A randomized multiple dose pharmacokinetic study of a novel PDE10A inhibitor TAK-063 in subjects with stable schizophrenia and Japanese subjects and modeling of exposure relationships to adverse events

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Supplementary Figures and Tables

Supplementary Figure 1. Study design

Pretreatment period		Treatment period			Follow-up
Screening washout[a]	**Check-in baseline assessments**	**TAK-063/placebo daily dosing study assessments**	**Study exit**	**Restabilization period[b]**	**Follow-up visit/telephone call[c]**
days -28 to -2	day -1	days 1-7	day 8	days 9-10	day 14 (±2)
	Confinement[d]				

[a]Subjects with stable schizophrenia underwent washout of their antipsychotic and other medications before dosing on day 1. If clinically warranted, subjects with stable schizophrenia might have checked in as early as day -4 for clinical monitoring and to ensure appropriate washout of medications. Baseline assessments occurred on day -1.
[b]Subjects with stable schizophrenia resumed their previous antipsychotic and other discontinued treatments as appropriate, and may have remained in the clinic up to day 10 (or longer if clinically warranted) during the restabilization period.
[c]Follow-up occurred by telephone unless abnormal, clinically significant findings were observed on discharge. In these cases, subjects were brought back to the clinic for re-evaluation at investigator's discretion.
[d]Confinement was from check-in (day -1) to the restabilization period (days 9-10).

Supplementary Figure 2. Dose escalation scheme

Cohort 1[a] →	**Cohort 2[a]** →	**Cohort 3[a]** →	**Cohort 4[a]** →	**Cohort 5[a]** →
3-mg TAK-063 or placebo	30-mg TAK-063 or placebo	100-mg TAK-063 or placebo	20-mg TAK-063 or placebo	10-mg TAK-063 or placebo
	Cohort 1[b] →	**Cohort 2[b]** →	**Cohort 3[b]**	
	3-mg TAK-063 or placebo	10-mg TAK-063 or placebo	20-mg TAK-063 or placebo	

[a]Subjects with stable schizophrenia.

[b]Healthy Japanese subjects.

Supplementary Table 1. Plasma PK parameters for TAK-063 M-I following ascending multiple doses in healthy Japanese subjects and subjects with stable schizophrenia on day 7

	Healthy Japanese subjects			Subjects with stable schizophrenia				
Parameter (mean [CV, %])	**3 mg (n=8)**	**10 mg (n=7)**	**20 mg (n=6)**	**3 mg (n=7)**	**10 mg (n=7)**	**20 mg (n=7)**	**30 mg (n=7)**	**100 mg (n=7)**
C_{max} (ng/mL)	15.1 (16)	38.2 (12)	70.9 (25)	19.2 (22)	74.8 (27)	123.6 (39)	108.5 (15)	127.7 (18)
t_{max} (h)[a]	3.0 (2.0, 4.0)	3.0 (1.5, 6.0)	3.0 (3.0, 4.0)	4.0 (2.0, 6.0)	3.0 (1.5, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
$t_{1/2}$ (h)	11.9 (31)	8.0 (28)	10.5 (6)	15.3 (34)	10.0 (18)	8.7 (27)	13.7 (34)	13.6 (44)
$C_{av,ss}$	6.5 (24)	15.8 (14)	33.6 (22)	9.1 (26)	32.8 (38)	57.8 (49)	57.1 (21)	66.6 (18)
AUC_{0-24} (ng·h/mL)	156.7 (24)	378.5 (14)	806.3 (22)	218.7 (26)	786.0 (38)	1387.2 (49)	1371.2 (21)	1598.4 (18)
$AUC_{(t)}$ (ng·h/mL)	156.7 (24)	378.5 (14)	806.5 (22)	218.9 (26)	786.3 (38)	1387.2 (49)	1371.2 (21)	1598.8 (18)
AR (AUC_{0-24})[b]	2.1 (19)	1.1 (14)	1.1 (20)	2.1 (30)	1.2 (26)	1.4 (26)	1.3 (15)	1.1 (22)
AR (C_{max})[c]	1.8 (22)	1.1 (17)	1.1 (17)	1.8 (29)	1.2 (15)	1.3 (23)	1.2 (20)	1.0 (12)
AUC_{0-24} (M:P) molar ratio[d]	0.5 (8)	0.5 (15)	0.5 (10)	0.8 (21)	1.1 (29)	1.0 (24)	0.7 (13)	0.6 (16)
C_{max} (M:P) molar ratio[e]	0.5 (13)	0.5 (13)	0.5 (10)	0.7 (22)	1.0 (22)	1.0 (19)	0.6 (13)	0.6 (18)

