

Application of allometric techniques to predict F10503LO1 PK parameters in humans

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INTRODUCTION

FAES FARMA is about to complete the preclinical development of a small molecules family of its own R&D portfolio, which has demonstrated an excellent *in vivo* *in vivo* activity on haematological and solid tumour cell lines as well as in animal models of several tumours, such as chronic lymphatic leukaemia, multiple myeloma, melanoma, colon cancer and ovarian tumours. One of these molecules, F10503LO1, is in late toxicology development and complete information about preclinical pharmacokinetics and toxicokinetics.

Proceeding from animal experiments into humans is a major problem in drug development. Therefore, making good predictions of clinical pharmacokinetics based on results from animal studies, would be of great importance to design first-in-man studies. Here an empirical interspecies approach, allometric escalation, was applied to support decision-making.

Consequently, the aim of this exercise was to predict the PK parameters of F10503LO1 in humans. For this purpose, information from PK in different species was gathered and analyzed in an allometric exercise with NONMEM.¹

MATERIALS AND METHODS

Three animal species (mouse, rat and dog) and a total of 294 plasmatic samples from different studies were included in this exercise. Plasmatic samples were obtained after bolus and intravenous infusion of the test item in both, male and female animals. Different doses in the range from 2 mg/kg to 12.5 mg/kg were analyzed: four doses in dog (2.5, 5, 10 and 12.5 mg/kg), two doses in rat (5 and 10 mg/kg) and one dose in mouse (2.5 mg/kg).

At an initial stage, the PK model that best described plasmatic observations was obtained. PK linearity within the range of doses assessed as well as the covariate effect of sex were explored. Then, correlation between parameters was evaluated, and finally the interspecies escalation was modeled.

Allometric escalation helped investigate correlation models of PK parameters between the analyzed species. The empirical approximation is based in an exponential function as follows:

$$Y = a \cdot W^x$$

where Y is the dependent variable (PK parameter), W (body weight)² the independent variable, and a and x are the allometric coefficient and exponent, respectively. Unfortunately, this approximation presents some weaknesses. Among others, it uses information of low weight species to estimate human PK parameters, and it involves the hazardous practice of projecting beyond the observed range. However, some authors consider that this risk is reduced by using a population approach.³

All data were fitted with a pharmacokinetic model using non-linear mixed-effect modelling implemented in NONMEM 7.2. This approach estimates coefficients and exponents that characterize the relationship between pharmacokinetic parameters and species features in a single step.⁴

The structural model selection was initially guided by a graphical exploration of individual concentration-time profiles. Inter-individual variability (IIV) was initially assumed for all structural parameters. PK parameters were presumed to follow a Log-normal distribution. Residual variance was estimated applying both sides logarithmic transformation.

For hierarchical models, the final model selection was based on the performance of the fit when a fixed effect is included into the overall model. Statistical significance was assessed using the likelihood ratio test (LRT). In addition, the improvement in the fit was evaluated by the reduction in the IIV and residual variability, the precision in parameter estimates, and the examination of diagnostic plots.

Finally, a nonparametric bootstrap was used as internal evaluation method to qualify the estimates of the PK model parameters by WINGS for NONMEM.⁵ Parameter precision was evaluated performing a 1000 dataset bootstrap. The mean and the 95% confidence intervals of the parameter estimates from the bootstrap replicates were compared with the estimated parameters from the original dataset. Visual Predictive Check (VPC) was used to explore the performance of the model selected. 1000 datasets with the same study design as the original dataset were simulated.

RESULTS

A two-compartment PK model with first-order elimination from central compartment was selected as the best model, describing F10503LO1 pharmacokinetics after intravenous administration in the 3 evaluated species. Results evidenced PK linearity within the range of doses evaluated.

Neither sex covariate effect on PK parameters nor correlation between PK parameters were statistically significant. Consequently, they were not included in the final model.

The goodness-of-fit plots for the final model are presented in Fig. 1 and show off-random uniform scatter around the line of identity, suggesting then absence of any trend or bias.

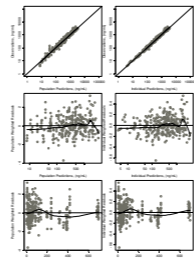


Figure 1. Goodness-of-fit plots for the single absorption population PK model: scatter plots of the observed plasma F10503LO1 concentration versus the population model prediction (panel A) and the individual model predictions (panel B). Scatter plots of the population weighted residuals versus the population model predictions (panel C) and of the individual weighted residuals versus the individual model predictions (panel D). Scatter plots of population weighted residuals versus time since last dose (panel E) and individual weighted residuals time since last dose (panel F).

