were assessed using literature data in humans. Measures of exposure (dose strength, AUC<sub>τ</sub>, CMAX<sub>τ</sub>, cumulative AUC, area under % inhibition curve (AUIC<sub>τ</sub>), maximum inhibition IMAX<sub>τ</sub>, cumulative AUIC) were tested for their ability to predict gastric ulceration in rodents as measured by % surface area of the stomach. Measures were compared for predictive performance with ulceration by modelling the exposure-risk relationship in NONMEM and comparing model diagnostics.

**Results:** The PKPD model showed good model performance and concordance with literature data in humans. The exposure-risk model with the best goodness-of-fit for gastric ulceration was cumulative TXB<sub>2</sub> inhibition.

**Conclusions:** NLME was used to characterise PK and PKPD relationships for relevant biomarkers without increasing the experimental burden of toxicity study protocols. Parameterisation of drug effects in terms of cumulative TXB<sub>2</sub> inhibition provided good prediction of the adverse events in rodents and predicted drug effect in humans. The use of systemic exposure as surrogate for target engagement in toxicology experiments must be revisited, as it may lead to inaccurate decisions regarding drug safety.

### **IV-07 Yi SoJeong Population Pharmacokinetics of a Novel Proton Pump Inhibitor, Drug Y, in Healthy Volunteers**

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**Objectives:** A new proton pump inhibitor (Drug Y) is under clinical development for management of gastroesophageal reflux disease. The aim of this study was to characterize pharmacokinetics of Drug Y by population approach following single and multiple oral doses in healthy volunteers.

**Methods:** In the first-in-human study of Drug Y, healthy volunteers were administered orally single or multiple dose of Drug Y (single dose, 30 to 800 mg; multiple dose, 100 mg once daily for 7 days). The effect of food on the pharmacokinetics was evaluated following single dose of Drug Y 600 mg. Nonlinear mixed effects modeling methodology was implemented in the population pharmacokinetic analysis using NONMEM<sup>®</sup> (version 6.2). After the Drug Y model was developed, food effects on drug absorption were investigated as categorical covariates. The first-order conditional estimation (FOCE) method was used to fit the plasma concentration-time data. Standard goodness-of-fit diagnostics and posterior predictive checks were used to evaluate the adequacy of the model fit and predictions.

**Results:** A two compartment model with first-order absorption, absorption lag time, and first-order elimination characterized the pharmacokinetics in 1175 concentrations of Drug Y from 63 healthy volunteers. Population mean estimates (standard error) of oral clearance (CL/F), central volume of distribution (V/F), inter-compartment clearance (Q), and peripheral volume of distribution (V<sub>2</sub>) were 473 (47.6) L/h, 99.1 (19.8) L, 269 (47.5) L/h, and 5930 (1470) L, respectively. Diagnostic plots results stratified by dose suggest that pharmacokinetic parameters are dose-independent within the dose range tested (30 to 800 mg). At fed status, relative oral bioavailability, absorption rate constant (k<sub>a</sub>), and absorption lag time were increased compared to those at fast status. Most of the data were within 5th and 95th percentile in visual predictive check, which indicated that the model describes the pharmacokinetics of Drug Y adequately.

**Conclusions:** The pharmacokinetics of Drug Y was characterized adequately by a two-compartment model with first-order elimination, and food intake affect absorption of Drug Y. This model can be used for modeling and simulation and to predict Drug Y exposure in patients.

## **IV-13 Andreas Steingoetter A population pharmacokinetic model for Gd-DTPA in DCE-MRI**

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**Objectives:** In dynamic contrast enhanced magnetic resonance imaging (DCE-MRI), the kinetics of an injected contrast agent (Gd-DTPA) can be simultaneously observed within multiple tissues. Due to MRI specific obstacles, however, kinetics in the plasma cannot directly be measured. In 2 compartment models commonly applied in DCE-MRI [1,2], these data are approximated from previous data and assigned to all subjects. These models disregard the individual variations in circulation time and those by systemic drug effects, and cannot model the multiple in normal and tumor tissue. The integration of multiple simultaneously acquired tissue concentration curves within a study population allows for the development of more complex models. Based on population nonlinear mixed effects modeling (popPK), this study was aimed at developing and evaluating a robust multi-compartment model for Gd-DTPA in a rat tumor model.

**Methods:** 33 data sets with concentration curves of tumor, muscle and liver were included for popPK modeling. Each curve consisted of 150 samples (every 6 sec). Tumors were classified into four levels of necrosis as determined by histology. All popPK analyses were performed with full MCMC Bayesian analysis method using NONMEM® 7.1. Initial parameter estimates were calculated by SAEM. The burn-in phase consisted of 3000 Bayes samples. Model parameters were estimated using 3000 Bayes samples. Structural model building was based on physiological and histological considerations, standard numerical criteria and supported by anatomical evidence. Bayesian chain plots (CP), CWRES, OFV, standard error (SE) of parameters and DIC were applied as selection criteria.

**Results:** With 3 observed compartments, the final model consisted of 3 serial muscle and liver compartments branching off the central compartment and 2 serial tumor compartments branching off the first liver compartment. CP, CWRES, OFV, SE and DIC confirmed the superiority of this final model in comparison to all reduced models. The covariate model building highlighted an effect of tumor necrosis as well as heart rate on the Gd-DTPA kinetics.

**Discussion:** A multi-compartment model for Gd-DTPA is presented. Based on standard numerical model building and selection criteria the presented model is not over-determined. Covariate analysis demonstrated that this model can detect changes in tissue structure and circulation.

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## **IV-22 David Ternant Influence of the FcγRIIIa genetic polymorphism on the effect of antithymocyte globulins on lymphocyte populations in kidney transplantation**

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**Objectives:** Polyclonal antilymphocyte globulins (ALG) have been used in transplantation for several decades but the sources of the interindividual variability of their effect are poorly understood. In vitro, ALG induce T lymphocyte depletion by apoptosis or by antibody-dependent cellular cytotoxicity (ADCC). We previously showed that polymorphism of FCGR3A, the gene that encodes FcγRIIIa receptor involved in ADCC, influences the relationship between horse ALG (h-ALG, Lymphoglobuline®) concentration and lymphocyte depletion in kidney transplanted patients [1]. The objective of this study was to confirm the influence of the FCGR3A genotype on the biological response to ALG treatment, using data from patients treated by rabbit ALG (r-ALG).

**Methods:** Among 194 patients kidney transplanted between 1998 and 2002 and treated with r-ALG (Thymoglobuline®), 69 were eligible and actually included in the study. Total lymphocyte count was used as a biomarker of effect and was followed until one year after the beginning of r-ALG treatment. All patients were genotyped for FCGR3A-158V/F polymorphism. Dose-effect data were analyzed using an indirect response model with inhibition of lymphocyte input. Since r-ALG concentrations were not available, a K-PD model was developed. The  $k_{in}$  and  $k_{out}$  parameters were lymphocyte input and output constants,  $R_0$  was the difference between initial and remote lymphocyte count, and EDK50 was the virtual infusion rate leading to 50% of lymphocyte depletion. A population approach was used. The influence of age, weight, concomitant immunosuppressive treatment and FCGR3A polymorphism on K-PD parameters was investigated.

**Results:** Lymphocyte count data were satisfactorily described using the K-PD model. Typical values (and interindividual CV%) were:  $k_{in} = 1750 \text{ mm}^{-3}\text{h}^{-1}$  (16.3%),  $k_{out} = 2.8 \text{ h}^{-1}$ ,  $R_0 = 860 \text{ mm}^{-3}$ . Patients with V allele were more sensitive to r-ALG treatment: EDK50 of FF, VF and VV patients were 0.35, 0.22 and 0.14 mg/h, respectively ( $p=5.1 \cdot 10^{-4}$ ). In addition,  $k_{in}$  was higher in patients co-treated with tacrolimus, and sensitivity to r-ALG treatment increased with age and body weight, and was higher in patients co-treated with sirolimus.

**Conclusions:** Our results confirm that FCGR3A genetic polymorphism influences r-ALG dose-effect relationship on lymphocyte count in kidney transplantation. This suggests that r-ALG act, at least in part, by ADCC.

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effect relationship of antilymphocyte globulins – a possible influence of FcγRIIIa genetic polymorphism. *Br J Clin Pharmacol* 2008; 1: 60–8.

#### **IV-26 Dorota Tomalik-Scharte Evaluation of Circadian Rhythms in Hepatic CYP3A4 Activity Using Population Pharmacokinetics of Midazolam**

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**Objectives:** Chronopharmacology deals with the impact of circadian rhythms on the pharmacokinetics and pharmacodynamics of different drugs. Diurnal changes in the activity of drug metabolising enzymes may be an important factor affecting the variability in drug disposition. The aim of this study was to evaluate the role of circadian rhythms in the activity of hepatic CYP3A4, metabolizing nearly 50% of currently prescribed drugs.

**Methods:** Sixteen healthy volunteers, males and females, were given a continuous intravenous infusion with low-dosed midazolam (M), a well established model substrate of CYP3A4 activity. Blood samples for measurement of M and its main metabolite 1-OH-M were drawn hourly for 24 hours following the achievement of a steady-state. Population pharmacokinetic analysis was performed using NONMEM. Plasma concentrations of M and 1-OH-M were fitted by a two-compartment base model (parent and metabolite) using first order conditional estimation. To evaluate circadian changes in CYP3A4 activity, the variability in the steady-state clearance of M was modelled by a cosine function with a 24-h period.

**Results:** The circadian model yielded an improvement of 92 points in the NONMEM objective function over the base model. The average clearance of M (%CV) was 22.4L/h (7%). The mean amplitude of the cosine function, describing the magnitude of the circadian variability in CYP3A4 activity, was 2.97L/h and the peak time, corresponding to the maximal clearance value, was at about 12:30.

**Conclusions:** The results of this pilot study provide evidence for a circadian variability in CYP3A4 activity, however, its effect seems to be moderate. Further population studies are needed to explore the clinical relevance of circadian rhythms in CYP3A4 activity for the treatment with drugs metabolized via this enzyme.

## **IV-32 Venkata Pavan Kumar Vajjah Effect of decontamination on the pharmacokinetics and pharmacodynamics of venlafaxine in overdose**

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**Background and Objectives:** Venlafaxine is a serotonin-noradrenalin reuptake inhibitor. The drug appears to be more toxic in overdose than other newer antidepressants, being associated with increased risk of seizures [1]. Patients ingesting an overdose of venlafaxine are treated with decontamination procedures. Single dose activated charcoal (SDAC), whole bowel irrigation (WBI) and a combination of both (SDAC/WBI) are the most commonly used decontamination procedures. The aims of the work were 1. To quantify the effects of decontamination procedures on the pharmacokinetics of venlafaxine in overdose; 2. To investigate the relationship between decontamination procedures and seizure events. 3. To determine the time at which 90% ( $T_{90}$ ) of patients would have had their first seizure in the presence and absence of decontamination.

**Methods:** The PK data included 339 concentration time points from 76 venlafaxine overdose occasions; 69 took a slow release formulation; the median dose in the PK study was 2625 (150-13,500mg). The PD data included 436 overdose occasions (including the PK data set). The median dose in the PD study was 1500 mg (75-13500 mg). Seizures occurred in 5% of patients. In both studies SDAC, WBI, and SDAC/WBI were administered to patients according to the treating clinician. Data were modelled using WinBUGS. Compartmental models were used to describe the PK of venlafaxine in overdose. Logistic regression and time to event analysis were used to investigate the PD data.

**Results:** A one-compartment model with first-order input and elimination provided an adequate description of the PK data. No evidence of nonlinearities in the PK profile were seen. SDAC increased clearance of venlafaxine by 35% and SDAC/WBI reduced the fraction absorbed by 29%, but the latter produced a greater reduction in maximum plasma concentration ( $C_{max}$ ) for a similar drop in area under curve (AUC). A linear logistic regression model without random effects described the PD data well. Simulation from the model showed that the probability of seizure was 0.05 (0.03-0.08) at 1000 mg, 0.19 (0.09-0.35) at 5000 mg and 0.75 (0.30-0.96) at 10000 mg. At a dose of 2100 mg the odds ratios in the presence of SDAC, WBI and SDAC/WBI were 0.48 (0.25-0.89), 0.71 (0.35-1.22) and 0.25 (0.08-0.62). Modified Gompertz model provided the best description of the time to seizures. Simulations from the time to event model showed that the  $T_{90}$  values for first seizure was 26 h at and was not affected by dose or decontamination procedure.

**Conclusion:** SDAC/WBI provided greater benefits than the sum of the independent effects of SDAC and WBI. The results of logistic regression analysis concur with the results from pharmacokinetic study. Patients should be observed for 24 hours based on the dose and risk of seizure occurring.

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#### **IV-49 Paweł Wiczling Pharmacokinetics and Pharmacodynamics of Propofol in ASA III Patients Undergoing Abdominal Aortic Surgery**

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**Objectives:** Available propofol pharmacokinetic protocols for target-controlled infusion (TCI) have been driven in healthy individuals. However, the disposition as well as the response to any given drug may be altered in clinical conditions. The aim of the study was to examine population pharmacokinetics (PK) and pharmacodynamics (PD) of propofol during total intravenous anesthesia (propofol/fentanyl) monitored by bispectral index (BIS) in ASA physical status III patients scheduled for abdominal aortic surgery.

**Methods:** Population nonlinear mixed-effect modeling was done using NONMEM IV. Data was obtained from ten male patients of 50 to 75 years age and weighing between 50 and 92 kg. The target-controlled infusion system (Diprifusor) was used to administrate propofol. Fentanyl at a dose of 2–3 µg/kg was administered whenever inadequate analgesia was assessed throughout the surgery. The bispectral index (BIS) served to monitor the depth of anesthesia. The propofol dosing was adjusted to keep BIS level between 40 and 60. Blood samples for propofol assay were collected from forearm veins at 0, 1, 3, 5, 10, 15, 30 minutes after the beginning of the infusion, then every 30 minutes until the end of anesthesia and after 1, 3, 5, 10, 15, 30, 60, 90, 120, 240 minutes after the termination of the propofol infusion.

**Results:** A two compartment model was used to describe propofol PK. Typical values of the central and peripheral volume of distribution, and the metabolic and inter-compartmental clearance were  $V_C = 24.7$  l,  $V_T = 112$  l,  $Cl = 2.64$  l/min and  $Q = 0.989$  l/min. Delay of the anesthetic effect, with respect to plasma concentrations, was described by the effect compartment with the rate constant for the distribution to the effector compartment equal to  $0.240 \text{ min}^{-1}$ . The BIS index was linked to the effect site concentrations through a sigmoidal Emax model with  $EC_{50} = 2.19$  mg/l. The body weight, age, blood pressure were not identified as statistically ( $p < 0.001$ ) significant covariates for all PK/PD parameters.

**Conclusions:** The population PK/PD model was successfully developed to describe the time course and variability of propofol concentration and BIS index in ASA III patients undergoing aortic surgery.

## **IV-52 Dan Wright Development of a Bayesian forecasting method for warfarin dose individualisation**

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**Objectives:** Warfarin is the most commonly prescribed oral anticoagulant worldwide. It is a difficult drug to dose accurately due to a large inter-individual variability in response and a narrow therapeutic range. Warfarin response is routinely monitored using the International Normalised Ratio (INR), a measure of blood clotting time. If the INR falls below 2, the patient is at risk of clotting while INRs above 4.5 carry an increased risk of major bleeding events. In addition, there is a delay between a change in the dosing regimen and achievement of the steady state INR which means that monitoring is often confounded by non-steady state conditions. Not surprisingly, warfarin dose individualisation constitutes a major challenge for clinicians, with reports suggesting that patients achieve therapeutic INRs only 50-60% of the time [1-4]. A simple tool for individualising warfarin dosages will therefore have significant benefits for healthcare.

The aim of this study was to develop a Bayesian dose individualisation tool for warfarin. This was incorporated into the freely available software TCIWorks (<http://www.tciworks.info/>) for use in the clinic.

**Methods:** All PKPD models of warfarin in the medical literature were identified and evaluated against two warfarin pharmacokinetic and pharmacodynamic datasets. The model with the best external validity was used to develop an optimal design for Bayesian parameter control. The performance of this design was evaluated using simulation-estimation techniques. Finally, the model was implemented in TCIWorks.

**Results:** A recently published warfarin KPD model was found to provide the best fit for the two external datasets [5]. Optimal sampling days within the first 14 days of therapy were found to be days 3,4,5,11,12,13 and 14. Simulations and parameter estimations suggested that the design will provide stable estimates of warfarin clearance and EC50. A single patient example showed the potential clinical utility of the method in TCIWorks.

**Conclusions:** A Bayesian dose individualisation tool for warfarin was developed. Further research to assess the predictive performance of the tool in warfarin patients is underway.

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### **IV-53 Rujia Xie Model based meta-analysis (MBMA) to support the development of decision criteria in dental pain studies**

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**Objectives:** Pre-specified decision criteria for go/no go decision-making of a compound are critical in drug development, especially for novel mechanisms. Model based meta-analysis (MBMA) is a key component in this process estimating a distribution of effects over placebo for the endpoints of interest from observed trials. This enables determination of which endpoint is most sensitive and also helps quantify what a meaningful effect may be. MBMA was used to integrate prior information of drugs studied in the post-surgical dental pain model to quantify an effect over placebo for the endpoint (last observation carried forward) LOCF-based TOTPAR (area under the Pain Relief (PR) curve).

**Methods:** Placebo controlled, post-surgical dental pain trials including NSAIDs, COX2 inhibitor or opiates reporting PR in subjects, following surgical extraction of at least 1 third molar post-operatively, were included in the meta-database. This consisted of 33 trials encompassing 102 treatment arms and 6188 subjects. A meta-analysis was conducted for both internal and literature data to analyse the efficacy endpoint of TOTPAR6 (0-6 hr post-treatment) and to determine its prediction interval for a given drug class. This information aided determination of a minimum meaningful target value (TV) of TOTPAR6 that would need to be observed in a dental pain study, with a certain level of probability, in order to further invest in the compound. Two decision rules governing the decision were evaluated for probability of being: i) superior to placebo; ii) greater than TV.

**Results:** The mean [95%CI] TOTPAR6 change from placebo for Ibuprofen 400mg was estimated to be 8.37 [7.45, 9.29] from the meta-analyses. Between study variability was described and an approximate predictive interval for the effect in an unspecified study could be 8.37 [4.83, 11.91]. Using this information, and considering the main objective of the study, it was determined that a TV of 6 would be used as part of the decision criteria to progress a compound to the next stage. The (posterior) probability of the true effect being 6 would need to be at least 25 %, as well as at least 95% (posterior) probability of the true effect being greater than placebo.

**Conclusions:** This meta-analysis provided a broad overview and understanding of effect size of different classes of analgesic drugs in order to develop quantitatively target values for endpoints in early phase efficacy studies that do not have pre-defined meaningful values.

#### **IV-55 Shuying Yang Predicting long term Placebo response based on short term observations: Meta-Analysis on FEV1 Response in Asthma Trials**

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**Objectives:** To characterise the early (week 2) and late (week 12) FEV1 (forced expiratory volume in 1 second) response with placebo in mild-to-moderate asthma population and to investigate the potential influential covariates. The final goals of the meta-analysis were:

1. To Identify criteria for population enrichment in novel trials in asthma population
2. To provide the necessary model-based support for the implementation of alternative study design (i.e., sequential adaptive, seamless, etc.)
3. To evaluate the expected outcomes of a Phase III program (including: benefit/risk and differentiating criteria), help in the definition of a preferred end-stage clinical development strategy including choice of the comparators, study population and experimental design.

**Methods:** Data from 11 large, well-defined historical 12-week clinical trials for the development of predictive models were utilised. Longitudinal placebo FEV1 data were collected in mild-to-moderate asthma patients. A total of over 1100 subjects' data were included in the analysis. This database includes baseline FEV1, demographics and disease history. All subjects were inhaled corticosteroid (ICS) naïve patients. The probability of the week 12 FEV1 change from baseline greater than a clinically relevant FEV1 response of 150mL (as an example) was modelled and predictive covariates on the FEV1 response was selected using stepwise logistic regression using proc logistic in SAS (1).

**Results:** The modelling results indicated that the early (week 2) FEV1 response in the subjects treated with placebo was significantly predictive of the FEV1 change at the end of the 12-week trials. In addition, the baseline percent predicted FEV1 (adjusted by age, gender and height) and age were also important covariates in the model. The predictability of the model was satisfactory (receiver operating characteristic curve (ROC) ~80%) for future potential application.

**Conclusions:** The late (week 12) FEV1 response with placebo was positively related to the early (week 2) FEV1 change. This finding has potential to be utilised as a rule to effectively select study population in asthma trials.

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**I-11 Paul Baverel A novel covariate search method intended for PKPD models with nonparametric parameter distributions**

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**Objectives:** To develop a new covariate modeling approach adapted for nonparametric parameter distributions and to evaluate its statistical properties in terms of power and type-I error rate of covariate inclusion.

**Methods:** The proposed methodology is articulated around the decomposition of the nonparametric joint density obtained in NONMEM into a set of unique individual probability density distributions. These individual probabilities are then exported into R and used as weighting factors of a generalized additive model (GAM) regressing support points on covariate distributions. A calibration of the method is undertaken by means of 1000 randomization tests automated with GAM analyses to derive a decision criterion based on the Akaike's information criterion (AIC) given the null hypothesis and a user-defined confidence level  $\alpha$ . Statistical properties of the proposed methodology were then evaluated through Monte-Carlo simulations with  $\alpha=5\%$ . Eight scenarios of 1000 stochastic simulations followed by estimations (SSEs) were performed under FOCE-NONP given a 1-compartment PK model and an informative design. Estimates of the statistical power of inclusion of both a continuous and a categorical covariate with varying correlation to CL were obtained with associated estimates of type-I error rate. A comparison was then performed with likelihood ratio test statistics (LRTs) given FOCE parameter distributions. Errors in estimates of correlation coefficients were further assessed.

**Results:** The methodology was successfully implemented by means of a Perl script calling PsN, NONMEM and R. Estimates of statistical power and type-I error rate of the proposed method were in close agreement with LRT statistics under ideal conditions of hypothesis-testing for the latter, and this, regardless of the correlation strengths and of the nature of the covariate distribution investigated. Estimates of regression coefficients presented negligible bias and were as precise as the ones obtained with parametric models.

**Conclusions:** The set of covariate analysis tools is extended with a new, calibrated, covariate identification technique intended for nonparametric population models.

### **I-13 *Benoît Beck* From the Experimental Model Settings to the Physical System for Interpretable Decision Making**

Benoit Beck

*Axiosis sprl & Arxios sprl - Bousval - Belgium*

**Objectives:** The presentation will emphasize the importance of putting the experimental settings in perspective to the physical studied system before taking any decision. This will be essentially done by going through different alternatives for evaluating the apparent permeability index obtained from in vitro CACO2 models. The comparison of these alternatives can be considered as an objective on its own.

**Methods:** The permeability index is used as part of a general screening process to study drug absorption. It is typically computed by adapting a straight line to the initial portion of the amounts in the receiver compartment; disregarding the first few points when lagging of the transfer process through the membrane is evident. Modeling the transfer process via a two-compartmental system yields an immediate analogue of the index as the initial slope of the receiver quantity, but the two-compartment model often does not match observations well. A three-compartment model, describing the cellular layer as well as donor and receiver compartments, typically better represents the kinetics, but has the disadvantage of always having zero initial flow rate to the receiver compartment!

**Results:** The alternative definition for the index proposed in Palumbo et al. [1] applicable for three-compartment models will be first assessed. That new definition will be shown to reduce to the classical formulation as the cellular layer's volume tends towards zero. We will discuss the fact that although mathematically well defined, the proposed alternative lacks of biological interpretations. We will then move to the concept of reformulating the model before taking decision. We will prove that by virtually assuming a continuous and instantaneous resetting of the donor and receiver concentrations, it is straightforward to obtain a computationally robust as well as biological interpretable general definition.

**Conclusions:** It is often critical to move from the model based on the experimental settings to another model representing the physical studied system in order to reach a robust conclusion. Making such clear distinction for the evaluation of the apparent permeability index has shown to be quite useful for obtaining a generic computational method that avoids any subjective interventions.

