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REGULAR RESEARCH ARTICLE

Translational Development Strategies for TAK-063, a Phosphodiesterase 10A Inhibitor

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Abstract

Background: TAK-063 is an inhibitor of phosphodiesterase 10A (PDE10A), an enzyme highly expressed in medium spiny neurons of the striatum. PDE10A hydrolyzes both cyclic adenosine monophosphate and cyclic guanosine monophosphate and modulates dopamine signaling downstream of receptor activation in both direct and indirect pathways of the striatum. TAK-063 exhibited antipsychotic-like effects in animal models; however, the translatability of these models to the clinical manifestations of schizophrenia and the meaningfulness for new targets such as PDE10A has not been established.

Methods: The TAK-063 phase 1 program included a comprehensive translational development strategy with the main objective of determining whether the antipsychotic-like pharmacodynamic effects seen in nonclinical models would translate to human subjects. To evaluate this objective, we conducted a single-rising dose study (84 healthy subjects), a positron emission tomography (PET) study (12 healthy subjects), a functional magnetic resonance imaging blood oxygen level-dependent (BOLD) study (27 healthy subjects), and a multiple-rising dose study that included people with schizophrenia (30 healthy Japanese subjects and 47 subjects with stable schizophrenia). In addition, assessments of cognition and electroencephalography (27 healthy subjects and 47 subjects with stable schizophrenia) were included.

Results: PDE10A engagement by TAK-063 was verified with a novel PET radiotracer for use in primates and humans. TAK-063 showed favorable pharmacokinetic and safety profiles in humans, and TAK-063 reduced ketamine-induced changes in electroencephalography and BOLD signaling in animal models and healthy human subjects. In addition, analogous effects on cognition were observed in animal models and human subjects.

Conclusions: Overall, the phase 1 results showed some consistent evidence of antipsychotic activity. This translational strategy may be valuable for the future development of novel therapeutic approaches, even when relevant nonclinical models are not available.

Keywords: schizophrenia, TAK-063, phosphodiesterase 10A

Introduction

Antipsychotic agents can address the positive symptoms of schizophrenia via partial agonism or full antagonism of dopamine receptor 2 (D2), but have little effect on negative and cognitive symptoms (Geyer, 2008; Citrome, 2014). In addition, side effects such as weight gain, extrapyramidal syndromes, hyperprolactinemia, and sedation can limit the tolerability of these agents (Ginovart and Kapur, 2012). Therefore, more effective treatments with improved safety profiles are needed.

Phosphodiesterase 10A (PDE10A) inhibition has been under investigation recently as an alternative therapeutic approach for schizophrenia. PDE10A hydrolyzes both cyclic adenosine monophosphate and cyclic guanosine monophosphate

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Significance Statement

The TAK-063 phase 1 program included a comprehensive translational development strategy with the main objective of determining whether the antipsychotic-like pharmacodynamic effects seen in nonclinical models would translate to human subjects. This strategy effectively guided clinical development, and findings in clinical studies were generally consistent with nonclinical findings. The approach to the TAK-063 development program provides a framework for the evaluation of new therapeutic approaches, even when relevant nonclinical models are not available.

(Fujishige et al., 1999) and is primarily expressed in medium spiny neurons (MSNs) of the striatum (Seeger et al., 2003). In autoradiography studies using mouse, rat, monkey, or human brain sections, radiolabeled T-773, a PDE10A specific tracer, selectively accumulated in the striatum; however, this selective accumulation was not observed in brain sections of PED10A-knockout mice. These results indicate that PDE10A is also primarily expressed in MSNs of the human striatum (Harada et al., 2015b; Takano et al., 2015). Striatal outputs originating in MSNs are mainly divided into 2 pathways: the D2-expressing indirect pathway and the dopamine receptor 1 (D1)–expressing direct pathway (Suzuki et al., 2015). PDE10A is expressed in both pathways, and PDE10A inhibition alters the levels of second messengers induced by activation of D1 and D2. By acting downstream of dopamine receptors in specific neuronal populations, PDE10A inhibition has the potential to provide a viable treatment option without some of the shortcomings experienced with traditional dopamine receptor–focused approaches.

