Dose-Response Analysis of the Effect of Carbidopa-Levodopa Extended-Release Capsules (IPX066) in Levodopa-Naive Patients With Parkinson Disease

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Abstract

Parkinson disease is an age-related disorder of the central nervous system principally due to loss of dopamine-producing cells in the midbrain. Levodopa, in combination with carbidopa, is widely regarded as an effective treatment for the symptoms of Parkinson disease. A dose-response relationship is established for carbidopa-levodopa extended-release capsules (IPX066) in levodopa-naive Parkinson disease patients using a disease progression model. Unified Parkinson Disease Rating Scale (UPDRS) part II plus part III scores from 171 North American patients treated with placebo or IPX066 for approximately 30 weeks from a double-blind, parallel-group, dose-ranging study were used to develop the pharmacodynamic model. The model comprised 3 components: a linear function describing disease progression, a component describing placebo (or nonlevodopa) effects, and a component to describe the effect of levodopa. Natural disease progression in early Parkinson disease as measured by UPDRS was 11.6 units/year and faster in patients with more severe disease (Hoehn-Yahr stage 3). Maximum placebo/nonlevodopa response was 23.0% of baseline UPDRS. Maximum levodopa effect from IPX066 was 76.7% of baseline UPDRS, and the ED_{50} was 450 mg levodopa. Equilibration half-life for the effect compartment was 62.8 days. Increasing age increased and being female decreased equilibration half-life. The quantitative model allowed description of the entire time course of response to clinical trial intervention.

Keywords

pharmacodynamics, IPX066, levodopa, Parkinson disease, disease progression

Parkinson disease (PD) is a neurodegenerative movement disorder characterized by the progressive loss of pigmented midbrain neurons in the substantia nigra pars compacta. Levodopa (LD) is a precursor of dopamine, that, when used with a peripheral dopa-decarboxylase inhibitor such as carbidopa (CD) or benserazide, is considered the "gold standard" in reducing motor symptoms associated with PD.[1–4] Immediate-release (IR) LD has a half-life of 1 to 3 hours and results in fluctuations in plasma LD concentrations that in turn result in variations in striatal dopamine concentrations and pulsatile stimulation of striatal dopamine receptors. Although controlled-release (CR) formulations of CD-LD are available, currently marketed products are associated with erratic absorption and variable LD plasma concentrations. In addition, due to slower absorption, current CR formulations have a longer latency to onset of motor improvement, and patients commonly supplement the CR regimen with IR doses, particularly for the first morning dose. A typical starting dose is one-half of a tablet containing 100 mg of LD and 25 mg of a dopa-decarboxylase inhibitor, taken 3 times daily for a total daily dose of 150 mg of LD. This may be titrated upward over several weeks to provide optimal clinical benefits with a total daily dose of 400 to 800 mg LD, divided into 3 or 4 doses.[5]

IPX066 (Rytary®) is an extended-release oral capsule formulation of CD-LD designed to provide a plasma profile characterized by a rapid initial increase in LD concentrations comparable to an IR dose, followed by sustained LD concentrations with minimal peak-to-trough fluctuations. This profile is expected to provide a rapid onset of effect and to minimize the "off" time in PD subjects. An open-label crossover phase 2 study in patients with idiopathic PD experiencing motor fluctuations on LD showed that IPX066 had a longer duration of effect than IR CD-LD.[6] Pharmacokinetic data in healthy subjects indicate that the initial increase in LD concentration was similar between IPX066 and IR CD-LD, and

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LD concentrations were sustained with IPX066, consistent with the pharmacodynamic effect. The efficacy of IPX066 in early and advanced PD patients has been demonstrated in randomized, double-blind studies.[7,8]

During development of a new therapeutic, it is important to have a quantitative understanding of the time course of disease endpoints and the effect of the therapeutic.[9] A number of studies have attempted to quantitatively characterize the time course of LD effects in PD.[10–14] In clinical practice and research, assessment of PD is typically carried out using rating scales such as the Unified Parkinson's Disease Rating Scale (UPDRS). The UPDRS has 4 components: part I, mentation, behavior, and mood (4 questions); part II, activities of daily living (ADL; 13 questions); part III, motor (14 questions); part IV, complications (11 questions).[15] Parts I through III of the UPDRS are scored on a 5-point Likert scale, with 0 representing "no impairment" and 4 representing "marked impairment." Changes in the UPDRS-ADL have been shown to correlate significantly with changes in the Hoehn-Yahr, a widely used staging system in PD,[16] and studies have suggested that UPDRS ADL serves as 1 of the most responsive measures of disease progression over time.[17,18] We present a quantitative model using UPDRS part II plus part III (total possible score of 108 with lower scores representing less disability) to characterize the time course of the effect of IPX066 in patients with early PD. Changes in UPDRS part II and part III are also accepted as validated scales for the assessment of motor function in PD by regulatory agencies.[19]

