

P-1_ Pharmacokinetics and bioavailability of new ciprofloxacin derivative (CNV 97101) in rat: repercussion of precipitation in stomach.

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poster

Purpose: A method of deconvolution by curve fitting is presented and applied to the estimation of oral absolute bioavailability of a ciprofloxacin derivative (CNV97101). The aim of the study was to explain the low oral bioavailability of CNV97101. In the study three different extrabasal routes has been used: oral, intraduodenal and intraperitoneal. Furthermore an in vitro study with the stomach content of fasted rats for 12/24 h was also developed.

Method: The concentration versus time plasma levels were obtained by administration of CNV97101 by four different routes: intravenous and the extrabasal routes described before. CNV97101 was dosed at 30mg/Kg, with two additional doses (oral and intravenous) at 15 mg/Kg. The same oral doses were also used to do the in vitro studies. Fitting procedures were performed using a non-linear mixed effect model in NONMEM assuming exponential models for intra and interindividual variability. The absorption phase was modeled considering a passive diffusion with an initial fraction of dose precipitated which was re-dissolved by a zero order process, and an absorption window which limited the absorption time. The fraction precipitated was fixed using the experimental results obtained from the in vitro experiment.

Results: The in vitro results showed the non precipitated fractions were 25% for 30 mg/Kg and 45% for 15 mg/Kg. However values for oral bioavailability were 49% and 58% respectively, furthermore a high fraction is re-dissolved and absorbed. In the case of intraduodenal administration, NONMEM estimates around 40% of the dose precipitates, but its final bioavailability is 93%.

Conclusion: The in vivo studies were developed with rats fasted for 12h, and as the in vitro study demonstrates this is the cause of the low oral bioavailability. However, in vitro studies with 24 h fasted rats showed a precipitation lower than 10%. So, the food interacts with CNV97101 making more difficult its absorption. As the proposed model indicates, CNV97101 is re-dissolved and absorbed for 1 hour along the small intestine.

P-2_ Age-related effects on nelfinavir - M8 pharmacokinetics - A population study in 182 children

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Objective: As a relationship between nelfinavir antiretroviral efficacy and plasma concentrations has been previously established, the large inter individual variability observed in children was analysed in order to optimise individual treatment schedule for this drug in a paediatric population.

Methods : A population pharmacokinetic model was developed in order to describe the concentration-time-course of nelfinavir and its active metabolite M8, in children. Individual characteristics, such as age or bodysize, that may influence the nelfinavir-M8 pharmacokinetics were investigated. Data from therapeutic drug monitoring in 182 children, aged from 3 days to 17 years, treated with nelfinavir were retrospectively analysed with the NONMEM program. Then FDA current recommendations were evaluated in 3 age groups : from 2 to 13 years, from 2 months to 2 years and younger than 2 months with twice- or thrice-daily regimens, estimating the percentage of children who reach the target minimum plasma concentration (0.8 mg/L), using Bayesian estimates.

Results: Nelfinavir pharmacokinetics was described by a one compartment model with linear absorption and elimination and M8 produced from the nelfinavir central compartment. Pharmacokinetic estimates and the corresponding inter-subject variabilities (%) for the model were: nelfinavir total clearance 0.92 L/h/kg (39%), volume of distribution 7.3 L/kg (112%), absorption rate 0.5 h^{-1} , formation clearance fraction to M8 0.025 and M8 elimination rate 1.86 h^{-1} (49%). Nelfinavir total clearance and volume of distribution decreased as a function of age. M8 elimination rate was increased by concomitant administration of nevirapine or efavirenz. A higher percentage of children had minimum plasma concentration above 0.8 mg/L with the thrice daily regimen than with the twice-daily regimen recommended by the FDA (especially in young groups). Our data confirm that the FDA recommendations i.e. 25 to 35 mg/Kg TID or 50 to 60 mg/Kg BID for children from 2 to 13 years, 40 to 50 mg/kg TID or 60 to 75 mg/kg BID for children from 2 months to 2 years are optimal. However in children younger than 2 months, the proposed nelfinavir newborn's dose of 40 mg/Kg BID is inadequate and we suggest to increase the dose to 50 to 60 mg/Kg administered thrice daily. This assumption should be further evaluated.

P-3_ High Inter-Patient Variability of Pharmacokinetics of Lamivudine (LMV), Stavudine (STV) and Zidovudine (ZDV) in HIV-Infected Patients treated with HAART (Cophar 1 - ANRS 102 Study).

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Objectives: Little is known about pharmacokinetic (PK) characteristics of combined nucleoside analogs (NA) in patients (pts) treated with HAART. Our objectives were 1/ to build a population pharmacokinetic model of ZDV, LMV and STV 2/ to estimate their inter-individual PK variability and 3/ to investigate the influence of different covariates.

Methods: The Cophar-1 study was a prospective, open, multicenter trial including pts with unchanged HAART containing either indinavir (IDV) or nelfinavir (NFV), and with a sustained virological response (viral load

Results: Mean parameters (CV%) of LMV, STV and ZDV were respectively: oral volume of distribution (V/F) 143L (49%), 24 L (82%) and 194 L (88%), oral clearance (Cl/F) 31 L/h, 21 L/h (77%) and 121 L/h (49%). For LMV, Tabs was 1.15 h (62%). For STV and ZDV, k_a was 0.46 h⁻¹ and 2.8 h⁻¹, respectively. The only significant covariate effect was combination with NFV vs IDV. In pts receiving NFV, Tabs of LMV is divided by 1.4 (p=0.002), Cl/F of STV is multiplied by 1.6 (p=0.001) and both V/F (p

Conclusions: This trial first designed to study protease inhibitor PK also gave us an estimation of PK parameters for the combined NA. We observed for the 3 NA a great variability of PK parameters and a systematic effect of NFV. This plasma concentrations variability may have consequences on the concentrations of intracellular active metabolites and requires further investigations.

P-4_ Model-based drug development of a new anti-HIV drug

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poster

Introduction: Maraviroc (UK-427,857) is an antiretroviral drug with a new mechanism of action. It is a CCR5 antagonist. Currently, maraviroc is entering phase 2B/3 clinical development. Throughout the development of this compound, it was decided to implement a model-based decision making approach. Modeling and simulation activities started during the pre-clinical development with the design of the proof-of-concept (POC) trial (1). Being the first in class, little information was available at that time. So an integrated semi-mechanistic PK-PD-disease model was developed based on prior knowledge in the field of HIV. On an ongoing basis relevant pre-clinical and clinical information generated during the development were implemented in the model. At each step of the development, the updated model was used to guide decisions.

Methods: A disease mechanistic model was developed to incorporate information from several sources (2). When clinical data from maraviroc POC trial became available (3), the model was updated and used to assess the impact of food and dosing regimens on viral load decline. These predictions were in agreement with the one measured in the trial (4). Simulations were performed to assess the ability of a study with maraviroc given as combination therapy to provide information to select phase 3 doses. Based on simulation results, we have decided not to do a stand-alone phase 2B and go straight to phase 2b/3. Compliance and trial outcome components were added to the PK-PD-disease model to simulate long-term outcome. The outcome of several doses, along with several scenarios was simulated to aid in the selection of doses for phase 2B/3. Doses were selected based on trade-off analysis carried out on predicted efficacy and adverse events profile from phase 1 studies.

Conclusions: The impact of uncertainties on dose-response curve was identified early in the development of maraviroc. A trial strategy was selected to cover for the uncertainties detected and characterize dose-response curve with reasonable precision.

Modeling allowed prediction of the effect on viral load of different maraviroc doses as monotherapy in this patient population. The use of a model-based approach for selecting doses can accelerate drug development, by predicting long-term response from short-term data and by replacing some arms or trials with simulations.

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P-5_ Vancomycin population pharmacokinetic analysis in patients with hematological malignancies

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poster

Introduction: The population approach and pharmacodynamic criteria have become available as tools in individualized antimicrobial therapy, leading to increased efficacy and reduced selection of resistance. However, little is known about the pharmacokinetics of vancomycin (VAN) in patients with hematological malignancies.

Objective: This study aimed to develop a VAN population pharmacokinetics model in a broad and representative sample of adult patients with hematological malignancies.

Methods: Sparse serum concentration data (n = 1128) from therapeutic drug monitoring of VAN were collected retrospectively from 274 patients. The dataset was divided into two groups according to a sequential time criterion. An index group of 286 courses administered to 215 patients was used for population PK modeling. The remaining 62 courses administered to 59 patients were used as a validation data set.

A one-compartment PK model was selected and population parameters were generated using the NONMEM program. A graphical approach and stepwise generalized additive modeling (GAM) were used to elucidate the preliminary relationships between PK parameters and the covariates: age, gender, weight, body surface area, serum creatinine, hemoglobin, albumin, time post-chemotherapy, hematology diagnosis, ECOG status, stage of antineoplastic treatment, autologous bone marrow transplantation, neutropenia and concurrent amikacin or amphotericin therapy.

Results: Covariate selection revealed that total body weight (TBW) affected V whereas renal function, estimated by creatinine clearance, and a diagnosis of acute myeloblastic leukemia (AML) influenced VAN clearance. We propose one general and two specific models customized for AML patients. The former was defined by: $CL (L/h) = 1.08 * CL_{cr, Cockcroft \text{ and } Gault} (L/h)$; $CVCL = 28.16 \%$ and $V (L) = 0.98 * TBW$; $CVV = 37.15 \%$. The AML models confirmed this structure but with a higher clearance coefficient (1.17).

The a priori performance of the models was evaluated in another 59 patients, and their clinical suitability was confirmed. The corresponding standardized prediction errors included zero and an SD close to unity.

Conclusions: The proposed models could be used to estimate appropriate VAN dosage guidelines, which are not clearly defined for this high-risk population. Their simple structure should allow easy implementation in clinical software and application in dosage individualization using the Bayesian approach.

P-6_ Population pharmacokinetics of tenofovir in HIV-infected patients taking highly active antiretroviral therapy.

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poster

Objectives: This study was performed to investigate the influence of renal function on tenofovir pharmacokinetics in HIV-infected adults with creatinine clearance higher than 50 mL/min.

Methods: A population pharmacokinetic model for tenofovir was developed from 193 adult patients by the use of a non-linear mixed effects modelling method performed with NONMEM.

Results: Tenofovir pharmacokinetics was well described by a two compartment open model in which the absorption rate constant was set to the distribution rate constant. Typical population estimates of apparent central distribution volume (V_c/F), peripheral distribution volume (V_p/F), intercompartmental clearance (Q/F) and plasma clearance (CL/F) were 534 L, 1530 L, 144 L/h and 90.9 L/h respectively. Apparent plasma clearance was related to bodyweight/serum creatinine ratio (BW/SCR) and to the existence of a tubular dysfunction. Concomitant treatment with lopinavir/ritonavir was found to decrease tenofovir clearance. Individual Bayesian estimates of CL/F were used to calculate the tenofovir area under the concentration-time curve from time zero to 24 h (AUC). In patients without tubular dysfunction, AUC values markedly decreased from 6.7 to 1.4 mg.h/L for BW/SCR increasing from 0.44 to 1.73.

Conclusion: BW/SCR was identified as a predictive factor of tenofovir AUC in HIV-infected patients. The relevance of a dosage adjustment based on BW/SCR should be further evaluated.

P-7_ Population pharmacokinetics of lopinavir in HIV-infected adults receiving lopinavir/ritonavir

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Objectives: Lopinavir (LPV) is an inhibitor of the protease of the human immunodeficiency virus (HIV). In order to exploit its pharmacokinetic (PK) profile, LPV is co-formulated with the cytochrome P450 inhibitor ritonavir (rtv). The aims of the present study were to develop a population PK model of LPV in HIV-1 infected adults receiving LPV/rtv, to assess the interindividual variability (IIV) in the PK parameters, and to identify possible covariates that could explain part of such variability.

Methods: The study included HIV-infected adults on stable therapy including LPV/rtv during at least 4 weeks. Blood samples were taken before and after drug administration at steady state to determine both LPV and rtv plasma concentrations. PK analysis was performed with the nonlinear mixed-effect modeling program (NONMEM v V) using FOCE method. The following covariates were evaluated in the analysis: age, sex, body weight, rtv AUC, rtv C_{min}, hepatitis C virus (HCV) co-infection, concomitant use of tenofovir (TDF), total plasma proteins, albumin, AST, or ALT. Before inclusion in the model, correlations between each individual parameter and covariates were tested using the stepwise generalized additive models implemented in Xpose.

Results: Fifty HIV-infected adults were enrolled in the study (men 76%, age 43.4± 8.2 years, body weight 67.9± 9.6 Kg, HCV co-infection 46%). LPV/rtv doses were 400/100 mg twice daily in 46 patients, 266/66 mg twice daily in 2 patients, and 800/200 mg once daily in 2 patients. A total of 391 blood samples were analyzed (7.8; range: 4-9 samples per patient). A one compartment model with first order absorption and elimination was the most suitable model to describe LPV plasma concentrations. IIV in PK parameters and the residual error were respectively described by exponential and additive models. LPV clearance was found to be exponentially related to ritonavir AUC: $TVCL=6.9*EXP(-0.07*AUC_{rtv})$; and volume of distribution was exponentially related to ritonavir minimum plasma concentration: $TVV=39.7*EXP(1.23*C_{MINrtv})$. IIV estimated for clearance, volume of distribution and absorption rate constant after the inclusion of the covariates was 21%, 23%, and 93%, respectively.

Conclusion: The population model developed with the present data could be used to estimate LPV/rtv appropriate dosage in HIV-infected subjects. The suitability of LPV/rtv dosage individualization in clinical practice needs to be confirmed in prospective clinical trials.

P-8_ Population pharmacokinetic modelling of gentamicin and vancomycin in patients with unstable renal function following cardiothoracic surgery

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Objectives: To describe the population pharmacokinetics (PopPK) of gentamicin and vancomycin in cardiothoracic surgery patients with changing renal function and to evaluate whether new methodologies¹ for handling time-varying covariates offer advantages in data fitting.

Methods: Data were collected from cardiothoracic surgery patients. PopPK analysis was performed using NONMEM. Covariates investigated for an influence on clearance (CL) and volume of distribution (V) were sex, age, weight, ideal body weight, height, body surface area, days of therapy, serum creatinine and creatinine clearance (CrCL). Two new approaches to modelling CL in terms of CrCL were examined:

1. CrCL was separated into a baseline (B_{CrCL}) effect and difference (D_{CrCL}) from baseline effect (ie. $CrCL - B_{CrCL}$). $P_{CL} = \theta_{CL} \times [1 + \theta_{B_{CrCL}} \times (B_{CrCL} - B_{MedianCrCL}) + \theta_{D_{CrCL}} \times D_{CrCL}]$.
2. The influence of CrCL on CL was allowed to vary between individuals by $\eta_{CrCL,CLi}$. $P_{CL} = \theta_p \times [1 + \theta_{CrCL} \times \exp(\eta_{CrCL,CLi} \times (CrCL - CrCL_{Median}))] \times \exp(\eta_{CLi})$.

Predictive performances of final models were evaluated using independent data.

Results: Model building data comprised 96 patients (gentamicin) and 102 patients (vancomycin). Subjects were aged 17 to 87 years, with CrCL estimates of 9 to 172 ml/min. Changes in CrCL ranged from -76 to 58 ml/min (gentamicin) and -86 to 93 ml/min (vancomycin). Both data sets were adequately described by a linear relationship between CL and CrCL. Inclusion of B_{CrCL} and D_{CrCL} improved gentamicin modelling but had little impact on vancomycin modelling. Inclusion of $\eta_{CrCL,CLi}$ resulted in a poorly characterised model for gentamicin and no improvement in fit for vancomycin. Comparison of population and individual parameter estimates using independent data from 39 patients (gentamicin) and 37 patients (vancomycin) indicated no bias in CL. Mean (95% CI) differences were 4% (-3 to 11%) for gentamicin and 2% (-7 to 10%) for vancomycin. Final CL estimates were: $CL_{Gent}(L/h) = 2.81 \times (1 + 0.015 \times (B_{CrCL} - B_{CrCL_{Median}}) + 0.0174 \times D_{CrCL})$. Interindividual variability (IIV) in CL was 27%. $CL_{Vanc}(L/h) = 2.97 \times (1 + 0.0205 \times (CrCL - CrCL_{Median}))$. IIV in CL was 27%.

Conclusion: An additional parameter to describe individual changes in CrCL with time leads to improved PopPK modelling of gentamicin but not vancomycin in clinically unstable cardiothoracic patients.

Reference:

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P-9_ Pharmacokinetics modelling and anti-Xa level simulation of enoxaparin used for venous thromboembolism prophylaxis after orthopaedic surgery

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Introduction: The use of enoxaparin to prevent venous thromboembolism after orthopaedic surgery at a fixed dose (40 mg subcutaneously once daily) leads to an important pharmacokinetic variability, which may have consequences on the treatment's efficacy. This variability is partly explained by covariates, however it still remains a residual variability.

Aim: To evaluate MAP (Maximum A posteriori Probability) Bayesian fitting, using one anti-Xa activity measured 3-4 hours after injection, to predict future anti-Xa levels.

Methods: Population pharmacokinetic parameters were estimated from clinical and biological data of 32 patients (group 1) receiving enoxaparin for venous thromboembolism prophylaxis after total hip replacement (NPEM2 program version 11.7). Future anti-Xa activities were simulated for 16 other patients (group 2) using USC*Pack following 3 methods: 1) MAP Bayesian procedure after one anti-Xa measurement (at day 1), 2) A priori method including body weight and creatinine clearance (AP1) and 3) A priori method without covariates (AP2). Simulated and measured anti-Xa levels at day 5 were compared (bias, precision).

Results: Age, gender, body weight and creatinine clearance were not statistically different between the 2 groups of patients. Simulations of anti-Xa activity by MAP Bayesian procedure, AP1 and AP2 showed respective bias \pm standard deviation : $0,03 \pm 0,12$, $0,08 \pm 0,12$ and $-0,10 \pm 0,11$ IU/mL, and precisions : $0,0148$, $0,0206$ and $0,0226$. No correlation was found between individual error by MAP Bayesian procedure and body weight ($r=0,028$; NS), age ($r=0,431$; NS) nor creatinine clearance ($r=0,369$; NS).

Conclusion: MAP Bayesian procedure seems to be the less biased and the most precise method to predict future anti-Xa activities for patients receiving enoxaparin at prophylactic regimen. Inclusion of covariates in the A priori model does not improve predictions. Further investigations may be required to evaluate the improvement of pharmacokinetic variability control by MAP Bayesian procedure.

P-10_ Population pharmacokinetics of enoxaparin used for thromboembolism prophylaxis after total hip replacement

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Introduction: Enoxaparin is usually given for venous thromboembolism prophylaxis in orthopaedic surgery, at a fixed dose of 40 mg subcutaneously once daily, without monitoring of anti-Xa levels. Pharmacokinetic variability of enoxaparin is now well documented in obese patients or in patients with chronic renal failure, but further investigations are required in a general population of in-patients.

Aim: To describe pharmacokinetic interindividual variability of enoxaparin used for venous thromboembolism prophylaxis after total hip replacement.

Methods: Three blood samples for anti-Xa activity measurement were taken in patients receiving enoxaparin during the study. Population pharmacokinetic analysis was performed using the NPEM2 program (version 11.7). A one compartment model was found to be the most suitable model to estimate population parameter values : clearance (Cl), apparent volume of distribution (Vol), elimination constant (Kel), absorption constant (Ka), weight-normalized volume of distribution ($V_s = \text{Vol}/\text{weight}$). Individual parameters were estimated by MAP (Maximum A posteriori Probability) Bayesian method. Correlations between each individual parameter value and covariates (body weight, ideal body weight, creatinine clearance) were tested.

Results: A total of 48 patients (men 54%, age 65 ± 13 years, body weight 79 ± 14 kg, creatinine clearance 78 ± 21 ml/min) were included in this study. The population estimates (median \pm standard deviation, coefficient of variation) were $Cl = 1,18 \pm 0,49$ L/h (41%), $Vol = 4,45 \pm 2,08$ L (49%), $Kel = 0,34 \pm 0,21$ h⁻¹ (80%), $Ka = 1,62 \pm 1,53$ h⁻¹ (95%), $V_s = 0,052 \pm 0,029$ L/kg (56%). Individual estimated Cl was strongly correlated with body weight ($r=0,715$, $p<0,001$), ideal body weight ($r=0,692$, $p<0,001$), but not with creatinine clearance ($r=0,170$, NS). Vol was poorly correlated with body weight ($r=0,288$, $p=0,03$) and ideal body weight ($r=0,314$, $p=0,03$). Kel was not correlated with creatinine clearance ($r=0,095$, NS) neither with body weight ($r=0,064$, NS). Estimated peak activity (C_{max}) ranged from 0,13 to 0,56 IU/mL, and was negatively correlated with body weight ($r=-0,454$, $p<0,001$). Estimated area under the concentration-time curve (AUC) ranged from 1,62 to 6,25 IU/mL.h.

Conclusion: Enoxaparin exhibits variable interindividual pharmacokinetics in a general population. Body weight is the best covariate which partly explains enoxaparin pharmacokinetic variability. Unfortunately, half of clearance variability remains unexplained.

P-11_ Use of an indirect effect model to describe the mobilization of progenitor cells induced by AMD3100

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poster

Background: AMD3100 is a small molecule CXCR4 antagonist that has been shown to induce the mobilization of hematopoietic stem cells (CD34+) from the bone marrow to peripheral blood. The purpose of this study was to characterize the exposure-response (ER) relationship of AMD3100 in mobilizing CD34+ cells.

Methods: AMD3100 concentrations and CD34+ cell counts obtained from 29 healthy subjects in a single dose, intensively sampled PK-PD study were analyzed using nonlinear mixed effects regression with the software NONMEM. FOCE with interaction was the estimation method and simultaneous PK-PD fitting was adopted.

Results: The PK of AMD3100 was described by a two compartment model with first order absorption. The population estimates for clearance (CL) and central volume of distribution (V) (\pm SE) were 5.17 L/hr (0.49) and 16.9 L (3.79) respectively. CD34+ cell mobilization was best described by an indirect effect model that stimulates the entry process of CD34+ from the bone marrow to peripheral blood in the form of sigmoid E_{max} model. The population estimates of E_{max} , EC_{50} and equilibration time (\pm SE) were 12.6 (4.89), 53.6 mcg/L (11.9) and 5.37 hours (1.31) respectively.

Conclusions: The ER relationship of AMD3100 in mobilizing CD34+ cells following subcutaneous administration was adequately characterized. Experimentation in patient populations is required to characterize the ER relationship further.

P-12_ Pharmacokinetic/Pharmacodynamic Modelling of the Anticoagulant Activity of Warfarin

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poster

Introduction: Racemic warfarin is the most widely prescribed anticoagulant drug for the prevention and treatment of thromboembolic disorders. Because of large interpatient variability in dose-anticoagulant effect relationship and a narrow therapeutic index, dosing is individually titrated by repeated measurements of INR (prothrombin time expressed as an international normalized ratio) to minimize the risk of serious bleeding events without compromising the anticoagulant effect. S-warfarin, the most potent enantiomer of warfarin, is metabolised by CYP2C9, and it has been suggested that genetic variation in the gene coding for this enzyme contributes significantly to the large interpatient variability in warfarin-dose requirements.

Objective: To develop a population PK/PD model for S-warfarin (S) and R-warfarin (R) and their anti-coagulant activity, and to use the model to estimate how much of the variability in INR response that is explained by variability in PK, with special emphasis on the contribution of CYP2C9 gene variation for clearance of S.

Method: The study population consisted of 57 Italian outpatients eligible for long-term warfarin anticoagulant therapy. CYP2C9 genotype was available for all subjects. Plasma concentrations of S and R and INR were measured following a 10 mg single dose and after attainment of stable maintenance dosing [median weekly dose (range): 28.75 (7.5-78.75) mg]. The analysis was performed in NONMEM in two steps. In the first step, the PK model was developed and pre-specified covariates tested. In the second step individually estimated S and R concentrations were used to drive the PD model.

Results: Disposition of S and R after oral administration was best described with a two- and a one-compartment model with first-order absorption, respectively. Estimated mean parameters (CV%) for S were: V_1/F 13.9 L (32%), V_2/F 3.9 L (91%) and Cl/F 0.30 L/h (32%), and for R: V/F 12.9 L (21%) and Cl/F 0.14 L/h (26%). Of the covariates tested, CYP2C9 genotype (*1/*3 and *2/*2 combined) was the only one identified as having a significant effect, with a 46% (14%) reduction in clearance for S as compared to wild-type (*1*1). The PD response was adequately described by a competitive agonist model with EC_{50} for S and R estimated to 0.16 mg/L and 0.35 mg/L, respectively. A transit compartment model with two parallel series of transit compartments, with mean transit times of approximately 10 and 70 h, respectively, described the time-delay in INR-response.

Discussion: The model suggests that variability in PK due to CYP2C9 polymorphism accounts for approximately 20% of the total variability in stabilised INR response in our study population. Even if the influence of genotype on the overall variability is relatively small, genotype may still be an important tool for identifying those patients most susceptible to adverse drug reactions due to impaired elimination of S, i.e. subjects with *1/*3, *2/*2, *2/*3 and *3/*3 genotypes.

P-13_ PK/PD-Modeling (PK/PD) and Clinical Trial Simulation (CTS) of Early Clinical Data of a New Oral Direct Thrombin Inhibitor (Dabigatran Etexilate)

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poster

Objectives: Dabigatran etexilate is an oral direct thrombin inhibitor undergoing evaluation for the prevention of venous thromboembolism following total hip and knee replacement. In order to optimise dose selection for phase III and to explore the effect of renal impairment PK/PD and CTS was used to analyse phase II data on dabigatran plasma concentrations, ecarin clotting time (ECT), incidence of venous thromboembolism (VTE) and bleeding events.

Methods: Study 1: A multicentre, open-label, dose escalation study with 314 patients and oral doses of 12.5, 25, 50, 100, 150, 200 and 300 mg bid or 150 and 300 mg od for a total of 6-10 days. Study 2: A multi-centre, parallel-group, double-blind study in 1973 patients with oral dosing of 50, 150, and 225 mg bid or 300 mg od or 40 mg enoxaparin for a total of 6-10 days .

Results: A two-compartment body model with first order absorption and elimination described the dose-exposure relationship well. Total body clearance was dependent on creatinine clearance.

The relationship between dabigatran plasma concentrations (CONC) and ECT was linear: $ECT = \text{BASE} + \text{SLOP} * \text{CONC}$. The typical values for BASE (baseline) and SLOP (slope) itself were a function of time after surgery. CTS was used to investigate the impact of renal impairment. A relationship of the incidence of bleeding events and VTE for the 50, 150, and 225 mg bid and 300 mg od dose groups of study 2 with dabigatran exposure was developed. Subsequently, the dose-exposure-effect models were used to explore different study designs for phase III clinical trials.

Conclusions: Population PK/PD-Modelling and clinical trial simulation was valuable in understanding the dose-exposure-effect relationship, exploring covariate effects and optimising trial designs.

P-14_ Population Pharmacokinetics of rHuEpo in Healthy volunteers.

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poster

Objectives. rHuEpo (Recombinant Human Erythropoietin-alpha) is approved in the US and EU for treatment of anemia in several indications, including anemia in patients receiving chemotherapy for cancer. The objectives of this analysis were to model rHuEpo pharmacokinetics after intravenous and subcutaneous administration, to quantify the associated variability and to examine the influence of demographic characteristics and other covariates on the pharmacokinetics.

