

Population Exposure–Response Analysis of “ON/OFF” Time in Patients With Parkinson’s Disease Following Preladenant Treatment

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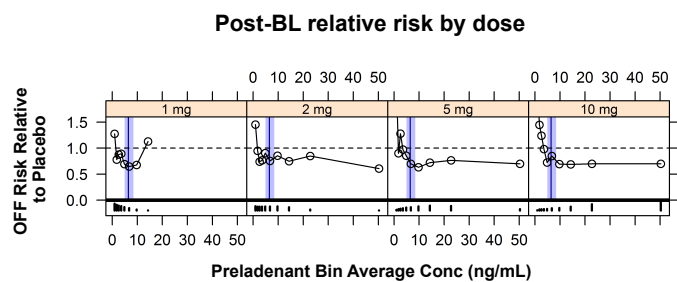
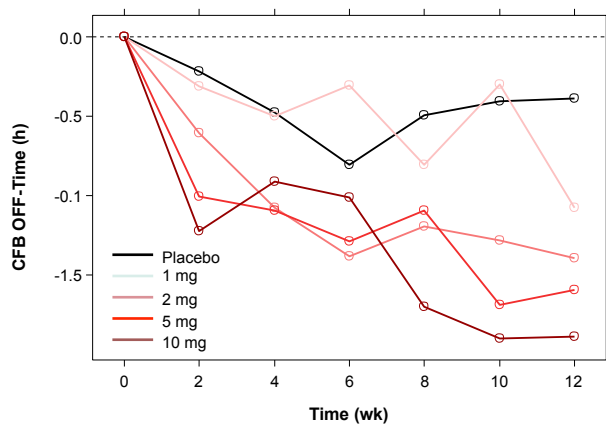
Objectives

Preladenant is an Adenosine type 2A (A2a) receptor antagonist that was in development for treatment of Parkinson’s disease (PD). Population analysis of ON/OFF data assessed: 1) Effects of concomitant anti-PD medication, 2) Efficacy of preladenant in Phase 2B patients with PD on stable L-Dopa/ dopamine therapy, 3) Interaction with concomitant anti-PD medication, 4) To support dosing recommendations for potential regulatory filings.

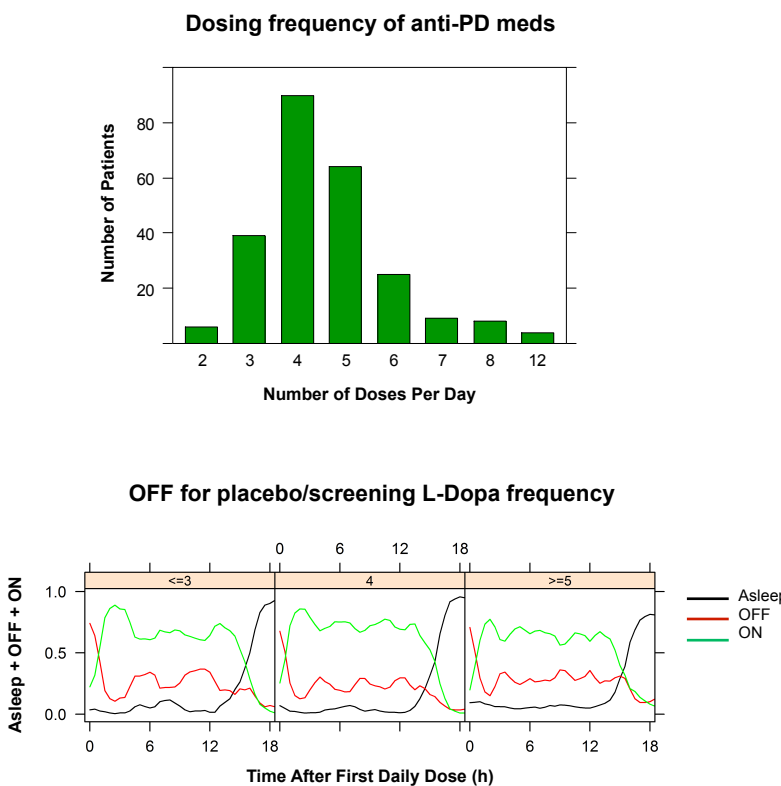
Context

- This analysis was supported by Phase 2B data composed of 235 patients with moderate to severe idiopathic Parkinson’s disease (PD). Patients received placebo or oral preladenant (1, 2, 5, 10 mg BID) in addition to a stable anti-PD treatment regimen. The concomitant regimen consisted of multiple daily doses of L-Dopa (in combination with carbidopa or other COMT inhibitor) or other anti-PD medication. The primary endpoint for this trial was reduction in average daily total OFF time
- ON/OFF status was assessed by the subject every 30 min over three days per assessment occasion and collected in a diary. The overall study period was 12 weeks. This yielded a rich dataset with over 130,000 observations of ON/OFF status
- Sparse PK measurements were available for each subject. Population PK model was developed from Phase I studies to supply individual preladenant levels

