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Population Pharmacokinetic-Pharmacodynamic Modeling of Istradefylline in Patients With Parkinson's Disease

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INTRODUCTION

- Istradefylline is a novel selective adenosine A_{2A} receptor antagonist with anti-parkinson's activities in rodent and primate models.
- Evidence indicates that A_{2A} receptors located on the striatopallidal medium spiny neurons, in the indirect pathway, are involved in motor control through the basal ganglia.
- Using istradefylline to block these receptors may reduce the excitability of the indirect pathway and thereby ameliorate Parkinson's disease symptoms.
- Recent randomized and controlled trials of istradefylline in Parkinson's disease patients have demonstrated effectiveness and tolerability when istradefylline is used in combination with other Parkinson's drug therapy.
- In an effort to describe the dose concentration-response relationship, population pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PK-PD) models were developed from istradefylline clinical trial data using non-linear mixed-effects modeling techniques.

OBJECTIVE

- The objective of the population PK-PD analysis was to develop exposure-response (ER) models describing the relationship between individual predicted istradefylline area under the curve (IAUC) at steady state and efficacy (percentage OFF [POFF] time) and safety (dyskinesia, nausea, and dizziness) end points.

METHODS

- Istradefylline ER data from 1760 (1181 istradefylline-treated, 579 placebo) patients were pooled across six Phase 2 and Phase 3 trials. The dose range was 5 to 60 mg administered once daily.
- IAUC, calculated for each patient based on the individual predicted apparent oral clearance from the final population PK model, was used as the exposure measure in the PK-PD analysis.
- Covariate data available for the analysis, distributions of continuous covariates, counts of categorical covariates, and continuous covariate correlations are listed in **Tables 1** and **2**.

Table 1. Summary of Continuous and Categorical PK-PD Covariates

PK-PD Continuous Covariates	Minimum	Maximum	Median	Mean
UPDRS subscale 2 score	1	40	17	17.6
Time since diagnosis of Parkinson's disease, y	0.09	36.8	8.32	9.17
Time since onset of motor complications, y	0.04	29.9	2.76	3.74
Baseline OFF time, h	0.25	17.8	6.30	6.39
Time since start of levodopa therapy, y	0.45	31.8	6.79	7.54

PK-PD Categorical Covariates	Concomitant Medications							
	Dopamine Agonists		COMT Inhibitors		Selegeline		Amantadine	
	No	Yes	No	Yes	No	Yes	No	Yes
Number	643	1117	1131	629	1523	237	1297	463
Percentage	37	63	64	36	87	13	74	26

	Hoehn & Yahr Score (HYSC)				
	HYSC Missing	Stage 2	Stage 2.5	Stage 3	Stage 4
Number	645	307	316	387	105
Percentage	37	17	18	22	6

N = 1760.
UPDRS = Unified Parkinson's Disease Rating Scale; COMT, catechol-*O*-methyltransferase.

Table 2. Correlation Coefficients of Continuous PK-PD Covariates

	UPDRS Subscale 2 Score	Time Since Diagnosis of Parkinson's Disease (TPD)	Time Since Onset of Motor Complications (TOMC)	Baseline OFF Time (BOFF)	Time Since Start of Levodopa Therapy (LYRS)
UPDRS	1	0.31	0.23	0.063	0.29
TPD, y	0.31	1	0.64	–0.061	0.88
TOMC, y	0.23	0.64	1	–0.088	0.69
BOFF, y	0.063	–0.061	–0.088	1	–0.097
LYRS, y	0.29	0.88	0.69	–0.097	1

UPDRS, Unified Parkinson's Disease Rating Scale.