Methods. A population pharmacokinetic analysis was performed using data from sixteen studies where healthy volunteers received doses of rHuEpo, ranging from 1 IU/kg to 160,000IU, as single or repeated administration. Data was available for 49 subjects who received intravenous administration, for 427 subjects who received subcutaneous administration, and for 57 subjects who received placebo. The pharmacokinetic data was rich, with an average of 27 samples per subject. Data was analysed using NONMEM with the first order method.

Results. Endogenous Epo concentrations displayed a diurnal variation, described by the sum of two cosine functions with periods of 24h and 12h. The disposition of rHuEpo was modelled using a two-compartment model with parallel linear and nonlinear clearance. The absorption after subcutaneous administration was described by a complex model, where the main fraction of the dose was absorbed via a short sequential zero-first order process and the remainder was absorbed via a long-lasting zero-order process. The bioavailability increased with increasing dose. Interindividual and interoccasion variability were characterized. The influence of several covariates on rHuEpo pharmacokinetics could be identified, the most important being the influence of age on the first order absorption rate.

Conclusions. This model establishes a model describing rHuEpo pharmacokinetics in healthy volunteers after both intravenous and subcutaneous administration, covering a very wide dose-range and a number of different treatment regimens. The model will serve as a basis for PK/PD modelling of rHuEpo, and for further establishing its pharmacokinetics in cancer patients.

P-15_ Population PK/PD model of GPI 15715 and GPI-derived propofol in sedation and comparison of PK/PD models for ordered categorical observations

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poster

Objectives: AQUAVAN^(r) Injection (GPI) is a water-soluble prodrug of propofol (PR). It was evaluated in an adaptive dose ranging colonoscopy study to produce a desired sedation level (MOAA/S score). A population PK model of GPI and GPI-derived PR and PK/PD model relating propofol concentrations to the MOAA/S scores were developed. Covariate predictors of PK and the effect were identified, and simplified dosing strategies were explored.

Methods: NONMEM analysis was performed using sparse plasma samples from 158 patients pre-medicated by i.v. fentanyl and receiving initial and up to 4 (mean 1) supplemental bolus doses of GPI (total 495-1675 mg). A linear model described PK of GPI (compartments 1, 2), PR (compartments 4, 5) and a GPI/PR concentration delay (compartment 3). Rich MOAA/S data and individual PR concentration predictions were used to develop PK/PD models. The effect compartment described a PK/PD delay. The probabilistic model described probabilities of being at each MOAA/S level while the continuous model described the expected MOAA/S scores. Predictive check simulations compared the models. Back-Step Method [1] was tried to improve the PK/PD estimates.

Results: Lean body weight (LBW) was the best predictor of PK. GPI and PR central volumes, and GPI clearance increased by 1.8%, 2.5%, and 1.4% per kg of LBW, respectively. Predicted PR C_{max} (at 4-5 minutes post-dose) was proportional to $1/LBW^{0.45}$. There was no effect of fentanyl, age or gender on PK. Individual predictions of the PK/PD models were similar and similar to the observed data. Predictive check simulations showed higher fraction of deeply sedated patients than observed, especially for the continuous model. Older patients (≥ 65 years) were estimated to have approximately 25% stronger effect at the same PR concentrations. No fentanyl or gender effect was detected.

Conclusions: 1. A linear PK model adequately described the data. 2. LBW was the best predictor of PR concentrations. Strictly weight-proportional dosing may overdose overweight individuals. Mg/kg dosing with an upper dose boundary, or fixed-dose (mg) in the ranges of weights may be preferable. 3. Age did not influence PK, but increased the PD effect. A dose reduction of about 25% is needed for patients over 65 years. 4. Fentanyl did not affect PK or PD. 5. Continuous and probabilistic PD models adequately described the data and the covariate effects; simulations demonstrated better predictive abilities of the probabilistic model.

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P-16_A mathematical model for paroxetine antidepressant effect time course and its interaction with pindolol

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poster

Background: Although selective 5-HT reuptake inhibitors (SSRIs) block monoamine uptake within hours of administration, their full clinical effect does not appear until 2-4 weeks after treatment onset. Pindolol, a betablocker with 5-HT_{1A} receptor antagonist activity has been shown to decrease the delay of action of SSRIs. However, the optimal dosing schedule of pindolol remains controversial.

Objectives: development of a new class of PK-PD models in order to fit the data of a published randomized trial and to simulate the influence of pindolol on paroxetine clinical response time course.

Methods: the model is based on the concept of homeostatic control mechanisms, in which SSRIs exert their antidepressant effect by increasing the transduction set-point of the postsynaptic 5-HT_{1A} receptor, and pindolol increases the rate of feedback mechanisms. The clinical response to paroxetine (assessed with the MADRS scale) is related to the level of post synaptic transduction by a Hill- type model. The parameters were estimated by non-linear regression using weighted least-squares. The objective function to be minimised was based on the comparison between the proportion of treatment responders observed at several time points in the study of Tome and the expected proportions estimated by population simulation based on the model. The goodness-of-fit was assessed by a predictive check. Finally, the score simulations on the MADRS scale with different doses of paroxetine and pindolol, were performed using ADAPT II software.

Results: The predictive distribution of the proportion of responders at each day of measurement was not significantly different from the proportions observed in the clinical trial . Since no lack-of-fit arises, the model and the parameter values are compatible with experimental data. The simulated MADRS total scores obtained after treatment with paroxetine alone (20 mg/d) or combined with different doses of pindolol (1.5 mg/d, 7.5 mg/d and 37.5 mg/d) supported that the reason for inconstant pindolol efficacy is that the 7.5 mg dose is too low.

Conclusion: The model seems to own a number of desirable features, allowing its use for clinical trial simulation or analysis. This kind of model could be applied to characterize time course of other antidepressants response ; currently , the ability of the model to describe the data of a trial of efficacy of the combination clomipramine plus lithium or placebo in the treatment of unipolar depression is ongoing .

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P-17_ A new CNS active drug and its metabolite: a population pharmacokinetic analysis

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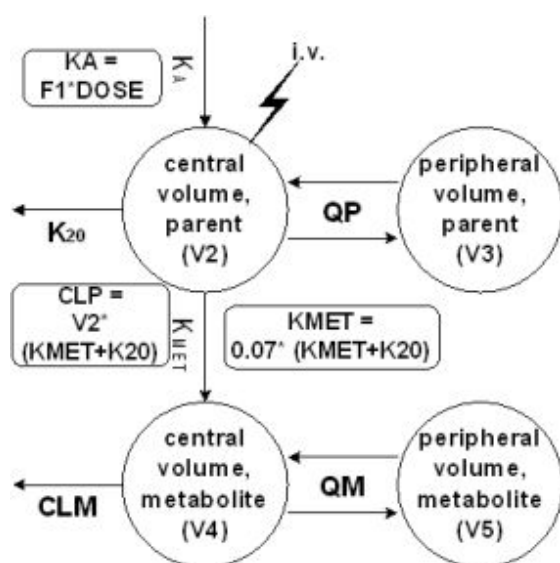
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poster

Objectives & Background: A population pharmacokinetic (PK) model for a new CNS active drug in clinical development and its metabolite was to be developed based on data from four phase I (healthy as well as renally impaired subjects) and two phase IIa studies (target population). The model development should also include an initial screening for covariates that might influence the PK characteristics of the drug and/or its metabolite.

Methods: Plasma data of 119 subjects (single and multiple oral dosing or iv infusion) consisting of 1819 parent and 1333 metabolite concentrations were fitted simultaneously. The analysis was performed using the FOCE INTERACTION estimation method implemented in NONMEM.



Results: Plasma concentration-time profiles (PCTP) were best described by a two compartment model for the parent compound as well as for the metabolite. Metabolic formation was accounted for by a transfer constant (K_{MET}) between the central volumes of both compounds. K_{MET} was fixed to a value reflecting the recovery of the metabolite in urine (7%). Interindividual variability could be included for CLP, CLM, V₂, V₄ and F₁. The estimates for parent drug and metabolite revealed large volumes of distribution and low clearances resulting in long half-lives. The initial covariate screening suggested that sex on F₁ has a significant influence on the PCTP which

warrant further investigations.

Conclusion: A population PK model has been successfully developed describing the plasma concentration of the parent compound and its metabolite. Influence of covariates will be further evaluated in a larger number of patients presumably exhibiting wider distributions of covariates. The model developed can serve as a tool to simulate and evaluate different dosing regimens for further trials for the drug under development.

P-18_ Population Pharmacokinetic/Pharmacodynamic Analysis of Different Subunit Selective GABAergic Ligands in an Animal Model of Epilepsy

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poster

Objectives: Changes in GABA_A-receptor functionality play an important role in many forms of epilepsy. One of the causes of these changes may be alteration in subunit composition of the receptor. In the present study the functionality of the GABA_A-receptor was studied *in vivo* in the post Status Epilepticus (post-SE) rat model, in which the SE was induced by *ip* injections of kainic acid (KA). Different subunit selective GABAergic ligands were used: midazolam (MDZ, selective for gamma₂), alphaxalone (ALP, selective for delta), and zolpidem (ZPD, selective for alpha₁).

Methods: A PK/PD experiment with a GABAergic ligand (MDZ, n=8, ALP, n=6, ZPD, n=4) was performed in male Sprague Dawley rats before and at 4 or 14 days after induction of SE. The power of β -frequency of the cortical EEG was used as a measure for the effect. The results were analysed using the mechanism based PK/PD model reported by Visser et al (JPET, 2002;302:1158-1167), comprising a separate characterization of the receptor activation process and the stimulus-response relationship. A single and unique stimulus-response relationship was assumed for all ligands. If only changes in subunit composition underly changes in functionality of the GABA_A-receptor in epileptic animals, this will be exclusively reflected in alterations in the *in vivo* intrinsic efficacy (e_{PD}).

Results: Analysis of the data resulted in a significant decrease in effect of MDZ and ZPD after induction of SE (e_{PD} = 39% or 87% of control respectively), whereas the effect of ALP was significantly increased (e_{PD} up to 129%). This is indeed in favour of an alteration in subunit composition, specifically an exchange of gamma-subunits to delta-subunits. Furthermore, the data indicate that the transducer function is altered as well by epilepsy. Further refinements of the model to characterize and explain these alterations are currently under investigation.

Conclusions: Using a mechanism based PK/PD model, subunit-selective alterations in epilepsy, expressed in changes in e_{PD} are shown. Moreover, as the model is able to distinguish between the receptor activation process and the stimulus-response relationship, analysis of alterations in the transducer function will provide deeper insight in the process of epileptogenesis.

P-19_ Population pharmacokinetics of paroxetine in the pediatric population

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poster

Aims: The aim of this work was to develop a population pharmacokinetic model for Paroxetine in pediatric patients and to use this model to assess individual exposure in pediatric patients enrolled in clinical trials for Major Depressive Disorder, Social Anxiety Disorder and Obsessive Compulsive Disorder for which only sparse plasma samples were collected.

Methods: The model structure was selected according to the PK profile obtained in 62 pediatric patients (27 children and 35 adolescents) in an intensive PK sampling study (8 PK samples per occasion) with paroxetine administered at 10 mg/day for the first 2 weeks 20 mg/day for the next 2 weeks, and 30 mg/day for the final 2 weeks, with PK assessment at the end of each dosing period. The effects of age, weight and gender on paroxetine pharmacokinetics were evaluated in this population. The resulting model was then used as a prior to obtain individual PK parameters in 131 pediatric patients for which only sparse (n=199) samples were available. Population pharmacokinetic analysis was performed on the data pooled from all studies using the nonlinear mixed-effects modelling program NONMEM Version V.

Results: The best model retained was single compartment with first order absorption and saturable first-pass effect and elimination. Both clearance and volume of distribution were found to be dependent on body weight according to the allometric model. The model enabled to assess individual paroxetine exposure in sparsely sampled children and adolescent patients.

P-20_ Retrospective Population Pharmacokinetic Analysis of Levetiracetam in Westerner and Japanese Adults

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poster

Objective: The aim of the analysis was to identify demographic and/or physiologic determinants of levetiracetam disposition in healthy subjects and in subjects with partial epilepsy, using two matched sets of studies performed in Japan and overseas.

Methods: 5408 plasma concentration-time data were available together with demographic variables and treatment information, from 524 unique subjects participating in six phase-I studies, and in two phase-III and two long-term follow-up studies in add-on treatment of partial epilepsy. The structural model was a one compartment model with first order absorption and elimination rates. Parameters were assumed log-normally distributed. Residual variability was modeled by two proportional error models, one for healthy and one for epileptic subjects. An inter-occasion variability term was used for K_a . Modeling was performed using NONMEM with FO estimation. The full data set was used for analysis and validation.

Results: Patients were taking one to three concomitant anti-epileptic drugs (AED) consisting mainly of carbamazepine, phenytoin, phenobarbital and valproate. Body weight, gender, creatinine clearance (CL_{cr}) and concomitant AEDs had a statistically significant effect on levetiracetam clearance. Weight, health status and valproate had a statistically significant impact on the volume of distribution. Food significantly decreased K_a . Ethnicity was not a statistically significant covariate. Clearance, typically 4.02 L/h in a 70 kg male subject with CL_{cr}=110 mL/min, varied by 20% at most when body weight was halved or doubled from the population mean (from 70 to 35 or 140 kg). Enzyme inducers increased levetiracetam clearance by 9%, while valproate decreased it by 19%. Clearance was 10% lower in females than in males, and 10% lower when CL_{cr} was decreased from 110 to 50 mL/min. Distribution volume, typically 52.7 L in a 70 kg epileptic subject, increased linearly with body weight, and decreased by 23% when levetiracetam was co-administered with valproate, probably as a consequence of body fat gain caused by valproate. Simulations from the final model showed that only body weight or valproate had a >20% effect on C_{max} and AUC_τ. These effects do not require dose adjustment, considering the low toxicity of levetiracetam and the recommended individual titration approach (from 1 to 3g daily).

Conclusion: Analysis of this large data set allowed the identification of several explanatory covariates that contribute to the modest pharmacokinetic variability of levetiracetam. Ethnicity was not statistically significant.

P-21_ Understanding the variability in clinical response to rufinamide, a new antiepileptic drug: a pooled PKPD analysis

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Background: Rufinamide is a new chemical entity developed for the treatment of epilepsy that modulates the activity of sodium channels, prolonging their inactive state. In phase II and phase III studies, rufinamide significantly reduced seizure frequency.

Objective: The objective of this analysis was to describe the exposure response (ER) relationship in patients with epilepsy (paediatric patients and adults) across a variety of doses, formulations, and concomitant anti-epileptic medications, over 10 years of development (1990-2000).

Methods: Studies were multicentre, double-blind, placebo-controlled (except for two studies), randomised, parallel-group, in patients with partial seizures, generalised seizures, and Lennox-Gastaut syndrome. Rufinamide was administered as oral tablets with different formulations, at daily doses: 100 to 7200 mg. In 6/7 studies, the clinical endpoint was seizure frequency, whereas one study endpoint was the time to meet one exit criteria. Seizure frequency was collected using diaries. Population PK and PKPD modelling used NONMEM. The analysis of total seizure frequency was performed after Log_e transformation of frequency per day.

Results: The PK population included 1072 patients. The PKPD population included 1725 patients (half males), with a total of 9881 PD observations. A one-compartment disposition model described rufinamide pharmacokinetics. The natural logarithm of total seizure frequency was described by the sum of an intercept (baseline frequency-prior to treatment initiation and at zero concentration of rufinamide), the effect of placebo and time in the study and a decrease proportional to rufinamide C_{avss} . Efficacy ER was not affected by formulation, study design (for identical endpoint) or concomitant medications. Differences in response among studies were explained by the relative bioavailability between formulations, by the baseline disease severity, and by the differences in placebo response between populations (children, adolescent, and adults).

Conclusions: This PKPD analysis allowed a complete bridging between formulations/doses, and a complete bridging between populations (adults and children) over 10 years of development.

P-22_ Population pharmacokinetics of lamotrigine in epileptic patients with data proceeding of therapeutic drug monitoring

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poster

Objective: This study aims to develop a population pharmacokinetic (PK) model of lamotrigina (LTG) in epileptic patients in order to implement it in Bayesian algorithms, to optimize LTG therapy.

Methods: The study was carried on 85 epileptic patients (1-86 years old) treated with LTG (200±150 mg/day). From routine clinical setting, 155 through plasma LTG concentrations were retrospectively collected at steady-state. Samples were analysed by HPLC-UV. The limit of sensitivity was .025 mg/mL. Inter- an intraday CV's were 8.4% and 5.2%, respectively. PK analysis was performed with a nonlinear mixed-effect modelling program (NONMEM V). Exponential error-models were assumed to describe interindividual and residual variabilities. The first-order conditional estimation was used throughout. A one-compartment model with first-order absorption and elimination was considered. Influence of age, gender, total body weight (TBW), body surface area and concurrent antiepileptic therapy with valproic acid (VPA) and inducers (IND) were analysed in the model. To elucidate preliminary relationship between clearance (CL) Bayesian estimated (POSTHOC) and covariates, a graphical approach exploratory data analysis and the stepwise generalized additive modelling implemented in Xpose were used.

Results. From the scatterplot of CL vs age a higher clearance in children than in adults was apparent, so we used two age groups, which got a better fit of data. TBW explained part of the interindividual variability of CL in both groups. In addition, the association with VPA produces a LTG delayed elimination. Only in adult population, IND showed significant influence on CL, because in children this covariate was not well represented (2%) Final regression models for CL were as follows:

Children £ 14 y old

$$CL (L/h)=(.038*TBW)*e^{-.763*VPA} \quad CV=38.3\% \quad CV_{residual}=35.6\%$$

Adults:

$$CL (L/h)=(.029*TBW)*e^{-.724*VPA}*e^{.444*IND} \quad CV=33.2\%$$

$$CV_{residual}=25.9\%$$

Where VPA and IND denotes presence (1) or absence (0) of associated medication

In the final model, the initial variability in CL was reduced by 39% and 42% for children and adults, respectively.

Conclusions: The population model proposed could be used to estimate LTG appropriate dosage regimens. Moreover their simple structure will allow an easy implementation in clinical PK software and their application in dosage individualization by Bayesian approach. A prospective study is necessary in order to confirm the suitability of this population model in clinical practice.

P-23_ Modelling of the Hamilton Depression Rating Scale in Unipolar Depression Trials

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poster

Objectives: Depression trials are known to show a large placebo response, which makes it very difficult to separate placebo effect from drug effect before 8 to 12 weeks treatment. The golden standard assessment tool in depression studies is the Hamilton Depression Rating Scale (HDRS), which consists of 17 items which are summed up to provide a total score. Thus far, little attention has been paid to the sensitivity of the HDRS to placebo response and no conclusive evaluation is available about the impact of disease severity on the onset and time course of depression symptoms. Objective of this investigation was to explore the sensitivity of HDRS to treatment effect and characterise the time course of response using retrospective data from clinical studies with SSRIs.

Methods: Data from 8-week to 12-week double blind, placebo-controlled studies were used. The HDRS was analysed to assess the importance of specific sub-scores and their sensitivity to drug efficacy (clinical response defined as >50% sustained decrease from baseline). Data exploration and sensitivity analysis was performed in R. K-PD modelling was performed using NONMEM V.

Results: Exploratory analysis of HDRS revealed that whilst some of the clinical items can clearly distinguish between responders and non-responders, many of the sub-scores do not show any sensitivity to response or variation over time. A sub-scale was developed incorporating only the sub-scores that showed a clear sensitivity to treatment response over time. The profiles and variability of in HDRS as well as the proposed sub-scale could be characterised by two types of population K-PD models. Mixture models were also evaluated to account for intrinsic differences in response profiles over time, i.e., to identify and separate responders from non-responders.

Conclusion: The assessment of net drug effect in depression trials requires incorporation of the time course of placebo response, rather than subtraction of average placebo response, and a separation of responders from non-responders.

P-24_ Population pharmacokinetics of the new antiepileptic drug lacosamide in healthy subjects with different age and gender

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Objectives: Characterization of population pharmacokinetics of the new antiepileptic drug lacosamide in young healthy male and elderly healthy male and female subjects in order to identify possible covariates that may have an influence on the pharmacokinetics (PK) of lacosamide.

Methods: 47 subjects received a single dose of 100 mg lacosamide or placebo on day 1 and day 8 and a multiple dose of 100 mg lacosamide bid or placebo on day 4 to day 7 in a single-center, double-blind, parallel group trial. Blood sampling was done after single dose on day 1 and after multiple doses following the last dose on day 8. Lacosamide concentration-time data were analyzed using nonlinear mixed-effect modeling (NONMEM). The parameters age, gender, body weight, height, and creatinine clearance (CL_{crea}) were tested as possible covariates to explain inter-individual variability in PK parameters of lacosamide.

Results: Lacosamide plasma concentrations were adequately described by a 1 - compartment model with low residual variability (CL_{crea} and gender were identified as covariates on k_e resulting in a reduction of inter-individual variability of k_e from 19% to 15%. The population mean of k_e for a subject with a median value of CL_{crea} of 89 mL/min was estimated to be 0.044 h^{-1} ($t_{1/2}$ of 15.8 h) for males and 0.051 h^{-1} ($t_{1/2}$ of 13.6 h) for females (=14% decrease), respectively.

Conclusions: An appropriate population PK model was successfully developed to characterize plasma concentration-time data of lacosamide after oral administration. Based on the results, the influence of the tested covariates on the PK of lacosamide could be described and quantified within the trial population of healthy subjects. A major part of the variability of V/f can be explained by differences in height and gender. The observed higher plasma concentrations of lacosamide in females were the result of the smaller V/f in this subpopulation. Additionally, as lacosamide is highly soluble in water and mainly distributes in extracellular fluid, changes in height are linked with changes in V/f. In summary, lacosamide was found to be a particularly suitable drug for population PK. As the inter-individual variability of V/f and k_e can be explained to a large extent and the identified covariates only have a minor influence on PK parameters, lacosamide is an antiepileptic drug with a highly predictable exposure in individual subjects.

The current model is capable of being used as basis for population PK evaluations in Phase 2/3 to verify the current results in the target patient population.

P-25_ Dose-response analysis of levetiracetam add-on treatment in patients with partial epilepsy

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poster

Objectives: The aim of this population analysis was to describe the individual change in seizure frequency from baseline after treatment with levetiracetam or placebo and to model the dose-response relationship and assess the impact of potential covariates.

Methods: Efficacy data from four double-blind, placebo-controlled parallel-group phase-III clinical trials were used. The final dataset used for the modeling of the dose-response relationship contained 4218 data rows for 958 individual epileptic patients with partial onset seizures. In the final model, the change in weekly seizure frequency for the improving patients was described by the following equation :

$$I = \text{Baseline} \times (1 - D_{\text{Placebo}}) \times [1 - E_{\text{max}} \times \text{Dose} / (\text{ED}_{50} + \text{Dose})] \times e^h$$

in which the drug effect was assumed to be an additional effect on top of a placebo effect D_{Placebo} . The changes in seizure frequency in patients improving or deteriorating on placebo and in patients deteriorating on levetiracetam, were described by dose-independent models. The number of seizures in an individual patient was modeled as a Poisson process and the seizure frequency between patients was assumed to be log-normally distributed. Modeling was performed using NONMEM version V.

Results: The final model successfully converged to an E_{max} dose-response relationship. A typical improving patient treated with placebo is predicted to have an 11% decrease in the seizure frequency from baseline, compared to 45% increase for a typical deteriorating patient. The typical value of the maximal reduction in seizure frequency from baseline in improving patients after treatment with Levetiracetam was estimated to be 72%. The typical value of ED_{50} (dose producing half of the maximum effect) was estimated to be 1408 mg/day. Neither gender, nor race, body weight, age or number of concomitant AEDs appeared to have an effect on the improvement or deterioration of patients.

Conclusion: Add-on treatment of levetiracetam demonstrates a dose-response relationship in approximately 75% of the patients with refractory partial seizures. The ED_{50} predicted by the model (1.4 g) corresponds to about half the current maximum recommended daily dose (3 g), and is close to the WHO 2005 Defined Daily Dose (1.5 g).

P-26_ PK and PK/PD Modelling of CNS Effects and Heart Rate After THC Administration in Humans

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poster

Introduction: Delta9-tetrahydrocannabinol (THC) is the most well known pharmacologically active cannabinoid, acting as a CB1 and CB2 agonist. Currently a large number of newly developed cannabinoid agonists and antagonists are under investigation as therapeutic agents. The clinical development of these is hampered by the lack of quantitative information regarding the pharmacokinetic/pharmacodynamic (PK/PD) properties of THC. We aimed to develop a model to investigate the potency and efficacy of agonists as well as to provide a framework to predict and quantify the pharmacological action of antagonists.

Aim: The purpose of this investigation was to develop a PK/PD model for the characterization of different central nervous system effects (CNS) and heart rate effects of THC in humans. This model should be capable to assist in the quantification of the PD interaction between THC and antagonists.

Methods: Inhaled rising doses of THC were administered using a Volcano(r) vaporizer (Storz-Bickel GmbH, Tuttlingen, Germany) to 12 subjects in a randomised order according to a placebo-controlled, two-way crossover design. The consecutive doses of THC (2, 4, 6 and 8 mg) were administered with 11/2 hour intervals and pharmacodynamic measurements were frequently obtained after each dose. Parameters demonstrating a clear dose-dependent THC effect were used in PK/PD modelling including visual analogue scales (VAS) for subjective effects on alertness, "feeling high" and external perception. Postural stability was assessed using body sway and cardiovascular effect were characterised using heart rate. Plasma THC and its major metabolites 11-OH-THC and 11-nor-9-COOH-THC were measured frequently after each consecutive dose. An integrated PK/PD model was used to analyse the data. Parameter estimation was performed using NONMEM (Version V, GloboMax, LLC, Hanover, MD).

Results: A four-compartment model simultaneously described the PK of THC and 11-OH-THC and of THC and 11-nor-9-COOH-THC. Both models revealed Michaelis-Menten elimination for THC. The effects of THC lagged behind the plasma concentration, revealing hysteresis which indicated a slow equilibrium between blood and effect compartment. VAS "feeling high", VAS external perception, body sway and heart rate were best described using an Emax model, while VAS alertness was best described by a linear model. Equilibration half-lives varied from 7.68 min for heart rate and from 39.2 to 84.8 min for the CNS parameters.

Conclusion: Suitable PK models were developed for THC and its major metabolites 11-nor-9-COOH-THC and 11-OH-THC. The PK/PD model developed was found to successfully predict the time course of VAS alertness, "feeling high", external perception, body sway and heart rate after non-steady state rising consecutive doses of THC. The difference in equilibration half-lives between heart rate and CNS effects, suggests two different physiological compartments, perhaps in combination with different mechanisms of action. This PK/PD model will be of value in the quantitative analysis of CB1 agonist and antagonist studies.

P-27_ Population PK/PD modeling of supine heart rate after oral administration of a new candidate antipsychotic drug

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poster

Objectives: In the first clinical studies with a new candidate antipsychotic, supine heart rate (HR) increased, which is thought to be related to its noradrenaline reuptake inhibiting properties. In order to help with the selection of doses that could be safely administered in subsequent clinical trials, a population PK/PD analysis was performed.

Methods: Data both from phase 1 and phase 2 trials were included in the population PK/PD analysis using NONMEM, and model-predicted concentrations at the time of the (supine) ECG measurements were used as drivers of the response.

Results: The effect of the drug on the supine HR was best described by a sigmoidal E_{max} model, and was assumed to be direct (no time delay) and constant over time (no tolerance). Other parameters affecting the HR were the diurnal rhythm, implemented as the sum of 2 cosine functions. Baseline HR was found to be different between healthy volunteers and patients (52 versus 64 beats/min in males), and within the patient population, between males (65 beats/min) and females (69 beats/min). E_{max} was estimated at 43.7% and EC_{50} at 31.5 ng/mL. Hill was lower than 1, indicative of the shallow relationship between plasma concentrations and increases in supine HR. Interindividual variabilities (IIV) were below 50%, except for E_{max} . With the exception of EC_{50} , and the IIV on Hill and on one of the amplitudes, all parameter estimates had relative standard errors below 50%.

