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A phase 2, randomized, placebo-controlled study of the efficacy and safety of TAK-063 in subjects with an acute exacerbation of schizophrenia

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ABSTRACT

Introduction: TAK-063 is a potent, selective inhibitor of phosphodiesterase 10A, an enzyme selectively expressed in medium spiny neurons of the striatum. This randomized, parallel-group study evaluated the efficacy and safety of 20-mg daily TAK-063 versus placebo in subjects with acutely exacerbated symptoms of schizophrenia (NCT02477020).

Methods: Adults aged 18 to 65 with diagnosed schizophrenia and psychotic symptoms that exacerbated within 60 days before screening were included. Subjects who discontinued psychotropic medications before screening were randomized 1:1 to 6 weeks of placebo ($n = 81$) or 20-mg TAK-063 ($n = 83$). Weekly efficacy visits were conducted during the treatment period, and dose de-escalation was allowed (blinded) to 10-mg TAK-063 for intolerability.

Results: The primary endpoint, change from baseline in the Positive and Negative Syndrome Scale total score at week 6, was not achieved (least-squares mean difference vs placebo [standard error] = −5.46 [3.44]; $p = 0.115$). Secondary endpoints were generally supportive of antipsychotic efficacy. Consistent with previous phase 1 studies, TAK-063 was safe and well tolerated, and most adverse events were mild or moderate in severity and did not result in discontinuation. No deaths occurred, and the incidence of akathisia and dystonia, categories of extrapyramidal syndromes, was more frequent in the TAK-063 group than placebo.

Conclusions: Although the study did not meet the primary endpoint (effect size = 0.308), the effects of TAK-063 on the primary and secondary endpoints may be suggestive of antipsychotic activity. Interpretation of these results is confounded by a relatively high placebo effect and a lack of dose-ranging or active reference.

1. Introduction

Schizophrenia is a chronic, debilitating disorder consisting of positive, negative, and cognitive symptoms (Citrome, 2014; de Araujo et al., 2012). Current antipsychotics, mainly D_2 receptor antagonists, address the positive symptoms associated with schizophrenia, but cognitive and negative symptoms are not effectively treated (Citrome, 2014; Leucht et al., 2009; Shekwahat and Jiloha, 2009). Current antipsychotics are associated with extrapyramidal syndromes (EPS) and metabolic and cardiovascular side effects (Citrome, 2014; Henderson et al., 2005; Scigliano and Ronchetti, 2013). The development of effective therapies with improved safety profiles would provide valuable new treatment options for schizophrenia.

TAK-063 is a potent, selective PDE10A inhibitor (Shiraishi et al., 2016; Suzuki et al., 2015). Phosphodiesterase 10A (PDE10A) is an intracellular enzyme that is selectively expressed in the medium spiny neurons of the striatum. PDE10A hydrolyzes the second messengers cAMP and cGMP that mediate intracellular signaling of G-protein coupled receptors, including D1 and D2 dopamine receptors, which are highly expressed in the direct and indirect pathways of the striatum, respectively (Fujishige et al., 1999). PDE10A inhibition can lead to striatum-specific elevation of cyclic nucleotide levels and potentially could have effects similar to D2 receptor antagonism on indirect pathways and to D1 receptor agonism on direct pathways of the striatum, thus activating both. By modulating integrated striatal outputs, pharmacologic inhibition of PDE10A could have procognitive effects on its own; in addition, by acting in a spiny neuron–specific fashion, it could augment the effects

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of other antipsychotic drugs, minimizing the exacerbation of side effects (reviewed in (Suzuki and Kimura, 2018)).

In this regard, preclinical studies in rats have suggested that TAK-063 treatment upregulates striatal cAMP/cGMP levels and could have efficacy in the treatment of positive and cognitive schizophrenia symptoms and that it does not increase glucose or prolactin levels (Suzuki et al., 2015). Investigation of murine models has also shown that combined treatment with TAK-063 and either haloperidol or olanzapine produced a potent, antipsychotic-like effect on MK-801–induced hyperactivity, without exacerbation of plasma prolactin levels or eliciting the cataleptic response associated with antipsychotic drugs (Suzuki et al., 2018).

