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Population pharmacokinetic and pharmacodynamic analyses of safinamide in subjects with Parkinson's disease

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Abstract

Safinamide is an orally administered α-aminoamide derivative with both dopaminergic and non-dopaminergic properties. Nonlinear mixed effects models for population pharmacokinetic (PK) and pharmacokinetic–pharmacodynamic (PKPD) analyses were developed using records from, respectively, 623 and 668 patients belonging to two Phase 3, randomized, placebo-controlled, double-blind efficacy studies. The aim was to estimate safinamide population PK parameters in patients with Parkinson's disease (PD) on stable levodopa therapy, and to develop a model of safinamide effect on the PD phase of normal functioning (ON-time). The final models were internally evaluated using visual predictive checks (VPCs), prediction corrected-VPC, and nonparametric bootstrap analysis. Safinamide profiles were adequately described by a linear one-compartmental model with first-order absorption and elimination. CL/F, Vd/F, and KA (95% confidence interval [CI]) were 4.96 (4.73–5.21) L/h, 166 (158–174) L, and 0.582 (0.335–0.829) h^{-1}, respectively. CL/F and Vd/F increased with body weight, while age, gender, renal function, and exposure to levodopa did not influence safinamide PK. The observed ON-time values were adequately described by a linear model, with time in the study period as dependent variable, and rate of ON-time change and baseline plus offset effect as slope and intercept parameters. Safinamide treatment resulted in an increase in ON-time of 0.73 h (week 4), with further ON-time increase with the same slope as placebo. The increase was not influenced by age, levodopa, or safinamide exposure. The population models adequately describe the population PK of safinamide and safinamide effect on ON-time. No dose adjustments in elderly and mild to moderate renally impaired patients are requested.

Abbreviations

BLQ, below the quantification limit; CI, confidence interval; CRLR, creatinine clearance; FOCEI, first-order conditional estimation method with interaction; IPRED, individual predicted concentrations; LC-MS, liquid chromatography-tandem mass spectrometry; OFV, objective function value; PC-VPC, prediction corrected VPC; PD, Parkinsos's disease; PIs, prediction intervals; PKPD, pharmacokinetic–pharmacodynamic; PK, pharmacokinetic; PRED, predicted concentrations; RSE, relative standard error; TRT, treatment variable; TVP, typical population value of the parameter; VPC, visual predictive check.

Introduction

Parkinson's disease (PD) is the second most common chronic progressive neurodegenerative disorder in the elderly after Alzheimer's disease (Yadav and Li 2015). The disease is characterized by dopamine deficiency resulting from progressive loss of nigrostriatal dopaminergic cells (Schapira 2011), and its diagnosis is mainly based on observational criteria of muscular rigidity, resting tremor, or postural instability in combination with bradykinesia (Grosset et al. 2010). Levodopa (L-dopa) is considered the most effective treatment for the motor symptoms of PD, but its long-term use is associated with motor fluctuations, that is, phases of normal functioning (ON-time, i.e., periods of good motor system control) that may alternate with decreased functioning periods (OFF-time, i.e., periods of poor mobility, slowness, and stiffness) (Shoulson et al. 1975). Furthermore, as a result of the use of high doses of L-dopa with increasing severity of the disease, many patients experience involuntary movements known as L-dopa-induced dyskinesia (Hauser 2009). Also, as the disease progresses, non-dopaminergic pathways (e.g, glutamate) become involved (Blandini and Armentero 2012) and patients require add-on therapy to improve motor fluctuations without exacerbating dyskinesia.

In 2015, safinamide (Xadago®, Zambon S.p.A., Bresso, Italy) was approved in the EU for the treatment of mid- to late-stage fluctuating PD as add-on therapy to a stable dose of L-dopa alone or in combination with other PD medicinal products (Fariello 2007; Schapira 2010; Singer 2012; Grégoire et al. 2013; Deeks 2015). Safinamide, an orally administered α-aminoamide derivative, uniquely combines potent, selective, and reversible inhibition of monoamino oxidase B (MAO-B), with blockade of voltage-dependant Na^+ and Ca^{2+} channels and inhibition of glutamate release (Pevarello et al. 1999; Salvati et al. 1999; Caccia et al. 2006; Binda et al. 2011), thus targeting both dopaminergic and glutaminergic systems (Onofrj et al. 2008; Cattaneo et al. 2015).

In Phase III trials, safinamide has been shown to increase total ON-time without increasing troublesome dyskinesia when used as an adjunct to L-dopa in patients with advanced PD and motor fluctuations (Borgohain et al. 2014a,b). Improvements in OFF-time, motor symptoms, daily living activities, depressive symptoms, and quality of life at 6 months remained significant at 24 months (Borgohain et al. 2014b).

The pharmacokinetics (PKs) of safinamide were investigated in Phase I studies (Marzo et al. 2004; Leuratti et al. 2013). Safinamide has a linear PK after single and multiple doses, is quickly absorbed (T_{max} 1–2.8 h in fasted state), has a high absolute bioavailability (95%) and its exposure is not affected by food (EMA CHMP 2014; Marzo et al. 2004). Safinamide is extensively metabolized and in humans is almost exclusively eliminated by metabolism, with <10% urinary excretion of unchanged safinamide. Safinamide elimination half-life is approximately 22 h. Steady-state is reached in 1 week (EMA CHMP 2014; Marzo et al. 2004; Leuratti et al. 2013).

The objectives of the present PK analysis were (1) to develop a population PK model for safinamide in adult PD patients based on data of two Phase III studies (Stocchi et al. 2012; Borgohain et al. 2014a); (2) to evaluate the influence of covariates; (3) to quantify the inter- and intrapatient variability; and (4) to obtain visit-specific predictions of individual safinamide exposure in patients, to be used in the development of a PKs pharmacodynamics (PKPD) model.

The aims of the PKPD analysis were (1) to develop a disease progression type exposure–response model of the effect of safinamide on the PD phase of normal functioning (ON-time) in patients with mid- to late PD on stable L-dopa treatment; and (2) to quantify the inter- and intrapatient variability in the rate of disease progression and response to safinamide.

Materials and Methods

In order to characterize the population PKs of oral safinamide administered as add-on therapy to levodopa (L-dopa) or dopamine agonists in patients with Parkinson's disease, safinamide PK data were combined from two Phase 3, randomized, placebo-controlled, and double-blind studies, that is, Study 015 (Stocchi et al. 2012) and Study 016 (Borgohain et al. 2014a).

The population PK pharmacodynamic analysis, describing the relationship between safinamide plasma concentrations (average concentration over 24 h) and the pharmacodynamic end point ON-time, used the data obtained from Study 016 only.

Study design

Study 015 included patients with early idiopathic Parkinson's disease receiving a stable dose of a single dopamine agonist for at least 4 weeks prior to baseline. Eligible patients received oral safinamide (as gelatin capsules containing safinamide methanesulfonate, Zambon S.p.A., Bresso, Italy) low dose (50–100 mg/day) or high dose (150–200 mg/day), or placebo for 24 weeks. Patients assigned to receive the low dose of safinamide started at a dose of 50 mg/day on Day 0/1, and were titrated up to their target dose of 100 mg/day on Day 14, provided there were no dose-limiting side effects. Patients assigned to the high-dose range started at a dose of 100 mg/day on Day 0/1, were titrated up to 150 mg/day on Day 7,

and were titrated up to their target dose of 200 mg/day on Day 14, provided there were no dose-limiting side effects. Titration was delayed, and/or maintenance doses were reduced or interrupted in case of intolerance. Blood samples were taken at baseline, 5 h after the first dose, and at each subsequent scheduled visit, that is, at weeks 2, 4, 8, 12, 18, and 24.

Study 016 included Parkinson's disease patients with motor fluctuations receiving a stable dose of L-dopa for at least 4 weeks prior to baseline. Eligible patients received oral safinamide (as tablets containing safinamide free base, Zambon S.p.A., Bresso, Italy) low dose (50 mg/day) or high dose (100 mg/day), or placebo for 24 weeks. For patients in the 100 mg/day safinamide group, dose was reduced to 50 mg/day if patients experienced intolerance.

The primary efficacy variable was the increase in mean daily ON-time (ON-time plus ON-time with minor dyskinesia) during a 18-h interval (0600–2400) recorded by the subjects in the Hauser patient diary (Hauser et al. 2000, 2004) at 30-min intervals each day during the L-dopa stabilization period and in the 5 days preceding each study visit (at least 2 and up to 5 recording days).

For safinamide determination, samples were collected at baseline, at 5 h after the first dose and at any time up to 8 h post-dose during the subsequent visits (weeks 4, 12, and 24).

Bioanalysis

Safinamide was analyzed in blood samples using a validated (FDA Guidance for Industry, 2001) liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantification was 20 ng/mL. For Study 015, inter- and intra-assay precision of measurements did not exceed 15% and mean accuracy values were within ±15%. For Study 016, inter- and intra-assay precision was within 7.9% and mean accuracy was between −2.3% and 0.2%.