TAK-063 is a potent and selective inhibitor of PDE10A (Harada et al, 2015a; Suzuki et al, 2015) that increases striatal cyclic adenosine monophosphate and cyclic guanosine monophosphate levels, which in turn increase the phosphorylation of key downstream substrates (Suzuki et al., 2015). TAK-063 demonstrated antipsychotic-like effects in methamphetamine- or MK-801–induced hyperactivity and prepulse inhibition in rodents (Suzuki et al., 2016); improved function in multiple cognitive domains—including recognition memory, attention, impulsivity, working memory, and executive function—in rodent paradigms (Shiraishi et al., 2016); and was shown to displace the binding of the PDE10A positron emission tomography (PET) radioligands [^{3}H]T-773 and [^{11}C]T-773 in rodents and nonhuman primates, respectively (Harada et al., 2015a; Takano et al., 2016a).

The development of PDE10A inhibitors faces several translational challenges. Compared with nonclinical models for dopamine receptor–targeting agents, nonclinical models for PDE10A inhibition and their relevance to clinical manifestations of schizophrenia have not been extensively characterized. Furthermore, assessing neurocognition in both animals and humans is particularly challenging with regard to construct validity and the selection of measures (Green and Braff, 2001). To address these challenges, a comprehensive translational development strategy was utilized to examine whether the findings in nonclinical studies of TAK-063 would extend to healthy human subjects and patients with schizophrenia.

Our translational phase 1 program was designed with the following objectives: confirming PDE10A engagement by TAK-063, establishing the pharmacokinetic profile of TAK-063, and evaluating the pharmacodynamic effects of TAK-063 that were observed in nonclinical studies. To guide the decision to proceed to a phase 2 trial, Go/No Go criteria were prospectively established for each phase 1 study (Table 1). The intention of this strategy was to demonstrate that the effects of TAK-063 observed in our phase 1 program were consistent with the data from our nonclinical studies. The strategy also required that we demonstrate sufficient evidence for antipsychotic activity in our target population (patients with schizophrenia) as a requirement for proceeding with the clinical development of TAK-063. Our prospective criteria were met, and TAK-063 proceeded to a phase 2 trial.

Materials and Methods

Nonclinical studies were mainly conducted at the Neuroscience Drug Discovery Unit of Takeda Pharmaceutical Company Limited and at the Karolinska Institute and King's College London. Clinical studies were conducted at multiple sites in the United States and Sweden, and PET studies were conducted at Karolinska Institute (Stockholm, Sweden). Clinical studies were designed to be relatively similar to their nonclinical counterparts.

Positron-Emission Tomography Studies

From a series of candidate compounds, [^{11}C]T-773, a novel PET radiotracer, was synthesized and developed for use in animals and humans (Harada et al., 2015a; Harada et al., 2015b; Stepanov et al., 2015; Takano et al., 2016a; Takano et al., 2016b). For PDE10A occupancy studies, displacements of non-radiolabeled T-773 and [^{11}C]T-773 were used as measurements to estimate PDE10A occupancy by TAK-063 (Takeda Pharmaceutical Company Limited; Fujisawa, Japan; Kunitomo et al., 2014) in rodents (n = 2 for 0.3 mg/kg dose; n = 3 for other doses) and nonhuman primates (n = 1 for each dose; Harada et al., 2015a; Harada et al., 2015b; Takano et al., 2016a), respectively. Binding kinetics of [^{11}C]T-773 were analyzed in nonhuman primates in pretreatment and displacement studies (n = 1 for each dose; Takano et al., 2015). In a PDE10A occupancy study using rodents, TAK-063 (0, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg) was orally administered to rats and 0.02 mg/kg of T-773 was administered by bolus intravenous injection via the lateral tail vein 90 minutes after TAK-063 administration. The rats were euthanized by cardiac perfusion with heparinized saline 30 minutes after T-773 injection, and the whole brains were isolated. The striatum and cerebellum were dissected from the brains. The concentration of T-773 was measured by mass spectrometry in each homogenate. Specific binding of T-773 (B_{SP}) to PDE10A in the rat striatum was represented as the difference between the T-773 concentration in the striatum and that in the cerebellum, which was used as a reference region because no specific binding of radiolabeled T-773 in the cerebellum was observed in the autoradiography studies using brain slices from multiple species, including humans (Harada et al., 2015b; Takano et al., 2015). PDE10A occupancy was calculated using the following equation: Occupancy (%) = $(B_{SP,base} - B_{SP,drug})/B_{SP,base} \times 100$. Here, $B_{SP,base}$ and $B_{SP,drug}$ are the concentrations at baseline (vehicle treatment) and at drug treatment, respectively. In a PDE10A occupancy study using nonhuman primates, 123-minute dynamic PET scans were performed with a High Resolution Research Tomograph (Siemens, Munich, Germany) after the