Conclusion: Predictions using the final population PK/PD model show that up to doses of 35-40 mg, less than half of the patients have increases in supine HR of 6 beats/min at peak. This range increases to 55-60 mg if average instead of peak steady-state concentrations are considered. Therefore, safety problems are to be anticipated only when doses higher than 40 mg/day are administered.

P-28_ Model Based Insights to Lamotrigine for Pain Associated with Diabetic Peripheral Neuropathy

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poster

Lamotrigine was studied for pain associated with diabetic peripheral neuropathy in replicate, randomized, double-blind, placebo (PBO) controlled, multicenter studies. Population PK/PD modeling was used to elucidate the exposure (post-hoc estimates of lamotrigine steady-state AUC) versus effect (response on an 11-point ordered categorical scale) as a function of time and baseline pain scores.

Methods: Each study included a 2-4 week screening phase; a 1-week baseline phase; a 7-week dose-escalation phase; and a 19-week treatment period. A total of 720 patients were enrolled in the 2 studies at doses of 0, 200, 300, and 400 mg/day (given BID). A longitudinal PK/PD model for ordinal response data was fit to individual patient diary pain data using NONMEM. The model accounted for the temporal profile of PBO response, individualized exposure to drug, and baseline pain status.

Results: The primary outcome, pain intensity change from baseline to week 19, was achieved for only the 400mg/day dose group in one of the two studies. Moreover, the dose-response relationship was not rank ordered in comparison to efficacy for 1 of the 2 trials. The PK/PD model was successful in characterizing the major features of trial results. Moreover, the model successfully accounted for the time profile and distribution of PBO response. Lamotrigine steady-state AUC and baseline were both strongly significant predictors of effect.

Conclusions: An exposure-response relationship was established for lamotrigine in painful diabetic neuropathy. The complexity of trial outcomes required a model-based approach to elucidate the exposure-response relationship and explore performance factors of the current trials, and mechanisms to improve upon the design of future trials.

P-29_ Clinical relevance criteria in covariate model building of population pharmacokinetic models -A phase III pharmacokinetic analysis of dofetilide

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poster

Objectives: To characterise the pharmacokinetics of dofetilide in patients and to identify clinically relevant covariates and their respective contribution to changes in pharmacokinetic parameters.

Methods: Pooled pharmacokinetic and covariate data from 1445 patients enrolled in 14 phase III clinical trials was used. A population pharmacokinetic model including interindividual variability, interoccasion variability and residual error was developed using NONMEM. Automated stepwise covariate model building was used to identify important covariates. The model fits were done using the first-order (FO) and the first-order conditional estimation (FOCE) method with interaction. During the covariate model building inclusion and exclusion of covariates was based on statistical significance with or without clinical relevance criteria, defined as either a reduction in interindividual variability in a parameter or a change in a parameter at the extremes (minimum or maximum).

Results: The data was adequately described by a one-compartment model with first order absorption. Two base models were developed, one where a joint clearance was estimated (Model 1), and one where the renal and the metabolic clearance values were estimated separately (Model 2). Splitting the clearance made it possible to investigate parameter-covariate relationships based on mechanistic plausibility. In this analysis more parameter-covariate relationships were identified in Model 2, and the objective function value was lower as compared to Model 1 both when statistical significance only was used and when it was combined with the clinical relevance criteria. All covariates found significant in Model 1 were also identified in Model 2. Both the full and the final covariate models contained less parameter-covariate relationships if the covariate model building was based on a combination of statistical significance and clinical relevance than if only statistical significance was applied. The parameter estimates of the resulting models were similar for the two estimation methods.

Conclusion: For data sets containing a lot of covariate information clinical relevance criteria is a valuable tool for identifying important covariates in the target population. The run times for models of this complexity in combination with large data sets are often long when the FOCE method is used. It is therefore not feasible to use statistical significance alone for covariate model building.

P-30_ Ivabradine and S18982 activities on heart rate: a population PK/PD analysis

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poster*

The ivabradine was developed for its heart rate decrease properties. The overall activity is related to both ivabradine and S 18982 (its active metabolite). Both entities have a similar intrinsic activity.

Aim: To establish the relationship between Ivabradine and S 18982 concentrations and heart rate in the phase II / phase III population.

Material and method: Population approach within NONMEM(r) Vers. V.1

Data: Eight phase II/III studies (1333 patients, 562 placebo & 771 Ivabradine). Ivabradine and S 18982 concentrations were measured as well as three different types of heart rate measurements: At rest in supine position (HRsp), at rest in standing position (HRsd) and during the exercise tolerance test (ETT, bicycle or treadmill test): 68887 heart rate measurements and 7411 plasma concentrations were available.

The model(s): Four stages: Firstly, the PK models. Ivabradine and S 18982 PK were modeled. Estimated parameters were integrated in the PK/PD model by fixing the populations estimates, empirical Bayes estimates were estimated simultaneously with PD. Secondly the relationship between the heart rate and the increase of the effort was established based on data before treatment. Thirdly, the placebo effect was graphical investigated over the different periods. Lastly, the PK/PD model included the impact of the concentrations of both entities on heart rate.

Results: Ivabradine and S 18982 PK were described using two two-compartment models with a first order absorption or formation for S 18982. The relation between HR and the increase of the effort was linear for both bicycle and treadmill test. A scaling factor was estimated between HRsp and HRsd.

No placebo effect was demonstrated and no clear non-responder population was identified.

The treatment impact was modeled using one effect compartment for Ivabradine and one for S 18982. The two entities acted through an inhibition Emax model, with a similar Emax and two different EC₅₀ expressed as a percentage of heart rate decrease.

Conclusion: Using the modeling approach, the information spread through the different phase II-phase III studies was combined in a single entity. It enabled to allowed to demonstrate a clear dose-response relationship between ivabradine administered dose and heart rate. This model was firstly, used through simulations to investigate any risk of serious bradycardia after Ivabradine administration in different situations. Secondly, it was also used as a basis to investigate the relationship between the Ivabradine plasma levels and the clinical end-point: Time to limiting angina (TLA), through a time-to event analysis.

P-31_ Strategies to Improve Model-based Decision-making During Clinical Development

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poster

Objectives: To assess the utility of a novel PK/PD-based modeling and simulation strategy as well as the utility of the Drug Model Explorer(tm) (DMX(tm)) technology for decision-making during early clinical development of CI-1027.

Background: CI-1027 was developed as a low-density lipoprotein cholesterol (LDL-C) lowering compound. The team was interested in assessing early the effect of CI-1027 plus statin combination compared with statin monotherapy or a key competitor plus statin combination. Given the LDL-C lowering effect across the CI-1027 plus statin doses range, should clinical development continue?

Strategy: A single Phase IIA trial was planned along with a dose-response surface meta-analysis of literature data on key competitors and CI-1027 data for several efficacy and safety endpoints. DMX software provided to the team an interactive, easy to use, query tool to compare treatments and make trade-off based on all endpoints.

Methods: The Phase IIA trial was a single 8-week, double-blind, study in hypercholesterolemic patients with placebo, three CI-1027 doses, three atorvastatin doses, and their respective combination. Summary data from the trial were combined with CI-1027 Phase I data and literature data from ezetimibe and statin trials. A nonlinear mixed effects regression analysis was undertaken to describe (1) the monotherapy dose-response for the non-statins, CI-1027, and ezetimibe, and (2) the dose-response for 5 statins as mono-therapy and in combination with a non-statin. Summary data from 21 clinical trials (~10,000 patients) were included for LDL-C. Emax models described the relationship between percent change in LDL-C and CI-1027, ezetimibe, and statin (mono-therapy) dose. Combinations were well described by adding a simple interaction term to the model.

Results: The predictive distribution of the dose-response surfaces was obtained from the models covariance matrix and uploaded into DMX. After selecting an endpoint, population, and treatment of interest the DMX system immediately displayed the corresponding quantitative result, including likely differences between CI-1027 and competitors. For LDL, the CI from the ANCOVA analysis of the Phase IIA trial overlaps that of ezetimibe. The CI from the meta-analysis does not overlap the ezetimibe CI clearly suggesting that CI-1027 is unlikely to lower LDL-C sufficiently to compete with ezetimibe.

Conclusion: In this case, the availability of integrated dose-response models for CI-1027 and competitors guided informed decision-making during early development. Based, in part, on the quantitative knowledge obtained through modeling all relevant data and made accessible via DMX, the development of CI-1027 was discontinued after one Phase IIA trial in the target population.

P-32_ Development and evaluation of a population pharmacokinetic model for cilobradine, an If channel blocker

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poster

Objectives: The If channel blocker cilobradine belongs to a class of bradycardic agents selectively decreasing heart rate by reducing the diastolic depolarisation rate in the sinus node. Hence, cilobradine might be beneficial in the treatment of cardiovascular diseases, e.g. ischemia. The objective of this study was to evaluate the population pharmacokinetic (PopPK) characteristics based on data of 6 clinical phase I trials with different formulations and to assess the predictive performance of the model developed.

Methods: Single doses of 1.25-40 mg cilobradine were administered as p.o. solution, p.o. capsule or 20 min i.v. infusion. The capsule was also given once daily (0.6-20 mg) for 7 or 15 days. PK profiles of 162 males with 2733 plasma samples were analysed (development data set). NONMEM, version V, level 1.1, with the FOCE interaction method was used for data fitting and assessment of several covariates by forward inclusion and backward deletion techniques. Model evaluation was performed using a new data set (evaluation data set) including 1713 plasma concentrations of p.o. solution over a dose range of 0.25-5 mg.

Results: The data were best described by a 3-compartment model with first-order absorption and elimination. The first distribution process revealed administration route-dependent characteristics; after i.v. dosing the initial distribution phase was faster than after p.o. dosing. Therefore, V_2 , V_3 and Q_3 were separately estimated for i.v. or p.o. data. Typical V_{sspo} and V_{ssiv} were large (95.8 L and 130.3 L, resp.), CL was 21.5 L/h and Q_3 15-fold higher for i.v. than for p.o. data (99.8 L/h vs. 6.61 L/h). Absolute bioavailability was significantly lower for p.o. solution than for p.o. capsule (34% vs. 43%); the capsule showed an additional lag time of 0.154 h. Covariate analysis revealed a statistically significant relation between K_A and dose. It was best described by a positive saturation function resulting in K_{Amax} of 0.43 h⁻¹ which was nearly reached at the dose of 5 mg, the dose at 0.5 K_{Amax} was 1.00 mg, i.e. the relation was primarily acting in the low dose range. Interindividual variability estimated for K_A , CL, F_1 and V_{2iv} was moderate (15% to 46%), residual variability was 26% (proportional random effect model). Imprecision of estimates was generally low with relative standard errors (RSE)

The estimates for the evaluation data set based on the final PopPK model were very similar to those of the development data set except of the covariate relation which was not supported by the evaluation data set. Simulations (n=500) of the evaluation data set based on the final PopPK model but without the covariate relation revealed that almost all observed concentrations of the evaluation data set were covered by the 90% prediction interval of the simulated concentrations.

Conclusions: A PopPK model has been successfully developed describing the plasma concentration-time course of cilobradine after administration of different formulations. As the covariate relationship found in the development data set was based on a limited number of data in the low dose range and could not be confirmed in the evaluation

dataset it should be revisited in a larger population, preferentially in the target patient population. The PopPK model was suitable to sufficiently predict concentrations of a different study design. Therefore, the model can serve as a tool to simulate and evaluate different dosing regimens for further clinical trials.

P-33_ Use of Time-to-event analysis to qualify activity of Ivabradine during exercise tolerance tests

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poster*

Ivabradine was developed for the treatment of angina pectoris. Its action combined to that of S 18982 (its active metabolite) results in a decrease of heart rate.

Objective: Assess efficacy of ivabradine and S 18982 during exercise tolerance tests (ETT) by investigating the relationship between dose-effect and clinical endpoint parameters (time of exercise duration -TED- and time to angina onset -TAO-).

Material and Method: In this present work, we used a PK/PD model previously developed from eight phase II/III studies to describe the impact of both ETT and plasma concentrations of ivabradine and S 18982 on heart rate.

In this model, the description of heart rate (HR) combines different parts: a linear effect of ETT on HR without treatment using two parameters: INIV (HR at rest) and SLOP (Impact of ETT on HR), and a treatment effect related to the plasma concentrations of ivabradine and S 18982 expressed through a parameter called INHIB (% of inhibition).

To determine impact of each patient's covariates on the overall risk of experiencing a TED or TAO in pooled repeated oral phase II and phase III studies, a time-to-event analysis was proposed, taken into account the actual times at which event didn't occur using a status "censored observation".

In this analysis, the risk related to each clinical endpoint depends on a combination of a basic risk with a regression model selecting covariates among individual demographic parameters and HR description parameters (INIV, SLOP and INHIB).

This analysis was performed using NONMEM(r) Vers. V.1, the risk function being modelled using a Weibull regression.

Results: We have established the relationship between dose-effect and clinical endpoint parameters. This relationship shows that the effect of ivabradine on these parameters is driven by its impact on heart rate in a concentration-related manner.

Conclusion: Through this time-to-event analysis, we were able to take into account all available ETT information, including both observed clinical endpoints, and unobserved ones describing them as censored observations. Moreover, this analysis allows demonstration of a risk function difference between the different doses, even for ETT performed at the trough of concentrations.

P-34_ The effect of rufinamide concentration on the QT interval in healthy subjects treated during 18 days with multiple ascending doses: a population PKPD analysis.

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poster

Objectives: A double-blind, placebo-controlled, ascending multiple dose study was performed to evaluate the cardiovascular safety, the tolerability, and the pharmacokinetics of rufinamide and determine the maximum tolerated dose in healthy subjects.

Methods: Fifteen healthy subjects received multiple ascending doses of rufinamide at 6 dose levels from 800 to 7200 mg per day. Drug was administered b.i.d. with a standardized meal as 400 mg film coated tablets over a period of 18 days with dose increases every 3 days. Five subjects received equivalent numbers of placebo tablets over 18 days. A predose PK sample was taken at the start of the study and nine PK samples were collected on the last day of dosing at each dose level giving a total of 55 samples per subject. 71 ECG/ subject were recorded before and during treatment. Population modelling of concentration and of ECG data was sequential, using NONMEM. Drug effect was estimated on heart rate and corrected QT (QTcF and study/subject specific (QTcSS)).

Results and conclusion: A one-compartment model with first-order absorption and elimination was used to predict the concentration data. Bioavailability decreased as dose increased. The effect of the dose on the bioavailability was described with an E_{max} model. Heart rate increased in placebo and rufinamide treated subjects. Using uncorrected QT, QTcF or QTcSS, rufinamide did not increase QT. On the contrary, rufinamide produced a small decrease of QT, QTcF and QTcSS, proportional to rufinamide concentration. For each 1 mg/mL, rufinamide decreased QTcSS by 0.5 ms, which equates to a decrease of 7.5 ms at a typical concentration in patients (15 mg/mL). The PK variability between subjects was very low and even with such a small sample size; NONMEM provided precise estimates of all parameters. The cardiovascular tolerability was excellent. Rufinamide was associated with a small decrease in QTcSS.

P-35_ A population PK model for nifedipine coat-core tablet

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poster

Objectives: Adalat CR(r) tablet, which has been marketed since 1998 in Japan, is a coat-core tablet of nifedipine, consisting of the "outer coating (coat part)" and the "inner core (core part)" with different release rate. We tried to define the pharmacokinetic model with population approach in order to demonstrate pharmacokinetic characteristics of the unique controlled release formulation of nifedipine.

Methods: Pharmacokinetic modelling was performed in 1314 plasma concentrations from 92 healthy male volunteers, who were administered 20mg once daily of Adalat CR(r) (Bayer Yakuhin, Ltd.). The pharmacokinetic analyses were performed using nonlinear mixed effect modelling with the NONMEM program version V on the validated Linux server farm environment.

Results: After administration of Adalat CR(r), dual absorption phase was observed in plasma concentration - time profile of nifedipine. According to the release characteristics of the drug, a modified 3-compartment model was applied; the 1st compartment for absorption from coat part which has slow release rate of nifedipine, the 2nd compartment for central compartment and the 3rd compartment for absorption from core part which has faster nifedipine release rate with a lag time. By combining of the drug concentration from 1st compartment and 3rd compartment, plasma concentration in central compartment was estimated, which fit well to the observed concentration.

Conclusion: Establishing pharmacokinetic model by applying commonly used non-compartment model is sometimes not easy for controlled release formulation. Therefore population approach, which can evaluate covariate effects and inter- and intra-individual variability, was applied.

P-36_ Use of an indirect effect model to describe the LDL Cholesterol lowering process by statins

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poster

INTRODUCTION: Statins (HMG-COA reductase inhibitors) are the most commonly prescribed agents for the treatment of hypercholesterolemia. This is due to their efficacy in reducing LDL cholesterol (LDL) level which is the primary goal of the treatment especially for patients with multiple risk factors or with established coronary heart diseases.

AIM: The aim of this study was to develop a K/PD model to describe the LDL lowering process in patients with hypercholesterolemia treated with atorvastatin, fluvastatin, simvastatin. This is in order to compare the kinetics of their effects with a view to optimise drug treatment.

Methods: 100 patients were studied retrospectively: 58 treated with atorvastatin, 25 with fluvastatin and 17 with simvastatin. The Lipid panels were obtained for each patient at the treatment initiation and then 1 to 9 other compliance panels were obtained at different time intervals. 618 LDL levels were measured and the data was analysed by NONMEM V.

Results: the data was best described by an indirect effect model with precursor compartment. 1- In the precursor compartment the LDL synthesis (K_{IN}) is inhibited with an Emax function that varied with the drug dose kinetics, 2- In the circulating LDL compartment the LDL clearance (K) increased with circulating LDL decrease (due to the LDL-receptor up-regulation). The equations that describe the model are:

$D(t) = f(AMT, K_{10}, K_A, t)$; the drug dose kinetics (1)

$dR1/dt = K_{IN} (1 - D(t)/(D(t) + D50)) - K \cdot R1$; the LDL variation (2)

$dR2/dt = K \cdot R1 - (1 - R1/(R1 + CHOL50)) \cdot K \cdot R2$; the circulating LDL variation (3)

At steady-state (ss), $dR1/dt = 0$ and $dR2/dt = 0$, $K = K_{IN}/BASE$ and $R2_{ss} = R1_{ss} = BASE$, where BASE is the LDL level at equilibrium before the treatment initiation.

The pharmacokinetic parameters were fixed to previously reported estimates as the data did not allow their estimation: $K_A = 36 \text{ d}^{-1}$, $K_{10} = 0.8, 1, 0.4 \text{ d}^{-1}$ for atorvastatin, simvastatin, fluvastatin respectively. The final estimates of the D50 parameters were 20 (± 1.3), 22 (± 2), 81 (± 9) mg for atorvastatin, simvastatin, fluvastatin respectively, K_{IN} was $26.6 (\pm 1) \text{ d}^{-1}$ and CHOL50 was $10.4 (\pm 0.3) \text{ g/L}$. The correlation coefficients between PRED and OBS were 0.723, 0.634 and 0.837 for atorvastatin, simvastatin and fluvastatin respectively. Gender, bodyweight, age, calories/day, sugar/day, lipids/day, hyperlipidemia types and waist /hip circumference did not have any effect on the pharmacodynamic parameters.

Conclusions: The pharmacodynamic parameters for the three statins were accurately estimated. The K/PD model developed successfully predicted the time course of LDL.

P-37_ Population pharmacodynamic modelling of lanreotide (Lan) autogel (ATG) in patients with acromegaly

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poster

Objective: To establish the concentration of Lan vs growth hormone (GH) response in patients with acromegaly over time.

Methods: A phase II, multicentre, randomised study was conducted in 108 patients with acromegaly who may or may not have been previously treated with a somatostatin analogue. Patients were randomised to receive placebo or Lan ATG 60, 90 or 120 mg once every 28 days by deep subcutaneous injection. The 52-week study had four phases: *i*) washout (weeks -12-0), for those previously treated; *ii*) double-blind, placebo-controlled (weeks 0-4), single dose of Lan ATG or placebo; *iii*) single-blind, fixed-dose (weeks 4-20), four injections; and *iv*) open-label dose titration (weeks 20-52), eight injections and two dose adjustments were allowed. Concentrations of Lan and mean serial measurements of GH in serum used for pharmacodynamic analysis were measured at washout and weeks 4, 13-16 and 52. Observed serum concentrations of Lan were used to build the population pharmacodynamic model for GH using NONMEM version V software programme.

Results: A total of 691 concentration-response pair data were used to develop the population model. GH levels were described as a function of observed concentrations of Lan using an inhibitory sigmoidal E_{MAX} model. The estimate of GH at baseline (GH_0) was higher for patients not treated with somatostatin analogues in the last 3 months (15.9 vs 8.74 ng/mL); the data supported the existence of two different sub-populations (responders and non-responders) with regard to IC_{50} [concentration of Lan eliciting a half-maximal decrease in GH (E_{MAX})]. Typical estimates were: 100 ng/mL (IC_{50} non-responders), 0.612 ng/mL (IC_{50} responders), 0.822 ng/mL (E_{MAX}) and 2.63 (sigmoidicity factor). No differences in E_{MAX} were found by pre-treatment status with somatostatin analogues in the previous 3 months.

The fraction of responders within the population was 0.863. The lower sensitivity found in the small proportion of non-responders indicates that these patients do not respond to Lan treatment even at high doses.

The degree of inter-patient variability in GH_0 , IC_{50} , and E_{MAX} was 85%, 43% and 17%, respectively. The model was internally (using the posterior predictive check) and externally (with data from another clinical trial) validated.

Conclusions: E_{MAX} was estimated as 82% demonstrating the efficacy of Lan, and 86% of patients responded to treatment. In those patients a Lan concentration of 0.612 ng/mL resulted in a 50% decrease in GH levels.

P-38_ Pharmacokinetic and pharmacodynamic modelling of the dual PPAR α/γ agonist tesaglitazar in patients with manifestations of insulin resistance

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poster

Objective: Tesaglitazar is a novel, dual peroxisome proliferator-activated receptor α/γ agonist under clinical development for the treatment of glucose and lipid abnormalities in patients with type 2 diabetes and metabolic syndrome. The aim was to characterize the pharmacokinetics (PK) of tesaglitazar and its pharmacodynamic (PD) effect on fasting serum-triglycerides (TG) in patients with manifestations of insulin resistance (IR).

Materials and methods: PK and TG data were collected from the Study in Insulin Resistance (SIR: SH-SBT-0001), a 12-week, randomised, double-blind, placebo-controlled study of tesaglitazar (0.1, 0.25, 0.5 or 1.0 mg once daily) in non-diabetic patients with manifestations of IR. In total, 389 patients were included in the analysis, and PK data were collected from 240 patients. Fasting TG was collected at 10 visits, and all observations were used in the analysis. Covariates evaluated were renal function, gender, age and body weight. Non-linear mixed-effects modelling, using NONMEM, was employed, first to describe the PK of tesaglitazar, and secondly to characterise the relationship between exposure of tesaglitazar and its effect on TG.

Results: The pharmacokinetics of tesaglitazar was well described by a one-compartment model with first order elimination. The mean oral clearance (CL/F) was found to be positively correlated to renal function, and was 0.13 L/h for an individual having a CrCL of 90 mL/min. The overall between patient variability in CL/F was 30 %, and decreased to 24 % when differences in renal function were accounted for. The mean oral volume of distribution (V_z/F) and half-life were 11.6 L and 63 h, respectively. None of the other covariates tested were found to affect CL/F when renal function was accounted for. No covariates influenced the other PK parameters. The relationship between exposure of tesaglitazar and change in TG was modelled with an indirect response model. The mean baseline TG was 2.8 mmol/L. The time to PD steady state was approximately 16 days and the mean maximal reduction in TG was 67%. The between patient variability in EC₅₀ decreased from 77% to 76% when including gender as a covariate in the model. The estimated EC₅₀ values were 0.76 and 0.38 μ mol/L for males and females respectively. None of the other covariates affected the PD parameters.

Conclusions: The pharmacokinetic/pharmacodynamic relationship of tesaglitazar was well characterised by population PK/PD modelling. This model provides an accurate description of the pharmacodynamic effect on triglycerides of tesaglitazar in patients with manifestation of IR.

P-39_ A pooled population pharmacokinetic analysis of tesaglitazar in patients with type 2 diabetes or with manifestations of insulin resistance

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poster

Objectives: Tesaglitazar is a dual peroxisome proliferator-activated receptor (PPAR) α/γ agonist under clinical development for the treatment of glucose and lipid abnormalities in patients with type 2 diabetes and metabolic syndrome. The aim of this analysis was to characterize the pharmacokinetics of tesaglitazar in the target patient populations.

Methods: Pharmacokinetic data were pooled from SH-SBT-0001 (SIR), a 12-week, randomised, double-blind, placebo-controlled study of tesaglitazar (0.1, 0.25, 0.5 or 1.0 mg once daily) in non-diabetic patients with manifestations of insulin resistance (IR), and from SH-SBD-0001 (GLAD), a 12-week, randomised, double-blind, placebo-controlled study of tesaglitazar (0.1, 0.5, 1.0, 2.0 or 3.0 mg once daily) in patients with type 2 diabetes. Pharmacokinetic data from 582 patients (2470 observations in total) were included. Covariates evaluated in the analysis were renal function (assessed as calculated creatinine clearance (CrCL) using lean body mass as a measure of body weight), gender, age, body weight, smoking status, patient population and serum-albumin. Non-linear mixed-effects modelling, using NONMEM, was used for the analysis.

Results: The pharmacokinetics of tesaglitazar were well described by a one-compartment model with first order absorption and elimination. The mean oral clearance (CL/F) was found to be positively correlated to renal function, and was 0.12 L/h for a individual with a CrCL of 76 mL/min. The overall between-patient variability in CL/F was 37 %, and decreased to 28 % when differences in renal function were accounted for. The mean oral volume of distribution (V_z/F) and half-life was 10.7 L and 61 h, respectively. The area under the concentration time curve, dose normalised to 1 mg, was approximately 20 μ mol h/L. None of the other covariates tested was found to affect CL/F when renal function was accounted for. No covariates were found to influence V_z/F.

Conclusion: The pharmacokinetics of tesaglitazar in patients with manifestations of IR or type 2 diabetes were well characterised by population modelling, and the results were in agreement with those previously reported in healthy subjects.

P-40 Treatment Efficacy of Combination-Therapy based on a Mechanistic Characterisation of Disease Processes in Type 2 Diabetes Mellitus over a two-year period

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poster

Objective Type 2 Diabetes Mellitus (T2DM) is a chronic progressive disease in which specific disease processes (i.e. progressive decline in *b*-cell function and insulin sensitivity) result in loss of glycaemic control. Information regarding these processes facilitates differentiation between drug efficacies on a mechanistic basis. By modelling the homeostatic feedback relationship between insulin and fasting plasma glucose such process-information on the time-course of the *b*-cell function and insulin sensitivity can be derived. Recently, a mechanistic disease progression model was established which jointly characterizes the trajectories of insulin, fasting plasma glucose and HbA_{1c} in relation to these specific disease processes. Treatments are incorporated into this comprehensive system at their corresponding target-site. In the current analysis this model was applied to evaluate the treatment effects on their ability to modify the disease processes in a new patient population of 1269 T2DM patients receiving combination-therapy during a period of two-years.