Software

The population PK and PKPD models were developed using a nonlinear mixed-effect modeling approach with the NONMEM® 6.2 software and NMTRAN pre-processor, Icon Development Solutions, Ellicott City, MD, USA (Beal et al. 1989-2006). PDx-Pop™ 3.0, Icon Development Solutions, Ellicott City, MD, USA (Bachman 2007), was used to run NONMEM, while models were run using the Intel Compiler 8, Intel Corporation, Santa Clara, CA, USA. Goodness-of-fit diagnostic plots were prepared with S-Plus 2000 Professional Release 3. All models were run using the first-order conditional estimation method with interaction (FOCEI).

PK model development

Structural model

A previous population PK analysis of Study 015 data alone (results not reported) suggested that a one-compartment model with first-order absorption and first-order elimination parameterized in terms of apparent oral clearance (CL/F) and volume of distribution (Vd/F) best described the safinamide data. Selection of the structural population PK model was driven by the observed data and was based on evaluation of goodness-of-fit plots (observed vs. predicted concentrations, weighted residual vs. predicted concentration or time, histograms of individual random effects), successful convergence (with at least three significant digits in parameter estimates), plausibility and precision of parameter estimates, and the minimum objective function value (OFV). Inclusion of a relative bioavailability factor (F_{rel}), where F_{rel} was set to 1 for the Study 015 and an estimate for Study 016, was evaluated.

Covariate model

Based on previous knowledge and scientific interest, the following covariates were included in the current population PK analysis: Age (AGE, years), Gender (GEND), Body weight (WGT, kg), Creatinine clearance (CRLR, mL/min), and Study (STUD). Race (RACE) was not included because it was only available for Study 016. Exposure to L-dopa at baseline (BLEV, mg/24 h), at each visit (LEVO, L-dopa dose rate/24 h), and as rate of change from baseline (LEVR) were listed and explored as covariates. They were equal to 0 for Study 015 as L-dopa was not administered.

For continuous covariates, a power function was utilized using the following equation:

$$\mathrm{TVP}_i = \theta_1 \times (\mathrm{COV}_i/\mathrm{COV}_{\mathrm{ST}})^{\theta_2} \quad (1)$$

where TVP_i is the typical value of a PK parameter (P) for an individual i with a COV_i value of the covariate, while θ_1 is the typical value for an individual with a standardized covariate value of $\mathrm{COV}_{\mathrm{ST}}$ and θ_2 is the power coefficient describing covariate parameter relationship.

Standardized values of the covariates were the values regarded as reference or normal in the general population. Reference values were 70 kg for body weight (median = 64 kg), 75 mL/min (median value) for CRCL, 60 years (median value) for age and 500 mg/24 h (median value) for LEVO.

For binary covariates, the fractional change in the typical parameter value was determined according to the following equation:

$$TVP_i = \theta_1 \times \theta_2^{IND_i} \quad (2)$$

where TVPi is as defined in equation 2 above, θ_1 is the typical value for an individual in whom the covariate takes the value 0 ($IND_i = 0$), and θ_2 is the fractional change in the typical value if the covariate takes the value 1 ($IND_i = 1$).

The covariate STUD was evaluated by calculating one typical value for the PK parameters of interest (clearance and volume of distribution) for the two studies included in the analysis.

A full model approach was implemented to test the covariate–parameter relationships, wherein all prespecified covariate–parameter relationships were entered in the model, and parameters were estimated. Insignificant or poorly estimated covariates (less than 6.63 points decrease of OFV for one parameter, and/or 95% confidence intervals (CIs) include null value, and/or high relative standard error (RSE) were then excluded from the model.

Diagnostic plots of interindividual random effects versus covariates were evaluated for the base and the final models, and if necessary, the model was refined based on the findings.

Intersubject variability

Distributions of interindividual random effects were assumed to be log-normal and were described by the following exponential error model:

$$P_i = TVP \times \exp(\eta P_i) \quad (3)$$

where P_i is the parameter value for an individual *i*, TVP is the typical population value of the parameter, and ηP_i (ETAs) are individual-specific interindividual random effects for an individual *i* and the parameter P. ETAs were assumed to be normally distributed with a mean of 0 and variances of ω^2: $\eta \sim N(0, \omega^2)$. For all PK parameters, interindividual random effects were estimated and variance of the interindividual random effects ω^2 was calculated.

Correlation

Initial base model building was performed using a diagonal covariance matrix of interindividual random effects. Correlations between interindividual random effects were then considered if warranted by the diagnostic plots.

Residual error

The residual error model was initially described by a combined additive and proportional error:

$$C_{ij} = \hat{C}_{ij} + \hat{C}_{ij} \times \varepsilon 1_{ij} + \varepsilon 2_{ij} \quad (4)$$

where C_{ij} is the measured plasma concentration of the individual I at time *j*, $\hat{C}_{ij}$ is the corresponding model predicted concentration, and $\varepsilon 1_{ij}$ and $\varepsilon 2_{ij}$ are the proportional and additive components, respectively, of the residual random error. Each of the residual error components was assumed to be independently normally distributed with a mean of 0 and variances of σ^2: $\varepsilon \sim N(0, \sigma^2)$.

The variances of additive and proportional terms of the residual intraindividual variability σ^2 were calculated.

PK analysis dataset

The NONMEM population PK dataset included dosing records and plasma concentration (ng/mL) records from safinamide treatment arms of the two studies (records of patients in the placebo arm were commented out). The data file was sorted by a univocal and increasing integer ID, derived from the study code, study site number, and patient identification number. An individual record was defined as all the data sharing the same ID. Individual concentration records consisted of a maximum of seven concentration records (i.e., Baseline [week 1] and weeks 2, 4, 8, 12, 18, and 24) for Study 015 and a maximum of four concentration records (i.e., Baseline [week 1] and weeks 4, 12, and 24) for Study 016. Actual times (calculated as the number of hours between the first dose and the actual time the PK sample was drawn) were associated with the concentrations (TIME variable). Dosing records included the amounts, actual times of dosing for administrations performed at the clinical center (study visits), and nominal times for home administrations. Series of identical dose records were replaced by a steady-state dose record with a dose interval set to 24 h. A categorical treatment variable (TRT) was used to identify patients receiving safinamide low (50–100 mg) or high (100–200 mg) doses in Study 015, and 50 or 100 mg doses or placebo in Study 016.

All patients who had taken the study medication and had at least one safinamide concentration measurement were included in the analysis. All pre-first dose concentrations and all concentrations below the quantification limit (BLQ) at other time points were not used. Missing drug concentrations were not imputed in the analysis. Concentration values were not used if the time of concentration measurement or preceding dose was missing. For visits other than the baseline visit, if PK sampling time for a concentration record occurred just before the dosing time on the same date, the preceding dose was assumed to be occurring 24 h prior to the recorded dosing time and this previous (unrecorded) dosing time was used to calculate the PK sampling times for that dose.

Covariate GEND was coded as 0 for males and 1 for females while STUD was set as 1 and 2 for Studies 015 and 016, respectively. The changes in L-dopa doses were made at week 4 and subsequent scheduled visits. Thus, the LEVR values were 1 for week 1 (baseline visit) and week 4, and were <1, 1, or >1 for subsequent visits (weeks 12 and 24) to reflect the time taken for the changed L-dopa dose to take effect following the change at week 4. There were no missing categorical covariates or missing AGE values in the data. For the time-varying continuous covariates (WGT and CRCL), if a baseline value was missing, screening or the next available value was used, if a week 24 value was missing, the preceding available value was used, if a week 4 or week 12 value was missing, the mean of the preceding and the succeeding values was used, if no value for a particular subject was available, a gender and week-specific median value was used.

PKPD model development

Structural model

The following assumptions were made:

- ON-time diminishes continuously during the 24 week study period due to the disease progression in the placebo patients, except possibly for the initial upward shift due to the placebo effect.
- In the study design, the natural disease progression may not be differentiated from the placebo effect.
- Safinamide effect would be tested on both offset and the slope of the disease progression. Presumably, these parameters would depend on the individual average safinamide plasma concentration (SAAV, ng/mL). If not, safinamide dose and/or treatment will be tested.

The selection of the base population PKPD model was done in two stages. First, a linear model with intercept and slope parameters (eq. 5) and the model with a delayed time-dependent offset (eq. 6) were tried for the placebo data as follows:

$$\mathrm{PD} = \mathrm{BL} + \mathrm{INT_{PLAC}} + \mathrm{SLOP_{PLAC}} \times \mathrm{TIME_{months}} \quad (5)$$

$$\mathrm{PD} = \mathrm{BL} + \mathrm{INT_{PLAC}} \times \mathrm{IN} + \mathrm{SLOP_{PLAC}} \times \mathrm{TIME_{months}} \quad (6)$$

where BL is an individual baseline ON-time value (at week 1), $\mathrm{INT_{PLAC}}$ is the offset effect, $\mathrm{SLOP_{PLAC}}$ is the slope of rate of ON-time change, $\mathrm{IN} = e^{(1-(\mathrm{INK}+\mathrm{TIME})/(1+\mathrm{TIME}))}$, and parameter INK describes the delay in the onset of the placebo effect.