In phase 1 clinical studies, TAK-063 was shown to be safe and well tolerated at single doses up to 1000 mg in healthy subjects and following multiple once-daily doses up to 100 mg for 7 days in subjects with stable schizophrenia (Goldsmith et al., 2017; Tsai et al., 2016). The most common treatment-emergent adverse event (AE) was somnolence, and TAK-063 did not increase prolactin or glucose levels or have other metabolic adverse effects that are associated with current antipsychotics (Henderson et al., 2005; Ishioka et al., 2015; Miyamoto et al., 2005; Tsai et al., 2016; Yurgelun-Todd et al., 2016). In the multiple-rising dose study, peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{24}) values on day 7 in the 20-mg group were comparable to the pharmacologically active exposures in non-clinical studies (Macek et al., 2016a). A positron emission tomography study conducted in healthy subjects to measure target engagement using a radiotracer ([^{11}C]T-773) (Takano et al., 2016a,b) predicted that relevant occupancies (>30%) would be achieved at doses of at least 10 mg (at steady state) (Takano et al., 2016a,b). A single-dose, ketamine-challenge functional magnetic resonance imaging study showed that the most consistent reversal of ketamine-induced increases in blood oxygen level dependency was observed in the 30-mg dose group, which approximates steady-state exposures of 20 mg (Macek et al., 2016a). The results of these studies, combined with pharmacokinetic data from the multiple dose study, were used to model pharmacokinetic/pharmacodynamic (PK/PD) relationships at steady state. Based on the PK/PD models and the tolerability profile observed in the single- and multiple-rising dose studies, 20 mg was considered to be the highest dose with a favorable tolerability profile that achieved relevant exposures and target occupancy while demonstrating pharmacodynamic effects consistent with potential antipsychotic effects (Macek et al., 2016a). Here we report the efficacy, safety, and tolerability of 20-mg TAK-063 administered over a 6-week period to subjects with acutely exacerbated symptoms of schizophrenia. To better characterize the effect size of TAK-063 treatment in a proof-of-concept study, the trial was designed to investigate TAK-063 as monotherapy rather than as a combination therapy.

2. Methods

2.1. Subjects and study design

This was a randomized, double-blind, placebo-controlled, multicenter, 6-week, parallel-group, phase 2 study conducted at 13 centers in the United States from July 1, 2015 to July 27, 2016 (Supplementary Fig. S1). The protocol was conducted in compliance with the Institutional Review Board, Good Clinical Practice regulations, and ethical standards of the Declaration of Helsinki. The methods were performed in accordance with relevant guidelines and regulations and approved by Quorum Review Institutional Review Board. None of the text, tables, and figures contains patient identifiers. Informed consent was obtained from all participants. The study is registered with the clinicaltrials.gov identifier NCT02477020.

Subjects aged 18–65 were eligible for the study if they had a primary diagnosis of schizophrenia ≥1 year before screening, a Positive and Negative Syndrome Scale (PANSS) total score ≥80 at screening and day 1, a score ≥5 (moderate-severe) on 3 or more key positive/psychotic symptoms of PANSS (delusions [P1], conceptual disorganization [P2], hallucinations [P3], suspiciousness [P6], unusual thought content [G9]), and Clinical Global Impression-Severity (CGI-S) ≥4 at screening and day 1. In addition, subjects were required to have an exacerbation of psychotic symptoms within 60 days before screening and body mass index between 18.0 and 35.0 kg/m^2 at screening. Exclusion criteria included a decrease of 20% or more in total PANSS score at day 1, moderate or severe substance use disorder, and a psychiatric disorder other than schizophrenia as primary diagnosis.

Patients referred from multiple settings (emergency departments, outpatient clinics, other) were included in the study. Patient eligibility was evaluated during a screening period prior to study entry (specified to last at least 3 days and no >8 days); during that time, subjects were hospitalized and had all psychotropic medications (including their current antipsychotic treatment) discontinued if applicable, consistent with labeling recommendations and conventional medical practice.

Prophylactic treatment of EPS was not permitted. For consistency within the study, propranolol (up to 120 mg/day) was recommended for the management of treatment-emergent akathisia, and benztropine (up to 6 mg/day) was recommended for other EPS (dystonia, dyskinesia, Parkinsonism).