Methods and Results Two Phase III studies were analysed, with one study comparing the efficacy of pioglitazone to metformin in combination-therapy of patients inadequately controlled by sulphonylurea. The other study compared pioglitazone to gliclazide in combination-therapy of patients inadequately controlled by metformin. The T2DM mechanistic disease progression model was able to adequately capture the characteristics of these newly acquired results. To evaluate drug effects on disease progression, the specific disease processes under influence of combination therapy were analysed. It was found that the treatment groups involving pioglitazone and the treatment group concerning sulphonylurea with metformin as add-on showed an improvement in *b*-cell function throughout the two-year trial period. In contrast, the combination of gliclazide added to metformin showed a continuing decline in *b*-cell function after a largely symptomatic effect on this disease process. All treatment groups, except for that with gliclazide, showed a symptomatic effect on insulin sensitivity and pioglitazone added to metformin showed a significant protective effect to loss of insulin sensitivity as compared to the other treatment combinations.

Conclusions In conclusion, the mechanistic disease progression model enabled the characterisation of the specific disease processes and the resulting biomarker dynamics in T2DM patients on combination-therapy over a period of two-years. Specifically, the model allowed the evaluation of combination-therapy efficacies on the time-course of the *b*-cell function and insulin sensitivity.

P-41_ A physiology based model for the glucose-insulin regulation in healthy volunteers and diabetic patients following intravenous glucose provocations.

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poster

Objectives: The aim of this project was to develop a physiology based model to simultaneously describe the glucose and insulin regulation following different intravenous glucose provocations in healthy volunteers and type II diabetic patients.

Methods: The model was developed based on mechanistic knowledge of the insulin-glucose regulation. Data without drug effect from 30 volunteers and 42 patients and four different trials were used. All individuals received an intravenous glucose provocation, with or without insulin infusion. The administered glucose was enriched with stable-labeled glucose. Blood samples were drawn pre-dose and until 240 minutes post-dose for the determination of plasma glucose, labeled glucose and insulin concentrations. Six individuals received a euglycemic and hyperinsulinemic clamp experiment from which only labeled glucose concentrations were available. Simultaneous analysis of all data by non-linear mixed effect modeling was done in NONMEM version 6.

Results: The glucose submodel contained a two-compartment disposition model with endogenous production and insulin dependent and independent elimination. The insulin submodel contained a one-compartment disposition model with endogenous production and release, distinguishing between the early and late phase of insulin secretion. Labeled glucose was assumed to have the same disposition properties as total glucose with the exception of endogenous production. Control mechanisms were incorporated into the model to account for the regulation of glucose and insulin production, dependent on glucose concentration, and glucose elimination, dependent on insulin concentration. Differences between volunteers and patients were identified and quantified. Goodness-of-fit graphs show that the model was able to describe the data well. Simulations from the model well mimicked concentration-time profiles of insulin and total glucose from the experiments. With design-specific estimates for insulin dependent glucose elimination clearance (mechanistically plausible as different tests give rise to different hepatic-to-peripheral insulin ratios) also labeled glucose was well simulated.

Conclusion: The model presented here allows the simultaneous prediction and simulation of glucose, labeled glucose and insulin in volunteers and patients following three different intravenous glucose provocation tests.

P-42_ Pharmacokinetics and Pharmacodynamics of Rocuronium bromide in patients undergoing brain surgery: Influence of chronic Phenytoin therapy

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poster

Objective: The characterization of the influence of Chronic Therapy with Phenytoin (CPT) in the Pharmacokinetics (PK) and Pharmacodynamics (PD) of Rocuronium in patients undergoing intracranial surgery. Background: Rocuronium bromide is a non depolarizing neuromuscular blocking agent (NMBA) widely used in anesthesia. Chronic therapy with phenytoin (lasting longer than 15 days) is known to affect the time course of effect of most NMBA requiring increments in dosing to achieve the same level of effect than patients without phenytoin therapy. This phenomenon could possibly be explained by PK or PD reasons, however in the case of rocuronium it has not been reported yet.

Methods: Under IRB approval and informed consent, 16 patients undergoing surgical craniotomy were included. All patients were routinely monitorized and anesthetized with propofol and remifentanyl to provide adequate hypnosis and analgesia. In each patient, an arterial line was inserted for hemodynamic control and for blood sampling. In addition, a microdialysis catheter was also inserted in the quadriceps muscle to allow the quantification of rocuronium concentrations in tissue. The effect was quantified by means of electromyography and the percentage of T1 with respect to supramaximal response (T1%), was the parameter used as effect measure. Rocuronium was administered as a bolus (weight adjusted) followed by a continuous infusion, which was adjusted to maintain a response of TOF. Data were recorded online on a computer by means using the software S5-Collect (DatexOhmeda). Nonlinear mixed effect modeling, using the program NONMEM (version V), was used to estimate the parameters of the PK and PD models.

Results: The best description, according to the value of the objective function and the standard errors (SE) of the parameters, was a two compartment model. Basic PK parameters were: V_c of 5.45 L (0.42) and CL of 0.17 L/min (0.04). When CPT was incorporated into the model as a categorical covariate associated to the clearance, the value of this parameter was increased (1.06 vs 0.17 L/min). A sigmoid EMAX model was linked to the PK using an effect site compartment with a value (SE) for ke_0 of 0.11 (0.008) min⁻¹. The influence of CPT on ke_0 or C_{50} was not significant.

Conclusions: Clearance of rocuronium in patients under CPT was higher (almost 90%) than in control patients (without phenytoin therapy). PD parameters for rocuronium did not change with CPT, although for vecuronium an increase in the C_{50} has been reported in the literature [1].

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P-43 _ Evaluation of an enterohepatic circulation model: predicting the influence of cholestyramine on the pharmacokinetics of meloxicam

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poster

Objectives & Background: Concentration-time profiles of drugs undergoing enterohepatic circulation (EHC) are often associated with multiple peak phenomena and a longer apparent half-life. Basic models describing EHC were reported in the literature [1]. Lehr et al. developed an EHC model considering the clock time as a control variable for the gall bladder emptying [2]. The objective of this study was to apply and evaluate the model by using data of a drug undergoing EHC (meloxicam [3]). Evaluation was to be performed by a) fitting the model to observed meloxicam plasma concentrations and b) by predicting the effect of interrupting the EHC on pharmacokinetics by co-administration of cholestyramine.

Methods: Plasma concentration-time profiles of 12 subjects treated with 30 mg meloxicam intravenously (bolus) either alone or concomitantly treated with 4 g t.i.d cholestyramine for four days were analysed. A three compartment model (central, peripheral and bile) with first order elimination was used to describe the data. The release of the bile compartment was controlled by a sine function model, switching the bile compartment periodically on and off. Interruption of EHC was mimicked by setting the rate transfer constant from bile to central compartment to zero.

Results: The model successfully described the plasma concentration-time profiles of all subjects including the multiple peak phenomena. Clearance and half-life of meloxicam after intravenous administration were determined to be 0.367 L/h and 20.1 h respectively. Simulating the interruption of the EHC resulted in a predicted increased clearance of 0.616 L/h and a shortened half-life of 11.0 h. These model-predicted values are in close agreement with the observed results from the compartmental analysis [3].

Conclusion: EHC of meloxicam could be successfully described by the model proposed by Lehr et al. Interruption of the EHC could be reliably predicted. Slight overestimation of clearance and half-life might be caused by an incomplete interruption of the EHC with cholestyramine.

The model might serve as a tool to describe the pharmacokinetics of drugs undergoing EHC and to assess the impact of interrupting the EHC e.g. by co-medication with cholestyramine or charcoal.

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**P-44_ Population Pharmacokinetics of Rituximab in RA (Rheumatoid Arthritis)
Patients: Combining two phase II studies**

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poster

Objectives: Rituximab (RTX; a CD20+-targeted therapeutic antibody) is currently licensed to treat non-Hodgkin's lymphoma using a body surface area (BSA)-adjusted dosing regimen. A fixed dose regimen of RTX, in combination with a short course of glucocorticoids (GC), is being explored as a novel approach to treating RA. The goal of this analysis was to explore the population pharmacokinetics (POP PK) of RTX using data from two Phase II studies in patients with RA.

Methods: Data were obtained from two studies: a Phase IIa study with frequent sampling (RTX 1000 mg x 2 infusion, 2 weeks apart) and a larger Phase IIb (RTX 500 vs 1000 mg infusion x 2, 2 weeks apart) with limited sampling. The effect of including various covariates, such as dose, concomitant medication, race, gender, prior anti-TNF α therapy, region, age, BSA and duration of RA disease, in the PK model was evaluated. A POP PK model was simultaneously fitted to the combined data from the two Phase II studies. The model consisted of two distribution compartments and a zero-order infusion. Potential influence of the covariates on the clearance (CL) and the central compartment volume of distribution (Vc) was evaluated. A bootstrap re-sampling procedure was used to validate the model stability and to estimate the 95% confidence intervals.

Results: A total of 3196 RTX concentrations from 423 patients was used in the analysis (1002 samples and 107 patients from the Phase IIa and 2194 samples and 316 patients from Phase IIb study). CL and Vc estimated using the combined data set were similar to the estimates from the Phase IIa data alone (291 mL/day and 3000 mL, for CL and Vc, respectively) (1). Gender and BSA significantly affected the CL and Vc, male had larger CL and Vc compared to female. Concomitant administration of high-dose GC (oral and IV) reduced the CL of RTX by 12% for a typical patient compared with no GC or only IV GC. There was no significant difference in CL between the two RTX doses.

Conclusions: PK parameters from the POP PK analysis of the combined data set did not differ from those published for the Phase IIa study alone. The effects of BSA and gender on the CL and Vc were confirmed. Concomitant administration of high-dose GC decreased RTX clearance by 12%. The PK parameters were not significantly different for the doses studied. The combined data from the two studies support the use of a fixed-dose regimen of RTX in RA.

Reference:

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P-45_ Meloxicam for juvenile rheumatoid arthritis patients: Is dosing on a mg/kg body weight basis justified?

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poster

Objectives & Background: Meloxicam is a nonsteroidal anti-inflammatory drug approved for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis in adults. These indications are planned to be expanded including the indication, signs and symptoms of juvenile rheumatoid arthritis (JRA). JRA patients were dosed on a mg/kg body weight basis in the safety and efficacy studies performed. The objective of the population pharmacokinetic analysis was to develop a common model describing all available pharmacokinetic data of juvenile rheumatoid arthritis patients and investigate whether dosing by kg body weight in JRA patients results in similar exposure as in adults.

Methods: The dataset for the population pharmacokinetic analysis included 47 JRA patients with 486 plasma concentration measurements. From 18 JRA patients plasma profiles after a single dose of 0.25 mg/kg were obtained and from 29 JRA patients steady state profiles following once daily dosing with 0.375 mg/kg were available. The demographic characteristics sex, race, age, weight, height, body surface area (BSA) and body mass index (BMI) as well as creatinine clearance were to be tested as covariates on the pharmacokinetic parameters. Based on the final model typical plasma concentration-time profiles for different doses (0.125 to 0.375 mg/kg once daily) and weight groups (10 to 90 kg) were simulated and overlaid with a typical plasma concentration-time profile obtained in adults. NONMEM, version V, level 1.1, with the FOCE interaction method was used for data analysis and simulation.

Results: The plasma concentration time profiles were best described by an one-compartment body model with sequential zero and first order absorption processes and first order elimination. Only weight was identified as a significant covariate on clearance and volume of distribution. The typical clearance (CL/F) and volume of distribution (V/F) estimates for a 34 kg JRA patient were 0.29 L/h and 6.2 L, respectively. These typical CL/F and V/F values increase/decrease by 2% and 2.5% per kg increase/decrease in body weight. 15.2% of the dose was absorbed by a zero order process over 0.7 h. The remaining 84.8% of the dose (F1) were absorbed by a first order absorption process with a rate constant of 2.13 h⁻¹ starting 0.834 h after administration. Estimates for interindividual variability were 44% in CL/F, 40% in V/F and 15% in F1. Residual variability was 27%.

The simulations showed that doses of 0.125 mg/kg, 0.250 mg/kg and 0.375 mg/kg once daily in JRA patients result in similar steady-state exposures as achieved with a 7.5 mg, 15 mg and 22.5 mg/kg in adults.

Conclusion: The pharmacokinetics in JRA patients were successfully described by an one compartment body model with sequential zero and first order absorption processes and first order elimination. As the steady-state exposures in JRA patients following once daily dosing of 0.125 mg/kg to 0.375 mg/kg meloxicam are comparable to the exposures seen in adults dosed with 7.5 mg to 22.5 mg the proposed dose individualisation on a mg/kg body weight basis is appropriate for JRA patients.

**P-46_ Mechanistic PK/PD modelling for signal transduction modulators.
Application to TGF-beta RI antagonists.**

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poster

Objectives: To develop a mechanistic PK/PD Model for a new Type I Receptor TGF- β Kinase Inhibitor using human xenografts.

Methods: Human xenografts (MX1-breast and Calu6-NSCLC) were implanted subcutaneously to nude mice. Experiments started 7 to 10 days after tumor implantation. Two different type of experiments were performed: (i) the PK/PD experiment providing information about the plasma levels of the Type I Receptor TGF- β Kinase inhibitor and the percentage change (inhibition) with respect to baseline of phospho-SMAD2,3 (PSMAD) in tumor, and (ii) the tumor growth experiment where the kinetics of tumor growth was followed during 25 to 30 days after the first drug administration. In both experiments drug or saline was administered orally in a single dose or in a multiple dosing design in a range from 10 to 300 mg/kg.

An indirect response model was used to relate the predicted plasma concentrations with the observed inhibition in PSMAD. The model assumes the existence of factors within the tumor cell responsible of the synthesis and degradation of PSMAD.

Tumor size (TS) in animals receiving saline did not reach a plateau and therefore a variant of the Gompertz model allowing for the switch from an exponential to a linear growth was used. Tumor growth inhibition observed in the animals receiving the new compound was linked to the inhibition of PSMAD through a delay in the propagation of the inhibitory signal which was modelled as a chain of transit compartments, and quantified by the mean signal propagation time (MSPT) parameter.

Results: Drug disposition was best described with a two compartment model. Dose and time did not show significant effects ($P > 0.05$) on the kinetics in plasma. The new compound showed very similar PSMAD effects for the two cell lines. Estimates of IC_{50} (μM) were 0.79 and 0.70 for Calu6-NSCLC and MX1-breast, respectively. The model predicted a complete inhibition of PSMAD at high drug concentrations, and a very rapid turnover rate [$t_{1/2}$ (min) = 18.6 (Calu6) and 32.0 (MX1)]. MSPT was estimated in 6.17 days for Calu6-NSCLC, which means that the drug will reach its steady-state effects after three weeks of continuous administration. For MX1 the estimate of MSPT was 28.7 days.

Conclusion: The integrated model was validated externally, and provided a tool to investigate different experimental scenarios as well as giving insights regarding the mechanisms of signal transduction in the cascade of events associated to the TGF- β membrane receptor.

P-47_ Population pharmacokinetics of high-dose methotrexate in osteosarcoma pediatric patients.

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poster

Introduction and Objectives: High-dose methotrexate (HD_MTX) is an efficient component of therapy in children with osteosarcoma. The aim of this study was to establish the population pharmacokinetics of HD-MTX in children with osteosarcoma and explore the influence of patient covariates and interoccasion variability on drug disposition.

Methods: Fourteen children (nine males and five females) treated in the "Hospital de la Santa Creu i Sant Pau" were eligible for this study. The demographic and biochemical data (age weight, height, body surface area, serum creatinine and creatinine clearance: CRCL) were recorded from the patient files. Patients received sixteen courses of MTX over a 4 hour intravenous infusion (mean dose, 11.19 g/m²) according to the Spanish Oncology Society guidelines. Blood samples were collected at 1,2,4,24,36 and 48 hr. after the start of infusion. Pharmacokinetic (PK) analysis was performed using the population approach by means of NONMEM V.

Results : According to previous data (1), the pharmacokinetics of MTX was best described by a two compartment open PK model with elimination from the central compartment. PK parameter variability was modelled as log-normally distributed. Intersubject variability (ISV) was included in total plasma clearance (10.3%) and in central compartment distribution volume (47.7%). Interoccasion variability (IOV) was only retained for CL (13.1%). Residual variability consisted of a proportional error of 53.1%. A covariate model based on creatinine clearance was identified as appropriate model to describe part of the variability in MTX clearance. The final estimates of fixed effect parameters (CL, total plasma clearance; V₁ and V₂, volumes of distribution of the central, and peripheral compartments, respectively; CL_{D1} intercompartmental clearance), were CL=55.5+52.2*(CRCL/134.83) L/day, 24.8 L and 1.23 L and 0.319 L/day, respectively.

Conclusion: A population PK model for MTX has been developed. It incorporates measure of renal function to predict total drug clearance. Validation of this model with external patients should be performed in order to assess the suitability of further MTX therapeutic drug monitoring.

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P-48_ Population Pharmacokinetic Model for Cremophor EL

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poster

Objectives: The pharmacologically active micelle-forming vehicle Cremophor EL (CrEL) has been shown to affect the pharmacokinetics of paclitaxel after Taxol^(r) administrations^[1]. CrEL micelle entrapment of paclitaxel within the plasma has been suggested as the primary underlying mechanism. The pharmacokinetics of CrEL has been shown to be schedule dependent and capacity limited elimination within the plasma has been suggested^[2]. The aim of this study was to develop a population pharmacokinetic model that could describe and predict CrEL plasma concentrations after Taxol^(r) administration and to investigate the critical aggregation concentration (CAC) in human plasma *in vitro*.

Patients and Methods: The learning data included 147 CrEL concentration-time profiles obtained from 116 patients receiving 1-, 3- or 24-hour infusions of Taxol^(r). CrEL concentrations were measured with a Coomassie Brilliant Blue G-250 colorimetric dye-binding assay^[3, 4]. The population pharmacokinetic analysis was performed in NONMEM. A validation data set with 45 individuals receiving 3-hour infusions of Taxol^(r) was used to investigate the predictive performance of the model. The apparent CAC was estimated by observing changes in plasma surface tension determined with a droplet weight method^[5], 1, 3 and 24 hours after addition of CrEL/EtOH/NaCl or Taxol^(r).

Results: A three-compartment model with capacity limited elimination with an additional linear elimination pathway as well as a separate volume of distribution for the 24-hour infusion schedule were required to describe all data of the learning data set. Body surface area was statistically significant ($P < 0.001$) as covariate on maximal elimination rate, volume of distribution of the central compartment and one of the peripheral compartments. The population model could adequately describe the concentrations of the validation data set where the prediction errors were similar as for the learning data. A previously published population pharmacokinetic model^[2], based on CrEL concentrations measured with another assay than the one used here, could not adequately describe our data. The apparent CAC in plasma was 0.39 mL/L, a concentration exceeded after Taxol^(r) administrations in patients, suggesting that CrEL form aggregates *in vivo*.

Conclusions: The population model developed on the present data could adequately predict and describe the CrEL concentrations after Taxol^(r) administrations. This model could be most useful when no CrEL concentration data is available and population pharmacokinetic models for paclitaxel including CrEL concentrations will be used.

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P-49_ Determinants of the pharmacokinetics of methotrexate and its metabolite 7-hydroxy-methotrexate following high-dose infusional methotrexate

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poster

Objectives: The identification of methotrexate (MTX) and 7-hydroxy-methotrexate (7-OH-MTX) pharmacokinetics and its determinants is very useful in providing guidelines to prevent potentially fatal nephrotoxicity from high-dose MTX (HDMTX) schedules. MTX is prone to drug interactions, particularly synergistic nephrotoxicity with non-steroidal anti-inflammatory drugs (NSAIDs), benzimidazoles, penicillin and sulphonamides among others.

Methods: Routine 24- and 48-hr blood samples were collected in 76 patients after having received a total of 308 courses of HDMTX (dose range 300mg/m² to 12g/m²). Intensive sampling was available from 21 patients. Leucovorin rescue was started 24 hrs after the start of MTX and continued dependent on MTX plasma levels. MTX and 7-OH-MTX concentration-time data were subjected to a population pharmacokinetic and covariate analysis using nonlinear mixed-effect modeling (NONMEM).

Results: Treatment-related mortality was 1.3% (1 patient with fatal renal failure). A three-compartment model best fitted the concentration-time data of MTX, while a two-compartment model best fitted the concentration-time data of 7-OH-MTX. Assuming 10% formation of 7-OH-MTX from MTX, MTX clearance (CL_{MTX}) was estimated at 8.85 L/hr, 7-OH-MTX clearance (CL_{7-OH-MTX}) at 2.00 L/hr. Creatinine clearance (CL_{CREA}) and comedication with benzimidazoles and NSAIDs were significant determinants of both CL_{MTX} and CL_{7-OH-MTX}. Comedication with NSAIDs led to a 16% reduction of CL_{MTX} and a 38% reduction of CL_{7-OH-MTX}, while comedication with benzimidazoles led to a 27% reduction of CL_{MTX} and a 39% reduction of CL_{7-OH-MTX}. A decrease of CL_{CREA} from a median of 87 ml/min to 60 ml/min (lower limit of normal) resulted in a 13% decrease of CL_{MTX} and a 20% decrease of CL_{7-OH-MTX}. Median MTX plasma concentrations at 24 and 48 hours were significantly higher in patients receiving benzimidazoles or NSAIDs as compared to patients without the respective comedication.

Conclusions: Coadministration of benzimidazoles or NSAIDs resulted in decreased CL_{MTX} and CL_{7-OH-MTX} and an increased risk for HDMTX-associated (nephr)toxicity. Patient self-medication of over-the-counter drugs should especially be assessed in this context, before HDMTX is started. The presented data suggest that the use of benzimidazoles and/or NSAIDs should be seen as a relative contraindication for HDMTX.

**P-50_ Population Based Pharmacodynamics for In Vitro Drug Sensitivity Assays:
Prediction of Model Based Parameters of Drug Activity and Relationship to
Clinical Outcome**

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poster

Background: Due to limited availability of patient tumor cells, predictive in vitro drug sensitivity assays often measures a variable effect at a few fixed concentrations. The information on the drug concentration-response relationship is not obtained and individual estimate of drug potency is limited.

Purpose: To develop a population-based pharmacodynamic model for the in vitro drug sensitivity of leukemic cell samples from patients with acute myelocytic leukemia (AML) to predict individual pharmacodynamic parameters for cytosine arabinoside (AraC) and daunorubicin (Dnr). Further to relate in vitro parameters to clinical outcome.

Methods: 179 consecutive samples of tumor cells from patients with AML were analyzed, with respect to respons to increasing concentrations of the drugs, using the fluorometric microculture cytotoxicity assay (FMCA). The population pharmacodynamic model was developed using the FOCE method in NONMEM. 124 samples were assigned to the learning data set and the final model was evaluated using another 30 samples. Additional 25 samples was added to the data set for the analysis of clinical outcome. The probability of clinical response was estimated using a logistic regression on in vitro parameter estimates of 46 individuals actually treated with the AraC+Dnr combination.

Results: The data was best described by an Emax model for AraC and a sigmoid Emax model for Dnr. The population mean values for Emax and EC50 were 78% and 0.30 µg/ml, and 90% and 0.11 µg/ml for AraC and Dnr, respectively. The prediction interval (10-90%) of individual EC50 for AraC and Dnr was 0.098-0.82 µg/ml and 0.022-0.57 µg/ml, respectively. The correlation between EC50 for the two drugs was low (0.04) whereas that for Emax was high (0.72). EC50 could be predicted with adequate precision from only one concentration. For patients treated with the AraC+Dnr combination, the probability of complete response was significantly ($p<0.05$) related to the product of the ratio of Emax to EC50 of the two drugs.

Conclusion: A joint pharmacodynamic model for AraC and Dnr including covariances across drugs, could adequately describe the in vitro sensibility data. Even with sparse sensitivity measurements adequate information on drug potency can be obtained. The model for clinical outcome is mechanistically reasonable and supports the dual therapy.

P-51_ PK-PD model compared with K-PD model to predict haematotoxicity induced by anticancer drugs.

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poster

Introduction: Pharmacokinetic-pharmacodynamic (PK-PD) models are available to predict haematological toxicity induced by anticancer chemotherapy, but they need pharmacokinetic knowledge. The aim of this work is to determine the feasibility of predicting haematological toxicity and to adapt dosage without pharmacokinetic information. This would be valuable in clinical practice.

Patients and methods: 28 patients treated for solid tumour received from 1 to 9 cycles of chemotherapy. Each cycle consists of a 15-min infusion of 40 mg/ m² of methotrexate (MTX) on day 1, and on day 8 of a 15-min infusion of 40 mg/m² of MTX followed by a 1-h infusion of docetaxel (TXT) given using a dose escalation scheme: TXT doses ranged from 60 and 100 mg/ m². Population pharmacokinetic was studied for both drugs on cycle 1 and 3, at days 1 and 8. HPLC was used to determine drug levels of both drugs. Blood counts were followed during the overall courses for PD analysis. The time course of blood counts could be analysed using a K-PD model based on an adapted indirect response model without drug concentrations (Jacqmin et al 2001). The performance of the K-PD model was compared with the classical approach using PK-PD model. Data analyses were performed using NONMEM version V.

Results: 22 patients out of 28 could be followed for pharmacokinetic determination of MTX and TXT (72 administrations of MTX and 38 of TXT). For both drugs, a 3-compartment model described adequately the data. No influence of TXT on MTX pharmacokinetic was showed (t-test, p<0.05). Creatinine clearance and body surface area improved the model for MTX, and AAG and proteinemia improved the model for TXT. AUC of TXT grew regularly from 60 to 80 mg/m², and then no further increase with doses was observed. The only significant PK-PD relationship was found between the AUC of MTX and blood counts nadir including all courses. Regarding the K-PD model, the best fit was obtained with a sigmoid Emax equation, and is in accordance with the PK-PD model.

Conclusion: In conclusion, we have shown that this mechanism-based approach allows an accurate prediction of the haematological toxicity after cancer chemotherapy. Validation of the model has to be performed in a prospective study.

P-52_ Pharmacokinetics of paclitaxel in liver transplantation cancer patients

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poster

The paclitaxel disposition is nonlinear and hepatic metabolism and biliary excretion have important roles. The influence of hepatic dysfunction on the pharmacokinetics and toxicities of the drug are not enough known. Some patients with hepatic metastases and/or elevated transaminase levels have been reported to have had increased toxicity and altered paclitaxel pharmacokinetics and there is limited data about the disposition of this drug in hepatic transplant recipients. Because paclitaxel has potential clinical utility for the treatment of several tumours, it was believed necessary to formally define paclitaxel dosification in this last population

Objectives: The aim of this study is to analyze the paclitaxel disposition in liver transplantation patients to optimize therapy and avoid infra and/or supradosification affecting the efficacy and toxicity of the treatment.

Patients and methods: Paclitaxel pharmacokinetic parameters of lung cancer patients (two men and a woman) with liver transplantation were estimated. All three patients received paclitaxel as a three hours intravenous infusion and carboplatin chemotherapy according to the protocol developed by the Oncology Department of the University Hospital of Navarra [1] . Blood samples were collected into heparinized glass tubes (Venoject) at different times during the first cycle of their corresponding treatment and were analyzed according to a high performance liquid chromatography (HPLC) method developed and validated by the pharmacokinetic laboratory of the Pharmacy Department at the University Hospital of Navarra. Paclitaxel pharmacokinetic parameters was carried out by noncompartmental analysis using software WinNonLin 3.0 (Scientific Consultants, NC, USA).

Results: The pharmacokinetic parameters obtained in this study were similar to the median values (range 17.4-22.8 L/h*m²) found by other researchers for patients with normal hepatic biochemistry [2-4] . Only the woman with elevated transaminase levels showed a total clearance lower (15.02 L/h*m² versus 18.04 L/h*m²). For hepatically metabolised drugs, those that are metabolised by CYP3A4 appear to be eliminated faster in women [5] ; so, in our experience, the lower value of clearance for the woman emphasize the effect of hepatic injury in the paclitaxel clearance.