Then, the data from safinamide treatment arms were added. Safinamide effect on intercept ($\mathrm{INT_{TREAT}}$) and slope ($\mathrm{SLOP_{TREAT}}$) was tested as follows:

$$\mathrm{PD} = \mathrm{BL} + (\mathrm{INT_{PLAC}} + \mathrm{INT_{TREAT}}) + (\mathrm{SLOP_{PLAC}} + \mathrm{SLOP_{TREAT}}) \times \mathrm{TIME_{months}} \quad (7)$$

Structural population PKPD model selection was based on evaluation of goodness-of-fit plots (observed vs. predicted ON-time score, weighted residual vs. predicted ON-time score or time, histograms of individual random effects, etc.), successful convergence (with at least three significant digits in parameter estimates), plausibility and precision of parameter estimates, and the minimum OFV of a NONMEM run.

Covariate model

All covariate–parameter relationships considered to be potentially significant during the screening process were included in the base PKPD model in a univariate manner. All relationships that decreased the OFV by more than 6.63 ($P < 0.01$) points (if any) were to be included in the full covariate model. For continuous covariates, a power function was utilized as described in equation 1, and for categorical covariates, the fractional change in the typical parameter value was determined according to equation 2. For the categorical effect of dose on slope parameter, an additive effect was utilized. In addition to the reference values listed for the population PK covariate modeling, the median SAAV value of 13 ng/mL was used as a reference value. As for the population PK model building, diagnostic plots of interindividual random effects versus covariates were evaluated for the base and the final models.

Intersubject variability

Distributions of interindividual random effects were assumed to be either log-normal, described by an exponential error model (eq. 3), or normal, described by an additive error model:

$$\mathrm{P}_i = \mathrm{TVP} + \eta \mathrm{P}_i \quad (8)$$

Parameters P_i, TVP, and $\eta \mathrm{P}_i$ were previously described. Interindividual random effects (ETAs), variance of the interindividual random effects (ω^2), and initial base model development remained as previously described for the population PK model.

Residual error

The residual error model was described by an additive error only:

$$C_{ij} = \hat{C}_{ij} + \varepsilon_{ij} \quad (9)$$

where C_{ij}, $\hat{C}_{ij}$, and ε_{ij} were as previously described. The variance of the residual intraindividual random variability (σ^2) was calculated.

PKPD analysis dataset

The NONMEM population PKPD dataset included the PD observation records from both placebo and safinamide treatment arms of Study 016, grouped and sorted by the individual ID and by TIME inside the individual records. The TIME of an observation record was calculated as the difference in hours of the time of the visit when the PD was recorded from the time of baseline PD visit. The PD observations were the ON-time values (h), which were the average over 2–5 recording days of the sum of duration of ON-time plus ON-time with minor dyskinesia during the 18 h of recording in the patient diary prior to a scheduled visit. The time of an observation record was calculated as the difference in hours of the time of the visit when the PD was recorded from the time of the baseline PD visit. An individual record consisted of maximally six observation records (weeks 1, 4, 8, 12, 18, and 24). The TRT followed the same rules of the PK dataset. The exposure to safinamide (average safinamide concentration over 24 h) was calculated by dividing the safinamide dose values at each visit by the individual clearance estimate (obtained from the PK analysis) at that visit. It was listed under the SAAV data item. SAAV was set as 0 for week 1 or placebo records and as >1 for weeks >1 and safinamide treatments.

All patients on placebo and safinamide treatments with evaluable PD data and the corresponding safinamide exposure data from population PK analysis were included in the population PKPD analysis. ON-time values were not used in the analysis if the time of measurement (Date) was missing or deemed not reliable.

PK and PKPD models internal evaluation

A visual predictive check (VPC) procedure was performed for the final population PK and PKPD models by simulating 200 datasets using the final model, covariates, sampling times, model PK or PD parameter estimates and the dosing histories contained in the dataset. The original data sets were compared with the 5th, 10th, 90th, and 95th percentiles for the simulated data for nominal times grouped within the bins (selected time after dose ranges were used for the bins). The percentage of observed points (plasma concentration values) that fell outside the 80% and 90% prediction intervals (PIs) were determined. A prediction-corrected VPC (PC-VPC) (Schapira et al. 2013) was also performed in order to avoid the misleading variability observed in the VPC that may be caused by factors other than the random effects (e.g., different covariate values within a bin). In PC-VPC, both the observed and the model predicted values were normalized by the typical model prediction in each bin. A comparison of the observed and simulated data was done similarly to VPC.

A nonparametric bootstrap analysis was performed by generating 1000 datasets through random sampling with replacement from the original data using the individual as the sampling unit. Population parameters of the final PK and PKPD models for each data set were estimated using NONMEM. Empirical 95% CI were constructed by obtaining the 2.5th and 97.5th percentiles of the resulting parameter distributions.

Results

Demographics and subject disposition

The PK analysis dataset included 624 patients contributing 2785 concentration records. Of these, 623 patients contributing 2719 concentration records were included in the population PK analysis. One hundred seventy-seven patients contributing 1099 concentrations were from Study 015 and 446 patients contributing 1620 concentrations were from Study 016. Summary of the demographic data for the subjects included in the development of the PK model are presented in Table 1. There were no patients with severe renal impairment (CRCL < 10 mL/min), 57 (9%) patients had moderate renal impairment (CRCL < 50 mL/min), 307 (49%) patients had mild renal impairment (CRCL = 50–80 mL/min), and 259 (42%) patients had normal renal function.

Observed plasma safinamide concentrations versus time for all patients are displayed in Figure 1.

The PKPD analysis dataset included 669 patients from Study 016 contributing 3607 observation records. Of these, 668 patients contributing 3603 observation records were included in the population PKPD analysis. Summary of the demographic data for the subjects included in the development of the PKPD model are presented in Table 2. The majority of the patients maintained the same L-dopa dose rate from baseline through the duration of the trial. Very few (N = 11/668, 2%) of the patients increased the dose of L-dopa during the trial. Among them, only two patients were in the 100 mg safinamide treatment arm (0.9%), three in the 50 mg treatment arm (1%), and six in the placebo arm of the study (3%). A few (N = 51/668; 8%) of the patients decreased the dose of L-dopa during the trial. Among them, 23 patients were in the 100 mg safinamide treatment arm (10%), 16 in the 50 mg treatment arm (7%), and 12 in the placebo arm (5%).

PK analysis and final model

The safinamide PK model building history and the associated changes in objective function (ΔOF) are presented in Table S1.

Table 1. Demographic profile summary for subjects included in model development: continuous and categorical covariates.

Covariate	Study 015 *n* = 177	Study 016 *n* = 446	All *n* = 623
Age (years)			
Median (range)	59.0 (31.0–82.0)	60.0 (35.0–80.0)	60.0 (31.0–82.0)
Baseline body weight (kg)			
Median (range)	70.0 (33.5–102)	61.1 (35.0–97.7)	64.0 (33.5–102)
Baseline creatinine clearance (mL/min)			
Median (range)	78.9 (25.3–201)	73.3 (27.5–146)	75.5 (25.3–201)
Gender, *n* (%)			
Male	112 (63)	319 (72)	431 (69)
Female	65 (37)	127 (28)	192 (31)
Race, *n* (%)			
Asian	NA	358 (80.3)	358 (57.5)
White	NA	87 (19.5)	87 (13.9)
Other	NA	1 (0.2)	1 (0.2)
NA	177 (100)	0	177 (28.4)

NA, not available.

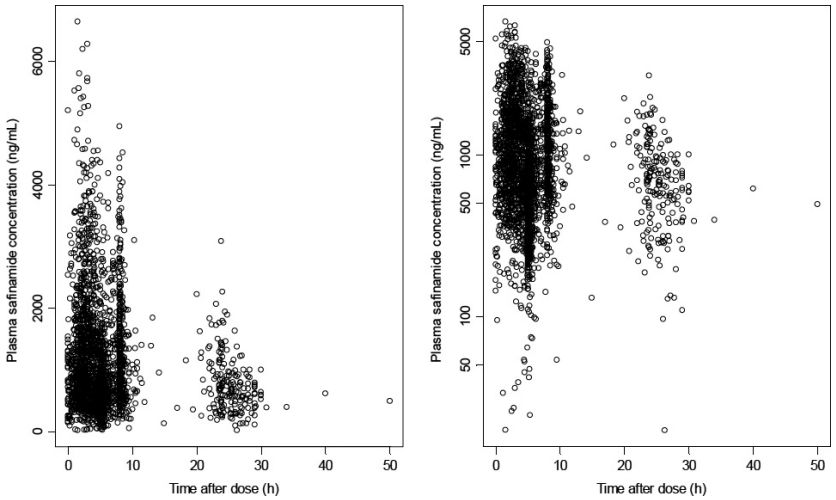

Figure 1. Observed plasma safinamide concentrations versus time after dose–linear and logarithmic scales.