Table 1. Decision Tree for Transition From Phase 1 to Phase 2 Clinical Trials

Study	Objectives	Go Criteria[a]
PET study	Proof of principle: confirm target engagement in humans • Assess central exposure, biodistribution, and target engagement of TAK-063 • Assist in dose selection for phase 2	Target occupancy >30% in PET study
fMRI BOLD study	Proof of mechanism: confirm PDE10A inhibition in humans • Assist in dose selection for multiple-rising dose study • Confirm findings from rats and monkeys demonstrating that TAK-063 ameliorates ketamine-induced fMRI BOLD effects	Evidence of changes in fMRI in TAK-063 alone, baseline BOLD measurements, or during ketamine challenge
SRD PK study	Characterize PK following single and multiple dosing of TAK-063	Half-life amenable to BID or QD dosing. Achieving clinical exposures comparable to minimally effective dose in animals (~1000 ng·h/mL)
SRD/MRD safety study	Establish safety in subjects with schizophrenia • Assess changes in exploratory endpoints with regard to symptoms of schizophrenia, EEG, and cognitive batteries	No intractable dystonia or other extrapyramidal syndromes. No unmanageable hematological effects, such as severe leukopenia or agranulocytosis. No significantly elevated prolactin, cholesterol, triglycerides, glucose, or weight gain.
MRD study	Evaluate tolerability and multiple-dose pharmacokinetics in healthy subjects and subjects with stable schizophrenia. Evaluate effects on measures of cognition and neurophysiological measures in patients with schizophrenia.	No severe or serious adverse effects that limit patient adherence, contribute to significant withdrawals due to adverse events, or limit patient exposures to less than the minimum effective dose. Demonstration of meaningful effects on EEG or other potential measures of pharmacodynamic effects (PPI).

Abbreviations: BID, twice a day; BOLD, blood oxygen level-dependent; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; MRD, multiple-rising dose; PET, positron emission tomography; PK, pharmacokinetic; PPI, pre-pulse inhibition; QD, once a day; SRD, single-rising dose.
[a]All "Go" criteria were met.

injection of [^{11}C]T-773 (141–166 MBq; specific radioactivity: >151 GBq/mmol; injected mass: less than 0.5 mg) under sevoflurane anesthesia. For each monkey, 2 brain PET measurements were performed. The first scan was made under baseline conditions and the next scan after intravenous administration. The doses of TAK-063 were 0.2, 0.8, and 1.6 mg/kg. TAK-063 was administered 35 minutes before the radioligand injection. The duration of the administration was 30 minutes using a syringe pump at a speed of 2 mL/kg/h. The administration of TAK-063 was finished 5 minutes before [^{11}C]T-773 injection. Arterial blood samples were taken continuously with an automated blood sampling system during the initial 3 minutes and were taken manually after 3 minutes. A metabolite analysis of the radioligand was performed to evaluate the fraction of the parent compound. After reconstruction of the PET images, time activity curves were generated for various brain regions, including the caudate, putamen, and cerebellum, which were delineated on the magnetic resonance imaging (MRI)/PET co-registered images. PET data were analyzed using a 2-tissue compartment model with a metabolite-corrected arterial plasma input function. The total distribution volume (VT) was calculated for each brain region. The specific binding part of the VT was calculated as the difference between the VTs of the target regions and the cerebellum. PDE10A occupancy was calculated as the percentage change from baseline of the specific binding part. PDE10A occupancy and dose were fitted to a hyperbolic function for determination of the dissociation constant (Takano et al., 2016a).