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## **I-17 Julie Bertrand Multiple SNP analysis with HyperLasso in Pharmacogenetic Studies using Nonlinear Mixed Effects Models**

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**Context:** To date the influence of genetic polymorphisms on concentration data is usually analyzed using the observed area under-the curve, maximal or minimal concentrations. Nonlinear mixed effects models (NLMEM) enable the analysis of all concentration versus time profiles, even on sparse data. This allows more flexibility in study design, for example to include additional subjects with fewer samples, making it easier for pharmacogenetic studies to meet the requirements of the medical authorities [1]. Lehr *et al.* [2] provide the first evaluation of the feasibility of, and potential benefits from, integrating multiple SNP data into NLMEM. However, their algorithm is a stepwise procedure which is known to have problems with correlated covariates. The HyperLasso approach [3] simultaneously analyses all SNPs using a prior with a sharp peak at zero and heavy tails.

**Objective:** To assess the type I error and power of HyperLasso and stepwise-based approaches for detecting a SNP effect on a pharmacokinetic parameter using NLMEM.

**Methods:** Two hundred data sets were simulated under both the null and an alternative hypothesis. Genetic polymorphisms were simulated using HAPGEN [4] approximating the design of the DMET chip [5] with about 1200 genetic polymorphisms across the all genome. Pharmacokinetic profiles were simulated using a two-compartment model with parameters based on real data [6]. Under the alternative hypothesis three causal variants were randomly associated to one or several PK parameters with a rare allele dosage effect size of 10 to 20%, so that the impact of the allele frequency and effect size could be investigated. PK modeling was performed using the Stochastic Approximation Expectation Maximisation algorithm implemented in Monolix 3.1.

**Results:** In average 830 over the 1252 genetic covariates were polymorphic in the population of 300 subjects per simulated data set. Under the null hypothesis of no gene effect in average [range], 4.5 [2-5] and 1.4 [0-8] polymorphisms were found associated to one or more of the 5 PK model parameters using the HyperLasso method on Empirical Bayes Estimates and a forward inclusion in the model, respectively.

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## **I-18 Bruno Bieth Using a Systems Biology Approach to Explore Clinical Diversity and Investigate Mechanism of Drug Action: Example of the RAAS System in Hypertension**

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**Objectives:** The complexity of the biological and pathophysiological mechanisms of disease, and the impact of therapies on disease progression, motivates the development and use of computational models as a way to integrate quantitative physiological knowledge.

Using biological and physiological prior knowledge, a detailed representation of the Renin-Angiotensin-Aldosterone System (RAAS) as well as the effect of anti-hypertensive therapies on long-term blood pressure regulation has been implemented into a large complex mathematical model to explore clinical variability in different populations and investigate mechanism of drug action.

**Methods:** The Systems Biology – Population software package (SBPOP) aims at providing a flexible computational framework in support of such model-based drug development. Virtual populations are created within this large-scale model to represent real patient subpopulations by matching the underlying individual characteristics to the observed clinical and pre-clinical data.

Different calibration methodologies have been developed to generate diverse phenotype of virtual populations. They consist in using different sampling algorithms of the model parameter space along with several physiological criteria for population selection (depending on the type of data available, e.g. longitudinal data with few patients typical of phase I-II, or few data points in large population typical of phase III).

**Results:** We will demonstrate how the RAAS platform combines with a set of virtual populations can describe: diverse baseline characteristics that correspond to inclusion criteria of patients recruited in clinical trials; disease progression patterns that take into account pathophysiological diversity of hypertensive and diabetic subjects; drugs therapy effects such angiotensin-converting enzyme inhibitors, angiotensin II Receptor Blockers and Renin inhibitor.

**Conclusions:** The platform provides a framework for integrating data in the context of the Hypertension disease, focusing on understanding and anticipating clinical responses to potential treatment through the generation of virtual populations.

## **I-19 Roberto Bizzotto Drug Effects on Sleep Data from a 28-Day Clinical Study in Insomniac Patients: Covariate Analysis Using a Multinomial Mixed-Effect Markov-Chain Model**

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**Objectives:** Sleep quality is objectively assessed through polysomnography (PSG), from which clinical efficacy endpoints like sleep latency (LPS) or wake time after sleep onset (WASO) are evaluated. In previous work a multinomial mixed-effect Markov-chain model has been validated for a thorough description of PSG data [1,2]. The aim of this work is the evaluation of drug effects on sleep architecture using this model.

**Methods:** 342 subjects with primary insomnia were enrolled in a 28-day placebo-controlled study evaluating the sleep effect of a NCE (two doses). PSG data from nights 1 and 27 were analyzed. Each individual sequence of sleep stages (initial sleeplessness IS, following wake AW, stage 1 ST1, stage 2 ST2, slow-wave sleep SWS and REM sleep) was treated as a Markov chain and transition probabilities were modeled through multinomial logit functions of nighttime and time after last sleep stage change ('stage time') [1,2]. Stepwise forward inclusion followed by backward elimination based on the log-likelihood ratio test [3] was used on the two nights separately to attempt the inclusion of plasma concentration effects. Linear and piecewise linear functions of concentration were added to the logits and estimated using NONMEM VI.

**Results:** Several statistically relevant effects were included in the final Markov-chain model, changing the probabilities of most transitions. In summary, in the first part of the night transitions from ST2 to SWS were promoted by lower exposures and reduced by higher exposures. In the later part of night 1, transitions from SWS to ST2 were more likely under drug treatment, mostly at low concentrations. In the second part of night 1 increasing plasma concentrations increased the transition probability ST2 to REM and decreased the transition probabilities ST2 to AW and ST2 to ST1 (the latter was higher at night 27). The probability of transitioning from ST1 to AW was reduced by increasing drug concentrations, at median stage time or high nighttime values.

**Conclusions:** Stepwise forward inclusion and backward elimination based on statistical criteria was able to develop a second-stage multinomial Markov-chain model including drug effects on many parameters. The final model provided a valuable explanation of the reducing effects observed on the clinical endpoints LPS and WASO and on the concentration-dependent tolerance observed on WASO. The multinomial Markov-chain model appeared a suitable tool for the exploration of drug effects on sleep architecture.

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## **I-20 Marcus Björnsson Performance of non-linear mixed effects models with and without taking informative dropout into account**

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**Objectives:** The objective of this simulation study was to investigate the performance of non-linear mixed effects models with and without taking informative dropout into account.

**Methods:** Simulations were performed using an inhibitory  $E_{\max}$  drug effect model combined with an exponential placebo effect model. Dropout was simulated using a hazard function in which the hazard was exponentially related to the individual predicted efficacy score, adapted from Björnsson and Simonsson [1]. The base scenario consisted of a placebo group and three active treatment groups, each with 45 subjects, and with a dropout rate between 25 and 55%. The simulated efficacy data were analysed using non-linear mixed effects modelling with or without including the dropout model. The impact of number of dose groups, number of subjects per group, number of observations per subject, dropout rate, and size of the placebo effect were investigated with respect to bias in the parameter estimates. The Laplacian estimation method in NONMEM 7 (ICON, Hanover, MD, USA) [2] and PsN [3] were used for the stochastic simulations and estimations.

**Results:** In the base scenario, bias was less than 5% in all fixed effects parameters when the same model, including dropout, was used for simulation and estimation. Bias was larger in  $EC_{50}$  when dropout was not included in the estimation model, although the bias was still less than 10% for the base scenario. The bias in  $EC_{50}$  increased with increasing dropout rate, increasing placebo effect and decreasing number of observations per subject. The increase in bias was larger when dropout was ignored. Bias in the rate constant for the onset of placebo effect was approximately 15-20% in most tested scenarios when dropout was not included in the estimation. Also in cases where parameter estimates were relatively accurate, simulation based diagnostics were poor when dropout was not accounted for.

**Conclusions:** Ignoring informative dropout can lead to biased parameter estimates, although the bias in many cases was found to be relatively low. The bias was dependent on dropout rate, placebo effect and number of observations per patient. Inclusion of a dropout model is essential in simulation based diagnostics when informative dropout is present, even when the parameters are estimated without bias.

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**I-25 Massoud Boroujerdi A Negative feedback model for a mechanism based description of longitudinal observations: application for bone turnover biomarkers.**

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**Objectives:** In modern medicine the initial diagnosis of an abnormal metabolic condition is based on blood borne measurements often involving multiple biomarkers. The biomarkers concentrations themselves would not be sufficient for providing a mechanism based description of mode of action. Estimates of clearance rates are the minimum requirement for a model based description of longitudinal observations.

**Methods:** A minimal negative feedback model is proposed for the description of longitudinal observations in clinical trials for treatment of osteoporosis in postmenopausal women. The negative feedback model is consisting of blood biomarker and a companion latent controller. By considering the above basal biomarkers values it is shown that the kinetics can be described by a second order differential equation without the involvement of biomarkers production rates. The second order differential equation is also analogous to classical servomechanism model with two parameters  $\omega_n$  and  $\zeta$ , the position being the above basal concentration. With the assumption that the rate constants defining the negative feedback model being equal  $\zeta$  would be 0.707 with only  $\omega_n$  to be estimated. The parameters of the servomechanism model namely  $\omega_n$  was estimated for each biomarker providing values for their clearance rates [1].

**Results:** The parameter of the negative feedback model was estimated for both lumbar spine bone mineral density and bone-specific alkaline phosphatase for the mean observations in four treatments groups over three years. The third year of treatment was a switch over among therapies (1) Placebo, (2) Alendronate, (3) Conjugated Estrogen (4) Combination therapy.

**Conclusions:** The clearance rate of bone-specific alkaline phosphatase was higher than the bone mineral density in all treatment groups. The linkage of the models indicate that the changes in bone mineral density modulates the feedback flux rate constant of bone-specific alkaline phosphatase with the modulation coefficient being slower in the switch over year from Alendronate to other therapies [2].

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**I-26 Marion Bouillon-Pichault Modeling Pain score in clinical trials using a joint survival-longitudinal mixed model with a Beta distribution in presence of missing values not occurring at random.**

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*Arlenda*

**Objectives:** In clinical trials investigating pain drugs, the pain is usually assessed by means of a score or a Visual Analogic Scale (VAS) always bounded in  $[0,10]$ . In such trials there are potentially two major sources of bias for estimating the real effect of a new drug assumed to decrease pain. The objective is to propose a method that allows an unbiased estimation of the treatment effect.

**Methods:** First, given the bounded nature of the Pain score, the use of a Beta distribution is preferred instead of a normal distribution that can lead to bias in estimates. For that purpose, a longitudinal mixed effect model with a Beta-Normal distribution has been developed to model pain score over the duration of the study.

Second, in this type of study in chronic or acute pain, the rate of dropouts by requiring rescue medication is in general large - from 15% to 35% - during the four first weeks and mostly linked to a lack of perceived efficacy, i.e. the dropouts are informative. In that case the data are missing not at random (NAR). To assess the efficacy of a new drug, the focus is on both the longitudinal data and the time-to-event, time to rescue medication here, with the aim to understand the association between both processes. Indeed a new pain drug will be declared more efficacious if time to rescue medication has been significantly prolonged and if pain score decreases more than placebo.

**Results:** The use of a Beta distribution for the pain scores and the joint modeling of both longitudinal and time to event data lead to unbiased treatment estimates. Ignoring the dropouts mechanism provides an underestimation of the treatment effect which can go up to 30% in some situations.

**Conclusions:** For the later, unbiased estimates for the longitudinal model in presence of missing values NAR can only be obtained if jointly modeled with the dropout mechanism.

### **I-31 Anne Brochot Specifying Models with Time Dependent Pharmacokinetic Parameters in NONMEM**

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**Objectives:** Time dependent parameters are sometimes required to describe the pharmacokinetics of a drug. NONMEM provides the user with a number of options in constructing a model with time dependent parameters. Two options using the PREDPP library were considered, one using the \$PK block and the other using the \$DES block. An example of time varying absorption previously presented [1,2] was investigated as well as other time varying pharmacokinetics.

**Methods:** The models studied have been implemented using either ADVAN6 (\$DES implementation) or ADVAN1 to ADVAN4 (\$PK implementation) in NONMEM (v. 7). The models have been fitted to simulated datasets and a comparison of the results was conducted.

**Results:** Depending on how the user introduces the time varying pharmacokinetic parameter, NONMEM will either use the analytic solution (ADVAN1 to ADVAN4) or numerically solve the differential equation(s) (ADVAN6). When using the analytic solution, NONMEM employs a step-function to approximate the change in the time varying parameter. How far this approximation differs from the real function depends on the number of TIME points included in the datafile. A large number of TIME records may provide a good approximation when using the analytic solution. However, if the individuals in the dataset differ with respect to their sampling times, then a different model will be fitted for each individual. The numerical solution using the NONMEM time variable T within \$DES provides sufficient integration steps to make the solution independent of the TIME record chosen.

**Conclusions:** The analytic solution using ADVAN1 to ADVAN4 in NONMEM uses an approximation when parameters are varying with time. The numerical differential equation solver in NONMEM uses the desired model but it is more computer intensive. If the analytic solution is used, the introduction of a sufficient number of time points is required to have an acceptable approximation.

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### **I-33 Vincent Buchheit Efficient quality review for modeling input dataset**

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**Objectives:** The objective of this poster is to share our experiences regarding modeling input dataset validation and to solicit feedback and collaboration from other Pharma industries.

**Methods:** Drug development is a succession of clinical trials, where statisticians and programmers play a major role in the data reporting and data analysis. In addition, pooling data across studies, within a compound, or across compounds is becoming nowadays a routine activity in most pharmaceutical companies, also in the Modeling and Simulation (M&S) Programming Group at Novartis. While we develop tools and methodologies to facilitate data pooling, we are still facing the following challenge: “How can we perform an efficient quality review of our pooled modeling input dataset, and therefore validate the data?”

**Results:** For this purpose, the double programming process is routinely applied in pharmaceutical industries. An independent programmer re-produces the same dataset based on data specifications. The validation is completed when both datasets match. It can take up to several weeks before completion. This Quality Control (QC) method is adequate to ensure that the data-generating program does what it is supposed to do. However, it does not guarantee that the data is scientifically accurate. From a modeling and simulation point of view, it's important to identify upfront most of the data issues that could impact the model development. The data issues are diverse: missing covariates, discrepancies between units and associated laboratory measurements, inconsistencies between dose history and pharmacokinetic samples, inconsistencies with the clinical studies report, different SAS(R) formats applied for the same variable (race, ethnicity) .... Some key graphics, such as the pharmacokinetic concentration data versus time since previous dose or plots from the scheduled timepoint against the calculated elapse time, or a summary table of all covariates by study and centers are efficient ways to identify potential issues. We will report on other graphical and statistical approaches, including the re-use of a qualified model on comparable data.

**Conclusions:** The use of Model Based Drug Development is more and more advocated in the pharmaceutical industry. The modeling approach contributes to answer some of the key questions, such as “What is the best dose?”, or “What is the best dose regimen?”. The matter of data quality is essential.

**I-42 Marylore Chenel BSA-adjusted dose? An old method to fight old bias**

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**Objectives:** By taking into account inter-individual variability in drug distribution, metabolism and/or elimination, individual dose adjustment lowers inter-individual variability in exposure. When given at a fixed dose, drugs with a wide therapeutic range, between effective dose and maximum tolerated dose (MTD), lead to a variable, but safe individual exposure. On the other hand in oncology, where therapeutic drug dose is closer to MTD, the therapeutic range is narrower. In this context, dose adjustment may help in reducing exposure variability, and better control the optimal dose in terms of efficacy and safety. Body surface area (BSA) is frequently used for dose-adjustment, as it has been shown to correlate with total blood volume, cardiac output and renal function [1]. Still, BSA-adjusted dose relies on a strong assumption on the linear relationship between exposure (*i.e.* drug clearance) and BSA. A different relationship may lead at best to unnecessary constraints on drug prescription and at worst to an increase of exposure variability across patients. Our work aims at evaluating the link between drug clearance and BSA, in order to choose the best dosing strategy in drug SX development.

**Methods:** PK data from two studies (49 patients, drug SX given intravenously and orally) was used to build a population model M0. Individual empirical Bayesian estimates (EBEs) of plasma clearance ( $CL_i$ ) were then computed. Model M1 was built, where clearance was supposed to be proportional to BSA, and was used to define a second set ( $CL_i'$ ) of EBEs. Naïve predictor prediction error and model prediction error were computed according to [2], using respectively ( $CL_i$ ) and ( $CL_i'$ ). The two predictors were then compared by computing median prediction error as a measure of bias and median unsigned prediction as a measure of precision. Graphical representation developed in [2] was used to allow a visual evaluation of comparative predictor performance. Models were also compared in terms of objective function values (OFV, = -2 log-likelihood). NONMEM VI FOCE-I, was used for model building.

**Results:** Models M1 and M0 gave similar population and individual estimates of parameters. A difference of 8 in OFV between M1 and M0 showed a significant effect of BSA on clearance. M0 and M1 gave respectively a prediction error on clearance of 38 % and 34 %.

**Conclusion:** In the context of early drug development in oncology, this work evaluated the relevance of dose adjustment based on BSA, in a quantitative and visually intelligible way. The reduction of variability induced by BSA-adjusted dose was found to be too small to justify dose adjustment in further development.

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### **I-43 S. Y. Amy Cheung Structural identifiability of parallel pharmacokinetic experiments as constrained systems**

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**Objectives:** Pharmacokinetic analysis using compartmental models can be restricted with respect to the estimation of parameter values. This is because the experimenter is only able to apply inputs and observations in a very small number of compartments in the system. This has implications for the structural identifiability [1] of such systems and consequently limits the complexity and mechanistic relevance of the models that may be applied to such experiments. A number of strategies are presented whereby models are rendered globally identifiable by considering a series of experiments in parallel [2].

**Methods:** Structural identifiability is the property of whether an experiment can uniquely identify the unconstrained model parameters. The 'same' experiment may sometimes be carried out several times on a system, in which it can be assumed *a priori* that some, but not all, of its rate constants change between experiments. The models representing each experimental observation thus share some common rate constant values depend on the dosing method and physiological nature of the model. This forms a much more constrained structure, encapsulates more information of the system and still can be readily analysed.

**Results:** The methodology is applied to a number of examples, including classic compartmental models and a series of mechanistic compartmental models such as parent-metabolite models [3]. It is shown that by considering parallel experimental strategies, individually unidentifiable or locally identifiable models, in many cases are rendered uniquely identifiable.

**Conclusions:** A formulation has been presented that places the concept of parallel experiments in the context of a single constrained model structure. Incorporation of prior knowledge into parallel experiment model structures with constrained parameterization allows sufficient information to be present in the input-output behaviour to give unique parameter estimates. The results show that the parallel experiment strategy can be very powerful in providing a globally uniquely identifiable model.

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## **I-52 Emmanuelle Comets A comparison of bootstrap approaches for estimating standard errors of parameters in linear mixed effects models**

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**Objectives:** Paired bootstrap which resamples the individuals from original data, has been used in PK/PD for estimating the standard errors (SE) of parameters in mixed-effects models (MEM) [1,2]. Alternative bootstrap methods, such as residual bootstrap and parametric bootstrap have been proposed to better take into account the hierarchical structure of multi-level data [3-6]. Our objectives are to study and propose appropriate bootstrap methods in MEM and to evaluate their performance by simulation. We present the results obtained with linear mixed-effect models, using an example of disease progression model in Parkinson's disease [7].

**Methods:** We implemented the paired, residual and parametric bootstraps in R, fitting the simulated data with the R function `lme`. We investigated corrections to residuals using the ratio between empirical and estimated variance-covariance matrix [6] to account for shrinkage. The bootstrap approaches were compared in term of bias, delta SE (difference between bootstrap and empirical SE), root mean squared error (RMSE), and coverage rate of the 95% confidence interval of all parameter estimates. A subset of a study describing the natural evolution of Parkinson's disease over a 2-year period was used to motivate the simulations and illustrate the results. The rich design (100 subjects and 7 samples per subject) and the sparse design (30 subjects and 3 samples per subject) were investigated by simulation using 1000 replicates and 1000 bootstrap samples per replicate for each bootstrap scenario.

**Results:** The paired and parametric bootstraps proved good approaches for both evaluated designs with small bias and RMSE of parameter estimates, SE close to empirical values and a good coverage rate. The residual bootstrap also performed well when resampling with corrected residuals. For these three approaches, the bias of all parameters were lower than 2.1% and 8%, and their SE remains within 6.4 and 10.4% of the true values, respectively for the rich and sparse design. The coverage rates obtained by bootstrap were better than the asymptotic coverage rates for random effects and residual error.

**Conclusions:** The paired bootstrap works as well as the residual bootstrap and the parametric bootstraps for both designs, although only the interindividual variability is resampled, possibly due to the large interindividual variability in the data. A correction was necessary for the residual bootstrap to account for the variance underestimation.

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### **I-53 Carolyn Coulter Utilising prior literature population models to inform clinical practice - a dosing regimen for immediate N-acetyl cysteine treatment of paracetamol overdose**

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**Objectives:** This research shows how a model from a prior population analysis can be used with clinical trial simulations to give a clinical rationale for a chosen dosing regimen. Here dosing of N-acetyl cysteine (NAC) after paracetamol overdose was investigated using this methodology. NAC acts to replenish glutathione which binds covalently to the toxic metabolite of paracetamol, N-acetyl-p-benzoquinone imine (NAPQI), preventing liver damage. The conventional dosing regimen of NAC is effective but incurs an initial delay of at least five to six hours post-overdose while a plasma paracetamol concentration is obtained; it then involves a complex three phase infusion. The first infusion uses a high dose rate of NAC which can lead to adverse reactions. The aim of this study was to develop a dosing regimen for NAC that can be administered immediately upon presentation post- paracetamol overdose that uses a low dose rate infusion. This methodology gave a new dosing regimen that should be as effective as the conventional regimen but is without the initial delay and reduces the initial high infusion rate.

**Methods:** In this study we used clinical trial simulation to explore the concentration-time profiles of different NAC dosing regimens including the conventional regimen. We used a published population pharmacokinetic model of NAC [1] and in MATLAB simulated 1000 virtual patients which we dosed in a cross-over design. We assumed that the AUC of NAC equates to the effectiveness of the regimen while the C<sub>max</sub> drives the risk of adverse effects. A hypothetical scenario was considered where the patient arrives 2 hours post-overdose and there is a 4 hour delay before NAC treatment is initiated; this is the best case scenario. The proposed infusion started immediately on presentation to hospital. The dose rate was selected to give an AUC that was the same or higher than the conventional regimen on 90% of occasions while reducing the C<sub>max</sub>.

**Results:** For the hypothetical scenario the conventional NAC regimen was replaced by an infusion of 200 mg/kg over 9 hours then 100 mg/kg over 16 hours. This regimen has a longer infusion duration and a greatly reduced C<sub>max</sub>, compared to the conventional regimen.

**Conclusions:** Our simulations suggest that immediate low dose rate infusions of NAC may be able to replace the complex conventional regimen. The proposed regimen needs to be assessed prospectively.

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## **I-55 Roosmarijn De Cock Maturation of GFR in preterm and term neonates reflected by clearance of different antibiotics**

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**Objectives:** Throughout infancy, renal function matures resulting in differences in glomerular filtration rate (GFR) at different stages of development. These developmental changes in GFR were previously quantified in (pre)term neonates aged up to 1 month on the basis of the clearance of amikacin. In this developmental renal excretion model (1), the maturation of GFR was predicted by birth weight (BWb) and postnatal age (PNA). The aim of this study is to assess model performance when this developmental renal excretion model (1) is used to describe maturation in clearance of other renally excreted antibiotics in (pre)term neonates. Using this approach a distinction is being made between system specific and drug specific information in paediatric pharmacokinetic models.

**Methods:** For the netilmicin dataset, 386 netilmicin concentrations were available from 97 (pre)term neonates (BWb 470-3000 g, PNA 1-30 days)(2). The vancomycin dataset contained 752 vancomycin concentrations from 273 preterm neonates (BWb 385-2550 g, PNA 1-30 days)(3).

A pharmacokinetic model was developed for both netilmicin or vancomycin using the developmental renal excretion model for amikacin clearance in neonates (1):

$$CL_i = CL_p * \{ ((BW_b / BW_{Bmedian})^{1.34}) * (1 + 0.213 * (PNA / PNA_{median})) \}$$

Using this approach,  $CL_p$  is considered a drug specific property and was therefore estimated for each of the drugs separately. The remaining information in this equation is considered system specific information which can be applied for all renally excreted drugs.

The descriptive and predictive performance of models developed using the developmental renal excretion model (1) were compared with comprehensive covariate models (4) for netilmicin or vancomycin respectively, by evaluation of the objective function (OFV), basic goodness-of-fit plots, NPDE and the individual and population parameter estimates versus most predictive covariate (4).