A one-compartment model with CL/F, Vd/F, and KA parameters and an allometrically scaled CL/F (with a scaling factor $(WGT/70)^{0.75}$) and Vd/F (with a scaling factor (WGT/70) was the starting point for the base population PK model development (model 100). Intersubject variability was estimated for CL/F, Vd/F, and KA using an exponential model. The residual error was described by a combined additive and proportional model.

There was a clear difference in concentration levels between the studies, therefore the effect of study was tested on CL/F, Vd/F, and KA and resulted in a lowering of the OFV from −83 to −156 points (depending on the parameter tested) with respect to model 100. Study effect (STUD) was then tested simultaneously on both CL/F and Vd/F (model 112). The model adequately described the safinamide concentration data, as indicated by the OFV change in comparison to model 100 (ΔOFV = −214) and by the diagnostic plot, and was chosen as the base model to test covariates.

Inspection of the plots of individual random effects against covariates (including RACE) showed no visible trend. However, AGE, GEN, CRCL, and LEVR were still tested on CL/F, and AGE and GEN were still tested on Vd/F. None of the tested covariates were significant, thus their inclusion did not improve the model fit (maximum drop of OFV was 4 points with respect to model 112).

Since Study effect was significant both on CL/F and Vd/F and the interstudy ratios were similar ($CL/F_{STUDY016/STUDY015}$ = 1.3 $Vd/_{FSTUDY016/STUDY015}$ = 1.6), STUD was also tested on the relative bioavailability factor (F_{rel})

Table 2. Demographic profile summary for subjects included in PKPD model development: continuous and categorical covariates.

Covariate	Study 016 *n* = 668
Age (years)	
Median (range)	60.0 (34.0–80.0)
Baseline body weight (kg)	
Median (range)	62.0 (33.5–120)
Baseline creatinine clearance (mL/min)	
Median (range)	73.5 (25.8–199)
Gender, *n* (%)	
Male	480 (71.9)
Female	188 (28.1)
Race, *n* (%)	
Asian	538 (80.5)
White	129 (19.3)
Other	1 (<0.01)

instead of on the two parameters (model 110). The new model showed a significant better fitting with respect to model 100 (ΔOFV = −191), and was simpler and more physiologically explainable than model 112 (even if with a slightly higher OFV), thus representing a better choice.

In model 110, interindividual random effects on KA and additive residual error were poorly estimated (RSE of 71 and 102%, respectively), the 95% CIs included the null value and the shrinkage value of interindividual random effects on KA was high (60%). For these reasons, in the final model (model 110a), ω^2 and σ^2 variance of the interindividual random effects on KA and additive residual error were fixed to 0. The modification had no effect on parameter estimates, predicted concentrations (PRED), or individual predicted concentrations (IPRED) and produced a small lowering of the OFV with respect to model 110 (ΔOFV = −26)

The parameters for Study 015 obtained from the final population PK model 110a are presented in Table 3. All parameters were estimated with good precision as indicated by the percentage of the RSE of the estimates (%RSE, Table 3). The interindividual variability of the CL/F (CV = 27.8%) and Vd/F (CV = 29.9%) parameters and the variability of the residual error (CV = 29.7%) were relatively low and estimated with good precision. Based on the estimate of F_{rel} (bioavailability factor), CL/F and Vd/F (95% CI) for Study 016 were calculated to be 4.96 (4.73, 5.21) L/h and 166 (158, 174) L, respectively. Oral clearance and volume of distribution increased with increasing body weight. CL/F and Vd/F estimates for the lightest (33 kg) and the heaviest patient (105 kg) were 2.04 and 4.87 L/h and 57 and 180 L, respectively.

The diagnostic plots for the final model are shown in Figure 2. The plots of population predicted versus observed safinamide concentrations and the individual predicted versus observed safinamide concentrations showed a symmetric distribution around the line of identity and so a good correspondence between observed and predicted concentrations and a good model fitting of the data. The plots of the conditional-weighted residuals versus population-predicted safinamide concentrations or time did not show any systematic bias in the model fit. The random effects were normally distributed, and were not correlated. The shrinkage of individual random effects was estimated as 18% for CL/F (7.2 and 23% for Study 015 and 016) and 31% for Vd/F (6.1 and 44% for Study 015 and 016). Higher shrinkage in Study 016 was possibly due to the fewer observed measurements. The residual error shrinkage was estimated at 12%.

PK model internal evaluation

The nonparametric bootstrap estimates (median) of the parameters and their 95% CI were very close to the

Table 3. Parameter estimates for the final safinamide population PK model and results of the bootstrap evaluation for the final model.

	NONMEM estimates				Bootstrap median	
Parameter	Point estimate	%RSE	95% confidence interval (CI)	CV%	Point estimate	95% CI
CL/F (L/h)	3.59	2.67	3.40–3.78		3.58	3.38–3.77
Vd/F (L)	120	4.38	110–130		120	107–129
KA (h^{-1})	0.582	21.6	0.335–0.829		0.572	0384–1.10
F (STUD016)	0.724	2.49	0.689–0.759		0.725	0.687–0.759
Interindividual variability						
ω^2_{CL}	0.0772	11.2	0.0602–0.0942	27.8	0.0759	0.0586–0.0942
ω^2_{Vd}	0.0892	17.2	0.0592–0.119	29.9	0.0855	0.0559–0.119
Residual variability						
σ^2prop	0.0885	5.11	0.0796–0.0974	29.7	0.0892	0.0805–0.0989

%RSE: percent relative standard error of the estimate = SE/parameter estimate*100, CL/F: Apparent clearance, Vd/F: Apparent volume of distribution; KA: absorption rate constant; F(STUD016): relative bioavailability of Safinamide in Study 016; σ^2prop: proportional residual error model. The reference population for PK parameters CL/F and Vd/F is a 70 kg patient.

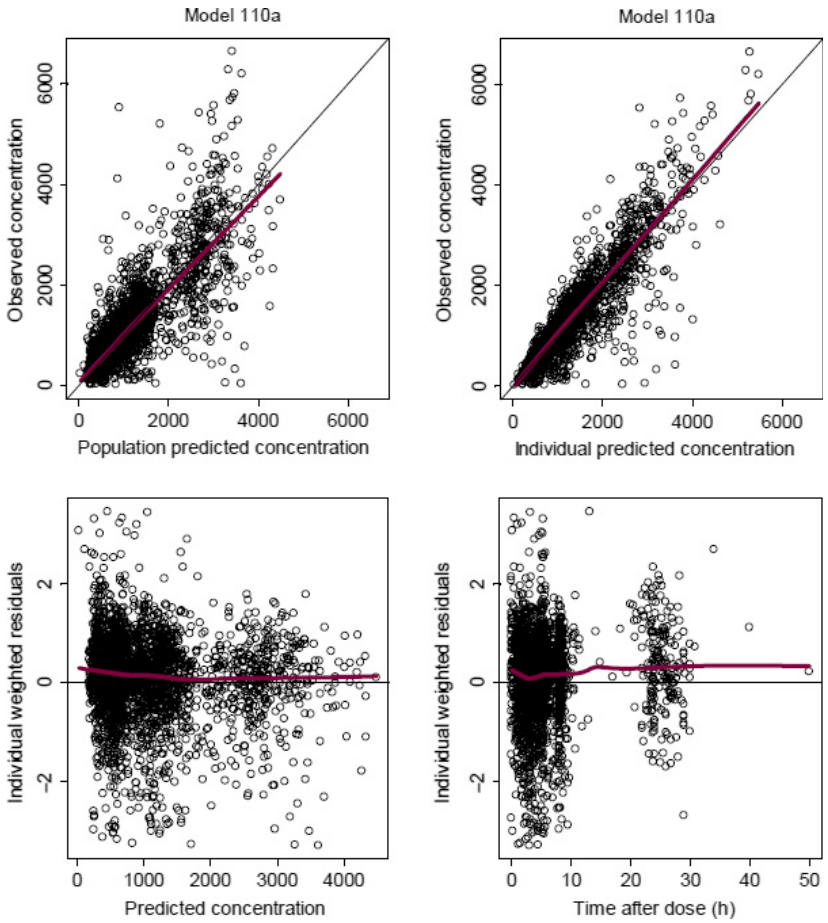

Figure 2. Observed versus population and individual predicted plasma safinamide concentrations–final population pharmacokinetic model (Model 110a).

respective values obtained with NONMEM from the original dataset (Table 3). Based on VPC and PC-VPC for all patients, only 7.9 and 9.4% of the observed concentrations fell outside the 90% PIs, confirming that the final model adequately describes the observed data (Fig. 3A and B). Two peaks of safinamide concentrations, which are also evident in the observed plasma concentration-time plots (Fig. 1) are apparent. The two peaks are possibly a result of the concentrations from a number of different occasions (visits) during the study, since the plots of observed plasma concentration time profiles by dose and visit do not show the presence of multiple peaks.

PKPD analysis and final model

A summary of the base population PKPD model development is presented in Table S2.

