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ARTICLE

# Population Pharmacokinetic and Exposure–dizziness Modeling for a Metabotropic Glutamate Receptor Subtype 5 Negative Allosteric Modulator in Major Depressive Disorder Patients

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**Dizziness, the most frequently observed adverse event in patients with major depressive disorder, was observed with basimglurant, a selective, orally active metabotropic glutamate receptor subtype 5 negative allosteric modulator. The potential relationship between dizziness and basimglurant exposure was explored. The pharmacokinetics of basimglurant was characterized with nonlinear mixed effects modeling using data from 288 trial participants enrolled in five clinical trials. The pharmacokinetics of basimglurant after daily oral administration of a modified release formulation was best described by a two-compartment disposition model with a transit compartment, lag time for the absorption, and first-order elimination. The largest covariate effects were the effect of smoking and male gender on apparent clearance followed by the effect of body weight on distribution volumes. Clearance was twofold higher in smokers and 40% higher in males. A logistic regression model showed a statistically significant correlation between basimglurant $C_{max}$ and incidence of dizziness. An increased risk of dizziness is predicted with increasing doses.**

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### Study Highlights

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**
✔ Empirical exposure–response modeling has been applied for treatment optimization of adverse effects, but examples of CNS effects such as dizziness are limited. Multiple methodologies have been published to characterize exposure–AE relationships for other drugs, including use of logistic regression models.

**WHAT QUESTION DID THIS STUDY ADDRESS?**
✔ What are the population PK properties of basimglurant, a selective mGlu5 NAM, and could a quantitative approach be applied for characterizing and predicting a common adverse effect for purpose of future drug development of an antidepressive drug?

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**
✔ A model-based approach for characterizing PK, adverse events, and analyzing dose recommendations for basimglurant in MDD patients.

**HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**
✔ The analysis illustrates the use of modeling for guiding dose recommendations for future trials based on an integrative analysis of available data.

Major depressive disorder (MDD) remains an area of considerable medical need despite the many agents approved for treatment of this illness. Response rates for initial treatment are estimated to be about 50%, while remission, considered to be the goal of treatment, ranges from 15–40%.[1] The metabotropic glutamate receptor 5 (mGlu5) receptor has emerged as an attractive target for the treatment of anxiety and depressive disorders based on its expression pattern in the brain and the efficacy of mGlu5 antagonists in various animal models.[2,3] Glutamate is the main excitatory neurotransmitter that mediates its effects via ionotropic glutamate receptors (i.e., N-methyl-D-aspartate (NMDA), $\alpha$-amino-3-hydroxy-5-methylisoazol-4-priopionate (AMPA) or kainate receptors) and G-protein-coupled receptors (e.g., mGlu receptors). The mGlu receptors are involved in learning, memory, anxiety, and the perception of pain.[4]

Basimglurant, a selective, orally active mGlu5 negative allosteric modulator (NAM),[5,6] was developed for the treatment of MDD. The safety data in both healthy subjects and MDD patients showed that basimglurant was safe and generally well tolerated. Consistent with the mechanism of action and as seen in other drugs of this class,[7–9] the most

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frequently observed adverse event (AE) in clinical trial participants was dizziness.[10] The incidence of dizziness was dose-related, with rates of 23.4% in the 1.5 mg basimglurant arm compared with 4.5% in the 0.5 mg arm. Relative to these the rate in the placebo arm was 5.5%. Dizziness occurred early during treatment, was mostly mild, transient, and self-resolving.[10]

Basimglurant administered as an immediate release (IR) formulation has a mean oral bioavailability of 67% (46–78%).[11] A modified release (MR) formulation was developed to reduce peak concentrations and therefore to improve safety and tolerability vs. the IR formulation. Administration of the MR formulation with food results in a modest reduction of maximum observed plasma concentration ($C_{max}$), an increase in time to $C_{max}$, but no impact on total exposure (area under the curve, AUC) compared with the IR formulation. Reduction of $C_{max}$ resulting in a decrease in the incidence of dizziness was considered a logical approach, as rapid absorption has been implicated in the onset of dizziness with another mGlu5 modulator.[7] The elimination of basimglurant is mainly mediated by cytochrome P450 (CYP) oxidative metabolism, followed by renal and fecal excretion with negligible parent drug found in urine. Carbamazepine decreased basimglurant plasma concentrations, likely by induction of CYP1A2 and/or CYP3A4 activity.[12] A dual inhibitor of CYP1A2 and CYP3A4, fluvoxamine, increased basimglurant plasma concentrations.[12] Ketoconazole (CYP3A4 inhibitor) had a modest to no impact on exposure of basimglurant.[11]

This article describes the population modeling approach used to characterize the pharmacokinetics (PK) of basimglurant administered orally using an MR formulation in healthy subjects and MDD patients, to estimate the between-subject variability (BSV) and to quantify the effects of possible covariates on the PK of basimglurant. Additionally, an exposure–safety analysis was conducted to examine the relationship between the basimglurant exposure metric, $C_{max}$ on Day 1, and the incidence of dizziness, the most frequently observed AE in patients with MDD. While dizziness was also an important AE in healthy subject trials, the exposure–dizziness model was limited to the patient population to avoid a potential confounding of this relationship by disease status and clinical setting. The risk for dizziness at higher doses not yet investigated was predicted based on these analyses.

