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Research Article

Development of a Population Pharmacokinetic Model for Taranabant, a Cannibinoid-1 Receptor Inverse Agonist

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Abstract. Taranabant is a cannabinoid-1 receptor inverse agonist developed for the treatment of obesity. A population model was constructed to facilitate the estimation of pharmacokinetic parameters and to identify the influence of selected covariates. Data from 12 phase 1 studies and one phase 2 study were pooled from subjects administered single and multiple oral doses of taranabant ranging from 0.5 to 8 mg. A total of 6,834 taranabant plasma concentrations from 187 healthy and 385 obese subjects were used to develop the population model in NONMEM. A standard covariate analysis using forward selection (α=0.05) and backward elimination (α=0.001) was conducted. A three-compartment model with first-order absorption and elimination adequately described plasma taranabant concentrations. The population mean estimates for apparent clearance and apparent steady-state volume of distribution were 25.4 L/h and 2,578 L, respectively. Statistically significant covariate effects were modest in magnitude and not considered clinically relevant (the effects of body mass index (BMI) and creatinine clearance (CrCL) on apparent clearance; BMI, age, CrCL, and gender on apparent volume of the peripheral compartment and age on apparent intercompartmental clearance). The pharmacokinetic profile of taranabant can adequately be described by a three-compartment model with first-order absorption and elimination. Clinical dose adjustment based on covariates effects is not warranted.

KEY WORDS: NONMEM; obesity; pharmacokinetics; population; taranabant.

INTRODUCTION

Taranabant is a potent and selective cannabinoid-1 receptor inverse agonist that has demonstrated a dose-dependent inhibition of food intake and weight gain, resulting in weight loss and decreased fat mass in preclinical models of obesity (1). In the clinical setting, taranabant reduced acute food intake over 24 h and increased energy expenditure between 2 and 5 h post-dose *versus* placebo in overweight and obese male volunteers (2). Taranabant also led to clinically significant, dose-dependent reductions in body weight and waist circumference in obese and overweight adults (3). Decreased food intake and increased energy expenditure are responsible for the weight loss observed with taranabant (2).

Pharmacokinetic (PK) data in humans indicate that taranabant is rapidly absorbed with the time of maximum plasma concentration occurring between 1 and 2.5 h. Taranabant plasma concentrations then decrease in a multiphasic manner, with an initial rapid decline followed by a slower decline with an apparent terminal half-life of ~70 to 100 h following single- or multiple-dose administration (4,5).

Taranabant is a lipophilic compound (ClogP=6.7) and distributes widely into adipose tissue (unpublished data). This is supported by the multiphasic decline in taranabant plasma concentrations indicating distribution into deep tissue compartments and subsequent elimination. *In vitro* studies indicate taranabant is highly protein bound (>98%) to both albumin and alpha$_1$ acid glycoprotein (unpublished data).

Following single-dose oral administration of taranabant, area under the plasma concentration–time curve ($AUC_{0-\infty}$) increases approximately linearly with doses up to 200 mg, with slightly less than dose-proportional increases in $AUC_{0-\infty}$ at higher doses. Maximum taranabant concentration (C_{max}) demonstrates similar increases with dose (4). Following multiple-dose administration of taranabant, the plasma concentration–time curve from 0 to 24 h (AUC_{0-24}) and C_{max} increase in a dose-proportional manner over the dose range of 5 to 10 mg, but increases are somewhat less than dose proportional at 25 mg, possibly due to autoinduction (5). Accumulation of plasma taranabant concentrations is approximately twofold after multiple-dose administration. When single oral doses of taranabant 25 mg were coadministered with a standard high-fat breakfast, there was a 14% increase in C_{max} and a 74% increase in $AUC_{0-\infty}$. Food status did not affect 24-h trough concentrations (4).

Taranabant is almost exclusively cleared by metabolism via cytochrome P450 3A4 with minimal renal excretion of the parent compound (4). Its primary active metabolite, M1, circulates in plasma with concentrations generally two to

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three times higher than taranabant and with a comparable apparent terminal half-life, suggesting formation rate-limited elimination (5).

The primary objectives of this analysis were to characterize the population PK of taranabant using pooled data from 12 phase 1 studies and one phase 2 study and to assess the influence of subject covariates on taranabant PK. The taranabant PK model described in this analysis was used to simulate 24-h trough concentrations for future phase 2 and phase 3 studies, which were subsequently used in exposure–response analyses of safety and efficacy.

METHODS

Study Design

Data from 12 phase 1 studies (full profile data) and one phase 2 study (sparse data) were used to develop the population PK model for taranabant (Table I). Subjects that received single doses of taranabant from 0.5 to 8 mg or multiple doses of taranabant from 0.5 mg to less than 10 mg daily were included in this analysis. Single doses greater than 12 mg were excluded from the analysis to more closely match the expected clinical dose range from the phase 2 and phase 3 studies (0.5 to 6 mg). Multiple doses greater than 10 mg were excluded in order to simplify the PK model because induction of metabolism may occur at these doses. Intravenous doses of taranabant were excluded because this formulation was not intended for clinical application and only a small number of subjects received this formulation relative to the total number of subjects included in the analysis.

The subjects in 10 of the 12 phase 1 studies were healthy men and women between 18 and 45 years of age. One phase 1 study also included subjects with renal insufficiency (creatinine clearance (CrCL) ≤80 mL/min). Another study contained 12 subjects with moderate hepatic insufficiency (Child Pugh Score of 7 to 9); however, subjects with hepatic impairment were excluded from this population PK analysis because demographic information related to liver function was not available for healthy subjects, and the effect of hepatic insufficiency could not be fully evaluated in the population PK model. The phase 2 study evaluated the safety and efficacy of taranabant in obese subjects (body mass index (BMI): 30 to 43 kg/m^2) between the ages of 21 and 65 years of age.

All subjects gave written informed consent and study protocols were approved by an investigational review board and conducted in accordance with the guidelines on Good Clinical Practice and with ethical standards for human experimentation established by the Declaration of Helsinki.

Pharmacokinetic Assessments

In the phase 1 studies, blood samples for PK analysis were collected at frequent intervals between 0.25 and 360 h post-dose. In the phase 2 study, most subjects had one blood sample collected 2 h post-dose at week 4, six samples collected at approximately 24 h post-dose at weeks 2, 4, 6, 8, and 12, and one sample collected approximately 28 days following the final dose of taranabant at week 16. It was assumed that 13 daily doses were received prior to the week 2 dose, while all other doses were assumed to be administered under steady-state conditions.