Similarly, for consistency within the protocol, the preferred treatment for anxiety/agitation was lorazepam (not >4 mg/day during screening and for the first 2 weeks of the treatment period and only 2 mg/day after week 3), and zolpidem was the preferred treatment for insomnia (not to exceed 12.5 mg/day and not more than twice weekly). Medications for the treatment of anxiety/agitation were not to be used in close temporal proximity (defined as administration within 4 h of each other) to any medication used for the treatment of insomnia. Anxiolytics were not to be administered within 6 h before the PANSS or cognitive assessments.

A 3-week inpatient hospitalization period was required after the initial screening period. Following screening, investigators or their designees used an interactive web response system (IWRS) to randomize subjects 1:1 to placebo or 20-mg TAK-063 daily. Double-blinding was maintained by the IWRS and was never to be broken. TAK-063 and matching placebo tablets were supplied to each study site. At the discretion of the investigator, subjects were eligible for hospital discharge at any time after completion of all assessments at the week 3 visit. Study medication was administered as a tablet once daily at night with food, preferably with the evening meal. If intolerable, down-titration of study medication to 10 mg/day was allowed (double-blind) at any time after the first dose. PANSS assessments were conducted at screening, on day 1, and at weeks 1–6 or at early termination. CGI-S was assessed as follows: screening, days 1 and 4, week 1, day 11, week 2, day 18, and weeks 3–6. CGI-Improvement (CGI-I) assessments were performed at weeks 1–6. Vital signs were assessed at screening, on day 1, and at weeks 1–6, and clinical laboratory samples were collected after a 6-h fast except at screening, when fasting was not mandated. Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A) assessments were conducted on day 1 and at weeks 1, 3, and 6. Twelve-lead electrocardiogram (ECG) was assessed at screening, on day 1, and at weeks 1, 3, and 6. All of the above assessments were conducted at early termination, as applicable. The Brief Assessment of Cognition in Schizophrenia (BACS) was conducted during screening, on day 1, and at weeks 3 and 6, while assessments on the Personal and Social Performance Scale (PSP) and the University of California San Diego Performance-based Skills Assessment - Brief (UPSA-B) took place on day 1 and at weeks 3 and 6. The Readiness for Discharge Questionnaire (RDQ) was administered for subjects while inpatient as follows: screening, day 1, day 4, week 1, day 11, week 2, day 18, and weeks 3–6.

2.2. Study endpoints

The primary endpoint was the change from baseline in total PANSS score at week 6. Secondary endpoints included the changes from baseline in PANSS subscales using the Marder 5-factor model, PANSS subscales (positive, negative, and general psychopathology), the Brief Negative Symptom Scale (BNSS), and the CGI-S. Additional secondary endpoints included the percentage of clinical responders based on total PANSS score (≥30% decrease from baseline in total PANSS), CGI-I, the percentage of CGI-I responders (subjects with a rating of "much" or "very much" improved), and change from baseline in BACS, PSP, and UPSA-B. Time to readiness for discharge as measured by the RDQ was an additional endpoint.

Safety endpoints included change from baseline on individual domain scores and CGI scores on the ESRS-A, vital signs, clinical laboratory findings (hematology, serum chemistry, and urinalysis), and change from baseline in ECG parameters. Additional safety endpoints included AE frequency, frequency and percentage of reasons for study discontinuation, frequency and percentage of subjects who decreased dose because of intolerability, and percentage of subjects who received pharmacologic treatment for EPS. Intensity of AEs was classified as "mild," "moderate," or "severe," and each AE was assessed for association with study drug.

2.3. Statistical analyses

The study was powered (80%) to detect a difference of 10 points with a common standard deviation of 20 points (effect size = 0.5) between treatment groups on the total PANSS at week 6. To reach 80% power, 128 subjects (64 per arm) were required. LS means, differences, and *p*-values were obtained using mixed models for repeated measures for total PANSS and PANSS Marder factors, CGI-S, and BNSS. Efficacy data are reported for the full analysis data set: all randomized subjects who received at least 1 dose of study drug for whom a baseline and at least 1 valid postbaseline value existed. The *p*-values for PANSS and CGI-I responders were obtained using a logistic regression model adjusting for treatment and the baseline PANSS or CGI-S score. All confidence intervals, statistical tests, and resulting change from baseline values were reported as 2-sided and assessed at $\alpha = 0.05$. No statistical adjustments were made for multiple comparisons.