## METHODS

### Patient population and study design

The PK data used in this analysis were collected in four healthy subject phase I studies and in one patient phase II study: i) an open-label, randomized, crossover study to compare two MR formulations of basimglurant to the IR formulation, and to estimate the effect of food on the PK from each new formulation (Institut de Pharmacologie Clinique Roche. Strasbourg, France); ii) two open-label, one sequence, crossover studies to investigate the effects of multiple doses of fluvoxamine and carbamazepine on the PK of basimglurant after single dose, NCT01665404, NCT01629368 (both at Biotrial, Rennes, France); iii) a double-blind, randomized, placebo-controlled study evaluating the PK, safety, and tolerability of basimglurant conducted in two parts: a single dose, crossover administration to healthy Japanese subjects and a multiple dose (14 days) administration to healthy Japanese and Caucasian subjects, NCT01368926 (Iberica, NY); and iv) a randomized, double-blind, parallel-group study to study the safety and efficacy of basimglurant vs. placebo, as adjunctive therapy in MDD patients with inadequate response to ongoing antidepressant treatment (6-week treatment period), NCT01437657.[10] Across the five studies, basimglurant was administered orally once a day (q.d.) with an MR formulation at doses of 0.2, 0.5, 0.7, 1, or 1.5 mg. The studies were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent, and the protocol was approved by independent Ethics Committees.

Full PK profiles after single and multiple doses were available in healthy subjects and sparse PK samples were collected in MDD patients at predose and at 4 and 6 hours postdose on Days 1, 42, at predose and at 4 hours postdose on Days 14 and 28 and at any time on Day 63.

### Analytical determination of basimglurant concentrations in plasma

Determination of the concentration of basimglurant in plasma samples was conducted with a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method using a Fluorophase PFP analytical column with ion spray mass spectrometric detection in the positive ion model. The limit of quantification was 0.05 ng/mL with a calibration range of 0.05 ng/mL to 25.0 ng/mL. Details of the bioanalytical method have been described previously.[11]

### Pharmacokinetics analysis

The population PK analysis of the pooled plasma concentration data applied the nonlinear mixed-effect modeling approach as implemented in NONMEM (v. 7.2.0 ICON Development Solutions, Dublin, Ireland).[13] All NONMEM runs were carried out using the first-order conditional estimation method with the interaction option.

The base PK model was initially developed on healthy subject data. PK profiles of basimglurant after single-dose administration display a multiexponential decay. Two- and three-compartment models with linear elimination were evaluated to describe the disposition of basimglurant. First-order, sequential zero- and first-order rate constant models or transit compartment models (with a chain of 2, 3, or 4 compartments)[14] were tested to describe the absorption of basimglurant. Considering the previously observed food effect on basimglurant absorption and the difference of the impact of food between Japanese and non-Japanese subjects observed in the phase I trial, food and Asian ethnicity (Japanese effect extended to Asian effect) effects on absorption parameters were considered part of the base model development. To describe the residual variability (RV), additive, proportional, or a combination of these were tested. The BSV in the model parameters were assumed to be log-normally distributed and were evaluated on all parameters. Further model investigations on the pooled data showed that the base PK model initially developed in healthy subjects described the MDD data adequately. Correlation among all