The analytical methods for determination of taranabant plasma concentrations have been described previously (4,5). The process included cohesive high-turbulence liquid chromatography for online extraction from plasma using turbulent flow chromatography, high-performance liquid chromatography for separation, and tandem mass spectrometry for detection in the positive ionization mode using a TurboIonSpray interface and monitoring the precursor–product ion in combination with multiple-reaction monitoring mode. The lower limit of quantification was 0.1 nM for taranabant with corresponding linear calibration range for taranabant was 0.1 to 100 nM. The accuracy ranged from 90.0% to 110.0%, with less than 8.8% coefficient of variation (CV). The mean recovery was 80.9%. Plasma concentrations below the lower limit of quantitation were removed from the analysis.

Population Pharmacokinetic Model Development

A population PK structural model was developed for taranabant. Metabolite concentrations were not modeled, as M1 is formation rate-limited and thus the concentrations always parallel parent concentrations with a high degree of correlation (5). All data preparation and presentation were performed using SAS® Version 9 (6) and/or S-PLUS Server Version 7.0 (7). Population PK modeling was performed using the computer program NONMEM®, Version VI, Level 1.0 with NM-TRAN, Version III, Level 1.1, and PREDPP, Version IV, Level 1.1 (8). Both two- and three-compartment structural PK models with first-order absorption and first-order elimination were initially evaluated. Taranabant elimination was parameterized in terms of apparent clearances (e.g., CL/*F*). Interindividual variability (IIV) for each PK parameter was estimated using an exponential error model while an additive plus proportional error model was initially used to describe residual variability (RV).

Model selection was based on standard goodness-of-fit plots, precision of the parameter estimates, changes in the estimates of IIV and RV for a specified model *versus* a comparator model, and the minimum value of the objective function (MVOF). The MVOF is a statistic that is proportional to minus twice the log likelihood of the data. In the case of hierarchical models, the change in the MVOF produced by the inclusion or deletion of an additional parameter when boundary conditions do not apply is asymptotically χ^2 distributed with the number of degrees of freedom equal to the number of parameters added to or deleted from the model. The magnitude of inherent Bayesian shrinkage was calculated for each parameter in which IIV was estimated (9).

A standard forward selection and backward elimination procedure was used to evaluate the effects of subject covariates on PK parameters. Covariates that were tested included age, BMI, body weight, CrCL, gender, and race. In the phase 2 data, BMI, body weight, and CrCL were non-stationary (i.e., changed with time). During forward selection,

Table I. Studies Available for the Population PK Analysis of Taranabant

Study No.	Study Title	Description of Subjects	Taranabant Dosing Strategy[a,b]
001	A Double-Blind, Randomized, Placebo-Controlled, Rising Single Oral Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of Taranabant in Healthy Male Volunteers	12 Healthy men; 18 to 45 years	Single oral doses of 0.5, 1, 2.5, 5, 12.5, 25, 50, 100, and 150 mg
003	A Double-Blind, Randomized, Placebo-Controlled, Staggered, Incremental Oral Dose, Parallel-Group Study to Assess the Safety, Tolerability, and Pharmacokinetics of Taranabant With Multiple-Dose Administration for 2 Weeks	54 Healthy non-obese men; 18 to 45 years	Single and multiple oral doses of 5, 7.5, 10, and 25 mg of taranabant
009[c]	A Randomized, Partially-Blinded, 2-Period, Fixed-Sequence Study in Healthy Subjects to Evaluate the Effects of Multiple Oral Doses of Ketoconazole (NIZORAL®) on the Single-Dose Pharmacokinetics of Taranabant	8 Healthy men and women; 18 to 45 years	Single oral dose of 2.5 mg taranabant followed by a single oral dose of 2.5 mg taranabant on Day5 after multiple doses of ketoconazole
010[c]	A Randomized, Partially-Blinded, 2-Period, Fixed-Sequence Study to Evaluate the Effect of Multiple Doses of Taranabant on the Pharmacokinetics of Midazolam in Healthy Adult Subjects	8 Healthy men and women; 18 to 45 years	Multiple oral doses of 6 mg taranabant daily on Days 1 to 28 and single doses of 2.0 mg midazolam syrup on Days 4 and 28
017[c]	A Randomized, Partially-Blinded, 2-Period, Fixed-Sequence Study to Determine the Effects of Diltiazem (CARDIZEM™ CD) on L-000899055 Pharmacokinetics in Healthy Subjects	12 Healthy men and women; 18 and 45 years	Single oral dose of 2.5 mg taranabant followed by a single oral dose of 2.5 mg taranabant on Day 5 after multiple doses of diltiazem
025	A Double-Blind, Randomized, Placebo-Controlled, Rising Single Oral Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics and Effect of Food on the Pharmacokinetics of Taranabant in Healthy Japanese Male Volunteers	18 Healthy Japanese men; 20 to 45 years	Single oral doses of 2, 6, 12, 24, and 36 mg of taranabant
026	A Double-Blind, Randomized, Placebo-Controlled, Double-Dummy, 4-Arm, Single-Dose Parallel Study to Assess the Effect of Taranabant on QTc Interval in Healthy Volunteers	80 Healthy men; 18 to 45 years	Single oral doses of 8 and 100 mg of taranabant
029	An Open-Label, Single-Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of Taranabant in Subjects With Renal Insufficiency	16 Men and women; 18 to 70 years 7 subjects with severe; 2 subjects with moderate; and 5 subjects with mild renal insufficiency; 2 healthy subjects	Single oral dose of 2 mg of taranabant
031[d]	An Open-Label, Single-Dose Study to Investigate the Pharmacokinetics of Taranabant in Subjects with Moderate Hepatic Insufficiency	16 Men and women; 18 to 75 years 8 subjects with moderate hepatic insufficiency; 8 healthy subjects	Single oral dose of 1 mg of taranabant
034	Taranabant Phase I Multiple Oral Dose Study: A Double-Blind, Randomized, Placebo-Controlled, 4-Panel, Multiple Oral Dose Study in Young Healthy Non-obese Japanese Male Subjects and Young Healthy Obese Japanese Male Subjects	27 Japanese men; 20 to 45 years Groups A to C: BMI $\geq$18 kg/m^2 and 25 kg/m^2 Group D: BMI $\geq$25 kg/m^2	Multiple oral doses Group A: 2 mg daily for 14 days Group B: 6 mg daily for 14 days Group C: 10 mg daily for 14 days Group D: 6 mg daily for 28 days
036[c]	A Randomized, Double-Blind, Double-Dummy, 3-Period, Fixed Sequence, and 2-Period Fixed-Sequence Study to Evaluate the Effects of Taranabant on Phentermine Pharmacokinetics and Safety and Tolerability After Coadministration of Taranabant and Phentermine in Healthy Subjects	10 Healthy men and women; 18 to 45 years	Multiple oral doses of 0.5 mg taranabant daily for 14 days Followed by 0.5 mg taranabant and 15 mg phentermine daily for 7 days
042[e]	A 2-Part, Partially-Blinded, Randomized, Placebo-Controlled, Intravenous Dose Escalation Study to Evaluate the Safety and Tolerability and Pharmacokinetics of Rising Intravenous Doses	30 Healthy men and women 18 to 60 years	Part 2: Single oral dose 3-period crossover A: 2 mg, fasting B: 2 mg with high-fat meal