3. Results

3.1. Demographics

Of 230 subjects assessed for eligibility, 164 were randomized and 106 completed the study (Fig. 1). A high proportion of subjects were black or African American (65.9%), and there was an imbalance of black subjects between the two treatment groups (placebo: 53.1%; TAK-063: 78.3%). Most white subjects were non-Hispanic (Table 1), and body mass index and gender were comparable between the placebo and TAK-063 groups.

Twenty-two subjects (11 in each treatment group) encountered at least one significant protocol deviation. The most reported deviation was "procedure not performed per protocol," although no deviation affected the study outcome.

3.2. Efficacy

The least-squares (LS) mean change from baseline in total PANSS score at week 6 was −14.1 in the placebo group ($n = 76$) and −19.5 in the TAK-063 group ($n = 80$) (95% CI: −12.26 to 1.35; effect size = 0.308) (Fig. 2). Although the effect on total PANSS score did not reach statistical significance, the differences in LS mean change in the TAK-063 group were consistently greater than in the placebo group at each assessment during the 6-week treatment period (Fig. 2). Overall, the LS mean change in total PANSS score in the placebo group was relatively large (−14.1 points) and showed substantial heterogeneity by site (Supplementary Fig. S2).

There was a numerically greater decrease on the PANSS positive, negative, and general psychopathology subscales favoring TAK-063 for most of the 6-week treatment period, although statistical significance was not achieved at week 6 (positive: LS mean difference = −1.60, SE = 1.09, 95% CI: −3.77 to 0.56, $p = 0.145$; negative: LS mean difference = −1.14, SE = 0.85, 95% CI: −2.83 to 0.54, $p = 0.182$; general psychopathology: LS mean difference = −2.44, SE = 1.73, 95%

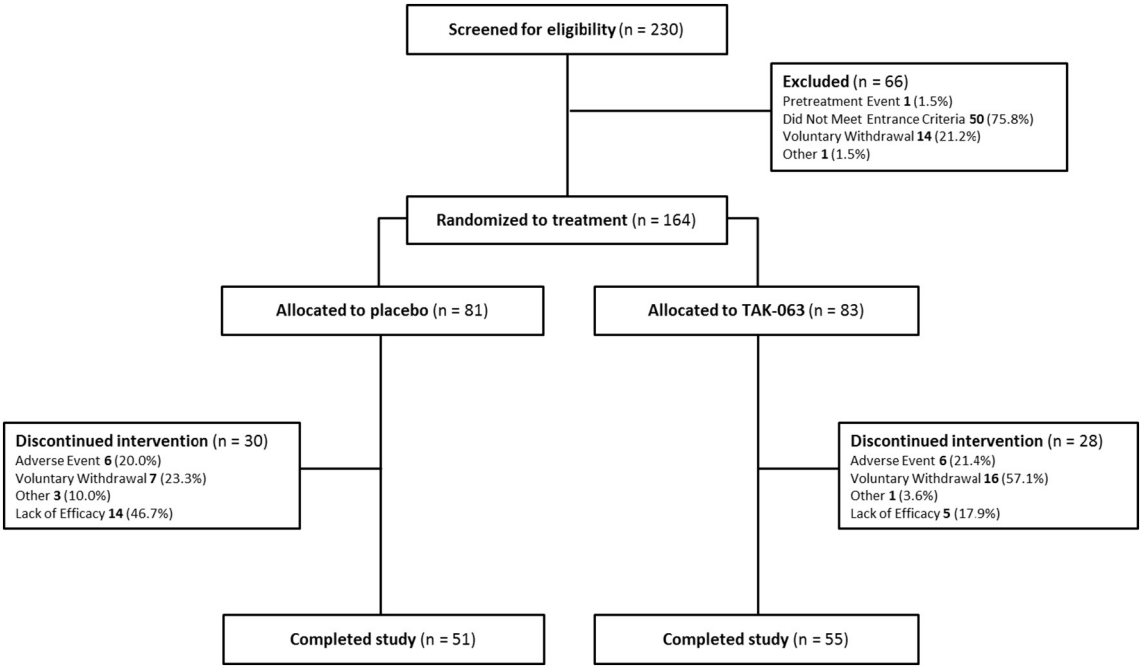

Fig. 1. Subject disposition.

Table 1
Demographic and baseline characteristics.