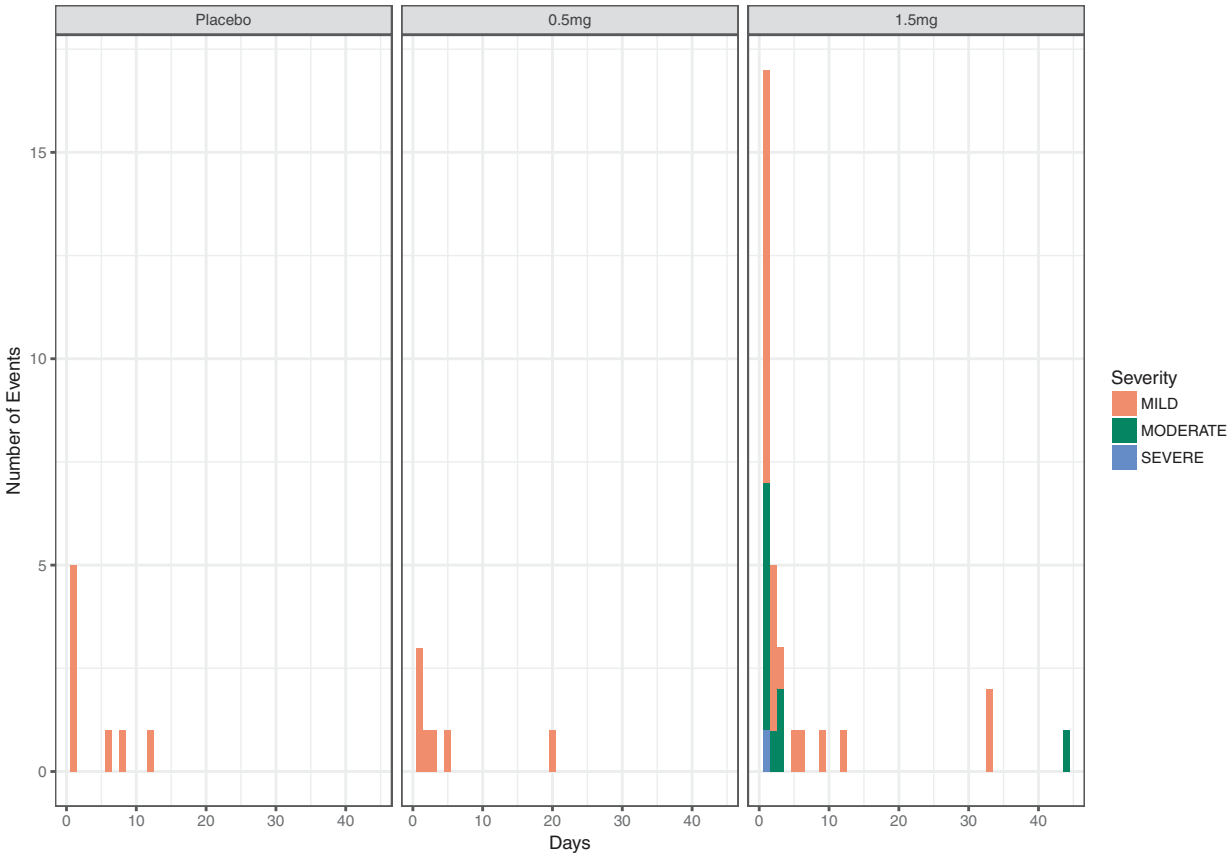


**Figure 1** Incidence of dizziness and the associated severity as a function of time in the phase II trial in MDD patients.

BSV components were investigated on the final model. The adequacy of the PK model to describe both populations was assessed by prediction-corrected visual predictive check (pcVPC).[15] The impact of the covariates was tested on the apparent disposition parameters, the apparent clearance (CL/F), the apparent central volume of distribution (Vc/F), the apparent intercompartmental clearance (Q/F), and the apparent peripheral volume of distribution (Vp/F). Covariate model building was performed in a stepwise fashion with forward inclusion at a *P*-value of 0.05 and backward deletion at a *P*-value of 0.01 using the Perl speaks NONMEM (PsN) toolkit.[16] The investigated covariates were limited to body weight, age, gender, Asian ethnicity, smoking status, and patient type (i.e., healthy subjects or MDD patients). As a last step, if a covariate was found to affect all or nearly all disposition parameters, i.e., volumes and clearances, in a similar direction and to the same magnitude, in the spirit of parsimony, the effect of that covariate was applied instead to apparent relative bioavailability rather than on each disposition parameter, following which the statistical significance was reassessed.

The model selection was based on various goodness-of-fit indicators, including visual inspection of diagnostic plots (e.g., observed vs. predicted concentration, conditional weighted residual vs. predicted concentration or time, histograms of individual random effects), plausibility of the parameter estimates, precision of the parameter estimates, and the objective function value (representing –2 log likelihood). All parameter estimates were reported with their 95% confidence intervals (CI).

The final PK model was qualified by a pcVPC in which 500 replicates were simulated to compute the 95% CI around the median, the 5$^{th}$ and the 95$^{th}$ percentiles of the simulated PK profiles, and for comparison to observed PK profiles.

### Exposure–safety analysis

Exposure–safety analysis was conducted in order to describe the relationship between basimglurant exposure, i.e., $C_{max}$ on Day 1 ($C_{max,Day1}$) and the occurrence of dizziness, the most frequently observed AE in MDD patients. Dizziness was reported as an AE by 37 out of the 333 randomized patients in the phase II study.[10] A total of 47 episodes of mild ($n = 36$ in 26 patients), moderate ($n = 10$ in 10 patients), or severe ($n = 1$ in one patient) dizziness was reported; most of these occurred early during treatment (>50% on Day 1, >90% by Day 12) (**Figure 1**); 29 patients reported only one episode while eight patients reported more than one episode of dizziness. Among the 37 patients reporting dizziness, six were on placebo, five received 0.5 mg, and 26 received 1.5 mg of basimglurant, suggesting a higher risk for dizziness with increasing dose. Consistent with higher drug levels, females showed a higher incidence of dizziness, three female patients at 0.5 mg and 20 at 1.5 mg reported dizziness, while no male patients at 0.5 mg and six at 1.5 mg reported dizziness.

While the underlying mechanisms for the cause of dizziness are likely to be multivariate,[17] the apparent dose response to dizziness indicated a strong likelihood of an exposure driver. To explore whether the higher incidence of dizziness could be explained by increasing exposure to basimglurant, individual exposure of $C_{max}$ on Day 1, predicted using the population PK model, were related to the occurrence of dizziness in a logistic regression analysis with a linear relationship between the logit of the probability of dizziness and $C_{max}$.

$C_{max,Day1}$ was selected over other exposure metrics such as AUC, $C_{trough}$, or average concentration on Day 1 because whenever it was reported (as a comment in the case report form) dizziness occurred within 2 hours and resolved within 4 hours after administration, which coincides with time of $C_{max}$. Individual $C_{max,Day1}$ estimates were derived from the individual predicted concentration–time profiles during the first dosing interval (0–24 hours on Day 1). For patients in the placebo group, these exposure estimates were set to zero for the analysis, whereas patients in the treatment groups without any PK observations were excluded from the analysis. Since 80% of the cases of dizziness occurred within the first 3 days of dosing, with 55% occurring on Day 1, and only few occurrences of multiple events, a longitudinal exposure–dizziness model wasn't attempted and only the first occurrence was considered in the regression analysis. As the majority of events were mild in nature, the severity was also not taken into account.