Overall Trial Results (I): Consistent Preladenant Dose and Exposure Response

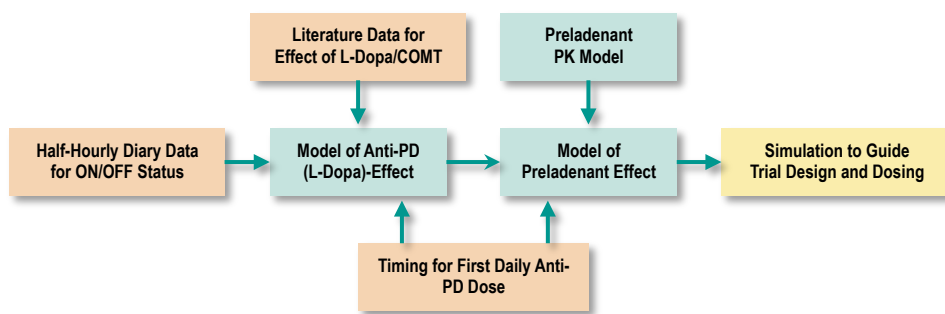


Overall Trial Results (II): Effect of Preladenant Is Confounded with Effect of L-Dopa



- Clearly see periodicity corresponding to expected anti-PD dosing times
- Main concomitant medication was combination L-Dopa + COMT inhibition
- PD patients are typically dosed to effect, so we don’t expect to see a dose response w/r L-Dopa (and we did not find one)

Flow of Modeling and Simulation Information



- Orange boxes represent input data while blue boxes represent models that were used to guide simulation trial and design

Initially Modeled Relationship Between L-Dopa and OFF for Screening and Placebo Data

L-Dopa/Placebo Model: Patient OFF behavior is complex and varies with L-Dopa dosing regimen, j , and time of day, t_k . We modeled the $\text{logit}(P_{OFF})$ as a function of L-Dopa Effect from the K-PD model. The maximal effect of L-Dopa had an associated IIV, η_i , and varies by dosing frequency, j . Further the first daily dose has increased effect, E_{D1} , and patient sensitivity to L-Dopa decreases (i.e. DE_{50} increases) over the course of the day:

$$\text{logit}(P_{OFF,j(i)k}) = \text{Int} + E_{Dopa,j(i)k} + E_{prelad,j(i)k}$$

$$E_{Dopa,j(i)k} = \frac{DE_{max,j(i)} \cdot D_{eff,j(i)}}{(DE_{50,j(i)} + D_{eff,j(i)})}$$

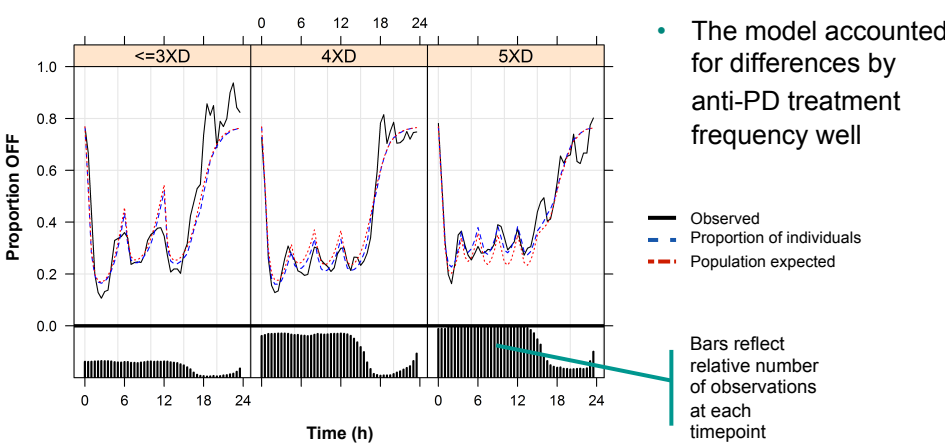
$$DE_{max,j(i)} = (DE_{max,Tvj} \cdot I_{j(i)}) \cdot (1 + E_{D1} \cdot I_{D1}) + \eta_i$$

$$DE_{50,j(i)k} = (DE_{50,j(i)} \cdot I_{j(i)}) \cdot [1 + f_1 \cdot (1 - e^{-t_k})]$$