Conclusion: Our results show that paclitaxel pharmacokinetic behavior in liver transplantation patients is similar to the control population with normal hepatic biochemistry test, so these cancer patients could receive paclitaxel with no recommendations on dosage reductions.

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P-53_ Tegafur and 5-Fluorouracil pelvic tissues concentrations in rectal cancer patients treated with preoperative chemoradiation. The processed sample stability investigation and their impact in the reability of data

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poster

Tegafur (Ftorafur), 1-(tetrahydro-2-furanyl)-5-fluorouracil, a oral prodrug of 5-fluorouracil (known radiopotentiating agent in preclinical models), has an efficacy similar to that of intravenous 5-Fu. Clinical experiences have explored with success the feasibility, tolerance and tumor response rate of oral Tegafur administered simultaneously with preoperative radiotherapy in rectal cancer [1] .

Objectives: The aim of this study was to measure Tegafur and 5-Fu concentrations in tissues of rectal cancer patients treated with preoperative chemoradiation and to correlate drug concentrations with cancer downstaging effects. Also was conducted a little stability study.

Patients and methods: Three tissue samples of 16 patients with locally advanced rectal cancer treated with preoperative pelvic irradiation sensitized with oral Tegafur before surgery (5 to 6 weeks after the completion of chemoradiation) were analyzed. Seven patients received a precharge dose of Tegafur 24 hours before surgery. Tegafur and 5-Fu concentrations, were determined according to a high performance liquid chromatography (HPLC) method developed and validated by the pharmacokinetic laboratory of the Pharmacy Department at the University Hospital of Navarra [2] . Stability study of processed samples was investigated, as a requirement of the analytical method validation, by reinjecting the samples (hold at room temperature in the auto-injector) at different time intervals during 16 days.

Results: In eight of the nine patients without precharge dose was possible obtained detectable levels of Tegafur but only in one patient 5-Fu levels were detectables. In Tegafur pre-charged patients both Tegafur and 5-Fu were present in all tissue samples with exception of 2 fat samples. Both, Tegafur and 5-Fu levels were higher in tumor samples than other sites and show a clear tendency toward a correlation between degree of 5-Fu present in the residual tumor and cancer downstaging. Stability study showed a progressive increase of 5-Fu levels with time with no change in Tegafur values; so we hypothesize about the presence of a chemically labile metabolic intermediates that spontaneously cleave to 5-Fu.

Conclusion: A prospective study with a larger cohort of patients is necessary to confirm these results and to evaluate if tumor uptake of fluoropyrimidine could be a prognostic indicator of downstaging. Research should also be required to characterize the metabolic intermediates found in the stability study.

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P-54_ Modelling and Simulation of the Telephone Sexual Activity Daily Diary (TSADD) Data of patients with female sexual arousal disorder (FSAD) treated with sildenafil (Viagra).

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poster

Objectives: To develop models to:

- i) Characterize the probability of sexual events and their satisfaction scores over time based on TSADD data obtained in Phase 2b/3 clinical studies of sildenafil in patients with FSAD without concomitant Hypoactive Sexual Desire Disorder (HSDD).
- ii) Simulate the expected dose-response in various patient populations to assess the impact of patient and disease characteristics on outcome.

Methods: Data were available on 493 patients with FSAD from three clinical studies. A parametric model was developed to describe the probability density function of the time between sexual events. Orgasm satisfaction scores (OS) and overall sexual satisfaction (SS) scores were modelled as 4 level-ordered categorical variables. The models were implemented in NONMEM. The following covariate effects were assessed (log-likelihood ratio test at $p < 0.05$): drug intake, drug dose, age, baseline diagnostic and satisfaction scores, menopausal status, and hormone levels. The models were qualified by posterior predictive check. Initial simulations were performed to evaluate the expected clinical response in the FSAD patient population.

Results: A Weibull distribution best described the probability density function of the time between sexual events. The median time between sexual events was 3 days and was not influenced by sex or orgasm satisfaction scores. Satisfaction scores were simultaneously modelled with overall sexual satisfaction conditional on orgasm satisfaction ($P(SS|OS)$).

- Satisfaction scores increased with time on study in a nonlinear fashion to achieve a plateau after 3 to 4 weeks on treatment.
- Sildenafil effect was dependent on dose, testosterone level and menopausal status.
- The probability of orgasm satisfaction scoring rates of 3 and higher was used as the clinical endpoint for simulations. The orgasm satisfaction rate ranged from 34.7% for placebo to 41.6% for 100 mg sildenafil. Absolute treatment effect (difference from placebo) was 6.9% for 100 mg dose of sildenafil, ranging from 0.6 to 24.7% for testosterone levels of 0.1 to 4pg/ml, respectively. The treatment effect for sildenafil in post-menopausal women was larger than in pre-menopausal women.

Conclusion: A modelling & simulation framework to support drug development in FSAD was developed. Sildenafil demonstrated a dose-dependent effect in female patients with FSAD.

P-55_ Modeling of circadian effect on lung function in patients with chronic obstructive pulmonary disease

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poster

Objectives: To model the circadian effect on lung function in patients with chronic obstructive pulmonary disease (COPD).

Methods: Lung function (FEV1 and FVC) was determined in 14 patients with COPD (mean (SD) age 63 (10) years, post-albuterol FEV1 49 (10) %predicted). FEV1 and FVC were measured at -1 hour pre-time zero, at 5, 15, 30 and 45 minutes post-time zero, and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 12 hours post-time zero on day -1 and day 9. Time zero was around 8:00AM. The change in lung function within 24 hours was analyzed by several models using a nonlinear mixed effects modeling program. Goodness-of-fit was assessed by evaluating diagnostic plots.

Results: The lung functions (FEV1 and FVC) followed a circadian rhythm in patients with COPD, and this process was adequately characterized using a cosine function. The typical rhythm-adjusted 24-hr mean baseline effect was related to gender, height and age. The typical amplitude for the cosine terms, which expressed as a change from the mean, was 139 mL for FVC and for 96 mL FEV1. The typical time shift for the cosine terms was 7.6 hour for FVC and 7.14 hour for FEV1. The goodness-of-fit plots indicated that the model provided a relatively unbiased fit to the data.

Conclusion: Lung function appeared to show a circadian effect in patients with COPD. It is important to consider this effect when calculating the post-dose drug effect for any drug to treat patients with COPD.

P-56_ Pharmacokinetics- guided targeting of mycophenolate mofetil (MMF) in combination renal transplantation treatment confirms the need for dose reduction

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poster

Purpose To use a prospective population pharmacokinetic (PK) method, and Bayesian estimates of the AUC, to optimize mycophenolate mofetil (MMF) dosing in maintenance combination therapy after renal transplantation.

Methods The patient cohort of 27 adult (19/8 male/female) renal transplant recipients, studied, had MMF administered with methylprednisolone (Md) in combination with sirolimus (SRL - 6 patients), cyclosporine (CsA - 13 patients), tacrolimus (Tac - 4 patients), tacrolimus without Md (2 patients) or MMF with Md alone (2 patients). The study started several months posttransplantation when patients were stable with serum creatinine (mean [range]) 1.9 (1.0 - 4.0) mg/dL, and albumin 4.2 (2 - 5) mg/dL. A total of 111 blood samples were analyzed from predose troughs (C₀), and 30 min (C₃₀) and 2 h (C₂) postdose, sampled from each patient, with 13 repeat occasions. A nonlinear mixed effects method (NONMEM) was used to build population pharmacokinetic (PK) priors for a two compartment oral absorption model with time lag, as patients entered the study, followed by Bayes estimation of individual patient PK parameters. Systemic clearance, CL, was used to titrate the dose for a putative target AUC (range) for MMF of 50 mg h/L (40 - 60 mg h/L). Demographic and biochemical variables were used for covariate modeling with the PK parameters.

Results The patients had, ages 41.5 (20 - 71) y and weights 68.8 (37 - 94) kg. Administered doses were 731.7 (250 - 1000) mg b.i.d., and AUC₀₋₁₂ of 63 (15.8 - 160.4) mg h /L. The bioavailability (F) - scaled NONMEM FOCE population PK parameters for MMF were (true value, interindividual coefficient of variation, CV%), for CL/F = 12.4 L/h (33%), central volume of distribution, V/F = 11.5 L (15%), intercompartmental clearance, Q = 20.2 L/h (45%), deep tissue volume of distribution, V₃ = 208 L (CV% not estimated), absorption rate constant, k_a = 2.27 h⁻¹ (CV% not estimated), and absorption time delay, Tlag = 0.35 h (CV% not estimated). The C₀ and the C₂ appear valid surrogates of the AUC, although the Bayes method is more reliable.

Conclusion Dosage was reduced overall in the patient group, after information from the population screen. TDM may be required for MMF in combination immunosuppression after renal transplantation.

P-57_ Optimal blood sampling time windows for parameter estimation using a population approach: design of a Phase II clinical trial

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poster

Introduction: A phase II dose-ranging study is planned for a drug in clinical development. The pharmacokinetics (PK) of the compound will be part of an ancillary study and will be considered as a secondary objective of the trial. The two aims of the PK analysis will be firstly to estimate PK parameters at steady state using a population approach in the concerned population, and secondly to investigate any potential PK/PD relationship between the exposure (Area Under the Curve) and the activity. As characterising the PK is at best a secondary objective in the clinical study, few samples can be drawn per patient for PK analysis and the sampling schedules must be as flexible as possible. Sampling time windows will be specified in order to get the maximum information from the samples without disturbing the trial too much and a population approach will be used for the PK analysis.

Aim: To determine the optimal blood sampling time windows for the estimation of PK parameters by a population approach under clinical constraints.

Methods: The clinical study will involve 3 dose levels (10, 30 and 90mg) and 150 patients per dose group. The drug will be administered orally once a day and the PK samples will be taken at steady state. All patients will be sampled just before drug administration (trough) and between 2 and 4h after dose. One third of patients in each dose group could as well be sampled between 4 and 10h after dose with a maximum number of samples equal to 6 per patient. Because the trial will be double blind, sampling time windows must be the same in each dose group. Based on previous data, the following model was shown to properly describe the PK of the compound: a 2-compartment model with a first order absorption constant (K_A); inter-individual variability (IIV) on the elimination and inter-compartmental clearances (CL and Q , respectively) and on the K_A . The residual variability was a combined error model. Based on this model two approaches were developed: M1 method where all parameters were estimated and M2 method where K_A and IIV on K_A were fixed. Optimal sampling times were determined by optimizing the population Fisher information matrix (PFIM) using PFIM 1.2 under MATLAB for the two approaches. The criterion used was D-optimality and the algorithm was a modified Fedorov exchange algorithm. Optimal sampling time windows were determined by allowing the D-optimal windows design to result in a specified level of efficiency when compared to the fixed-times D-optimal design. Finally, the D-optimal sampling time window design was evaluated, after MATLAB simulations and NONMEM estimation with the FOCE interaction method, by computing the relative error of estimations.

Results: According to the coefficients of variation of the standard error (CVSE) given by PFIM for each parameter, the best results were obtained when K_A and IIV on K_A were fixed (M2 method). Windows were determined with the M2 approach and 4 optimal sampling time windows : at trough, between 2 and 4h after dose for all patients and only 2 sampling time windows between 4 and 10h after dose for 1/3 of patients;

equal to [4h - 5h05'] and [9h10'-10h]. These sampling time windows obtained with a 90% level of efficiency and a uniform sampling distribution are wide enough to be useful in a clinical trial. The trends of CVSE values given by the PFIM are in full agreement with the simulations of 100 datasets with the selected design. Mean population parameters, such as the CL, were quite well estimated but the relative error was high for the IIV on Q, and for the additive random error.

Conclusion: An optimal sampling time windows strategy under clinical constraints was implemented for a Phase II study. Sampling time windows were designed and the PK sampling schedule was evaluated by simulation. As previously described with fixed effect models, the number of samples per patient is equal to the number of fixed parameters, and consequently in the present case only 4 sampling times windows were necessary to estimate parameters as there were 4 mean population PK parameters in the model. The weakness of the design was the lack of information about the absorption phase which might be overcome with a Bayesian approach. However, characterising the absorption phase is not a major concern for the proposed trial as the clinical study will mainly focus on exposure. Therefore, the sampling time windows will then be suggested to define the sampling schedule in the phase II study to come. Without this approach, the PK sampling schedule would be made empirically and results would be at best similar to those described here.

P-58_ Population pharmacokinetics of S-mephenytoin and its metabolites S-nirvanol and S-4-hydroxymephenytoin in CYP2C19 poor, intermediate and extensive metabolizers.

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poster

Objectives: The aim of this study was to develop a model to describe the pharmacokinetics of S-mephenytoin, a probe of CYP2B6 and CYP2C19 activities, and its metabolites S-nirvanol and S-4-hydroxymephenytoin in healthy volunteers.

Methods: The population pharmacokinetics of S-mephenytoin and its metabolites were described by nonlinear mixed effects modeling using NONMEM. Data were pooled from two studies. One dataset contained rich data from 14 healthy male volunteers, who had received a single oral dose of 200 mg racemic mephenytoin. The second dataset contained sparse data from 74 healthy volunteers, who had received a single oral dose of 100 mg racemic mephenytoin.

Results: The pharmacokinetics of S-mephenytoin and its metabolites were described by multi-compartment models incorporating first-pass formation of S-4-hydroxymephenytoin.

The final model contained estimation of three subpopulations using the \$MIXTURE subroutine. The formation clearance of S-4-hydroxymephenytoin was estimated separately for the extensive metabolizers (EMs), intermediate metabolizers (IMs) and was fixed to zero in poor metabolizers (PMs). S-4-hydroxymephenytoin first-pass formation was estimated only for EMs. Bioavailability of mephenytoin was fixed to 1 for PMs and was estimated relative to PMs in the rest of the population. The percentage of subjects estimated to be EMs, IMs and PMs were about 70, 13 and 17%, respectively, which is consistent with literature reports of the distribution in Asians.

The population estimate of mephenytoin bioavailability was about three fold lower in EMs and IMs compared to PMs. The formation clearance of S-4-hydroxymephenytoin was about 2 fold higher in EMs compared to IMs.

Conclusion: The presented model adequately describes the population pharmacokinetics of S-mephenytoin and its metabolites S-nirvanol and S-4-hydroxymephenytoin and confirms the presence of the three subpopulations of CYP2C19 phenotype described in the literature. This model will be developed to be able to assess the inductive/inhibitory effect of CYP2B6 and CYP2C19 activity by various drugs.

P-59_ Population Optimal Design for Multivariate Response Pharmacokinetic Models

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poster

Objective: To develop a methodology for individual and population multivariate response design for pharmacokinetic models. To suggest optimal sampling times for a *restrospective* iv bolus study for the disposition kinetics of tolcapone and its two metabolites in healthy volunteers.

Methods: We aim to design a study for efficient estimation of tolcapone and its metabolites, by employing a D-optimal design criterion. This criterion minimises the volume of the joint confidence region by maximising the determinant of the Fisher information matrix (FIM) (inverse of variance-covariance matrix). It was further assumed that measurements made at distinct times are independent, but measurements made of each drug tissue concentrations are correlated with a constant variance-covariance matrix. Following population data analysis in NONMEM, models for the univariate responses, e.g. considering only tolcapone disposition, and for the multiresponse situation, i.e. simultaneous analysis of tolcapone and its metabolites, were identified. Subsequently optimal sampling times were suggested for both individual and population designs. The effects of design variables, such as response covariance matrix, number of sampling times and structure of residual model were investigated. To determine the D-optimal design the determinant of the FIM has to be maximised over the whole design space. Unfortunately the surface of this determinant was very convoluted which places additional requirements on any optimiser. A number of optimisation methods (downhill simplex, simulated annealing, adaptive random search, exchange) were used.

Results: The exchange algorithm and a hybrid scheme consisting of simulated annealing followed by downhill simplex performed the most consistently well. D-optimal sampling times for individual and population designs were obtained.

Conclusions: A methodology for population multivariate response design for PK experiments was suggested. This was illustrated by a retrospective study of the disposition of tolcapone and its metabolites in healthy volunteers.

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P-60_ Simultaneous population D-optimal designs for contrast enhanced MRI measurements of atherosclerotic plaque neovasculature.

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poster

Objectives: Atherosclerotic plaque is a common cause of stroke. Furthermore, histology studies have shown a strong correlation between stroke and the number and size of neovessels in surgically removed carotid plaques^[1]. Thus, there has been interest in using the quantification of neovasculature in carotid plaques *in vivo* as a biomarker to assess long-term prognosis and weigh treatment options. In previous work we have shown that contrast-enhanced (CE) MRI techniques have the ability to identify and quantify plaque neovascularization^[2]. In that work we used a simplified Patlak model^[3] to describe the pharmacokinetics of the contrast agent in carotid plaques based on dynamic CE-MRI data. We were able to show that parameters in the model correlate well with *ex vivo* histological measurements of plaque neovascular area and could be used to examine the link between neovasculature and plaque vulnerability. However, the comparison between the *in vivo* model parameters and the *ex vivo* histological measurements depend on the accuracy of the estimated model parameters. If our model parameters have a high degree of variability, then any existing correlation between the *in vivo* and *ex vivo* measurements could be missed. As such, in this work we explore the extent to which simultaneous population optimal experimental design techniques could improve our comparisons of model parameters and histological measurements.

Methods: We compute simultaneous population D-optimal designs using the optimal design program PopED^[4] and the procedures described in Hooker *et al.*^[5]. We then simulate and estimate model parameters on numerous replicate experiments (using the assumed true parameter values) based on these D-optimal designs. From an optimal design standpoint, this problem is interesting because simultaneous optimal design techniques must be used due to the fact that both PK and PD measurements must be made at the same time.

Results: We show that by utilizing these optimal design techniques the number of images required per experiment could be cut in half, thus allowing for higher resolution in each image and thus better correlation between the *ex vivo* and *in vivo* measurements.

Conclusions: These results suggest that simultaneous population D-optimal design techniques could contribute to *in vivo* quantification of plaque neovasculature, which could aid in investigating the likelihood of stroke and possibly treatment effectiveness.

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P-61_ Optimising PK sampling under the constraint imposed in later phase clinical trials

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poster

Objectives: When collecting pharmacokinetic (PK) data in a clinical trial an important design factor is the number and times when blood samples are taken. Given prior information on the expected drug concentration-time relationship, theory for computing D-optimal designs is available and gives sampling times that maximise the collected PK information. The usual assumption is that subjects have blood samples taken at the same fixed times post dose. However, fixed sampling times for each subject rarely happen in later phase clinical trials (Phases 2 & 3) so designs obtained using mathematical theory may not be optimal given such a constraint. The purpose of this presentation is to describe a simulation method that aims to maximise the PK information collected given the practical constraints of later phase clinical trials.

Typical characteristics of later phase clinical trials are that the collection of PK is not the primary objective, blood sampling is sparse (*e.g.*, two sampling times during two clinic visits per subject), there are restraints on when sampling can be done and there is a lack of patient compliance. Such characteristics introduce uncertainty in the sampling times. For example, within a clinic visit the first sampling time may occur randomly within a protocol-specified visit widow (*e.g.* dose taken between 1 and 2 hours before clinic visit) and the second sampling time is conditional on the first plus some additional clinic assessment time. Consequently, all subjects potentially have different sampling times, but hopefully constrained within specified visit windows. Progress is being made but standard optimal designs obtained via theory fail to incorporate this random component in sampling times and may be sub-optimal from a practical viewpoint.

Methods: We describe the use of simulation to account for the randomness in sampling times. As an illustrative example, a first-order absorption one-compartment PK model was assumed. A grid of sampling windows was created, derived from possible visit windows that could be realistically specified in a study protocol. For each possible sampling window combination, random sampling times for n subjects were simulated (2 samples x 2 visits). The data derived were used to fit the PK model and the efficiency of each sampling window combination estimated. The highest efficiency, having lowest standard error, was used to determine the optimum sampling window combination. This optimum sampling window was compared to a D-optimal design (PFIM [1]) and the loss of efficiency due to the randomness in sampling times was estimated.

Conclusion: Advantages of the simulation method over theoretical designs will be discussed but the former does represent a cost in terms of time and resource. It is recommended that a combination of both optimal design theory and simulation is the best compromise as it will lead to both a faster and more applicable design solution.

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P-62_ Randomized exposure-controlled trials; impact of randomization and analysis strategies - from a toxicity perspective

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poster*

Objectives: It has previously been shown[1] that the most beneficial parallel group trial design and analysis strategy from a statistical power perspective is a randomized dose-controlled trial (RDCT) and a model-based analysis (MBA) with an independent variable as highly correlated to the clinical endpoint as possible. It has been argued on the basis of a traditional statistical analysis approach that there are situations where a randomized concentration-controlled trials (RCCT) is a better trial design compared to an RDCT[2]. One of the perceived advantages is the lower risk of toxicity. Given that a higher statistical power leads to smaller group size it is not at all clear that an RCCT with traditional analysis will result in fewer toxicity events than an RDCT with model based analysis. The aim of this study was therefore to investigate, through simulations, how the randomization scheme and analysis strategy can influence the number of toxicity events in a clinical trial.

Methods: A simulation framework was set up with a dose leading to a plasma concentration (one-compartment model at steady state), leading to a change in a biomarker (E_{max} model) and the biomarker leading to a response in a dichotomous clinical endpoint (linear-logistic model). There was also a link between the plasma concentration and a toxicity response (T_{max} model, adverse event $T \geq 0.75 T_{max}$). Three factors were varied across simulations: TC_{50} , variability in TC_{50} and variability in CL. Two randomization schemes were simulated; RDCT and RCCT, and two analysis methods were used; group-wise analysis (GWA) and a MBA. In the MBA three independent variables were used; dose, concentration and biomarker. Each combination of randomization scheme and analysis strategy was simulated with a number of subjects that yielded an 80 percent statistical power to detect a treatment effect in the clinical endpoint.

Results: An RDCT with model based analysis using the biomarker typically required less half the number of subjects of an RCCT with GWA. These represent the most and least efficient design/analysis options, respectively. For situations with low variability in CL, the former also results in a lower number of adverse events. As variability in CL increases, the number of adverse events in an RDCT increases relative an RCCT. At higher variability in CL the design/analysis option resulting in the lowest number of adverse events is an RCCT with MBA, about half that of an RCCT with GWA.

Conclusions: This demonstrates that under reasonable conditions and maintaining equal power across trial designs and analysis options, an RDCT may well result in fewer adverse events than an RCCT. A MBA will result in a higher statistical power and therefore smaller group sizes compared to a GWA, given the same randomization scheme.

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P-63 _ Relevance of the use of population design evaluation and optimisation methods in the context of drug development projects in Roche

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poster

Context: Population designs evaluation and optimisation methods have been widely developed in the last few years. Based on the population Fisher information matrix approach [1, 2], for which relevant results have been shown [3, 4], PFIM and PFIMOPT Splus functions have been proposed for population designs evaluation and optimisation respectively [5]. However, the use of those functions in a daily routine for design determination is still very few and demonstration of their usefulness in the context of drug development projects is still required.

Objective: The objective was to explore the relevance of using PFIM and PFIMOPT in the context of drug development projects in Roche. The idea was to appreciate, for a given good level of parameter estimates precision, both the number of samples that could be saved and then the diminution of design cost that Roche could expect by using those tools.

Method: Four projects with completed studies (including population PK analyses) have been selected for a retrospective analysis of their population designs. Those studies occurred at different stages of the drug development (phases II and III) and had different ways of administration, IV or PO. Their population designs were given in two different forms, either by fixed sampling times or by sampling windows; moreover they involved full PK profile samples (most with around 10 samples per patients) sometimes combined with a peak and trough strategy at different occasions.

For each study, the same strategy was used. First a priori knowledge on the PK of the drug was collected from previous studies (phase I) in order to mimic the knowledge of the pharmacologist at the time of the choice of the design. Based on that knowledge, the efficiency of the population design, in term of precision of the parameter estimates, was then evaluated with PFIM. In order to try to improve the efficiency of the design and / or to reduce the number of samples per subject, the optimal sampling times were computed using PFIMOPT. Based on those a "compromised" design taking into account the clinical constraints was derived. The gain of efficiency and the study cost reduction using the compromised design were then appreciated.

Results: Results given by PFIM on the efficiency of each population design were in accordance with the different level of difficulties encountered during the modelling of the data with NONMEM (2 studies over the 4 with SE% > 100% on most of the parameters). Optimisation of those designs has allowed derivation of compromised designs, with reasonable expected precision of parameter estimates, but also less costly, with a reduction of the number of samples per subject up to near 45%.

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P-64_ Designs in nonlinear mixed effects models: application to HIV viral load decrease with evaluation, optimization and determination of the power of the test of a treatment effect

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poster

Context: We have proposed Splus and R functions, PFIM and PFIMOPT, for respectively designs evaluation and optimization in nonlinear mixed effects models (NMEM) [1]. These functions rely on an approximation of the Fisher information matrix using a first order linearization of the model [2]. Optimisation is based on the D-optimality criterion and uses a simplex algorithm. More recently, we have extended the expression of the Fisher matrix for models including the influence of covariates [3] and have implemented the Fedorov-Wynn algorithm for optimisation.

Objective: Our objectives were to apply and to illustrate this method to the example of a biexponential model of HIV viral load decrease under antiretroviral treatment [4]. This model involves four fixed effects, four additive random effects and an additive homoscedastic error. An additional fixed effect of the antiretroviral treatment on the first rate-constant is also considered.

Methods: We evaluate with PFIM a design of two groups of 100 patients with the same 6 sampling times per group and compare the empirical standard errors (SE) found with simulations with the SE predicted either with the nlme function of Splus or with MONOLIX, the new SAEM algorithm for NMEM estimation without any linearization [5-6]. We also use MONOLIX with one simulation of 5 000 patients to estimate the variance matrix and thus the expected Fisher information matrix under asymptotic convergence assumptions; we then derive the expected SE for smaller data sets. We apply the Fedorov-Wynn algorithm to optimise a design for a model without treatment effect and for a model where the treatment effect is estimated. We compare the optimised designs to those found with the Simplex algorithm. Last, from the predicted SE we compute and compare the power of a Wald test for the treatment effect under an alternative hypothesis for this parameter; this is performed for several empirical and optimised designs with either different total numbers of patients or different numbers of observations per patient.

Results: Regardless of the method, the SE were all very close which illustrates the usefulness of PFIM. For instance, for a treatment effect of 30%, the SE predicted for this parameter is 0.079 with PFIM and 0.078 with MONOLIX. The power computed from the SE given by PFIM is 92% for 100 patients per group and is reduced to 57% for 40 patients per group as in [4]. Optimisation with the Fedorov Wynn algorithm was faster and more robust than with the Simplex algorithm and led to a similar group structure and efficiency. Designs with fewer samples per patient but still reasonable power were optimised. For example, we showed that for a total number of patients of 100 per group, the power of an optimised design with 3 samples per patient divided into 4 sub-groups can be nearly as good as that of a design of 6 identical samples per patient chosen empirically: 87% versus 92%. This illustrates the consequence of the choice of the design on the number of samples and patients needed for a given power.

Conclusion: We illustrated the usefulness of PFIM and PFIMOPT on this new example and we showed that the Fedorov-Wynn algorithm is a good algorithm for design optimisation.

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P-65_ Designing Sparse-Sampling Schemes for Population PK Study of a Highly Variable Drug.

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poster

Objective: Design a sparse sampling scheme for a population PK component of an efficacy trial of an anti-tumor drug. Due to predisposition to bleeding of the study patient population, the optimal sampling scheme should incur a minimal number of blood draws per patient. The data collected will augment available PK data and allow for identification and testing of covariates for this highly variable drug.