Table I. (continued)

Study No.	Study Title	Description of Subjects	Taranabant Dosing Strategy[a,b]
	of Taranabant and the Definitive Absolute Bioavailability/Food Effect of Taranabant Final Market Image Capsules in Healthy Adult Subjects		C: 2 mg with light meal Part 2, Period 4: 1 mg IV infusion, fasting
006	A Phase II Study to Evaluate the Safety and Efficacy of Taranabant in Obese Subjects	400 Obese men and women 21 to 65 years BMI 30 to 43 kg/m^2	Multiple oral doses of 0.5, 2, 4, and 6 mg of taranabant once daily for 12 weeks

BMI body mass index
[a] Only those subjects, drugs, formulations, and study periods available for the present analysis are included; subjects who received placebo or other drugs alone are not included. The number of subjects planned in the study protocol may not be the same as the number of final subjects included in the present analysis
[b] Single doses greater than 12 mg and multiple doses greater than or equal to 10 mg were excluded from the analysis
[c] Only PK data following administration of taranabant alone was utilized in these drug–drug interaction studies
[d] Data from subjects with hepatic insufficiency was not utilized in this analysis
[e] PK data obtained following intravenous administration of taranabant was not used in this analysis

a covariate contributing at least a 3.84 unit change in the MVOF (α=0.05, one degree of freedom) and a decrease in IIV on the PK parameter of interest was considered statistically significant. During backward elimination, a covariate was considered significant if it contributed at least a 10.83 unit change in the MVOF (α=0.001, one degree of freedom) when removed from the model.

The adequacy of the final population PK model was investigated using a visual predictive check. The fixed and random effect parameters from the final model were used to simulate 1,000 replicates of the observed dataset. The 5th, 50th (median), and 95th percentiles of the distributions of the simulated concentration values at each sampling time (binned when necessary) were calculated. These percentiles of the simulated data were plotted (overlaid) on the original observed data to visually assess concordance of the model-based simulated and observed data. The model was considered adequate if approximately 90% of the data fell within the 5th to 95th percentiles.

Individual predicted steady-state trough concentrations at 24 h ($C_{ss(24)}$) were generated using the empiric Bayesian PK parameter estimates and the final PK model equations. Individual steady-state AUC ($AUC_{ss(0–24)}$) was calculated by dividing dose by the individual subject's apparent clearance (CL/*F*). For the phase 2 data, the geometric mean of CL/*F* was used for this calculation in order to produce a time-averaged CL/*F*.

Covariates included in the final model were tested to determine if the magnitude of the covariate effect was clinically significant. An approximate twofold increase or 50% decrease in the population mean value of $AUC_{ss(0–24)}$ was defined as a clinically meaningful change in taranabant exposure. The bounds were determined based on all available safety and efficacy data from phase 2 and phase 3 clinical studies. Reference ratios of the typical population values of $AUC_{ss(0–24)}$ were calculated. For dichotomous covariates, the ratio compares the population mean values with or without the covariate. For continuous covariates, the ratio compares the population mean values for the model-predicted steady-state exposures at a specific value in the covariate distribution compared with a reference value of the covariate. The reference values were selected based on the available covariate distributions in the phase 1 and phase 2 studies. Covariates other than the covariate of interest were set to the median value.

RESULTS

Data and Demographic Characteristics

The analysis dataset used to develop the population PK model included 6,834 plasma taranabant concentrations from

Table II. Baseline Demographic Characteristics for the Phase 1 and Phase 2 Subjects

Subject Characteristic	Phase 1	Phase 2	Pooled Phase 1 and 2
Age (years)			
Mean (SD)	33.5 (11.6)	42.3 (10.18)	39.5 (11.4)
Median	32.0	41.0	39.0
Min, Max	18.0, 69.0	21.0, 65.0	18.0, 69.0
n	187	385	572
Baseline BMI (kg/m^2)			
Mean (SD)	25.0 (3.2)	35.4 (3.8)	32.0 (6.1)
Median	24.8	35.0	32.5
Min, Max	18.9, 34.3	28.4, 43.4	18.9, 43.4
n	187	385	572
Baseline CrCL (mL/min)			
Mean (SD)	95.6 (26.3)	73.3 (16.2)	80.6 (22.6)
Median	96.7	70.7	78.4
Min, Max	5.1, 171	33.9, 125	5.1, 171
n	187	385	572
Baseline Weight (kg)			
Mean (SD)	74.3 (12.0)	97.1 (14.4)	89.7(17.4)
Median	73.7	96.1	88.9
Min, Max	50.0, 111	67.5, 151	50.0, 151
n	187	385	572
Race, *n* (%)			
White	91 (15.9)	263 (46.0)	354 (61.9)
Black	17 (3.0)	80 (14.0)	97 (17.0)
Asian	34 (5.9)	1 (0.2)	35 (6.1)
Hispanic	45 (7.9)	37 (6.5)	82 (14.3)
Other	0 (0.0)	4 (0.7)	4 (0.7)
Gender, *n* (%)			
Male	150 (26.2)	54 (9.4)	204 (35.7)
Female	37 (6.5)	331 (57.9)	368 (64.3)

572 subjects. The phase 1 data consisted of 4,282 taranabant plasma concentrations from 187 subjects with each individual subject contributing between 8 and 44 blood samples. The phase 2 data consisted of 2,552 taranabant plasma concentrations from 385 obese subjects with each individual subject contributing between 1 and 8 blood samples.

Subjects in the phase 1 studies were primarily white males with a median BMI of approximately 25 kg/m^2 and a median age of 32 years. A limited number of subjects with renal insufficiency were included in the phase 1 data. Creatinine clearance ranged from <10 to 171 mL/min. Subjects in the phase 2 trial were predominately white females with a median BMI of approximately 35 kg/m^2 and a median age of 41 years. Creatinine clearance ranged from 33.9 to 125 mL/min in the phase 2 subjects. Baseline demographic characteristics for the subjects in the phase 1 and phase 2 studies are provided in Table II.

