

Modelling of Pharmacokinetics and the Incidence of Adverse Events of the PDE-10A Inhibitor TAK-063

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Introduction

- TAK-063 is a novel, potent, and selective inhibitor of the phosphodiesterase (PDE10A) enzyme that is expressed primarily in the striatal medium spiny neurons of the basal ganglia. Based on its potential effects on striatal function, TAK-063 is being developed for the treatment of schizophrenia.
- This analysis characterizes the clinical pharmacokinetics of TAK-063 and the relationship between exposure and adverse events (AEs) observed in healthy subjects and those with schizophrenia.

Methods

Study Design

- Two placebo-controlled, double blind, dose-escalation studies were conducted to evaluate the safety, tolerability, and pharmacokinetics (PK) of TAK-063. Routine safety and tolerability assessments were measured throughout the trials, along with extensive PK sampling.
 - Study 101 Single Rising Dose (SRD): Single oral-dose administration under fasted conditions in healthy Japanese and non-Japanese subjects. Subjects (n=14/cohort; 6 Japanese, 8 non-Japanese) were randomized and received 3, 10, 30, 100, 300, or 1000 mg TAK-063 or placebo as a suspension in a 5:1 active : placebo ratio for Japanese and 6:2 for non-Japanese.
 - Study 104 Multiple Rising Dose (MRD): Repeated daily oral-dose administration under fed conditions for 7 days in healthy Japanese subjects and in non-Japanese subjects with stable schizophrenia who were washed out from their current antipsychotic medications. Subjects (n=10/cohort) were randomized and received TAK-063 or placebo in an 8:2 active : placebo ratio. Dose levels of 3, 10, 20, 30, and 100 mg in subjects with stable schizophrenia and 3, 10, and 20 mg as tablets in healthy Japanese volunteers, respectively, were explored.

Population PK Analysis

- 1 or 2 compartment models with linear or saturable kinetics were evaluated as candidate structural PK models using nonlinear mixed effect approaches. Between-subject and residual variability were estimated using exponential and proportional error models, respectively.
- Potential covariates consisted of subject demographics such as age, body weight (BW), BMI, lean body mass (LBM), creatinine clearance (CrCL), sex, race, and disease status (healthy or schizophrenia subjects). Covariate screening and functional relationship between covariates were graphically evaluated followed by covariate analysis performed using univariate stepwise forward addition ($\alpha = 0.01$) followed by backward elimination procedure ($\alpha = 0.001$).

PK/AE Analysis

- Logistic regression analysis was conducted to evaluate the incidence of the common AEs and characterize the relationship with exposure to TAK-063.
- The incidence of AEs was modeled using a logistic regression model given by the expression: $f[P(AE_i=1)]=\log[p/(1-p)] = \beta + f_{exp}$ where AE_i takes a value of 1 if subject i has an AE at some time during the study and 0 otherwise. The parameter β denotes the logit for subjects not on drug (placebo). The function f_{exp} represents the function describing the exposure response relationship and can take linear (SLOPE*PK) or E_{max} [E_{max}*PK/(PK+EC₅₀)] forms where PK represents individual C_{max} and AUC values estimated using non-compartmental methods.
- All modeling analyses were conducted using NONMEM or R. Data processing, and graphs were produced using SPLUS or R.

Results

Study Population

- SRD: 36 Japanese (17 male/19 female) and 48 non-Japanese (26 male/22 female) healthy subjects were enrolled and randomized to placebo or TAK-063.
- MRD: 47 subjects with stable schizophrenia (31 male/16 female) and 30 (27 male/3 female) healthy Japanese subjects were enrolled and randomized to placebo or TAK-063.

Safety and PK

- TAK-063 was safe and well tolerated, following single- and repeated-dose administration.
- The most common treatment-emergent AE reported was somnolence in subjects treated with TAK-063, occurring in subjects with schizophrenia as well as in healthy Japanese and non-Japanese subjects (**Tables 1-2**).
- Extrapyramidal symptoms (EPS), which include akathisia, dyskinesia, dystonia, and parkinsonism, were primarily observed in the subjects with schizophrenia (**Table 2**).
- The frequency of somnolence and EPS (schizophrenia only) appeared to increase with increasing dose; however, somnolence and EPS were observed in subjects receiving placebo (**Table 2**).
- TAK-063 PK was consistent across all subjects and between studies (**Figure 1**).