The plots in Figure 4 suggested that there was a small placebo effect that was increasing linearly during the whole treatment period. The effect of safinamide treatment appeared to increase faster than placebo during the first 8 weeks, and then to grow with the slope similar to the placebo arm, with very little difference between the safinamide treatment arms. The plots also indicated that the variability of the ON-time did not differ between the treatment arms and that the variability in the ON-time response was not dependent on safinamide exposure, as suggested from the plots displayed in Figure 5.

Initially, the placebo data alone were modeled using a linear disease progression model (model 805) with the slope and intercept parameters, where the placebo effect (intercept) could be time-dependent. The parameters included the baseline ON-time value (BL), the intercept parameter (INT_{PLAC}), the constant (INK) describing time-dependent onset of the placebo effect (see eq. 6), and slope ($SLOP_{PLAC}$) of disease progression. The individual random effects were estimated for all the PD parameters, and the residual error was described by an

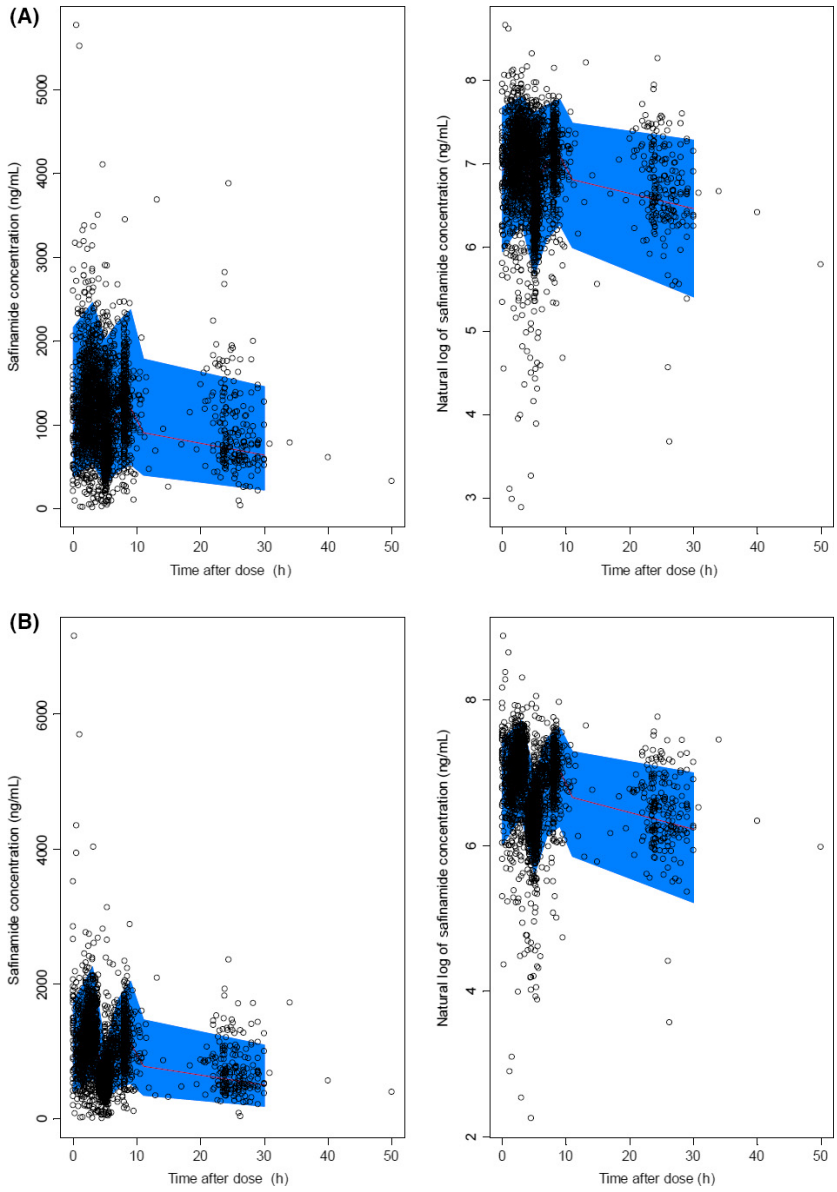

Figure 3. (A) Visual predictive check (VPC) for the final population pharmacokinetic model, all patients (Model 110a). (B) Prediction-corrected VPC for the final population pharmacokinetic model, all patients (Model 110a).

additive model. Since the natural disease progression assumes ON-time values to decrease with time, the typical value of $SLOP_{PLAC}$ was constrained to be negative to describe a decrease in ON-time with time in models with placebo data only. In the first and in all the subsequent models, the typical value for BL was not estimated. Instead, BL utilized the individual observed ON-time baseline values, and interindividual variability on BL was described by an exponential error model. The interindividual variability for $SLOP_{PLAC}$ and INT_{PLAC} parameters were described by additive error models. The typical value for $SLOP_{PLAC}$ and interindividual variability on BL approached 0 and the covariance step was not implemented. Fixing both the typical value for $SLOP_{PLAC}$ and interindividual random effect on BL to 0 (model 806), there was no change in OFV compared to the first model. The estimate of INK was very low (6.77 h) suggesting that a time delay in the onset of the placebo effect was not required.

Therefore, a simple linear model with constant intercept and slope was applied to the placebo data as described in equation 5 (Model 903). The interindividual random effect on BL was fixed to 0. $SLOP_{PLAC}$ was allowed to have a positive or negative value. The OFV

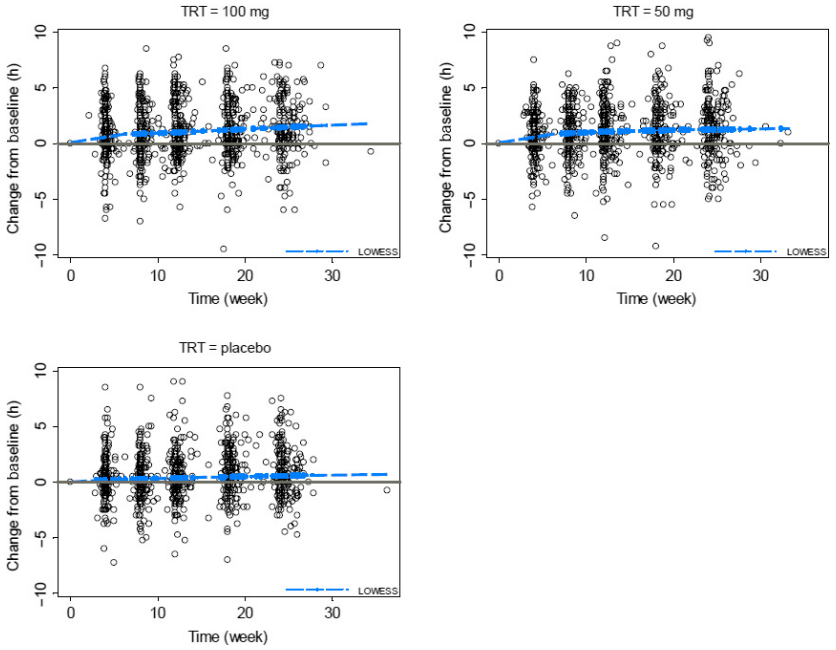

Figure 4. Observed ON-time value and change from baseline versus time by treatment.

was 13 points lower compared to the previous model. $SLOP_{PLAC}$ (95% CI) was estimated to be 0.116 h/month (0.0476, 0.184) and was estimated with reasonably good precision (RSE = 30.1%). In contrast, INT_{PLAC} was poorly estimated (RSE = 62.3%), and was small (0.231 h), and thus the 95% CI (−0.0512, 0.513) included the null value. Interindividual variability on both parameters was estimated with good precision (RSE = 19.2 and 17.8% for $SLOP_{PLAC}$ and INT_{PLAC}, respectively) and their SDs were 0.333 h/month and 1.61 h, respectively.

Then, the data from all treatment arms were combined. First, the same linear model was applied (model 904), followed by adding safinamide treatment effect on the intercept (INT_{TREAT}) and slope ($SLOP_{TREAT}$) parameters (model 907, see eq. 7). One additive interindividual variability term was used to describe interindividual variability on the sum of INT_{TREAT} and INT_{PLAC} and another additive interindividual variability term was used to describe interindividual variability on the sum of $SLOP_{TREAT}$ and $SLOP_{PLAC}$. Inclusion of these two parameters decreased the OFV by 9 points. The mean estimate of INT_{TREAT} (95% CI) was 0.505 (0.148, 0.862) while the estimate of $SLOP_{TREAT}$ approached 0. Fixing the $SLOP_{TREAT}$ to 0 (model 908) did not change the OFV. As stated earlier, INT_{PLAC} (95% CI) was small (0.238 h) and poorly estimated, with a 95% CI (−0.0207, 0.497 h) that included the null value. INT_{PLAC} was thus fixed to 0 (model 915), increasing the OFV by 3 points. All model parameters were estimated with good precision, and this model was chosen as the base model.