Population Pharmacokinetic Model

Taranabant PK was described by a three-compartment model with first-order absorption and first-order elimination using the first-order conditional estimation method with interaction in NONMEM. Numerous more complex absorption models including combined first- and zero-order absorption processes and transit compartment absorption models were evaluated in order to characterize the highly variable absorption process noted with taranabant; however, none of these models provided an acceptable alternative to first-order absorption based on a lack of improvement in goodness-of-fit plots or failure to minimize successfully in NONMEM. The population PK model was parameterized is terms of absorption rate constant (k_a), CL/F, apparent central volume of distribution (V_2/F), apparent volume of distribution for the first peripheral compartment (V_3/F), apparent intercompartmental clearance between the central compartment and the first peripheral compartment (Q_3/F), apparent volume of distribution for the second peripheral compartment (V_4/F), and apparent intercompartmental clearance between the central compartment and the second peripheral compartment (Q_4/F).

Pharmacokinetic parameters were assumed to have a log-normal distribution, and IIV was estimated on k_a, CL/F, V_2/F, Q_3/F, V_4/F, and Q_4/F using exponential error models. Covariance was estimated between the IIV terms for k_a and Q_3/F and k_a and Q_4/F, as well as Q_3/F and Q_4/F. A time-dependent RV model was used for the phase 1 data to account for differences in the magnitude of RV between taranabant absorption and disposition [10]. A step function was used to partition the magnitude of RV whereby separate proportional error models were estimated for PK observations collected less than 2 h after the administration of a dose and greater than or equal to 2 h after the administration of a dose. Two hours was selected as the time point for the change in variance because absorption was completed by this time in

Table III. Parameter Estimates and Standard Errors for the Taranabant PK Model Estimated Using the Phase 1 and Phase 2 Data

Parameter	Final parameter estimate		Magnitude of interindividual variability (%CV)	
	Population mean	%SEM	Final estimate	%SEM
Absorption rate constant (k_a; 1/h)	2.73	18.1	73.0	38.5
Apparent clearance (CL/F; L/h)	25.4	2.1	44.1	7.8
Apparent central volume of distribution (V_2/F; L)	175	4.3	29.7	18.8
Apparent volume of distribution for compartment 2 (V_3/F; L)	273	10.5	NE	NE
Apparent intercompartmental clearance 3 (Q_3/F; L/h)	24.6	5.6	37.2	28.8
Apparent volume of distribution for compartment 3 (V_4/F; L)	2130	7.7	33.3	20.5
Apparent intercompartmental clearance 4 (Q_4/F; L/h)	30.4	5.2	35.9	24.3
Exponent for relationship between V_4 and BMI (L/(kg/m^2))	1.38	18.6	NA	NA
Exponent for relationship between CL and BMI ((L/h)/(kg/m^2))	-1.11	10.0	NA	NA
Change in CL per unit change in CrCL ((L/h)/(mL/min))	0.0668	27.1	NA	NA
Exponent for relationship between Q_4/F and age ((L/h)/year)	0.357	24.0	NA	NA
Intercept for age on V_4/F (L)	752	28.2	NA	NA
Exponent for relationship between V_4/F and age (L/year)	2.10	26.6	NA	NA
Additive shift on V_4/F for female subjects (L)	643	26.0	NA	NA
Change in V_4 per unit change in CrCL (L/(mL/min))	12.5	24.8	NA	NA
cov (IIV on k_a, IIV on Q_3/F)	0.0901	62.5	NA	NA
cov (IIV on k_a, IIV on Q_4/F)	0.0676	44.4	NA	NA
cov (IIV on Q_3, IIV on Q_4/F)	0.0764	28.7	NA	NA
Proportional RV (Phase 1, TSLD <2 h)	0.407	11.4	NA	NA
Proportional RV (Phase 1, TSLD ≥2 h)	0.0526	10.5	NA	NA
Proportional RV (Phase 2)	0.126	7.3	NA	NA
Additive RV (Phase 2)	0.00385	35.8	NA	NA
Minimum value of the objective function = 10,510				

%CV percent coefficient of variation, *%SEM* percent standard error of the mean, *F* bioavailability factor, *IIV* interindividual variability, *TSLD* time since last dose, *RV* residual variability, *NA* not applicable, *NE* not estimated

%CV for Proportional RV (Phase 1, TSLD <2 h)=63.80%CV, %CV for Proportional RV (Phase 1, TSLD ≥2 h)=22.93%CV, and %CV for Phase 2 is 71.48%CV at 0.1 nM, 36.03%CV at 1 nM, 35.50%CV at 10 nM, 35.50%CV at 100 nM, and 35.50%CV at 1,000 nM

Vd_{ss}/F=2,578 L, $t_{1/2\alpha}$=1.40 h, $t_{1/2\beta}$=11.2 h, and $t_{1/2\gamma}$=114 h for the typical 39-year-old, male subject with a body mass index of 31.5 kg/m^2 and creatinine clearance of 80.6 mL/min

most individuals. A separate additive plus proportional residual error model was used for the phase 2 data but because there was limited plasma concentration data prior to 2 h, the RV did not vary with time.

The effects of age, body weight, BMI, CrCL, race, and gender were tested using standard forward selection and backward elimination procedures. Although, the effects of BMI and body weight were tested on each parameter, after evaluation of the MVOF and IIV either BMI or body weight was selected for any individual parameter. Despite the knowledge that food had a significant impact on taranabant $AUC_{0-\infty}$ (4), the effect of food was not maintained in the final model because it was shown to have a limited impact on taranabant C_{24}, the exposure measure targeted for future pharmacokinetic–pharmacodynamic analyses. In addition, information concerning food intake was not available for the phase 2 study as dosing was administered without regard to food.

Seven statistically significant covariates were included in the final model following backward elimination including the effect of BMI and CrCL on CL/*F*, the effect of BMI, age, CrCL, and gender on V_4/F, and the effect of age on Q_4/F. The parameter estimates and precision of these estimates from the final model are provided in Table III. Equations for the typical value of CL/*F*, Q_4/F, and V_4/F are:

$$\mathrm{TVCL}/F_{ij}(\mathrm{L/h}) = 25.4 \cdot \left(\frac{\mathrm{BMI}_{ij}}{31.5}\right)^{-1.11} + 0.0668 \cdot \left(\mathrm{CrCL}_{ij} - 80.6\right) \quad (1)$$

$$\mathrm{TVQ_4}/F_{ij}(\mathrm{L/h}) = 30.4 \cdot \left(\frac{\mathrm{AGE}_i}{39}\right)^{0.357} \quad (2)$$

$$\mathrm{TVV4}/F_{ij}(\mathrm{L}) = 2130 \cdot \left(\frac{\mathrm{BMI}_{ij}}{31.5}\right)^{1.38} + 752 \cdot \left(\frac{\mathrm{AGE}_i}{39}\right)^{2.10} + 643 \cdot \mathrm{SEX}F_i + 12.5 \cdot \left(\mathrm{CrCL}_{ij} - 80.6\right) \quad (3)$$

