Population PK Analysis in Sparse Data and Flexible Sampling Time Conditions

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Objective

Characterize the pharmacokinetics including effects of covariates of a tested drug, based on a phase II dose-ranging study.

Material and Methods

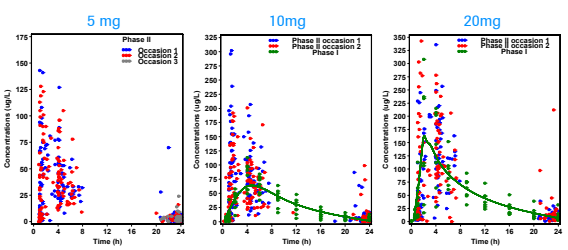
- Study conditions: Three doses 5, 10 and 20 mg
  Once daily administration
  Target population
- Blood samples were taken at steady-state
  - 3 at occasions 1 and 2: predose, 1 between 1-3 h and 1 between 1-8 h postdose, based on investigators' choice
  - 1 at occasion 3: predose
- Analytical method: LC-MS/MS with 0.1 ng/mL as LOQ
- Increase information for the structural model definition by adding data from phase I study in patients
- 1829 exploitable concentrations from 209 patients
- Non-linear mixed effects model approach using NONMEM V1.1.:
  - The inter-individual variability (IIV) on each structural parameter was described with an exponential model : $P_i = TVP \times \exp(\eta_i)$
  - The same model was used to describe the interoccasion variability (IOV). IOV was only tested on CL/F
  - The residual variability was characterized by a proportional error model: $ym_{ij} = yp_{ij} \times (1+\varepsilon_{ij})$

Results

Population

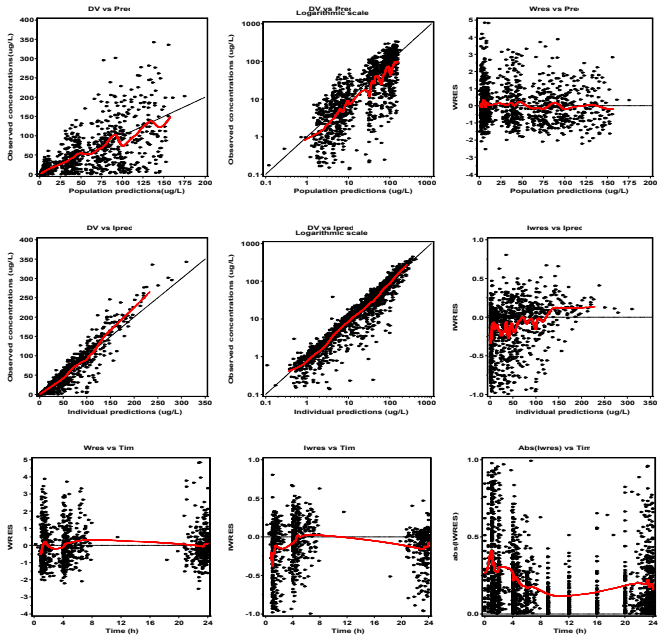
Gender:	92 female, 117 male
Age:	35-75 years
BMI:	20-40 Kg/m²
AST/ALT:	6-50 / 6-66 IU/L
Creatinine CL:	53-225 mL/min
Albumin:	28-49 g/dL
Bilirubin:	0.37 – 21 µmol/L
Dose:	3-40 mg
Time:	single dose / steady state
Comedication:	ACE-Inhibitors
CYP2C19 Genotype:	156 homozygous EM 50 heterozygous EM pooled with 3PM (EM=extensive metabolizer, PM=poor metabolizer)

PK Profiles

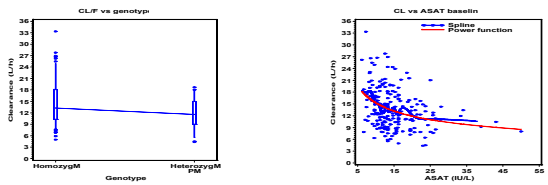


Parameter		Value	IIV (%)	IOV (%)
CL/F	(L/h)	14	39	19
V_2/F	(L)	51		46
Q/F	(L/h)	4.5		
V_3/F	(L)	38	100 FIX	
ka	(h^{-1})	0.66	87	
t_{lag}	(h)	0.37	70 FIX	
F1_20 mg; F1_40 mg		0.78; 0.64		
ASTb on CL/F		-0.32		
Genotype on CL/F		-0.13		
Residual Error	(%)	37		

Goodness of Fit for Phase II Study



Apparent Clearance Versus Potential Covariates



Discussion and Conclusion

- Modeling aspect:
  The model described the PK data in patients well, however, the variability of the PK profiles made the model unstable. The large variability may reflect intrinsic variability as well as errors such as mistakes in sampling or drug intake time records.
- Sampling strategy:
  As the blood sampling times were partly left to the investigators' choice, many samples were drawn at the same time. Only the inclusion of prior information from a phase I study allowed an appropriate structural model to be chosen. The proposal for future studies would be:
  - Randomized and individualized sampling scheme for each patient
  - Feasibility questionnaire driving the selection of centers for PK
  - More intense training for the clinical center staff on PK
- The PK of this compound in patients is simple. The parameters are constant over time and no drug accumulation is expected.
- Covariates and Concomitant medication:
  - Genotype was found to be a relevant factor for PK. Following this finding, the genotype (PM excluded) was tested on the primary efficacy criterion. No statistically significant difference in PD was found.
  - ASTb had a statistically significant influence, however the effect is small and not expected to be of clinical relevance.
  - No signal for interaction with ACE-inhibitors
- The high residual variability is partly attributed to the fragmentary PK design

In conclusion, despite sub-optimal sparse sampling and large PK variability, it was possible to derive an adequate model that described the PK in the patient population and that was able to identify important co-factors. Future population PK analysis will be conducted with improved methods in order to expand on this analysis.