The relationship between $C_{max,Day1}$ and the occurrence of dizziness (any severity) was investigated in a regression analysis considering the following link functions for the transformation of the binomial dependent variable: logit, probit, complementary log–log, using the generalized linear models (glm) function in R (v. 3.3.1, Vienna, Austria). In addition, for the logistic regression, nonlinear relationships with exposure were investigated in NONMEM. The performance of the PK/safety model was evaluated using model parameter estimates and their corresponding precision (SE), Akaike information criterion, and the ability of the model to describe the data.

To assess the risk for dizziness associated with doses up to 4 mg q.d., PK profiles were simulated for a large patient population ($N = 5{,}000$) using the population PK model and the covariates distribution in the phase II MDD population. $C_{max,Day1}$ were derived to estimate the probability of dizziness using the final regression model.

## RESULTS

### PK results

The population PK data set was composed of a total of 3,533 plasma samples from 288 individuals treated with MR basimglurant, of which there were 88 healthy subjects and 200 MDD patients. The majority of the analysis population ($N = 273$) received basimglurant with food, 35 individuals were fasted, and 20 received basimglurant with and without food on two occasions. Overall, 58% of the individuals were female and 17% were Asian. At baseline, the analysis population had a median weight of 71.9 kg and a median age of 43.5 years.

**Table 1** Model parameter values in the final population PK model

| Parameter | Estimate | RSE (%) |
|---|---|---|
| ***Fixed effect parameters***[a] | | |
| Clearance (CL) [L/h] | 8.87 | 6.58 |
| Volume of distribution of the central compartment (Vc/V4) [L] | 231 | 4.13 |
| Intercompartmental clearance (Q) [L/h] | 31.0 | 6.23 |
| Volume of distribution of the peripheral compartment (Vp/V5) [L] | 1140 | 5.08 |
| Ktr under fasted state [h-1] | 4.52 | 12.8 |
| Ktr under fed state [h-1] | 0.999 | 5.46 |
| Lag time under fasted state [h] | 0.212 | 10.6 |
| Lag time under fed state [h] | 0.120 | 9.25 |
| ***Covariate effect parameters*** | | |
| Ethnicity on Ktr_fasted | 0.588 | 15.2 |
| Gender on CL | 0.401 | 33.5 |
| Smoking status on CL | 1.08 | 20.0 |
| Body weight on Vc/V4 | 0.879 | 17.5 |
| Smoking status on Vc/V4 | 0.397 | 34.5 |
| Gender on Q | –0.213 | 33.5 |
| Body weight on Vp/V5 | 1.71 | 9.29 |
| Gender on Vp/V5 | –0.434 | 9.38 |
| Ethnicity on relative bioavailability (F) | 1.26 | 6.75 |
| ***Random effect parameters*** | | |
| BSV on CL [% CV] | 71.3 | 9.12 |
| BSV on Vc/V4 [% CV] | 25.9 | 23.9 |
| BSV on Q [% CV] | 36.3 | 23.3 |
| BSV on Vp/V5 [% CV] | 37.4 | 11.9 |
| BSV on Ktr_fasted [% CV] | 41.9 | 37.5 |
| BSV on Ktr_fed [% CV] | 53.8 | 10.4 |
| Correlation between BSV on CL and on Vc/V4 | 0.651 | 20.2 |
| Correlation between BSV on CL and on Q | 0.518 | 25.6 |
| Correlation between BSV on CL and on Vp/V5 | 0.248 | 24.1 |
| Correlation between BSV on Vc/V4 and on Q | 0.721 | 41.1 |
| Correlation between BSV on Vc/V4 and on Vp/V5 | 0.350 | 45.9 |
| Correlation between BSV on Q and on Vp/V5 | 0.550 | 34.4 |
| Proportional residual error [% CV] | 0.262 | 0.831 |

BSV, between-subject variability; CV, coefficient of variation; RSE, relative standard error.
[a]All clearances and volumes are apparent.

PK of basimglurant was best described by a two-compartment disposition model with a transit absorption compartment model (a chain of three compartments, including the depot compartment)[11] with a lag time and a first-order elimination. The residual variability (RV) was modeled with a proportional error model, and BSV was estimated on all PK parameters except lag time. Correlations among disposition parameters were found to be statistically significant.

The final PK model included the effects of food (FOOD) and Asian ethnicity (ETHN) on the absorption transit rate (Ktr), the effect of food on the lag time (Tlag), the effects of gender (SEX) and smoking status (SMOK) on apparent clearance (CL/F), the effect of body weight (WT) and SMOK on apparent central volume of distribution (Vc/F), the effect of SEX on apparent intercompartmental clearance (Q/F), the effects of