$j = 0$: TID
 $j = 1$: QID
 $j = 2$: 5XD

Parameter	Description
$P_{OFF, j(i)k}$	Probability of OFF State for patient i with anti-AD regimen j , at time k , in week i
Int	Baseline (at wakeup) OFF Intercept
$E_{Dopa,j(i)}$	L-Dopa effect on OFF for subject i with anti-AD regimen j
$DE_{max,j}$	Maximum L-Dopa effect for subject j
$DE_{50,Tvj}$	Typical maximum L-Dopa effect for L-Dopa treatment frequency j
D_{eff}	Prior L-Dopa effect on UPDRS (from K-PD model)
E_{D1}	Sensitivity to L-Dopa at wakeup; D_{eff} at half-maximal L-Dopa effect
f_1	Added effect of 1 st daily L-Dopa dose
t_k	Indicator variable for L-Dopa regimen or 1 st dose
r	Maximum fold change in L-Dopa sensitivity
t_k	Time k after wakeup
i	index for patient
$j(i)$	index on regimen for patient i
k	index for observation time
i	index for study week

Qualification of Model Describing Relationship Between L-Dopa and OFF for Screening and Placebo Data



- The model accounted for differences by anti-PD treatment frequency well

Modeling Preladenant Effect

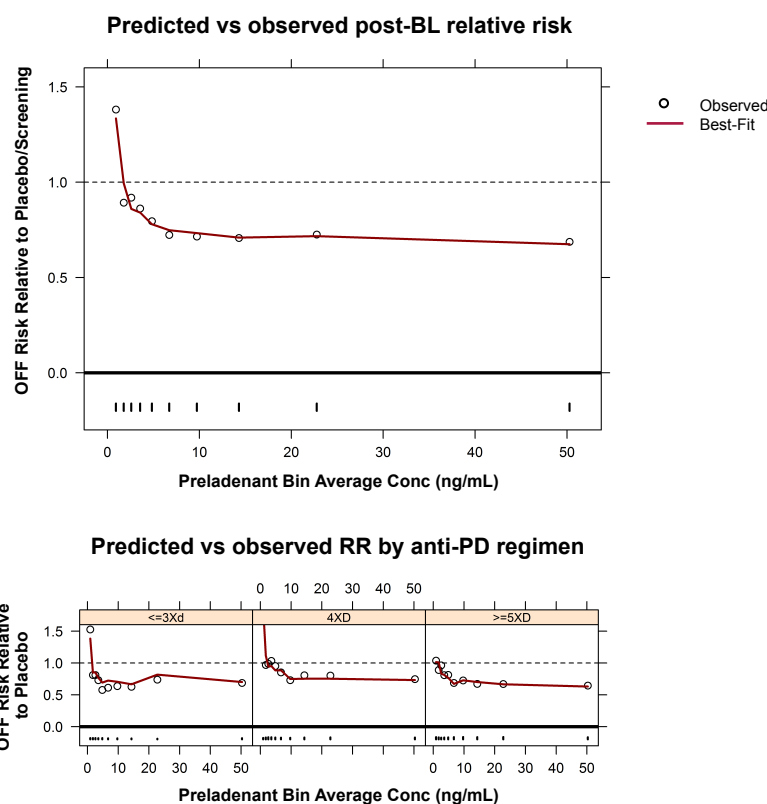
Model of Preladenant Effect: The effect of preladenant was considered to be additive to the placebo/L-Dopa effect on the logit scale. We also noted that the effect of preladenant increased over the treatment period. Inter-individual variation was handled by the use of individual estimates of preladenant concentration over time. Thus the effects of preladenant are functions of individual PK predictions, time of day, $t_{day,k}$, and the week of treatment, WK_i :

$$\text{logit}(P_{OFF,j(i)k}) = \text{Int} + E_{Dopa,j(i)k} + E_{prelad,j(i)k}$$

$$E_{prelad,j(i)k} = \frac{P_{max} \cdot C_{PR,k}}{[EC_{50} + C_{PR,k}]} \cdot (WK_{50} + WK_i)$$