	Placebo (n = 81)	TAK-063 (n = 83)	Total (N = 164)
Age (years), mean (SD)	41.2 (10.4)	42.3 (10.4)	41.8 (10.4)
Gender, n (%)			
Male	67 (82.7)	65 (78.3)	132 (80.5)
Female	14 (17.3)	18 (21.7)	32 (19.5)
Race, n (%)			
American Indian or Alaska Native	1 (1.2)	0	1 (0.6)
Black or African American	43 (53.1)	65 (78.3)	108 (65.9)
White	33 (40.7)	16 (19.3)	49 (29.9)
Ethnicity, n (%)			
Hispanic or Latino	14 (17.3)	6 (7.2)	20 (12.2)
Non-Hispanic and Latino	67 (82.7)	77 (92.8)	144 (87.8)
Other[a]	4 (4.9)	2 (2.4)	6 (3.6)
BMI (kg/m^2)	27.8 (4.4)	27.2 (4.2)	27.5 (4.3)
Initial diagnosis of schizophrenia, n (%)			
≤5 years before informed consent	8 (9.9)	2 (2.4)	10 (6.1)
>5 years before informed consent	73 (90.1)	81 (97.6)	154 (93.9)

Note: BMI, body mass index; SD, standard deviation.
[a] Includes Asian, Native Hawaiian or Other Pacific Islander, and multiracial groups.

CI: −5.87 to 0.98, $p = 0.161$). PANSS Marder factors also consistently favored TAK-063 but did not reach statistical significance at week 6 (Table 2). The percentage of PANSS total responders in the TAK-063 group was consistently greater than in the placebo group during the 6-week treatment period (Supplementary Fig. S3).

Nominal significance favoring TAK-063 was observed in the CGI-S at week 6 (LS mean difference = −0.43; SE = 0.20; 95% CI: −0.83 to −0.03; $p = 0.035$; effect size = 0.413) (Table 2). The CGI-I score also nominally favored the TAK-063 group at week 6 (LS mean difference = −0.66; SE = 0.24; 95% CI: −1.15 to −0.18; $p = 0.007$), and the percentage of CGI-I responders was greater in the TAK-063 group than in the placebo group at week 6 (placebo: 29.4%; TAK-063: 58.2%; 95% CI: 1.52 to 7.77; $p = 0.003$) (Supplementary Table S1). The difference from baseline in BNSS total score at week 6 also favored TAK-063 but was not statistically significant (Table 2). Similarly, the change from baseline for both BACS total score and PSP favored TAK-063 at week 6 but did not reach statistical significance (95% CI: −1.30 to 5.69 and −1.96 to 7.19, respectively), and the difference between the placebo and TAK-063 groups for the UPSA-B was not statistically significant at week 6 (95% CI: −5.00 to 3.92) (Table 2). The number of subjects deemed ready for discharge on RDQ favored TAK-063 but was not significant at the end of the mandatory hospitalization phase (week 3) nor at any other time point except for week 5 (15.0% vs 3.9%; $p = 0.018$).

When efficacy results were analyzed according to race subgroups, there were differences in efficacy in black vs non-black patients. For the primary endpoint (the week 6 difference in LS mean change from baseline in PANSS total score between TAK-063 and placebo), dichotomized by race, the results were −9.16 (SE = 4.13; $p = 0.029$) for black patients and 6.53 (SE = 6.10; $p = 0.291$) for non-black patients.

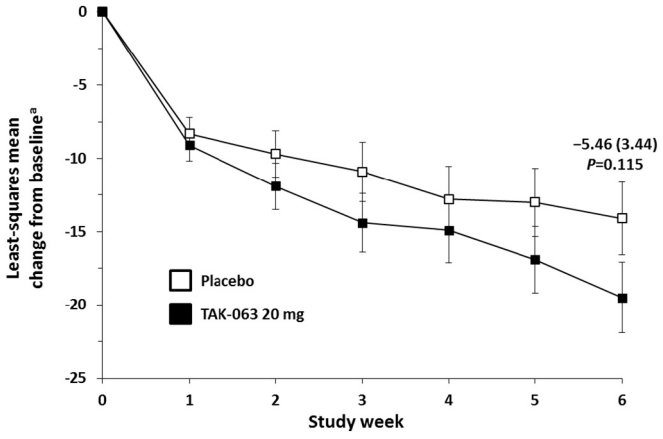

Fig. 2. Change from baseline in PANSS total score by study week. [a]Points indicate least-squares (LS) mean change from baseline at weeks 1–6 of the treatment period. Numbers at week 6 report LS mean difference (standard error). p-Values were derived from the LS mean difference between TAK-063 and placebo, which was obtained using a mixed model for repeated measures with baseline PANSS total score as a covariate, and pooled center, week, and treatment as fixed factors. Unstructured covariance was assumed. PANSS, Positive and Negative Syndrome Scale.