Methods

Patients and Data
The study was conducted under the principles of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, according to Good Clinical Practice guidelines, and was approved by the appropriate institutional review board or ethics committee at each study site, and all subjects provided written informed consent.

UPDRS data were obtained from the North American cohort (56 centers in the United States and Canada) of a randomized, placebo-controlled, fixed-dose, parallel-arm phase 3 study comparing 3 doses of IPX066 (145 mg, 245 mg, and 390 mg LD) to placebo, each administered 3 times a day approximately every 6 hours for 30 weeks (clintrials.gov NCT00880620). Details of the study design and the efficacy results have been reported previously.[7] Briefly, the study was conducted in North America and Europe, with the majority of subjects enrolled in North America. Subjects were at least 30 years of age at PD diagnosis, Hoehn-Yahr stage 1, 2, or 3, and were LD naive (defined as not having taken LD for more than 30 days and not within the 4 weeks prior to enrollment). Anticholinergics, amantadine, and MAO-B inhibitors were allowed, but dosages had to be stable for 4 weeks prior to the study and unchanged throughout the study. Mini-Mental State Examination score had to be ≥26, and the sum of UPDRS part II and part III scores had to be ≥18. Eligible subjects were equally randomized into the 4 treatment groups (Placebo, 145 mg, 245 mg, and 390 mg LD administered 3 times a day) within each of 2 strata: subjects who had never taken any PD medications (stratum 1) and subjects who had previously taken or were using allowed non-LD medications for PD (stratum 2). Subjects were evaluated at baseline and weeks 4, 9, 16, 23, and 30.

Parkinson Disease Progression and Drug Effect Model
The state of a disease at any time, S(t), may be described as the combination of the natural progression of the disease, any modulation due to placebo, and any drug effects.[20]

$$S(t) = NDP(t) + EP(t) + ED(t) \tag{1}$$

where NDP(t) represents the natural progression of disease, EP(t) the placebo (or effect due to allowed non-LD PD medications), and ED(t) represents the drug effect.

The UPDRS score is the most widely used scale in clinical studies of PD and has been applied to track the temporal progression of PD. For simplicity, we assume that the natural progression of PD is linear (at least over the duration of the observation period of the trial)

$$NDP_i(t) = S_{0i} + \alpha_i \cdot t \tag{2}$$

where $NDP_i(t)$ is the UPDRS part II plus part III score at time t for the i-th subject, S_{0i} is the score at the beginning of the study (screening), and α is the slope (rate) of disease progression per unit of time.

The placebo effect was modeled as

$$EP_i(t) = S_{0i} \cdot P_{max,i} \cdot (1 - e^{-k_{pl} \cdot t}) \tag{3}$$

where $EP_i(t)$ is the placebo effect for the i-th subject, P_{max} is the maximum percentage change from baseline (S_0) due to placebo, and k_{pl} is the rate constant to reach the steady-state maximum placebo effect. The placebo effect may also include any non-LD effect. In the current study, subjects were allowed to continue specified stable non-LD therapy such as anticholinergic agents, amantadine, or monoamine oxidase type B inhibitors. Because these regimens were stable for at least 4 weeks prior to entry into the study, any non-LD

effect was assumed to be already reflected in the baseline UPDRS.

For subjects treated with IPX066, the dose response of the drug effect was modeled as an E_{max} function

$$ED_i(t) = S_{0i} \cdot \frac{E_{max,i} \cdot D_{E,i}}{(ED_{50,i} + D_{E,i})} \qquad (4)$$

where $ED_i(t)$ is the effect due to IPX066 for the i-th subject; E_{max} is the maximum drug effect expressed as a percentage of the baseline UPDRS part II plus part III score; ED_{50} is the effect compartment LD dose producing 50% of E_{max}. The effect compartment LD dose, D_E, may be predicted as

$$\frac{d(D_{E,i})}{dt} = k_{eo,i} \cdot (Dose_i - D_{E,i}) \qquad (5)$$

where $Dose_i$ is the LD daily dose for the i-th subject, and k_{eo} is the first-order equilibrium constant for the effect site, assuming the effect compartment LD dose is equivalent to the systemic dose at steady state.

