Evaluation of the Relationship Between Sumanirole Exposure and Orthostatic Hypotension

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PHARMACIA

ABSTRACT

PURPOSE: Sumanirole is a selective D_2 receptor agonist in development for treatment of Parkinson's disease (PD). This agent is expected to have a better safety profile compared to other dopaminergic agents due to receptor selectivity. Using a previously developed population pharmacokinetic (PPK) model, PK/PD analyses were performed on Phase II data to evaluate the relationship between sumanirole exposure and the occurrence of orthostatic hypotension (OH).

METHODS: Data were obtained from two double-blind, placebo-controlled trials of sumanirole: alone in early PD, or with levodopa for advanced PD. Patients received twice-daily extended-release oral sumanirole doses (2–48 mg/d). Subject-specific Bayesian estimates of area under the concentration-time curve (AUC) were generated based on the PPK model, with creatinine clearance and gender as significant covariates of sumanirole clearance. OH occurrence (systolic blood pressure (SBP) change of ≥20 mm Hg with supine-to-standing position change) was recorded for 11 weeks. Longitudinal logistic regression analyses were performed to evaluate AUC, study, and dose duration as predictors of OH occurrence.

RESULTS: A total of 1980 SBP observations from 214 patients on placebo and 3974 from 378 patients on sumanirole were available. The overall proportion of OH occurrences was significantly higher (P=0.01) in patients treated with placebo (18% of observations) compared with patients treated with sumanirole (15% of observations). However, within the sumanirole-treated patient group, logistic regression identified sumanirole AUC as a significant predictor of OH occurrence, where OH was more likely to occur with higher AUCs. The predicted probabilities of OH ranged from 0.14 at a sumanirole AUC of 0 ng•h/mL to 0.35 at an AUC of 2300 ng•h/mL. Study and dose duration were not significant predictors.

CONCLUSIONS: These results suggest that OH occurrence in patients receiving placebo was significantly higher than in patients receiving sumanirole, although a relationship between sumanirole AUC and OH was detected in the sumanirole treatment group.

INTRODUCTION

- For many years, the mainstay of treatment for Parkinson's disease (PD) has consisted of dopamine replacement therapy; however, the occurrence of late side effects in patients on long-term levodopa prompted a search for novel antiparkinsonian drugs.
- Sumanirole (PNU 95666E), a selective D_2 receptor agonist within the D_2 receptor family, is currently in development. Because of its selectivity for the D_2 subtype, sumanirole is predicted to have fewer side effects than other dopaminergic agents used in the treatment of PD.
- In a Phase I multiple-dose pharmacokinetics (PK) study, mean oral clearance of sumanirole was 38.9 L/h, and mean apparent volume of distribution (V/F) was 197 L, resulting in a mean elimination half-life of 3.5 hours.
- This poster further describes the disposition of sumanirole based on population PK analyses and the resulting drug exposure-safety relationship.

OBJECTIVES

- To develop a population pharmacokinetic model to describe the disposition of sumanirole after oral administration in subjects with PD
- To assess the relationship between sumanirole exposure and the occurrence of orthostatic hypotension (OH)

METHODS

Population Pharmacokinetic Model

Data

- Data pooled from 2 Phase II trials and 1 Phase I trial
- Sampling design: Study 009—5 to 6 blood samples obtained after dose at Visit 8, 1 sample at Visit 9, and 1 (217 subjects) or 9 (50 subjects) samples at Visit 11; Study 010—single blood samples at Visits 9 and 11; Study 020—full profile (13 samples) after 5 days

Pharmacostatistical Model

- NONMEM®, version 5.1.1
- PK model: one-compartment model with first-order absorption and elimination
- Interindividual error determined by the exponential error model
- Residual variability determined with the proportional error model
- Creatinine clearance (CrCL) and gender were included as significant covariates of clearance (CL/F)
- CrCL estimated using the modified Cockcroft and Gault method[1]

Statistical Analyses

- Statistical significance: univariate forward-selection analyses: P=0.05; backward elimination: P=0.001
- Goodness-of-fit of each NONMEM® analysis assessed by examination of:
  - Scatterplots of predicted vs measured concentrations and vs weighted residuals
  - %SEMs of the parameter estimates
  - Changes in the estimates of the interindividual and residual variability