**Results:** The descriptive and predictive properties of the models developed using the developmental renal excretion model, were similar compared to the comprehensive covariate models for basic goodness-of-fit plots and NPDE. In agreement the models that were developed

using the developmental renal excretion model, in the comprehensive covariate models BWb and PNA were identified as most predictive covariates for clearance. The comprehensive covariate models had only a slightly lower objective function (netilmicin  $p < 0.05$ , vancomycin  $p < 0.001$ ) compared to the models using the developmental renal excretion model.

**Conclusions:** Use of the developmental renal excretion model quantifying maturation in GFR mediated amikacin clearance for the analysis of netilmicin and vancomycin clearance in neonates, results in adequate descriptive and predictive performance. We conclude that the application of system specific information may lead to optimization of sparse data analysis in children.

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**I-58 Maud Delattre Pharmacokinetics and stochastic differential equations : model and methodology.**

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**Objectives:** A recent evolution of the traditional PK models based on ordinary differential equations (ODEs) consists in adding a system noise to the ODEs to account for more intra-individual variability (see [1], [2], [3]). However, the frequently proposed linear SDE system turns out to be irrelevant. First, it gives an overly erratic description of the evolution of the drug concentrations within the compartments of the human body. Second, it does not comply with some constraints on the biological dynamics (sign, monotony,...).

The objective of this contribution is to present new SDE models that would best reflect the PK reality. Some specific maximum estimation procedure for the population parameters are also developed in a population approach.

**Methods:** Assuming that the diffusion process randomly perturbs the transfer rate constants of the system is more realistic and allows a more accurate representation of the biological system. When it is possible to come down to a linear SDE model by some appropriate transformations of the original SDE system, we suggest estimating the population parameters by combining the SAEM algorithm with the Kalman filter. This methodology was implemented in a working version of MONOLIX and tested on some simulated basic examples.

**Results:** The simulated datasets show that this new model more faithfully mimics the biological dynamics. Based on these simulated examples, the proposed estimation methodology also gives encouraging results. On particular, the population parameters are estimated with little bias and the estimated standard errors for each parameter are low.

**Conclusions:** We have proposed a new category of mixed-effects models based on SDEs for PK modeling and our maximum likelihood estimation procedure shows quite good practical properties. We aim to extend in a next future the present approach to more complex compartment models. Defining the transfer rate constants as stochastic processes often leads to highly non linear models, in which the present estimation methodology based on the Kalman filter cannot be used. A SAEM based method using the extended Kalman filter or a particle filter should rather be considered.

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## **I-65 Aris Dokoumetzidis Multiple dosing for linear fractional pharmacokinetic systems**

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**Objectives:** We investigate the implementation of multiple dosing in pharmacokinetic systems including fractional rates.

**Methods:** One of the problems of fractional calculus is the initialisation of fractional differential equations because of the time memory effects, which may have consequences in the implementation of multiple dosing systems. In this poster we investigate the implementation of a multiple dosing scheme in a one compartment model (i.e. a Mittag-Leffler (ML) function), with two methods, which both work in the classic, non-fractional case: (i) Considering each additional dose by reinitialization i.e. with ML functions where the initial value of each is the final value of the previous one; and (ii) implementing the multiple dosing by adding up several single dose profiles, using the superposition principle. We assess whether these techniques work for fractional systems by comparing them to the limit case of a one-compartment fractional model with constant infusion which has an analytical solution.

**Results:** We derive the analytical solution of a PK model with fractional elimination and constant infusion which involves a Mittag-Leffler function. A multiple dose system is implemented by reinitialization and by superposition. The two methods give the same profiles only when the order  $\alpha=1$ . For a fractional  $\alpha=0.5$  the 2 methods give different profiles and only the superposition method gives profiles which follow the constant infusion model in the limit when the dose and the dosing interval become very small. The reinitialization method fails to do that. Both the constant infusion and the multiple dose system demonstrate the lack of a steady state and the ever ending accumulation of drug as a result of the presence of fractional kinetics. In the case of the constant infusion where there is analytical solution we prove mathematically that for infinite time the solution goes to infinity and not to a steady state. This is an important clinical implication of the presence of fractional kinetics.

**Conclusion:** Multiple dosing in linear pharmacokinetic systems with fractional rates can be implemented using the superposition principle exactly the same way as in ordinary PK systems, however the reinitialization method fails. The important implication of lack of a steady state for constant rate multiple dosing (or infusion) is also pointed out.

## **I-64 Aris Dokoumetzidis Numerical solution of nonlinear fractional compartmental systems**

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**Objectives:** We present a method to formulate and solve numerically, nonlinear pharmacokinetic systems which include fractional rates. As an example we consider the fractional Michaelis - Menten (MM) kinetics.

**Methods:** In [1] a method of formulating compartmental systems with linear fractional differential equations (FDE) was introduced with applications in pharmacokinetics. Here we extend this formulation to nonlinear FDEs. We further report a method to solve numerically such systems by finite differences (FD) based on [2] but with modifications to account for the special form of the equations that we use. A simple linear FDE of a one-compartment PK model with fractional elimination and constant infusion which has an analytical solution was solved with the FD algorithm and the numerical solution was compared to the analytical one. Further, a nonlinear model of a two compartment model with fractional MM elimination of order  $\alpha$  was solved with the FD method. The special case when the order was set to  $\alpha=1$  was also compared to the output of a Runge - Kutta algorithm, MATLAB ode45.

**Results:** Since the formulation of our FDEs includes derivatives on the left and the right hand side, the original algorithm of [2] had to be modified. The finite differences scheme became implicit instead of the explicit of [2] and therefore an additional step of numerically solving an algebraic equation was introduced at each step of the integrator. The FD numerical algorithm gave identical results to the analytical solution of a linear FDE, proving that it works well, for linear systems. The FD algorithm provided a solution for a nonlinear system of FDEs. In the case where the order of the FDEs was set to 1, the FD algorithm provided the same result as a common Runge - Kutta routine. This algorithm can also be used for linear systems as an alternative to the Numerical Inverse Laplace Transform method that we proposed in [1] since it may be faster and more stable.

**Conclusion:** An algorithm to solve numerically nonlinear systems of FDEs was shown to perform well. This algorithm can be considered as general purpose and may be used for linear systems too.

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## **II-13 Axel Facius Modelling and Simulation based Techniques to support Trial Design and Submission of Daxas**

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Roflumilast, an oral selective PDE4 inhibitor has been recently approved in EU, US and Canada as treatment that reduces the rate of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Model based techniques were used to describe the primary clinical endpoint (reduction in the number of exacerbations) and secondary endpoint (change from baseline (cfb) FEV<sub>1</sub>) in two pivotal phase III trials.

**Objectives:** The objectives of this analysis were to develop statistical models to describe the effect sizes in both clinical endpoints and to simulate these outcomes in two pivotal trials.

**Methods:** Data from six phase II/III trials (~5600 patients) were used to develop a nonlinear mixed effects model describing FEV<sub>1</sub> with time. Data from two phase III trials (~2500 patients) were used to develop a generalized linear model (negative binomial model) to describe exacerbation rates per patient per year. The models were qualified using posterior predictive checks.

**Results:** The FEV<sub>1</sub> model described the data from all six trials very well. Significant covariates were dose (PK information was not available), baseline FEV<sub>1</sub> % pred., reversibility, and the symptom (cough and sputum) score. The predicted effect size for the two pivotal trials was 47.2 mL difference between placebo and treatment.

The initial exacerbation model did describe the data with relatively large variability. The exacerbation data contains comparatively little information because there is only one value per subject and the response variable is categorical. PK information was not available to develop a PK/PD model. We used the strong correlation between the effect sizes on predicted mean cfb FEV<sub>1</sub> and exacerbations as an additional source of information by adding the predicted change from baseline FEV<sub>1</sub> as covariate. The final exacerbation model included predicted mean cfb FEV<sub>1</sub>, baseline FEV<sub>1</sub> % pred, symptom score, ICS pre-treatment, gender and dose. The model predicted effect size was 16.7%.

**Conclusions:** Mean cfb FEV<sub>1</sub> could be used as a marker of exacerbation rate. Combining correlated endpoints might substantially increase model quality and precision of predictions when used as additional sources of information about individual effect sizes. The model predictions were very accurate: Observed effect sizes were 48 mL (FEV<sub>1</sub>) and 17% (exacerbations) in recently completed Phase III studies.[1]

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## **II-19 Christina Friedrich Comparison of Statistical and Physiological Modeling Methods Using Examples in Drug Discovery and Development**

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**Objectives:** Both statistical (e.g., NLME) and physiological (systems biology ODE models based on physical laws and physiological knowledge) modeling methods can be used to support decision-making in drug discovery and development. There is a lack of clarity in the field about which method is appropriate under what conditions. This study delineates (1) what questions can be addressed, (2) what data are needed, (3) how hypotheses are used and tested, and (4) how to build confidence in each kind of model.

**Methods:** The authors systematically reviewed ten examples from their modeling disciplines in similar therapeutic areas to address the research questions above.

**Results:** (1) Statistical modeling is best suited to quantify pharmacokinetic/pharmacodynamic processes and to separate/quantify different sources of variability. Physiological modeling is ideal for exploring mechanistic connections between pathophysiology, therapeutic pathways and outcomes. (2) Statistical models are fully inferred from clinical or pre-clinical data sets with most model parameters being estimated; the model complexity is determined by the data. Physiological models start with knowledge and hypotheses of biological processes. Many types of data are used to inform and parameterize the models. (3) The statistical modeling process is guided throughout by the hypotheses to be tested: for model building, addition of mechanistic components, covariate relationships etc. In physiological models, scope is guided by the decision to be made, modeling uncovers knowledge gaps, and the models facilitate investigation of the systemic implications of alternative hypotheses. (4) For statistical models, many tools are available to evaluate models internally and externally and assess goodness of fit. For physiological models, matching data is also critical, and additional criteria must be met to ensure that the model is relevant and adequately addresses uncertainty and variability.

**Conclusion:** Statistical and physiological modeling methods in drug discovery and development share some attributes, which should help make each method conceptually accessible to practitioners of the other. There are also distinguishing features that could inform choice of approach and interpretation of results. Based on our exercise, we conclude that the methods are complementary. Additional work is under way to crisply define hand-off points and methodologies to optimize overall use of modeling in drug discovery and development.

## II-47 Vijay Ivaturi Selection Bias in Pre-Specified Covariate Models

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**Objectives:** Often covariate parameter relations are chosen *a priori* such as in the full model[1] approach or the partial stepwise covariate model building (SCM)[2] approach where covariates are investigated for some parameters only. The relations chosen may overlook true relations, which exist between an available covariate and a parameter of the model. The objective of this work was to investigate the risk of bias of parameter estimates and inflated Type I error, when a true covariate relation is ignored. A secondary objective was to explore potential base-model predictors which can be used to predict risk of parameter bias and false positive relations in such situations.

**Methods:** Sparse and rich data were simulated from PK and PD models with a true covariate parameter relationship. Estimation models where the true effect was ignored and the covariate was included on other parameters were fit to these data. Type 1 error and bias in parameter estimates of covariate relations were assessed for these estimation models where the true covariate relation was ignored. The predictors evaluated for Type I error inflation included: richness of the data, correlation between estimates, shrinkage, magnitude of covariate effects and sample size. These methods were also evaluated on real datasets.

**Results:** In general when a true effect was ignored, but the covariate was included on another parameter, there was a substantial bias in the estimated covariate relation. There was also an increased Type I error for the estimated covariate parameter relation. No explanatory variables were selected as reliable predictors of this increased false positive risk but in general, sparseness of data and correlation between the false and true thetas correlated positively with risk of bias and false positives. These results were consistent when evaluated on real datasets.

**Conclusions:** When choosing covariate relations *a priori* such as in the full model or the partial SCM approach, there is an increased risk of bias on covariate effects or false positives respectively. In case of the full model approach a way to avoid risk of bias could be to always include covariates of interest on all parameters of the model. For the partial SCM, it is relatively easy to extend the scope of models to test after the initial search. In that second search covariates found on some parameters should then be tested on those not explored during the initial partial SCM.

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## II-53 Åsa Johansson Comparison of methods for handling missing covariate data

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**Background:** Inclusion of important covariates in non-linear mixed effects modelling will reduce the unexplained inter-individual variability and improve the predictability of the model. Missing covariate data is a common problem and the method chosen for handling missing data can be crucial for the outcome of the study. Missing data can be divided into three categories: missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) [1]. For MCAR, the missingness does not depend on any observed or unobserved data; for MAR, the missingness depends on observed data but not on unobserved data; and for MNAR, the missingness depends on the unobserved missing data itself. The underlying mechanism of the missingness is usually unknown but will affect the predictability of the model if wrong assumptions are made.

**Objective:** The aim of this study was to implement and compare different methods for handling missing categorical covariate data under different mechanisms of missingness.

**Methods:** A simulation model was set up to generate data for 200 individuals. 60% of the individuals were assigned to be males and 40% females. Weights were simulated according to truncated lognormal distributions where the sex-specific means and variances had been estimated from a big dataset with 1022 males and 423 females. The PK model was a constant infusion model with a 100% difference in CL between males and females (estimated as two fixed effects), an inter-individual variability of 30% and a residual variability of 20%. Three different types of missingness were simulated; MCAR, MAR and MNAR. For each type of missingness, 50% of the individuals were assumed to lack the covariate sex. For MCAR, all individuals had the same probability to miss sex information; for MAR, the underlying mechanism gave a higher missing probability with increasing weight; and for MNAR, the underlying mechanism gave a three times higher missing probability for males than females. Different methods for handling missing covariates were compared: multiple imputation (MI), modelling with \$MIX based on observed WT (MOD) [2] and modelling with \$MIX based on observed WT with estimation of an additional fixed effect (EST). For comparison purposes, estimation with all data (ALL) was carried out and also with simpler imputation algorithms, but the relatively poor performance of the latter is not reported below. Implementation of MI, MOD and EST needed additional estimations, and for MI additional simulations had to be carried out. The function  $p(\text{male}|\text{WT})$  was estimated prior to estimation with MOD and EST, as a logit-transformed linear regression equation (incorrect regression function), or as a more appropriate probability density function based on estimated lognormal WT distributions for males and females, respectively. MI was a modified version of the method described by Wu and Wu [3]. The covariate imputation was preceded by an estimation of the PK model without inclusion of any covariates followed by an estimation of the probability curve for  $p(\text{male}|\text{WT}, \text{EBE})$ , where EBE is the Empirical Bayes Estimate estimated from the base model, and the two WT functions described above were explored in parallel. Prior to the estimations with MI simulations took

place to impute the missing sex values based on the probability functions and the individual WT and EBE values. The imputation step followed by estimation was repeated six times after which the mean value of each parameter was calculated. A Stochastic Simulations and Estimations (SSE) analysis was utilized to compare the methods. 200 datasets were simulated and the methods were compared according to bias and precision of parameter estimates. The OFVs obtained with MOD and EST were compared and a significant drop in OFV was taken as an indication of data being MNAR and/or a probability equation with poor predictability. In those cases when a significantly lower OFV was obtained with EST parameter estimates obtained with this method was used for calculation of bias and precision, otherwise estimates obtained with MOD were used. Root mean squared error in  $\theta$  estimates were evaluated for each parameter in each method and were expressed as % of RMSE compared to ALL (rRMSE).

## Results:

**MCAR:** MI gave unbiased estimates for all parameters and the precision was almost as high as for estimation with all data even when the regression curve was used to describe  $p(\text{male}|\text{WT})$  (114-124% rRMSE). MOD/EST gave slightly biased estimates of the fixed effects when the regression curve was used (122-133% rRMSE) whereas MOD/EST gave unbiased and precise estimates of the fixed effects when the probability density function was used. When the probability was described with a regression equation, 25.5% of the simulated datasets were estimated with a significantly lower OFV for EST compared to MOD whereas 1.5% were estimated with a significantly lower OFV for EST when the probability density function was used.

**MAR:** The results were similar to MCAR, but both MI and MOD were more sensitive to the misspecification of the regression equation.

**MNAR:** An overprediction of CL for both males and females was observed for MI when the regression curve was used (208-209% rRMSE). EST had a significantly lower OFV in 99.5% of the simulated datasets when the regression curve was used and MOD/EST resulted in a small downward bias (114-123% rRMSE). When the probability density function was used, 48.5% of the simulated datasets had a significantly lower OFV for EST and an upward bias was observed for the fixed effects (132-138% rRMSE).

**Discussion:** With an increase in the use of combined analysis, appropriate handling of missing covariates is likely to be of increasing importance. Simplistic strategies like data omission, imputation of mode or other single imputation methods were, as expected, found to be suboptimal compared to MI and MOD/EST (not shown). Estimation of a regression curve for the missing covariate based on observed covariates is a commonly used method but this study shows that erroneous assumptions about the probability curve may have a substantial effect on the parameter estimates for all underlying mechanisms of missingness. The problem is less pronounced for MI where the EBEs stabilize the regression curve. The MI method used assumes low EBE shrinkage and higher EBE shrinkage will lead to greater bias and lower precision for MI.

**Conclusions:** When covariate missingness is important to handle appropriately, MI and/or MOD/EST may be appropriate but the methods differ in their robustness to misspecification of the relation to known covariates, missingness mechanism and data richness. This work outlines the relative merits of these methods.

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## **II-57 Takayuki Katsube Evaluation of Stepwise Covariate Model Building Combined with Cross-Validation**

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**Introduction:** Covariate models are often built using a stepwise covariate model building (SCM), a procedure which is not intrinsically designed for providing good predictive performance. Cross-validation (XV) is a procedure for estimating the prediction error using multiple subsets of a dataset and may be used to select an appropriate model size [1]. If the main goal is predictive modeling, SCM combined with XV for determining model size may be useful.

**Objectives:** The objective of this study is to evaluate covariate model building using SCM combined with XV.

**Methods:** Five-fold XV was used in this study. The dataset was randomly split into 5 parts with approximately equal number of subjects. Each part and the remaining 4 parts were used as test data and training data, respectively. Using each training data, covariate models were built using SCM with or without linearization (a further development of [2] using the FOCE approximation). At each step in the SCM, the objective function values on the corresponding test data (XV OFV) were calculated without re-estimating (MAXEVAL=0 in NONMEM), to evaluate the predictive performance. The datasets were randomly split 3 times. Consequently, the sum of XV OFV on 15 test data sets was calculated by the number of relations. The number of relations where the sum of XV OFV was minimal was taken to be an appropriate model size. Pharmacokinetic datasets for phenobarbital (4 test relations), moxonidine (13 test relations) and pefloxacin (14 test relations) were used to evaluate the procedure.

**Results:** The sums of XV OFV were minimal at 2 relations for phenobarbital and moxonidine, while for pefloxacin, the minimum of sum of XV OFV was at the maximal number of relations. The results in terms of optimal model size were the same for SCM and linearized SCM. In that respect, there were larger differences in prospective OFV between random splits within a method, than between the linearization or not. The optimal number of relations predicted by SCM combined with XV was the same (phenobarbital and moxonidine) or larger (pefloxacin) than when using standard SCM (forward addition ( $p < 0.01$ )).

**Conclusions:** These results suggest the possibility of covariate model building using SCM combined with XV. Using XV to determine suitable model size is expected to give better predictive model performance. Using the linearized SCM speeds the process up and makes SCM combined with XV feasible for real world problems.

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## **II-58 Ron Keizer The bootstrap of Stepwise Covariate Modeling using linear approximations**

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**Background:** Stepwise covariate modeling (scm) is a tool for automatized building of a covariate model on top of a base structural model [1]. Previously we have shown that using a linear approximation to the base model in the scm provides similar results compared to an scm based on the original model, while greatly reducing computation times [2]. Performing a bootstrap analysis of the scm can provide valuable information, e.g. about the type I error of covariate inclusion (through inclusion of a random covariate), correlations between covariate inclusions, and influential individuals. However, a bootstrap of a regular (non-linearized) scm may require considerable computation time, easily taking up to weeks or months depending on model complexity and size of the dataset. A bootstrap of a linearized scm can be performed much faster, typically within a day.

**Objectives:** To compare results obtained with the linearized and non-linearized bootstrap-scm.

**Methods:** Two real datasets were used for which a structural model had been developed earlier. Dummy covariates were introduced into the datasets based on the randomized original covariates, to allow for investigation of type I error for covariate inclusion. Three methods of performing the bootstrap-scm were implemented: (i) linearized scm, with bootstrap based on the original dataset, (ii) linearized scm, with bootstrap based on the dataset with derivatives obtained from linearizing the base model and fitting the original dataset (for a faster, but more approximate, linearized scm), (iii) non-linearized scm with bootstrap based on the original dataset.

Results obtained with the linearized and non-linearized bootstrap methods were compared using histograms of covariate inclusion and plots showing the distribution of covariate model size. Based on the full covariate models constructed for each bootstrap sample, several additional diagnostic plots were constructed to study the variability and correlations in covariate inclusion, and the prevalence of influential individuals in the dataset. Additionally, the 200 final covariate models obtained in the bootstrap-scms were re-estimated using the original dataset, and the OFV compared to the OFV of the final models obtained from the scm on the original dataset.

**Results:** Covariate inclusion rates were very similar between the two linearized bootstrap-scm methods. Generally, the linearized bootstrap-scm showed slightly lower covariate inclusion rates than the non-linearized scm. Distributions of covariate model sizes were highly similar between the two linearized methods, and were also similar to the non-linearized bootstrap-scm. Diagnostic plots for the bootstrap-scm included covariate inclusion rates for single covariates, inclusion rates for combinations of covariates (correlation), histograms of the most common combinations of covariates, the distribution of covariate model size, and plots to study influential individuals. Overall, these plots showed similar results for the linearized and non-linearized

bootstrap-scm. Interestingly, a small fraction (~10% for both datasets) of the final full covariate models obtained in the bootstrap procedures showed a lower OFV than the final model in the original scm, when the final (non-linearized) model was refitted on the original dataset. For both datasets, the linearized methods both completed within a day, while the non-linearized bootstrap-scm took several days to complete. The linearized bootstrap based on the dataset with derivatives (ii) was fastest.

**Conclusion:** This analysis showed that linearization of the model allows the implementation of a bootstrap-scm within a reasonable time-span, while producing results comparable to a bootstrap-scm based on the original non-linearized model. Several diagnostic plots were proposed for the bootstrap-scm to aid the construction of the covariate model.

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## **II-62 Akash Khandelwal Influence of Correlated Covariates on Predictive Performance for Different Models**

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**Objectives:** To compare the predictive performance of different model building methods in the presence of covariate correlation.

**Methods:** A one compartment first-order absorption model was used to simulate concentrations. A dataset comprising of 100 individuals, each with 3 sampling times and 2 normally distributed covariates (COV1 and COV2), was simulated 100 times under different scenarios: (A) COV1, but not COV2 is related to CL, (B) both COV1 and COV2 are related to CL, (C) neither COV1 nor COV2 are related to CL i.e. the base model. Each scenario is simulated with different correlation between COV1 and COV2 (0, 0.3, 0.5, 0.7 and 0.9). Each scenario was analyzed using models including: no covariate, COV1, COV2, or both COV1 and COV2. In addition stepwise covariate model building (SCM; likelihood ratio test; p

**Results:** The addition of a false covariate to a model with a true covariate effect lowers the predictive ability of the model as evidenced by the increase in the prospective OFV (albeit similar for different strengths of correlation). Best predictive performance came from the use of the true covariate model. Second best predictive performance was provided by SCM, regardless of scenario. When a covariate containing information is not included in the model the prospective OFV is higher than the model with included covariate, regardless of correlation to informative covariate.

**Conclusions:** The selection of a covariate model can be pre-defined or data-driven. In this limited case it was shown that unless the true model is pre-selected, the data-driven approach provided the best predictive performance regardless of covariate correlation. When either of two correlated covariates may contain information about the parameter in question, pre-selection of one may harm the predictive performance of the resulting model.

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### III-11 *Natacha Lenuzza* Development of a PK library of parent drug/metabolite integrated models

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**Objectives:** Variations of drug metabolism in patients can prevent therapeutic efficacy or lead to toxicity. The CIME cocktail [1] has been designed to measure *in vivo* the phenotypes of 10 major enzymes involved in drug metabolism (Cytochromes P450, glucuronyl transferase, active transporters) by simultaneous quantification of 10 substrates and their main metabolites, and subsequent estimation of appropriate PK parameters by non-linear mixed-effect modelling. However, no models combining both the parent drug and its metabolite are yet available in the main PK software. We have thus developed and validated such a library in the PK-PD MONOLIX reference software [2].

