# Population pharmacokinetic-based interspecies allometric scaling and prediction of first-in-human (FIH) pharmacokinetics of a new anticancer agent

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## INTRODUCTION AND OBJECTIVES

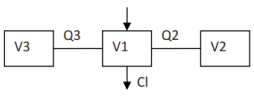
The FIH-studies design should always be supported on preclinical safety and PK data. Interspecies allometric scaling is used to extrapolate PK parameters from animals to man [1]. In the classical two-steps approach PK parameters must be first determined in each species and then scaled accounting for species body weight differences [2]. However, individual animal data available from preclinical PK studies often are imbalanced and sparse. A single-step approach based on nonlinear mixed effect modeling of pooled individual data of all animals allows simultaneous interspecies scaling of PK parameters and simulation of different dosing scenarios for FIH [3,4,5].

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

## RESULTS

A three-compartment mammillary model (Figure 1) with linear elimination from central compartment and additive residual error in log domain was shown to adequately describe four-species pooled concentration-time data (Table 2). Including all five preclinical species resulted in a deficient fit, thus mini-pigs were excluded from the final model (Figure 4). Further model fit improvement was archived (Figures 2-3) accounting for the presence of a small subpopulation of monkeys with low clearance and low central compartment volume of distribution. No other covariates (gender, BrW, MLS or fu) were retained in the final model. The final PK model allowed extrapolation of PK parameters from preclinical mammals to man (Figure 4). Subsequent simulations performed using an in-house dataset of phase I trials patients (n=199) were used to inform the design of FIH dose-scaling clinical trial (Figure 5) and to assist bioanalytical method development.

**Figure 1.** Structural model




**3-compartmental system**
linear elimination from central compartment

**Allometric scaling equation**

$$y = aWT^{b}$$

Where ***y*** is the dependent biological variable of interest (CL or Vd), ***WT*** is the body weight, and ***a*** and ***b***, the coefficient and exponent, respectively.

**Covariates checked:**
- Brain weight (BrW)
- Gender (0 male, 1 female)
- Maximum life-span (MLP)
- Monkey PK Outliers (OTL)

**Table 2.** Final model parameters

| Parameter | Units | Parameter estimate | RSE (%) |
|---|---|---|---|
| Coefficient (*a*) | | | |
| CL | (L/h*kg) | 0.2662 | 8.5 |
| V1 | (L/kg) | 0.004162 | 20.1 |
| Q2 | (L/h*kg) | 0.04349 | 23.6 |
| V2 | (L/kg) | 0.02487 | 21.9 |
| Q3 | (L/h*kg) | 0.03318 | 17.7 |
| V3 | (L/kg) | 0.2755 | 15.4 |
| Exponents (*b*) | | | |
| ECL | | 0.7161 | 5.1 |
| EV1 | | 0.5624 | 15.1 |
| EQ2 | | 0.467 | 20.7 |
| EV2 | | 0.5459 | 18.0 |
| EQ3 | | 0.542 | 14.5 |
| EV3 | | 0.6156 | 11.2 |
| Covariates | | | |
| OTL-V1 | | -0.5071 | 17.8 |
| OTL-CL | | -0.7445 | 3.6 |
| Inter-subject variability | | | |
| BSV-CL | | 0.3006 | 9.3 |
| BSV-Q2 | | 0.2773 | 16.2 |
| Residual variability | | | |
| Additive error in log domain (%) | | 27.5 | 4.9 |

**Figure 3.** Some fitted indiv. PK profiles

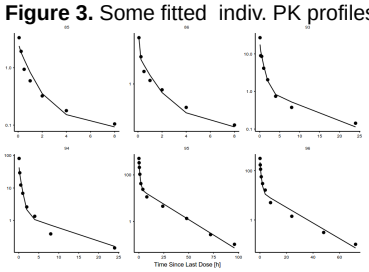
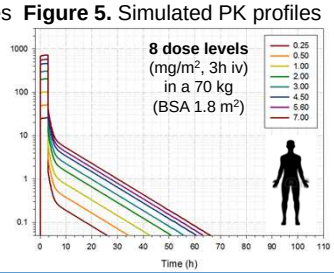