PET imaging was also conducted in 12 healthy volunteers to evaluate [^{11}C]T-773 kinetics in the brain and test-retest the reproducibility of [^{11}C]T-773 (ClinicalTrials.gov ID: NCT02370602). Subsequently, PDE10A occupancy by TAK-063 was measured by TAK-063 displacement of [^{11}C]T-773 by a 75-minute dynamic PET scan (n = 3 for 30 mg and 100 mg doses; n = 2 for 3 mg, 10 mg, and 1000 mg doses; Takano et al., 2016b).

Electroencephalogram Studies

Extensively validated techniques, such as electroencephalograms (EEGs), were utilized to assess the effects of TAK-063 on neurological deficits associated with schizophrenia (Light and Swerdlow, 2015). EEG studies were performed in awake rats (n = 4 for each dose; a recording electrode and a reference electrode were positioned on the prefrontal cortex and the cerebellum, respectively) and monkeys (n = 6 for each dose; an EEG montage was obtained using frontal and occipital cortex electrodes; Tomimatsu et al., 2016). After 5 minutes of baseline recording, rats were treated with vehicle or TAK-063 (0.03–3 mg/kg orally) and monkeys were administered vehicle or TAK-063 (0.2 or 0.8 mg/kg/h intravenously for 30 minutes) after 5 minutes of baseline recording and a 15-minute non-treatment phase. Rats received 10 mg/kg of ketamine subcutaneously 90 minutes after TAK-063 administration, and EEG signals in rats were filtered at 0.1–1 kHz, amplified, and digitized at 500 Hz. Monkeys received 1 mg/kg ketamine intramuscularly 10 minutes after TAK-063 administration, and EEG signals in monkeys were filtered (0.5–100 Hz), amplified, and digitized online. Fast Fourier transformations were performed, and the total power in gamma (30–80 Hz) frequency was calculated for both rats and monkeys.

EEG studies were also conducted in subjects with stable schizophrenia (SSS) who were on stable antipsychotic monotherapy and received 3, 10, 30, or 100 mg TAK-063 during a 7-day multiple-rising dose study (Macek et al., 2016a); according to

Goldsmith et al. (2017), SSS can be defined as an individual on stable antipsychotic monotherapy for ≥1 month before screening, who had a Clinical Global Impression of Severity score ≤4, and a total Positive and Negative Symptom Scale score ≤70 at screening and check-in (Day -1; Macek et al., 2016a; Goldsmith et al. 2017). Additionally, an EEG was assessed in healthy subjects who received 3, 10, and 30 mg TAK-063 in an incomplete crossover, ketamine-challenge, functional MRI (fMRI) study (Yurgelun-Todd et al., 2020); ClinicalTrials.gov ID: NCT01892189), and EEG recordings were made after the imaging battery was complete, which was approximately 5 hours after the administration of study medication (n = 14 for 3 mg and 10 mg doses; n = 15 for 30 mg dose). In the multiple-rising dose study, 10-minute samples of 19-channel EEG recordings were taken while subjects were either (1) seated with eyes closed (resting condition) or (2) presented with high-frequency auditory stimuli at 40 Hz in blocks (40-Hz condition; n = 9 for placebo; n = 7 for 100 mg dose). Digital filtering techniques were used to remove artefacts, and data were subsequently transformed using the Fast Fourier method to obtain the following bands: delta (0–3.5 Hz), theta (4–7.5 Hz), alpha (8–12 Hz), beta (13–25 Hz), global gamma (30–50 Hz), and high gamma (40–50 Hz). Spectral power in each frequency band was quantified in topographic displays, as well as in 5 extracted regions—frontal, central, parietal, occipital, and temporal—each as the median of a cluster of electrodes per subject and per time point. The timing and extent of gamma band amplitude increases due to auditory stimulation were also examined during 30-, 40-, and 50-Hz high-frequency stimulation EEG recordings.