**Methods:** Analytical solutions were obtained by using the Laplace transform, and identifiability was assessed by similarity transform approach or by integro-differential algebra using DAISY software [3]. Both solutions and equations were implemented in MLXTRAN. To illustrate the use of our library, we carried out a simulation study with the acetaminophen parent drug and its metabolite acetaminophen glucuronide (which are both measured in the CIME approach). The selected model (2-compartments/1-compartment with Tlag for the parent drug absorption) was chosen to generate data, according to different sampling schemes (rich or sparse), a log-normal distribution of random effects and a proportional residual error model. Parameter estimations were performed with MONOLIX and results were evaluated in terms of bias, standard error (SE) and relative efficiency to evaluate the reliability of estimations. To assess the robustness of MONOLIX estimations, misspecified models were also evaluated (*i.e.* normal distribution of random effect, or additive residual error).

**Results:** Models accounting for 1/1, 1/2, 2/1 and 2/2 compartments, with or without Tlag, first-pass effect and equal volumes, for either a single-dose intravenous or oral administration, were implemented. Our simulation study shows good convergence and reliable, robust estimations of parameters with MONOLIX. Interestingly, by using ordinary differential equations (ODE) instead of analytical solutions, we observed smaller SE in the case of rich data and higher efficiency in the case of sparse data.

**Conclusions:** A comprehensive library of integrated parent drug/metabolite models has been developed and validated. Such models will be of high interest to quantify drug metabolism and drug-drug interactions in human.

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### **III-18 Eleonora Marostica Population state-space modelling of patient responses in antidepressant studies**

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**Objectives:** A major challenge posed by the analysis of the clinical scores used to assess the disease status in depression trials is the lack of "first principles" from which response models can be derived. The state-space framework, which is based on a set of differential (or difference) equations that describes the evolution of one or more variables characterizing the patient's health state [1], represents an appealing and more mechanistically driven approach to describe these data. In order to develop a comprehensive state-space approach, we address two main questions: (i) do state-space models give adequate descriptions of the clinical response? (ii) how should flexible dosing schedules be handled within a state-space framework?

**Methods:** A double-blind, randomized, placebo controlled, flexible dose depression trial was used as a benchmark for alternative state-space approaches. Discrete- and continuous-time stochastic processes (i.e. integrated random walks and integrated Wiener processes [2, 3]) were used to describe the time-course of the HAMD score, within the framework of population modelling. In particular, each individual curve was expressed as the sum of an average curve and an individual shift, both described as random processes whose statistics were specified through hyperparameters. Dose changes were modelled as impulses on the second derivative of the patient's score. According to an empirical Bayes paradigm, hyperparameters were estimated through Maximum Likelihood. Estimation and post-processing were carried out with R 2.10.0 [4].

**Results:** Even low-order discrete- and continuous-time state-space models were able to fit very satisfactorily the whole range of shapes observed in individual responses. Moreover, the explicit description of dose changes improved the performances in terms of residuals. The continuous-time model appears to be marginally superior to the discrete-time one.

**Conclusions:** The results demonstrate that state-space approaches not only provide adequate description of population responses but are also easily adapted to account for possible dose changes during the trial. Among the advantages, there is the possibility to model the presence of random perturbations that affect the patient's health state. A further step to explore is the development of an integrated response and dropout model within the state-space framework.

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### **III-19 Hafedh Marouani Kinetic nomograms assist individualization of drug regimens**

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**Objective:** The aim of this work is to propose a rapid and simple drug dosage adjustment method. Develop a useful tool in achieving individual drug blood levels within its therapeutic window with few samples and in a short period of time, rendering the procedure a simplified bedside application.

**Methods:** The procedure is codified by kinetic nomograms. To obtain these, statistical description of the inter-individual variability provided by the population pharmacokinetic study (prior information) and assayed drug concentrations from two blood samples in a given individual (individual information) are required. The kinetic nomogram is built as a collection of time-concentration curves following a fixed "identification protocol". The time-concentration curves divide the "time-concentration space" in several areas each of them corresponding to a given adjusted dose. One has only to locate the assayed drug concentration and then, read the dose corresponding to the area containing this location. Kinetic nomograms are simplified alternatives to the Bayesian procedure [1] followed by dosage adjustment procedures. Evaluation of kinetic nomogram performances was done by a simulation study using as example rapamycin (sirolimus®), an immunosuppressant drug indicated for the prophylaxis of renal allograft rejection [2]. All calculations were performed with the MATLAB software [3].

**Results:** The simulation study confirmed the need for individual dosage adjustment, 71.6% of individuals underwent modification of the identification protocol of 1 mg b.i.d. in order to reach steady-state trough levels at 8 ng/ml. When regimens were adjusted by kinetic nomograms and Bayesian procedure, the minimum steady-state concentrations of sirolimus showed low variability (CV of 23.4 and 18.2%, respectively) as compared to those obtained by standard recommended protocols of 4 mg o.i.d. (68.6%). Doses adjusted by kinetic nomograms and Bayesian procedure are linearly linked and highly correlated ( $r = 0.97$ ), and both provided efficient control (87.9 and 99.6% of cases between 6 and 20 ng/ml respectively).

**Conclusion:** Kinetic nomograms allowing rapid dosage adjustment after beginning the drug therapy represent reliable alternatives to the cumbersome Bayesian procedure. They could be tailored for several clinical situations and different schedules. The presented kinetic nomograms can highly promote other population studies aiming at dose individualization with direct application in current clinical settings.

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### **III-23 Christophe Meille PK/PD Model of skin toxicity in animal reported as binary outcome**

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**Objectives:** Develop a PK/PD model for skin toxicity in animal and provide a quantitative basis for preclinical safety assessment.

**Material and Methods:** The PK and tolerability of drug X targeting the ERK pathway was investigated in rats ( $n = 150$ ) in a repeated oral dose toxicology study with 4 week recovery period. Drug X was administered once daily for 4 weeks orally by gavage at dosage levels 0.25, 1, 4, 16 mg/kg/day. For each individual, the skin toxicity was reported daily as a binary outcome. The number of incidences of skin toxicity was dependant of the administration protocol. Decrease of skin toxicity frequency was observed during the recovery period. PK samples were collected in a satellite group on the first and last administered dose. A PK/PD model was used for describing damage kinetics function of time and binary outcome. The structural model was built of 1) the PK model, 2) the skin damage model and 3) the probabilistic model. For PK a 1 compartment model with first order absorption and elimination was used. The skin damage model is represented by an indirect response model. In this model, concentration of the drug blocks damage compartment elimination through an  $I_{max}$  model (Dc50 parameter). The damage value is the input function to a Logit model which describes the probability of the toxic event function of the damage value. Model parameters were identified to the observed data using population approach with Monolix 3.2 software [1].

**Results:** All PK and PD parameters were well identified, with a Dc50 of 0.1 ug/ml and  $k_{out}$  of  $0.0012 \text{ h}^{-1}$ . Gender was identified as a relevant covariate on clearance. An overlay of the predicted probability of skin toxicity and observed frequency for each dosing group showed the model flexibility to describe the observations. Simulations are done to show risk profile for different protocols.

**Conclusion:** This example shows the fit of a PKPD model on binary outcome data. Logit model can easily be extended to more categories, describing different grades with ordered categorical data. The model can be applied across various species.

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### III-61 *Klaas Prins* Use of a generalized poisson model to describe micturition frequency in patients with overactive bladder disease.

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**Objectives:** Daily micturition frequency is a key endpoint for assessing overactive bladder disease activity. Micturitions are count data and are commonly modeled assuming the Poisson distribution, which assumes equidispersion, meaning that mean and variance are the same. However, observed within-individual variance is consistently lower than within-individual mean micturition frequency. Being encouraged by a recent study addressing underdispersion in Likert pain rating scales [1], we evaluated model fit attributes of the same structural micturition model while comparing a generalized Poisson (GP) that flexibly describes under and over dispersion versus the standard Poisson (PS) distribution.

**Methods:** Placebo micturition count data from 3058 patients participating in 7 studies were modeled as  $\text{mict} = \text{mict}(\text{base}) * (1 - \text{plmax} * (1 - \exp(-k * t)))$ , in NONMEM7, with METHOD=SAEM followed by MCMC Bayesian. Parameter plmax was logit-transformed to ensure that predicted mict never went below zero. Lognormal between subject variability (BSV) was assumed on  $\lambda$  (PS) or  $\lambda_1$  (GP) and additive BSV was assumed on plmax (PS, GP). In the generalized Poisson equation [2], a  $\lambda_1$  and a dispersion factor  $\lambda_2$  are estimated, where the mean of the distribution is  $\lambda_1 / (1 - \lambda_2)$  and the variance is  $\lambda_1 / (1 - \lambda_2)^3$ . In the special case of  $\lambda_2 = 0$ , the GP model collapses to a PS. Models were compared by Objective Function Value (OFV), ability to capture mean trends and observed variability using Visual Predictive Check (VPC), and precision of parameter estimates.

**Results:** The mean trend in the data was equally well captured by both models. The GP model was significantly better than the PS model as compared by the lower mean OFV (104,822 vs. 93,612) which is a >11,000 point drop. The VPC showed that the PS model under predicted the 5<sup>th</sup> and over predicted the 95<sup>th</sup> confidence interval, while the GP model captured them remarkably well. Parameter estimates of the placebo model were 5% (plmax), 51% (k), 19% (BSV  $\lambda$  or  $\lambda_1$ ), and 32% (BSV plmax) more precise for the GP model than those of the PS model.

**Conclusions:** The GP model was found to be superior to the PS model in describing the variability observed in micturition count data and yielding more precise parameter estimates. The GP model will as such provide more accurate inferences, such as drug efficacy predictions and clinical trial simulations.

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### **III-60 Klaas Prins Modeling urge urinary incontinence data acknowledging non-Poisson dispersion of counts within individual provides a major model fit improvement.**

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**Objectives:** Daily number of urge urinary incontinence (UUI) episodes is a count endpoint for assessing overactive bladder disease activity and commonly modeled using Poisson (PS) regression. PS assumes equi dispersion, meaning that mean is equal to the variance. However, UUI data are over-dispersed, i.e. individual variance > individual mean. The observed UUI distribution is very skewed and contains a large number of zeroes, which result in poor model fits under the standard PS models. The generalized Poisson (GP) distribution flexibly handles over-, equi- as well as underdispersion, and recently successfully described underdispersed Likert pain scores [1]. We wanted to evaluate if the GP distribution could also successfully describe the distribution of overdispersed count data in a model of UUI.

**Methods:** Placebo UUI count data from 200 patients participating in 2 studies were modeled as  $UUI = UUI(\text{base}) * (1 - \text{plmax} * (1 - \exp(-k * t)))$  in WinBUGs assuming PS or GP count distribution. Parameter plmax was logit-transformed to ensure that predicted UUI did not go below zero and a Gamma distributed between subject variability was assumed on  $\lambda$  (PS) or  $\lambda_1$  (GP),  $\lambda_2$  (GP) and plmax (PS, GP). The GP equation [2] features a lambda ( $\lambda_1$ ) and a dispersion factor ( $\lambda_2$ , with  $\lambda_2 < 0$  pointing to under-,  $\lambda_2 = 0$  being equi- and  $\lambda_2 > 0$  indicating over dispersion), where the mean is defined by  $\lambda_1 / (1 - \lambda_2)$  and the variance by  $\lambda_1 / (1 - \lambda_2)^3$ . In case  $\lambda_2 = 0$  the GP model collapses to a PS. Models were compared by the significance of the dispersion parameter estimate, the Deviance Information Criterion (DIC) and ability to capture mean trends and observed variability using VPC.

**Results:** The mean trend in the data was equally well captured by both models. The GP model estimated a  $\lambda_2$  of 0.37 (SE 0.02) that was highly significantly different from zero, thus confirming within-subject over dispersion of counts. Furthermore, the DIC of the GP model dropped a few hundred points indicating a highly significant model fit improvement over the PS model. The VPC showed that the PS model under predicted observed variance, while the GP model captured variance remarkably well.

**Conclusions:** The GP model was found to be superior to the PS model in terms of describing the variability observed in UUI count data and yielding a significantly positive dispersion parameter. The GP distribution for UUI data will as such provide more accurate inferences, such as between treatment comparisons and clinical trial simulations.

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### III-62 Patanjali Ravva Covariate Modelling in Aggregate Data Meta Analysis: A Simulation Study Evaluating Performance of Model Linearization

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**Objectives:** This simulation study evaluated a proposed method based on second order Taylor series approximation for fitting covariate models to aggregate data (AD) or combined AD and individual patient level data (IPD), as analyzing AD data with IPD models leads to biased parameter estimates [1,2].

**Methods:** This simulation study is motivated by the meta-analysis of HbA1c lowering (% change from baseline) at 12 weeks following treatment using DPP4 inhibitors. An Emax model with effects of Baseline HbA1c and Age on Emax parameter described well the individual patient data from an internal compound.

IPD of a continuous clinical endpoint (CFB) for 5 drugs (A to E) of similar class were simulated using an Emax dose response model. The model incorporated effects of two continuous covariates on Emax parameter using a power function. A total of 18 studies (2, Drug A; 4, Drugs B to E) each with 5 dose groups (including placebo) and 50 individuals per group were simulated.

A total of 9 scenarios exploring the combination of effects (small, moderate and large) of varying degree of nonlinearity with respect to covariates, and of between study to within study covariate variability were performed (500 per Scenario). For each simulation run, two additional datasets were created by reducing IPD to AD and by combining AD and IPD from Drug A (ADIPD).

Four models were proposed to analyze these data. IPD was modelled with an IPD model (original model); AD was modelled with an AD model (similar to IPD model, with summary values in place of individual values and residual error appropriately corrected for sample size). Additionally, an aggregate model (AD\_Lin) was derived using a second order Taylor series approximation of the IPD model and fit to AD. Finally, ADIPD were modelled using a combination of IPD and AD\_Lin models.

The bias and precision in parameter estimates under four models were assessed.

**Results:** The bias in estimated Emax parameter under various simulation scenarios are presented below

		Model	Nonlinearity		
			Small	Moderate	Large
Between Study to Within Study	Small	IPD	<1%	<1%	<1%
		AD	3%	24%	70%
		AD_Lin	<1%	2.04%	9%
		ADIPD_Lin	<1%	2%	8%

Variability	Moderate	IPD	<1%	<1%	<1%
		AD	2%	12%	32%
		AD_Lin	<1%	2%	5%
		ADIPD_Lin	<1%	1%	4%
	Large	IPD	<1%	<1%	<1%
		AD	1%	6%	16%
		AD_Lin	<1%	1%	3%
		ADIPD_Lin	<1%	1%	3%

**Conclusions:** Parameter estimates from the AD model can be severely biased. The proposed linearization method based on Taylor series approximation adequately addresses the issue of bias when modelling aggregate data using nonlinear models.

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#### **IV-01 Alberto Russu Integration of response, tolerability and dropout in flexible-dose trials: a case study in depression**

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**Objectives:** The difficulties arising when analyzing depression trials are manifold, as a comprehensive model, in addition to the efficacy endpoints, should account for: (i) flexible dosing schemes, (ii) dropout events, and (iii) drug-related adverse effects. Simplified modelling approaches that neglect some of the above aspects may yield biased results. In this work we investigate an integrated approach based on the joint population modelling of response, tolerability and dropout. The proposed methodology is used to analyse data from a flexible-dose, placebo-controlled, Phase II depression trial. As an extension of previous work [1,2], in this study we account for flexible dosage regimen and adverse events as covariates in the dropout model.

**Methods:** The time course of the HAMD score was described as the sum of a Weibull and a linear function [3]. The dose escalation was included in the model as a covariate on two of the four structural parameters. We investigated three different dropout mechanisms: missing completely at random (MCAR), at random (MAR) and not at random (MNAR) [4]. The dropout probability was modulated using three covariates: the time course of the clinical outcome, dose escalation, and the occurrence of clinically relevant adverse events in the drug arm. The population model was implemented in WinBUGS 1.4.3 [5].

**Results:** With respect to previous approaches [1,2], which used only the HAMD score as a covariate in the hazard model, the proposed method achieved comparable goodness-of-fit to HAMD data. However, the inclusion of dose escalation and drug-related adverse events in the hazard function yielded a substantial benefit in the description of the dropout process, as witnessed by the Deviance Information Criterion [6], parameter estimates, and the modified Cox-Snell residuals [4]. Comparison of the dropout mechanisms suggested a MNAR dropout process in both treatment arms. The ability of the proposed model to reproduce realistic dropout patterns was assessed via Kaplan-Meier visual predictive checks [7].

**Conclusions:** Our results show the feasibility of a joint model accounting for the HAMD time course, discontinuities in the dosing schedule, dropouts and adverse events. Indeed, in the study here analyzed, the dropout process was influenced by all the above aspects. Thorough modelling approaches that integrate all the relevant information are necessary to provide a more comprehensive assessment of antidepressant drug response.

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## **IV-14 Doerthe Steller Extension of Continuous-Time PK/PD Markov Models to Published Count Data**

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**Objectives:** Availability of rich clinical data forms the basis of reliable PK/PD modeling. Incorporation of literature data is an important goal whenever individual study data is sparse or erratic. Joint (Meta) analysis of data from multiple sources provides reliable models capable for further simulations and decisions over subsequent study designs and trial success. Markov models have been successfully applied in several categorical PK/PD modeling tasks for individual data. Aim of this work was hence to extend the Markov approach to aggregated data settings.

**Methods:** Markov modeling techniques had to be developed and refined for summarized rather than individual categorical data. This was exemplified by published Infliximab data from the studies ACT1 and ACT2 for the treatment of Ulcerative Colitis (UC) [1, 2]. Literature data was processed for Markov model needs, i.e. subjects in the states of 'remission', 'no 'remission' and 'dropout' were summarized at the time points given. A structural PK/PD model was established with continuous transitions between those discrete model states and incorporation of a stimulating drug effect.

Markov models were implemented in NONMEM 7.1.2 via the Kolmogorov backward equations [3]. Since published count data instead of individual data formed the base of analysis, a binomial likelihood was to be minimized for the parameter estimation process. Model quality was assessed by simulations with Trial Simulator software (Version 2.2.1, Pharsight Corporation, Mountain View, CA).

**Results:** The continuous-time Markov approach was successfully transferred and adapted from the individual to the aggregated categorical data setting. A three-state Markov model on the basis of published mean data only was built which adequately described disease progression as shown by VPCs. This comprehensive model could then be used for simulations of different scenarios and comparison to other treatments of UC (competitive profiling).

**Conclusions:** We have developed Markov modeling and simulation techniques for individual, aggregated or combined categorical data and encourage its use and further exploration.

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### **IV-23 Nadia Terranova A non parametric population approach for selecting biomarkers of a drug action**

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**Objectives:** Intravenous treatment with a candidate drug administered at its optimal pharmacological dose was evaluated in healthy mice and in mice exposed to an inflammatory insult, with respect to a broad panel of inflammatory biomarkers. Three groups of animals were considered: two different groups were exposed to inflammatory insult 3h before the intravenous treatment with the investigated compound or its vehicle, one additional group was exposed to saline (that does not cause inflammation) 3h before the treatment with the same compound. Inflammatory biomarker concentrations were measured at different time points using a serial sacrifice design (6 mice for each time point for each group). The objective of the study was to determine which inflammatory biomarker was modulated by the compound under investigation.

**Methods:** The concentration curves, both typical and individual ones, were modeled as stochastic processes, in which the only requirement was a certain degree of regularity of the time profiles. A Markov Chain Monte Carlo algorithm was applied to perform the Bayesian estimation of typical and individual Areas Under the concentration-time Curves (AUCs) [1]. A comparison with the Bailer method was also performed.

**Results:** The method was applied to real data-sets. For each biomarker, the typical AUC and corresponding confidence interval in the three different groups were computed. Then, they were compared to find those biomarkers that were differently expressed in the three groups. They represent the best candidates to assess the drug effect.

**Conclusions:** The best experimental design and then the number of samples is usually limited by many practical factors, i.e. costs and ethical issues. This work presents an application of a nonparametric Bayesian approach for estimate the distribution of the AUC of a typical subject in a population study with a destructive sampling protocol. The method allows a sound comparison of different experimental conditions to select suitable biomarkers of the compound action. This method has a wide applicability in several (similar) situations involving sparse sampling and population studies.

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#### **IV-25 Michel Tod A meta-analysis regression model for quantitative prediction of the impact of polymorphism on drug exposure**

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**Objectives:** A framework to predict quantitatively the impact of CYP2D6 polymorphism on drug exposure is proposed. The metrics of interest is the ratio of drug AUC in mutant to wild-type patients. A model was derived to rely the AUC ratio with two characteristic parameters, one for the drug (the fraction metabolized by CYP2D6 in vivo, CR), the other for the genotype (the fraction of activity with respect to the homozygous wild type, FA). Any combination of alleles, as well as duplications, may be accommodated. The model allows to combine all available data arising from all drugs and genotypes.

**Methods:** The primary goal of the analysis was to estimate the CRs and FAs for 40 drugs and 5 classes of genotypes respectively, including poor, intermediate, and ultra-metabolizers. Data were available for 73 (drug, genotype) couples. A three-step approach was applied. First, initial estimates of CRs and FAs were obtained by several methods, using data from the literature. Second, an external validation of these initial estimates was carried out, by comparing the AUC ratios predicted by the model equation to the observed values, using a second set of published data. Third, refined estimates of CRs and FAs were obtained by a bayesian orthogonal regression, using all the data and initial estimates of CRs and FAs from step 1. The posterior distributions of the AUC ratios, CRs and FAs were obtained by Monte Carlo Markov chain simulation by using WinBugs 1.4.

**Results:** With the refined estimates, the mean prediction error of AUC ratios was -0.05, while the mean prediction absolute error was 0.20. The model may be used to predict the variations of exposure for all 200 combinations between drugs and genotypes. An application to a rare combination of alleles (\*4\*10) is described.

**Conclusion:** The predictive performances of the model were good. The method is very easy to use, once the characteristic parameters (CRs and FAs) have been established. This framework may be easily applied to other polymorphisms.

## **IV-29 Kuenhi Tsai Evaluating Bootstrap Methods in Nonlinear Mixed Effect Models (NMEM) Using a PK Model**

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**Objectives:** The bootstrap methods in PK/PD studies have not investigated the bias and reliability of various bootstrap confidence interval (CI) methods or the application of using the parametric (residual) bootstrap method performed [1]. In addition, the bootstrap distribution and CI of PK/PD parameters are often compared to the parameter estimation and its derived CI of the original data as a tool of model validation. The legitimacy of this approach is explored here. The objectives are (1) to utilize statistical criteria to investigate the bias and reliability of popular bootstrap CI methods, (2) to compare nonparametric and parametric bootstrap (residual) methods, and (3) to assess whether bootstrap distribution and CI can be used for model validation.

**Methods:** Nonparametric (sample with replacement) and parametric (residual) bootstrap methods are investigated. Bootstrap confidence intervals were constructed using percentile, t interval, bias-corrected, bias-corrected and accelerated, and hybrid approaches. The simulated PK model was a one compartment model with first-order absorption. Two sampling schemes with small and moderate number of subjects were investigated. 100 replicates of the dataset were generated for each scheme with 100 times of bootstrapped samples for each replication. The parameters were assessed using bias, standard deviation, root mean squared error, and the coverage probability of 95% CIs. The performance of bootstrapping was also evaluated in the event that an inter-subject variability on the absorption rate was incorrectly specified.

**Results:** The nonparametric method is superior to the parametric method in bias and CI coverage of the clearance and its inter-subject variability. The standard normal method has a better coverage than the rest of the methods. All bootstrap CI methods perform equivalently well in the nonparametric method. When the model is incorrectly specified in the smaller random error case, all parameters except the intra-subject variability term have a good coverage with all the methods. The coverage of the CIs for the intra-subject variability is low for the standard normal method and all bootstrap CIs.

**Conclusions:** The nonparametric method is concluded to be better than the parametric method may be due to the limitation of the current parametric bootstrap method that only resamples the intra-subject random error. However, the coverage is no better than the standard normal method in both rich and sparse sampling. Since most PK/PD models assume normal or log-normal distribution random errors, application of the bootstrap CI methods to get better estimation of CI is questionable. The similar parameter estimation and CI coverage of the original data set and bootstrap data in misspecification results show bootstrap CIs cannot serve as a tool for model validation if the model is incorrectly specified in the original data.