Where:

TVCL/F_{ij} the typical value of the apparent oral clearance for the *i*th subject at the *j*th observation

Table IV. Summary Statistics of Individual Bayesian Estimates Stratified by Phase

Parameter	Phase 1	Phase 2	Pooled Phase 1 and 2
CL/*F* (L/h)			
Geometric Mean (%CV)	35.6 (50.8)	22.4 (43.7)	26.1 (52.0)
Median	35.8	23.2	25.9
Min, Max	6.1, 103	5.2, 80.6	5.2, 103
n	187	385	572
k_a (1/h)			
Geometric Mean (%CV)	2.49 (56.0)	2.76 (19.2)	2.67 (35.0)
Median	2.58	2.84	2.83
Min, Max	0.7, 6.5	1.3, 4.1	0.7, 6.5
n	187	385	572
Q_3/F (L/h)			
Geometric Mean (%CV)	24.2 (32.5)	24.6 (12.0)	24.5(20.8)
Median	24.3	25.0	24.9
Min, Max	6.0, 72.9	13.9, 32.7	6.0, 72.9
n	187	385	572
Q_4/F (L/h)			
Geometric Mean (%CV)	28.1 (36.5)	31.0 (17.1)	30.0 (25.3)
Median	28. 3	31.3	31.0
Min, Max	6.2, 58.6	14.6, 48.3	6.2, 58.6
n	187	385	572
V_2/F (L)			
Geometric Mean (%CV)	172 (22.5)	173 (7.1)	173 (14.0)
Median	170	175	175
Min, Max	102, 384	120, 221	102, 384
n	187	385	572
V_3/F (L)			
Geometric Mean (%CV)	273 (0.00)	273 (0.00)	273 (0.00)
Median	273	273	273
Min, Max	273, 273	273, 273	273, 273
n	187	385	572
V_4/F (L)			
Geometric Mean (% CV)	2,403 (37.0)	3,764 (24.6)	3,250 (36.6)
Median	2,463	3,824	3,518
Min, Max	730, 5,865	1,146, 9,171	730, 9,171
n	187	385	572

TVQ_4/F_{ij} the typical value of the apparent distributional clearance to the third compartment for the *i*th subject

TVV_4/F_{ij} the typical value of the apparent peripheral volume of distribution of the third compartment for the *i*th subject at the *j*th observation

AGE_i age (year) in the *i*th subject

$SEXF_i$ indicator variable for gender in the *i*th subject where $SEXF_i$=1 for females and 0 for males

$CrCL_{ij}$ creatinine clearance (mL/min) for the *i*th subject at the *j*th observation

BMI_{ij} body mass index (kg/m^2) for the *i*th subject at the *j*th observation.

Summary statistics of time-averaged individual Bayesian parameter estimates stratified by phase (Table IV) indicate that subjects in phase 1 studies had larger CL/*F* estimates and a smaller V_4/F than obese subjects in the phase 2 study. The individual Bayesian PK parameter estimates were used to generate predicted $C_{ss(24)}$ and $AUC_{ss(0–24)}$.

Body mass index and CrCL were statistically significant predictors of CL/*F* and accounted for much of the observed difference between CL/*F* for phase 1 and phase 2 subjects. Since taranabant is primarily metabolized, with renal clearance accounting for only a small percentage of overall elimination (less than 1%) (4), it was not expected that CrCL would be a significant covariate on CL/*F* (unpublished data). This finding may be more likely secondary to other physiologic changes, such as altered protein binding associated with renal disease.

In addition, V_4/F increased with increasing BMI, age, and CrCL and was also higher in females compared to males. The effect of gender on V_4/F was small (≈22% increase for females) and explained a small portion of the interindividual variability (IIV on V_4/F reduced by 1.56 percentage points) compared to the effect of BMI on V_4/F indicating that the difference in V_4/F is likely attributable to BMI differences

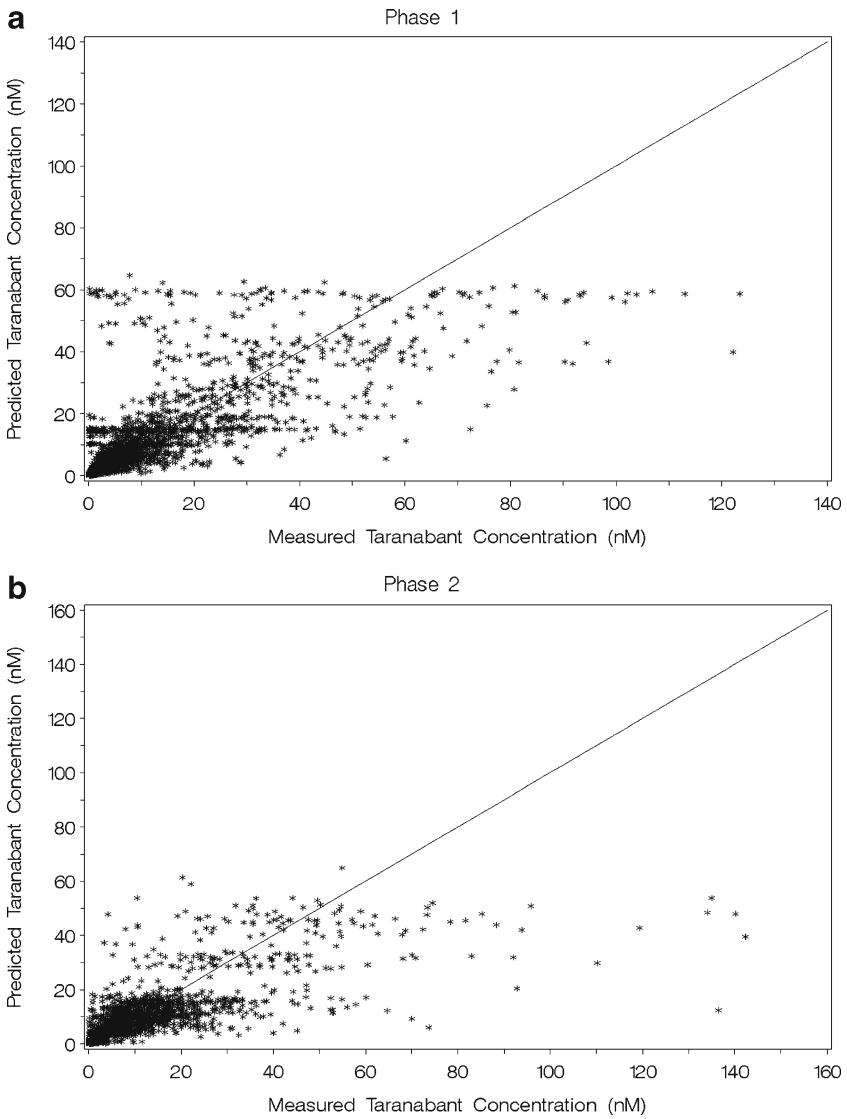

Fig. 1. **a** Predicted taranabant plasma concentration *versus* measured taranabant plasma concentration for phase 1 from the final model **b** Predicted taranabant plasma concentration *versus* measured taranabant plasma concentration for phase 2 from the final model

between patients and healthy volunteers. Age was found to have a statistically significant effect on Q_4/F, with Q_4/F increasing with increasing age.