3.3. Safety

No clinically relevant or consistent differences were observed between groups for hematologic, renal, or hepatic lab test results, vital signs, or ECG. Most subjects reported AEs that were mild or moderate in severity (placebo: 46 of 50 subjects; TAK-063: 56 of 65 subjects) (Table 3), and the AEs reported in this study were generally consistent with previously conducted phase 1 studies (Goldsmith et al., 2017; Tsai et al., 2016). AEs experienced by ≥5% of subjects in the TAK-063 group were akathisia (placebo: 4.9%; TAK-063: 13.3%), somnolence (placebo: 2.5%; TAK-063: 12.0%), dyspepsia (placebo: 7.4%; TAK-063: 10.8%), headache (placebo: 11.1%; TAK-063: 7.2%), nausea (placebo: 6.2%; TAK-063: 6.0%), dystonia (placebo: 1.2%; TAK-063: 6.0%), and decreased appetite (placebo: 1.2%; TAK-063: 6.0%). The rate of discontinuation due to AEs was similar between groups (placebo: 7.4%; TAK-063: 7.2%) (Table 3), while the rate of discontinuation due to lack of efficacy was higher in the placebo group (46.7% vs 17.9%). Although serious AEs (SAEs) were experienced by 2 of 81 subjects in the placebo group (2.5%) and 4 of 83 subjects in the TAK-063 group (4.8%), none were considered related to study drug. SAEs reported in the placebo group were cellulitis (1 subject) and agitation (1 subject), and those reported in the TAK-063 group were agitation (1 subject), worsening of schizophrenia (2 subjects), and suicidal ideation (1 subject). Two subjects in each group discontinued treatment because of SAEs (Table 3), and 1 dose down-titration occurred in the TAK-063 group.

The overall incidence of EPS was 12.3% in the placebo group and 27.7% in the TAK-063 group. The most common categories of EPS AEs as identified by the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query for EPS (broad search) were dystonia (placebo: 7.4%; TAK-063: 15.7%), akathisia (placebo: 4.9%; TAK-063: 13.3%), and Parkinson-like events (placebo: 6.2%; TAK-063: 6.0%) (Supplementary Table S2). However, most cases of EPS resolved with minimal or no treatment. The frequency of propranolol and benztropine use (initiated post-baseline) for EPS treatment was lower than the incidence of EPS AEs and was greater in the TAK-063 group than in the placebo group (propranolol: 6.0% [5 patients] vs 3.7% [3 patients]; benztropine: 10.8% [9 patients] vs 1.2% [1 patient]). During the treatment period, the average daily propranolol dose for subjects experiencing EPS was 6.5 mg/day in the placebo group and 5.3 mg/day in the TAK-063 group, while the average daily benztropine dose was 0.8 mg/day in the TAK-063 group compared with 0.2 mg/day in the placebo group. Very few (2) discontinuations occurred because of EPS, with 1 in the placebo group (akathisia) and 1 in the TAK-063 group (dystonia). The absolute change from baseline for any ESRS-A domain was no >0.1 at any study time point for either treatment group.

4. Discussion

These results, together with the phase 1 safety data, suggest that TAK-063 was safe and well tolerated. No deaths occurred, and most AEs were mild or moderate in severity and did not result in study discontinuation. AEs associated with EPS were likewise mild or moderate

Table 2
MMRM analysis of select secondary endpoints at week 6.