Pharmacological and Functional Magnetic Resonance Imaging Blood Oxygen Level-Dependent Studies

Pharmacological MRI (PhMRI) studies in Sprague-Dawley rats were conducted at King's College London (Tomimatsu et al., 2016). The ketamine-challenge fMRI study was a 3-period, incomplete crossover study that enrolled 27 healthy volunteers. In this clinical study, subjects were randomized to receive single oral administrations of placebo and 2 of 3 doses of TAK-063 (3, 10, or 30 mg), with an approximately 1-week washout period between administrations. Sub-anesthetic ketamine doses were administered intravenously approximately 4 hours after the administration of TAK-063 to achieve a plasma concentration of 75 ng/mL (Macek et al., 2016b). Changes in blood oxygen level-dependent (BOLD) signals pre-ketamine and post-ketamine were compared with those of subjects receiving placebo. EEG recordings were made after the imaging battery was complete, approximately 5 hours after the administration of study medication, and were generally similar to the EEG methods used in the multiple-rising dose study. The fMRI BOLD signal was assessed during the resting state and a working memory activation task (the expectancy AX Continuous Performance Test paradigm, for 15 minutes; Yurgelun-Todd et al., 2020). BOLD echo planar images were obtained during a 20-minute resting-state sequence using a 3 Tesla Siemens Verio scanner (repetition time = 2 s, echo time = 28 ms, 40 slices, 3 mm slice thickness). The fMRI images were analyzed using SPM8 and Matlab. The percentage signal change for resting state data was calculated between the pre-ketamine and post-ketamine infusion based on a priori regions of interest using SPM's Anatomy Toolbox.

Single- and Multiple-Rising Dose Pharmacokinetics, Safety, and Tolerability

The single-rising dose study was a double-blind, placebo-controlled study in 84 healthy Japanese subjects (HJS) and non-Japanese subjects who received 3 (n = 11), 10 (n = 11), 30 (n = 11), 100 (n = 11), 300 (n = 11), or 1000 mg (n = 11) TAK-063 or placebo (n = 18; 3 patients per cohort; Tsai et al., 2016). The multiple-rising dose study was a double-blind, placebo-controlled study in 77 subjects (n = 30 HJS and n = 47 SSS). HJS were administered placebo (n = 15) or 3 (n = 8), 10 (n = 8), or 20 mg (n = 8) TAK-063. SSS were administered 3 (n = 7), 10 (n = 8), 20 (n = 7), 30 (n = 8), or 100 mg (n = 8) TAK-063 (Goldsmith et al., 2017; ClinicalTrials.gov ID: NCT01879722). The dose levels selected for investigation in the multiple-rising dose study were based on the safety findings from the single-rising dose study. In both studies, validated liquid chromatography-tandem mass spectrometry was used to determine TAK-063 concentrations (Tsai et al., 2016; Goldsmith et al., 2017). Safety parameters, including adverse events (AEs) and clinical laboratory tests, were examined at specific intervals during the studies (Tsai et al., 2016; Goldsmith et al., 2017).

Cognition Studies

Cognitive studies were conducted in Institute of Cancer Research mice, Long-Evans rats, and hooded Lister rats. The performance of experimentally naive rats, phencyclidine (PCP)-treated rats and mice, and MK-801–treated rats was evaluated in tasks assessing recognition memory, spatial working memory, attention and impulsivity, and executive function (Shiraishi et al., 2016).