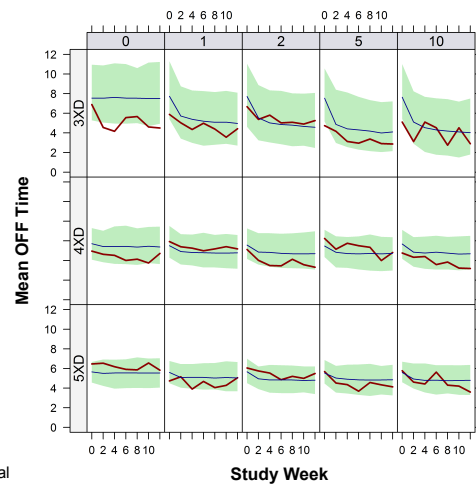
- The model estimated an EC_{50} for the preladenant effect on P (OFF) of 2.4 ng/mL
- Some evidence of synergistic interaction effect of preladenant with other anti-AD meds

Predicted Risk of OFF Relative to Placebo Was Well Estimated by the Model



Simulation Agrees Well With Phase 2B Trial Results

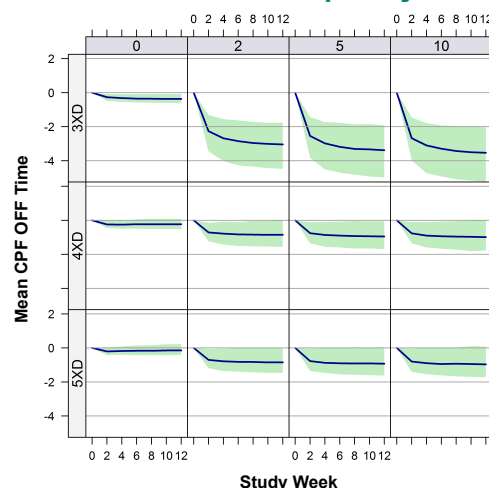
- Simulation includes effects of model uncertainty and interpatient variability
- Observed response is quite variable between dose groups, and between L-Dopa dosing frequencies
- We have good agreement between observed OFF time and predicted OFF time



There Was a Difference In Baseline and Larger Effect of Preladenant In Patients Given TID Dosing

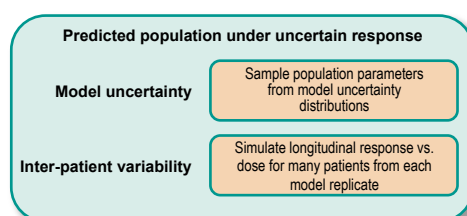
CBF OFF time vs time by dose and comedication frequency

- This resulted in QID and 5XD patients showing substantially smaller effect of preladenant than TID



Simulation Scenarios to Inform Future Clinical Trial

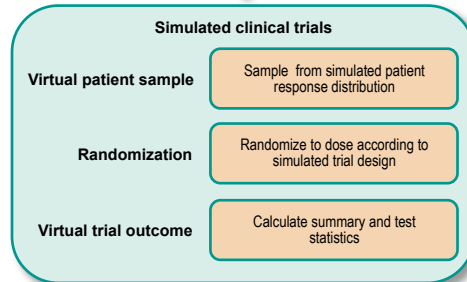
- Final model was used to simulate the efficacy response for subjects under possible treatment scenarios
 - Dose levels, dosing regimen, and treatment duration



- Virtual trials were constructed from samples of virtual patients

Question of interest:

- Probability and/or size of a clinically important or detectable difference in response between different treatments, doses, or observation times



Simulation Scenarios to Inform Future Clinical Trial Determine That Patients Given QID or 5XD (or More) L-Dopa Are Unlikely to Yield a Positive Trial Result for Preladenant

Daily Frequency for Anti-Parkinson's Drug	Sample Size				
	20/grp	50/grp	100/grp	150/grp	200/grp
TID	0.80	>0.99	>0.99	>0.99	>0.99
QID	0.10	0.19	0.30	0.46	0.66
5XD	0.10	0.18	0.30	0.52	0.62
Equal mix of all	0.22	0.62	0.90	0.99	0.99

Conclusions

- Treatment with SoC in PD presents a complex nuisance factor confounding assessment of the efficacy of a new treatment
- By comprehensively modeling placebo and concomitant treatment we accounted for these complex phenomena
- We were also able to estimate the concentration-response relationship for a preladenant in an adjunctive therapy setting
- The simulation performed in this analysis identifies that patients given QID or 5XD (or more) L-Dopa were unlikely to yield a positive trial result for preladenant
 - Much of the efficacy was driven by the TID patients
- This model provides a quantitative framework in support of PD dosing and development recommendations.