All fixed and random effect parameters were estimated with good precision (%SEM <30) with the exception of IIV on k_a, covariance between IIV on k_a and IIV on Q_3/F, covariance between IIV on k_a and IIV on Q_4/F, and the additive component of RV for phase 2 data, which were estimated with moderate precision; only the covariance between IIV on k_a and IIV on Q_3/F was estimated with relatively poor precision. The magnitude of IIV on CL/F was moderate at 44.1%CV, and Bayesian shrinkage on this parameter was minimal (3.6%) suggesting that individual subject-specific exposure measures for $AUC_{ss(0-24)}$ and $C_{ss(24)}$ were acceptable. The magnitude of IIV on the other parameters, however, must be interpreted with caution given the relatively large degree of Bayesian shrinkage observed for these parameters (V_2/F=53%, V_4/F=33%, k_a=53%, Q_3/F=44%, Q_4/F=39%). The condition number of the final model was 225. Residual variability was large (63.8%CV) for concentrations obtained prior to 2 h after a dose in the phase 1 data, but was moderate for observations obtained after 2 h following a dose (22.9%CV). Residual variability for the phase 2 data was moderate at high concentrations (35.5%CV), but was relatively large near the lower limit of quantitation (71.5%CV).

Goodness-of-fit plots of population predicted *versus* measured taranabant concentrations for phase 1 (Fig. 1a) and phase 2 (Fig. 1b) show a large but equal spread around the line of unity indicating that the degree of IIV explained through covariate analysis was small in magnitude relative to the total variability observed in taranabant PK. Plots of the individual predicted *versus* measured taranabant concentrations for phase 1 (Fig. 2a) and phase 2 (Fig. 2b) show a bias in which some low measured concentrations at early time points were overpredicted while some high measured concentrations (peaks) were underpredicted and further highlight the difficulty encountered in fitting the complex and variable

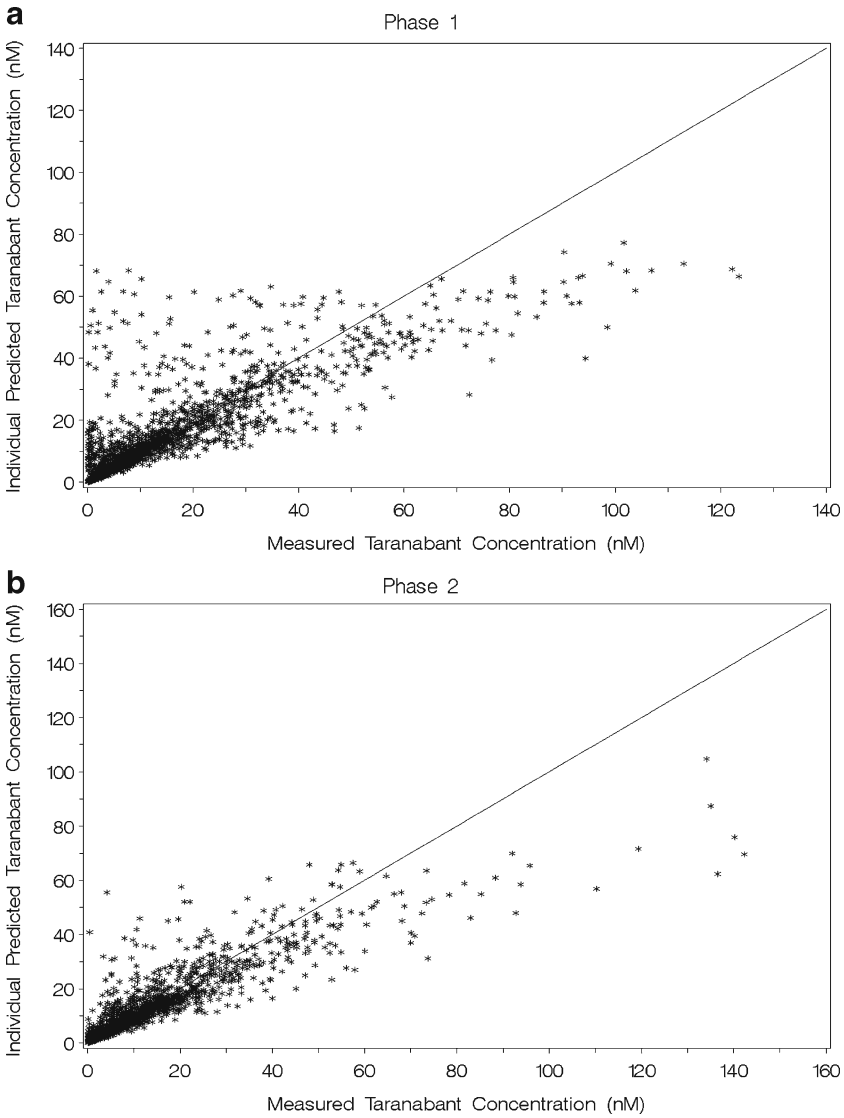

Fig. 2. **a** Individual predicted taranabant plasma concentration *versus* measured taranabant plasma concentration for phase 1 from the final model **b** Individual predicted taranabant plasma concentration *versus* measured taranabant plasma concentration for phase 2 from the final model

absorption of taranabant. Plots of weighted residuals *versus* population predicted taranabant concentrations and weighted residuals *versus* time since last dose (not shown) show that the majority of observations (97.4%) were within the expected three standard deviations and have an equal distribution around zero.

Model qualification was assessed using the visual predictive check method. The dose-normalized 5th, 50th, and 95th percentiles were plotted for single-dose phase 1 data (Fig. 3a), multiple-dose phase 1 data (Fig. 3b), and phase 2 data (Fig. 4), and the corresponding dose-normalized observed concentrations from the analysis dataset were overlaid. The visual predictive check shows that despite some clear bias to under predict peak taranabant concentrations, most of the data in the disposition phase fell within the 5th and 95th percentiles, indicating that the model developed for taranabant is acceptable for simulating 24-h trough concentrations of taranabant after single and multiple doses.

