Development of PK/AE Models in Subjects With Schizophrenia and in Healthy Japanese and Non-Japanese Subjects

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Introduction

- Current antipsychotics are generally less well tolerated in healthy subjects vs. subjects with schizophrenia and in Asian vs. non-Asian subjects, though very few studies have directly compared antipsychotic tolerability within these populations.
- TAK-063 is a 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. Preclinical data suggest this novel mechanism of action may impart a different propensity for adverse events (AEs) in humans than do current antipsychotics; however, to date, the relationship between exposure and AEs has not been reported.

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.

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: $f[P(AE_i=1)]=\log[p/(1-p)] = \beta + fexp$ 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 fexp represents the function describing the exposure response relationship and can take linear (SLOPE*PK) or E_{max} $[E_{max}*PK/(PK+EC_{50})]$ 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, though the oral bioavailability under fed conditions was approximately twice that of fasted conditions compared at the same dose level (**Figure 1**).

PK/AE Analysis Results

- The frequency of somnolence and EPS generally increased with increasing exposure (**Figure 2**).
- 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 3**.
- 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 Adverse Events

TEAEs for Healthy Japanese Subjects								
	TAK-063							
AE	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)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	4 (80.0)	2 (40.0)	3 (60.0)	10 (33.3)
Orthostatic tachycardia	1 (16.7)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)	3 (60.0)	5 (16.7)
Orthostatic hypotension	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	2 (40.0)	4 (13.3)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)	2 (6.7)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (3.3)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (3.3)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (3.3)
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Muscle tightness	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
TEAEs for Healthy Non-Japanese Subjects								
	TAK-063							
AE	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)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	3 (50.0)	3 (50.0)	3 (50.0)	12 (33.3)
Orthostatic tachycardia	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	4 (66.7)	8 (22.2)
Orthostatic hypotension	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	2 (5.6)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (2.8)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (2.8)
Dysarthria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (2.8)
Headache	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (2.8)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (2.8)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (2.8)
Blurred vision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (2.8)

Data in parentheses indicate percentages.

Table 2. MRD Summary of Adverse Events

	TAK-063						
Preferred Term/Group	Placebo (n=9)	3 mg (n=7)	10 mg (n=8)	20 mg (n=7)	30 mg (n=8)	100 mg (n=8)	All TAK-063 Subjects (N=38)
Subjects With Schizophrenia							
Subjects with any TEAEs	5 (55.6)	4 (57.1)	7 (87.5)	5 (71.4)	6 (75.0)	8 (100.0)	30 (78.9)
Somnolence	2 (22.2)	2 (28.6)	3 (37.5)	4 (57.1)	4 (50.0)	8 (100.0)	21 (55.3)
Akathisia	0	0	2 (25.0)	1 (14.3)	2 (25.0)	1 (12.5)	6 (15.8)
Orthostatic Hypotension	0	0	2 (25.0)	1 (14.3)	2 (25.0)	1 (12.5)	6 (15.8)
Extrapyramidal Disorder	0	0	0	0	3 (37.5)	2 (25.0)	5 (13.2)
Headache	0	0	0	1 (14.3)	2 (25.0)	1 (12.5)	4 (10.5)
Anxiety	1 (11.1)	0	1 (12.5)	0	0	2 (25.0)	3 (7.9)
Oromandibular Dystonia	0	0	0	1 (14.3)	0	2 (25.0)	3 (7.9)
Constipation	0	0	0	0	1 (12.5)	1 (12.5)	2 (5.3)
Dizziness	0	0	0	1 (14.3)	0	1 (12.5)	2 (5.3)
Dizziness Postural	0	1	0	0	1	0	2 (5.3)
Dyskinesia	0	0	0	0	2	0	2 (5.3)
Dystonia	1 (11.1)	0	0	2 (28.6)	0	0	2 (5.3)
Nausea	0	0	1 (12.5)	0	0	1 (12.5)	2 (5.3)
Orthostatic HR Response Increased	0	0	1 (12.5)	0	0	1 (12.5)	2 (5.3)
Healthy Japanese Subjects	**(n=6)**	**(n=8)**	**(n=8)**	**(n=8)**	**NA**	**NA**	**(N=24)**
Subjects with any TEAEs	3 (50.0)	4 (50.0)	5 (62.5)	5 (62.5)	–	–	14 (58.3)
Somnolence	2 (33.3)	3 (37.5)	4 (50.0)	5 (62.5)	–	–	12 (50.0)
Headache	0	1 (12.5)	0	1 (12.5)	–	–	2 (8.3)
Nausea	0	1 (12.5)	0	1 (12.5)	–	–	2 (8.3)
Restlessness	0	0	0	1 (12.5)	–	–	1 (4.2)

Data in parentheses indicate percentages.