Variability
Intersubject variability in the pharmacodynamic parameters was modeled by an exponential term

$$\theta_i = \theta_T \cdot e^{(\eta_i)} \qquad (6)$$

where θ_i is the parameter for the i-th subject, θ_T is the typical value of the parameter in the population, and η_i is a random intersubject effect with mean 0 and variance ω^2. Random intersubject effects were estimated for k_{eo}, P_{max}, and ED_{50}. Parameters were log-transformed, and E_{max} was constrained to be between 0 and 1.

A combined proportional and additive model was used to describe the residual variability:

$$y_{ij} = \hat{y}_{ij} \cdot (1 + \varepsilon_{1ij}) + \varepsilon_{2ij} \qquad (7)$$

where y_{ij} and $\hat{y}_{ij}$ represent the j-th observed and predicted responses, respectively; for the i-th subject, ε_{1ij} and ε_{2ij} denote the residual intrasubject random errors for the proportional and the additive components, each with mean 0 and respective variances σ_1^2 and σ_2^2.

Covariate Effects
The effects of continuous covariates were modeled as follows:

$$\theta_i = \theta_{pop} \cdot \left(\frac{Cov_i}{Cov_{pop}}\right)^{k_{cov}} \qquad (8)$$

and the effect of categorical covariates was modeled as follows:

$$\theta_i = \theta_{pop} \cdot e^{k_{cov} \cdot X_i} \qquad (9)$$

where θ is a model parameter, Cov represents a continuous covariate, X represents a categorical variable, i is an index for each subject, pop is an index describing the usual value of this covariate for the population, and k_{cov} is a coefficient describing the strength of the covariate effect.

Model Development
The pharmacodynamic model was developed in a step-wise fashion. First, an initial model of disease progression and the placebo effect was developed using data from subjects randomized to the placebo treatment. Then, data from the IPX066 treatment arms were added to build a comprehensive structural model with disease progression, placebo, and drug effect. Parameters for the structural model were estimated using data from all patients in the placebo and IPX066 treatment arms.

During model development, various model structures were examined, including using a sigmoid E_{max} model or E_{max} model to describe the IPX066 dose response, varying the onset and offset of the placebo effect, and using the observed baseline or the Hoehn-Yahr stage as a covariate to predict the baseline UPDRS.

Covariates were added to the structural model using a forward addition and backward elimination approach. Significant covariate relationships in the univariate screening were assessed using the likelihood ratio test at the $P < .01$ level of significance (change in objective function >6.64 for 1 degree of freedom). A full model was constructed by incorporating all significant covariates into the base model. Elaboration of the final model was done by a stepwise backward elimination process. Starting with the full model, the final model was obtained by removing each covariate one at a time. The covariate with the smallest change in the minimum objective function (MOF) was removed from the model, and the process was repeated. The level of significance to retain a covariate was $P < .001$ using the maximum likelihood test.

Evaluation of the Model
A visual predictive check (VPC) was conducted to evaluate the final model. A total of 1000 replicates of the trial were simulated. The areas covering the 90% confidence intervals of the median and the 5th and 95th percentiles of the predicted UPDRS scores and the 5th and 95th percentiles of the observed data were plotted for each treatment group. The extent of shrinkage for the final model was assessed for η of each parameter as well as for ϵ using the method of Savic et al.[21]

The disease progression model was developed using a population-modeling approach with the NONMEM software (version 7.2.0, ICON Development Solutions, Ellicott City, Maryland). The first-order conditional

estimation (FOCE) method was used for parameter estimation. Graphical representations, exploratory analysis, model diagnosis, simulation, and covariate selection were performed using the R, PsN, and xpose software.

Results

There were 171 subjects (111 males, 60 females) enrolled in the North American cohort. The median age of the population was 66 years, and the median number of years since diagnosis of PD was 1 year. The mean baseline UPDRS part II plus part III score was 34.1 with a majority of subjects rated as Hoehn-Yahr stage 2 (72.5%). Subjects were naive to LD (defined as less than 4 weeks exposure), with 101 of the 171 patients receiving some non-LD therapy for PD.