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**IV-48 Thomas Wendl Modeling of renal failure, dialysis, inhalation and mechanical ventilation: Development of a whole-body physiologically-based pharmacokinetic (PBPK) model for ICU patients with and without renal failure receiving inhalatively administered Amikacin via a tracheal tube.**

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**Objectives:** Aim of this study was to establish a whole-body PBPK model for inhalative administration of Amikacin to renally impaired volunteers and to intubated and mechanically ventilated ICU patients with ventilator associated pneumonia (VAP).

**Methods:** : A whole-body PBPK model for inhalative administration of Amikacin to healthy volunteers was parameterized using the software tools PK-Sim® and MoBi® [1] to account for renal failure and inhalation via a tracheal tube, common findings in intensive care unit (ICU) patients. Renal failure was taken into account by reduction of glomerular filtration rate (GFR), a continuous veno-venous hemodiafiltration (CVVHDF) by insertion of an additional clearance into the venous blood plasma and hemodialysis by a temporary operation of a plasma clearance process. Systemic uptake from alveolar lining fluid (ALF) was adjusted to measured concentration time profiles in ICU patients after inhalation of Amikacin via the tracheal tube [2, 3].

**Results:** The whole-body-PBPK model for inhaled Amikacin combined with a reduction of renal clearance and in some cases inclusion of hemodialysis is able to describe the measured plasma concentration-time profiles of Amikacin in renally impaired volunteers. To describe inhalation in intubated and mechanically ventilated ICU patients, a reduction of the fraction deposited in the alveoli as well as an increase in paracellular lung uptake is necessary. An increase of paracellular uptake could be explained by inflation of the lungs through the ventilator. A model accounting for both, the reduced clearance of renally impaired and fast systemic uptake in mechanically ventilated ICU patients is able to predict the PK of Amikacin in intubated and mechanically ventilated ICU patients with acute renal failure with great accuracy. This is shown in a visual predictive check with clinical data.

**Conclusions:** The established PBPK model can be used to predict time-resolved concentrations of Amikacin in pulmonary lining fluids, lung interstitium and lung cells of intubated and mechanically ventilated ICU patients, and therefore, allows for estimation of local efficacy.

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### **I-01 Leon Aarons Population Pharmacokinetic Analysis of Ropivacaine and its Metabolite PPX from Pooled Data in Neonates, Infants and Children**

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**Objectives:** The aim of the present study was to characterize ropivacaine and PPX pharmacokinetics and factors affecting them in paediatric anaesthesia.

**Methods:** Population pharmacokinetics of ropivacaine and its active metabolite PPX were estimated following single and continuous ropivacaine blocks in 192 patients aged 0-12 years from six pooled published studies. Unbound and total ropivacaine and PPX plasma concentration and PPX urinary excretion data were used for non-linear mixed effects modelling by NONMEM. Covariates included age, body weight, gender, ethnic origin, ASA, site and method of administration and total dose.

**Results:** One-compartment first-order pharmacokinetic models incorporating linear binding of ropivacaine and PPX to  $\alpha 1$ -acid glycoprotein were used. After accounting for the effect of body weight, clearance of unbound ropivacaine and PPX reached 41% and 89% of their mature values, respectively, at the age of 6 months. Ropivacaine half-life decreased with age from 13 h in the newborn to 3 h beyond 1 year. PPX half-life differed from 19 h in the newborn to 8 - 11 h between 1 and 12 months to 17 h after 1 year. Simulations indicate that for a single caudal block the recommended dose could be increased by a factor of 2.9 (0 to 1 month group) and 6.3 (1 to 12 year group) before the unbound plasma concentrations would cross the threshold for systemic toxicity. Corresponding factors for continuous epidural infusion are 1.8 and 4.9.

**Conclusion:** Ropivacaine and PPX unbound clearance depends on body weight and age. The results support approved dose recommendations of ropivacaine for the paediatric population.

## I-04 *Hesham Al-Sallami* A semi-mechanistic model for estimating fat free mass in children

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**Objectives:** Body size correlates with clearance and can be used to scale drug doses. Lean body weight (LBW) has been proposed to be a better size descriptor than other measures of weight. Mathematical models for estimating LBW (approximated by fat free mass, FFM) have been developed in adults. There are currently no models available to predict in children. The aim of this project is to develop a semi-mechanistic model to quantify FFM in paediatric patients.

### Methods:

- A general model for maturation was developed for FFM using NONMEM VI. An index dataset (496 females and 515 males) containing demographic data and body composition measurements was used to estimate model parameters. Missing data were imputed.
- An empirical model for FFM was developed using STATA 11.
- The predictive ability of the adult model (Janmahasatian et al, 2005) and the general maturation model were evaluated with respect to the empirical model using the mean squared error (MSE).
- A test dataset (90 females and 86 males) was used to evaluate the general maturation model.

### Results:

- A semi-mechanistic sigmoid Emax maturation model was developed:

$$\text{FFMchildren} = \text{FFMbaseline} + \frac{\text{AGE}^{\text{GAMMA}}}{(\text{AGE}^{\text{GAMMA}} + \text{AGE50}^{\text{GAMMA}})} \times (\text{FFMadults} - \text{FFMbaseline})$$

- An empirical model with 9 terms (including interactions) was developed using mixed-effect linear regression.
- Using the index dataset, the adult model had a variance of 15 kg<sup>2</sup> whereas the maturation model had a variance of 12 kg<sup>2</sup>. The increment in MSE using the adult model in relation to the empirical model (which had a variance of 6 kg<sup>2</sup>) was 146%; the increment in MSE using the maturation model in relation to the empirical model was 99%.
- Using the test dataset, the adult model had a variance of 16.5 kg<sup>2</sup> whereas the maturation model had a variance of 12.2 kg<sup>2</sup>. The increment in MSE using the adult model in relation to the empirical model (which had a variance of 8.5 kg<sup>2</sup>) was 94%; the increment in MSE using the maturation model in relation to the empirical model was 44%.

**Conclusions:** The adult model provided an unbiased descriptor of FFM in children. The general model for maturation for FFM provided a more precise estimate of FFM in children than the adult model. The loss of predictive performance was significantly less for the general model for maturation compared to the adult model for both internal and external evaluation.

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## **I-27 Marion Bouillon-Pichault Pharmacokinetic design optimization in children and estimation of maturation parameters: example of cytochrome P450 3A4**

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**Objectives:** The pharmacokinetics of drugs in children is different from those in adults, because of growth and maturation. It is commonly accepted that clinical investigations with children are difficult, in particular because of recruitment difficulties. Metabolic pathways have maturation patterns that change from one another. The aim of this work was to determine whether optimizing the study design in terms of ages and sampling times for a drug eliminated solely via cytochromes P450 3A4 (CYP3A4) would allow us to accurately estimate the pharmacokinetic parameters throughout the entire childhood timespan, whilst taking into account age- and weight-related changes.

**Methods:** A linear monocompartmental model with first-order absorption was used successively with three residual error models and previously published pharmacokinetics parameters ("true values"). The optimal ages were established by D-optimization using the CYP3A4 maturation function to create "optimized demographic databases". The post-dose times for each previously selected age were determined by D-optimization using the pharmacokinetic model to create "optimized sparse sampling databases". We simulated concentrations by applying the population pharmacokinetic model to the optimized sparse sampling databases to create optimized concentration databases. The latter were modelled to estimate population pharmacokinetic parameters. We then compared true and estimated parameter values.

**Results:** The established optimal design comprised four age ranges: 0.008 years old (i.e. around three days), 0.192 years old (i.e. around three months), 1.325 years old and adults, with the same number of subjects per group and three or four samples per subject, in accordance with the error model. The population parameters that we estimated with this design were precise and unbiased (root mean square error [RMSE] and mean prediction error [MPE] less than 11% for clearance end distribution volume and less than 18% for  $k_a$ ), whereas the maturation parameters were unbiased but less precise (MPE<6% and RMSE<37%).

**Conclusions:** Based on our results, taking growth and maturation into account a priori in a pediatric pharmacokinetic study is theoretically feasible. However, it requires that very early ages be included in studies, which may present an obstacle to the use of this approach. First-pass effect, alternative elimination routes and combined elimination pathways should also be investigated.

### **I-36 Massimo Cella Implementation of Pharmacokinetic Bridging for Drug Combinations in Children**

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**Objectives:** The aim of this investigation is to show the relevance of adaptive protocols for dose selection in paediatric trials in early clinical development. The combination of antimalarial drugs atovaquone (ATV) and proguanil (PGN) was used as paradigm for the purposes of our evaluation.

**Methods:** Population pharmacokinetic models were developed for ATV and PGN using historical data in adults. Target exposure values for ATV and PGN were considered comparable in adults and children. Using simulations, a paediatric population (n= 40) was evaluated according to a range of scenarios in which clearance varied from 20% to 100% of the adult values, or allometrically correlated with body weight. The same initial dose was administered in all scenarios and the simulated concentration time profiles were then fitted using the SAEM method in NONMEM 7. Doses were adapted, if necessary, based on the individual AUC estimates.

**Results:** Systemic exposure expressed as AUCs (geometric means + percentiles) was significantly different across scenarios. Despite the evidence for higher exposures when the clearance was lower than in adults and high variability in drug disposition across the population, adaptation (titration) procedures were effective in ensuring target exposure was achieved in each individual patient.

**Conclusions:** An adaptive trial protocol is critical for accurate paediatric dose selection when evaluating drug combinations. It enables implementation of bridging concepts, taking into account the impact of covariates and other sources of variability on systemic exposure, which cannot be factored in a typical fixed design protocol. In contrast to current beliefs regarding the use of allometric methods only, flexible trial protocols are required to ensure target exposure is achieved for both active moieties.

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### **I-38 Pascal Chanu A dose selection rationale based on hemodynamics for sildenafil in pediatric patients with pulmonary arterial hypertension (PAH)**

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**Objectives:** The efficacy of medications in PAH is mainly based on improvements in exercise capacity: six-minute walk distance (6MWD) or peak oxygen consumption (pVO<sub>2</sub>) in adults. In children  $\geq 7$  y, 6MWD is not well reproducible and pVO<sub>2</sub> is thus the preferred test. In younger patients an exercise capacity test is not doable and hemodynamic endpoints may be used to assess efficacy [1, 2]. A recent FDA analysis [3] showed a relationship between changes from baseline in 6MWD and pulmonary vascular resistance index (PVRI) in the adult PAH population. Sildenafil (REVATIO®), 20 mg TID, received approval for the treatment of adult PAH in the US based on 6MWD data. The objective of this analysis was to support the dose selection of sildenafil in the pediatric PAH population using a model-based approach to pulmonary vascular resistance (PVR) outcomes bridging efficacy from adults to children.

**Methods:** A population PK/PD analysis of PVR data from two pivotal sildenafil trials in adult [4] (n=218) and pediatric patients [5] (n=219, 1-17 y) was performed in NONMEM 7. A model was developed to characterize the relationships between PVR, baseline pathophysiological covariates and sildenafil exposure (obtained using a previously developed population PK model [6, 7]). Simulations based on clinically defined success criteria to achieve similar hemodynamic responses in children compared to those seen in adults under the labeled dose were conducted to support the dose selection in pediatric PAH patients.

**Results:** PVR was modeled as a function of baseline covariates (functional class, etiology, age, body surface area, ability for exercise capacity assessment) and sildenafil exposure. Model based simulations suggested that for children a dose of 10 mg TID up to 20 kg and 20 mg TID beyond achieves a comparable PVR response to adults at the labeled dose of 20 mg TID, i.e., a 20% improvement in change from baseline in 40% of patients. Clinical results and similar analyses [8, 9] on pVO<sub>2</sub> data in children 7-17 y confirmed the selected regimen.

**Conclusions:** A recent FDA assessment of the relationship between 6MWD and PVRI proposes the use of HD endpoints to support drug development in PAH especially in the pediatric population. Leveraging the FDA assessment, contrasting it with Pfizer's sildenafil data, and utilizing model based simulations of HD endpoint outcomes allowed bridging efficacy from adults to children supporting dose recommendations for sildenafil in pediatric PAH patients.

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## **I-48 Karina Claassen Evaluation of a PBPK Model for Preterm Neonates by Predicting Paracetamol Pharmacokinetics**

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**Objectives:** This work aimed to validate the recently developed physiologically-based pharmacokinetic (PBPK) model for preterm neonates [1] by predicting the pharmacokinetics of paracetamol, a drug that undergoes hepatic clearance processes in addition to the renal excretion.

**Methods:** The recently presented model for preterm neonates has been extended by integrating information about hepatic enzyme ontogeny in fetuses and neonates. Propacetamol, a prodrug of paracetamol, was chosen as a model drug due to the multitude of processes involved in its elimination (renal excretion and hepatic metabolism via cytochrome P450 2E1, sulfotransferase 1A1, and UDP-glucuronosyltransferase 1A6) and the availability of therapeutic drug monitoring (TDM) data in 48 neonates reported by Allegaert et al. [2-3]. In this study, preterm neonates with a postmenstrual age of 27 to 43 weeks of gestation and a postnatal age of one to 76 days were given either single (n=30) or multiple doses (n=18) of propacetamol as an infusion over 15 minutes. Pharmacokinetics of paracetamol were predicted on the basis of a previously established paracetamol model for adults taking into account the anatomy and physiology of preterm neonates and postnatal changes such as body weight gain, changes in organ composition and blood flow changes.

**Results:** After integration of the developmental changes in preterm neonates that occur after birth and data on enzyme ontogeny, the extended PBPK model for preterm neonates could successfully predict individual paracetamol plasma concentrations for all postmenstrual and postnatal ages included in this study.

**Conclusions:** The good prediction of paracetamol elimination indicates a reasonable description of the ontogeny of the eliminating organs and the enzymes involved. In the future, this PBPK model might help to facilitate dose and dosing regimen decisions in preterm neonates.

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## II-05 *Cyrielle Dumont* Design optimisation of a pharmacokinetic study in the paediatric development of a drug

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**Objectives:** In the context of the Paediatric Investigation Plan [1] in place since 2007, pharmacokinetic (PK) studies in children are strongly supervised. Indeed, the blood volume, which can be taken in a child, is limited and studies are analysed by NonLinear Mixed Effect Models (NLMEM) [2,3]. The choice of the PK design has an impact on the precision of parameters estimates. To that end, approaches based on the evaluation of the Fisher information matrix (MF) [4] are used and implemented in software packages, as PFIM [5,6] in R. Our aim was to optimise the PK sampling time design for the paediatric trial of a drug X in development, taking into account clinical constraints. To evaluate designs, a priori information is needed. For the present study, we used 'simulated' plasma concentration in children, obtained via the SIMCYP software from knowledge of the drug in adults and its physico-chemistry properties [7,8].

**Methods:** The molecule breaks down into parent drug and its metabolite, which is active. A first work was performed to find the starting dose of the drug X in the paediatric trial [9]. The PK model, obtained from the 'simulated data' with the software NONMEM, using a joint model for the parent drug and its metabolite as in adults, was a model with four compartments. The PK design, for a future study in 82 patients receiving a single dose of the drug, was then optimised by PFIM, considering several clinical constraints, as the number of groups, the timing of the clinical examination and the duration of stay at the hospital. Limit of quantification (LOQ) was not taken into account for design optimisation, as the simulated observation had no LOQ. For final evaluation of the proposed design, we used an approach based on the simulated proportion of LOQ at each sampling time to predict data below LOQ for the metabolite.

**Results:** Reaching a compromise between PFIM results and clinical constraints, the optimal design is composed of four samples at 0.1, 1.8, 5 and 10 h after drug injection. Concerning LOQ, we showed its limited influence on the design.

**Conclusions:** PFIM was a useful tool to find an optimal design in children, considering clinical constraints. Even if it was not forecast in the initial design at the beginning, it was necessary to include a late time at 10 hours for all children. Finally, we proposed to carry out an adaptive design after the inclusion of 20 children.

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## II-08 Esther Encinas Fentanyl pharmacokinetic and pharmacodynamic (PK/PD) estimation in neonates and infants using allometric and ontogeny methods

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**Background:** Use of fentanyl for prolonged sedation in neonates and infants has become increasingly widespread. Usually, dose schedules are extrapolated from adults, but this is questionable because dramatic age-related changes on PK/PD take place after birth.

**Objectives:** The aim of this study was to develop and validate a predictive PK/PD model of fentanyl for sedation in neonates and infants, based on the integration of knowledge on the drug behaviour in adults and physiological changes during development.

**Methods:** Two approaches were used for estimation of tricompartamental PK parameters [1] [2]. A) Allometric equations based on body weight and postmenstrual age were used for all volumes of distribution (V) and clearances (Cl). B) Physiologically based ontogeny: V1 and V2 were estimated from the extracellular and total body water content, respectively. V3 was obtained from the adult ratio V1/Vss and V3/Vss (assumed to be constant at all ages). Intercompartmental clearances (CLd1 and CLd2) were related to cardiac output. Factors accounting for age-related changes on  $\alpha_1$ -glycoprotein (AAG), CYP3A4 and liver blood flow were estimated [3] and applied for obtaining the intrinsic and systemic Cl in each age range. Simulations on different ages and dosing protocols were performed in NONMEM using the estimated parameters. A semiparametric model [4] was used for PD, after scaling of the effect compartment equilibrium rate constant (Keo) according to brain perfusion.

**Results:** Parameters obtained by approaches A and B were compared with those described in the literature [5], although published data were scarce and heterogeneous. In contrast to the allometric method, physiologically based model seemed a good predictor as bias was statistically different from zero. For a representative newborn, the following parameters were obtained: 1.26, 2.63, 22.02 and 25.90 L for V1, V2, V3 and Vss, respectively; 0.03, 0.44 and 0.21 L/min for Cls, CLd1 and CLd2, respectively. PK/PD integration suggests that neonates and infants could not reach the target concentration in the effect compartment early after general schedules for sedation.

**Conclusions:** The developed physiologically based model satisfactorily predicts PK/PD in the studied ages, which allows proposals of new dosing regimens. However, given the important variability observed in this subpopulation, monitoring of plasma levels is highly recommended. In this sense, the present model could aid in optimizing the sampling protocol.

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## II-12 David Fabre Population Pharmacokinetics of Alfuzosin in children and adolescents

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**Objectives:** The objective of this analysis was to develop and qualify a combined PopPK model for two formulations (solution and sustained release tablets) of alfuzosin administered in children and adolescents, and to investigate the influence of key demographic parameters (i.e., body weight, age, sex, race) and renal function (measured by  $Cl_{CR}$ ) on alfuzosin PK.

**Methods:** The analysis was based on plasma samples from 3 pediatric clinical studies using the NONMEM computer program (version VI level 1.2) running on LINUX. All runs were performed using the FOCE method. Mono- and bi-compartmental models with and without lag time with zero or first order absorption were evaluated. Formulation was included as a straightaway covariate on  $K_a$ , in order to be able to develop a PopPK model for solution and tablet formulations, according to:  $ka(L/h)=TVKa+\theta(6)*(1-Form)$ .

**Results:** The data Set was composed of 209 patients (841 samples, age ranging from 2 to 17 years, weight from 10 to 90 kg), 134 receiving the solution (572 samples) and 75 the tablet (269 samples). The structural PK model was a bi-compartment model with a formulation-dependent absorption constant ( $K_a$ ,  $0.0.0990\text{ h}^{-1}$  for tablet and  $0.293\text{ h}^{-1}$  for solution), characterizing the first-order absorption process from the depot to the central compartment. Oral clearance was  $7.88\text{ L/h}$  and was related to body weight according to:  $CL/F(L/h)=7.88+0.535*WT$ . Oral distribution volume  $V2/F$  was  $12.9\text{ L}$ . The peripheral compartment was related to the central one by an inter-compartmental clearance  $Q/F$  of  $5.7\text{ L/h}$  and described by an apparent distribution volume  $V3/F$  of  $185\text{ L}$ . Inter-patient variability in the  $CL/F$ ,  $V2/F$  and  $V3/F$  and  $ka$  was about 42.2 %, 57.5 %, 159 % and 39.0 %, respectively. The residual variability was about 36.5 %. Sex, Age, Race,  $Cl_{CR}$  and Dose (0.1 or 0.2 mg/kg/day) had no influence on alfuzosin PK.

**Conclusions:** A PopPK model was developed and validated with data from 209 patients of 3 pediatric studies treated with alfuzosin solution or tablet formulations at 0.1 or 0.2 mg/kg/day. This model, parameterized as a 2-compartment model with first-order formulation-dependent absorption process, showed a good agreement between predicted and observed plasma concentrations for solution and tablet.

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## II-32 *Andreas Velsing Groth* Predicting paediatric PK in order to investigate it

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**Objectives:** Scaling of PK parameters for a given drug from adults to children is typically done using standard allometric scaling exponents (0.75 and 1 for CL and V, respectively). However, if the drug bears similarities in chemical structure and likely clearance mechanisms to another drug with both adult and paediatric PK data available, assuming an adult-paediatric PK parameter relationship similar to that of the well-known drug may be a better prediction for the new drug than using standard scaling parameters.

The objective of the present work is to investigate the use of prior PK data to predict paediatric PK in order to improve the quality of paediatric PK assessments and hence paediatric dose and therapeutic results [1].

**Methods:** The population PK analyses were performed in NONMEM VII using adult and paediatric PK data with 7 samples per subject for the 1<sup>st</sup> generation drug and adult PK data with 14 samples per subject from 2<sup>nd</sup> generation drug.

The sample size N required to achieve a 95% confidence interval within 60-140% of the point estimate of the population value is calculated as  $N = (CV/\log(1.4)/t(0.975, N-1))^2$ , where CV is the coefficient of variation of the relevant PK parameter to be estimated.

**Results:** The estimated allometric exponents for CL and V from the combination of adult and paediatric PK data of the 1<sup>st</sup> generation drug were 0.577 (95% CI: 0.37-0.79) and 0.77 (95% CI: 0.55-0.99), respectively. These estimated exponents were subsequently used for the estimation of the 2<sup>nd</sup> generation drug's PK parameters, leading to estimates for unexplained between subject variability of 12 and 10 CV% for CL and V, respectively.

Assuming rich PK sampling in children (7 samples per child), the estimated paediatric sample size required to achieve 95% confidence intervals within 60-140% of the point estimate for the population typical values of CL and V with the 2<sup>nd</sup> generation drug was 3 children in each age group defined as 2-<6 and 6-<12 years.

A proposed sparser sampling schedule (4 samples per child) focusing on the early part of the plasma profile was predicted to increase the required recruitment to 4 children per age group.

**Conclusions:** Using prior adult and paediatric PK data, a paediatric PK study of a 2<sup>nd</sup> generation drug was designed to get adequate PK information with feasible sample size and sampling. The proposed method of designing paediatric PK studies ensures informative paediatric data is acquired to inform dose selection and labelling.

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## II-39 Anna-Karin Hamberg Predictions of warfarin exposure and INR response in children

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**Background:** Warfarin therapy is challenging due to its narrow therapeutic range and pronounced inter-individual variability in dose requirements. Numerous studies have investigated causes of dose variability in adults, but there is still a paucity of data from warfarin treated children. It has been suggested that the PK in children  $\geq 2$  years in general can be predicted from prior information on adult PK parameters and body-weight adjustment. Hence, the main challenge with regard to dosing in children is to elucidate whether the PKPD relationship differs between adults and children [1]. We have published a population model for warfarin in adults [2], which after minor revisions could form the starting point for a pharmacometric model applicable to both adults and children.

**Objectives:** To assess whether allometric weight scaling of a published population model for warfarin can predict exposure and INR response in children.

**Methods:** The published PK and KPD models were adapted for allometric scaling by weight. The revised models were used to predict a sparse PKPD dataset from 52 Japanese children aged 1-18 years old that were genotyped for CYP2C9 (\*1/\*1 n=45, \*1/\*3 n=7) but not for VKORC1 [3]. When predicting INR, all children were assumed to be VKORC1 A/A, the dominant genotype (>80%) among Asians. VPCs were used to assess the predictive performance of the models [4] in both adults and children.

**Results:** The PK model performed well in the prediction of S-warfarin exposure in Japanese children aged 1-18 years old. Preliminary results with the KPD model also indicate a reasonably good agreement between predicted and observed INR response in children.