In the multiple-rising dose study, cognitive function was examined in HJS receiving 3, 10, or 20 mg TAK-063 and in SSS receiving 3, 10, 20, 30, or 100 mg TAK-063. Cognitive function and postural sway were assessed using the Cognitive Drug Research test battery on Days 1, 2, 4, 6, and 7 predose and at 2 and 6 hours postdose, and statistical analyses were conducted (Macek et al., 2016c).

The study protocols were approved by the institutional review boards at all participating institutions, and the study procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki. All patients provided written informed consent before any study procedures were performed. No formal assessment of maintenance of the double-blind was utilized in any of the double-blind studies.

RESULTS

Single- and Multiple-Rising Dose Pharmacokinetics

The objectives of the single- and multiple-dose pharmacokinetic studies were to determine the pharmacokinetics of single and multiple doses of TAK-063 in healthy subjects and subjects with schizophrenia, and to confirm that the half-life was suitable for once- or twice-daily dosing. Because food may affect the rate of absorption and the pharmacokinetics of drugs administered orally, we evaluated the food effects on pharmacokinetic parameters of 100 mg TAK-063 in the single-rising dose study. TAK-063 exposures were increased slightly under fed versus non-fed conditions in HJS, and exposure increased in a dose-dependent manner (Tsai et al., 2016). As in the nonclinical studies, TAK-063 exhibited slower absorption and increased oral bioavailability in the fed state. In humans, the mean elimination half-life of TAK-063 under fasting conditions ranged from 15–25 hours across dose groups. In the multiple-rising dose study, TAK-063 exposure (maximum serum concentration [C_{max}] and area under the curve [$AUC]_{0-24}$) increased dose proportionally up to 30 mg in SSS and up to 20 mg in HJS on Day 1 (Goldsmith et al., 2017). On Day 7, C_{max} (~100 ng/mL) and AUC_{0-24} (~1000 ng·h/mL) in the 20-mg TAK-063 group were comparable to the pharmacologically active exposures in nonclinical studies (Goldsmith et al.,

2017; Tohyama et al., 2018). Taken together, the dose-exposure relation from the single- and multiple-rising dose studies supported once- or twice-daily dosing and achieved target plasma concentrations of TAK-063, leading to the decision of continued clinical development (Table 1).

Single- and Multiple-Rising Dose Safety and Tolerability

It has been reported that in pharmacokinetic studies of antipsychotics, there may be differences in the tolerability of these agents in healthy volunteers versus in patients with schizophrenia (Cutler, 2001). In the single- and multiple-rising dose studies, TAK-063 was generally safe and well tolerated in the single- and multiple-rising dose clinical studies. No serious or dose-limiting AEs and no clinically significant changes in hematology, clinical laboratory tests, or electrocardiograms were reported in either HJS or SSS (Tsai et al., 2016; Goldsmith et al., 2017); similar to nonclinical studies, there were no increases in prolactin or glucose (Tsai et al., 2016, Goldsmith et al., 2017, Suzuki et al., 2015), and the most frequent AE in both studies was somnolence. In the multiple-rising dose study, most TAK-063–related AEs in SSS occurred at doses of 30 mg or higher, and most extrapyramidal syndrome (EPS) events in SSS were of mild or moderate severity. In HJS, most TAK-063–related AEs were mild or moderate in severity, and 1 subject in the 20-mg TAK-063 group experienced EPS (Goldsmith et al., 2017). Although the durations of the single- and multiple-rising dose studies were relatively brief, TAK-063 did not produce signs of adverse metabolic effects in HJS or SSS (Tsai et al., 2016; Goldsmith et al., 2017).

As reported in these studies, the safety and tolerability data supported once-daily dosing, and the incidence of EPS was acceptable at TAK-063 doses of 30 mg or less (Tsai et al., 2016; Goldsmith et al., 2017), leading to the decision to continue clinical development (Table 1).