Parameter		LS mean (SE)			*p* value	95% CI	Effect size
		Placebo ($n = 76$)	TAK-063 20 mg ($n = 80$)	Difference			
PANSS Marder factors	Positive	−5.33 (0.80)	−7.23 (0.78)	−1.90 (1.12)	0.092	(−4.11, 0.31)	0.330
	Negative	−3.38 (0.68)	−4.11 (0.66)	−0.73 (0.94)	0.441	(−2.58, 1.13)	0.150
	Disorganized	−1.90 (0.58)	−3.16 (0.57)	−1.26 (0.80)	0.119	(−2.85, 0.33)	0.305
	Hostility	−1.16 (0.48)	−2.28 (0.46)	−1.12 (0.65)	0.088	(−2.41, 0.17)	0.334
	Anxiety	−3.66 (0.46)	−4.34 (0.45)	−0.68 (0.64)	0.288	(−1.93, 0.58)	0.207
BNSS total		−4.93 (1.508)	−7.80 (1.45)	−2.87 (2.05)	0.163	(−6.93, 1.18)	0.273
CGI-Severity		−0.76 (0.15)	−1.19 (0.14)	−0.43 (0.20)	0.035	(−0.83, −0.03)	0.413
CGI-Improvement		3.46 (0.18)	2.80 (0.17)	−0.66 (0.24)	0.007	(−1.15, −0.18)	0.530
BACS		2.33 (1.29)	4.52 (1.25)	2.20 (1.77)	0.216	(−1.30, 5.69)	0.245
PSP		9.65 (1.69)	12.27 (1.61)	2.62 (2.31)	0.260	(−1.96, 7.19)	0.220
UPSA-B		3.97 (1.66)	3.43 (1.59)	−0.54 (2.26)	0.812	(−5.00, 3.92)	0.047

Note: BACS, Brief Assessment of Cognition in Schizophrenia; BNSS, Brief Negative Symptom Scale; CGI-I, Clinical Global Impression Scale-Global Improvement; CGI-S, Clinical Global Impression Scale-Severity of Illness; LS, least-squares; MMRM, mixed model for repeated measures; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale; SE, standard error; UPSA-B, The University of California San Diego Performance-based Skills Assessment - Brief. LS means, differences, and *p*-values were obtained using a mixed model for repeated measures with baseline score for the indicated parameter as covariate and pooled center, week and treatment as fixed factors. For UPSA-B, the baseline UPSA-B composite score was used as a covariate and pooled center, week, and treatment as fixed factors. Unstructured covariance was assumed.

in the TAK-063 group, and consistent with findings from the phase 1 multiple-rising dose study. In most cases, EPS resolved with minimal or no intervention. Notably, the lower rate of somnolence observed in this study relative to the phase 1 studies in which TAK-063 was administered during the day may support nighttime dosing (Goldsmith et al., 2017; Tsai et al., 2016). Although the study did not meet its primary endpoint, the 20-mg dose was previously shown to achieve target engagement predicted to be efficacious (Macek et al., 2016a; Takano et al., 2016a,b) and pharmacodynamic effects in phase 1 studies that may be predictive of efficacy in the treatment of schizophrenia: increases in EEG gamma power in subjects with schizophrenia, reversal of ketamine-induced increases in functional magnetic resonance BOLD signal, and improvements in cognition (Macek et al., 2016b,c; Tsai et al., 2016; Yurgelun-Todd et al., 2016).

The study was powered to detect a difference in total PANSS between TAK-063 and placebo of 10 points, with a common standard deviation of 20 points (effect size = 0.5). Overall, the study did not meet its primary endpoint; the difference in total PANSS had an effect size of 0.308. The magnitude of the effect size observed on the primary endpoint (0.308) was generally consistent with the effects on secondary endpoints including PANSS Marder factors, PANSS subscales, and BNSS, but also did not reach statistical significance. Three secondary endpoints (CGI-S scores, CGI-I scores, and the percentage of CGI-I responders) were nominally better with TAK-063 treatment than with placebo at week 6. In addition, the observed effect size of 20-mg TAK-063 on the difference from placebo in total PANSS in this study was comparable to the range of effect sizes (0.33–0.88) reported in a meta-analysis of randomized trials of 15 antipsychotics (Leucht et al., 2013).

Several factors are likely to have a role in the failure to detect a difference between the active and placebo arms of this study, most notably the magnitude of the change in total PANSS score in the placebo group at week 6 (−14.1), with the largest between-week change observed at week 1 (−8.3). Heterogeneity in placebo response across sites was apparent as early as week 1, with some subjects showing decreases in total PANSS at week 1 of approximately 40 points, while 3 sites reported mean placebo responses >38 points at week 6 (Supplementary Fig. S2). High placebo responses have been reported in a number of US schizophrenia trials, and placebo response appears to be increasing (with the relative benefit of medication compared to placebo decreasing) over time in trials of antipsychotics (Chen et al., 2010; Kemp et al., 2010; Kinon et al., 2011). Several multi-trial analyses have investigated this trend, most comprehensively a meta-analysis of 105 trials of antipsychotics reporting a statistically significant increase with time in the size of the placebo response from years 1960–2014 ($p < 0.001$) (Chen et al., 2010; Kemp et al., 2010; Kinon et al., 2011; Rutherford et al., 2014). This trend has been associated with factors such as multiple study sites, short trial duration, and short disease history (Weimer et al., 2015).