**Conclusions:** Allometrically scaled models developed from adult data appear to be a viable approach to overcome the paucity of warfarin data in children and should prove useful as a basis for individualised dosing recommendations in children. Additional data from warfarin treated children from all phases of therapy, especially start of treatment, and from different ethnic groups with diverse genetic profiles, are warranted for further evaluation of the predictive performance of the KPD model in children.

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## II-41 Sarapee Hirankarn Population K-PD Model of Sodium Nitroprusside in Neonates and Children During Anesthesia or Sedation

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**Objectives:** Sodium nitroprusside (SNP) is an effective hypotensive agent. Due to a short half-life and chemical instability, measurement of SNP concentration *in vivo* is not practical. The kinetic-pharmacodynamic (K-PD) model offers an approach that circumvents the absence of pharmacokinetic (PK) data. The objective of this analysis is to use a K-PD model to describe mean arterial pressure (MAP) response to SNP in neonates and children.

**Methods:** A total of 3038 MAP measurements were collected from 202 patients following IV administration of SNP. A population K-PD model was developed using NONMEM VI (FOCE). A one compartment disposition model with a nominal distribution volume of 1 L/70kg was assumed for SNP. Size and maturation differences in CL and V were described using theory based allometry and a sigmoid hyperbolic function [1]. An inhibitory sigmoidal  $E_{\max}$  model was used to describe the effect of SNP. The effect on MAP was assumed to be proportional to the amount in the effect compartment. The infusion rate producing 50% of  $E_{\max}$  ( $ER_{50}$ ) at steady state was calculated from the product of the nominal  $EC_{50}$  and CL. A power function of age was used to describe age related differences in baseline MAP. A mixture model was used to explain the wide variability in MAP response.

**Results:** The K-PD model with a mixture model on  $EC_{50}$  described the data with adequate precision. Population mean parameters (RSE) for baseline MAP,  $E_{\max}$ , low  $ER_{50}$ , and high  $ER_{50}$  were estimated to be 77 (1.4%) mm Hg, 19 (7%) mm Hg, 0.9 (14.8%) mg/h/70kg and 4.3 (21.0%) mg/h/70kg, respectively. The percentage of the sub-population with a high  $EC_{50}$  was 45% (13.3%). Baseline MAP increased with age. The estimated time for this population to reach 50% of mature CL is 107 (25%) weeks post-menstrual age. The effect compartment half-life of SNP was 6 (14.2%) minutes.

**Conclusions:** In the absence of PK data, the K-PD model provided plausible parameter estimates. The finding of two phenotypes with a 5 fold difference in infusion rate to reach the same MAP fall indicates that dose individualization based on MAP response is essential. These phenotypic differences may be due to a polymorphism in either clearance or  $EC_{50}$  or in both parameters.

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## II-45 Ibrahim Ince Population PK of midazolam from preterm neonates to adults, a maturation model

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**Objectives:** : A previous investigation showed major impact of critical illness on midazolam clearance, however no influence of age-related changes on the cytochrome P450 (CYP) 3A4/5 mediated clearance of midazolam was found in children between 1 month to 17 years of age.<sup>1</sup> In this analysis we aimed to develop a maturation model for CYP3A4/5 enzyme activity using midazolam clearance as *in vivo* probe, for preterm neonates from 26 weeks gestational age (GA) onwards to adults.

**Methods:** : Pharmacokinetic data after intravenous midazolam were obtained from 6 previously reported studies. Subjects were 32 non-ventilated preterm neonates (26-33.5 weeks GA and 3-11 days PNA)<sup>2</sup>, 24 preterm neonates with respiratory distress syndrome (26-37 weeks GA and 0-1 days postnatal age (PNA))<sup>3</sup>, 23 children after elective major craniofacial surgery (3-23 months)<sup>4</sup>, 18 pediatric intensive care (a term) patients (2 days to 17 years)<sup>5</sup>, 18 pediatric oncology patients (3-17 years)<sup>6</sup> and 20 healthy male adults (20-31 years)<sup>7</sup>. Population PK modeling was performed using NONMEM v6.2. In a systematic covariate analysis, the influence of PNA, GA, postmenstrual age, body weight (BW) and PELOD score (organ failure) was investigated.

**Results:** Upon inclusion of preterm neonate datasets, BW proved a significant covariate for clearance in a two-compartment model. The influence of BW was best described using an allometric equation with a BW-dependent maturational exponent (BWME):  $BWME = Coeff_1 \times BW^{exp2}$ , in which  $Coeff_1$  is the coefficient of the exponential function,  $exp2$  is the additional exponent of the exponential function. It was shown that BWME changed from 0.84 in preterm neonates to 0.44 in adults, with a  $Coeff_1$  of 0.8 (CV of 9.1%) and  $exp2$  of -0.141 (CV of 32.1%). BW was also linearly correlated with midazolam central volume of distribution.

**Conclusions:** A maturation model for midazolam clearance from preterm neonates to adults has been developed showing that CYP3A4/5 activity rapidly matures from (preterm) neonates up to children of 0.77-10 kg. Thereafter, maturation slows down resulting in minimal increase between 10 and 81 kg of body weight.

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## **II-56 Nastyia Kassir An Optimal Sampling Strategy for Tacrolimus in Pediatric Liver Transplant Recipients Based on a Population Pharmacokinetic Model**

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**Objectives:** Trough concentration is commonly used for tacrolimus (TAC) dosing optimization despite its inadequacy in predicting correct drug exposure. Although tacrolimus systemic exposure may be best reflected by AUC, extensive blood sampling is not suitable for outpatient monitoring. Instead, a model based AUC is being considered. Objectives were to 1) develop a population pharmacokinetic (PK) model for TAC in pediatric liver transplant patients; and 2) determine a limited sampling strategy that accurately predicts TAC exposure.

**Methods:** Study included 28 patients receiving TAC orally twice daily. Median patient age and weight were 7.3 years old, and 20.4 kg, respectively. A population PK model was fitted to whole blood concentration data (Phoenix<sup>TM</sup> NLME). Covariate analysis was performed using a stepwise forward additive and a backward elimination approach. Influence of the following covariates was explored: body weight, body mass index, age, gender, type of transplant (full or cut-down liver), liver function tests, hematocrit, hemoglobin, drug interactions, and time post-transplantation. Using the final model, a practical optimal sampling strategy was developed using WinPOPT software. The best limited sampling strategy among combinations of a maximum of four sampling time-points was tested. Precision of individual parameter estimates was obtained using simulation and re-estimation using a candidate design.

**Results:** Concentration-time profiles of TAC were adequately fitted by a 2-compartment model with first order absorption. Weight was found to be significant on both oral clearance (CL/F) and central volume of distribution (Vc/F). Although not statistically significant, CL/F had a trend to be higher in patients transplanted with full liver, as compared to those who received a cut-down liver. Estimates of CL/F and Vc/F for a patient weighing 20 kg were 16.9 L/h and 47.5 L, respectively. Based on the optimized sampling strategy, the expected standard error on population CL/F and AUC<sub>0-12</sub> was very low (1.9 %). This design also enabled the estimation of empirical Bayesian estimates of interest (CL/F and AUC<sub>0-12</sub>) with good precision.

**Conclusions:** The population PK model of tacrolimus, and empirical Bayesian estimates based on three or four blood concentration measurements, represent an accurate and convenient method to predict tacrolimus AUC<sub>0-12</sub> in pediatric liver transplant recipients, despite high inter-individual variability in PK and patient demographics.

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## II-63 *Sung Eun Kim* Population Pharmacokinetics of Theophylline in Premature Korean Infants

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**Objectives:** The aim of this study was to investigate the population pharmacokinetics of theophylline in premature Korean infants and to assess the influence of demographic and clinical covariates.

**Methods:** Forty-eight premature infants (24.4 - 36.6 weeks of gestational age (GA)), who received intravenous aminophylline or oral theophylline approximately every 8 or 12 hours were included in the population analysis. Trough levels (128 observations) and peak levels 1 to 4 hours after dosing (46 observations) were obtained from all infants. Body weight (BW), height, postnatal age (PNA), conceptional age (GA + PNA), presence of oxygen support, sex, delivery mode, serum AST, ALT, BUN, and creatinine (Cr) levels were included in the dataset for covariate analysis. Population pharmacokinetic models were built using NONMEM<sup>®</sup>, version VI).

**Results:** Theophylline population pharmacokinetics was described by a one-compartment model with rapid absorption ( $k_a=100$ ) and first-order elimination using the subroutines ADVAN2 and TRANS2. Regarding covariate selection, the effects of BW and serum Cr level were found significant for clearance and the effects of BW were found significant for volume of distribution, with BW most significant. The final estimates of pharmacokinetic parameters were  $CL (L/h) = 0.03 \cdot (BW/1.3)^{1.15} \cdot (Cr/0.54)^{-0.382}$  and  $V (L) = 1.7 \cdot (BW/1.3)^{1.82}$ . Interindividual variabilities (CV%) were 17% and 47% for clearance and volume of distribution, respectively.

**Conclusions:** The final model represented that BW and serum Cr level had significant effects on the theophylline pharmacokinetics in Korean premature infants. Further studies will be needed in a larger population to validate these results.

## II-64 *Holly Kimko* Disease-Drug Model of Methylphenidate (MPH) in Children with Attention Deficit Hyperactivity Disorder Via Longitudinal Meta-analysis

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**Objectives:** To develop disease (placebo)-pharmacokinetic-pharmacodynamic (D-PK-PD) population models that relate MPH concentration-time profiles from formulations with various release patterns and placebo with time courses of PD measures (i.e., SKAMP-Composite, PERMP-Attempted, and PERMP-Correct), using a meta-analytic approach to predict the time course of PD measures of any MPH formulation in a pediatric ADHD population.

**Methods:** Mean MPH concentration-time data from adult healthy volunteer studies of four MPH formulations (Concerta<sup>®</sup>, Ritalin LA<sup>®</sup>, Focalin XR<sup>®</sup> Metadate CD<sup>®</sup>); mean PD measures versus time data (and the number of subjects represented at each point) from pediatric efficacy trials of the MPH formulations; individual PD data for Concerta<sup>®</sup> (OROS methylphenidate) from 3 pediatric trials were used.

The pediatric PD data were used to build mixed effects models from the mean data. The observed SKAMP-Composite score was modeled as the sum of placebo and drug effects. The daily variations of the score for the placebo treatment were described by an indirect response model with the score linearly related to B, which is being produced with the constant rate  $k_{out}$  and is eliminated with the time-dependent rate  $\alpha(t) k_{out} B$  where  $\alpha(t)=1$  at night, and it has different values at two (final model) stretches of the day between waking up and going to bed. The drug effect was described by the  $E_{max}$  function of MPH concentrations with acute tolerance. Acute tolerance was accounted for by dependence of  $EC_{50}$  on *time* from the morning dose. Similarly, PERMP-Attempted and -Correct scores were jointly modeled.

The final meta-analysis models were used to construct the patient-level population models. Covariate and inter-individual random effects, and the residual variability were estimated.

**Results:** In total, 11 meta-patients were available. The estimated  $EC_{50}$  value was approximately 7.6 ng/mL, which is close to the MPH  $C_{max}$  at an intermediate (36-40 mg) dose of extended release MPH in adults. Modeling supports presence of time-dependent tolerance.

**Conclusions:** The models of the three PD measures have been developed using the meta-analysis and the patient-level population analysis. Internal and external evaluation demonstrated the ability of the models to predict mean time-course of the PD measures and their variability in the target population.

### III-03 *Elke Krekels* Maturation of glucuronidation; a system specific property

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**Objectives:** The maturation of morphine and propofol glucuronidation in children younger than 3 years was found to be best described by a bodyweight-based exponential equation with a similar exponents of 1.44 and 1.45 respectively<sup>1,2</sup>. This function is hypothesized to be a 'system specific' rather than a 'drug specific' property, which would imply that it can be extrapolated to other drugs that are metabolized through glucuronidation. This hypothesis is tested in the current study.

**Methods:** The current analysis was based on a dataset containing 473 zidovudine concentrations and 173 zidovudine-glucuronide concentrations collected in 29 individuals varying from term neonates to infants up to 5 months of age<sup>3</sup>. Two models were fit to these data, the first model used the developmental glucuronidation covariate model obtained previously with morphine. In this model, maturation of glucuronidation was described by bodyweight in an exponential equation with an exponent of 1.44 with reduced clearance capacity in neonates younger than 10 days. For the second model a comprehensive covariate model was developed using a systematic covariate analysis, this provides the best possible description of the data and therefore the comprehensive covariate model served as a reference model. In the comprehensive covariate model the most predictive covariate for glucuronidation maturation in the current dataset was postnatal age in a sigmoidal equation.

**Results:** Despite the different determinants for maturation of glucuronidation clearance between the two models, the developmental glucuronidation model obtained with morphine had similar descriptive and predictive properties compared to the fully optimized reference model, based on basic goodness-of-fit plots and NPDE analysis. The difference in the obtained covariate relationships are probably the result of the high correlation between bodyweight and age and the differences in age-range in the datasets on which the covariate models are based.

**Conclusions:** These findings support our hypothesis that maturation of drug metabolism is a system specific property. Provided a model is based on a sufficient number of individuals, broad range in covariate values and fully validated, use of information on maturational processes obtained in one drug, can significantly reduce time and costs of paediatric model development for new drugs.

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### **III-20 Amelie Marsot Population pharmacokinetics of Phenobarbital in neonates and infants.**

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**Objectives:** Phenobarbital is widely used for treatment of neonatal seizures and the prevention of neonatal hyperbilirubinaemia. A pharmacokinetic model of phenobarbital in 35 neonates and infants was described in 2005 by Yukawa et al., studying oral and rectal routes. A new model in a similar population is proposed for intravenous administration.

**Methods:** 27 neonates and infants (weight: 1.2-10.0 kg; PNA: 0-466 days) hospitalized in a pediatric intensive care unit, were studied. Total mean dose of 194 mg (40-450mg) was administered by 30-min infusion. Blood phenobarbital concentrations were determined by immunoassay method. Pharmacokinetic analysis was performed by using a non linear mixed-effect population model. Data analysing included calculation of performance error (PE), median performance error (MDPE) and median absolute performance error (MDAPE). A bootstrap was used as internal validation.

**Results:** Data were modelled with an allometric pharmacokinetic model using three-fourths scaling exponent for clearance and parameters. This one-compartment model gave the following results. The population typical mean (percent relative standard error (%RSE)) values for clearance (CL) and apparent volume of distribution (Vd) were 8.70 mL/H/kg (10.4%) and 1.44 L/kg (15.1%), respectively. The interindividual variability of Vd (%RSE) and intraindividual variability (%RSE) were 60% (25.0%) and 42% (27.9%), respectively. The indicators of predictive performance gave the following results: MDPE (range) was -9.5% (-74.4 to 131.7%) and MDAPE (range) was 30.1% (3.9 to 131.7%).

**Conclusions:** The pharmacokinetic parameters of intravenous phenobarbital in neonates and infants were estimated. The predictive performance was acceptable with a small bias. These intermediate results should be confirmed by the inclusion of new patients.

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### III-45 Parul Patel Dried Blood Spots and Sparse Sampling: A perfect combination for minimally invasive PK/PD studies in children

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**Background:** Dried blood spots (DBS) have recently received considerable interest for application to PK studies. The technique requires a micro (~50µl) blood-volume sample, and is therefore particularly advantageous to studies involving children and neonates. In-vitro validation of DBS based quantification techniques indicate a comparable performance to methods based on large blood-volumes. However, validation in the clinic is necessary to ascertain the robustness of the DBS sampling methodology as a means of generating population PK data in children.

**Objective:** To perform a clinical validation of the DBS technique in preterm neonates receiving caffeine therapy for apnoea of prematurity.

**Method:** In a prospective study, between 1-10 (15µl) DBS samples (total 338) were collected opportunistically from 67 preterm neonates at random times intervals post caffeine dose. Neonates received oral and iv caffeine doses according to the local protocol. Caffeine exhibits low plasma protein binding, does not bind to red blood cells (RBC) and has a blood-to-plasma ratio of 1. Therefore conversion of blood values for comparison was not necessary. The DBS caffeine concentration data was used to develop a Pop-PK model, and compared with a previously reported model based on conventional plasma caffeine concentrations.

**Results:** A 1 compartmental model with zero and first order absorption described the DBS data well. Parameters derived from DBS data were estimated with precision (RSE <10%) and were comparable to CL and V estimates from plasma (6.83 vs. 6.96ml/h/kg and 614 vs. 851ml/kg, respectively). Weight and postnatal age were the most influential covariates in the CL model which is in accordance to previous findings (Charles, 2008). Similar to Charles et al. the BOV in CL (31.2%) was higher than the BSV in CL (24.7%) which has important implications for caffeine TDM. Model evaluation using bootstrap and PC-VCP confirmed the robustness of the model.

**Conclusion:** The DBS based population model enabled precise estimation of caffeine PK parameters in preterm neonates. Furthermore, estimates were comparable to plasma literature values derived from a demographically similar neonatal population. DBS is potentially a more practical and ethical sampling technique in PK /PD studies involving young children provided there is sufficient understanding of the behaviour of the drug with respect to RBC association and protein binding.

**Reference:**

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### III-53 Chiara Piana Impact of non-adherence to antiretroviral therapy in HIV-infected children

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**Objectives:** Data exist showing failure of treatment with antiretrovirals due to inadequate adherence to the prescribed dosing regimen. Several studies have been performed to assess whether high rates of adherence are necessary to achieve and maintain viral suppression during the course of therapy [1, 2, 3]. However, none of these studies have explored compliance in a systematic manner, identifying which drugs are more likely to be affected by poor adherence. The aim of this investigation was therefore to evaluate the forgiveness of antiretroviral therapy to variable compliance, taking into account the differences in pharmacokinetics and pharmacodynamic properties of currently used drugs.

**Methods:** Simulation scenarios were evaluated using a hypothetical population of HIV-infected children (n=100) aged between three months and eleven years. Published pharmacokinetic and pharmacodynamic models were integrated with an established model for viral replication to predict treatment outcome based on different degrees of adherence to therapy for each class of drugs used in first-line therapy (non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors). The measures of interest were viral load and CD4 cell count. Text regarding objectives. Text regarding methods.

**Results:** Preliminary results suggest that efavirenz, a non-nucleoside reverse transcriptase inhibitor with long half-life and high potency, allows for variable quality of compliance, such as delays in drug administration, whilst it is more susceptible to interruption of therapy for long periods (2-3 weeks).

**Conclusions:** Despite its relevance in therapeutics, the implications of poor compliance and most importantly the degree of forgiveness of antiretrovirals has not been assessed in a quantitative manner. Our results show that simulations can be applied as a tool to explore non-adherence to treatment. The use of this model-based approach provides a framework for the optimisation of the dosing regimens for antiretroviral drugs, unravelling the set of pharmacokinetic and pharmacodynamic properties that are required for forgiveness.

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## IV-10 Ivy Song Dose Selection of Dolutegravir (DTG, S/GSK1349572) in Pediatric Studies

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Medicine, University of Alabama at Birmingham, Birmingham, AL, USA*.

**Objectives:** DTG is an unboosted, once daily integrase inhibitor currently in late stage clinical development for the treatment of HIV infection in adults. Evaluation of DTG in the pediatric population is now warranted necessitating the need for dosing recommendations. This analysis presents various methods used for the selection of dosing strategies and initial doses in an upcoming study in HIV-infected children and adolescents.

**Methods:** Target exposure of DTG was determined using pooled adult pharmacokinetic (PK) data obtained in Phase II. Initial dose(s) in various age ranges were proposed and justified based on review of approved pediatric doses versus adult doses of currently marketed antiretroviral agents as well as the predicted exposure in pediatric subjects through allometric scaling of adult PK parameters. Monte Carlo simulation was also performed to predict exposure at the proposed doses by weight band and to demonstrate the simulated exposure matches the pre-determined target exposure.

**Results:** Upon review of recommended dosing regimens of approved antiretroviral agents, the preferred dosing strategy in children was to dose DTG at fixed doses by weight band using either an adult tablet formulation or an alternative pediatric formulation. This approach generally makes prescribing much easier for clinicians and is expected to provide convenience and enhance compliance in pediatric subjects on HIV therapy. The following once daily doses were proposed for 6-18 years old children based on allometric scaling and Monte Carlo simulation: 50mg for subjects with weight of  $\geq 40$  kg; 35 mg for 30-<40kg; 25mg for 20-<30kg; and 20mg for 15-<20kg. Dosing in children younger than 6 years old has more weight cut-offs and will require a pediatric-friendly formulation to allow more dosing flexibility relative to the tablet formulation.

**Conclusions:** Fixed doses by weight band were selected for the planned pediatric study. In order to provide more flexible dosing, three different tablet strengths (10, 25, and 50mg) were recommended and are available to support the proposed dosing strategy in 6-18 years old children. The selected dosing strategy will serve as initial doses and real-time PK will be collected for area-under-the-curve targeted dose optimization.

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### **IV-31 Wanchana Ungphakorn Population Pharmacokinetics and Use of Monte Carlo Simulation To Determine Optimal Dosing Regimen of Oral Ciprofloxacin in Paediatric Patients with Severe Malnutrition**

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**Objectives:** Oral ciprofloxacin has been considered as an alternative antimicrobial agent for severely malnourished children. However, to date, there are no pharmacokinetic data in this patient population and an appropriate dosing regimen is not well defined. The aims of this study were to determine the influence of clinical characteristics on the population pharmacokinetics of oral ciprofloxacin in paediatric patients with severe malnutrition and consequently to define the optimal dosing regimen.

**Methods:** The study was conducted at Kilifi District Hospital, Kenya. Ciprofloxacin 10 mg/kg was administered 12 hourly for 48 hours and up to 4 samples were withdrawn at various times. The data were analysed with NONMEM [1] Version VI using FOCE with interaction. First order, zero order, and transit compartment absorption models were compared. Allometric relationships between oral clearance (CL/F) and volume of distribution (V/F) and weight were included in the base model. A range of clinical characteristics was examined for their influence on ciprofloxacin pharmacokinetics. A 10,000-patient Monte Carlo simulation was performed to determine the probability of achieving the target AUC of at least 125 and 35 for gram-negative and gram positive organisms, respectively. The cumulative fraction of response (CFR) were calculated [2].

**Results:** The data comprised 202 ciprofloxacin concentration measurements from 52 infants and children aged 8 to 102 months. A one compartment model with first order absorption and a lag adequately described the data. A combination of high mortality risk and serum sodium concentration provided the best fit for CL/F and sodium concentration for V/F. Inclusion of these factors reduced between subject variability in CL/F from 50% to 38% and in V/F from 49% to 43%. Absorption rate was poorly estimated and highly variable. Bootstrap, pc-VPC and npde results were satisfactory. With the current regimen, the breakpoint MIC was <0.06 mg/L for gram-negative organisms and was <0.25 mg/L for gram-positive organisms. The overall responses were >75% against *Salmonella* spp., *K. pneumoniae*, and *E. coli* but least than 50% against *P. aeruginosa* and *S. pneumoniae*. Higher doses provided a little advantage.

**Conclusions:** The findings suggest that the pharmacokinetics of oral ciprofloxacin in malnourished children are influenced by weight, serum sodium, and presence of high mortality risk. Oral ciprofloxacin with a dose of 20 mg/kg/day achieves adequate concentrations for some

organisms but other drugs should be considered for *P. aeruginosa* and *S. pneumoniae* infections in this patient population.

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### **IV-33 Pyry Välitalo Pharmacokinetics of Oxycodone in Labouring Women With Preliminary Estimates of Neonatal Exposure**

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**Objectives:** Oxycodone has been the most commonly used opioid in treatment of post-operative pain in Finland for the last 50 years. There have been no previous studies about the pharmacokinetics of oxycodone in labouring women. Based on case reports of neonatal oxycodone abstinence syndrome [1], it seems that oxycodone can permeate placenta. This study was set up to investigate the pharmacokinetics of oxycodone in labouring women and to preliminarily quantify the neonatal exposure to oxycodone following maternal administration.

**Methods:** Fifteen women were included in the study. The participants were previously healthy and their pregnancies were normal. The women received an initial dose of 780 µg of free oxycodone base and the dose was repeated as necessary in five minute intervals (up to a maximum of 3.9 mg). Venous blood samples were taken 5 minutes after each oxycodone administration, at 10, 30, 60 minutes after the last oxycodone dose, and after that at every 60 minutes until birth. The umbilical cord was clamped at delivery, and venous and arterial blood samples were drawn. The samples were analyzed with a highly sensitive LC-MS/MS method [2].

