

Physiologically-based pharmacokinetic (PBPK) and population PK (PPK) modeling for basimglurant : assessment of predicted variability by the PBPK model and its utility

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1 – Background and Methods

Simulated between-subject variability (BSV) is frequently taken into account when using PBPK models to predict ADME process and DDI and extrapolating PK to special populations. However the assessment of the predictions is rarely done. In this study, the ability of a PBPK model to predict BSV was evaluated by comparison to the variability estimated through a PPK model using basimglurant as an example. Subsequently, utility of the PBPK model to assist in sample size calculations for a DDI study was investigated.

Basimglurant is currently being investigated for the treatment of major depressive disorder¹. It is a weakly basic and lipophilic compound (LogP > 3). Pharmacokinetics of basimglurant after i.v. administration in 6 healthy individuals is characterized by a CL of 11.8±7.4 L/h and a V_{ss} of 677±229 L² (mean±SD). The elimination is via hepatic metabolism mainly through CYP enzymes 1A2 and 3A4.

A PPK model was developed using NONMEM (Version 7, level 1, double precision) based on 3762 basimglurant plasma concentrations collected in 164 individuals receiving oral administration of an immediate release (IR) formulation.

An initial PBPK model was constructed using SimCYP versions 12 and 13 based on physicochemical properties and in vitro data (f_{up}, B/P partition coefficient etc.). This model was further developed using clinical PK data (oral single and multiple dose studies and an intravenous study) and based on in vitro experiments³ a fraction metabolized by CYP1A2 (f_m_{CYP1A2}) of 70% and a f_m_{CYP3A4} of 30% were assigned. This model was then used to investigate the DDI risk. BSV of basimglurant was predicted by the approach implemented in SimCYP^{4,5}.

Abbreviations. ADME: absorption, distribution, metabolism and elimination, AUC: area under the curve, B/P: blood to plasma, BSV: between-subject variability, CL: clearance, C_{max}: maximum plasma concentration, CYP: cytochrome p450, DDI: drug-drug interaction, f_m: fraction metabolized, f_{up}: unbound fraction in plasma, pc-VPC: prediction corrected visual predictive check, RSE: relative standard error, V_{ss}: volume of distribution at steady state

2 – Population PK model of basimglurant IR formulation

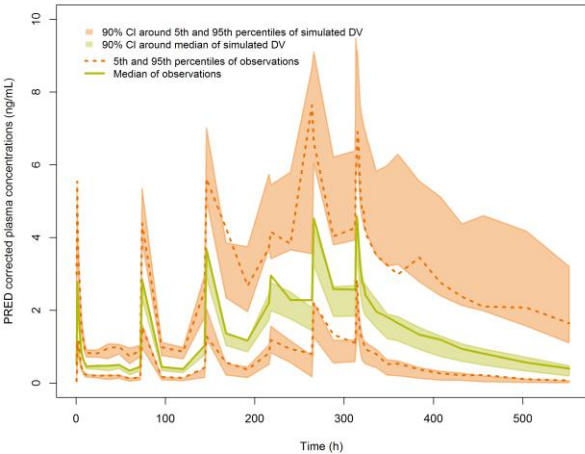
The best structural PK model fitted to the basimglurant concentrations was a 3-compartment mammillary disposition model with first-order elimination kinetics and a sequential zero- and first-order absorption process. The PK model parameters were well estimated with RSE ranging from 3.1 to 15.1%. The PK parameters, BSV and identified covariates are shown in Table 1. The pc-VPC shown in Figure 1 indicates that the model adequately captures both the central tendency and the BSV of basimglurant pharmacokinetics after oral administration of the IR formulation.

Table 1. Summary of the final PPK model parameters

Parameters and values (unit)		BSV*
K _a	0.949 (1/h)	78.5
D1	1.59	52.5
CL/F	8.62×(1 + 0.564×SEX) (L/h)	49.4
V2/F	114 × (WT/75) ^{0.861} (L)	16.7
Q3/F	20.3 × (WT/75) ^{1.39} (L/h)	41.8
V3/F	669 × (WT/75) ^{1.52} (L)	36.9
Q4/F	20.7 (L/h)	21.7
V4/F	146 (L)	
Proportional residual error	18.3 (CV%)	
BSV on proportional residual error	32.9 (CV%)	

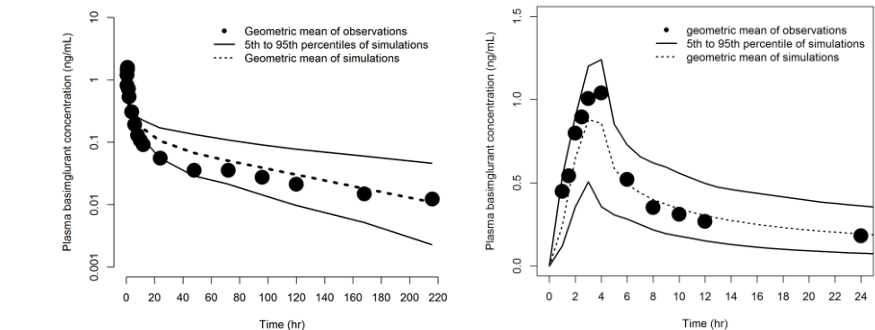
*, %CV

Fig1. pc-VPC of the final PPK model parameters



3 –PBPK model of basimglurant

The disposition of basimglurant implemented in the PBPK model was verified using the PK data after i.v. administration in 6 healthy men (Fig 2, left). The PBPK model also predicted PK after oral administration of basimglurant adequately (Fig 2, right).