A summary of the covariate model development is also presented in Table S2. None of the covariate–parameter relationships appeared significant. However, LEVO, LEVR, SAAV, AGE, and the categorical covariate of safinamide dose were tested univariately on $SLOP_{PLAC}$ and INT_{TREAT} parameters in different ways. In addition, LEVO and AGE were tested, also univariately, as covariates on INT_{PLAC}. None of the models improved upon the base model. In addition, in all the models, there was no decrease in inter- or intraindividual variability, most of the covariate parameters were poorly estimated and their 95% CIs contained the null values. With the exception of the model with LEVO on $SLOP_{PLAC}$, the OFV decreased by less than 6 points in all the models. In model 931, the effect of LEVO on $SLOP_{PLAC}$ was estimated to be negative (−0.779) and the OFV decreased by 7.6 points. It was determined that very few patients ($n = 8$) with LEVO < 200 mg/24 h influenced the model. Without this influence, the effect of LEVO disappeared. Therefore, the base model was chosen as the final population PKPD model.

The parameters of the final population PKPD model are presented in Table 4. The condition number for the final model was low (2.3) and well below 1000. $SLOP_{PLAC}$ (95% CI) was small and positive, 0.117 (0.0780, 0.156) h/month, representing an increment of 0.7 h at the end of the 6 months study period for the patients in the placebo group. The instantaneous (within 4 weeks) safinamide treatment effect, INT_{TREAT}, was 0.728 (0.514, 0.942) h. The interindividual variability values

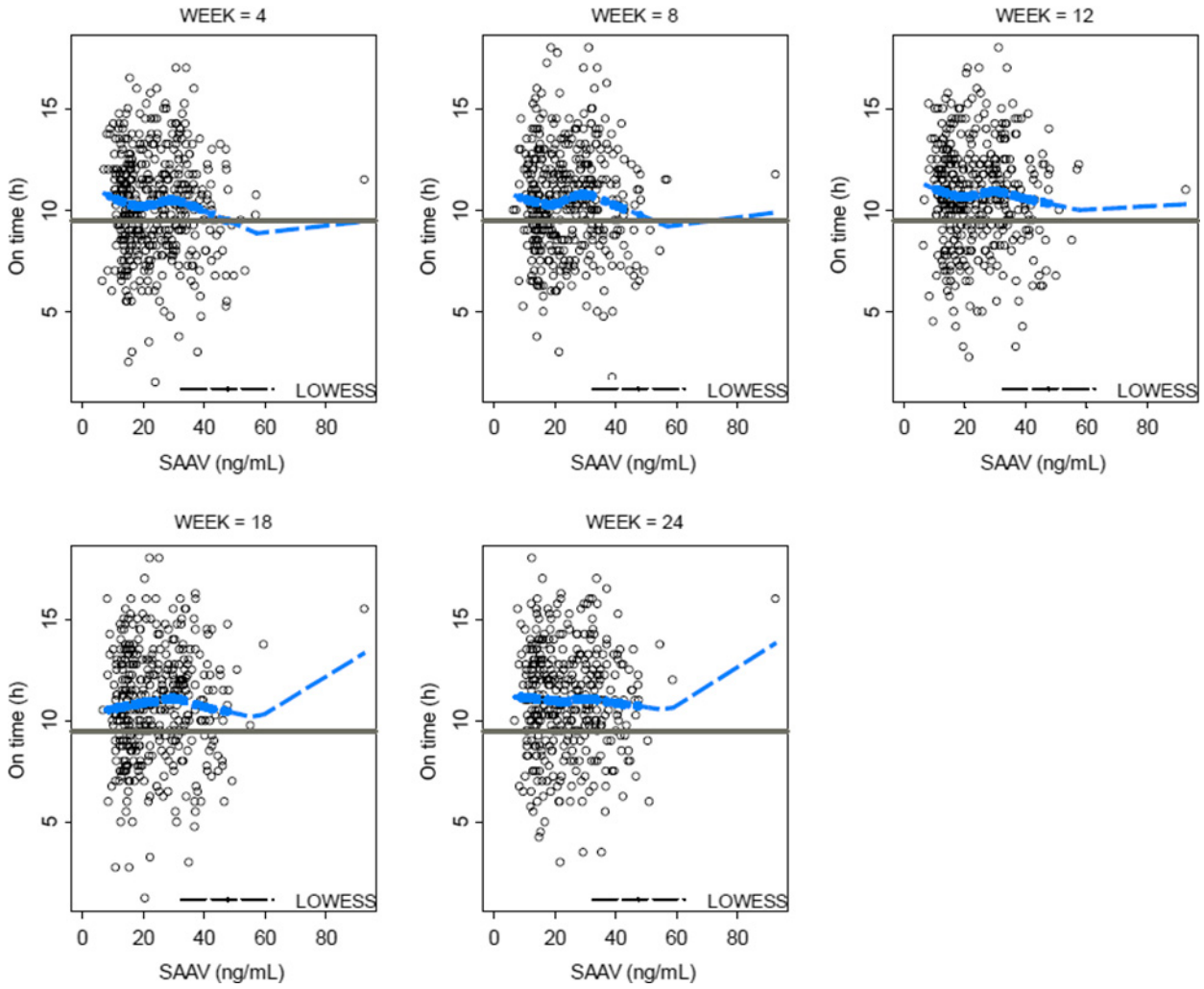

Figure 5. Observed ON-time value and change from baseline versus average 24 h safinamide concentrations (SAAV) by visit.

were large, with SD equal to 0.361 for $SLOP_{PLAC}$, 1.81 for INT_{PLAC}, and 1.09 h for the residual error. All parameters were estimated with good precision, with RSE between 8% and 17%. The shrinkage of individual random effects was estimated as 25% for $SLOP_{PLAC}$ and 12% for INT_{PLAC}.

The diagnostic plots for the model are presented in Figure 6. The distributions of the random effects were close to normal, and they were not correlated.

PKPD model internal evaluation

No bias was evident in any of the VPC (Fig. 7A) and PC-VPC plots (Fig. 7B). While variability of the model was slightly overestimated according to VPC (overall, 3.8 and 10.9% of the observed values fell outside the 90 and 80% PIs, respectively), the PC-VPC procedure showed that the variability was estimated correctly (overall, 7.5 and 14.5% of the observed values fell outside the 90 and 80% PIs, respectively). Thus, PC-VPC confirmed that the final model adequately described the data, including its variability.

The parameter estimates and 95% CI from the bootstrap analysis were very close to the NONMEM estimates obtained from the original dataset (Table 4).

Discussion

The plasma concentrations of safinamide were adequately described by a one-compartment model with first-order absorption and first-order elimination. The structural model parameters and the associated inter- and intraindividual variability were estimated with good precision.

For a typical patient of 70 kg weight in Study 015, the apparent oral clearance (CL/F) and volume of distribution (Vd/F) estimates were 3.59 (95% CI: 3.40, 3.78) L/h and

Table 4. Parameter estimates for the final safinamide population PK PD model and results of the bootstrap evaluation for the final model.

	NONMEM estimates				Bootstrap estimates	
Parameter	Point estimate	%RSE	95% confidence interval (CI)	SD	Point estimate	95% CI
Intercept (INT_{PLAC}) (h)	0 FIX	NA	NA		0 FIX	NA
INT_{TREAT} (h)	0.728	15.0	0.514–0.942		0.727	0.505–0.943
Slope ($SLOP_{PLAC}$) (h/month)	0.117	17.0	0.0780–0.156		0.116	0.0769–0.154
Interindividual variability						
ω^2BL	0 FIX	NA	NA	–	–	–
ω^2SLOP_{PLAC} (h/month)	0.130	10.5	0.103–0.157	0.361	0.129	0.104–0.156
ω^2INT_{PLAC} (h)	3.29	7.93	2.78–3.80	1.81	3.29	2.79–3.81
Residual variability						
σ^2add	1.19	5.59	1.06–1.32	1.09	1.18	1.05–1.32

Model description: PD=BL + INT_{PLAC} + INT_{TREAT} + $SLOP_{PLAC}$*$TIME_{months}$. %RSE, percent relative standard error of the estimate = SE/parameter estimate*100; SD, √coefficient of variation; BL, baseline of the ON-time, observed baseline values used in the model; INT_{PLAC}, intercept of placebo effect; ω^2INT_{TREAT}, variance of the intercept of the placebo effect; INT_{treat}, intercept of Safinamide treatment effect; $SLOP_{PLAC}$, slope of the effect, the same for placebo and Safinamide treatments; σ^2add, additive residual error model; NA, not applicable.