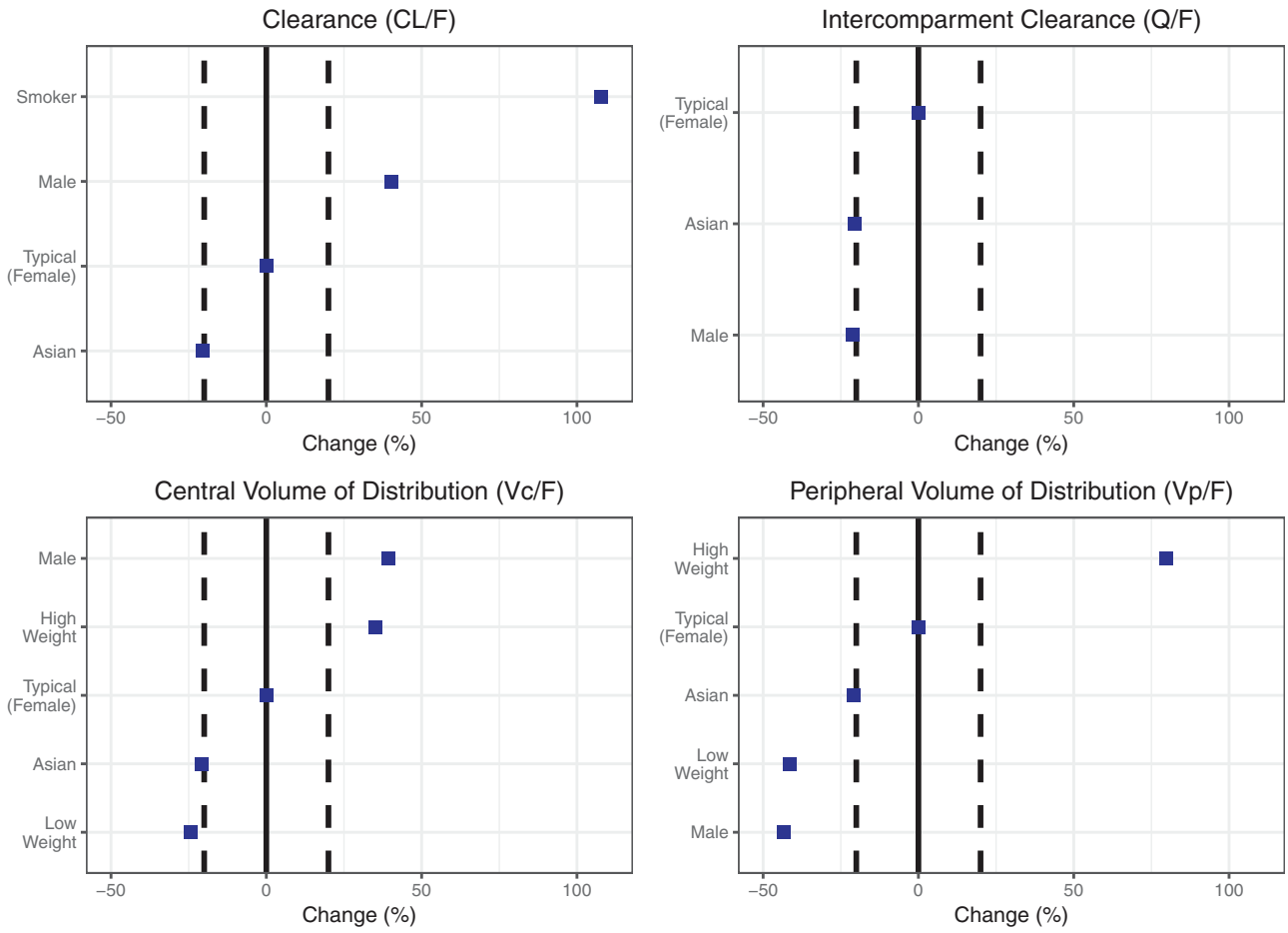


**Figure 2** Impact of covariate effects on the population PK parameters. Symbols represent the covariate effects as percent change from the value for a typical subject (i.e., female, non-Asian, nonsmoker with 71 kg body weight), the solid lines are the zero reference lines, the dashed lines represent a change of ±20%. The Low and High Weight category are fixed to 52 and 100 kg, respectively; the values correspond to the 5$^{th}$ and 95$^{th}$ percentiles of the weight distribution.

WT and SEX on apparent peripheral volume of distribution (Vp/F), and the effect of ETHN on the relative bioavailability (F). The equations of the final covariate models are presented below:

$$Ktr = 4.52 \cdot (1 - FOOD) \cdot (1 - 0.588 \cdot ETHN) + 0.999 \cdot FOOD$$

$$Tlag = 0.212 \cdot (1 - FOOD) + 0.12 \cdot FOOD$$

$$CL/F = 8.87 \cdot (1 + 1.08 \cdot SMOK) \cdot (1 + 0.401 \cdot SEX)$$

$$Vc/F = 231 \cdot \left(\frac{WT}{71}\right)^{0.879} \cdot (1 + 0.397 \cdot SMOK)$$

$$Q/F = 31.0 \cdot (1 - 0.213 \cdot SEX)$$

$$Vp/F = 1140 \cdot (1 - 0.434 \cdot SEX) \cdot \left(\frac{WT}{71}\right)^{1.71}$$

$$F = 1 + 1.26 \cdot ETHN$$

All population parameters were well estimated, with relative standard errors (RSE) below 35% for the fixed effect parameters. Parameter estimates with RSE are shown in **Table 1**.

Food slows down the absorption transit rate (Ktr) of basimglurant, while the absorption starts slightly earlier with food. **Figure 2** shows the percentage changes in the population disposition parameters from the typical value due to covariates and **Figure 3** illustrates the combined effect of the significant covariates, smoking, gender, and race, on the population PK profile at steady state.