Results from the nonparametric bootstrap analysis further confirmed absence of bias in the estimation of model parameters (Table 1). Parameter estimates of the final population pharmacokinetic model were very similar to the median of the non-parametric bootstrap replicates, and all were contained within the 95% confidence intervals obtained from the bootstrap analyses. The precision of the NONMEM parameter estimates was also good, since the relative standard error from the bootstrap analysis for the majority of fixed and random effects was lower than 15 and 50%, respectively. Only some difficulties were observed for the estimation of C₂ inter-individual variability, where few bootstrap runs presented difficulties to estimate this variability.

Table 1. Population pharmacokinetic parameters of F10503LO1 after intravenous administration in three different species.

Parameter	Original dataset		Non-Parametric Bootstrap	
	Median (95% CI)	Relative SE (%)	Median (95% CI)	Relative SE (%)
Concentration				
C (ng/mL)	87 (2.88)	47.2 (8.6)	88	79
C ₁ (ng/mL)	2810 (7.24)	2810 (8.32)	3069	49.0
C ₂ (ng/mL)	148 (11.06)	142 (11.41)	112	176
V _d (mL)	7756 (5.94)	7752 (5.88)	7659	87.0
Elimination				
Cl _{CR} (mL/min)	0.796 (1.42)	0.796 (18.7)	0.719	20.04
V (mL)	0.801 (3.70)	0.817 (3.13)	0.758	8.88
C ₁ (ng/mL)	0.771 (8.48)	0.778 (7.14)	0.701	8.82
V _d (mL)	0.987 (3.85)	0.975 (3.05)	0.819	1.82
Inter-individual variability (%)				
ω _{Cl}	15.1 (28.81)	15.28 (9.85)	11.45	18.85
ω _V	26.89 (47.48)	26.79 (35.52)	23.30	48.08
Residual error (%)				
Additive	20.02 (12.80)	18.46 (8.56)	17.72	21.68

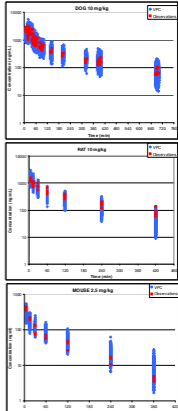


Figure 2. Results from the Visual Predictive Check in blue versus the observations in red. This figure includes one panel per species, showing as an example only one dose for species. In the upper panel (A) results for 10 mg/kg in dog, in the medium panel (B) results for 10 mg/kg in rat, and the lower panel (C) results for 2.5 mg/kg in mouse.

Visual predictive check evidences that the model developed is appropriate to describe plasmatic concentrations of F10503LO1 in the three different species, establishing the influence of weight in the PK parameters estimation. For example, Figure 2 depicts the results of VPC for only one dose in each species (10 mg/kg in dog, 10 mg/kg in rat and 2.5 mg/kg in mouse). Similar results to the ones presented in the poster were obtained for the rest of doses analyzed.

The coefficient and exponents estimated by the model will be applied to simulate PK parameters of F10503LO1 in man and to evaluate different scenarios.

CONCLUSIONS

The model selected describes plasmatic observations in the 3 evaluated species correctly, and allows the extrapolation to PK parameters in humans. These parameters in combination with information of its *in vitro* efficacy and pharmacology security will be applied for simulation of different scenarios and to select first-in-man dose.

References:

1. S. D. G. Shaw, J. B. Baker, J. A. B. B. (Eds.). NONMEM Users Guide, 1989-1991, Icon Development Solutions, Ellicott City, Maryland, USA.
2. Coxson V, Fauran E, Chrythopoulos C, Day A. Mixed effect modeling of sumatriptan pharmacokinetics during drug development. I: interspecies allometric scaling. *J Pharmacokinetics Biopharmaceutics*. 2007; 35: 149-67.
3. Jolliffe K, Perez-Risco JJ, Henegrych A, Vermeulen A, Grayson T. Mixed effects modeling of the interspecies pharmacokinetic scaling of pegaptanib human erythropoietin. *Eur J Pharm Sci*. 2005; 26: 465-75.
4. N. Holford, version 705, Auckland, New Zealand.

Acknowledgements: We thank Herten Laboratories Ltd. for their technical support in sample preparation.