- The PK-PD database contained 9108 measurements of POFF and 1890 measurements for each safety/tolerability end point.
- Data processing and graphics were performed using R software (Comprehensive R Network; http://cran.r-project.org/). POFF data were analyzed with the use of non-linear mixed-effects modeling (NONMEM), and safety data were analyzed using a naive-pooled approach with NONMEM V, level 1.1 (GloboMax/ICON, Ellicott City, Maryland).
- Placebo data were used to develop a disease progression/placebo response (DP-PR) model for POFF. A model describing the effect of IAUC on POFF was incorporated into the DP-PR model, and all parameters of the combined model were simultaneously estimated.
- Each of the safety end points was expressed as a dichotomous categorical variable representing the occurrence of an adverse event (AE), such as dyskinesia, nausea, and dizziness, with scores of 1 for yes and 0 for no. These data were viewed as a probabilistic outcome and were analyzed using a logistic regression model with IAUC as the predictor.
- Covariate effects were assessed according to a full-model approach. The clinical importance of covariate effects was based on point and interval estimates of parameters rather than on stepwise hypothesis testing.
- Final full-model goodness-of-fit was evaluated using typical diagnostic plots. Final models were also investigated for any remaining trends between random effects and all covariates in the population PK-PD database.
- Parameters of the final model (and asymptotic standard errors) for each end point were estimated, and 95% confidence intervals were obtained by non-parametric bootstrap. One thousand bootstrap data sets were generated and analyzed for each model to assess parameter precision.
- The adequacy of the final models and parameter estimates was also investigated with a predictive check method. The final model was used to simulate 100 trials, and the simulated data were compared with the data observed during the actual trial.
- PK and PK-PD models were used to simulate the effects of treating each patient in the Phase 2/3 studies at doses of 5, 10, 20, 40, 60, and 80 mg/day istradefylline on POFF and the safety/tolerability end points.

RESULTS

- An E_{max} model based on time and proportional to the baseline POFF was used to describe the disease progression/placebo data, and an E_{max} model based on IAUC was used to describe the effect of istradefylline on POFF (**Equation 1**).

Equation 1. Full Covariate Model for Percentage OFF Time

$$
\begin{aligned}
EO_i &= \theta1_{EO} \bullet (UPDS/17)^{\theta6} \bullet (TOMC/2.8)^{\theta7} \bullet \theta8^{DOPA[DOPA1]} \bullet \theta9^{COMT[COMT1]} \bullet \theta10^{SELG[SELG1]} \bullet \\
&\quad \theta11^{AMAT[AMAT1]} + \eta^{E0} \\
E_{max}P_i &= \theta2_{E_{max}P} \bullet (UPDS/17)^{\theta12} \bullet (BOFF/6.3)^{\theta13} \bullet (TOMC/2.8)^{\theta14} \bullet \theta15^{DOPA[DOPA1]} \bullet \\
&\quad \theta16^{COMT[COMT1]} \bullet \theta17^{SELG[SELG1]} \bullet \theta18^{AMAT[AMAT1]} + \eta^{E_{max}P} \\
ET_{50_i} &= \theta3_{ET_{50}} \\
E_{max}I_i &= \theta4_{E_{max}I} \bullet (UPDS/17)^{\theta19} \bullet (BOFF/6.3)^{\theta20} \bullet (TOMC/2.8)^{\theta21} \bullet \theta22^{DOPA[DOPA1]} \bullet \\
&\quad \theta23^{COMT[COMT1]} \bullet \theta24^{SELG[SELG1]} \bullet \theta25^{AMAT[AMAT1]} + \eta^{E_{max}I} \\
EC_{50_i} &= \theta5_{EC_{50}} \\
PDDP_{Ei} &= E0_i \times (1 + E_{max}P_i \times Time_i/[ET_{50_i} + Time_i]) \\
I_{Ei} &= E_{max}I_i \times IAUC_i/(EC_{50_i} + IAUC_i) \\
POFF_i &= PDDP_{Ei} + I_{Ei} \\
POFF &= POFF_i \exp(\varepsilon_1) + \varepsilon_2
\end{aligned}
$$

E0, baseline percentage OFF time; UPDS, UPDRS subscale 2 score; PDDP, disease progression/placebo response; $E_{max}P$, maximum DP-PR effect; ET_{50}, time to reach 50% of maximum DP-PR effect; $E_{max}I$, maximum istradefylline effect; EC_{50}, AUC that results in 50% of maximum istradefylline effect; POFF, percentage OFF time. Covariate abbreviations are as described in Table 4.

- Structural model parameters for the base model were estimated with good precision with the exception of EC_{50} (RSE = 45%), whereas estimates of random effects demonstrated significant interindividual variability (**Table 3**).