Overall, the goodness-of-fit plots presented in **Figure S1** showed good agreement between observed and predicted data, with a slight deviation from the unity line for predicted concentrations above ~10 ng/mL. The plots of conditional weighted residuals vs. time or vs. population prediction showed a random distribution of data points around the zero line, with the majority of data within two SD and a slight deviation from the zero line for late timepoints. The distribution of the conditional weighted residuals did not indicate any major deviation from normality. The results of the visual predictive check on the phase II study (**Figures S1** and **S2**) confirmed that the model captured both the central tendency and the BSV of basimglurant PK except for the late timepoints collected at follow-up visit. The shrinkage for CL/F, Vc/F, Q/F, and Vp/F was 3.4, 26, 31, and 29%, respectively, indicating

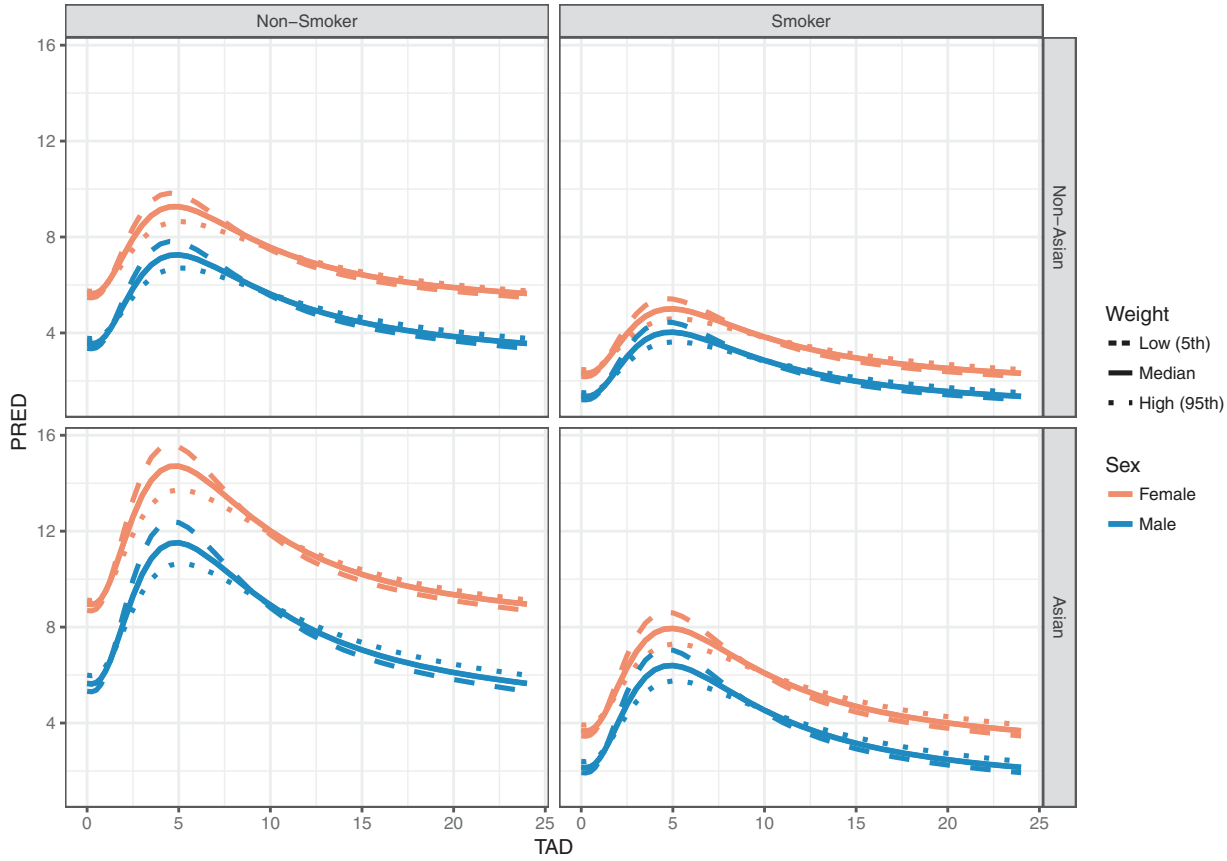


**Figure 3** Impact of the covariate effects on the population PK profiles at steady-state. Low, Median, and High weight are equal to 52, 71 and 100 kg, respectively.

**Table 2** Evaluation of the relationship between $C_{max,Day1}$ and the risk of dizziness

| Model | Parameter | Estimate (standard error) | *P* value | Odds ratio estimate (95% confidence interval) |
|---|---|---|---|---|
| With $C_{max,Day1}$ | Intercept | −2.970 (0.301) | <0.0001 | 1.510 (1.279–1.802) |
| | Slope | 0.412 (0.087) | <0.0001 | |

that the sampling scheme was informative to derive individual disposition parameter estimates. The shrinkage for Ktr in fed condition was 30%, while in fasted condition it was 67%, likely due to a less informative sampling scheme to describe the absorption in fasted subjects.

### Exposure–safety results

In all, 310 patients, 110 in the placebo group (among whom 6 reported dizziness), 99 in the 0.5 mg dose group (among whom 3 reported dizziness), and 101 in the 1.5 mg dose group (among whom 26 reported dizziness), were included in the analysis. The median (minimum–maximum) values of $C_{max,Day1}$ in MDD patients were 1.21 ng/mL (0.42–3.26 ng/mL) at 0.5 mg and 3.47 ng/mL (1.04–9.62 ng/mL) at 1.5 mg.