Disease Progression

The population parameter estimates describing the effect of IPX066 in patients with early PD as measured by UPDRS are summarized in Table 1. Baseline Hoehn-Yahr scores met significance criteria for incorporation in the model to describe the rate of disease progression. The estimated rate of disease progression was 11.6 units per year (95% confidence interval: 6.4, 20.8 units) in patients with Hoehn-Yahr scores of 1 or 2, with the rate of progression being 83% faster in patients with more advanced disease (Hoehn-Yahr score of 3).

Placebo Effect

The maximum placebo effect was 23.0% of the baseline UPDRS score with a half-life to maximum effect of 62.8 days. Age, body weight, sex, duration of disease, baseline UPDRS, and Hoehn-Yahr score did not reach significance for incorporation into the placebo model. During the model-building process, placebo effects for stratum 1 subjects (those who had never taken PD medications) and stratum 2 subjects (those who had previously taken and continued to take non-LD medications) were compared, and no difference was noted in the response for the 2 groups.

IPX066 Drug Effect

The biophase equilibrium half-life for a typical patient (65-year-old male) was 62.8 days. Age and sex reached significance for inclusion in the drug effect model. The equilibrium constant varied by $(\frac{AGE}{65})^{-3.93}$; thus, a 70-year-old male had a k_{e0} that was 75% of that for a 65-year-old male, and the equilibration rate was 3.4 times faster in women than in men. IPX066 had a maximum effect (E_{max}) of 76.7% of baseline (equivalent to a reduction of ~26.1 units) with an ED_{50} of 450 mg/day. None of the other covariates met the threshold for inclusion in the model.

The adequacy of the final model was assessed by its ability to describe the time course of UPDRS part II plus part III for individual patients. This is illustrated

Table 1. Parameter Estimates for Disease Progression Model Using UPDRS Parts II and III in Subjects With Early Parkinson Disease Following IPX066

| Parameters	Unit	Estimate [95%CI]	Bootstrap Median [95%CI]	Shrinkage (%)
Baseline UPDRS				
HY* = 1		23.3 [20.9, 26.1]	23.3 [21.5, 26.1]	
HY = 2		34.1 [32.3, 36.1]	34.2 [32.6, 35.7]	
HY = 3		40.9 [36.3, 46.0]	41.1 [37.3, 45.2]	
Slope of disease progression	units/year			
HY = 1,2		11.6 [6.5, 20.8]	11.5 [5.95, 17.16]	
HY = 3		21.1 [11.5, 38.9]	20.4 [4.1, 32.4]	
Maximum placebo effect (P_{max})	% of baseline	23.0 [13.0, 40.7]	23.9 [12.4, 40.6]	
$t_{1/2}$ for the onset of placebo effect	days	62.8 [30.5, 127.6]	65.9 [31.0, 147.6]	
Maximum drug effect for IPX066 (E_{max})	% of baseline	76.7 [41.5, 93.8]	80.1 [59.5, 100]	
$t_{1/2}$ of the onset of IPX066 effect (65-year-old male)	days	62.8 [28.2, 138.0]	62.5 [30.7, 128.8]	
IPX066 dose to achieve 50% of E_{max} (ED_{50})	mg/day	450 [171.4, 1184]	471 [192, 923]	
Coefficient of age on k_{e0}		−3.93 [−6.24, −1.62]	−3.80 [−8.52, −1.20]	
Coefficient of female sex on k_{e0}		1.22 [0.44, 2.00]	1.24 [0.40, 2.21]	
Interindividual Variability				
Maximum placebo effect (ω^2_{pmax})		0.561 [0.282, 0.838]	0.588 [0.330, 1.00]	31.4
Equilibrium constant for effect site compartment ($\omega^2 k_{eo}$)		2.70 [0.642, 4.76]	2.4 [0.501, 4.99]	41.8
ED_{50} ($\omega^2 ED_{50}$)		0.406 [0.00, 0.815]	0.430 [0.067, 1.20]	57.7
Baseline UPDRS				
[HY = 1]		0.0514 [0.095, 0.093]	0.0484 [0.0078, 0.0938]	70.6
[HY = 2,3]		0.0917 [0.0692, 0.114]	0.0908 [0.0689, 0.112]	9.6
Residual Variability				
Proportional error (δ_1^2)		0.0136 [0.0064, 0.0208]	0.0133 [0.0055, 0.0210]	16.6
Additive error (δ_2^2)		6.46 [2.48, 10.4]	6.56 [2.99, 11.3]	16.6