Population PK Analysis

- TAK-063 PK was best characterized using a transit compartment model for absorption and a two compartment model for disposition.
- The oral bioavailability was dose-dependent and decreased with increasing dose. A proportional increase in central volume of distribution (V₂) with BMI was noted [ie V₂=154*(1+0.454*(log(BMI)-log(25.9)))]; no other covariates including disease status were statistically significant.
- Model parameters were estimated with good precision and presented in **Table 3**. Model demonstrated a reasonable goodness-of-fit and is presented in **Figure 2**.

PK/AE Analysis Results

- The frequency of somnolence and EPS generally increased with increasing exposure (**Figure 3**).
- Linear models demonstrated adequate goodness-of-fit with no substantial model improvement using E_{max} functions. Parameter estimates for each population are presented in **Table 4**.
- Using a chi-squared test to evaluate nested models, disease status as a covariate was significant for EPS but not for somnolence. Also, race in healthy subjects was not significant for somnolence.

Table 1. SRD Summary of Somnolence Treatment Emergent Adverse Events

Preferred Term/Group	TAK-063							
	Placebo (n=6)	3 mg (n=5)	10 mg (n=5)	30 mg (n=5)	100 mg (n=5)	300 mg (n=5)	1000 mg (n=5)	TAK-063 Overall (N=30)
Healthy Japanese Subjects	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	4 (80.0)	2 (40.0)	3 (60.0)	10 (33.3)
	Placebo (n=12)	3 mg (n=6)	10 mg (n=6)	30 mg (n=6)	100 mg (n=6)	300 mg (n=6)	1000 mg (n=6)	TAK-063 Overall (N=36)
Non-Japanese Subjects	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	3 (50.0)	3 (50.0)	3 (50.0)	12 (33.3)

Data in parentheses indicate percentages.

Table 2. MRD Summary of Somnolence and Extrapyramidal Treatment Emergent Adverse Events

Treatment-Emergent EPS by Category	Placebo	TAK-063					
	n=9	3 mg n=7	10 mg n=8	20 mg n=7	30 mg n=8	100 mg n=8	All Subjects N=38
Somnolence	2 (22.2)	2 (28.6)	3 (37.5)	4 (57.1)	4 (50.0)	8 (100.0)	21 (55.3)
Subjects with any EPS	1 (11.1)	0	2 (25.0)	3 (42.9)	5 (62.5)	4 (50.0)	14 (36.8)
Akathisia	0	0	2 (25.0)	1 (14.3)	2 (25.0)	1 (12.5)	6 (15.8)
Dyskinesia	0	0	0	0	2 (25.0)	0	2 (5.3)
Dystonia	1 (11.1)	0	0	3 (42.9)	0	2 (25.0)	5 (13.2)
Other EPS	0	0	0	0	4 (50.0)	2 (25.0)	6 (15.8)
Healthy Japanese Subjects	n=6	n=8	n=8	n=8	NA	NA	N=24
Somnolence	2 (33.3)	3 (37.5)	4 (50.0)	5 (62.5)	—	—	12 (50.0)
Subjects with any EPS	0	0	0	1 (12.5)	NA	NA	1 (4.2)
Akathisia	0	0	0	1 (12.5)	NA	NA	1 (4.2)

Data in parentheses indicate percentages. Extrapyramidal symptoms include akathisia, dyskinesia, dystonia, or other extrapyramidal disorders.

Table 3. Parameter Estimates and Standard Errors For TAK-063 PK Model

Parameter	Final Parameter Estimate		Interindividual Variability/Residual Variability	
	Typical Value	%SEM	Magnitude	%SEM
KA (absorption rate constant, 1/hr)	7.00	FIXED	45.1 %CV	13.7
CL (oral clearance, L/hr)	11.1	4.80	26.7 %CV	18.4
V2 (central volume of distribution, L)	154	4.03	0 %CV	FIXED
D50 (dose at 50% maximal effect on oral bioavailability, mg)	72.2	10.9	NE	NA
Proportional residual error	0.0834	6.84	NE	NA
Q (distribution clearance, L/hr)	2.73	10.4	NE	NA
V3 (central volume of distribution, L)	1620	43.6	NE	NA
Effect of BMI on V2	0.454	32.3	NE	NA
GAMMA (shape factor)	1.64	14.9	NE	NA

NA: Not Applicable; NE: Not Estimated.