The extent of DDI with ketoconazole (CYP3A inhibitor), fluvoxamine (CYP1A2 inhibitor) or carbamazepine (CYP1A2 and CYP3A inducer) were adequately predicted by the PBPK model, indicating the f_m_{CYP1A2} and f_m_{CYP3A4} of basimglurant were relevant for in vivo pharmacokinetics.

Table 2. Observed and predicted AUC and C_{max} ratios of DDIs

Perpetrators	Observations		Simulation	
	C _{max} ratio	AUC ratio	C _{max} ratio	AUC ratio
Ketoconazole	1.03	1.24	1.14	1.49
Fluvoxamine	1.11	1.60	1.10	1.78
Carbamazepine	0.782	0.63	0.88	0.64

4 – Comparisons of between subject variability simulated with PBPK and PPK models

Simulations for 0.5 mg basimglurant once daily for 14 days were performed with the PBPK and the PPK models for 1000 virtual individuals with exactly the same distributions of demographics. The median and 5th-95th percentiles of simulated basimglurant plasma concentration profiles as well as distributions of simulated C_{max} and AUC_τ at steady state were compared between the models.

The median and 5th-95th percentiles of simulated plasma concentrations profiles of basimglurant (full profiles on days 1 and 14, trough on days 2 to13) using the PBPK and PPK models were similar (Fig 3). Distributions of simulated C_{max} and AUC_τ at steady-state were also comparable between the models (Fig 4 and Table 3).

Fig3. Comparison of simulated PK profiles between PBPK and PPK models

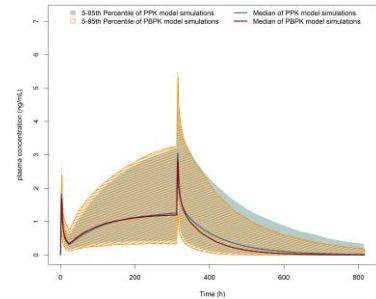


Fig4. Comparison of distributions of simulated PK parameters between PBPK and PPK models

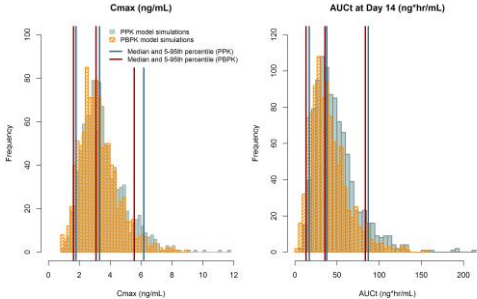


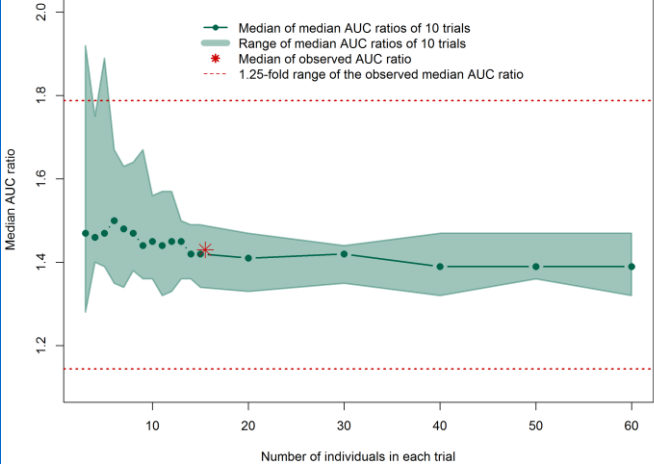
Table 3. Median [5th – 95th percentiles] of simulated C_{max} and AUC_τ

Models	C _{max,ss} (ng/mL)	AUC _{τ,ss} (ng • hr/mL)
PPK	3.31 [1.79 – 6.17]	43.1 [19.4 – 99.0]
PBPK	3.09 [1.63 – 5.55]	40.6 [15.1 – 95.0]

5 – Simulation of DDI with ketoconazole

A ketoconazole DDI trial with the number of subjects varying between 3 to 60 was simulated 10 times. The median and range of the median AUC ratios of basimglurant in the absence and presence of ketoconazole were examined in relation to the number of subjects in each trial (Fig 5). The range of the median AUC ratios of basimglurant in trials with 3 to 10 subjects was larger and fluctuated more widely than in the trials with more than 10 subjects. Constant median AUC ratios were seen in trials with 14 to 60 individuals per trial and showed good agreement to the observed median AUC ratio which was investigated in 15 individuals.

Fig5. Simulated AUC ratios of ketoconazole DDI trial with varying number of subjects



- The range of median AUC ratio is maintained between sample size from 14 to 60, indicating that a sample size of 14 would be sufficient to investigate the DDI with reasonable confidence.
- Possibility for AUC ratio being outside of 1.25-fold range of the observed value was indicated for trials with sample size less than 6 which might influence on characterization of in vivo f_m_{CYP3A4}.

6 – Conclusion

- The PBPK model predicted BSV of basimglurant was in accordance with the estimates made with the PPK model
- Utility of the PBPK model to determine an appropriate sample size for a DDI study with ketoconazole was shown for basimglurant.
- PBPK model based sample size calculation would be useful for metabolic DDI studies particularly when characterization of in vivo fraction metabolized based on the study outcome is expected

Reference

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