Safety Assessment

- Exposure measure: $AUC_{0\text{-}12}$, Calculated using the trapezoidal rule on the predicted concentration-time profile. Bayesian parameter estimates from the PK model were used to predict each subject's concentration-time profile.
- Safety measure: OH, defined as a decrease in systolic blood pressure of at least 20 mm Hg with a position change from supine to standing.
- Logistic-regression analyses with backward elimination (level of significance, 0.05).
- Potential predictors of OH occurrence evaluated: $AUC_{0\text{-}12}$, study, and number of weeks on a specific dose.

RESULTS

Pharmacokinetic Model

- Total of 2594 sumanirole concentrations from 378 patients and 20 healthy volunteers: Study 009 (267 subjects with 2134 concentrations), Study 010 (111 subjects with 200 concentrations), and Study 020 (20 subjects with 260 concentrations) (Table 1; Figure 1)
- One-compartment PK model with first-order absorption (Table 2; Figure 2)
- V/F was fixed to a constant 300 L because of correlation with the absorption-rate constant

Table 1. Studies Included in the Population Analyses

Protocol	Study Design	Treatment Regimen
M/2760/0009	Double-blind, placebo-controlled, dose-response study of sumanirole tolerability, safety, and efficacy in patients with early PD	Dose escalating up to groups: 0 mg (placebo), 2, 8, 24 or 48 mg/d
M/2760/0010	Safety, tolerance, and efficacy evaluation of sumanirole as an adjuvant to levodopa in advanced PD	Dose escalating to any of 1, 2, 4, 8, 16, 24, 32, or 48 mg/d
666E-CNS-0075-020	A single-blind, placebo-controlled, randomized parallel group and crossover study to investigate pharmacokinetics and adverse event profile of sumanirole given in an extended release formulation to Caucasian healthy volunteers	Multiple-dose (twice daily) administration of placebo, 1-mg, or 2-mg doses

Figure 1. Sumanirole concentrations vs time since last dose for all dose groups.

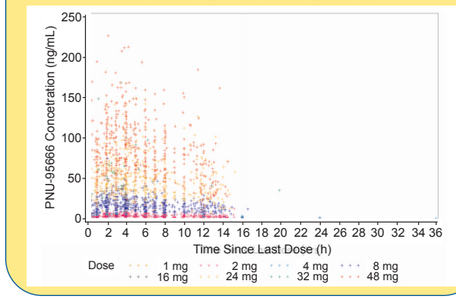


Table 2. Predicted Parameter Estimates from the Final PPK Model

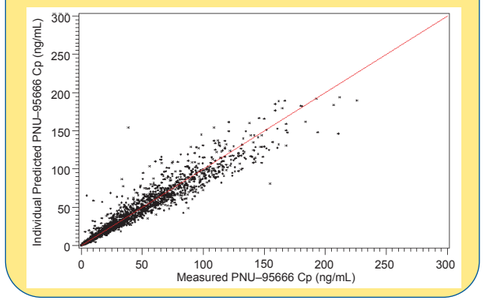
Parameter	Population Mean Estimate	%SEM*
CL/F coefficient (L/h)†	20.1	2.8%
Power for CrCL effect on CL/F†	0.622	10.0%
CL/F shift for males† (1/h)	2.96	27.6%
V/F (L)	300	Fixed
ka (1/h)	0.379	4.6%
IIV‡ CL/F (%CV)	32.6%	12.3%
IIV‡ ka (%CV)	39.1%	30.8%
Residual variability (%CV)	21.1%	7.7%

* % SEM = Standard error of the estimate divided by the population mean estimate times 100%, a measure of the relative precision of estimates.

† $CL/F = \left[\theta_1 \cdot \left(\frac{CrCL}{75.8}\right)^{\theta_2} + \theta_3 \cdot SEXM\right] * e^{\eta_1} = \left[20.1 \cdot \left(\frac{CrCL}{75.8}\right)^{0.622} + 2.96 \cdot SEXM\right] * e^{\eta_1}$

‡ IIV = Interindividual variability.