Methods: A population PK model was developed based on the data from 7 Phase I clinical trials, wherein patients (n=68, 40% female, 60% male) were given twice-daily doses of 200, 250 or 300 mg. A total of 727 plasma concentrations (n=7-14/patient) were available for 12 or 24hr post-dose at steady-state. Model performance was assessed by evaluation of diagnostic plots and the final model was identified. For each sparse sampling scenario, individual patient's PK profile was bootstrapped to generate 100 datasets. The population PK model was fit to each bootstrapped dataset and accuracy and precision of resulting parameter estimates were compared to those from the original model. All data modeling and simulations were performed using S-Plus v 6.0 and resampling using SAS 8.

Results: A steady-state one-compartment with an additive interindividual random variability and residual error model best described the data. The final model did not have any covariates due to limited diversity of covariate data (race, gender and weight). The likelihood of a successful model fit to the bootstrapped datasets was related to the number of sampling points in the design. The percentage of datasets with successful model fits ranged from 70%-95% for the different sampling scenarios. For the designs under consideration, the scaled mean squared error (MSEs) for the population model parameters ranged from 0.0056 to 0.0171.

Conclusions: The ease and flexibility of proposed methodology allowed for evaluation of various sampling scenarios which were subsets of the original design. The obtained estimates of each model fit were used for computation of standard metrics of model prediction errors and design efficiency.

P-66_ Patients' Non-compliance with Drug Administration Times and Optimal Population Design in Pharmacokinetics.

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poster

Objectives: Optimal designs in population pharmacokinetics (PK) usually assume that drug administration times are fixed in the trial. However, the fact that patients take the drug later or earlier than specified by the experimenter shifts post-dose measurements to suboptimal times. The problem occurs when patients administer the drug unsupervised before coming to the clinic, as in certain Phase 2/3 trials.

In this setting, experimenter specifies *how long before each clinical visit the patients should take the drug so as to maximise the precision of the population parameter estimates*. Mathematically, the design problem is to find the optimal times to be specified, given the random error caused by patients' non-compliance (cf. Pronzato, 2001). The problem is related to that described in Johnston et al. (2005). However, their study considers sampling windows rather than times, and additional clinical constraints (cf. also Green and Duffull, 2003).

The purpose of the presentation is to assess information loss arising from patients' non-compliance with specified administration times. The assessment is made assuming realistic time compliance for a simulated D-optimally designed trial. To reduce information loss, compliance-based designs and compliance improvement measures are suggested.

Methods: In the simulation, the same patients are instructed to take a drug at a specified time before each of their three clinical visits. At the clinic, a single sample is taken at the beginning of each visit. The distributions of administration times with non-compliance were based on the data from actual clinical trials. The data contained patients' dosing histories collected by an electronic monitoring device, the use of which is also assumed in the simulated trial. Consequently, the actual administration times are random at the design stage, but known for estimation purposes.

For the assumed first-order absorption one-compartment PK model (cf. Retout and Mentré, 2003) with perfect compliance, a three-point D-optimal population design was found using Matlab. The optimality criterion value was calculated for both perfect and empirically-based compliance, assuming that the three-point D-optimal design is used.

Results: The criterion value dropped between 25% and 40%, depending on the pattern of non-compliance. The largest decrease occurred at about the first optimal time post-dose. The smallest decrease occurred at about the third optimal time, suggesting varying significance of compliance for different visits.

The next stage of the research considers compliance-based adjustments to optimal design algorithms. First, the D-optimality criterion was optimised over a prior population distribution of administration times. The algorithm thus differed from current standard methods, which assume fixed design times. For the considered empirical-based distributions, designs different from the standard D-optimal one were obtained, and the criterion value increased by between 6% and 10%. Second, since the same patients attended all three clinical visits, an optimal design with respect to

individual distributions of administration times was considered. The optimisation resulted in individualised time specifications, based on the mean and variance of each patient's administration time. The individualised optimisation produced a higher increase in the criterion value than did the first, population-based, algorithm. The drawback is that collection of patients' dosing histories is required before conducting a PK trial. However, such collection may be feasible in clinical trials, especially since compliance itself can be an important end-point, and is crucial for determining the efficacy of a drug.

In addition to design adjustments, cost-efficient measures aimed at compliance improvement are considered. Based on individual dosing histories, patients can be classified into compliers and non-compliers, and group-specific motivational measures implemented. For instance, medical personnel can make phone calls reminding the non-compliers to take the medication at the specified time. Alternatively, since compliance is particularly crucial for the earliest post-dose measurement time, the drug could be administered at the clinic before the first sample is taken. If the number of visits is limited to one or two per patient, the earliest part of the drug concentration profile (when compliance has the most effect on the accuracy of the results) should be constructed using the measurements from compliers, whereas the later part constructed predominantly from non-compliers' data.

Conclusion: The simulations using empirically-based non-compliance showed up to a 40% decrease in the D-optimality criterion value. Designs based on a prior distribution of random administration times can mitigate some of the decrease. The design approach considered in the research may be applicable to the specification of the optimal sampling intervals, as in the sampling windows examples. The compliance improvement measures suggested may also enhance trial results. The decision to implement a particular improvement measure would depend on prior compliance information, available resources, and the trial's objectives. The accuracy of Phase 2/3 PK trial results should be substantially improved by making provision for patients' imperfect administration time compliance in trial design.

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P-67_ Analyzing Multi-response Data Using Forcing Functions: illustrated in pharmacokinetic physiological flow modeling

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poster

Objectives: To analyze multi-response data, a multivariate output model can be fit to all the response components simultaneously (SIM), or each response component can be fit separately to a univariate output model, conditioning on the non-modeled components, the so-called forcing function approach (FFA). Focusing on a special case of multi-response model corresponding to a pharmacokinetic physiological flow model (PFM), the aims of this study are to provide an algorithm for applying FFA, examine its performance, and make recommendations regarding its use.

Methods: The basic PFM has 4 homogenous compartments. All are sampled: arterial blood (A), non-eliminating tissue (N), eliminating tissue (E), and venous blood (V), which is also the drug dosing site. Parameters are blood flow rates to E and N, volumes of distribution of A, E, N, V, elimination rate constant from E, and observation error variances. Observations from a generic individual under various study designs and parameter values are simulated. Using data-analytic models both the same as, and different than the data simulation model, SIM fits the PFM to all data simultaneously; FFA first fits each type of response (one per tissue) separately, approximating the tissue's input by linearly interpolating the observed concentrations from the donor tissue(s), estimates the identifiable parameter combinations for the response type, and then solves the simultaneous equations linking these across tissues, to obtain the primary model parameters of interest. This simulation and analysis steps are repeated to generate reliable performance statistics. Performance measures include parameter estimation error, prediction error, and the ability to identify the correct analytic model.

Results and Conclusions: When data-analytic model is correct, FFA's parameter estimation errors are generally about 2 times greater than those with SIM, and FFA's prediction errors are about 10 times greater than those of SIM. When data-analytic model is misspecified, FFA's prediction errors are about 3 times greater than those of SIM. However, SIM fails to identify the correct analytical model twice as often as FFA. The study suggests FFA's final parameter estimates cannot be trusted when the multi-response system being modeled involves feedback, despite its greater convenience for model building, and its clear advantages for model identification. A test is proposed to indicate when FFA's final estimates may be trustworthy.

P-68_ Bioavailability of gabapentin assessed by cumulative urine sampling compared with a model for the saturated absorption of gabapentin.

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poster

Introduction: Gabapentin has a demonstrated analgesic effect in patients with chronic neuropathic pain states¹ and is well established in the treatment of seizures. Gabapentin does not bind to plasma proteins and is excreted unchanged in the kidneys. Gabapentin displays dose dependent, saturable absorption. This is believed to include an active transport process mechanism by an L-amino acid transporter². This absorption pattern is believed to explain lack of effect in many patients due to sub-optimal dosing, but also low toxicity since high doses will be less absorbed³.

Methods: Patients with chronic, neuropathic pain receiving gabapentin as their main pain treatment were included in the study. The subjects were monitored during one dose interval (6-8 h) when in steady state. The bladder was emptied before the gabapentin dose was taken. Total urine volumes were measured and gabapentin concentrations measured by LC/MS-MS⁴. An estimate of excreted gabapentin pr 24 h were calculated based on the length of urine collection, urine volume and concentration of drug in the urine. An estimate for bioavailability estimated from urine collection (F_U) was calculated by using the following formula:

$$F_U = (\text{amount excreted in urine in mg/24 h})/DD$$

where DD is daily dose of gabapentin. These estimates were compared to estimates found by using a model for gabapentin absorption developed by Gidal et al.⁵ These authors report a Michaelis-Menten relationship between F and DD where the bioavailability estimated by the model (F_M) was found to be:

$$F_M = D_{\max} / (D_{50} + DD), D_{\max} = 2720 \text{ mg/day and } D_{50} = 4080 \text{ mg/day.}$$

Results: A good agreement was found between the two estimates of F. The model was able to predict an estimate of F close to the measured value in five out of seven patients. Average bioavailability for the seven patients was almost the same for model and urine collection, 42.5% and 43.7% respectively.

Conclusions: These results demonstrate that the absorption model can be included in pharmacokinetic models to be used in the monitoring of gabapentin.

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P-69_ Separating Signal from Noise: PK/PD modelling of QT-interval prolongation

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poster

Background: The presence of a prolonged QT-interval has become an identifier for the risk of a unique form of polymorphic ventricular tachycardia, Torsade de Pointes (TdP). Since this finding can be a serious safety issue, policies and guidelines have been proposed to ensure that the effects of non-cardiovascular drugs on QT-interval are accurately characterised. Such policies have assumed that ECG measurements are highly reproducible. However, there is convincing evidence from clinical research that QT-interval assessments can show high variability if considered over a wide time span. Therefore, any meaningful attempt to characterise drug-induced changes in ECG parameters requires identification of variability sources, as they will have major impact on clinical study design and sample size.

Objective: The primary objective of this investigation was to develop a pharmacokinetic / pharmacodynamic (PK/PD) model to describe the time course and variability of QT-interval in healthy subjects. In addition, it was our aim to establish the relevance of external factors on the accuracy and reproducibility of ECG measurements.

Methods: 30 healthy subjects were given a single oral dose of 160 mg d, l-sotalol, a beta-blocker well known to produce clinically significant QT prolongation, according to a double-blind, randomised, placebo-controlled, crossover study design. Pharmacokinetic sampling was performed at various times up to 24 h after dosing. 12-lead ECG was monitored continuously throughout the study and recordings were made at different time points before and after dosing. QT-intervals were read from automated recordings as well as from manual assessments, as defined by a cardiographer. The pharmacokinetics of sotalol was described according to a two-compartment model with first order absorption. To account for the effect of heart rate on QT-interval, the relation between QT and RR was modelled as $y = x^a \cdot b$. Drug effect was then characterised as a covariate on the intercept. Various models were explored to define the underlying exposure-response relation for d,l-sotalol. Data analysis was based on non-linear mixed effects modelling (NONMEM v5.1).

Results: We have derived a population-based correction model to estimate the QT/RR relation and subsequently estimate drug effect on corrected QT-interval. We found clusters causing major discrepancies in the reproducibility of recordings derived from automated measurements. An iterative mixture model was implemented to account for data clustering and estimate a QT/RR relation for each individual subject. Circadian patterns in HR and the QTc/RR relationship were characterized using harmonic Fourier functions. A direct effect model using an Emax link function was sufficient to characterise the QT response on d,l-sotalol exposure.

Conclusion: High variability exists in QT-interval measurements despite the careful control of the likely sources of noise in a clinical setting. In addition, there are major differences in the measurements and variability from automated readings, as compared to manual ones. A population-based correction factor improves the estimates of drug-induced effect on QT-interval and accurately characterises variability in ECG measurements. In contrast to the currently accepted statistical methodology for assessing drug-induced QTc prolongation, PK/PD modelling identifies the contribution of the various factors to mitigate QTc liability of new chemical entities.

P-70_ Structural identifiability analysis of some semi-physiologically based and whole body physiologically based (WBPBPK) pharmacokinetic models.

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Objectives: It is essential to establish the importance and raise the awareness of structural identifiability analysis [1] of system models as the prerequisite for population PK/PD experimental design. The analysis should be performed prior to the planned experiment to identify whether the internal structure includes assumed unknown pathways and parameters values that can be uniquely globally determined by input-output experiments. A locally identifiable model is one that consists of a finite set of parameter values, which indicates there is a finite set of estimated parameters. An unidentifiable model consists of infinite sets of parameters values and is not suitable for system identification in which the proposed model would require modification such as reparametrization or redesign of the intended experiments. These concepts are demonstrated through the investigation of the structural identifiability analysis of two linear models: a semi-physiologically based drug-metabolite model of dextromethorphan (DEX) and dextrorphan (DOR) [2] and a whole body physiologically based pharmacokinetic model (WBPBPK) of diazepam [3].

Methods: The exhaustive modelling or similarity transformation approach [4] was chosen from other existing methods [1] to use for the structural identifiability analysis for both linear systems due to its robustness and the efficiency in handling a large number of input-output measurements. The models also underwent controllability and observability checks to verify the complete controllability and observability of the models when using the similarity transformation approach. Analysis was carried out on variant models with different model structure assumptions to ratify the dependence of model assumptions in relation to the identifiability results. The similarity transformation approach was carried out using the symbolic calculation software, MATHEMATICA.

Results: The result of the semi-physiologically based model studies shows the impact of modification and simplification of the model in relation to the level of structural identifiability. The structural identifiability of the WBPBPK model was ascertained. The cases where hepatic intrinsic clearance was known and unknown a priori were considered.

Conclusions: The prior consideration of the structural identifiability is shown to be an important part of PK/PD experimental design lead to an understanding of the relationship between input-output experiments and the internal structure of the proposed model. This allows development of the model before any actual experiment is carried out.

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P-71_ Producing NONMEM dataset using a standard SAS(r) program

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Objectives: The overall objective is to implement a system which will ensure results from NONMEM analysis to be ready in time for decisions made about drug development. One main problem is a bottleneck in the data building part of the process especially with the large datasets in phase 2 and 3. The aim of this project is to greatly reduce the time taken to prepare a dataset for NONMEM from the raw data in the database.

Method: Standard specification for the required structure of NONMEM dataset was developed to minimise changes in what is required between studies. Key data components were identified. Date/time and value of PK and/or PD observations (plasma and urine) and the dosing history and route (non steady state and/or steady state; intravenous and/or extravascular administration) formed the main body of the dataset. The covariates are from demographic, laboratory, co-medications and adverse events data. These covariates were grouped as follows: covariates that only exist once per patient, covariates that change once per visit, and covariates like co-medications which can start and stop at various times throughout the study. Standard rules for replacing missing covariates were also defined. A SAS programme was developed to reflect the standard requirements of a NONMEM dataset.

Result: Six standard input datasets are created from the various source datasets within the study database. These are then used in the rest of the program which will remain mainly unchanged. The standard datasets contain dosing data, observation (PK and PD) data, time-independent covariates (e.g. sex or race), time-dependent covariates (e.g. weight), laboratory data and co-medication data.

The dosing and observation data is set together to create the main body of the NONMEM dataset. The demographic covariates are prepared by replacing missing values, and then merged together by patient number. The time-dependent covariates are then merged by patient and visit number, and the missing values replaced by carry forward and carry backward method. Laboratory covariates are then merged and missing values are once again replaced. Finally the co-medications are merged and flags are assigned if the patient was taking a particular medication at each time when there was a dosing or observation measurement.

Conclusion: The time taken to produce the NONMEM dataset was reduced to a quarter of what it took in the past. This has ensured the NONMEM analysis can be performed very soon after the database is locked, and in time for decisions made about future drug development.

P-72_ Building a pharmacogenetic model to describe the pharmacokinetics of digoxin

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Objectives: Over the past few years pharmacogenetic data has become increasingly available. In pharmacokinetic (PK) or pharmacodynamic (PD) studies, the focus is on a small number of Single Nucleotide Polymorphisms (SNP) or haplotypes to explain part of the interindividual variability.

The objectives of this work were, first, to review the literature on the statistical methods in this field, second, to apply model building strategies to study the pharmacokinetics of digoxin, a well-known probe for the activity of P-glycoprotein (PgP).

Methods: Papers dealing with pharmacogenetics and pharmacokinetics, published in Clinical Pharmacology and Therapeutics between 2003 and 2004, were retrieved based on the table of contents and the abstracts. In a second search, we scanned PubMed to retrieve all the papers using nonlinear mixed effect models (NLMEM) for pharmacokinetic modelling in the presence of genetic data.

The pharmacokinetics of digoxin have been previously analysed using non-compartmental methods [1], pooling three drug interaction studies in 32 healthy volunteers with extensive pharmacokinetic sampling. All patients were genotyped for the two main mutations in the MDR-1 gene which controls the expression of PgP (C3435T in exon 26 and G2677T/A in exon21). We used several approaches to include the genetic covariates in the pharmacokinetic model: stepwise selection with log-likelihood ratio tests, exhaustive search using the Bayesian Information Criterion (BIC) or the Akaike Information criterion (AIC), backward selection from a full model where covariates were selected using the Wald test. We used FO (NONMEM) and SAEM (MONOLIX) as estimation methods.

Results: In 2003-2004, 28 papers and 22 abstracts including pharmacogenetics and pharmacokinetics were published in Clinical Pharmacology and Therapeutics. A vast majority (93%) used non-compartmental analysis or observed data such as maximum concentrations and performed standard statistical tests. We found 15 papers in PubMed where NLMEM have been used, but they showed a variety of ways to deal with the categorical nature of pharmacogenetic data, resulting in different coding schemes. Model building strategies were also variable.

The PK model for digoxin was a two-compartment model. Using stepwise selection with NONMEM we found that carriers of the TT genotype on exon 26 exhibited an increase of 30% in bioavailability compared to the other genotypes. We did not find any other effect when treating the genetic data as haplotype instead of SNPs, but because of linkage disequilibrium there was limited additional information in haplotypes when compared to exon 26 alone. We will illustrate the differences in covariate selection with the other approaches, using both FO and SAEM.

Conclusion: A wide array of methods have been used to deal with pharmacogenetic data when studying the pharmacokinetics of drugs, with no standard approach. NLMEM can provide a better understanding of the influence of genetic data on pharmacokinetics. For digoxin, NLMEM showed an increase in bioavailability in homozygote carriers of

the T allele for the exon 26 polymorphism in MDR-1, explaining the differences in AUC observed previously [1].

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P-73_ Modelling placebo response in depression using a mechanistic longitudinal model approach

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poster

Background and Objectives: Depression is one of the most common and treatable of mental illness. In any six-month period, 340 million people in the world suffer from this disease. Eighty to 90 percent of those who suffer from depression can be effectively treated, and nearly all people who receive treatment derive some benefit. Placebo effect is an important component of the efficiency of antidepressant drug that has to be taken into account when predicting the time course and the variability of the drug effect. The objective is to develop a placebo response longitudinal model in depression as measured with the Hamilton depression scale accounting for dropout.

Method: Placebo data from a 6-week double blind, placebo-controlled study were used. Hamilton depression scale measurements were obtained before the start of the treatment and at week 1, 2, 3, 4, and 6 during the treatment period. Modelling was performed using NONMEM V. Since the problem of missing data is almost ever-present in clinical trials, alternative methods for analysing longitudinal data in presence of dropout were explored.

Results: Indirect-response model was used to describe the time course of the Hamilton depression scale. The time course of HAMD is determined as the net resultant of an onset (kin) and a loss rate (kout) process. Placebo produces indirect action on the inhibition of the onset response rate.

Placebo effect can be characterised by the administration of a "virtual" drug with unknown PK using a K-PD model strategy. This approach enables placebo effect to be linked to a dose regimen. Alternative mechanisms of dropping out were also investigated by exploring the Missing Completely At Random, the Missing At Random and the Informative Dropout possible mechanism. The most informative dropping out model was selected based on the log-likelihood ratio test.

Conclusion: This PKPD model allows the description of placebo related change in Hamilton depression scale with a mechanistic approach rather than a descriptive approach.

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P-74_ Propagation of population PK and PD information using a Bayesian approach: dealing with non-exchangeability

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Objectives: To implement a conservative prior that safeguards against population non-exchangeability of prior and data likelihood, in the framework of population pharmacokinetic / pharmacodynamic analysis, incorporating multi-level hierarchical modelling.

Methods: Three different exercises were performed: (i) We investigated the use of parametric priors in the multilevel hierarchical modelling framework. (ii) We assessed the average performance of the a multilevel hierarchical model compared to the standard mixed effect model, considering also some interesting extreme cases. (iii) We implemented an application with a small Proof of Principle (PoP) study, which demonstrates the propagation of information across PD studies using multilevel modeling.

Results: Fitting with the 4-stage model and informative parametric priors performed similarly with meta-analysis of the test datasets combined with datasets that the priors came from, demonstrating that parametric priors can be used alternatively to meta-analysis. Further, the 4-stage model gave posterior distributions which have larger uncertainty but at the same time are unbiased, compared to the 3-stage model, and therefore implements a more conservative prior in a formal way, which is appropriate when the prior and the test populations are not exchangeable. For the application with PoP study, the statistical power of detecting the difference in potency of two drugs, when inter-study variability was present, was much greater when an extra stage in the hierarchical model to account for it, was used.

Conclusions: by applying the prior one hierarchical level above the level of the parameters of interest, we implemented a more conservative prior, compared to applying the prior directly on the parameters of interest. The approach is equivalent to Bayesian individualization, offers a safeguard against bias from the prior and also avoids the danger of the data being overwhelmed by a strong prior.

P-75_ A Semi-Mechanistic Model For Quantification Of Lean Body Weight

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Introduction: Lean body weight (LBW) has been recommended to scale drug dose. The current estimate of LBW [1] however inconsistent at extremes of size [2] and could be misleading with respect to interpreting weight-based regimen.

Aim: To develop a semi-mechanistic model to predict Fat Free Mass (FFM) from subject characteristics in a population that includes extremes of size. Fat free mass (FFM) is considered to closely approximate LBW. There are several reference methods for assessing FFM, whereas there are no reference standards for LBW.

Methods: A total of 373 patients (168 men, 205 women) were available for study. These data arose from two data sets. Data set A [index data set] contained anthropometric characteristics, fat-free mass (FFM) estimated by dual-energy X-ray absorptiometry (DXA - a reference method) and bioelectrical impedance analysis (BIA) data. Data set B [test data set] contained the same anthropometric measures and FFM data as data set A, but excluded BIA data. The patients in data set A had a wide range of age (18-82 years), weights (41 - 196 kg) and BMI values (17.1-69.9 kg/m²). Patients in data set B had BMI values of 18.7-38.4 kg/m². A two stage semi-mechanistic model to FFM was developed from the demographics from data set A. For stage one, a model was developed to predict impedance (Z). For stage two, a model that incorporated predicted impedance was used to predict FFM. These two models were combined to provide an overall model to predict FFM from patient characteristics. The developed model for FFM was externally evaluated by predicting into data set B.

Results: The semi-mechanistic model to predict Z incorporated sex, height and weight. The developed models provide a good predictor of the impedance for both males and females ($r^2 = 0.78$, ME = 2.30×10^{-3} , RMSE = 51.56 [$\sim 10\%$ of mean]). The final model for FFM incorporated sex, height and weight, where sex and BMI were the basis for prediction of Z and height was additionally required to predict FFM from Z. The developed model for FFM provided a good predictive performance for both males and females ($r^2 = 0.93$, ME = -0.77, RMSE = 3.33 [$\sim 6\%$ of mean]). In addition, the model predicted accurately the FFM of subjects in data set B ($r^2 = 0.85$, ME = -0.04, RMSE = 4.39 [$\sim 7\%$ of mean]).

Conclusions: A semi-mechanistic model has been developed to predict FFM (and therefore LBW) from easily accessible patient characteristics. This model has been prospectively evaluated and shown to have good predictive performance.

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P-76_ Robust fitting of pharmacokinetic models to Phase II/III clinical trial data

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poster

Pharmacokinetic analysis of Phase II/III trial data is often hampered by uncertainties in the data. This is not so much due to errors in the observations, but more so due to the non-compliance to the planned doses and the in-correct (unwitnessed) recording of dose events by the subjects enrolled in the trial. Ignoring these errors can result in biased parameter estimates. Various approaches have been proposed to overcome this issue, including the modelling of non-compliance. An alternative way to reduce the influence of the uncertainties in the dosage is by reversing the viewpoint. This considers the observations that are extremely remote from the results of model predictions as being indicators of a mismatch between assumed and applied dosage. By allowing a separate residual error for these observations their influence on the estimated parameters is reduced, thus improving the statistical inference. This approach is comparable to the concept used in robust regression techniques. An iterative procedure is proposed for identifying the remote observations using outlier criteria and refitting the model, until the identified residual variability accounts for all identified remote observations. The technique is explored and illustrated by Monte Carlo simulations under various non-compliance scenarios and sparse sampling schedules, and back fitting the model on the simulated datasets. A comparison is made between the bias of the back-fitted models with and without applying the robust fitting approach.

P-77_ Implementation of variability in a physiologically-based pharmacokinetic approach for simulating the first-in-animal study.

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poster

Objectives: The objective of this study was to evaluate the influence of different sources of variability in a basic, generic physiology-based pharmacokinetic (PB-PK) model used for simulating the first-in-animal study.

Methods: The basic model (1), partially modified from the one developed by Poulin & Theil (2), comprised a system of differential equations describing 13 tissue compartments. The model was based on physiological parameters, such as tissue volumes, weights, composition and blood flows, and compound-specific parameters (logP, pKa, hepatocyte intrinsic clearance, fraction unbound in plasma) obtained in vitro or estimated in silico. The variability of these input parameters were derived from the literature (3) and from the experimental data, respectively. Stochastic simulations of plasma concentration-time curves were generated using Matlab.

Results: Normal or log-normal distributions were implemented for describing the variability of parameters. Preliminary data suggest that the variability of physiological data is less important than the variability of the compound-specific input parameters. The basic model was also modified to consider alternative administration routes, such as inhalation. The approach provided results in good agreement with those reported in the literature (4).

Conclusions: The implementation of stochastic simulations into the basic PBPK model allowed to simulate not only the average pharmacokinetic profile, but also the dispersion of the data, considering the different sources of variability in the model parameters.

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P-78_ NMQual: A Tool to Automate Installation and Facilitate Qualification of NONMEM

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poster

Objectives: Keeping NONMEM installations up to date with known bugfixes can be challenging due to the nature of the procedure (e.g. manually modifying and compiling code according to bug-fix documents), and the lack of an automated method to update the source files with the bugfixes prior to compilation. In addition, presentations at recent industry meetings have indicated that a "validated" install of NONMEM is likely to be required by regulatory authorities in the future. The goal of this work was to develop a tool (NMQual) to facilitate the automated installation and qualification of NONMEM on a PC running MS Windows or Linux.

Methods: NMQual was developed according to modern software life-cycle practices. User requirements for NMQual included the ability to update the NONMEM source code with all bugfixes at the time of installation, implement any user or site specific changes, install NONMEM with minimal user intervention, maintain an electronic trail of all changes made during the installation, qualify the NONMEM installation, and allow a NONMEM run to be linked to an installation and any related code changes. Requirements also included the automated implementation of several NONMEM test cases, which were compared to reference results. The Perl programming language was ideally suited for the development of NMQual, due to its cross-platform compatibility, scripting capabilities, and ease of use.

Results: NMQual validation tests indicated successful implementation of all user requirements on both Linux and WindowsXP. Bugfixes and user requested changes are implemented via XML-formatted files read by Perl. All source code changes are tracked within the source files via inserted comments and externally using an installation log. NONMEM runs can be started from any directory on the computer using an installation-generated Perl script. Prior to the execution of NONMEM a checksum is run against the install directories to ensure that source code has not been modified since the last qualified installation. Each NONMEM output file includes the complete installation log appended after the standard output.

