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 disorder. It is a weakly basic and lipophilic compound (LogP > 3). Pharmacokinetiks of basimglurant after i.v. administration in 6 healthy individuals is characterized by a CL of 11.8±7.4 L/h and a Vf of 677±229 L (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 in vitro experiments in vivo fm of 30% were assigned. This model was then used to investigate the DDI risk. BSV of basimglurant was predicted by the approach implemented in SimCYP4.

Abbreviations: ADME: absorption, distribution, metabolism and elimination. AUC: area under the curve. B/P: blood to plasma. BSV: between-subject variability. CL: clearance. CYP: cytochrome p450. DDI: drug-drug interaction. fm: fraction metabolized. IR: immediate release. PK model parameters were well estimated with RSE of 78% and a fm of 30%. This model was then used to investigate the DDI risk. BSV of basimglurant was predicted by the approach implemented in SimCYP4.

2 Population PK model of basimglurant IR formulation

The best structural PK model was fitted to the basimglurant concentrations was a 3-compartment mammalian 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 6.5%. The PK parameter 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.

3 PBPK model of basimglurant

Using Virtual Human Populations, 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 (CYP3A4 inhibitor), fluvoxamine (CYP1A2 inhibitor) or carbamazepine (CYP2B6 and CYP3A4 inducer) were adequately predicted by the PBPK model, indicating the fm of CYP3A4 and fm of CYP3A4 of basimglurant were relevant for in vivo pharmacokinetics.

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 95th-99th percentiles of simulated basimglurant plasma concentration profiles as well as distributions of simulated Cmax and AUC were at steady-state were compared between the models.

The median and 95th-99th percentiles of simulated plasma concentrations profiles of basimglurant (full profiles on days 1 and 14, trough on days 2 to 13) using the PBPK and PPK models were similar (Fig 4). Distributions of simulated Cmax and AUC at steady-state were also comparable between the models (Fig 4 and Table 3).

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 PK parameter 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.

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.

PPK 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