*HY, Hoehn-Yahr score.
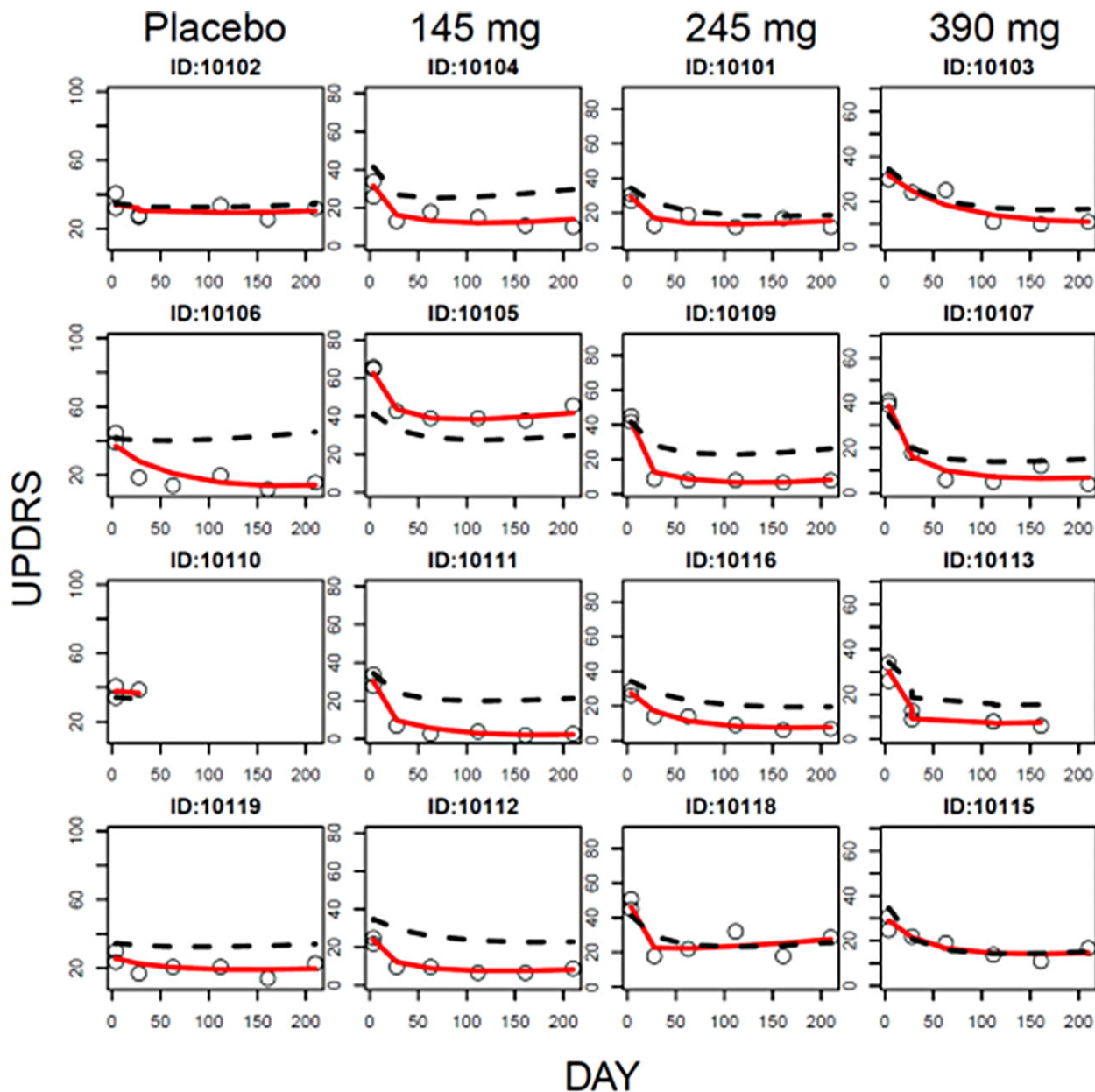
Figure 1. Predicted and observed UPDRS part II plus part III in representative individual subjects caption. Data for 4 representative subjects in each dose group are presented. Solid lines represent the model-predicted individual fits, and dashed lines represent the population fits.

in Figure 1 for 4 representative patients in each dose group. The predictions matched quite closely with the observed values. In addition, visual and numeric predictive evaluation indicated that the model adequately describes the data for the population over the duration of the study (Figure 2). The lines describing the central tendency (median) and the 5th and 95th percentiles of the predictions fell well within the area covering 90% of the observations. All parameters were estimated with adequate precision. Generally shrinkage estimates were low except for baseline UPDRS scores in patients with Hoehn-Yahr scores of 1 and ED_{50} (Table 1).