Figure 2. Individual predicted sumanirole concentrations vs measured sumanirole concentrations.



Safety Assessment

- A total of 5954 blood pressure observations from 592 patients were analyzed for OH (Table 3).
- 3974 observations from 378 patients occurred during active drug therapy (Table 4; Figure 3).
- OH occurred in approximately 15.5% of observations (615/3974) for patients administered sumanirole, and 18.1% of observations (358/1980) during placebo administration; the proportion of observations in which OH occurred was significantly higher (P=0.01) during placebo treatment (Table 4).
- As shown in Figure 4, the range of AUCs for patients with OH remained within the range of AUCs for patients who did not experience OH.
- Logistic regression analyses identified sumanirole AUC as a statistically significant predictor of OH occurrence, where OH was more likely to occur with higher AUCs (P=0.0001).
- The median AUC values at the 8- and 16-mg dose levels were 198.5 and 372 ng•h/mL, respectively; the associated probabilities of OH were 0.16 and 0.17 (Figure 5).

Table 3. Number of Observations at Each Dose Stratified by Protocol—All Patient Observations for OH Analysis

	Protocol					
	M/2760/0009			M/2760/0010		
Dose	No OH	OH	Total	No OH	OH	Total
0 mg	556	91	647	1066	267	1333
1 mg	244	23	267	115	13	128
2 mg	715	136	851	112	13	125
4 mg	164	28	192	120	17	137
8 mg	529	85	614	149	21	170
16 mg	144	34	178	168	44	212
24 mg	295	62	357	152	16	168
32 mg	78	28	106	105	29	134
48 mg	164	39	203	105	27	132
Total	2889	526	3415	2092	447	2539

Figure 3. Frequency distribution of grouped AUC stratified by OH.

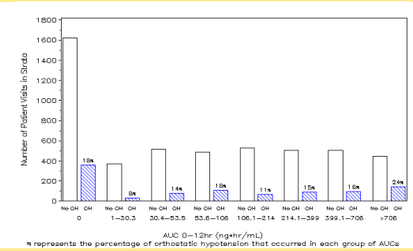


Table 4. OH Occurrence for Sumanirole and Placebo

OH	Compound Sumanirole	Compound Placebo	Total (%)	P
Occurrence				
Frequency	615	358		
Percent	10.33	6.01	973 (16.34)	
Row Percent	63.21	36.79		
Column Percent	15.48	18.08		0.010
No Occurrence				
Frequency	3359	1622		
Percent	56.42	27.24	4981 (83.66)	
Row Percent	67.44	32.56		
Column Percent	84.52	81.92		
Total (%)	3974 (66.75)	1980 (33.25)	5954 (100)	

Figure 4. Sumanirole AUC vs dose stratified by OH.

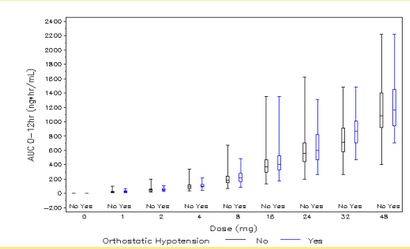
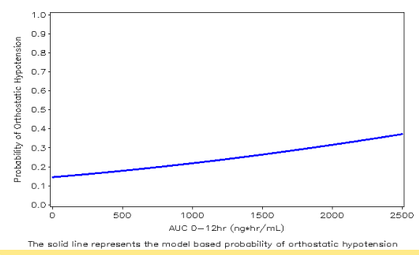


Figure 5. Probability of OH vs sumanirole AUC.



CONCLUSIONS

- The population pharmacokinetics of sumanirole were best described using a one-compartment model with first-order absorption and elimination.
- Orthostatic hypotension occurrence was more common in PD patients receiving placebo than in patients receiving sumanirole, although a relationship between sumanirole AUC and the occurrence of OH was detected in the sumanirole treatment group.

REFERENCE

1. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.

Presented at the November 2002 annual meeting of the American Association of Pharmaceutical Scientists.