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Table 3. MRD Parameter Estimates for 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

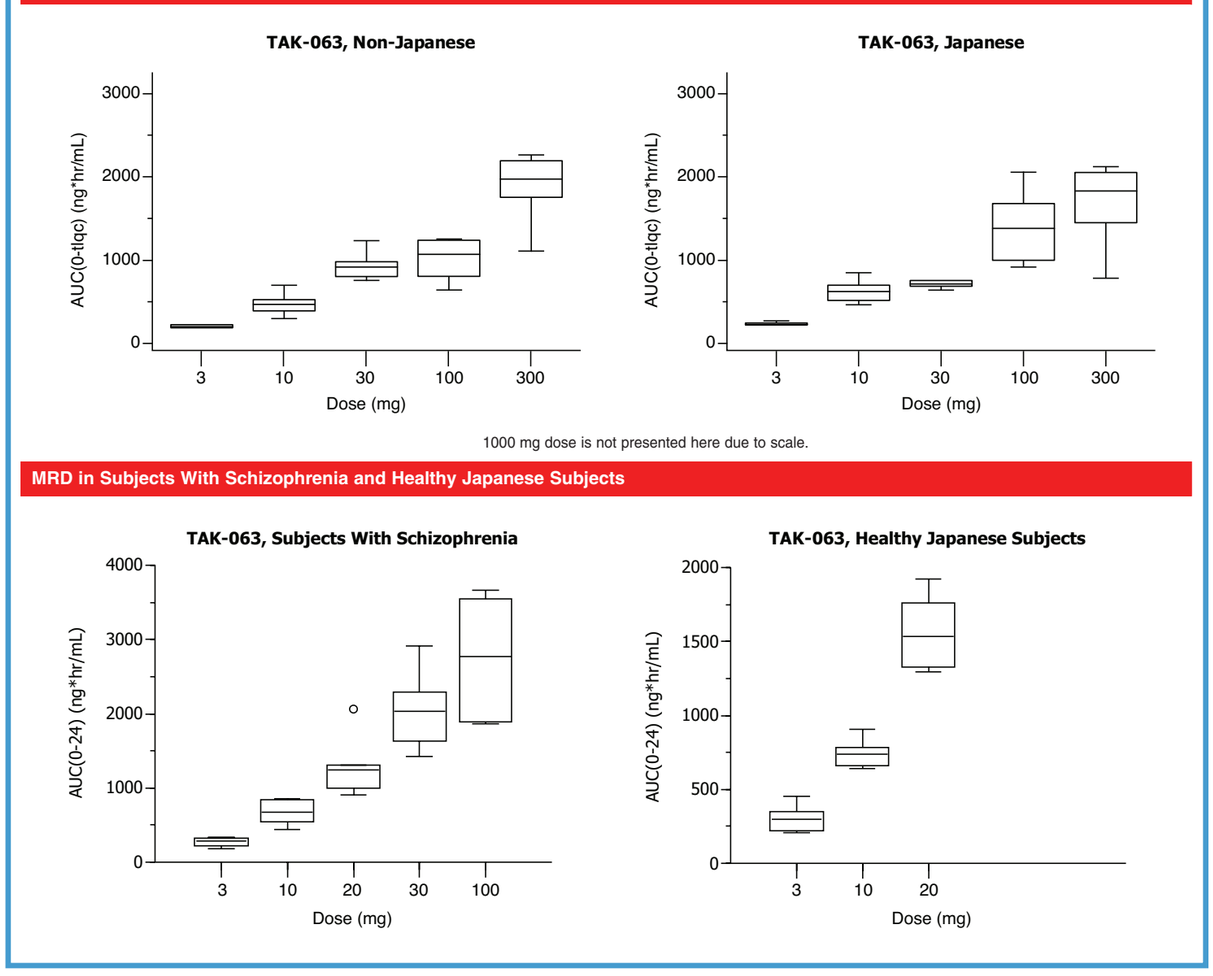
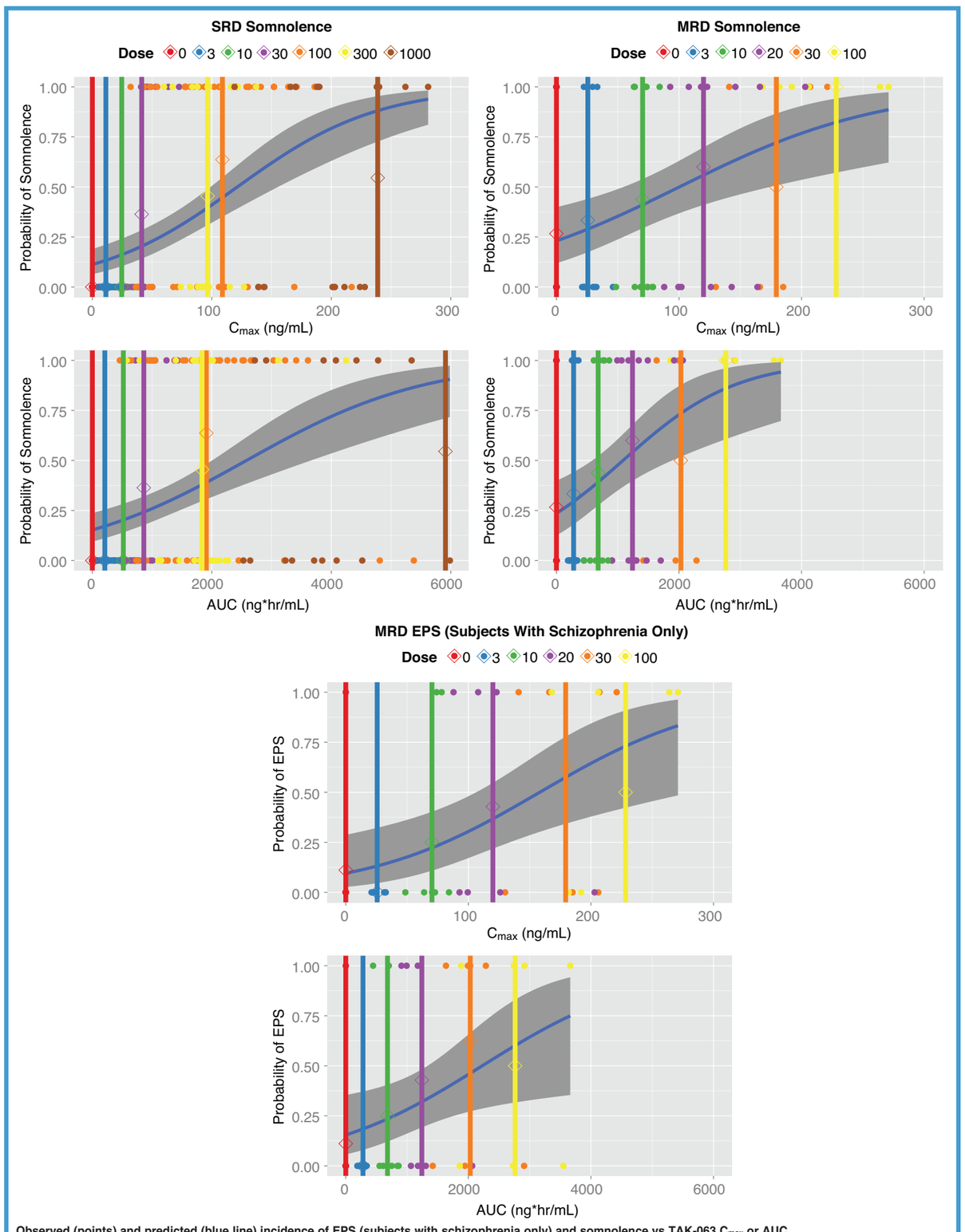


Figure 2. Probability of Adverse Event Occurrence vs. TAK-063 Exposure



Observed (points) and predicted (blue line) incidence of EPS (subjects with schizophrenia only) and somnolence vs TAK-063 C_{max} or AUC.
Note: Vertical lines denote the mean TAK-063 C_{max} or AUC by dose; shaded regions denote the 95% confidence interval; x-axis was truncated to maintain consistent scale.

Discussion

Our preliminary results show that 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.