The results of the logistic regression analysis indicate that $C_{max,Day1}$ was statistically correlated with the occurrence of dizziness and that rates of dizziness increased with increasing basimglurant $C_{max,Day1}$ ($P < 0.0001$, **Table 2**). Besides $C_{max}$, none of the other covariates were statistically significant. The risk of dizziness at the doses investigated in MDD patients (i.e., 0.5 and 1.5 mg) was predicted at 9% and 24%, respectively. The exposure–response relationship is illustrated in (**Figure 4**).

The availability of a model also allowed for estimating simulated exposure from daily doses up to 4 mg and the associated risk for dizziness (**Table 3**). The predicted probability of dizziness is 66% for a dose of 3 mg and 87% for a dose of 4 mg, indicating higher doses may not have acceptable tolerability unless some alterations, such as titration, were introduced.

## DISCUSSION

The objectives of the presented analysis were to characterize basimglurant population PK in healthy subjects and in patients with MDD and to explore the relationship between basimglurant exposure and dizziness, the most frequently observed AE in MDD patients treated with basimglurant.

The inspection of the goodness-of-fit plots and of the prediction-corrected visual predictive check (pcVPC) plots demonstrated that overall the final PK model was able to describe and reproduce the data and therefore could be used for simulation. However, some deviation from the

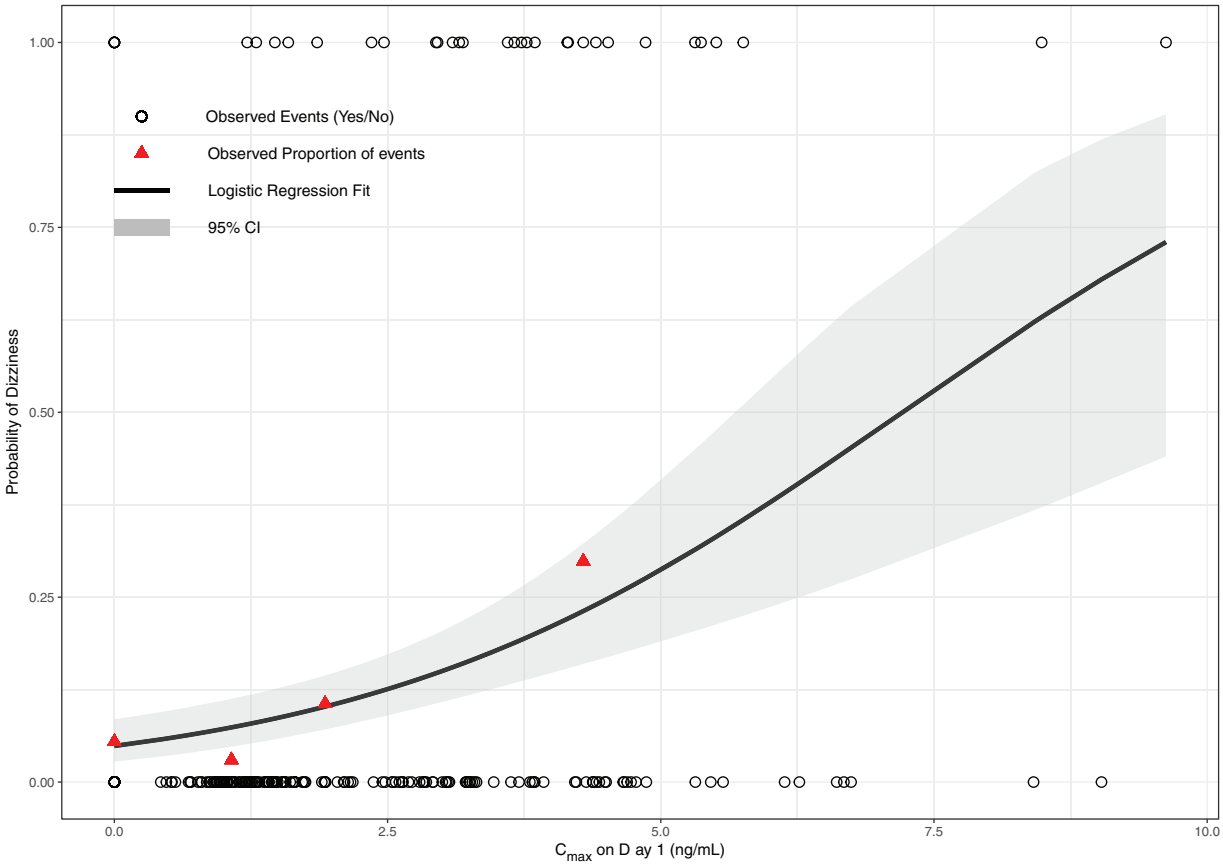


**Figure 4** Exposure–response relationship for the risk of dizziness. The solid line and shaded region indicate the model prediction and 95% CI for the logistic regression.