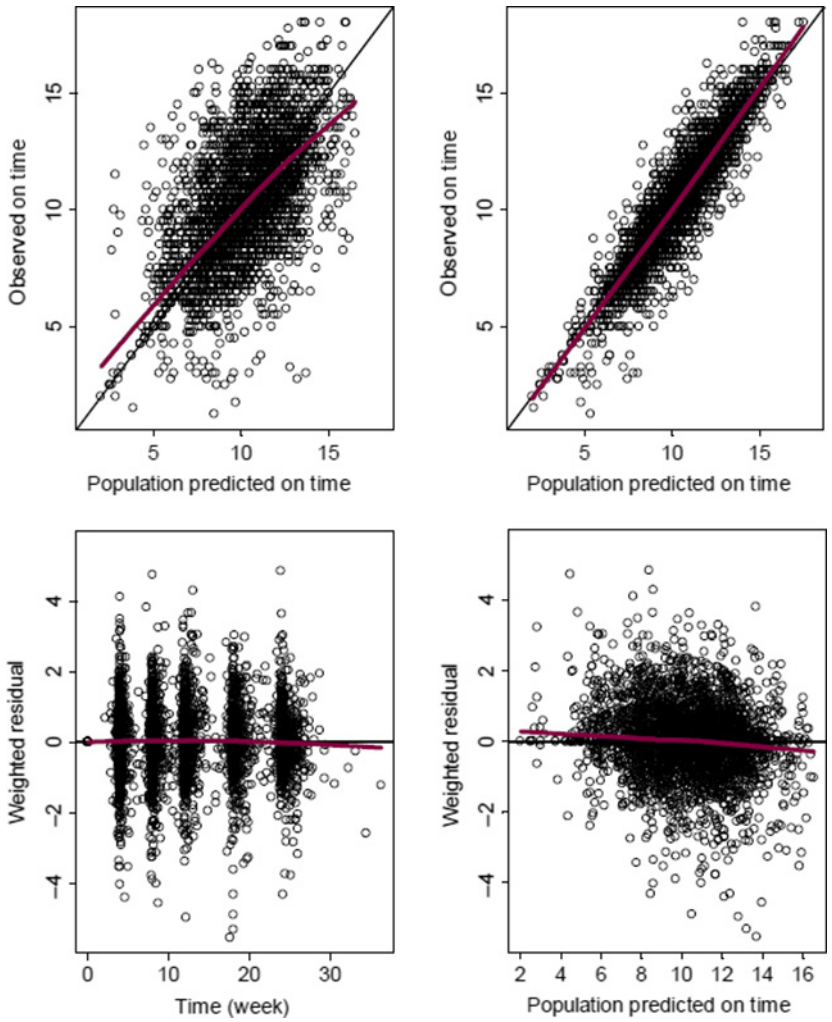

Figure 6. Observed versus population and individual predicted ON-time–final population pharmacokinetic–pharmacodynamic model (Model 915).

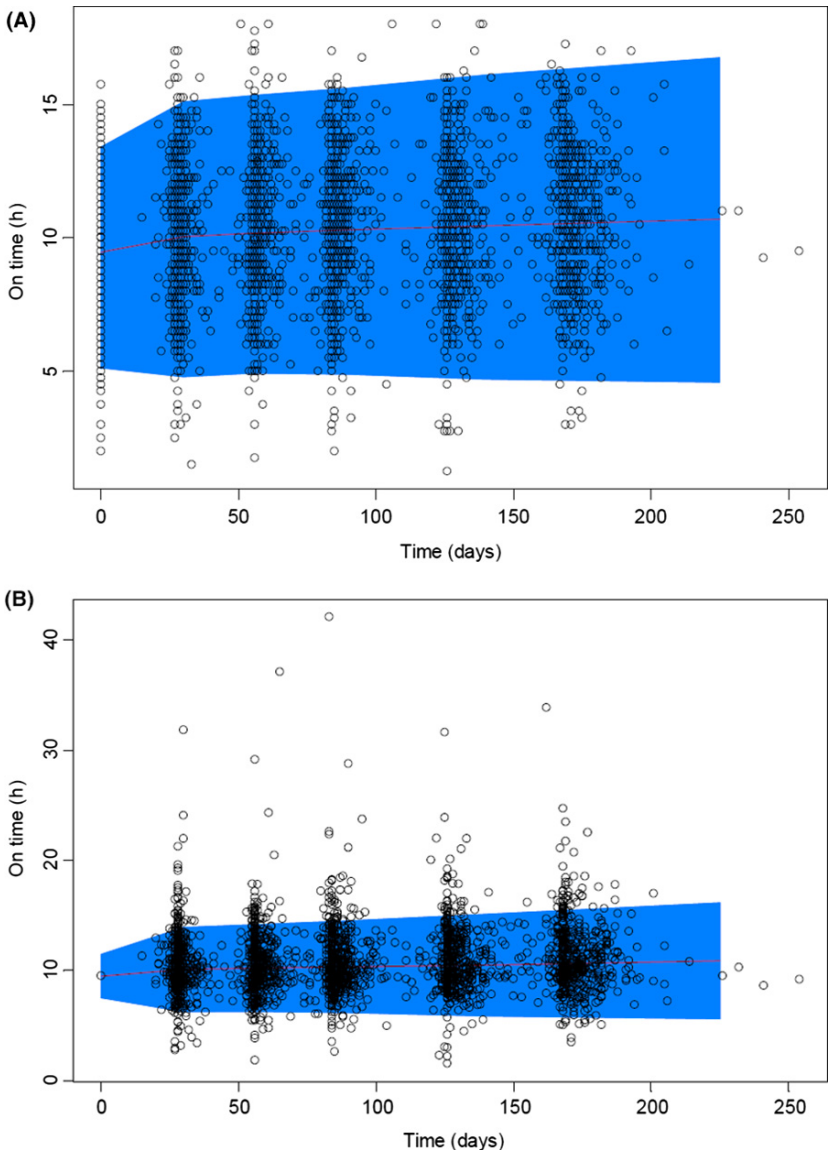

Figure 7. (A) Visual predictive check (VPC) for the final population pharmacokinetic–pharmacodynamic model, all patients (Model 915). (B) Prediction corrected VPC for the final population pharmacokinetic–pharmacodynamic model, all patients (Model 915).

120 (95% CI: 110, 130) L, respectively. The clearance and volume of distribution for a typical patient in Study 016 were 4.96 (95% CI: 4.73, 5.21) L/h and 166 (95% CI: 158, 174) L, respectively.

The absorption was fast with KA estimate of 0.58 h^{-1}. Both CL/F and Vd/F increased allometrically (linearly for Vd/F and with a power coefficient of 0.75 for CL/F) with increasing body weight. For the lightest (33 kg) and the heaviest patients (105 kg) in the analysis, the estimates of CL/F and Vd/F were 43% lower and 36% higher (2.04 and 4.87 L/h) and 53% lower and 50% higher (57 and 180 L), respectively, than for a typical patient.

Observed safinamide plasma concentrations were approximately 30% lower in Study 016 compared to Study 015. The observed difference in concentrations was implemented in the population PK model as a difference in bioavailability. Interestingly, this difference is consistent with the difference in molecular weight between safinamide-free base and safinamide methanesulfonate, suggesting a systematic error. A difference of the same order of magnitude was observed between Study 015 and its own follow-up Study 017 (Schapira et al. 2013). Thus, an effect resulting from the different populations or different population trial design is

considered unlikely. Safinamide plasma concentrations were analyzed in different laboratories but with a very similar validated analytical method.

The apparent oral clearance of safinamide estimated from the present population PK model in subjects with Parkinson's disease in Study 016 is comparable to that obtained in healthy volunteers by noncompartmental analyses (ranging between 4.7–5.8 L/h across various studies) (Marzo et al. 2004; Leuratti et al. 2013). The oral clearance process comprises loss of the parent molecule by metabolism and renal excretion. However, considering that approximately 90% safinamide is metabolized (Marzo et al. 2004; Leuratti et al. 2013), only a small portion of the drug is excreted as unchanged in urine.

The apparent volume of distribution estimate from Study 016 in the current population PK analysis is also comparable to the apparent volume of distribution estimated during the terminal phase (ranging between 150–200 L across various studies) (Marzo et al. 2004; Leuratti et al. 2013). Vd/F values (>100 L independently of the F factor) exceed reference subjects' body weights and indicate an extensive organ (s)/tissue(s) distribution of the drug, with organ/tissue safinamide in equilibrium with safinamide in blood according to a one-compartment open model, substantiated by the observed monoexponential elimination of unchanged safinamide ($t_{1/2}$ approximately 22 h).

Both the estimates of apparent oral clearance and volume of distribution corresponding to Study 015 were slightly lower compared to the estimates from Study 016 and previous studies possibly due to the observed differences in the safinamide bioavailability between Study 015 and Study 016/other studies.

Weight, renal function, age, and gender were explored as covariates on CL/F and Vd/F. In Study 016, levodopa was administered to all the patients and levodopa doses were only allowed to be changed if necessary based on tolerability or worsening motor function throughout the study period. Levodopa dose at baseline, and change in levodopa dose rate was also tested as a covariate for Study 016. None of the covariates except weight were found to have an effect on safinamide PK parameters. This result is in line with the expectations since for many metabolized drugs, there is a close relationship between body weight and clearance. The absence of significance of the covariate CRCL, a metric of the renal function, in this analysis confirms the notion of the limited renal clearance of safinamide reported in the literature. Thus, renal impairment should have only a minor impact on safinamide PK and no dose adjustment is needed in patients with mild and moderate renal impairment.