Table 4. Parameter Estimates and Standard Errors for TAK-063 PK/AE Models

Study	Adverse Event	Population	PK	β (SE)	Slope (SE)
SRD	Somnolence	Japanese healthy subjects	C _{max}	-1.49 (0.40)	0.01 (0.003)
			AUC	-1.45 (0.38)	0.0006 (0.0002)
		Non-Japanese healthy subjects	C _{max}	-2.03 (0.40)	0.015 (0.004)
			AUC	-1.75 (0.37)	0.0006 (0.0002)
MRD	Somnolence	Japanese healthy subjects	C _{max}	-0.61 (0.60)	0.004 (0.008)
			AUC	-0.72 (0.60)	0.0005 (0.0007)
		Non-Japanese subjects with schizophrenia	C _{max}	-1.61 (0.58)	0.016 (0.005)
			AUC	-1.46 (0.55)	0.001 (0.0004)
	EPS	Non-Japanese subjects with schizophrenia	C _{max}	-1.95 (0.62)	0.01 (0.004)
			AUC	-1.70 (0.56)	0.0007 (0.0003)

Figure 1. SRD and MRD Summary of TAK-063 Exposure

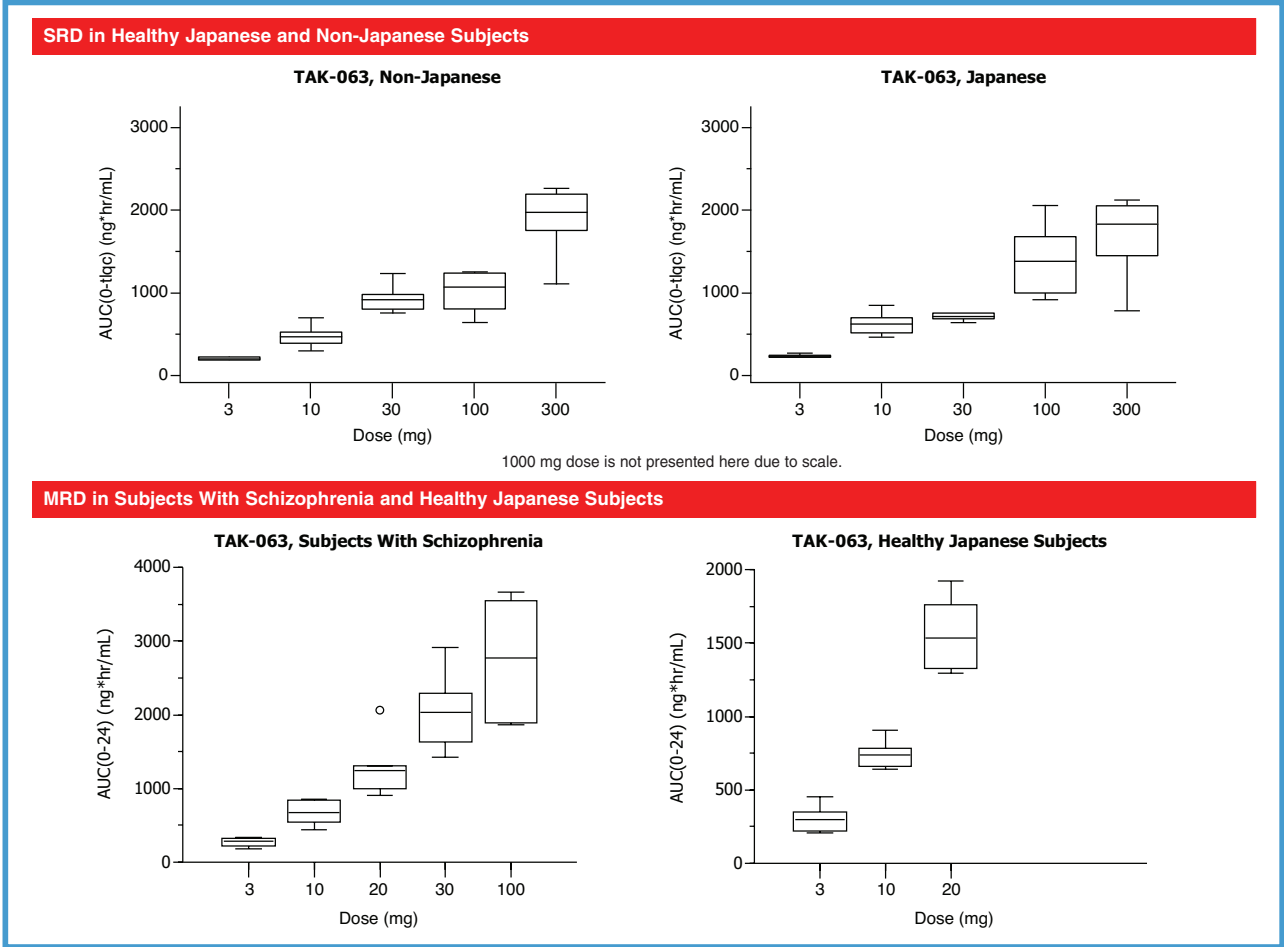


Figure 2. Diagnostic Plots for TAK-063 PK Model

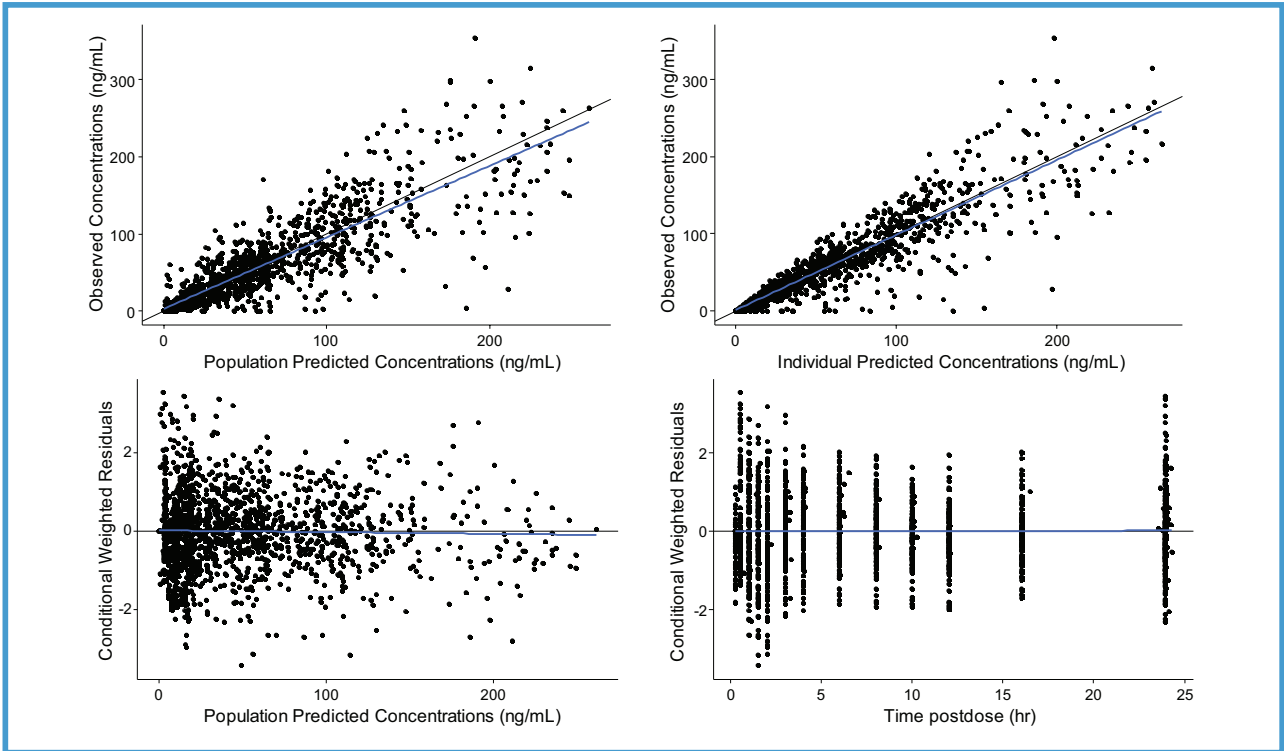
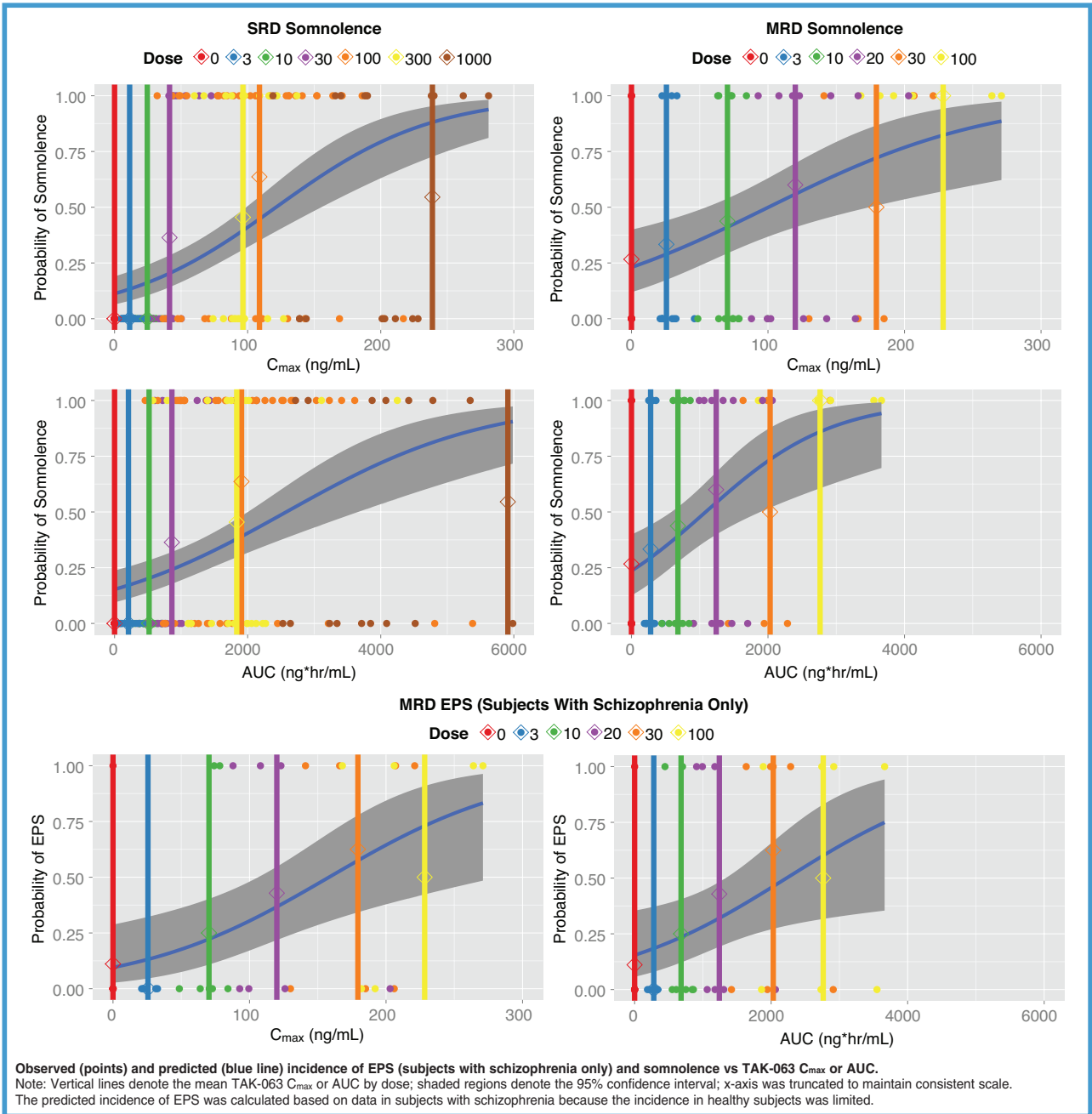


Figure 3. Probability of Adverse Event Occurrence vs. TAK-063 Exposure



Discussion

Our preliminary results show that the population PK model adequately characterized the PK data and demonstrated no substantial differences between healthy subjects (Japanese and non-Japanese) and subjects with schizophrenia. The PK/AE models described the incidence of somnolence and EPS well. The incidence of EPS and somnolence increased with increasing exposure to TAK-063, though a non-zero event rate was noted in placebo subjects. The reasons for the higher rates of EPS in subjects with schizophrenia currently remain unclear, but may be due to sensitization from the washout of prior antipsychotic medications. These models will be refined with emerging data to predict AEs for future clinical trial designs for TAK-063, with the aim of understanding the exposure-AE profile associated with PDE10A inhibition.

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