Table 3. PK-PD Percentage OFF Time Base Model Parameters for the Placebo and Istradefylline Effect Models

Parameter	Fixed-Effect Parameter (% SE)
E0 = θ1	37.9 (1)
$E_{max}P$ = θ2	–0.152 (11)
ET_{50} (days) = θ3	19.3 (34)
$E_{max}I$ = θ4	–5.79 (15)
EC_{50} (ng/mL/h) = θ5	1690 (45)
	Interindividual Variance (% SE)
ω^2_{E0}	107 (7) SD = 10.3
$COV_{E0\text{-}E_{max}P}$	(54) *r* = 0.11
$\omega^2_{E_{max}P}$	0.117 (14) SD = 0.341
$\omega^2_{E_{max}I}$	17.5 (96) SD = 4.18
	Residual Variance (% SE)
ω^2_{add}	51.8 (9) SD = 7.20
ω^2_{exp}	0.0212 (23) CV% = 14.5

E0, baseline percentage OFF time; $E_{max}P$, maximum DP-PR effect; ET_{50}, time to reach 50% of maximum DP-PR effect; $E_{max}I$, maximum istradefylline effect; EC_{50}, AUC that results in 50% of maximum istradefylline effect; COV, covariance; add, additive error; exp, exponential error; % SE, percentage standard error; *r*, correlation coefficient; SD, standard deviation; CV%, percentage coefficient of variation.

- Goodness-of-fit plots demonstrated a good fit to the data and a lack of bias (**Figure 1**).
- The addition of individual-specific covariates to the model resulted in some improvement in goodness-of-fit plots and only a small decrease in interindividual variability (**Figure 2**), whereas covariate effects were estimated with varying degrees of precision (**Table 4**).

Figure 1. Goodness-of-fit plots for percentage OFF time base model.

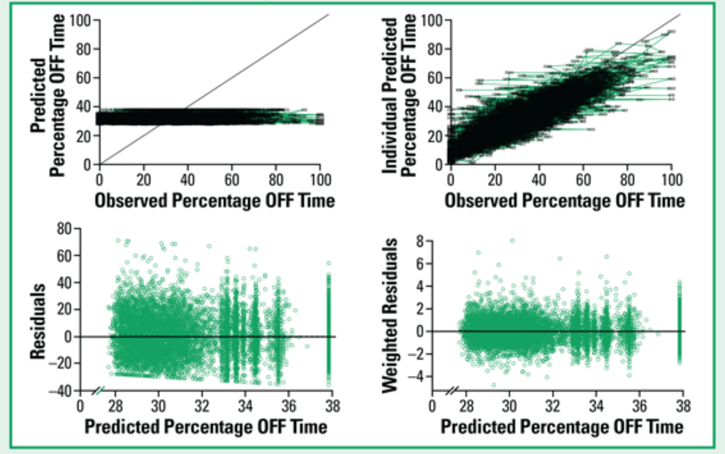
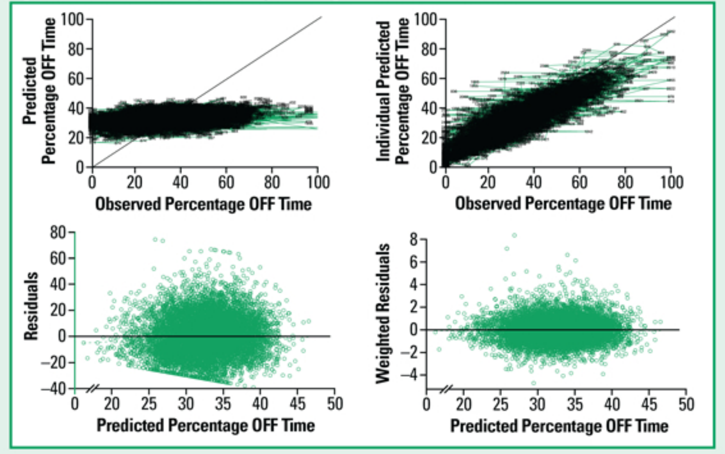


Table 4. PK-PD Percentage OFF Time Final Model Parameters for the Placebo and Istradefylline Effect Models