Discussion

This report outlines the development of a population pharmacodynamic model to describe the disease progression and the LD dose response relationship for IPX066 on UPDRS part II plus part III scores in patients with PD who were naive to LD. This model-based approach allowed estimation of the natural progression of disease and quantitation of the dose-response relationship.

The pharmacodynamic parameters estimated for IPX066 in the present study for UPDRS part II plus part III are consistent with those reported for
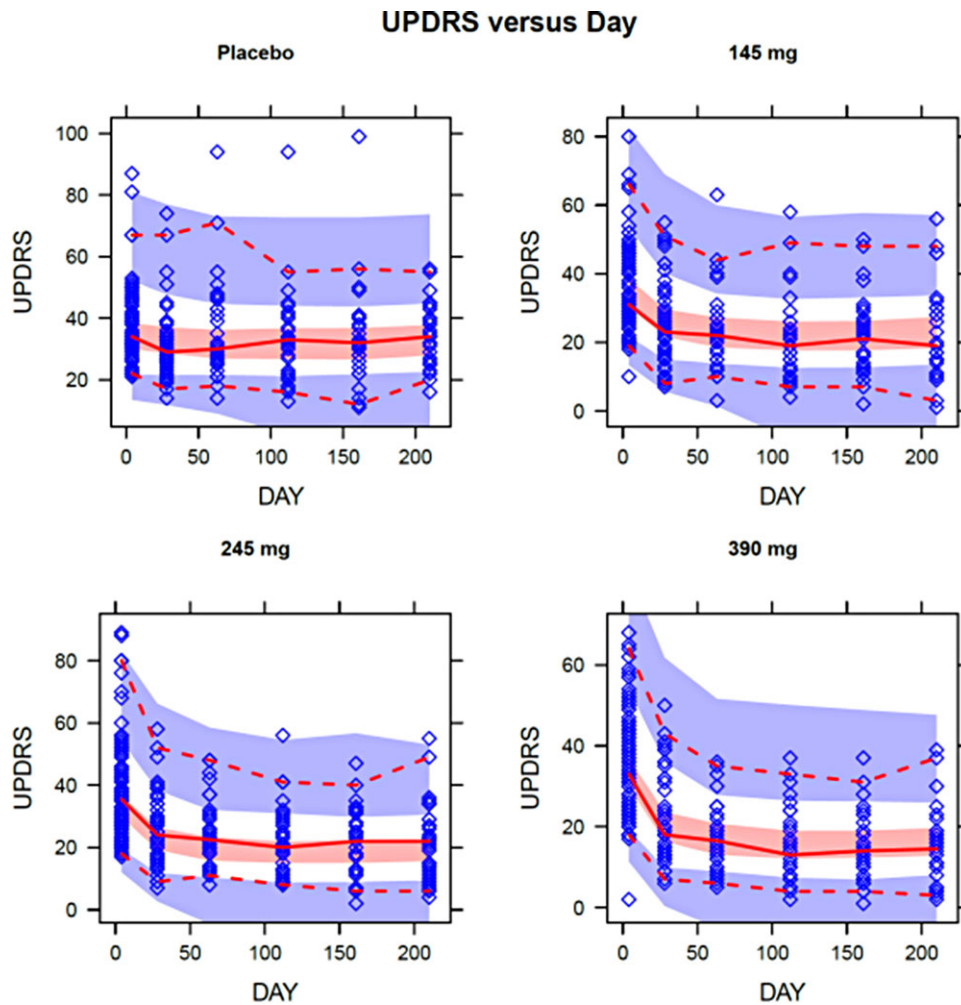
Figure 2. Visual predictive check of disease progression model for IPX066 in patients with early Parkinson disease. Symbols represent individual observations. Solid lines represent the median predictions, and the dashed lines represent the 5th and 95th percentiles of the model prediction. The shaded area represents the 90% prediction bands.