[a] t_{max} is presented as the median (minimum, maximum).
[b] Day 7 AUC_{0-24} (ng·h/mL)/day 1 AUC_{0-24} (ng·h/mL).
[c] Day 7 C_{max}/day 1 C_{max}.
[d] AUC_{0-24} TAK-063 M-I (nM.h)/AUC_{0-24} TAK-063 (nM.h).
[e] C_{max} TAK-063 M-I (nM)/C_{max} TAK-063 (nM).

AR, accumulation ratio; AUC_{0-24}, area under the plasma concentration-time curve from time 0 to 24 h postdose; AUC_t area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{avss}, average plasma concentration at steady state; CL/F, oral clearance; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; M-I, metabolite-I; M:P, molar metabolite to parent; PK, pharmacokinetic; $t_{1/2}$, elimination half-life; t_{max}, time to reach maximum observed plasma concentration.

Supplementary Table 2. Urine PK parameters for TAK-063 M-I on days 1 and 7 following once daily oral doses in healthy Japanese subjects and subjects with stable schizophrenia

Healthy Japanese subjects				**Subjects with stable schizophrenia**				
Day 1 (mean [CV, %])	**3 mg (n=8)**	**10 mg (n=8)**	**20 mg (n=8)**	**3 mg (n=7)**	**10 mg (n=8)**	**20 mg (n=7)**	**30 mg (n=8)**	**100 mg (n=7)**
Ae_{24} (ng)	0.000 (NA)	10488 (56)	26557 (45)	0.000 (NA)	9099 (38)	16880 (48)	24302 (52)	52683 (28)
CL_R[a] (mL/h)	NC (NC) (n=0)	38.0 (43) (n=7)	39.9 (40) (n=8)	NC (NC) (n=0)	15.9 (67) (n=8)	20.4 (39) (n=6)	25.6 (36) (n=7)	36.8 (32) (n=7)
Day 7 (mean [CV, %])	**3 mg (n=8)**	**10 mg (n=7)**	**20 mg (n=6)**	**3 mg (n=7)**	**10 mg (n=7)**	**20 mg (n=7)**	**30 mg (n=7)**	**100 mg (n=7)**
Ae_{24} (ng)	1024 (163)	14140 (58)	35341 (36)	630 (179)	11709 (60)	25328 (50)	35462 (33)	67768 (54)
CL_R[a] (mL/h)	14.2 (48) (n=3)	42.8 (33) (n=6)	45.5 (38) (n=6)	11.3 (60) (n=2)	16.9 (92) (n=7)	21.7 (41) (n=6)	26.4 (33) (n=7)	41.4 (41) (n=7)

[a]For CL_R data, the number of eligible subjects is provided below the values.

Ae_{0-24}, total amount excreted in urine from time 0 to 24 h; CL_R, renal clearance; CV, coefficient of variation; M-I, metabolite-I; NA, not applicable; NC, not calculated; PK, pharmacokinetic.

Supplementary Table 3. Calculated probabilities based on PK/AE models

C_{max} vs somnolence			**AUC vs somnolence**			**C_{max} vs extrapyramidal syndromes**			**AUC vs extrapyramidal syndromes**		
Dose	Prob	SE	Dose	Prob	SE	Dose	Prob	SE	Dose	Prob	SE
0	0.228	0.071	0	0.236	0.070	0	0.125	0.068	0	0.154	0.073
3	0.288	0.069	3	0.295	0.068	3	0.158	0.071	3	0.185	0.074
10	0.411	0.064	10	0.392	0.064	10	0.232	0.073	10	0.235	0.073
20	0.562	0.075	20	0.542	0.073	20	0.340	0.080	20	0.320	0.076
30	0.727	0.092	30	0.735	0.094	30	0.492	0.109	30	0.463	0.106
100	0.829	0.089	100	0.860	0.085	100	0.620	0.137	100	0.601	0.144

AE, adverse event; AUC; area under the plasma concentration-time curve; C_{max}, maximum observed plasma concentration; PK, pharmacokinetic; Prob, probability; SE, standard error.