Conclusion: NMQual, a validated tool for the automated installation and qualification of NONMEM, provides a simple mechanism to improve the quality control of NONMEM installations.

P-79_ Topical Corticosteroid Bioequivalence - An Evaluation of the FDA Guidance

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poster

Objective: The US FDA has issued a guidance describing a methodology for the conduct and analysis of clinical studies aiming to establish bioequivalence of topical corticosteroids (1). The guidance and a subsequent report from FDA authors (2) recommend that bioequivalence is based on skin blanching observations obtained with an application duration ("ED50") estimated to produce 50% of the maximum area under the blanching effect curve (AUEC) after removal of the formulation. A population analysis of data provided in the guidance was used to evaluate the robustness of the "ED50" estimate to the estimation method and model assumptions. A simulation study was undertaken to explore the rationale for the choice of the "ED50" as the optimal design point for detecting differences in rate and extent of absorption.

Methods: NONMEM was used to estimate the "ED50" using different models and estimation methods. The uncertainty of the "ED50" estimate was evaluated by bootstrapping the data.

A semi-physiological compartmental model was constructed to simulate the rate and extent of absorption from the epidermis to skin vasculature. Corticosteroid loss from the vasculature was assumed to be determined by blood flow so that vasoconstriction induced by a corticosteroid would affect the time course of skin blanching. An Emax model was used to describe the relationship between corticosteroid concentration at the vasculature and changes in blood flow. Skin blanching was assumed to be proportional to the effect of the corticosteroid on blood flow.

Results: The estimate of "ED50" reported in the FDA guidance is 1.89 h. NONMEM estimates ranged from 0.7 to 3.73 h depending on the model and estimation method. Using a model similar to that proposed in the guidance and the FOCE method the median "ED50" was 2.54 with 90% confidence interval of 0.88 to 8.06 h.

The simulation study showed that AUEC reflected differences in extent of bioavailability (0.8 - 1.25 x reference) and potency (0.5 - 2 x reference) but was insensitive to the choice of the duration of application. With a 60 min reference absorption half-life differences in test absorption half-life (30 - 120 min) were detected with increasing sensitivity to AUEC as duration of application increased. AUEC was insensitive to application duration with rapid absorption half-life (10 min reference).

Conclusion: The method proposed in the FDA guidance for estimation of "ED50" is not robust. Differences in rate and extent of absorption of topical corticosteroids are largely insensitive to the timing of the AUEC design point unless absorption is slow. There is no mechanistic support for choosing the "ED50" as the optimal design point for assessment of bioequivalence.

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P-80_ Simultaneous modelling of disease progression and time to event with NONMEM - likelihood ratio test criteria for random and informative dropout models and an evaluation of two methods affecting the quality of parameter estimates

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Objective: An important challenge for clinical pharmacologists is to be able to describe the time course of disease progression biomarkers and link this to the probability of clinical outcome events. A common event in clinical trials is subject dropout. Hu & Sale (1) described a joint modeling method for describing informative dropout using observations of a disease status biomarker and a subject dropout interval (the exact time of dropout was not known) or censoring time. They used NM-TRAN to construct code for -2 times the log likelihood (-2LL) for each type of observation. The objective of this study is to compare the NM-TRAN method with using a modified CCONTR subroutine to compute the objective function contributions and to evaluate the use of the likelihood ratio test for model discrimination.

Methods: The -2LL method has been compared with the CCONTR method using NM-TRAN to compute the likelihood for dropout and censoring events and the more usual predicted value for the continuous scale disease status. Biomarker status, dropout and censoring event data were simulated with NONMEM. Data was simulated and parameters estimated using a linear time course for the disease status and 3 dropout models (completely at random, random and informative). NONMEM was used to estimate parameters of the joint model. A randomization test was used to generate null distributions for the likelihood ratio (LR) obtained from data simulated with completely random dropout.

Results: The CCONTR method had more successful runs (79% vs 44%) and was 10% faster (100 runs) than the NM-TRAN method. The estimates of slope and parameter variability of the disease status were unbiased for both methods. The CCONTR method estimates of baseline hazard and informative dropout hazard were also unbiased but the NM-TRAN method estimates were significantly biased (+15% and -2% respectively). The root mean square error of all parameters was less than 20%. The null distribution of the LR obtained from random and informative dropout models fitted to completely random dropout data was similar to the chi-square distribution.

Conclusion: NONMEM can be used to estimate hazard function parameters for dropout models with acceptable bias and imprecision. The CCONTR method is preferable to NM-TRAN coding of -2LL for joint models. Model discrimination can be performed by assuming the likelihood ratio is approximately chi-square distributed.

Reference:

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P-81_ A New Model to Describe the Bradycardic Effects of If channel blockers in Healthy Volunteers

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poster*

Purpose: To develop a pharmacokinetic/pharmacodynamic model capable to describe simultaneously and semi mechanistically the time course of the heart rate response measured at rest (HR_{rest}) and at end of exercise (HR_{exe}) after administration of Cilobradine.

Methods: 96 healthy female and male volunteers, receiving once daily oral doses of Cilobradine at dose levels of 0.25, 0.5, 1, 2 and 5mg or placebo over a period of two weeks, were included in the analysis. Plasma samples and response measurements were taken extensively during the first and the last day of administration, as well as trough values in-between. A total of 1173 plasma concentration values (C), 3312 HR_{rest} and 1467 HR_{exe} measurements were used to build the PK-PD models. All the analyses were performed under the population approach using the FOCE method implemented in NONMEM V.

Results: Absorption process and disposition of Cilobradine in plasma were best described through a first order absorption and a three compartment body model respectively. HR_{rest} and HR_{exe} data were fitted separately with an EMAX model relating drug effects with the predicted effect site concentrations. The estimates of EC₅₀ and ke₀ were very similar for the two responses, 4.57 and 5.16 ng/mL and 0.009 and 0.0147 h⁻¹, respectively. The derived t_{1/2ke0} values predict that distribution equilibrium between plasma and biophase will be achieved after three weeks of continuous treatment, a very unlikely phenomena taking into account the site of action for this type of drugs. Probably such a delay is due to another mechanisms different from drug distribution. A standard indirect response model was used to describe regulation of heart rate. The increase in response after 3 min of exercise was modeled as an increase of θ magnitude in the zero order rate constant of synthesis (k_{syn}) for a period of 3 min. A slow adaptation process, governed with the k_{adapt} rate constant and including two transit compartments, served to relate drug effects with the inhibition in k_{syn}. The decrease in k_{adapt} as a function of C was found to be linear.

Conclusions: The model shows an example of how to deal with responses that are experimental and temporally altered during the study period.

P-82_ Prediction of drug-drug interactions and their associated variability in human populations: Application to erlotinib and its coadministration with ketoconazole and rifampicin

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Background: Drug-drug interactions (DDIs) mediated by cytochrome P450 enzymes are a potential cause of toxicity with co-medications. For this reason the quantitative prediction of DDIs in general as well as for the individual is of great importance. SimCYP^(r) is a commercially available computer-based tool developed for this purpose [1]. This software enables the prediction of the metabolic clearance of drugs (before and after administration of an inhibitor or inducer) in human populations using in vitro metabolism and inhibition data [2,3,4].

Objectives: The aim was to investigate the ability of SimCYP^(r) to predict clinical DDIs (i.e. AUC ratio of the substrate with and without the inhibitor/inducer) and their associated variability using erlotinib (TarcevaTM, invented by OSI Pharmaceuticals; co-developed by OSI Pharmaceuticals, Genentech and Roche).

Methods: A SimCYP^(r) model for erlotinib was developed using available in vitro data. The prediction of clearance for erlotinib and the influence of inhibition by ketoconazole and induction by rifampicin on its metabolism were assessed using the model. Simulations were performed using a virtual population (demographic characteristics: North-European Caucasians aged between 20 and 50), constituting 100 trials of 10 subjects. Simulated data were analysed and compared with clinical data. Sensitivity analyses were used to determine the impact of any parameter uncertainty on the simulated results.

Results/Conclusion: The population-predicted CL/F for erlotinib was similar to observed values (obs. CL/F: 5.2-15L/hr; pred. CL/F: 9L/hr). In agreement with clinical observations, SimCYP^(r) predicted a mild interaction with ketoconazole (obs. AUC ratio: 1.9, mean, 1.5-2.4, 90% CI; pred. AUC ratio: 2.0, median, 1.3-3.3, 90 percentile range) and a mild induction by rifampicin (obs. AUC ratio: 0.33, mean, 0.26-0.41, 90% CI; pred. AUC ratio: 0.40, median, 0.23-0.64, 90 percentile range). The sensitivity analyses indicated that certain parameters (e.g. in vitro inhibition constant) had a greater impact on the simulation than others (e.g. absorption rate constant). This work shows that SimCYP^(r) has the potential to be used successfully for the prediction of DDIs and could also be used to assist in the design of clinical trials (i.e. to power a DDI study).

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P-83_ The Efficiency of Mixed Effect Modelling to Detect Metabolism-Based Drug-Drug Interactions (mDDI)

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poster

Purpose. To assess, by simulation, factors that influence the detection of mDDIs in phase 2/3 clinical trials using population pharmacokinetics (POPPK).

Method. Steady state plasma concentrations of a hypothetical drug in the presence and absence of enzyme inhibitors, were generated from in vitro data using the Simcyp program. Population (Caucasian, 50% male, 20-50 y) size was varied from 80 - 2000. The compound was metabolized mainly by CYP3A4 with a contribution from CYP2D6. Concomitant medications (COMEDs) with different I_u/K_i ratios (I_u = population average unbound plasma concentration, K_i = inhibition constant)(0.006, 0.026, 0.38, 3.3, 11, 22 for CYP3A4; 0.06, 0.9, 6.75, 13.5 for CYP2D6) were evaluated. The frequency of COMED was varied from 1.25% - 10%. The extent of interaction was determined using NONMEM ($p > 0.001$ backward; $p > 0.01$ forward selection of covariate).

Results. No false negative ($I_u/K_i = 0.38$) or false positive ($I_u/K_i < 0.38$) interactions were detected using a population size of 2000. However, at $I_u/K_i = 0.38$ (e.g. fluconazole 50 mg/day) and COMED level of 2.5%, a statistically significant interaction could only be detected using > 480 subjects.

Conclusion. Simulations are recommended to define the size of study populations necessary to detect mDDIs with confidence using the POPPK approach.

P-84_ Modeling Discontinuation of Treatment in Non-Ignorable Situations

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Objectives: Clinical studies mostly generate incomplete data. The fraction of non-available data can range from small to substantial, and the reasons can be manifold: The data was not recorded, the data was lost on its way to the clinical database, or patients discontinued treatment. In all those cases there is no problem in analyzing the complete data only if the missingness is completely random.

However, if partial or missing data is dependent on other variables, that process must be modeled in order to correct for the bias that would otherwise result.

This poster outlines a recent study planning using modeling and simulation. In the anticipated scenario,

- 30 percent of patients enrolled are perceived to discontinue treatment before the end of the study
 - the probability of discontinuation depends on the well-being (or not) of a patient
- In other words, it was anticipated that a patient that does not respond well to treatment has a higher likelihood of discontinuing the treatment.

Methods: The model approach is a longitudinal mixed effects model with some model assumptions on the discontinuation process. Subjects are assumed to have a linear disease progression with different slopes for treatment groups. If a subject discontinues treatment, the subject will instantaneously switch from a treatment profile to a placebo profile. To enable building a placebo model, subjects discontinuing the drug will be asked to continue with the scheduled visits.

The anticipated study setup, conduct, and disease progression were simulated 1,000 times, and discontinuation was simulated with probabilities varying due to individual disease progression. The individual probabilities of discontinuation are based on a function of the random effects, the individual deviations from the population average. Subjects with better than population average disease progression were assigned lower chances of discontinuation, subjects with worse than population average disease progression were assigned higher probabilities of discontinuation. Discontinuation was simulated and the effect on the final parameter estimates were assessed.

The evaluations of the incomplete data as observed (simulated) are contrasted against the known true complete data evaluations using a mixed effects model and a standard per-protocol analysis based on complete patient records only (since drug discontinuation is regarded as protocol violation).

Results: In this particular setup we show that using a per protocol analysis results in an underestimation of the treatment effect of 50 percent with a corresponding loss in power.

Using the model-based approach, the primary parameter (difference of treatment to placebo) was estimated as 117 percent of the value as simulated (averaged over 1,000 simulations), whereas the per protocol estimate yielded an estimate of 49.6 percent of the simulated value. Powers (fractions of hypothesis rejections in the simulations) were estimated as 80 and 61 percent, respectively.

For further study parameters, the model-based approach is much closer to the simulated

values, whereas the per protocol analysis consistently underestimates by 50 percent. Interestingly, only a fraction of all model estimation runs converged, between 20 and 100 percent depending on the parameter. The accuracy (deviation of the model-based estimates from the original values) increases with the fraction of converged model runs (using SAS PROC NLMIXED). This result seems to suggest that whether or not a model estimation converges successfully might partially depend on the underlying model parameter values.

Conclusions: If a study yields more than just a few incomplete data records, it must be investigated if the reason for missingness is related to the absence or presence of a treatment effect (or other circumstances). Presence of non-ignorable missingness leads to modeling the process of discontinuation of treatment.

Using a per protocol analysis (complete cases only) or imputation by LOCF (Last Observation Carried Forward) can result in severely wrong results, as shown in this particular study setup where the treatment effect would be underestimated by about 50 percent.

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P-85_ Estimation of population pharmacokinetic parameters of saquinavir in HIV patients and covariate analysis with MONOLIX

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Context: We developed the software MONOLIX which implements an algorithm for maximum likelihood estimation in nonlinear mixed effects models without linearization. The algorithm combined the SAEM (stochastic approximation version of EM) algorithm [1], with a Markov Chain Monte Carlo procedure [2]. This Matlab software is available at <http://www.math.u-psud.fr/~lavielle/monolix/logiciels>.

Objectives: Our objectives were 1) to apply and illustrate MONOLIX on a real data set; 2) to estimate the population pharmacokinetic parameter of saquinavir in HIV patients; 3) to test the effects of several covariates on saquinavir pharmacokinetics.

Methods: Concentration data were obtained after single administration of 600 mg of saquinavir alone in 100 HIV patients who never received protease inhibitor before [3]. In order to evaluate the influence of several covariates, three groups of patient were enrolled in this prospective trial: asymptomatic patients (N = 30), AIDS symptomatic subjects without diarrhea (N = 37) or with diarrhea (N = 33). Each patient had three samples collected in 3 periods: 0 to 1.5 h, 2 to 4 h, and 5 to 12 h. There was a total of 240 concentrations, i.e. it was a rather sparse design. A one compartment model with first order absorption after a time-lag was used, with exponential random effects for each PK parameter (V/F, CL/F, k_a and Tlag). We defined the best error model and then construct the covariate model using a systematic ascending procedure based on BIC. Eleven covariates were tested: gender, age, BMI, creatinine clearance, diarrhea, mean weight of stools per 24 h, plasma albumine, xylose, lactulose/mannitol ratio, alkaline phosphate level, CD4 count.

Results: The best error model was an homoscedastic error model. Although several covariates were significantly related to CL/F in the univariate LRT or Wald tests (BMI, diarrhea, CD4 count, creatinine clearance, xylose), the best model from BIC had only a BMI effect on CL/F and no further covariate effect on none of the parameters. The final population parameters were CL/F = 1210 L/h (SE=169), V = 738 L (SE= 192), k_a = 0.55 h⁻¹ (SE =0.04) and Tlag= 1.12 h (SE = 0.10). The variances (and their SE) of all the random effects were estimated and were 1.34 (0.26) for CL/F, 2.78 (0.68) for V/F, 0.20 (0.05) for k_a and 0.48 (0.11) for Tlag. The variance of the residual error was 85.9 (ng/ml)² (SE=11.8). CL/F increases with BMI (fixed effects of 0.11 with SE of 0.03) which confirms the enhancement of saquinavir exposure in patients with low BMI [3].

Conclusions: MONOLIX is a fast and efficient algorithm as illustrated in this real example with a sparse design and large inter-patient variability. We will show, on the saquinavir example, the estimation capabilities of this software from several initial parameters values and display the graphs produced.

Acknowledgements: We thank Dr Trout and Pr Bergmann, Lariboisière Hospital, Paris, for the access to the data of the PK trial on saquinavir.

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P-86 _ Assessment of the potency of a metabolite relative to the parent compound using a population PK/PD model for the inhibition of a neurotransmitter re-uptake transporter in mice

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Objectives & Background: Drug X is a new CNS active compound which is currently under clinical development. X inhibits the re-uptake transporter of the neurotransmitter W and is mainly metabolised to Y, which is the only metabolite found in human plasma. Y shows significant in vitro activity, but has never been administered to any species, so its pharmacokinetic (PK) properties and also the in vivo activity are unknown. In order to investigate the in vivo contribution of the metabolite to the observed pharmacodynamic (PD) effect an animal study was performed to determine the potency and effect-time course of drug X and metabolite Y.

The objective of the data analysis was to develop a population PK/PD model in order to assess the potency of metabolite Y relative to parent drug X.

Methods: Single doses of drug X or its metabolite Y were administered intravenously (0.3-10 mg/kg) or orally (1-20 mg/kg) to 132 female NMRI mice, 64 female NMRI mice were treated with placebo and served as control group. Samples for PK (X and Y) and PD were taken at 0.75, 1.5, 3, 16 and 17.5 h after administration. The PD effect was determined by the competitive inhibition of the re-uptake transporter of the neurotransmitter W by substance Z in mouse brain after administration of X or Y. Like X and Y, substance Z inhibits the re-uptake transporter W and was administered intravenously in a dose of 2.0 μ Ci as a tritium labelled molecule 45 minutes before the mice were decapitated. Selected areas of the mice brains were dissected and the amount of radioactivity per mg tissue was determined. Thus, the inhibition of the in vivo binding of drug X and metabolite Y by substance Z was determined. Overall, 197 plasma concentrations (65 drug X, 132 metabolite Y) and 132 PD measurements, from 132 mice, were available for developing the PK/PD model. The analyses were performed using the FO estimation method supplied by NONMEM version V, combined with graphical visualisation methods. Model development was performed in a sequential way, starting with a PK model for the metabolite after intravenous administration. Next, PK data from other administrations were added and the respective PK/PD models were built. The final model was to describe the complete PK/PD data of the 132 mice treated with drug X or Y.

Results: Plasma concentration-time profiles of drug X and metabolite Y were best described by one compartment models with saturable Michaelis-Menten (MM) elimination kinetics. Absorption of drug X after oral administration was best described by a first-order process combined with a MM process accounting for the first-pass metabolism. Absorption of Y could be modelled using a first-order absorption process. Metabolic formation of Y out of X was accounted for by a MM metabolism step. Volumes of distribution were found to be large with 17.7 L/kg (X) and 13.6 L/kg (Y) suggesting an extensive distribution into tissues. Within the linear PK range of X and Y, the parameters clearance and half-life could be derived from the estimated MM parameters. Clearances were found to be high with 5.3 L/h/kg (X) and 1.9 L/h/kg (Y)

which resulted in half-lives of 2.3 h (X) and 4.9 h (Y), respectively.

The PD effect was best described by an extended Emax model which accounted for the competitive interaction of drug X and its metabolite Y. It was assumed that the efficacy (Emax) was equal for both compounds and that the maximum effect achievable by X and Y was a 100% inhibition of the neurotransmitter W re-uptake transporter. To account for the time delay in the PD, effect compartments were introduced in the model. KEO values were estimated to be 0.555 1/h for drug X and 0.878 1/h for the metabolite Y. EC50 values estimates were 72.3 nM for drug X and 363.1 nM for the metabolite Y.

Conclusion: A PK/PD model was successfully developed describing the plasma concentration-time profiles of the parent compound X, its metabolite Y and the inhibition of the neurotransmitter W re-uptake transporter simultaneously.

Pharmacokinetics of drug X and its metabolite Y exhibited non-linearity which had never been noticed before in any species treated. Simulations performed with parameters obtained from this data analysis showed that MM kinetics have only an impact on high concentrations caused by high doses administered in this trial. However, non-linearity in human PK has not been observed so far and is not expected to occur within the effective plasma concentration range.

Pharmacodynamic investigations revealed a 4.1 - 5.0 fold higher in vivo potency of drug X in comparison to metabolite Y regarding the inhibition of the neurotransmitter W re-uptake transporter in mice. Comparison of EC50 values of iv data and iv plus po data indicated that no additional active metabolites were built during the first-pass metabolism of drug X. Since under steady state conditions in humans plasma concentrations of the metabolite Y were approximately 3 fold lower than that of the parent compound X, and since the in vivo potency of Y is 5 fold lower the contribution of the active metabolite Y to the overall efficacy might be low.

P-87_ Exposure-Response Analysis Using Time to Event Data: An Example Using Sleep Onset.

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poster

Background/Aims: Exposure-response analysis of different types of clinical data (e.g., continuous, categorical, count) requires different modeling approaches. The time required to fall asleep is used as the primary endpoint in assessing sleep onset in insomnia patients. The aim of the analysis was to develop a dose-response model to describe latency to sleep (LS).

Methods: Data from 6 studies were combined (773 patients) and analyzed using a survival model in NONMEM. The Weibull distribution is used to describe the time to an event, such as LS and is described by 2 parameters: f , the median time to event, and g . When $g=1$, <1 or >1 , the probability of the event remain constant, decreases or increases, respectively, over time. In addition, an Emax model was used to describe drug effect. As a posterior predictive check, LS data were simulated (N=100 trials) based on final parameter estimates and compared to observed data.

Results: The shape parameter g was 1.33 indicating an increased probability with time: the longer the patient is awake, the more likely it is that he/she will eventually fall asleep. Median time to fall asleep (f) at baseline was dependent on study population (patients with difficulty falling asleep [$f=34.0$ min] vs. difficulty maintaining sleep [$f=21.5$ min]). Placebo response averaged 12%, while Emax was 72% and was greater in elderly patients. Simulated and observed LS by dose were in good agreement.

Conclusions: The Weibull distribution was successfully implemented to describe time to event data (such as LS) in NONMEM.

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P-88_ A Semi-Mechanistic Pharmacokinetic-Pharmacodynamic Model for Antibiotics

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poster

Objectives: In vitro time-kill studies are commonly used in the assessment of efficacy of antimicrobial agents. The aim of the present study was to develop a general semi-mechanistic Pharmacokinetic-Pharmacodynamic model that describes the killing of bacteria using data from time-kill experiments.

Methods: Time-kill curves were performed in which cultures of *Streptococcus Pyogenes* (M12 NCTC P1800) were exposed to constant concentrations of five different antibiotics; benzylpenicillin, cefuroxime, erythromycin, moxifloxacin, and vancomycin. The concentrations ranged from 0 to 64 times the minimum inhibitory concentration (MIC) and samples for viable count were taken at time points 0, 1, 2, 4, 6, 9, 12, 15, 18 and 24 h after start of experiments. In total 135 experiments were performed resulting in 2526 samples for viable counts. The data was modeled using NONMEM (version VI beta) using first-order conditional estimation method. All data was modeled simultaneously and the parameters in the model were specified as either bacterial or drug specific. Model performance was assessed by evaluation of diagnostic plots and precision of parameter estimates.

Results: A two compartment model was developed where the total bacterial population was divided into two subpopulations, one growing drug sensitive population (S) and one resting insensitive population (R). The total number of bacteria triggers the transfer rate from S to R. This model described well that bacteria exposed to low or none concentration of antibiotics will grow exponentially until reaching a maximum level of bacteria and then a stationary phase is reached. The tolerance development often seen in bacterial time-kill studies was also explained using the transfer between the different compartments.

Conclusion: The developed PK-PD model could describe both the early rapid killing and the late tolerance development seen after exposure of antibiotic to bacteria in an in vitro system. The model allows an efficient summarization of time-kill data and could be of use for prediction of better dosing strategies of antibiotics as well as for synergy studies of poly antibiotic treatment.

P-89_ Indirect-response model for the analysis of concentration-effect relationships in clinical trials where response variables are scores

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poster

Effectiveness of many drugs can only be assessed in terms of scores quantifying a clinical status of patients (symptoms' intensity). Scores can often be considered as continuous variables, however, they are constrained and never exceed lower and upper limits that may create problems for data modeling.

Recently, a general indirect response model for clinical efficacy data has been proposed [1] that expresses the rate of patient status change as a balance between the rate of deterioration (vD) and amelioration (vA):

$$dR/dt = vD - vA \quad (1)$$

R is a score of interest, and increased R means worsening. Initial conditions are $R(0) = R_0$ ("baseline"). The drug effect is aimed to either vD (slowing down) or vA (accelerating). The model version presented here assumes that vA is proportional to the current value of R , and the rate constant K indicates how fast the system stabilizes after perturbation. vD is a (constant) rate that may be affected by a drug:

$$dR/dt = E*vD - K*R \quad (2)$$

where E is a function of drug concentration. $E=1$ means no drug effect; $E<1$ means improvement. Since R is constrained dR/dt should tend to 0 at $t \rightarrow \text{Inf}$. In the absence of drug the ultimate R value is due to DP : $R \rightarrow RP$. From Eq 2 it follows that $vD = K*RP$, and Eq 2 becomes:

$$dR/dt = E*K*RP - K*R = K*(E*RP - R) \quad (3)$$

Basic parameters of model 3 are K , R_0 and RP . The latter two have to be constrained to assure that model predictions remain within the natural range of scores. This can be achieved via logit transformation.

As an example we present the concentration-response analysis of efficacy data collected in two Phase 3 trials conducted in different centers. Study designs were identical: patients were randomized into placebo and active treatment groups. Thus, DP and placebo effect could not be differentiated, and RP corresponded to both. During the first 4 weeks the daily dose was 8 mg, and then was increased up to 16 or 24 mg. Clinical status was assessed at randomization and after 4, 12 and 22 weeks of treatment. Plasma samples were collected at each visit, and drug concentration was assayed. The population PK analysis provided individual predictions of steady-state plasma concentrations (C_{ss}) that were used in E . An E_{max} model ($E=1-E_{max}*C_{ss}/(C_{50}+C_{ss})$) was better than a linear one ($P<0.05$). No difference in terms of drug efficacy was found between trials ($E_{max}=0.3$ and $C_{50}=80$ ng/mL), however, R_0 was lower in one of the trials, and this accounted for an apparent worse clinical outcome of this trial according to the standard endpoint analysis.

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P-90_ The Lasso - A Novel Method for Predictive-Covariate Modelling of Population Pharmacokinetics/Pharmacodynamics

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poster

Objectives: To implement a new method (the LASSO) for covariate selection within NONMEM and to compare this method to the commonly used stepwise-covariate modelling (SCM).

Introduction and Theory: Identification and quantification of covariate relations is an important part of population pharmacokinetic/pharmacodynamic (pop PK/PD) modelling. The covariate model is often built with stepwise-covariate-selection procedures such as SCM (1). However, the problems of using stepwise regression and other subset selection methods have been debated for decades and in the area of pop PK/PD it has recently been shown that these selection methods often are inappropriate for small- to moderately-sized datasets (< 100 individuals), where the covariate model may even reduce the predictive performance (2).

One method for obtaining a more predictive model in linear regression is "Ridge regression". This method mainly shrinks the covariate coefficients and does not provide the big picture of which covariates are important by selecting among the many potential covariate relations one may wish to investigate. The LASSO is a similar and increasingly popular method which performs both selection and shrinkage of the covariate coefficients simultaneously.(3)

The lasso-estimate of the covariate model is the maximum-likelihood estimate subject to the restriction: absolute-sum of the covariate coefficients $\leq t$. The t-value will determine the amount of shrinkage and the model size. An optimal t-value can be estimated using cross validation.