CD-LD in the literature. In the present analysis, with the natural progression of disease described using a linear relationship, the basal progression was 11.6 units/year. Holford and colleagues reported a progression rate of 14 units/year, 12.5 units/year, and 12.1 units/year using the placebo-LD, placebo-deprenyl, and the full data sets from the DATATOP study.[11,22] Similarly, Bhattaram et al have reported a progression rate that ranged from 0.11 units/week to 0.27 units/week (corresponding to 5.7 to 14.0 units/year).[23] In a review by Chan et al, the authors reported placebo treatment rates of progression in PD for the total UPDRS ranging from 13.11 to 14.02 units/year.[24] Analysis of the DATATOP study, which extended for 8 years, showed that the rate of disease progression changes over time and was best described by a nonlinear function.[11] The analyses by Holford and colleagues also showed that the rate of progression was approximately linear for the first 2 years.[11] The short duration of the current

trial limited examination of more complex models such as an asymptotic model using an exponential or a Gompertz function. Holford and colleagues noted that a Gompertz growth model best described the full data from the DATATOP study that extended for 8 years. However, although their model was predictive for the first year, subsequently the predicted median and upper bound of the predicted variability were greater than observed. The use of a linear relationship to describe disease progression in the current analysis may be justified because the duration of the study (approximately 210 days) was shorter than 2 years. Data in the IPX066-treated groups were also limited to less than 2 years, so it is not expected that a pooled analysis with longer-term data for the placebo group would help refine the pharmacodynamic parameters for the IPX066 treatment.

A single rate of progression was estimated for patients with Hoehn-Yahr stage 1 and 2, whereas the estimated rate of progression was faster in patients
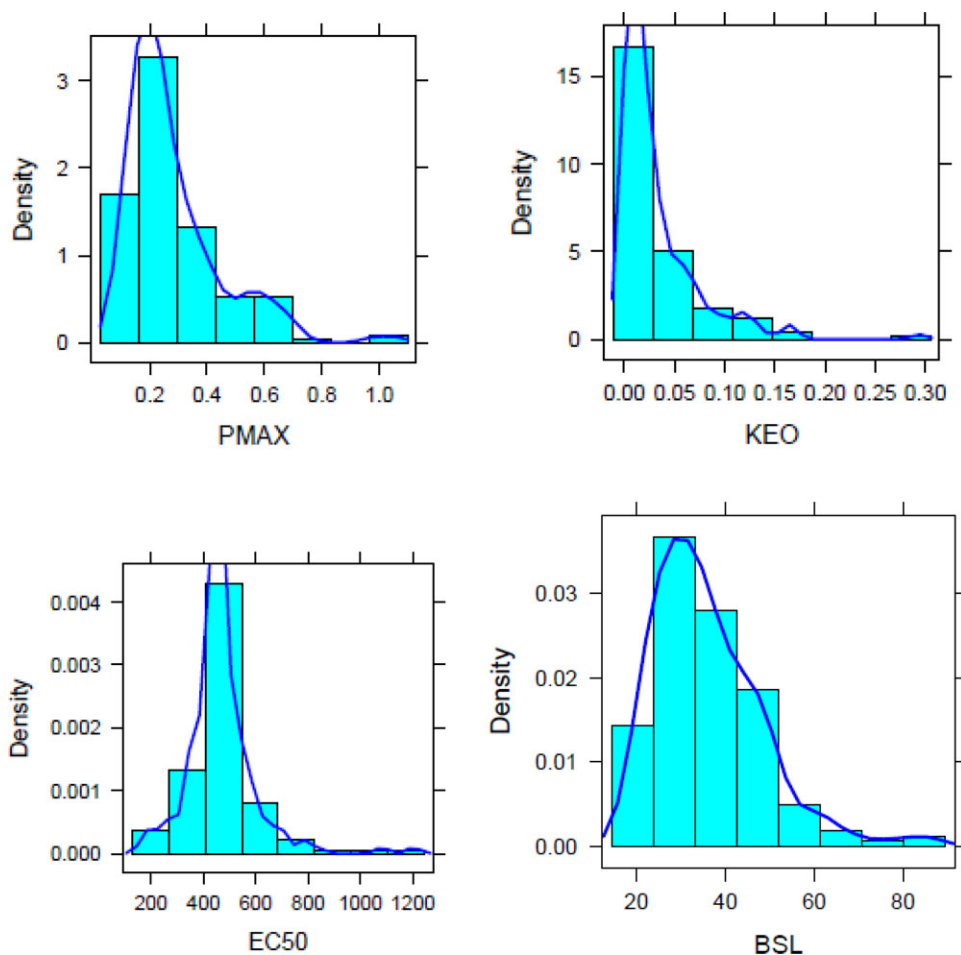
Figure 3. Distribution of model parameter.