Parameter	Fixed Effect (%)	Bootstrap 95% CI
E0 = θ1	39.5 (2)	38.3, 40.7
$*(UPDS/17)^{\theta6}$	0.0998 (20)	0.0583, 0.140
$*(TOMC/2.8)^{\theta7}$	–0.0388 (–23)	–0.0550, –0.0226
$*\theta8^{DOPA[dopamine\ agonists\ yes]}$	0.974 (2)	0.941, 1.01
$*\theta9^{COMT[COMT\ inhibitors\ yes]}$	0.960 (2)	0.929, 0.993
$*\theta10^{SELG[selegeline\ yes]}$	0.976 (2)	0.933, 1.03
$*\theta11^{AMAT[amantadine\ yes]}$	0.967 (2)	0.929, 1.01
$E_{max}P$ = θ2	–0.147 (–20)	–0.204, –0.0881
$*(UPDS/17)^{\theta12}$	0.227 (91)	–0.226, 0.663
$*(BOFF/6.3)^{\theta13}$	–0.494 (–35)	–1.25, –0.251
$*(TOMC/2.8)^{\theta14}$	–0.0672 (–197)	–0.277, 0.241
$*\theta15^{DOPA[dopamine\ agonists\ yes]}$	1.33 (24)	0.642, 2.14
$*\theta16^{COMT[COMT\ inhibitors\ yes]}$	0.569 (31)	0.237, 1.11
$*\theta17^{SELG[selegeline\ yes]}$	0.961 (36)	8.60e-11, 1.72
$*\theta18^{AMAT[amantadine\ yes]}$	0.865 (26)	0.408, 1.33
ET_{50} (days) = θ3	17.8 (31)	10.6, 33.4
$E_{max}I$ = θ4	–3.57 (–24)	–5.37, –1.41
$*(UPDS/17)^{\theta19}$	–0.0767 (–255)	–0.500, 0.361
$*(BOFF/6.3)^{\theta20}$	–0.134 (–157)	–0.529, 0.46
$*(TOMC/2.8)^{\theta21}$	0.163 (87)	–0.108, 0.521
$*\theta22^{DOPA[dopamine\ agonists\ yes]}$	1.24 (26)	0.792, 4.23
Interindividual Variance (% SE)		
ω^2_{E0}	98.1 (7) SD = 9.90	83.9,111
$COV_{E0\text{-}E_{max}P}$	(463) *r* = 0.0120	–0.545, 0.405
$\omega^2_{E_{max}P}$	0.118 (13) SD = 0.343	0.0921, 0.160
$\omega^2_{E_{max}I}$	14.2 (118) SD = 3.77	3.34e-09, 48.9
Residual Variance (% SE)		
σ^2_{add}	51.8 (9) SD = 7.20	43.1, 61.3
σ^2_{exp}	0.0215 (22) CV% = 14.7	0.0128, 0.0301

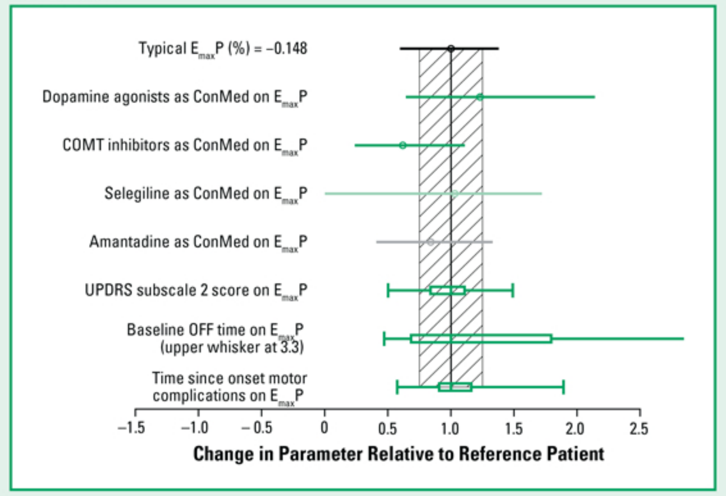
UPDS, UPDRS subscale 2 score; TOMC, time since onset of motor complications; COMT, catechol-*O*-methyltransferase; BOFF, baseline OFF time; COV, covariance; CV%, percentage of coefficient of variation.