Another factor that could have confounded the overall results is the imbalance in the proportion of black patients across study arms, because a subanalysis indicated that there might be efficacy differences for TAK-063 between black and non-black patients. Although there is an emerging body of research exploring the potential effects of genetic

Table 3
Summary of treatment-emergent adverse events.

	Placebo ($n = 81$)		TAK-063 20 mg ($n = 83$)		Total ($N = 164$)	
	Events	Subjects, *n* (%)[a]	Events	Subjects, *n* (%)[a]	Events	Subjects, *n* (%)[a]
Treatment-emergent AEs	137	50 (61.7)	170	65 (78.3)	307	115 (70.1)
Related	44	26 (32.1)	71	38 (45.8)	115	64 (39.0)
Not related	93	24 (29.6)	99	27 (32.5)	192	51 (31.1)
Mild	100	31 (38.3)	114	35 (42.2)	214	66 (40.2)
Moderate	32	15 (18.5)	44	21 (25.3)	76	36 (22.0)
Severe	5	4 (4.9)	12	9 (10.8)	17	13 (7.9)
Leading to study discontinuation		6 (7.4)		6 (7.2)		12 (7.3)
Serious treatment-emergent AEs	2	2 (2.5)	4	4 (4.8)	6	6 (3.7)
Not related	2	2 (2.5)	4	4 (4.8)	6	6 (3.7)
Related	0	0	0	0	0	0
Leading to study discontinuation		2 (2.5)		2 (2.4)		4 (2.4)
Deaths		0		0		0

AE, adverse event.
[a] Percentages are based on the total number of subjects in the safety analysis set for each treatment group.

factors on the variability of race-specific responses to schizophrenia treatments (Fijal et al., 2009; Huang et al., 2016), the specific reasons for these differences in our study are unknown.

The interpretation of this study is limited by a lack of dose-ranging and active reference. Therefore, an absolute determination of a negative study versus a failed study cannot be made. The overall development strategy for the program was a "best dose forward" approach, in which a single dose level is explored in a proof-of-concept study for decision making. TAK-063 20 mg/day was chosen for this study, as it was considered to be the highest, best tolerated dose that achieved target occupancy, plasma concentrations, and pharmacodynamic effects consistent with preclinical data and antipsychotic efficacy. The limitations of this strategy, especially with unprecedented mechanisms like PDE10A inhibitors, are that it is not possible to determine where these results may lie within the dose-response relationship in humans, as well as the unknown relevance of the preclinical models used as predictors of preclinical efficacy to the potential efficacy in humans. An active reference would have been beneficial to serve as a measure of assay sensitivity and provide some within-study benchmark for estimation of relative efficacy and safety and tolerability. It is unknown whether higher or lower doses would have demonstrated similar, lesser, or greater magnitude of differences in effect sizes of primary and secondary endpoints. In summary, while TAK-063 did not meet the primary efficacy study endpoint and interpretation of the results of this study is confounded by the lack of dose-ranging comparisons and an active reference, TAK-063 exhibited a favorable safety and tolerability profile and showed some evidence of potential efficacy in subjects with an acute exacerbation of schizophrenia.

Contributors

Thomas A. Macek, Maggie McCue, Elizabeth Hanson, John Affinito, and Atul R. Mahableshwarkar designed the study or were primarily responsible for oversight and conduct of the study. Paul Goldsmith conducted the pharmacokinetic analyses while Xinxin Dong conducted the statistical analysis.

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Conflict of interest

Maggie McCue, Elizabeth Hanson, and John Affinito are employees of Takeda Development Center Americas, Inc., Deerfield, IL. Thomas A. Macek, Xinxin Dong, and Atul R. Mahableshwarkar were employees of Takeda Development Center Americas, Inc., Deerfield, IL, at the time of this study. Paul Goldsmith was an employee of Takeda Development Centre Europe Ltd., London, UK, at the time of this study. All authors have contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.08.028.

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