Method: A method for performing the LASSO in NONMEM was implemented in Perl using the Perl-speaks-NONMEM-software package (4,5). The implemented method was applied to a real PK dataset (6) investigating 20 parameter-covariate relations and the procedure was compared to the SCM (forward selection at $p < 0.05$). The comparison was made on run times, which covariates were selected and the magnitude of the covariate coefficients.

Results: The LASSO method required only half the run time for the SCM. The LASSO retained the two most important covariates selected by the SCM. As expected the retained covariate coefficients were shrunken when using the LASSO method.

Conclusion: In this example the LASSO selected the two most important covariates, as identified by the SCM. The LASSO required only half the computer-run time and shrank the two selected coefficients compared to the SCM. We believe this shrinkage is necessary to improve the predictive performance of the model considering that 20 covariate relations have been investigated in a dataset with only 64 individuals. However, an evaluation on external data must be performed to assess predictive performance.

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P-91_ Generalisation of the SAEM algorithm to nonlinear mixed effects model defined by differential equations : application to HIV viral dynamic models

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poster

Objectives: We consider parametric mixed models whose regression functions are solution of an ordinary differential equation (ODE). Maximum likelihood estimation in nonlinear mixed effects models (NLMEM) cannot be directly performed as the likelihood has no close form. Kuhn and Lavielle [1] proposed the SAEM algorithm, implemented in the Matlab function MONOLIX. We adapt the SAEM algorithm to models defined by ODE. We illustrate the method on a simulated pharmacokinetic (PK) dataset, with comparison to NONMEM, and on a real dataset of HIV dynamics.

Methods: Classical ODE numerical solving methods such as Runge-Kutta can be included in SAEM. We propose an original Local Linearisation (LL) scheme to solve the ODE taking advantage of the specific structure of the MCMC algorithm included in SAEM. The LL scheme reduces significantly the computational time. We prove the convergence of this algorithm and bound the error deriving from the numerical integration of the ODE.

We simulate one dataset of 20 patients with a one-compartment PK model with first order absorption and saturable Michaelis-Menten elimination, mimicking an anti-cancerous drug [2]. We compare the estimates obtained by SAEM and NONMEM. SAEM converges and provides accurate estimates, whereas NONMEM fails to converge

Applications: We analyse simultaneously HIV viral load decrease and CD4 increase after treatment in HIV patients, using the model proposed by Perelson et al. [3]. We consider data of 32 patients until week 16 of the COPHAR2-ANRS 111 trial. We obtain a NLMEM defined by ODE, including 7 population parameters, 7 random effects, and two residual errors. The SAEM algorithm converges and provides accurate estimates of the 16 parameters.

Conclusions: The extension of SAEM to ODE model using the LL scheme is a powerful tool to provide accurate estimation on NLMEM.

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P-92_ Prediction of Clearance in Children Using a Combined Physiology-based and Enzyme Ontogeny Approach

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poster

Objective: Clearance is a critical pharmacokinetic concept for scaling dosage, understanding the risks of drug-drug interactions and environmental risk assessment in children. Clearance in children is dependent upon the physiological maturity and enzymatic ontogeny of the responsible elimination processes. This study aimed to predict clearance through the scaling of various individual elimination pathways in the age range from premature neonates to sub-adults.

Methods: Accurate clearance scaling to children requires prior knowledge of adult clearance and the age-dependence of physiological and enzymatic development. Using experimental adult and children clearance values for eight single elimination pathway compounds plus in vitro data, a model for the ontogeny of renal clearance (glomerular filtration and tubular secretion), CYP3A4, CYP2E1, CYP1A2, UGT2B7, UGT1A6, sulfonation and biliary clearance was developed. Six compounds that demonstrate multiple pathways of elimination were used to test the ontogeny models. Each pathway was individually scaled to the desired age inclusive of protein binding prediction and summed to generate a total plasma clearance.

Results: Although interindividual variability was higher in studies using children in comparison to adult data, the age-dependence of clearance of all processes followed a similar pattern. Clearance in premature neonates was usually much lower than the adult clearance. With proceeding maturation, weight normalized clearance in children exceeded that in adults and gradually reached adult levels in the early 20's. There was excellent correlation between experimental and predicted clearances for the training ($R^2 = 0.957$) and test sets ($Q^2 = 0.854$). Clearance in premature neonates could also be well predicted (training $R^2 = 0.921$; test $Q^2 = 0.810$).

Conclusion: Using this information, the scaling of clearance to children would be a first step towards the development of dosing regimes for clinical trials in children and for examining the developmental extent of drug-drug interactions in paediatric patients.

P-93_ Predicting pharmacokinetics in children using PK-Sim(r)

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poster

Objective: Approaches that are able to predict potential differences in the pharmacokinetic behavior of a compound in children compared to adults are highly desirable for dosage adjustment, therapeutic response analysis and risk assessment. Physiology-based pharmacokinetic (PBPK) modeling allows for the simulation of concentration-time profiles in plasma and other organs based on a combination of physiological parameters such as organ volumes and blood flow rates with substance specific parameters including organ/plasma-partition coefficients, permeability coefficients and elimination rate constants. PK-Sim^(r) is a software tool designed to account for age dependent physiology from birth to sub-adults, which are critical elements for PK prediction in children (1). The objective of this study was to determine the appropriateness of PK-Sim^(r) to correctly predict plasma concentration-time curves and PK parameters (volume of distribution, elimination half-lives) of model compounds such as morphine and levofloxacin.

Methods: Experimental plasma concentration-time data and PK parameter information following intravenous administration was gathered from the literature for various age groups. Predictions were generated in PK-Sim^(r) for each literature study using the mean age and weight of the subjects, as reported. Additional input information comprised of physio-chemical properties, clearance, administration regime and protein binding prediction (2).

Results: Trends associated with the differing age groups as well as experimental plasma concentration-time curves were extremely well represented by PK-Sim^(r) predictions. Preterm and term neonates had greater plasma concentrations in comparison to children 6 months of age and older. Children greater than 6 months had lower plasma concentrations in comparison to adults. This is a result of both the age-dependence of clearance and disposition.

Conclusion: PK-Sim^(r) is very well suited for the prediction of plasma concentration-time data and PK parameters in children from birth to sub-adults. This approach will not only aid in clinical trial development but has the potential to reduce the number of required subjects.

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P-94 _ Counting events: population approaches using NONMEM

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poster

Objectives: In drug development, there are examples in which pharmacotoxicological or clinical endpoints are expressed in terms of counts (e.g., number of epileptic, vomiting or diarrhoea episodes, neuronal firing, etc.). These events are typically described as arrivals in a Poisson process, the intensity of which can be modulated, depending on the cases, by pharmacological actions, disease progression or variations in external stimuli. Some examples of such analyses (1-3) made use of homogeneous Poisson processes, with constant intensity either in the whole observation interval or in a time interval. Whilst time-invariant intensity is correct in most cases, this approach cannot be easily applied to cases where large and rapid variations of intensity are expected (e.g., those obtained following a single, rapid, pharmacokinetic impulse). In these conditions an inhomogeneous Poisson process may be considered. In this study we compared the outcomes obtained using the homogeneous and inhomogeneous Poisson approaches.

Methods: We interpreted our count data as arrivals of a non-homogeneous Poisson process with a non-linear intensity function whose parameters were estimated by NONMEM. Firstly we used as objective function $-2 \log$ -likelihood of the Poisson density function, assuming a homogeneous Poisson process within a defined time interval. Secondly we used $-2 \log$ -likelihood of an inhomogeneous Poisson process where the intensity varies instantaneously.

Results: Provided that the time interval is appropriately chosen, the intensity profile obtained with the first approach is consistent with the more accurate estimate of the second approach. This approach can also be useful for optimizing the experimental design with the appropriate choice of the time interval that allows the application of the homogeneous approach.

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P-95_ Cluster analysis : an alternative method for covariate selection in population pharmacokinetics modeling

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poster

Objectives: A high covariate number could become problematic when one needs to determine the most significant variable combination, in order to reduce the inter-individual variability (IIV). Alternatively to multiple introductions of single variables, we propose a single introduction of one multivariate variable: hierarchical cluster analysis (HCA) is a stratification method combining the initial single covariates to build a multivariate categorical covariate.

Methods: HCA stratifies the population into homogeneous and non-overlapping groups (clusters) according to similarities from the set of covariates. This uses a distance measure and a linkage algorithm. HCA approach is illustrated by a database of plasmatic cortisol in 82 patients after intravenous bolus administration of synacthen. Using NONMEM, a basic infusion model was initially achieved, and then a classical covariate selection was applied to improve IIV. Alternatively, a categorical covariate was built by HCA from the initial database containing 6 continuous covariates. Such categorization was carried out using Euclidean distance and complete-linkage algorithm. The new covariate was then included into a population PK model, and the PK results were compared to those of the basic and classical covariate models.

Results: With a classical covariate selection, the best fit was between the elimination rate constant k and the body mass index (BMI), which improved IIV of k compared with the basic model. HCA stratified the 82 patients into 5 dissimilar clusters that differed by increasing BMI, obesity duration, and waist-hip ratio. The dispersion of k according to the 5 clusters showed 3 distinct variation ranges a priori, which corresponded a posteriori (after NONMEM modeling) to 3 sub-populations of k . After grouping the overlapped clusters for k , we obtained three final clusters representing non obese, intermediate, and extreme obese sub-populations. The PK model based on 3 clusters was better than the basic model, similar to the classical covariate model, but had a stronger interpretability: it showed that the stimulation and elimination of cortisol were higher in the extreme obese followed by intermediate then non obese subjects.

Conclusions: HCA is proposed as an alternative approach for covariate selection in population pharmacokinetics, particularly when the initial covariates are numerous.

P-96 _ A Novel Method for Simulation of Correlated Continuous and Categorical Variables Using A Single Multivariate Distribution

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poster

Introduction: Covariate distribution modeling (CDM) is used to generate virtual patients (covariate vectors), based on data from an existing patient population. Covariates may be continuous (weight) or categorical (sex); mixed covariate types present a challenge when creating a CDM.

In the standard (Discrete) method (DM), the population is subdivided by each unique combination of categorical covariates, each with a separate multivariate normal distribution (MVND) for the continuous covariates. However, when there are many categories, some subgroups have insufficient data to build a representative model. Therefore, a novel (Continuous) method (CM) was conceived in which complete covariate vectors, including both continuous and categorical covariates, could be sampled from a single MVND.

Methods: A MVND is comprised of a mean vector and a variance-covariance matrix (VCVM). In the DM, categorical covariates are sampled from their individual distributions; continuous covariates are then generated from the proper subgroup's MVND. In the CM, all covariates are treated as continuous; the resultant single MVND is used to generate complete patient covariate vectors. Since categorical covariates (e.g., X) will have continuous values, cutoff values to assign the categorical levels are defined as the inverse of the LN cumulative distribution with mean(lnX), sd(lnX), and cumulative probability r. The CM and DM were applied to real and simulated data sets to compare their abilities to generate matching virtual patient distributions.

Results: For the real data, both methods accurately generated the summary statistics (continuous) and proportions (categorical) of the covariates, with high precision and negligible bias. The DM results, however, were based on incomplete data. Because there were $<N+1$ subjects in 1/3 of the subgroups (where N is the number of covariates in the MVND), the VCVMs for these subgroups were singular, and the continuous covariates could not be generated. For the simulated data sets, the CM performed as well as the DM, except when the subgroups had markedly different continuous covariate means, for which we are aware of few clinically relevant examples.

Conclusions: Compared to the DM, the CM's benefits result from analyzing the whole population instead of subsets. Including a large amount of data in the creation of the MVND enhances its stability and, as a consequence, the reliability of the generated covariate combinations. In addition, by allowing all covariates to be described by a single MVND, the number of analyses that must be performed is reduced, increasing efficiency. The CM appears to generate unbiased, precise covariates for the purposes of simulating covariate vectors in a clinical trial simulation.

P-97_ Non-Adherence to Prescribed Therapy is a Major Obstacle for Population PK/PD Studies

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poster

Background: The extent of non-adherence to prescribed therapy in ambulatory patients is too often overlooked and ignored in the analysis of clinical trials. From clinical studies whose sponsors have concurred with entering their anonymized data into a common archive, we have recently finished the assembly and begun the analysis of data on 15214 ambulatory patients whose dosing histories during studies of varying lengths have been electronically compiled.

Methods: Electronic Medication Event Monitors were used to record the times and dates of package entry during the course of 87 drug studies performed between 1990 and 2004. Chapter headings in the British National Formulary served to categorize fields of treatment.

Results: Study durations ranged from 30 to 1400 days. Patterns of deviation from prescribed dosing regimens varied widely, but were almost entirely markedly skewed toward longer dosing intervals than prescribed, i.e. under-dosing, in every field of treatment.

On average, only during 60% of the study days was the prescribed dosing regimen executed correctly. In studies continuing beyond 6 [12] months, almost 30% [40%] of trial participants had stopped taking the trial medication, despite a prescription that called for continued taking of the drug. Drug holidays (3 or more consecutive days without drug intake) occur at least once a year in 50% of patients. Holidays occur monthly in 2% of the patients, and quarterly in an additional 10% of patients. With QD BID regimens, 20% [40%] of doses were not taken on schedule.

Conclusions: Underdosing, drug holidays, and early cessation of dosing are common features of clinical trials, and likely are frequent sources of low response and high variability in response to the protocol-specified dosing regimen. These dosing errors are usually grossly underestimated by counting returned, untaken dosage forms or by asking patients to fill out diaries or questionnaires. In the presence of non-adherence, missing or biased information on the dosage schedule leads to biased PK-PD analysis [1,2] and more unfortunately it forces one to discard up to 35 % of collected PK data [3]. The above findings highlight the needs for reliable assessment of dosing histories in clinical trials.

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P-98_ The influence of an increase in plasma protein binding on the pharmacokinetics and pharmacodynamics of S(-)-Propranolol

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poster

Objectives: Protein binding can have a major impact on a drug's pharmacokinetics (PK) and pharmacodynamics (PD). At present the theoretical basis of the influence of plasma protein binding on PK is well-established¹. The role of plasma-protein binding on pharmacodynamics however has so far not been established in a systematic manner. The objective of this research is to determine the influence of alterations in plasma protein binding on the PD *in silico* and corroborate the findings *in vivo*.

Methods: In order to determine the influence of the affinity of the drug for both protein and receptor on *in vivo* drug effects a sensitivity analysis in berkeley madonna was performed, on the basis of a mechanism-based pharmacodynamic receptor interaction model.

The PK-PD of S(-)-Propranolol was investigated under varying plasma protein levels in rats. Heart rate under isoprenaline-induced tachycardia was used as a biomarker for receptor occupancy.

Results: Simulations show that in case of high receptor affinity protein binding has minimal effect on the target occupancy. For S(-)-propranolol the model showed that changes in plasma protein levels result in a slight rightward shift of the concentration-effect curve. This indicates that the pharmacodynamics are largely non-restrictive. All pharmacokinetic profiles were described with a 3-compartment model using alpha-1-acid glycoprotein levels as a covariate on V2. The population analysis of the pharmacodynamic data is still in progress of the pharmacodynamic data is still in progress.

Conclusion: Simulations show that the role of plasma protein binding in *in vivo* pharmacodynamics can be identified using a mechanism-based PD model. For drugs with a high receptor affinity protein binding can be non-restrictive for the pharmacodynamics.

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P-99_ Predicting recovery progression in acute stroke using the Barthel Index

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poster

Objectives: This study was designed to refine analytical techniques for describing and predicting disease progression in acute stroke, by modelling scores measured on the Barthel Index, a categorical scale for assessing functional independence in recovering stroke patients, while addressing the statistical problem of dropout.

Methods: Scores assessed on four occasions over a 120-day period in 775 acute stroke patients were used to model the time course of recovery using NONMEM. Participating patients were recruited during the control arm of a double-blind, multinational, multicenter, placebo-controlled investigation of the efficacy of a novel acute stroke compound. At each measurement occasion, four discrete events were possible: attainment of a maximum score on the scale ('healing'), improvement, decline, or dropout (the premature exit of a participant in the study). Each of these possible events had a probability and a score change magnitude associated with it. Scores were transformed - to constrain the predictions to the scale - and used to model the system. Time-related variables, including previous score magnitude and time elapsed since the previous observation, were considered as predictors, as well as physiological and demographic covariates such as age.

Results: To accommodate the non-monotonic nature of these transitions, it was necessary to develop a strategy that considered both the longitudinal, continuous aspects and the probabilistic characteristics of the data simultaneously. A basic framework incorporating both of these features was developed, and used to model the trajectory of disease progression using the scale scores. The final model's predictive and descriptive abilities were good, and included covariate terms for previous score magnitude, time elapsed since previous observation, and age.

Conclusions: The model has a wide range of potential applications, including longitudinal analysis of stroke scale data, clinical trial simulation, and prognostic forecasting. This modelling approach is likely to be adaptable to other clinical assessment scales, such as those used in psychiatry and multiple sclerosis. Its use has great promise in reducing sample sizes and costs in clinical trials of drugs for the treatment of acute stroke, and thereby increasing the viability of research in this critical area.

P-100_ Modelling time varying kinetics using time dependent feedback control on clearance

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poster

Objectives: A population pharmacokinetic model for a new compound under development in psychiatry was built based on data from three Phase I studies. The compound exhibited time dependence pharmacokinetics showing less than expected accumulation at steady state. The objective of the analysis was to characterize the time dependency in the pharmacokinetics of the compound.

Methods: Plasma concentration profiles from 71 healthy volunteers were included in the analysis. Subjects were dose for were dosed for 28 days and plasma concentration time profiles were obtained on days 1, 14 and 28. Data from four different dose levels were available. The analysis was conducted using NONMEM. A mechanistic model implementing a time dependent feedback control on clearance was developed.

Results: A two compartment model in which clearance was assumed to be affected by the amount of enzyme in a hypothetical compartment was used to characterize the time dependency. The change of enzyme over time was characterized by a turnover process in which the compound was able to inhibit the elimination of the enzyme.

Conclusion: The proposed model was able to successfully capture the time dependence in the pharmacokinetics of the compound. The model will serve as a based model in the population PK analysis of the Phase II trials.

P-101_ Use population approach to characterize PK time-course with erratic absorption

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poster

Objectives: Characterization of population pharmacokinetics of a new CNS compound explored in neurological and psychiatric disorder accounting for intra and inter-subjects variability from a single ascending dose study.

Methods: Twenty subjects received a single dose from 10 to 250 mg. Each subject received ascending doses up to four different occasions. High intra-subjects variability (40-60%) mainly due to PH-dependent absorption was observed in the majority of subjects. Concentration-time data were analyzed using nonlinear mixed-effect modeling (NONMEM) assuming a variable rate and extent of absorption from occasion-to-occasion.

Results: Initially, a two compartmental model with first order absorption accounting only for inter-individual variability (IIV) has been used. Then, the same structural model including also inter-occasions variability (IOV) in both k_a (rate of absorption) and extent of absorption has been developed. Different models including IOV on absorption rate and/or extent of absorption have been tested. The model selection has been done using diagnostic plots and statistical criteria (log-likelihood and posterior predictive check). The comparison between all the different models led to select the one accounting for IOV in both rate and extent of absorption. Moreover, the highest source of variability has been identified in the inter-occasion variability for the extent of absorption suggesting the critical role of relative bioavailability for the future development of this compound.

Conclusions: An appropriate population PK model was successfully developed to characterize plasma concentration-time data of the drug after oral administration. Based on the results, the influence of the erratic absorption profiles on the PK after repeat dose has been predicted using a simulation approach assuming time independent behaviour.

P-102_ Modelling a spontaneously reported side-effect by use of a Markov mixed-effects model

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poster

Objectives: To present a method for analyzing side effect data where change in severity of the side effect is spontaneously reported during the experiment.

Methods: A clinical study in 12 healthy volunteers aimed to investigate the concentration-response characteristics of a CNS-specific side effect was conducted. After an open session where the subjects experienced the side effect and where the individual pharmacokinetic parameters were evaluated they were randomized to a sequence of three different infusion rates of the drug in a double-blinded crossover way. The infusion rates were individualized to achieve the same target concentration in all subjects and different drug input rates were selected to mimic absorption profiles from different formulations. The occurrence of the specific side effect and any subsequent change in severity was self-reported by the subjects. Severity was recorded as 0 = no side effect, 1 = mild side effect and 2 = moderate or severe side effect.

Results: The pharmacokinetics was described with a two-compartment model and the side effect data were analyzed using a transition model with Markov elements. The observed numbers of transitions between scores were from 0 to 1: 24, from 0 to 2: 11, from 1 to 2: 23, from 2 to 1: 1, from 2 to 0: 32 and from 1 to 0: 2. The side-effect model consisted of an effect-compartment model with a tolerance compartment. The proportional odds model as previously implemented for ordered categorical pharmacodynamic data [1, 2, 3] assumes that observations are independent under the model. For frequently measured categorical type data, there is a clear correlation between neighbouring observations that a standard proportional odds model could not predict. For such situations, transition models including Markov elements have been used [4, 5]. Such models, usually implemented with one model for each transition, were not considered appropriate, as the data set was not sufficiently informative-rich to allow appropriate estimation of all resulting parameters and the graded nature of the scores not naturally recognized. A different approach by using a transition model but also recognising the ordered nature of the data in the parameterisation of the model was therefore applied. This model estimates the probabilities of a having a certain side effect score conditioned on the preceding observation. The model is a hybrid between the proportional odds model and the transition model and it can therefore also be viewed as a proportional odds model where the probabilities are dependent on the preceding stage through a first-order Markov element. The predictive performance of the model was investigated by a posterior predictive check (PPC), where 100 datasets were simulated from the final model. Average number of the different transitions from the PPC was from 0 to 1: 26, from 0 to 2: 11, from 1 to 2: 25, from 2 to 1: 1, from 2 to 0: 35 and from 1 to 0: 1.

Conclusions: This approach of incorporating Markov elements in an analysis of spontaneously reported categorical side-effect data could adequately predict the time course of the observed data and could be considered in analyses of categorical data where dependence between observations is an issue.

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P-103_ Agonist-antagonist interaction models with slope factor: implications of an alternative derivation

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poster

Objectives: The method developed by Schild [1] to determine the equilibrium dissociation constant of a competitive antagonist (K_B) has been a cornerstone of quantitative pharmacological research. On the basis of this method, Waud [5], Leff and Dougal [4] proposed a model to describe the interaction of an agonist and a competitive antagonist in terms of an sigmoidal E_{max} model and antagonist potency and Schild slope factor (b). A key feature of this model and the Schild equation is that they are 'null methods' and provide antagonist potency estimates independent of the slope of the E_{max} model (n_H). Holford and Sheiner [3] proposed a generalized model for the competitive interaction between two ligands, which reduced to the case of an agonist and a competitive antagonists results in an equation similar to that of Waud, with the exception of the positions of the two slope factors, n_H and b . Interestingly, it can be shown that the Holford and Sheiner model predicts that the Schild analysis is no longer a null method and is sensitive to the value of n_H . More recently, Zuideveld *et al.* [6] and Cheng [2] independently derived a third parameterization of the interaction model, with a slightly different effect of b compared to the reduced Holford and Sheiner model and again predicts dependency of the Schild method on n_H . Despite the fact that their work appears to challenge one of the most fundamental methods in pharmacology, Holford and Sheiner, Zuideveld *et al.* and Cheng failed to describe this implication of their model modifications. This poster therefore describes the implication of the model as described by Zuideveld *et al.* and Cheng, using simulations and several examples from literature.

Methods & Results: Sensitivity analysis of the new model has shown that slope factor (n_H) of the agonist has to be large (>3) before a change would be observed in a Schild analysis plot. Simulations taking into account typical inter-individual variability and residual error further show that it is difficult to prove that the antagonist slope factor, b , deviates significantly from 1, which may be the reason that the vast majority of experimental data appears to support the null method assumption behind the Schild analysis.

Conclusions: Based on the model and literature examples, it is predicted that a significant increase in K_B is to be expected where antagonist are evaluated with agonist with an associated $n_H > 1$.

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P-104_ Metrics based on objective function for external validation of a population pharmacokinetic model

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poster

Objectives: An important step in population pharmacokinetic model building is to evaluate the model's adequacy. We propose 3 metrics based on objective function for external validation. These metrics were applied to four validation datasets: three simulated datasets and a dataset from a phase I study.

Methods: Let M^B be a model and V a validation dataset. We defined 3 metrics for model validation based on the objective function: 1) Prediction Error on Objective Function (PEOF), which is the difference between the objective function (OF) determined in V with M^B before fitting (OF_{nofit}^V ; all parameters fixed) and after fitting (OF_{fit}^V ; all parameters estimated); 2) Prediction Error on Objective Function with Simulation (PEOFS), in which OF_{nofit}^V is compared to the posterior predictive distribution of the objective function estimated from k datasets simulated with M^B ; 3) A third approach compares the PEOF with the posterior predictive distribution of the difference between OF_{nofit}^V, k and OF_{fit}^V, k for the k^{th} simulated dataset ($\Delta OF^V, k$). In the present case, M^B was a one-compartment model with zero-order absorption and first-order elimination, built from two phase II studies. The metrics defined above were applied on 4 validation datasets, the real data (V_{real}) and 3 datasets simulated according to the design of V_{real} : the first (V_{true}) was simulated using M^B ; the second and third datasets were simulated using the same model, but with a bioavailability multiplied by two (V_{false1}) or divided by two (V_{false2}).

A likelihood ratio test was performed for PEOF with a p-value of 0.05. For the metrics with simulations, we calculated the p-value based on the empirical distribution. The pharmacokinetic evaluations and simulations were performed with NONMEM and SAS was used for statistical tests.

Results: The 3 metrics performed similarly on the 4 datasets. They all rejected V_{false1} , V_{false2} ($p < 0.001$) as well as V_{real} , but not V_{true} . When plotting the empirical posterior distribution of the two metrics based on simulations (PEOFS, ΔOF^V), ΔOF^V appeared to have a better discriminant power. Also, as it is applied on exactly the same k^{th} simulated dataset, this metric handled BQL observations more appropriately than PEOFS. PEOF provides a simple alternative in this example and was efficient here to detect model inadequacy.

P-105_ The Visual Predictive Check - Superiority to Standard Diagnostic (Rorschach) Plots

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poster

Objective: NONMEM users typically demonstrate the adequacy of a model by displaying plots of PRED vs DV or IPRED vs DV along with weighted and unweighted residuals. These are often called the standard diagnostic plots. An alternative way of evaluating a model is to simulate from the final estimates and compare the distribution of the observations with the simulated distribution. A plot of the time course of the observations and prediction interval for the simulated values provides a visual predictive check. The objective of this report is to compare the standard diagnostic plots with the visual predictive check in terms of their ability to suggest improvements to the model structure and confirm the suitability of the final model.

Methods: Plasma warfarin concentrations and effects on prothrombin complex activity have been reported by O'Reilly et al. (1, 2). These data were fitted with a one compartment disposition model with first-order input and elimination plus either an immediate effect model, an effect compartment model or a turnover model. The turnover model is known *a priori* to be the most appropriate mechanistic model.

Results: The standard diagnostic plots did not give a clear indication of the best model. There was some indication in the residual plot that the immediate effect model was not performing well at the time of the earliest post treatment prothrombin complex observation. The visual predictive check demonstrated the lack of fit of the direct and effect compartment models both for structural and stochastic components.

Conclusion: The standard diagnostic plots should be called Rorschach plots because their interpretation is dependent on the mind of the observer. The visual predictive check is diagnostic of both the fixed and random effects parts of a PKPD model.

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