A total of 171 venous plasma samples from mothers, 15 arterial and 14 venous umbilical cord samples were above limit of quantitation. The pharmacokinetics of oxycodone in mother was characterized by a two-compartment model. In addition, umbilical vena, the neonate, and umbilical artery were implemented as separate compartments.

**Results:** The clearance of oxycodone was 0.84 L/min/(70kg)<sup>0.75</sup>. The central and peripheral volumes of distribution were 79 and 88 L/70kg, respectively. The inter-compartmental clearance was 2.9 L/min/(70kg)<sup>0.75</sup>. The transfer rate from mother to neonate was similar to the transfer rate from neonate to mother. The residual error was 12% for venous mother concentrations and 32% for umbilical cord concentrations. All fixed-effects parameters were fairly well estimated (RSE < 25%).

**Conclusions:** The pharmacokinetics of oxycodone in labouring women was similar to that in healthy volunteers [3]. Oxycodone permeates the placenta and distributes into the neonate. Since the number of subjects in this study was small, these results should be considered preliminary.

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**IV-39 Sven van Dijkman Optimal design for a dexmedetomidine pharmacokinetic trial in mechanically ventilated neonates with single organ respiratory failure.**

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**Objectives:** The European legislation has created an increased demand for clinical trials in neonates and infants. However, paediatric protocols still rely on feasibility and empiricism rather than clinical pharmacology principles. The objective of this investigation was to illustrate how protocol design can be optimised in terms of patient numbers and sampling times to obtain well-estimated pharmacokinetic parameters, whilst ensuring minimal discomfort and limited blood withdrawal. A pilot study with dexmedetomidine has been selected to demonstrate the advantages of the approach. Data from the optimised pilot study will be used to support the design of an efficacy trial with 30 neonates.

**Methods:** Number of patients and sampling times were optimised with the ED optimality methodology in PopED using a pharmacokinetic model developed by Potts et al. (1). Simulated concentrations at the optimal sample times were used to re-estimate model parameters in NONMEM 7® according to an automated procedure in PsN. The parameters of interest were clearance, volume of distribution and inter-compartmental clearance. The concordance between original and re-estimated parameters was assessed by graphical and statistical diagnostic measures.

**Results:** Preliminary results show that model parameters and concentration curves over time (with 90% CI) can be accurately characterised with as few as 5 patients. SME and RE of parameter estimates showed acceptable values in all simulated scenarios. NONMEM minimisations were successful in 67-93 % of the cases.

**Conclusions:** Our analysis showed that as few as 5 blood samples from 6 patients are sufficient to allow accurate estimation of the parameters of interest. In contrast to current beliefs, the use of optimal design concepts is critical for the implementation of pharmacokinetic studies in neonates. Uncertainty and bias in parameter estimates due to empirical sampling may lead to under or overestimation of clearance and consequently yield inappropriate dosing recommendations.

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#### IV-44 Katarina Vucicevic Population Pharmacokinetic Modelling of Amikacin in Neonates

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**Objectives:** The aim of this study was to explore the influence of demographic and clinical covariates, and hence to develop population pharmacokinetic (PK) model of amikacin in neonates with suspected or proven sepsis.

**Methods:** In total 39 neonates born at term ( $\geq 37$  weeks gestational age, GA) were included in the study. Amikacin was administered over 1 h infusion, using multiple or once-daily dosing schedule, with daily dose of 15 mg/kg (if postnatal age, AGE  $\leq 7$  days) or 20 mg/kg (if AGE  $> 7$  days). Two samples were taken per patient, corresponding to the peak and trough serum concentration. The population PK analysis was performed using NONMEM® software (ver.6.2). Internal validation was performed.

**Results:** Linear one-compartment model with a proportional interindividual error and combined residual error model were used to describe PK of amikacin. The final population model for clearance is:  $CL(l/h) = 0.12 \cdot (TM/4) \cdot 0.75 \cdot 1.31 \cdot GA \cdot 1.33 \cdot AGE$ , where GA=0 for 37-38 gestational weeks, GA= 1 for 39-42 gestational weeks; AGE=0 for postnatal age  $\leq 7$  days, AGE=1 for postnatal age  $> 7$  days; whereas volume of distribution was weight normalized, and interindividual error was not modeled. The results show that clearance is increased in average by 31 % in neonates of 39-42 gestational weeks compared to neonates of 37-38 gestational weeks, and it was increased in average by 33 % with postnatal age  $> 7$  days. The estimate of clearance for a typical patient was 0.12 (0.106 - 0.134) l/h, while interindividual variability of clearance in the studied population was 24.72 (11.79 – 32.91) %, the residual variability estimated the proportional error at 54.41 % and additive error 61.07  $\mu\text{g/mL}$ .

**Conclusions:** The results suggest that amikacin elimination increases with gestational and postnatal age presumably owing to the process of maturation that is extensively carried out in the first weeks of life. Final population pharmacokinetic model for amikacin can be used to predict the individual concentration of amikacin in neonates, and individualization of therapy.

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#### **IV-46 Chenguang Wang The allometric exponent for maturation in propofol clearance varies with age**

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**Objectives:** For scaling propofol clearance between (preterm) neonates, infants, children, adolescents and adults, an allometric model with an exponent that matures with bodyweight (bodyweight dependent maturational exponent model, BWME-model) was developed leading to improved model performance compared to a  $\frac{3}{4}$  allometric scaling model [1]. To explain this result, an in-depth study of the allometric exponents in different age combinations was performed.

**Methods:** We systematically selected two out of six studies comprising neonates, infants, toddlers, children, adolescents or adults [2,3,4,5,6,7,8] and performed a population pharmacokinetic analysis using NONMEM VI on each of these combined datasets. A three-compartment model together with an allometric scaling model for clearance was applied to estimate the value for the exponent of the allometric equation for clearance in every combined dataset.

**Results:** The value for the allometric exponent for maturation in propofol clearance was found to vary mostly when the young age range (with bodyweights less than 6 kg) was included in the dataset resulting in estimated exponent values above 1. In older children (with bodyweights greater than 6 kg) and adults, the values for the allometric exponent were lower than 1. The allometric scaling exponents between the paediatric population and the adult population were in accordance with the exponent values that were identified in the BWME- model. However, the allometric scaling exponents of the combined datasets within the paediatric population were different from the results of the BWME-model.

**Conclusions:** Different allometric exponents for maturation in propofol clearance were identified depending on the included age-range, with values higher than 1 in young infants and values lower than 1 in older age ranges. Our findings confirm that allometric exponent changes across age-ranges and explain the fact that the  $\frac{3}{4}$  allometric scaling model performs well in some of paediatric studies and fails in others.

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#### **IV-64 Wei Zhao Individualized therapy and Bayesian estimator of ganciclovir exposure after oral administration of valganciclovir in pediatric renal transplant patients**

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**Background:** A population pharmacokinetic study of valganciclovir, the prodrug of ganciclovir active against cytomegaloviruses, was previously conducted in pediatric renal transplant patients (referred below as the building group including 22 patients and 164 concentrations)[1]. Individualized therapy of valganciclovir was developed based on modeling strategy and validated in the present study.

**Methods:** The Bayesian estimator of valganciclovir exposure was obtained from the population pharmacokinetic parameters of the model building group. External validation was performed in an independent validation group, which consists of pharmacokinetic profiles from 15 patients (7 samples per patient).

**Results:** The target area under the curve (AUC<sub>0-24</sub>) of 40 to 50 $\mu\text{g}\cdot\text{h}/\text{mL}$  is recommended in both adult and pediatric organ transplant patients. The current pediatric dosage regimen (Pediatric Dose (mg) = 7 x BSA x Creatinine clearance) does not always allow to reach the target but may be associated with either under or overdosing, even when taking into account identified covariates such as creatinine clearance and body surface area. The individual observed concentrations were well predicted by the model in the validation group. The Bayesian estimator of exposure using T<sub>0</sub>, T<sub>2</sub> and T<sub>4</sub> gave the best prediction of individual AUC. Mean prediction error was 0.1% [95%CI -4.1% to 4.0%] and mean prediction precision was less than 21.3%. Bland and Altman analysis showed that the average difference between measured and estimated AUCs was -0.27 $\mu\text{g}\cdot\text{h}\cdot\text{ml}^{-1}$  (range -8.9 to 9.0 $\mu\text{g}\cdot\text{h}\cdot\text{ml}^{-1}$ ).

**Conclusion:** AUC based dosage adaptation was necessary to optimize individual therapy in paediatric renal transplanted patients as variability is high. The Bayesian estimator of valganciclovir exposure, using three concentrations measured just before (T<sub>0</sub>) and 2 and 4 hours after drug intake was validated in the present study and can be used to accurately predict individual AUC. It will be useful to individualize valganciclovir therapy in pediatric renal transplant patients.

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## **I-08 *Claus Andersen* Trial Sample Size Estimation and Study Design Assessment using Monte Carlo Sampling**

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**Objectives:** Construct a simulated clinical trial as close to clinical reality as possible benefitting from available clinical information.

**Methods:** To simulate a trial in Huntington's Disease we brought together patient data and trial design to simulate the patient population distributions using Monte Carlo sampling. This started from the patient inclusion criteria and the randomization protocol, covering possible dosing regimens, and balanced as well as unbalanced study designs. Finally the primary end-point measured in terms of Total Functional Capacity (TFC)[1] was statistically assessed using various methods (ANCOVA, t-tests and Mann-Whitney U-test) after 5000 simulated trials.

**Results:** The trial simulations could faithfully include key elements of the trial design, thus proposing a change of inclusion criteria (excluding patients with TFC=13), and showed that a balanced design (same number of placebo as treated patients) increases power with respect to unbalanced designs. The sample size estimates showed that a 92% power could be obtained with 444 enrolled patients (222 in placebo and treated groups) assuming a 10% drop out rate and a 40% attenuation of decline in TFC. This was optimally assessed by an ANCOVA with  $\alpha=0.05$  and baseline TFC as covariate).

**Conclusions:** Constructing simulations of a trial allows the inclusion of design aspects which can influence the trial outcome just as much as sample size. Considering the investment by all stakeholders in a clinical trial the cost of simulating its key aspects are warranted, and allows design questions to be addressed scientifically and identification of some issues before the trial is run.

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## **I-12 Caroline Bazzoli New features for population design evaluation and optimisation with R functions: PFIM Interface 3.1 and PFIM 3.2**

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**Objectives:** To develop the free R function PFIM [1] for population design evaluation and optimization and to illustrate the use of PFIM Interface 3.1 and PFIM 3.2.

**Methods:** Compared to PFIM Interface 2.1, the new PFIM Interface version 3.1, dedicated to design evaluation and optimisation for multiple response models, incorporates the features that were previously released in version 3.0 of PFIM [2]. Furthermore, the library of "classical" pharmacokinetic (PK) models has been completed by the three compartment models and a library of pharmacodynamic (PD) models is now available. PFIM Interface 3.1 can handle either a block diagonal Fisher matrix or the complete one. Regarding the R scripts version, the key new feature of PFIM 3.2 is the computation of the Fisher information matrix for models including fixed effects for the influence of discrete covariates on the parameters [3] and/or inter-occasion variability (IOV) [4]. The predicted power of the Wald test for a given distribution of a discrete covariate as well as the number of subjects needed to achieve a given power can be computed. Examples of the use of both versions of PFIM are presented in the context of warfarin PKPD.

**Results:** We used the standard example of warfarin PKPD where warfarin is administered as a single oral dose to 32 subjects. Plasma concentration and effect on prothrombin complex activity (PCA) are measured. A one compartment PK model with first order absorption and elimination is used and the effect on PCA is described by a turnover model with inhibition of the input. First, using PFIM Interface 3.1, we evaluated the empirical rich design and compared it to a design optimised using the Fedorov-Wynn algorithm. With 2.1 less samples than the empirical design, the optimal design provides similar predicted standard errors for the fixed effects. Then, we wanted to evaluate designs with a genetic covariate effect on clearance using PFIM 3.2. With the optimal design and a clearance assumed to decrease by 50% for patients with a mutant genotype, only 8 subjects are needed to obtain a power of 90% for the comparison test detecting the genetic effect. Finally, we planned a crossover PK study to assess the absence of interaction of drug X on warfarin absorption rate-constant ( $k_a$ ).

**Conclusions:** We illustrated the use of the new versions PFIM 3.2 and PFIM Interface 3.1. They are great tools to evaluate and/or optimise designs for multiple response models and for more complex models quantifying the influence of discrete covariate and/or inter-occasion variability.

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### **I-34 *Núria Buil Bruna* The feasibility of model-based exposure calculations in preclinical toxicology**

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**Objectives:** An important part of drug development involves the establishment of safe exposure levels in humans. Preclinical experiments often use an empirical non-compartmental approach to the calculation of drug exposure. This has a variety of limitations including the difficulty to extrapolate to clinical exposure levels. Pharmacokinetic modelling can address these shortcomings, however the sparse pharmacokinetic sampling that is often used in these experiments calls into question the feasibility of a model-based approach. The aim of this study was to evaluate the expected model parameter precision from preclinical designs and explore the possibility of reductions to the numbers of animals used.

**Methods:** Expected parameter precision was determined by calculation of the expected Fisher Information Matrix (FIM) in the software PopED, for 9 different hypothetical drugs. These drugs were described by a variety of structural PK models and parameter values. Models tested included non-linear kinetics and distribution to a peripheral compartment. Experimental designs matched standard practices and included sparse and serial sampling designs. Reduced designs with fewer animals were also tested. The secondary parameters, AUC and CMAX were calculated from the primary PK parameters using NONMEM VI. Acceptable precision was defined as CV < 30% for fixed effects and CV < 50% for random effects.

**Results:** The results show that secondary parameter precision remained below 35% in all cases. A reduction of animals used in composite designs by 2/3 yielded no significant loss in expected precision.

**Conclusions:** The use of pharmacokinetic modelling to characterise toxicokinetic exposure is feasible without changes to toxicity study protocols. Significant reductions to the numbers of animals for sparse designs may be possible using an integrated approach. The FIM-based approach used here, can be used as alternative to lengthy simulation/re-estimation for the calculation of expected parameter precision.

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## II-04 Anne Dubois Evaluation of designs for biosimilarity crossover trials analysed by nonlinear mixed effects models

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**Objectives:** To assess the similarity between different formulations of a biologic drug, a pharmacokinetic (PK) bioequivalence trial is usually performed as for chemical drugs [1,2]. Nonlinear mixed effects models (NLMEM) can be used to analyse such data [3,4]. Before performing these trials, it is important to define an appropriate design which has an impact on the precision of parameter estimates and the power of tests. The approach for design evaluation and optimisation based on the expression of the Fisher information matrix (MF) was extended to NLMEM including within subject variability (WSV) and discrete covariates changing between periods [5]. The power of equivalence Wald test can be computed using the predicted standard error (SE). These developments are implemented in the R function PFIM 3.2 [6]. Our objectives were to evaluate and apply this evaluation design approach to biosimilarity crossover trials.

**Methods:** We simulated 1000 replicates of crossover trials using simulation settings of Dubois et al [4]. Crossover trials with 2 and 4 periods were simulated under the equivalence test  $H_0$  with different numbers of subjects (N) and of samples, and two variability levels. We estimated the NLMEM parameters by the SAEM algorithm implemented in MONOLIX 2.4 [7,8]. We compared the predicted SE obtained by PFIM to the distribution of SE estimated by MONOLIX and the corresponding empirical SE. We then computed the power of equivalence test on clearance (CL) for different  $H_1$  and simulated designs. We applied this approach to a crossover trial on 16 monkeys comparing 2 formulations of drug X. We evaluated then optimised its design by NLMEM using about twice less samples than originally.

**Results:** For all simulated scenarii, the predicted SE computed by PFIM and the empirical SE obtained from simulations are close, for all fixed effects including treatment, period and sequence effects. For variance parameters, predicted SE of WSV are slightly underestimated even for 4-period trials. The power of equivalence test decreases with N or for high variability. For the application, the predicted power of the equivalence test on CL is 90% and 85%, for the original and optimised designs.

**Conclusion:** This extension of MF for NLMEM is relevant to predict SE of treatment effect and power in crossover trials. PK similarity trials analysed through NLMEM allow sparse designs and can be performed in patients. PFIM can be used to efficiently design these trials.

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## II-06 *Cyrielle Dumont* Design evaluation in nonlinear mixed effect models: influence of covariance between random effects

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**Objectives:** Nonlinear mixed effect models (NLMEM) are increasingly used during drug development and for analysis of longitudinal data obtained in clinical trials or cohorts. For design evaluation, an alternative to cumbersome simulations is to use the Fisher information matrix (MF). Its expression for NLMEM was derived using a first-order approach [1,2] and is implemented in the R function PFIM [3,4] as well as in several software. Our aims were i) to study the impact of the size of covariance on the standard errors (SE) and on the amount of information; ii) to show how we can analytically predict the SE in the framework of rich individual data without using the model; iii) to study the influence of the covariance on the optimal design and on the corresponding SE. We illustrate the results applying this extension to the design of a pharmacokinetic (PK) model of a molecule in development in children.

**Methods:** The development of MF for NLMEM including covariance between random effects was implemented in a working version of PFIM. For the PK example, we predicted the SE on fixed effects and on variance components assuming different values of correlations between the two random effects. We also evaluated the total information through the determinant of MF ( $\det(\text{MF})$ ). Assuming rich individual data, one can assume that individual parameters could be observed, and we then derived analytically the predicted SE for fixed effects and variance components. Lastly, we compared optimal designs with and without covariance and their respective SE.

**Results:** We found that changes in covariance between the two random effects of the PK model did not affect the values of the SE of the fixed parameters nor of the variance parameters for design evaluation. However, the amount of information (i.e.  $\det(\text{MF})$ ) increases when covariance increases. We also found, on the rich individual design, that the SE obtained directly are similar to those given by PFIM. These values are lower bound of SE that could be obtained by population approach. In the framework of optimization, the results showed that optimal designs and the SE are different if the covariance is taken into account or not.

**Conclusions:** This extension of MF taking into account covariance between random effects will be included in the next version of PFIM. For design evaluation, including covariance has no influence on the predicted SE but has one on the amount of information and therefore on the optimal designs [5].

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## **II-30 Gordon Graham An Application of Optimal Design to Dose Selection and Sample Size Determination with a Negative-Binomial Exposure-Response Model for a Phase IIb Study**

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**Objectives:** Previously, late stage clinical trials had been performed with drug Tx, enabling the development of an exposure-response model for a count endpoint, R. However, the drug exposure range from these studies did not adequately cover the range of concentrations below the IC50. The objective of this work was to determine the doses and sample size per dose for an additional study into drug Tx to better characterise the exposure-response relationship at concentrations below the IC50.

**Methods:** Doses of Tx were selected based on maximising the determinant of the information matrix, and sample size was based on the estimated relative standard error (RSE) on IC50 being less than 50%. [1] was used for developing the information matrix for the negative binomial exposure-response model. As a sensitivity analysis, doses and sample sizes were also assessed using a Poisson model for the count endpoint, R. The power of testing for a difference between dose groups was also performed based on model simulations.

**Results:** The selection of doses corresponding to concentrations mostly below the IC50 greatly improved the precision of the IC50 and other exposure-response model parameters. However, the RSE was not less than 50% for doses: 0Tx, 0.25Tx, 0.5Tx and 1Tx, where 1Tx is a reference dose group, and a total sample size of 1750 in a ratio 1:2:2:2. Combining the planned study with previous studies leads to a RSE for IC50 of 49.9% and allows the sample size to be reduced to 650 in a ratio of 1:5:5:2. The power of detecting a difference between 0.5Tx and 1Tx was low, but high power of comparing 0Tx and 1Tx.

**Conclusions:** Optimal design techniques were useful for assessing dose selection and sample size of this clinical trial.

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## **II-54 Matts Kågedal Improved study design in phase IIb by the use of optimal design, focusing on the precision of dose finding**

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**Objectives:** The objective of dose finding studies is to identify the relationship between dose and efficacy to guide selection of doses to be further studied in phase III. Not all parts of the dose exposure response curve are of equal importance and it may be difficult to predict how the precision in parameter estimates translates in to precision in dose-selection. Thus if optimal design methods are used it is important to have a parameter in the model that has a direct relevance for dose selection and to optimize the study design w.r.t. the precision of that parameter.

The objective of this work was to investigate if the design of a dose finding study could be improved by the use of a re-parameterized Emax model by applying the Ds and D-optimal criteria.

**Methods:** An alternative parameterisation of the sigmoid Emax model, described by Groth, was used [1] where one of the parameters ( $D^*$ ) is the dose corresponding to a particular treatment effect ( $E^*$ ). In the optimization, the optimal design tool PopED [2] was used. The D-optimal criteria was used as well as the Ds criteria with  $D^*$  as the parameter of interest. Assumptions with regards to steady state pharmacokinetics and the shape of the exposure response curve was based on a drug intended for the treatment of neuropathic pain where pain is assessed using a numerical rating scale graded 0-10. The Ds and D-optimal designs were subsequently evaluated by means of simulation to estimate the probability of correctly estimating the dose corresponding to a treatment effect of 1 versus placebo. Correct estimation of dose was defined as being in the interval 6-24 mg and the true dose was 12 mg.

**Results:** The optimal design based on the Ds-optimal design was 0, 0.1, 9 and 18 mg and the D-optimal design was 0, 1.5, 7.5 and 18 mg. The probability of correct estimation of dose was 61% based on the Ds-optimal design and 54% based on the D-optimal design.

**Conclusions:** The re-parameterized sigmoid Emax model provides a means of optimizing dose finding studies for correct dose identification, since the model has a parameter with direct relevance for dose selection. Ds-optimal design can be useful in improving design performance for dose finding by focusing on the parameter of interest ( $D^*$ ).

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## **I-07 Anders Kristoffersson Optimal design of in vitro time kill curve experiments for the evaluation of antibiotic effects.**

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**Objectives:** In order to integrate information of antibiotic effects from *in vitro* time kill curve experiments semi-mechanistic pharmacokinetic-pharmacodynamic (PKPD) models are of interest [1]. While informative compared to basic MIC measurements, that provide only a point estimate of the antibiotic effect, these experiments are labour intensive as bacteria counts are measured at a range of different concentrations and time points. This work therefore aims at evaluating currently used experimental designs and providing generalized and efficient experimental plans for future time-kill curve experiments of antibiotics.

**Methods:** A previously developed model [1] was implemented in the PopED optimal design software [2]. The original experimental design for five different antibiotics includes 9 unique sampling points studied at 9-10 concentrations. The optimization of the sampling schedule incorporated all five antibiotics in order to give a general design. A D-optimal design criterion with a reduced FIM calculation was utilized with parameters independent across sub-models. Designs were compared based on efficiency (the ratio of the FIM determinant between the optimized and the base design raised to the inverse of the number of unfixed parameters). Time dependent autocorrelation between sample points within one experiment was evaluated by implementing AR(1) residual autocorrelation [3] for the PKPD model using NONMEM 7 [4].

**Results:** The autocorrelation in the original model was high, a half-life of 7.5 h was estimated for these 24 h experiments and the impact on the optimal design was pronounced. When autocorrelation was considered the number of unique sample points increased from five to seven. The efficiency for the optimal design developed without consideration of autocorrelation was 102% when evaluated on a model with autocorrelation while the corresponding efficiency for the design that considered autocorrelation was 120%.

**Conclusions:** Inclusion of autocorrelation had a pronounced influence on the design. A design produced without consideration of autocorrelation had low performance on a model with autocorrelation. The determined general experimental setup for *in vitro* time kills curve experiments provided increased power at decreased experimental cost by a reduction of sampling points and a decrease in estimated parameter uncertainty. The proposed design was sufficient for a wide range of antibiotic classes, indicating the potential for application to novel antibiotics not previously studied.

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## **II-12 Karl-Heinz Liesenfeld Modeling and simulation to optimise the study design investigating the hemodialysis of dabigatran in patients with end stage renal disease (ESRD)**

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**Objectives:** To define a study design that allows investigation of the influence of hemodialysis on the steady state exposure of dabigatran in ESRD patients. As redistribution after stop of hemodialysis may result in a clinically relevant increase in plasma concentrations the proposed study design should especially allow a comprehensive investigation of this redistribution effect.