**Figure 5.** Simulated PK profiles




## METHODS

Preclinical PK studies conducted on athymic nude mice, Sprague Dawley rats, Beagle dogs, Göttingen mini-pigs and Cynomolgus monkeys involving 122 animals with 416 plasma concentrations were available for interspecies scaling (Table 1). In mice and in rats, each plasma concentration corresponds to a unique animal, whereas in the remaining species the individuals contributed with several plasma concentrations. The new anticancer compound was administered intravenously over wide range of doses (0.005 to 1.25 mg/kg) to animals with body weight ranging from 0.02 kg in mice to 20 kg in mini-pigs. Animal plasma concentrations were pooled and fitted in one step to a PK model using non-liner mixed-effects modelling implemented in NONMEM v7.3. Allometric equations were contained into the PK model to allow individual body weight PK parameters scaling. The incorporation into de model as covariates of gender, brain weight (BrW), maximum lifespan (MLS) and unbound plasma fraction (fu) was investigated.

**Table 1.** Species and PK studies used for allometric scaling

| Animal species | Gender (n) | Body weight (kg), median (range) | Single dose iv bolus (mg/kg) | Number of animals (n=122) | Time points (h) | Number of plasma concentrations (n=416) |
|---|---|---|---|---|---|---|
| Mice | Female (32) | 0.023 (0.020-0.028) | 1.25 | 32 | 0, 0.083, 0.25, 0.5, 1, 2, 4, 8, 24 | 32 |
| Rat | Female (24)<br>Male (24) | 0.147 (0.115-0.186) | 0.10 | 48 | 0, 0.083, 0.25, 0.5, 1, 2, 4, 8, 24 | 48 |
| Dog | Female (3)<br>Male (3) | 9.50 (7.61-11.55) | 0.005 | 6 | 0, 0.083, 0.25, 0.5, 1, 2, 4, 8, 24 | 44 |
| Monkey | *Study 1*:<br>Female (3)<br>Male (3)<br>*Study 2*:<br>Female (12)<br>Male (12) | 7.03 (6.35-8.20)<br><br>3.30 (3.0-4.0) | 0.020<br><br>0.104, 0.208, 0.292 | 6<br><br>24 | 0, 0.083, 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72, 96<br>0, 0.083, 0.25, 0.5, 1, 2, 4, 8, 24 | 246 |
| Mini-pig | Female (3)<br>Male (3) | 19.70 (18.90-21.10) | 0.020 | 6 | 0, 0.083, 0.25, 0.5, 1, 2, 4, 8, 24 | 49 |

**Figure 2.** Scatterplots illustrating good model fitting

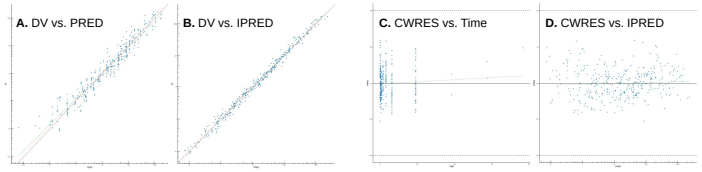
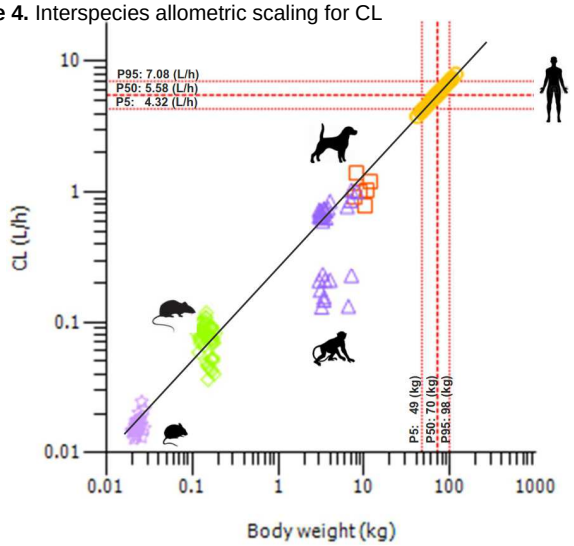



**Figure 4.** Interspecies allometric scaling for CL




## CONCLUSIONS

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

## REFERENCES

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