**Table 3** Predicted dizziness probability for $C_{max,Day1}$ at different dose levels

| Dose | $C_{max,Day1}$ (ng/mL) | Predicted dizziness probability in % |
|---|---|---|
| 0.5 mg | 1.47 (0.592–3.73) | 8.6 (6.1–19) |
| 1.5 mg | 4.42 (1.77–11.2) | 24 (9.6–84) |
| 2.0 mg[a] | 5.89 (2.37–14.9) | 37 (12–96) |
| 2.5 mg[a] | 7.36 (2.96–18.6) | 52 (15–99) |
| 3.0 mg[a] | 8.83 (3.55–22.4) | 66 (18–100) |
| 4.0 mg[a] | 11.8 (4.73–29.8) | 87 (27–100) |

[a]Assuming linear pharmacokinetics at higher doses. Data for $C_{max}$ shows median (95% PI). Data for predicted dizziness show the probabilities for the respective percentiles of $C_{max}$ (i.e., median, 2.5th and 97.5%).

identity line in the DV vs. PRED plot at low concentrations and a poorer performance of the model in describing late timepoints collected at follow-up visit in the phase II trial have been observed. The discrepancies seen on the pcVPC of the phase II trial could be explained by the fact that PK samples at those late timepoints were collected in only 40% of the MDD population.

During the covariate search no difference in the PK of basimglurant between healthy subjects and MDD patients was detected. An effective half-life of 107 hours in a typical MDD female patient and of 49 hours in an MDD typical male patient were estimated, both of whom represent non-smoking, non-Asians, and weight 71 kg.

The elimination of basimglurant is mainly mediated by oxidative metabolism; *in vitro* enzyme phenotyping and kinetics studies have demonstrated that at the concentrations attained clinically, basimglurant metabolic clearance is catalyzed mainly by CYP1A2[12]; this was confirmed in a clinical study using a CYP1A2 inhibitor, fluvoxamine, and lack of effect with a CYP3A4 inhibitor, ketoconazole. It is therefore not surprising that the covariates affecting CL/F directly, i.e., smoking status and gender and indirectly via the relative bioavailability, i.e., Asian ethnicity, are related to this metabolic pathway. Smoking increased CL/F by more than twofold, resulting in 52% lower AUC at steady state and a shorter terminal half-life, 76 hours vs. 129 hours in a smoker vs. non-smoker; nicotine induces cytochrome P450 (CYP450) isoenzymes,[18] especially CYP1A2. In males, AUC and $C_{max}$ at steady state were 30% and 20% lower, respectively, and the terminal half-life decreased from 129 hours in females to 63 hours in males; it is known that gender has an effect on CYP1A2 activity, with males having a higher activity.[19–21] Asians have slightly higher bioavailability (26%) compared with non-Asians. This may be due to the ethnic differences in CYP1A2 metabolic capabilities resulting in lower intrinsic clearance of CYP1A2.[22] A confounding effect between weight on the one hand and gender or smoking

status on the other can be ruled out, as the distributions of weights in women and men or in smokers and nonsmokers largely overlap (**Figure S3**). The large BSV on CL/F (71%) may be due to a wide interindividual variation in CYP1A2 activity, which in turn may be due to environmental factors.[23]

A body weight effect on the central and peripheral volumes of distribution was identified. Higher body weight was associated with longer terminal half-life and lower $C_{max}$, while AUC at steady state was not influenced by body weight.

Food intake was found to slow down the absorption, with a reduced $C_{max}$ by ~30% and delayed $T_{max}$ by 2.5 hours compared with fasted state on Day 1. Ethnicity influences the absorption only under fasted condition, with the absorption delayed by 1.5 hours in Asian subjects.

A logistic regression model was selected for characterizing the exposure–dizziness relationship. The results showed a highly significant relationship ($P < 0.0001$) with $C_{max}$ on Day 1 with an odds ratio of 1.510 (95% CI: 1.279–1.802). The clinical data showed an exposure-dependent incidence of dizziness soon after basimglurant administration of 9% (CI: 6–13) and 24% (CI: 16–34) at the two doses tested in MDD patients. Due to only trends of efficacy noted in the clinical trial,[10] the risk of dizziness at higher doses was investigated for future dose exploration. Due to a limited number of high-exposure values, the uncertainty around the prediction of the probability of dizziness is larger for high exposure. Thus, extrapolation of the risk at exposure levels that were higher than observed in the patient trial should be interpreted with caution, but can still provide a prediction of risk. Predictions of dizziness rates at higher, untested doses ranged from 37–87%. Further investigation into the time course of dizziness showed that there was rapid onset (peak around Day 1) and spontaneous resolution (within 4–5 days, **Figure 1**). Taken together, the important relation of exposure to dizziness and the observed pattern of spontaneous resolution, it is anticipated that consistent with previous attempts with other drugs in this class[24] the risk of increased frequency or severity of dizziness at higher doses could be mitigated by titration. This hypothesis was tested in a subsequent trial conducted to explore higher doses in healthy subjects and patients with MDD (NCT02433093, Collaborative Neuroscience Network, CA, USA). In the patient cohort ($n = 6$ on active, 2 on placebo), a top daily dose of 2.5 mg was administered for 22 days titrated up from a starting dose of 1.5 mg. Rates of dizziness were markedly reduced compared with the predictions from the phase II trial, with only one patient reporting dizziness (unpublished results). While the small cohort size limits the clinical interpretation, conceptually, the titration scheme provided a proof-of-concept for the titration approach.

In conclusion, population PK of basimglurant in healthy subjects and MDD patients was characterized by means of a nonlinear mixed effects model. The PK model identified significant effects of ethnicity on absorption and gender, smoking status, and body weight on disposition parameters. The exposure–dizziness model predicted a steep increase in incidence of dizziness with increasing exposure. This prediction, along with the observation of tolerance to dizziness with time, warrants the recommendation of a dose titration strategy in future studies to keep the incidence of dizziness to low levels while achieving higher exposures for maintenance of efficacy.

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