The clinical relevance of the covariates included in the final model was evaluated using the typical population PK parameters and model equations. For a particular covariate, $C_{ss(24)}$ values were predicted at a reference covariate value and at specific values throughout the covariate distribution. The ratio between a specific $AUC_{ss(0–24)}$ and a reference $AUC_{ss(0–24)}$ value was also calculated for those covariates that affect CL/*F*. The reference ratio of all covariate effects were

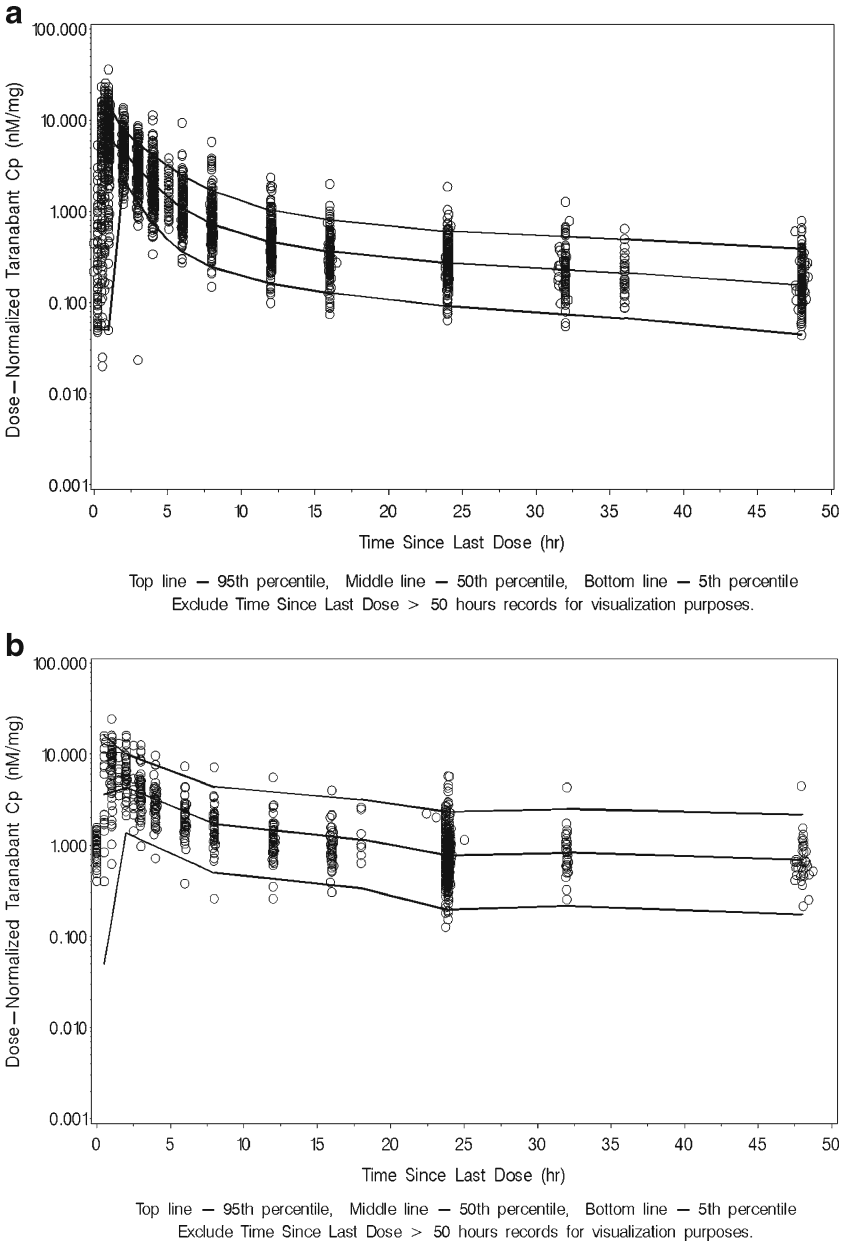

Fig. 3. **a** Plots of dose-normalized simulated 5th, 50th, and 95th percentiles and actual dose-normalized taranabant plasma concentrations (Cp) *versus* time since last dose for phase 1 single-dose data **b** Plots of dose-normalized simulated 5th, 50th, and 95th percentiles and actual dose-normalized taranabant plasma concentrations (Cp) *versus* time since last dose for phase 1 multiple-dose data

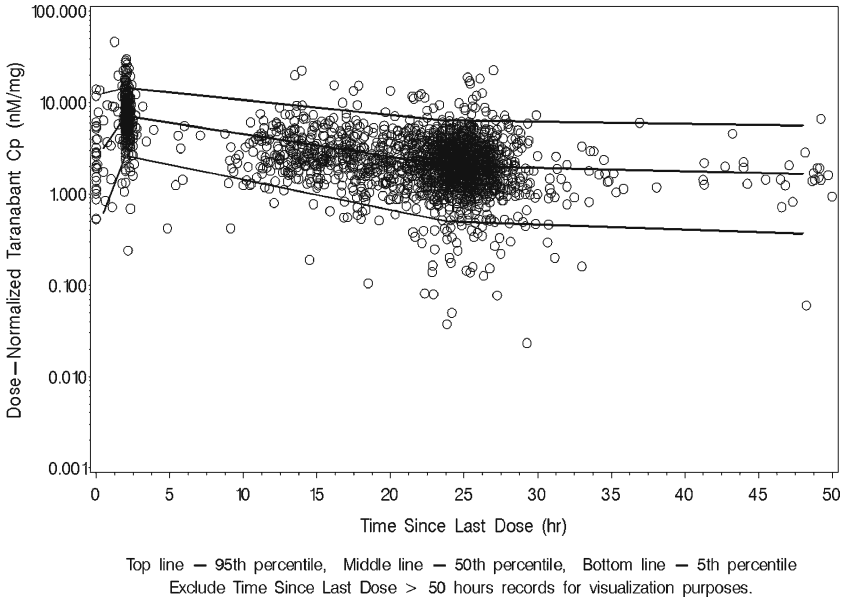

Fig. 4. Plots of dose-normalized simulated 5th, 50th, and 95th percentiles and actual dose-normalized taranabant plasma concentrations (Cp) *versus* time since last dose for phase 2 data

maintained within the bounds of 0.5 to 2 and were, therefore not considered clinically relevant (Table V).