Positron-Emission Tomography Studies

In mice, [^{3}H]T-773 accumulated in brain regions with high PDE10A expression (Harada, et al., 2015b), while PDE10A-knockout mice showed no [^{3}H]T-773 or [^{11}C]T-773 binding in the brain (Harada, et al., 2015b; Tóth et al., 2015; Supplementary Figure S1a). Similarly, [^{11}C]T-773 accumulated in the striatum of monkeys (Harada et al., 2015b; Supplementary Figure S1b). In agreement with these nonclinical studies, [^{11}C]T-773 accumulated to high levels in the striatum of healthy subjects (Takano et al., 2015; Takano et al., 2016b; Supplementary Figure S1c) and showed distribution patterns similar to those observed in animal models. Similar to mice and monkeys, displacement of [^{11}C]T-773 by TAK-063 was demonstrated in healthy subjects (Tóth et al., 2015; Takano et al., 2016a; Takano et al., 2016b).

In nonclinical studies, potential antipsychotic and pro-cognitive effects were demonstrated at a PDE10A occupancy of approximately 26% in animal models (Harada et al., 2015a; Suzuki et al., 2015; Suzuki et al., 2016; Shiraishi et al., 2016). The objective of the clinical PET study was to determine whether a level of occupancy consistent with nonclinical studies could be achieved. Using concentration:occupancy modeling, similar occupancies were predicted to be achieved at a steady state at doses of 10 mg TAK-063 (Macek et al., 2016b). Upon confirmation of PDE10A engagement and the achievement of approximately 30% PDE10A occupancy in human subjects, the decision to proceed to clinical development was consistent with the Go/No Go criteria developed for the compound (Table 1).

Electroencephalogram Studies

Findings from clinical, pharmacological, and genetic studies have led to the proposal of the N-methyl-D-aspartate (NMDA) receptor hypofunction hypothesis to help understand the etiology and pathophysiology of schizophrenia (Snyder and Gao, 2013). In fact, NMDA receptor antagonists such as ketamine, phencyclidine, and MK-801 transiently induce schizophrenia-like symptoms in rats and monkeys, and sub-anesthetic doses of ketamine are an accepted means of modeling schizophrenia symptoms in healthy human subjects (Abi-Saab et al., 1998; Lahti et al, 2001; Frohlich and Van Horn, 2014). TAK-063 has shown antipsychotic-like and pro-cognitive effects in NMDA antagonist-induced rodent models of schizophrenia (Suzuki et al., 2015; Shiraishi et al., 2016); we therefore used ketamine to assess the effect of TAK-063 in these studies. Oral administration of TAK-063 was shown to reduce ketamine-induced increases in resting gamma power in rat nonclinical models. Similarly, ketamine-induced increases in gamma power were reduced by intravenous administration of 0.2 and 0.8 mg/kg TAK-063 in awake monkeys (Tomimatsu et al., 2016).

As in rats and monkeys, ketamine-induced increases in gamma power in the human ketamine challenge study were significantly attenuated in healthy human subjects who received a single dose of 30-mg TAK-063 during the eyes-closed task (n = 14 for 3 mg and 10 mg doses; n = 15 for 30 mg dose), which approximates the steady state exposures of 20 mg (Macek et al., 2016b; Supplementary Figure S2).

Deficits in gamma power have been reported in people with schizophrenia and are thought to be reflective of impairments in cognition (Minzenberg et al., 2010). To explore these effects on EEG activity in patients with schizophrenia, the effects of TAK-063 on EEGs in SSS were assessed as an exploratory endpoint during the phase 1 multiple-rising dose study. TAK-063 increased gamma power in several brain regions of SSS after 40-Hz stimulation on Day 1 (n = 9 for placebo; n = 7 for 100 mg dose; Figure 1), but not on Day 7. These generally consistent results in ketamine studies across healthy human subjects, rodents, and nonhuman primates suggest that TAK-063–attenuated changes in EEG are associated with schizophrenia, and met the Go criteria established for the compound.