Figure 2. Goodness-of-fit plots for percentage OFF time final model.



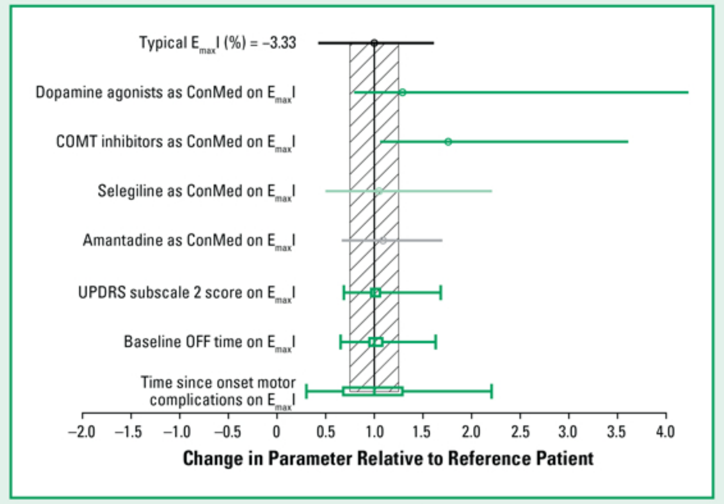
- The most influential covariate on the POFF PK-PD model was smoking status (IAUC decrease by 38% based on the PK model), whereas the effect of COMT inhibitors on POFF trended in opposite directions for placebo compared with istradefylline (**Figures 3** and **4**).

Figure 3. Covariate effects for maximum effect of placebo ($E_{max}P$) for percentage OFF time PK-PD model.



Solid vertical line represents $E_{max}P$ point estimate, and horizontal black line represents 95% CI. For categorical covariates, point estimates are represented by the open circles, and 95% CI is represented by the horizontal bar. For continuous covariates, box and whisker plots represent the spread of point estimates, with 50% of data within the box and the remaining 50% between the ends of the box and whisker plots. Hatched area represents typical value ±25%. COMT, catechol-*O*-methyltransferase; UPDRS, Unified Parkinson's Disease Rating Scale.

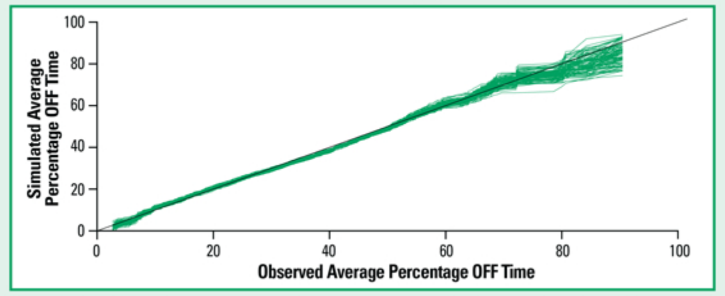
Figure 4. Covariate effects for maximum effect of istradefylline exposure ($E_{max}I$) for percentage OFF time PK-PD model.



Solid vertical line represents $E_{max}I$ point estimate, and horizontal black line represents 95% CI. For categorical covariates, point estimates are represented by the open circles, and 95% CI is represented by the horizontal bar. For continuous covariates, box and whisker plots represent the spread of point estimates, with 50% of data within the box and the remaining 50% between the ends of the box and whisker plots. Hatched area represents typical value ±25%. COMT, catechol-*O*-methyltransferase; UPDRS, Unified Parkinson's Disease Rating Scale.