DISCUSSION

A population PK model for taranabant was developed using phase 1 and phase 2 data from healthy volunteers and obese subjects. The model was used to estimate taranabant PK parameters, assess the influence of subject covariates on taranabant PK, and simulate 24-h trough concentrations for subsequent exposure–response analyses of efficacy and safety.

A three-compartment model with first-order absorption and first-order elimination was used to characterize taranabant PK. The population PK model was parameterized in terms of k_a, CL/*F*, V_2/F, V_3/F, Q_3/F, V_4/F, and Q_4/F. Interindividual variability was estimated for k_a, CL/*F*, V_2/F, Q_3/F, V_4/F, and Q_4/F using exponential error models. Covariance was estimated between IIV on k_a and IIV on Q_3/F, IIV on k_a and IIV Q_4/F, and IIV on Q_3/F and IIV on Q_4/F. A time-dependent residual variability model was employed for the phase 1 data, which allowed for differences in the magnitude of residual variability between absorption and disposition data. A separate additive plus proportional error model was used for the phase 2 data. Although several statistically significant covariates were identified, an assessment of clinical significance using typical population exposure measures shows that none of the covariates had a clinically relevant effect on exposure based on clinical significance bounds of 0.5 to 2. These bounds assume that changes in exposure of greater or lesser magnitude may be associated with an increased likelihood of adverse or subtherapeutic drug effects.

The parameter estimates from the model were generally estimated with good precision and were consistent with the current understanding of taranabant PK. Following intravenous (IV) administration of taranabant (1 mg) in healthy non-obese subjects, the average clearance from plasma was 9.9 L/h. A similar plasma clearance value of 9 L/h was derived by multiplying the mean CL/*F* (39 L/h) value estimated in phase 1 subjects by the absolute bioavailability (0.23) of the taranabant oral formulation (unpublished data). Furthermore, the mean CL/*F* value (Table IV) for the phase 1 subjects in this analysis is close to the CL/*F* estimate following multiple dose oral administration of taranabant 5 mg once daily in healthy male volunteers (37 L/h) (5). In addition, the

Table V. Ratio of Typical Population Exposure Measures

Exposure Measure	Ratio of Typical Population Exposure			
for BMI (kg/m^2)				
	22:32	28:32	38:32	42:32
AUC_{ss} (nM × hr)	0.659	0.862	1.21	1.35
$C_{ss(24)}$ (nM)	0.543	0.810	1.30	1.51
for CrCL (mL/min)				
	50:80			
AUC_{ss} (nM × hr)	1.09			
$C_{ss(24)}$ (nM)	1.12			
for Gender				
	Male:Female			
AUC_{ss} (nM × hr)	NA[a]			
$C_{ss(24)}$ (nM)	0.997			
for Age (year)				
	25:45		60:45	
AUC_{ss} (nM × hr)	NA[a]		NA[a]	
$C_{ss(24)}$ (nM)	0.952		1.03	

Typical CL/*F* values for the covariate value of interest (e.g., BMI=22) were calculated using the equations from the final PK model. Typical AUC_{ss} was calculated from dose (nmol) divided by CL/*F*. Typical $C_{ss(24)}$ values were predicted in NONMEM using the final model parameter estimates and equations as well as the covariate value of interest. Other covariate values were set to median values

[a] AUC_{ss} was not assessed for this covariate because it was not present on CL/*F* in the final model

large peripheral volume of distribution is consistent with the results from a study in which taranabant was administered intravenously and is not unexpected given the high lipophilicity of taranabant. The long terminal half-life observed with taranabant may reflect the slow release of drug from adipose tissue back into the vasculature. A tissue distribution study in rats showed that following IV administration of (^{14}C) taranabant (2 mg/kg), concentrations in fat exceeded those in plasma with fat-to-plasma concentration ratio values of 26, 33, and 83 at 4, 8, and 24 h post-dose, respectively (unpublished data).

The population PK model presented in this manuscript has several limitations but was judged to be acceptable based on the ability of the model to meet the objectives of the analysis. For example, goodness-of-fit plots and visual predictive checks demonstrated poor agreement between model predictions and observed concentrations for the ascending portion of the concentration–time curve suggesting that simulation of peak plasma taranabant concentrations would generally be inappropriate. However, despite the poor performance of the model for peak plasma concentrations, the model did an adequate job in characterizing the disposition phase of the taranabant concentration–time profile. As such, simulated C_{24} concentrations provided useful input for exposure–response analyses of safety and efficacy. In addition, because the model adequately described the disposition of the compound, the model was useful in identifying selected covariate effects which influenced taranabant disposition parameters (e.g., CL/*F*).

Another limitation of the PK model described in this analysis was the reduced dosage range that was investigated. The range of doses examined in this analysis was scaled down in order to avoid the addition of model complexities which would have been required had higher doses been included (e.g., autoinduction of metabolism). As a result, this model cannot extrapolate taranabant exposures outside the range of 0.5 to 8 mg; however, given that the intended clinical dose range based on safety and efficacy data was 0.5 to 6 mg and that future phase 2 and phase 3 trials did not investigate doses outside of this intended clinical dose range this limitation is of minor relevance.

A third model limitation involved the known food effect on taranabant. A standard high-fat breakfast resulted in a 14% increase in C_{max} and a 74% increase in $AUC_{0-\infty}$ but did not affect 24-h trough concentrations when compared to drug administration in the fasted state. The effect of food was not included in the model as a covariate because the food status in future phase 2 and phase 3 studies was unknown. Since taranabant was administered in the fasted state for most of the studies included in the analysis the model will have a tendency to under predict C_{max} and AUC in subjects that received taranabant with a high-fat meal. However, because 24-h trough concentrations were similar between fasted subjects and fed subjects, simulated C_{24} values for exposure–response analyses could be utilized.

Volume of distribution typically increases for lipophilic drugs in subjects with obesity compared to non-obese subjects, whereas observed differences in metabolic or renal clearance for specific drugs may depend on factors such as the primary CYP enzyme pathway responsible for elimination, extent of obesity, or underlying organ function (11). The healthy subjects included in this analysis had a larger CL/*F* than the obese subjects but had a smaller peripheral volume of distribution (V_4/F). The differences in these two parameters likely account for some differences in measured taranabant trough concentrations between healthy volunteers and obese subjects. The decrease in CL/*F* observed in obese subjects may be the result of increased protein binding or a decrease in CYP3A activity, both of which have been reported in the literature (11).

CONCLUSION

In summary, a three-compartment model with first-order absorption and first-order elimination was used to characterize the taranabant PK data obtained from 12 phase 1 studies and one phase 2 study. No covariates were determined to have a clinically significant impact on taranabant exposure. The model qualification results suggest the model was adequate for the purpose of simulating 24-h trough concentrations for exposure–response analyses in future studies.

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