with Hoehn-Yahr stage 3. These findings are consistent with published reports of a faster progression in more severe patients[16,25] and correlate favorably with clinical practice, where mild or early PD generally has been defined operationally as Hoehn-Yahr stages 1 and 2.[26]

In the present analysis the maximum placebo effect was 23.0% of baseline, and the onset equilibrium half-life of the placebo effect was 62.8 days. The maximum effect (E_{max}) of IPX066 on UPDRS part II plus part III was 76.6% of baseline (corresponding to a decrease of 26.1 units from baseline). The estimated equilibration half-life for the effect compartment was 63 days for a 65-year-old male. For women of comparable age, the equilibration half-life was decreased to 18 days. The results indicated that a 1-decade increase in age above 65 years results in a 1.2-fold increase in the equilibration half-life.

These pharmacodynamic findings are consistent with those reported with other formulations of CD-LD. Ploeger and Holford noted a maximum placebo effect of 23.6% of baseline value and an onset equilibrium half-life of placebo effect of 51 days.[13] Holfold and Chan reported a maximum LD drug effect of 23.3 units,

a disease progression of 13.11 to 14.02 units/year, and an equilibrium half-life of 0.211 years.[11]

Following adjustment for the bioavailability of IPX066 relative to IR LD, the ED_{50} value estimated in the present study was equivalent to a systemic LD dose of 305 mg, which is comparable to a median LD dose of 300 mg/day in the DATATOP study. Interestingly, in an analysis of the DATATOP data by Holford et al,[11] the estimated ED_{50} was 9.63 mg/day using the full data set of their model and 90 mg/day using the shorter 2-year subset study of LD alone. In a subsequent report,[12] the same authors employed an ED_{50} estimate of 0.0376 units per 0.3 g/day (corresponding to 11.28 mg/day) to simulate disease progression. These estimates of ED_{50} are all lower than the values noted in the present analysis and also less than the normal LD doses of 300 to 1600 mg per day used clinically.[27]

In the current analyses a significant sex effect was noted on the effect site equilibrium rate constant. Although we do not attribute a physiologic reason for this, there may be several potential causes for this finding. Women are reported to have 16% higher striatal [^{123}I]FP-CIT binding than men at onset and throughout

the course of disease.[28] Female patients exhibit greater striatal dopamine transporter (DAT) activity compared with male patients in all striatal subregions.[29] Clinically, women with PD exhibit less severe PD motor features and show greater LD responses with more severe LD-induced dyskinesia.[30,31] Female sex has been associated with a shorter time to LD-induced dyskinesia.[32] Female sex hormones (ie, estrogen) are thought to play an important role in the sex differences observed in PD.[33] Finally, women require lower doses of LD than men for a comparable response, and for a given dose of LD, women tend to have higher systemic concentrations compared to men, due to lower body weight.[34,35] It should also be noted that differences in the k_{e0} half-life would reflect differences in the time to reach steady state and do not signify differences in onset of effect or in the overall magnitude of effect.

Limitations

We assumed an empirical linear function to describe the natural progression of disease. As noted, published reports indicate that over at least 2 years, and possibly up to 5 years, disease progression may follow a linear trend.[11,23] Inclusion of data over a longer duration would allow potential nonlinearities in disease progression to be modeled. The present analysis was also limited to the North American cohort of patients enrolled in the study. Visual examination of the time course of response from patients enrolled in Eastern Europe showed that all 3 doses of IPX066 in these subjects had fairly comparable and robust effects, suggesting that these doses may be on the asymptote of the dose-response relationship. Regional differences in the responses are not uncommon, particularly on instruments such as the UPDRS. The IPX066 doses chosen in the study were guided in part by the goal of matching the exposures corresponding to the LD doses studied in the ELLDOPA trial.[36] Finally, we assumed an asymptotic response for the placebo effect. Although it is recognized that a placebo effect will abate with time, the current model did not include an offset of the placebo effect because the UPDRS part II plus part III response for the placebo treatment had not reverted back to the baseline value by the completion of the study.

Despite these assumptions, the model provides a good description of the time course of effects as noted by robust predictions of the response for individual subjects.

Conclusions

This model-based approach allowed description of the full-time course of disease progression and the effects of an extended-release capsule formulation of CD-LD in early PD. The pharmacodynamic response for IPX066 as measured by UPDRS part II plus part III compares favorably with published data for other formulations of LD.

Declaration of Conflicting Interests

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