**Methods:** Based on a population pharmacokinetic (PK) model of a phase III study in patients with atrial fibrillation and on information from a dedicated phase I study where dabigatran was administered to ESRD subjects undergoing hemodialysis a PK model including dialysis clearance was developed. In a first step simulations were performed to obtain a dosing schedule for ESRD patients that leads to the same steady-state trough concentrations as in the patient population (~ 90 ng/mL). In a second step the impact of three conditions, start of hemodialysis relative to intake of dabigatran etexilate (0-10 hours (h)), dialysis clearance (100-300 mL/min), and dialysis duration (1-8 h) were simulated to elucidate their influence on exposure and on the extent of redistribution.

**Results:** A dosing schedule for ESRD patients resulting in an inter-dialysis (3 days) steady-state trough concentration of ~ 90 ng/mL was developed. Using a typical dialysis duration of 4 h exposure might be reduced by 60 to 75% of the initial value assuming dialysis clearance values between 160 and 240 mL/min. The extent of redistribution depends on all three investigated conditions. The later the start of the hemodialysis, the higher the dialysis clearance and the longer the duration of hemodialysis the larger was the redistribution. A hemodialysis start of 8 h after the last dose results in a redistribution effect of dabigatran which is close to the maximum effect. Nonetheless, only a relatively small redistribution effect of about 7 ng/mL was predicted. In addition the late start of hemodialysis will allow a better separation of the variability caused by absorption and by dialysis.

**Conclusions:** Informed by the simulation results the study design consists of a hemodialysis duration of 4 h which should result in a sufficient reduction of the dabigatran concentration and thus allows a precise estimation of the dialysis clearance without burdening ESRD subjects. The start of dialysis 8 h after the last dose should allow to describe the maximum redistribution effect and to estimate the variability in the dialysis clearance.

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### III-24 France Mentré Comparison of results of the different software for design evaluation in population pharmacokinetics and pharmacodynamics

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**Objectives:** To compare the standard errors (SE) and criterion provided by the different software for population designs on two examples: a simple pharmacokinetic (PK) model and a complex pharmacokinetic-pharmacodynamic (PKPD) example.

**Methods:** Following the first theoretical work on optimal design for nonlinear mixed effect models, this research theme has rapidly grown in methodological and application developments. There are now several different software tools that implement an evaluation of the Fisher information matrix for population PKPD models. Five software tools were evaluated (in alphabetical order): PFIM (C. Bazzoli & F. Mentré), PkStaMP (S. Leonov, A. Aliev), PopDes (K. Ogungbenro), PopED (J. Nyberg & A. Hooker), and WinPOPT (S. Duffull). Each of the software uses approximations in the evaluation of the Fisher Information Matrix. The comparison was performed using two models: i) a simple one compartment PK model used for warfarin; ii) a more complex PKPD model for Peg-interferon with both concentration and response of viral load of hepatitis C virus (HCV). The HCV model was written as a system of differential equations. A fixed design was used for both examples (i.e. no optimization was considered). The results of the software were compared in terms of SE and were also compared to the empirical SE obtained in a clinical trial simulation with 1000 replications analyzed both by the SAEM algorithm in MONOLIX and the FOCEI algorithm in NONMEM.

**Results:** For the warfarin PK model, when the block diagonal Fisher Information Matrix was obtained using the first order approximation, all software gave identical SE very close to those obtained through simulation. Simulation-estimation performed in both MONOLIX and NONMEM gave similar results. Different approximations to the information matrix provided different SE even for the simple PK example. For the more complex PKPD model, similar trends are observed with good prediction of the SE of all PKPD parameters even using a first order approximation.

**Conclusions:** When similar approximation of the Fisher Information Matrix is used, all software provided identical results and were close to those obtained by clinical trial simulation. Statistical work is ongoing to improve the calculation of the Fisher Information Matrix for highly nonlinear

models. For most PKPD model, using one of these various available software tools will provide meaningful results avoiding cumbersome simulation and allowing design optimization.

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### III-32 *Thu Thuy Nguyen* Evaluation of Fisher information matrix using Gaussian quadrature in nonlinear mixed effects models: application to dose-response trials

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**Objectives:** Nonlinear mixed effects models (NLMEM) can be used to analyse dose-response trials where each patient received several doses. Design in NLMEM can be evaluated/optimised using the population Fisher information matrix ( $M_F$ ), with first order approximation of the model [1,2]. This approach was implemented in the R function PFIM [3,4] and in other software. Adequacy of this approximation is however influenced by model nonlinearity. We aim to: i) propose a new approach to evaluate  $M_F$  in NLMEM without linearisation, based on Gaussian quadrature [5]; ii) evaluate this method by simulations and compare it to first order approximation for dose-response sigmoid Emax models with various nonlinearity levels.

**Methods:** In NLMEM, the likelihood expressed as an integral has no analytical form. We approximate it by quadrature rule [6] using Gauss-Hermite nodes and weights [7]. We then can derive the expression of  $M_F$  without linearising the model. We evaluate the relevance of this method and compare it to the linearisation approach for dose-response sigmoid Emax models, inspired from a previous example [8]. Various nonlinearity levels of the model are studied with different sigmoidicity factors  $\gamma$  (the larger  $\gamma$  is, the more nonlinear is the model). Dose-response trial simulations are performed for a rich design (7 doses) as well as for a sparser design (4 doses). For each scenario, we simulate 1 trial of 10000 subjects then 1000 trials of 100 subjects. We compare the standard errors (SE) obtained from different approaches: simulations analysed in MONOLIX 3.2 [9] with SAEM algorithm [10] vs. linearisation approach in PFIM vs. Gaussian quadrature.

**Results:** We have implemented this new method using the function *gauss.quad* of the R package *statmod* to calculate Gauss-Hermite nodes and weights in a working version of PFIM. For  $\gamma = 3$ , with the rich design, the SE predicted by linearisation approach are very close to those obtained from simulations. However, with the sparser design, we observe large differences in SE of fixed effects between linearisation approach and simulations.

**Conclusions:** The linearisation approach seems to work well for a great nonlinearity level with a very rich design but not with a sparse design. We propose an approach without linearisation to evaluate  $M_F$  in NLMEM for designing dose-response trials. This approach, if relevant, can be applied to more complex models with great nonlinearity level and will be implemented in a future version of PFIM.

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### III-33 Thu Thuy Nguyen Designing a dose-response study analysed by nonlinear mixed effects models

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**Objectives:** Nonlinear mixed effects models (NLMEM) can be used to analyse dose-response trials with several doses in each patient. The choice of design beforehand has important impact on study results as on the precision of parameter estimates and on the power of tests. Design in NLMEM can be evaluated/optimised using the population Fisher information matrix, with first order approximation of the model [1,2]. This approach was implemented in the R function PFIM [3,4] as well as in other software. We aim to design a dose-response trial using PFIM 3.2.

**Methods:** To design this dose-response study, we use an Emax model inspired from a previous example [5]. We assume an exponential random effect model and an additive residual error model. In PFIM 3.2, we can include a covariate effect on the parameter D50 (dose to reach 50% of maximal effect). To study the design influence on the criterion and the precision of D50 estimation, we consider various designs with 100 or 200 subjects receiving 7, 4 or 2 doses as given in the example or optimised with Fedorov-Wynn algorithm [6]. To examine the covariate influence on optimisation, we compare the optimal designs obtained for a model without and with covariate effect decreasing D50 by 50% in half of the subjects. Using the standard error (SE) of covariate effect, we compute the power of the Wald test for D50 comparison and the number of subjects needed (NSN) for a power of 90%.

**Results:** As expected, the richer is the design, the larger is the criterion and the more precise is the estimation of D50. For the sparse design with 2 doses, the relative SE of D50 is 37% with the optimal design vs. 50% with the given design. The optimal design with 4 doses has 2 groups for the model without covariate but has 1 group for the model with covariate. With 2 times less samples than the given design with 4 doses, the optimal design with 2 doses provides an expected power remaining above 80% to detect a covariate effect decreasing D50 by 50%. In term of power, there is not much difference between the design with 100 subjects, 7 doses and the one with 4 doses; but there is one between the design with 2 doses, 200 subjects and the one with 100 subjects. It emphasises the impact of the number of subjects in power of tests.

**Conclusions:** We have illustrated different steps in designing a dose-response study using PFIM 3.2. It is a useful tool for design allowing users to take into account discrete covariates and to compute power and NSN.

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### III-38 Joakim Nyberg Parallelization in optimal experimental design using PopED

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**Objectives:** Optimal design for population models can be quite time consuming. A natural way to decrease the computer time is to execute the optimization and Fisher Information Matrix (FIM) calculation in parallel and take advantage of multiple core and cluster systems. This is especially suitable for the population FIM, since it is the sum of individual FIMs. The objective in this work is to parallelize the open source optimal design tool PopED [1], preferably without the need of extra Matlab licences and additional software cost.

**Methods:** Open MPI [2] was chosen as the message passing interface because; 1) it is open source, 2) it is available for most operating system and 3) it uses a distributed memory architecture which is the most common cluster architecture and will also work well for multiple core computers. A Matlab shared library was built to execute the FIM calculations using the free Matlab Compiler Runtime (MCR). This is automatically accomplished in PopED by 1) compilation of the defined model into a shared library and 2) compilation of the Open MPI interface into an executable that calls the Matlab shared library. The number of cores/processors ( $n_{\text{units}}$ ) to use is dynamic and defined in PopED prior to every run, where one unit is dedicated to be a job manager and the remaining,  $n_{\text{units}}-1$ , are workers. To have even more flexibility the number of designs to execute on a worker node before communicating with the job manager can be defined ( $n_{\text{chunk}}$ ). For users with the Matlab Parallel Computing Toolbox (PCT) an option is available to use this method instead of the Open MPI.

Parallelization performance  $\delta_{\text{exp}} \leq n_{\text{units}}-1$  was defined as the execution time relation  $t_{\text{serial}}/t_{\text{parallel}}$  where  $\delta_{\text{exp}}=n_{\text{units}}-1$  is the theoretical best performance for MPI and  $\delta_{\text{exp}}=n_{\text{units}}$  for PCT, which can only be achieved by embarrassingly parallel methods with the time<sub>MPI</sub>=0. FIM for two models ( $M_{\text{fast}}$ ,  $M_{\text{slow}}$ ) with different execution times (~1 sec and ~60 sec) were evaluated with 231 random designs and  $n_{\text{chunk}}=7$ .

**Results:** All of the search methods, Random Search, Stochastic Gradient, Line Search, Modified Fedorov Exchange Algorithm, available in PopED were successfully parallelized. For the two test models;  $M_{\text{fast}}$ :  $\delta_{\text{exp}}=[2.1, 2.4, 2.3]$  for  $n_{\text{units}}=[4,8,34]$  with MPI,  $M_{\text{slow}}$ :  $\delta_{\text{exp}}=[2.7,6.3,26.7]$  for  $n_{\text{units}}=[4,8,34]$  with MPI. For PCT:  $M_{\text{fast}}$ :  $\delta_{\text{exp}}=2.7$  for  $n_{\text{units}}=4$  and  $M_{\text{slow}}$ :  $\delta_{\text{exp}}=4$  for  $n_{\text{units}}=4$ .

**Conclusions:** The optimal design tool PopED has been parallelized which enables time consuming models to be executed within a more reasonable time frame without the loss of any accuracy.

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### III-39 Joakim Nyberg Population optimal design with correlation using Markov Models

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**Objectives:** Incorporating correlation for continuous data in optimal design has shown to be important [1]. Therefore; different ways of incorporating correlation into discrete type data are investigated using Markov models.

**Methods:** A Dichotomous model with a Markov element on the baseline effect of the drug was used. One elementary design with 200 individuals and 20 observations per individual were used. The observations were split into a first dose (10 first obs.) and a second dose (10 last obs.) Four parameters (3 fixed effects and 1 random effect) are included in the model. The Markov element is constructed so that the probability of having a response at time  $i$  ( $DV_i$ ) increases if the previous observation ( $DV_{i-1}$ ) was a response.

Three Fisher information matrix (FIM) calculations are investigated: S1) The  $FIM_M$  given the complete Model with Markov Element, S2) The  $FIM_S = FIM_1 + FIM_2$  when splitting the Model into two models,  $FIM_1$  from model1 were  $DV_{i-1}$  was a response and  $FIM_2$  from model2 were  $DV_{i-1}$  was a non-response and S3)  $FIM_D$  with a dichotomous model without Markov elements were the probability of having a response versus dose was the same as in the Markov model. S1 had to be implemented with a high order approximation of the likelihood, i.e. a Laplace (Lap) approximation and/or Monte Carlo (MC) integration technique [2], but with S2 and S3 an analytic approximation (AA) without correlation of the random effects could also be used [3]. Optimal designs for the two doses were found using a discrete grid (25\*25) between 0-1 units. PopED 2.11 [4] was used for all computations.

**Results:** For S1, the standard by which other methods should be compared, the optimal doses were (0, 0.25). With AA; S2 and S3 had optimal doses (0, 0.38) and (0, 0.50) respectively while both Lap and MC approximations had optimal doses (0, 0.42) and (0, 0.63). S2 shows more similarities with the optimal design from S1 while using a dichotomous model (S3) appears less similar.

**Conclusion:** Optimal designs were different if Markov elements were included in the model. For S1; the slower Lap or MC methods had to be used, while, the faster AA could be used in the S2 and S3 calculations. S2 appear to better approximate the S1 method. With the proposed methods a first order Markov Model was used, but any Markov order is possible within this framework of calculating FIM. Moreover, models without any known link functions could be used, with the drawback of an increased calculation time using the Lap or MC methods.

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2. J. Nyberg, M. O. Karlsson and A. C. Hooker. Population optimal experimental design for discrete type data. PAGE 18 (2009) Abstr 1468 [[www.page-meeting.org/?abstract=1468](http://www.page-meeting.org/?abstract=1468)].
3. Longford N.T. (1994). Logistic regression with random coefficients. Computational Statistics & Data Analysis 17, 1-15.
4. PopED, version 2.11 (2011) <http://poped.sf.net/>.

### III-59 *Italo Poggesi* Efficiency criteria generated by optimal design tools should be evaluated in the light of study objectives

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**Objectives:** The definition of an optimal sampling schedule is of particular importance in applying sparse sampling strategies in clinical studies [1]. The objectives of this study were to assess the efficiency of different pharmacokinetic sampling strategies - logistically constrained or optimal - as estimated using WinPOPT [2] and to further assess these designs using population analyses of simulated datasets.

**Methods:** An hypothetical compound ( $k_a$  1 h<sup>-1</sup>, CL 650 L/h, V<sub>c</sub> 4500 L, Q 785 L/h, V<sub>p</sub> 12800 L, log-normal inter-individual variability (IIV) and proportional residual variance) was assumed to be given every 48 h. Two designs for the collection of plasma samples were considered: (i) {0.5, 2, 4 h after the first dose and predose, 0.5, 2, 4 h at steady state} and (ii) {1, 6, 12 h after the first dose and predose, 1, 6, 12 h at steady state}. The designs were evaluated using the WinPOPT software [2]. The same program was used for selecting the optimal design. Simulations were performed using NONMEM [3], and the plasma concentrations were extracted at the relevant times and used to re-estimate the population and individual parameters, which were compared with the 'true' ones.

**Results:** Based on the WinPOPT-generated efficiency value and considering all parameters, schedule (ii) was approximately 70% more efficient than schedule (i). The optimal design {3, 9, 22 h after the first dose and 0.236, 2.97 (twice), 48 h after the 11<sup>th</sup> dose} was 236% more efficient than schedule (i). When the optimization was focused on CL and V<sub>c</sub> only, schedule (ii) and the optimal design were 30% and 345% more efficient than schedule (i), respectively. Although less efficient in terms of uncertainty of the parameter estimates, the non-optimal designs provided population and individual parameters in reasonable agreement with the true values. Population clearance in particular was estimated with low bias (-6%) also with the least efficient schedule. Bias for V<sub>c</sub> was generally higher, but still within ±20%; slightly larger biases were observed for IIV.

**Conclusions:** The minimization of the uncertainty around parameters can be an aim of the design of a study (e.g., in pediatric PK studies). However, when accurate individual PK parameters have to be used in a sequential PKPD approach, bias should be also considered. The available optimality sampling design tools are useful in exploring the precision given a sampling schedule and proposing schedules to be assessed using simulations.

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### **III-64 Elba Romero PK/PD sampling design optimization following a sustained release formulation of triptorelin using optimal experimental design**

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**Objectives:** Sustained release administrations of drugs have improved long-term treatments for the patient. However, the design of clinical trials in such situations is complex due to the high number of samples required to obtain a precise prediction of the drug response. In the case of triptorelin (TPT) administered to suppress testosterone (TST) levels in prostate cancer patients the study duration was 4 months and involved 32 samples per patient. Therefore, the aim of this work was to use optimal design theory to reduce the number of samples per patient based on a previously developed receptor-based pharmacokinetic/pharmacodynamic (PK/PD) model for the TST effects of TPT.

**Methods:** Pharmacometric Model: Data (CTPT and CTST) from a population of advanced several prostate cancer patients from four clinical trials were used to develop a receptor-based pharmacokinetic/pharmacodynamic model [1]. Data from one of these studies (n=24), where a slow release formulation was tested, were used to test the optimal design theory. Optimal Design: The PK/PD model was implemented in PopED [2] and optimization was performed using the D and Ds optimality criteria. For the later, only the PD parameters were considered interesting. Modified Fedorov Exchange algorithm with a grid of one sample per day and no replicates was used for the optimization.

**Results:** Comparable coefficients of variations as for the original design were obtained with 62.5 % optimal samples. Similarly, to achieve 100% efficiency only 11 samples with optimal time were needed. Focusing on the PD parameters using Ds optimality permitted a reduction to 87.5 % of the initial number of samples while maintaining 100% efficiency.

**Conclusions:** Using optimal design theory the number of samples in a long term sustained release trial could be substantially reduced, lowering both costs and patient burden.

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## IV-20 Amit Taneja Optimisation of Screening Experiments for the Assessment of Analgesic Effects

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**Objectives:** Experimental protocols in preclinical drug screening are often based on empirical criteria such as best guess approaches. Practical constraints prevent the use of a model-based approach, which can have major impact on the ranking of compounds at this early stage of development. In the current investigation, we apply robust ED-optimality in a prospective setting for a new chemical entity (NCE) wherein prior information from a paradigm compound is used to optimise the study design, and thereby accurately estimate the parameter of interest (EC50).

**Methods:** We demonstrate the advantages of the concept based on two compounds commonly used in neuropathic pain treatment, namely gabapentin (reference) & pregabalin (NCE). We apply a logistic regression model, under the assumption that EC50 is the only unknown parameter. Initial estimates for the NCE were based on an in vitro potency ratio of 2:1. The design variables for optimisation include the PK sampling times and doses. Uncertainty of 50% is assumed for the between-subject variability as well as in the parameter EC50. The design was validated using a simulation/estimation study (SSE) with n=500. The precision and bias of parameter estimates for standard and optimised protocol designs were then compared. Simulated PKPD profiles of each design were also compared. POPEd 2.10/ MATLAB 7.9 were used for the optimisation procedures, whilst NONMEM 6 was used for simulation purposes.

**Results:** The ED-optimal doses for the paradigm (5-150mg/kg) were lower than the original doses (30-300mg/kg). Optimal sampling times were around the expected EC50. Relative standard errors for the optimal design were 32.33(14.7%) vs. 79.3(123.30)% for the original protocol. For the NCE, the EC50 estimates were close to the hypothesised true estimate, 108ng/ml, while modelling of experimental data yielded estimates of 3200 (110-7000) ng/ml. The RSE for this parameter was also considerably lower after optimisation.

**Conclusions:** We show that a model-based approach can be used to optimise the screening of NCEs. Empirical protocols for the assessment of drug potency in the presence wide parameter uncertainty leads to biased estimates and inaccurate ranking of candidate molecules. The use of ED-optimality concepts support the design of more informative experimental protocols, since it can warrant sampling times and dose selection that support the estimation of EC50, taking into account its uncertainty. .

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## **IV-24 Donato Teutonico Multivariate patient simulation for clinical trial optimization in COPD**

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**Objectives:** Clinical Trial Simulation (CTS) can be a valuable tool to improve drug development [1]. However, in order to obtain realistic simulation scenarios, the patients included in the CTS process must be representative of the target population. This is particularly important when covariate effects exist that may affect the outcome of a trial. The objective of this exercise is to evaluate the performance of different methods to simulate demographic covariates of patients for a Chronic Obstructive Pulmonary Disease (COPD) trial.

**Methods:** *Virtual* patients with varying demographic characteristics were simulated by re-sampling with replacement, sampling from a univariate distribution and sampling from a multivariate distribution. Simulations of continuous and categorical covariates were performed in R according to the method described by Tannenbaum et al. [2]. A KPD model was used to generate FEV1 responses in the COPD trials and results compared with the data from a real patient population.

**Results:** Covariate simulation using a multivariate distribution allows covariate correlations to be characterised using an empirical distribution. Moreover using the multivariate distribution is also possible to simulate new populations stratifying for specific covariates of interest.

**Conclusions:** Multivariate distribution methods may be applied to continuous and categorical covariates. This procedure is valuable for the optimisation of the design of clinical studies in which covariate effects are known to influence treatment outcome (pharmacokinetics or pharmacodynamics).

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## IV-43 *Camille Vong* Optimal Design of Anticancer Regimens

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**Objectives:** Anticancer regimens are often a delicate compromise between dose intensity and acceptable toxicity, for example neutropenia. The aim of the present study was to develop methods in an optimal design approach to select the optimal dosing and sampling strategies within clinical restrictions, based on predictions of nadir neutrophil counts.

**Methods:** A semi-physiological PK/PD model for docetaxel's haematological toxicity [1, 2] was used to determine the population mean value of nadir concentration and time of nadir. An optimization on both time and size of dosing was performed in PopED v.2.11 [3]. The optimizations maximized the expected nadir value given a set of clinical constraints using a penalty function. Constraints investigated included 1) 5 doses of 20 mg/m<sup>2</sup> given within 21 days (optimization on dose time) and 2) 5 doses fixed to be given on day 1 then every 5 days with a total dose of at least 100 mg/m<sup>2</sup> (optimization on dose size). Sampling schedules were also optimized to allow for model identification of the nadir value using a C-optimal criterion [4] and by using a Sample Reuse Simulation approach [5].

**Results:** Suitable dosing schedules were found for the different scenarios specified above. For scenario (1) optimized dosing times were found to be 1, 5, 11, 16 and 21 days, resulting in a nadir value of 2.0 x 10<sup>9</sup>/L. For scenario (2) optimized doses were found to be 27.0, 19.5, 21.8, 10.4, and 33.5 mg/m<sup>2</sup>, resulting in a nadir value of 1.9 x 10<sup>9</sup>/L. Nadir was estimated more precisely with the optimized time points compared to a typical D-optimal design.

**Conclusions:** Optimal design methodology can be applied for toxicity monitoring within clinical constraints in oncology studies. Future optimal dosing designs will incorporate both efficacy and toxicity and incorporate between subject variability.

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## IV-56 Shuying Yang Using Placebo FEV1 Response to Improve the efficiency of clinical trials in Asthma

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**Objectives:** To evaluate the efficiency of new clinical trial design in asthma where subjects are randomised to study treatments based on their placebo response at the end of a run-in period.

**Methods:** A novel approach based on population enrichment for designing and analysing clinical trials for asthma is proposed. The study design consists of two parts: a two-week run-in period where all subjects are treated with placebo, and a randomised period where subjects follow their randomised treatment (active/placebo) for certain period of time. The selection of subjects for second part of the trial is based on their FEV1 response at the end of run-in period. Clinical trial simulations (CTS) are utilised to investigate the validity and the benefits of the proposed study design. The advantage and gain of the proposed design over the conventional approach where all subjects included in the analysis regardless are explored. The simulations are conducted in R (1) with the aid of functions in MSToolKit (2).

**Results:** Outcomes from the clinical trial simulations suggested that the study power was significantly improved under the proposed study design. Similar study efficiency was attained with about half of the subjects with this new design when compared to the conventional method. The benefit of the new design was more evident for scenarios where the true effective size (active-placebo) depends on the effect of placebo at the run-in period. The risk of an inflated Type I error associated with the proposed trial design was assessed using Clinical Trial Simulation. Randomised two-arm placebo controlled trials were simulated under the assumption that the active drug was ineffective (effect size equals to 0). The results obtained in absence of population enrichment were compared to the results obtained after population enrichment. The results indicated that the proposed methodology preserved the Type I error showing no estimation bias.

**Conclusions:** The new design with a two-week placebo run-in period in asthma trials is valid, sufficient, and more efficient in terms of study power or sample size for detecting the potential drug effects.

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