Before the start of the PKPD analysis, the assumption was that ON-time would decrease during the trial due to disease progression. Placebo effect (confounded with the effect of changing levodopa dose during the 4 weeks of the stabilization phase before the start of study treatment) was expected to first increase (possibly with some delay) and then wane. This did not happen. The placebo data were described by the linear model of time, with no offset added to the intercept and a shallow positive slope of 0.117 h/month (95% CI: 0.0780, 0.156) that would lead to an average increase of 0.70 h over the duration of the study. Therefore, the natural disease progression could not be differentiated from the placebo effect of the study and the long-term effect of Levodopa stabilization. It is unexpected for a placebo effect to last that long.

The data of patients in the safinamide treatment arms were described by the same linear model. The offset effect on the intercept was modified by the treatment, but the slope was the same as for the placebo patients (the effect on the slope due to safinamide was estimated to be not significant). This would mean that the safinamide symptomatic effect is already fully attained by the first post-baseline visit (4 weeks). After that the increase of ON-time with time is the same as in the placebo patients. The immediate safinamide effect was estimated to be 0.728 h (95% CI: 0.514, 0.942) and the total mean increase of ON-time in patients in the safinamide treatment arms at the end of the trial was estimated to be 1.43 h as opposed to 0.70 h for placebo. Thus, at the end of the 6 months of study, "ON time" duration after safinamide treatment was two times longer than after placebo administration.

There was very high interindividual variability in the model, with interindividual CV for the estimated parameters (defined as SD/Estimate) ranging between 250% and 300%. The intraindividual variability measured as the SD of the residual error in the model was also high and estimated to be 1.09 h.

There was no trend detected for safinamide exposure–response relationship in the plots. Incorporation of safinamide exposure as a covariate in the model did not improve the fit. The CIs of the estimates of the SAAV effect and safinamide dose effect on the offset and the slope parameters included the null values, suggesting that there was no safinamide exposure effect in the present patient population.

None of the other covariates (age, safinamide dose, levodopa exposure, and change in levodopa dose rate) had any significant influence on the instantaneous increase of ON-time or the rate of ON-time change during the trial. Safinamide PK variability did not contribute to the variability in the response. However, the high variability in response and the limited duration of the study in relation to the persistence of the placebo effect reduce the possibility to deeply evaluate the effect of the different safinamide doses on the ON-time parameter.

In conclusion, plasma concentrations of safinamide were adequately described by a linear one-compartmental model with first-order absorption and first-order elimination. Age, gender, renal function, and exposure to levodopa did not influence safinamide PK, suggesting that dose adjustment in elderly and mild to moderate renally impaired patients is not requested. In addition, the observed ON-time values were adequately described by a linear model of time in the study period with slope and intercept parameters. The model-based analysis showed that safinamide treatment resulted in an instantaneous increase in ON-time of 0.73 h, reached by the first post-baseline evaluation at week 4, with further increase of ON-time with time, with the same slope as in the placebo patients. This increase was not influenced by age, L-dopa, or safinamide exposure.

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References

Bachman WJ (2007). PDx-Pop™ User Manual. Icon Development Solutions, Ellicott City, MD, USA.

Binda C, Milczek EM, Bonivento D, Wang J, Mattevi A, Edmondson DE (2011). Lights and shadows on monoamine oxidase inhibition in neuroprotective pharmacological therapies. Curr Top Med Chem 11: 2788–2796 Review.

Blandini F, Armentero MT (2012). New pharmacological avenues for the treatment of L-dopa-induced dyskinesias in Parkinson's disease: targeting glutamate and adenosine receptors. Expert Opin Investig Drugs 21: 153–168. doi:10.1517/13543784.2012.651457 Epub 2012 Jan 11.

Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D, et al.; Study 016 Investigators (2014a). Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. Mov Disord 29: 229–237. doi:10.1002/mds.25751.

Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt MH, Chirilineau D, et al.; Study 018 Investigators (2014b). Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. Mov Disord 29: 1273–1280. doi: 10.1002/mds.25961. Epub 2014 Jul 10.

Caccia C, Maj R, Calabresi M, Maestroni S, Faravelli L, Curatolo L, et al. (2006). Safinamide: from molecular targets to a new anti-Parkinson drug. Neurology 67(7 Suppl 2): S18–S23.

Cattaneo C, Ferla RL, Bonizzoni E, Sardina M (2015). Long-term effects of safinamide on dyskinesia in mid- to late-stage Parkinson's disease: a post-hoc analysis. J Parkinsons Dis 5: 475–481. doi:10.3233/JPD-150569.

Deeks ED (2015). Safinamide: first global approval. Drugs 75: 705–711.

Fariello RG (2007). Safinamide. Neurotherapeutics 4: 110–116 Review.

FDA Guidance for Industry (2001). Bioanalytical method validation.

Grégoire L, Jourdain VA, Townsend M, Roach A, Di Paolo T (2013). Safinamide reduces dyskinesias and prolongs L-dopa antiparkinsonian effect in parkinsonian monkeys. Parkinsonism Relat Disord 19: 508–514.

Grosset DG, Macphee GJ, Nairn M; Guideline Development Group (2010). Diagnosis and pharmacological management of Parkinson's disease: summary of SIGN guidelines. DG BMJ 340: b5614. doi: 10.1136/bmj.b5614.

Hauser RA (2009). Levodopa: past, present, and future. Eur Neurol 62: 1–8. doi:10.1159/000215875 Epub 2008 Sep 9.

Hauser RA, Friedlander J, Zesiewicz TA, Adler CH, Seeberger LC, O'Brien CF, et al. (2000). A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. Clin Neuropharmacol 23: 75–81.

Hauser RA, Deckers F, Lehert P (2004). Parkinson's disease home diary: further validation and implications for clinical trials. Mov Disord 19: 1409–1413.

Leuratti C, Sardina M, Ventura P, Assandri A, Müller M, Brunner M (2013). Disposition and metabolism of safinamide, a novel drug for Parkinson's disease, in healthy male volunteers. Pharmacology 92: 207–216. doi:10.1159/000354805 Epub 2013 Oct 11.

Marzo A, Dal Bo L, Monti NC, Crivelli F, Ismaili S, Caccia C, et al. (2004). Pharmacokinetics and pharmacodynamics of safinamide, a neuroprotectant with antiparkinsonian and anticonvulsant activity. Pharmacol Res 50: 77–85.

Beal SL, Sheiner LB, Boeckmann AJ (1989-2006). NONMEM Users Guides. Icon Development Solutions, Ellicott City, MD, USA.

Onofrj M, Bonanni L, Thomas A (2008). An expert opinion on safinamide in Parkinson's disease. Expert Opin Investig Drugs 17: 1115–1125.

Pevarello P, Amici R, Bonsignori A, Caccia C, Amici R, McArthur RA, et al. (1999). Sodium channel activity and sigma binding of 2-aminopropanamide anticonvulsivants. Bioorg Med Chem Lett 9: 2521–2524.

Salvati P, Maj R, Caccia C, Cervini MA, Fornaretto MG, Lamberti E, et al. (1999). Biochemical and electrophysiological studies on the mechanism of action of PNU-151774E, a novel antiepileptic compound. J Pharmacol Exp Ther 288: 1151–1159.

Schapira AH (2010). Safinamide in the treatment of Parkinson's disease. Expert Opin Pharmacother 11: 2261–2268.

Schapira AH (2011). Monoamine oxidase B inhibitors for the treatment of Parkinson's disease: a review of symptomatic and potential disease-modifying effects. CNS Drugs 25: 1061–1071.

Schapira AH, Stocchi F, Borgohain R, Onofrj M, Bhatt M, Lorenzana P, et al.; Study 017 Investigators (2013). Long-term efficacy and safety of safinamide as add-on therapy in early Parkinson's disease. Eur J Neurol 20: 271–280. doi:10.1111/j.1468-1331.2012.03840.x.

Shoulson I, Glaubiger GA, Chase TN (1975). On-off response. Clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients. Neurology 25: 1144.

Singer C (2012). Managing the patient with newly diagnosed Parkinson disease. Cleve Clin J Med 79(Suppl. 2): S3–S7.

Stocchi F, Borgohain R, Onofrj M, Schapira AH, Bhatt M, Lucini V, et al.; Study 015 Investigators (2012). A randomized, double-blind, placebo-controlled trial of safinamide as add-on therapy in early Parkinson's disease patients. Mov Disord 27: 106–112. doi:10.1002/mds.23954.

EMA, Committee for Medicinal Products for Human Use (CHMP) (2014). Xadago 50 mg and 100 mg film-coated tablets. Summary of product characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002396/WC500184965.pdf

Yadav HP, Li Y (2015). The development of treatment for Parkinson's disease. Adv Parkinsons Dis 4: 59–78. doi:10.4236/apd.2015.43008.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Safinamide population pharmacokinetic model building history and associated changes in NONMEM objective function (OF).

Table S2. Safinamide population pharmacokinetic–pharmacodynamic model building history and associated changes in NONMEM objective function (OF).