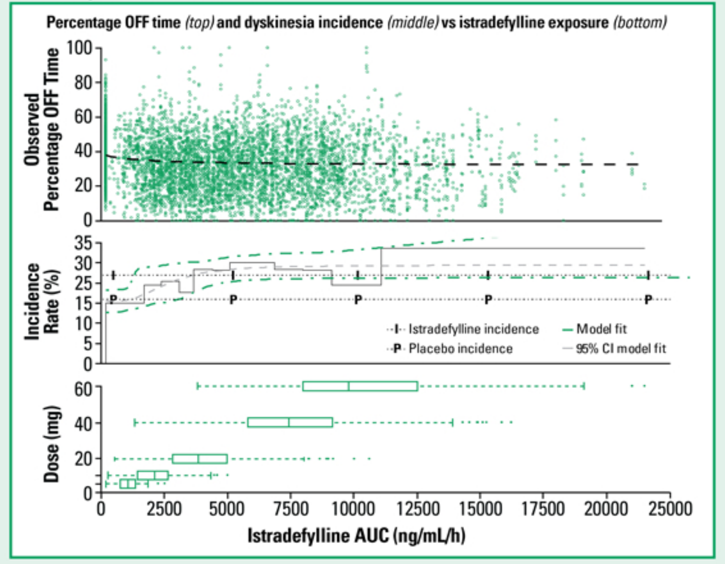
- Model evaluation results (non-parametric bootstrap and predictive check) demonstrated that the final model provided a good description of the data (**Figure 5**).

Figure 5. Model evaluation predictive check for average percentage OFF time: Q-Q plot.



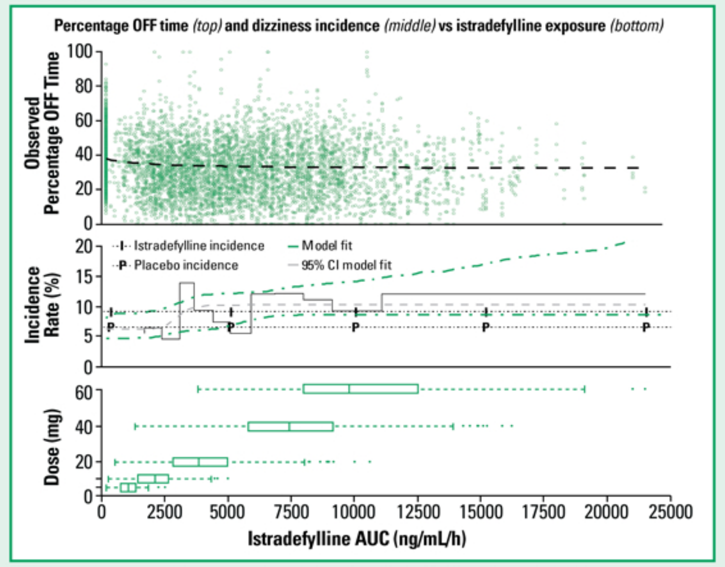
Distributions of simulated average percentage OFF time within each patient (POFFavg) are compared with the actual observed distribution of POFFavg values from the population PK-PD database. Quantile–quantile plots for each of the 100 simulation replicates are depicted by a gray dashed line and are overlaid on this plot. The black solid line represents a reference line of identity.

Figure 6. Integrated plot of observed data and PK-PD model predictions for percentage OFF time and dyskinesia adverse events.



(top) Observed percentage OFF time versus IAUC. Black dashed line is PK-PD model prediction of percentage OFF time. *(middle)* Observed incidence rate and model predicted probability of dyskinesia versus IAUC. *(bottom)* Box and whisker plots of IAUC by dose.

Figure 7. Integrated plot of observed data and PK-PD model predictions for percentage OFF time and dizziness adverse events.



(top) Observed percentage OFF time versus IAUC. Black dashed line is PK-PD model prediction of percentage OFF time. *(middle)* Observed incidence rate and model predicted probability of dizziness versus IAUC. *(bottom)* Box and whisker plots of IAUC by dose.

- A sigmoid E_{max} model was used to describe the relationship between IAUC and the probability of experiencing dyskinesia and between IAUC and the probability of experiencing dizziness (**Table 5**).

Table 5. Parameter Estimates for Dyskinesia, Dizziness, and Nausea PK-PD Models

Dyskinesia Logit Parameters	Fixed-Effect Parameter (% SE)	Dizziness Logit Parameters	Fixed-Effect Parameter (% SE)	Nausea Logit Parameters	Fixed-Effect Parameter (% SE)
$E_{max}PD$ = θ1	0.57 (28)	$E_{max}PDZ$ = θ1	0.538 (35)	SLOP = θ1	0.00218 (403)
$EC_{50}D$ = θ2	2380 (44)	$EC_{50}DZ$ = θ2	2770 (29)	Power = θ2	0.635 (68)
Gamma = θ3	2.94 (75)	Gamma = θ3	10 (227)	BNS0 = θ3	–2.62 (6)
BD0 = θ4	–1.7 (6)	BDZ0 = θ4	–2.71 (5)		

$E_{max}PD$, maximum dyskinesia probability; $EC_{50}D$, AUC resulting in 50% of $E_{max}DYS$; Gamma, Hill coefficient; BD0, baseline dyskinesia probability; $E_{max}PDZ$, maximum dizziness probability; $EC_{50}DZ$, AUC resulting in 50% of $E_{max}DZ$; Gamma, Hill coefficient; BDZ0, baseline dizziness probability; SLOP, slope of nausea probability; Power, power term; BNS0 = baseline nausea probability; $E_{max}PDZ$, maximum dizziness probability; $EC_{50}DZ$, AUC resulting in 50% of $E_{max}DZ$; Gamma, Hill coefficient; BDZ0, baseline dizziness probability; SLOP, slope of nausea probability; Power, power term; BNS0 = baseline nausea probability.

- Based on the model predictions and the median exposure of istradefylline at each dose investigated, the probability of experiencing a dyskinesia or dizziness AE reached a plateau by 40 mg/day (**Figures 6** and **7**).
- A power model best describes the relationship between IAUC and the probability of experiencing nausea (**Table 5**).
- The precision of the estimates for the full covariate model for all the AE end points was poor, limiting the information that could be extracted from the model.
- Efficacy, as measured by the percentage of patients experiencing a change in actual OFF time at the end point of ≥30 minutes, began to plateau at doses greater than 40 mg/day (**Table 6**).

Table 6. Integrated Percentage OFF Time and Dyskinesia, Dizziness, and Nausea PK-PD Model Results by Dose

Dose, mg[a]	Change in Percentage OFF Time End Point, %	Change in Actual OFF Time End Point, h	Patients With ≥30-Minute Decrease in Actual OFF Time End Point, %	Dyskinesia Incidence Rate	Dizziness Incidence Rate	Nausea Incidence Rate
5	–2.2 (–2.8, –1.6)[c]	–0.35 (–0.45, –0.25)	57.5	16.3 (13.4, 20.9)	6.3 (4.8, 8.9)	8.2 (6.5, 10.8)
10	–3.2 (–4.1, –2.3)	–0.51 (–0.66, –0.37)	61.5	18.6 (15.0, 24.2)	6.7 (5.1, 9.5)	8.9 (7.1, 11.3)
20	–4.0 (–5.1, –2.9)	–0.64 (–0.81, –0.46)	64.7	22.5 (18.6, 25.4)	9.3 (6.1, 11.9)	9.9 (7.9, 12.1)
40	–4.7 (–6.0, –3.4)	–0.75 (–0.96, –0.54)	67.3	24.1 (21.0, 27.5)	10.7 (8.6, 13.2)	11.8 (9.5, 14.1)
60	–4.9 (–6.3, –3.6)	–0.79 (–11.01,	68.4	24.3 (21.3, 28.1)	10.9 (8.6, 14.1)	13.0 (10.6, 16.2)
80[b]	–5.1 (–6.6, –3.7)	–0.82 (–1.04, –0.59)	68.9	24.4 (21.3, 30.0)	11.0 (8.7, 15.8)	15.2 (11.1, 20.1)

[a] Median AUC and bootstrap results at each dose used to calculate end point data.
[b] 80-mg dose extrapolated based on 60-mg data.
[c] Median (95% CI).

CONCLUSIONS

- The typical maximum decrease in POFF attributed to IAUC would be 5.79% (4.09%-7.49%), with half the maximum effect reached at an exposure of 1690 (199-3180) ng/h/mL.
- Incidence rates of dyskinesia and dizziness would be expected to plateau at 40 mg/day, but the incidence rate of nausea may continue to rise with each dose increase.
- Integration of the efficacy and safety ER models indicates an incremental regimen benefit at 40 mg/day compared with 20 mg/day.
- Consideration should be given to increasing the starting dose from 20 mg/day to 40 mg/day in Parkinson's disease patients who smoke.

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