Pharmacological and Functional Magnetic Resonance Imaging Studies

Ketamine is reported to induce aberrant cortical activation that is similar to that associated with schizophrenia (Driesen et al., 2013; Hunt and Kasicki, 2013). PhMRI and fMRI signals are changed by ketamine treatment (Deakin et al., 2008; Chin et al., 2011). In rats, the subcutaneous administration of ketamine (10 mg/kg) increased the BOLD signal across many brain regions, and TAK-063 reversed the ketamine-induced BOLD signal changes in the cortex, brainstem, and cerebellum (Tomimatsu et al., 2016).

To extend the phMRI findings in rodents, TAK-063 was investigated in ketamine-treated healthy human subjects (Yurgelun-Todd et al., 2020). Compared with placebo, TAK-063 reduced ketamine-induced increases in BOLD signal across all brain regions analyzed during the working memory task (Figure 2; Supplementary Figure S3) in a dose-dependent manner (Yurgelun-Todd et al., 2020). The most consistent reversal of ketamine-induced effects in fMRI was observed in the 30-mg TAK-063 dose group, which approximates the steady state exposure of 20 mg (Macek et al., 2016b). These outcomes indicate that TAK-063 exhibited antipsychotic-like effects in nonclinical models of psychosis and in healthy human subjects experiencing schizophrenia-like symptoms, consistent with the Go criteria established for the compound (Table 1).

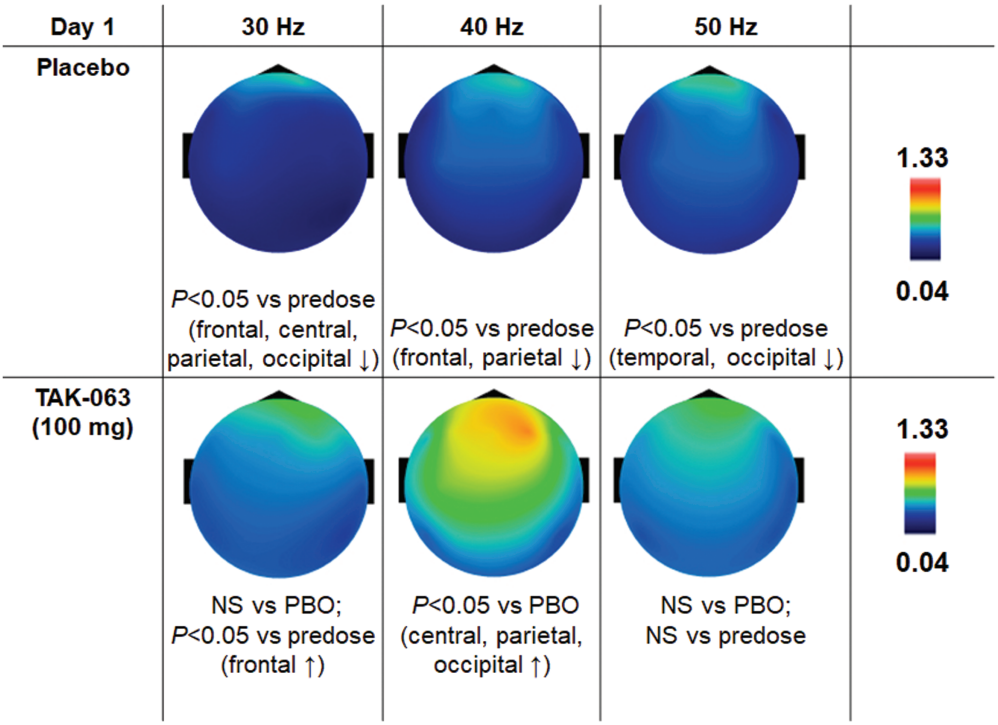


Figure 1. Modulation of gamma power by TAK-063 in subjects with stable schizophrenia. Abbreviations: NS, not significant; PBO, placebo.

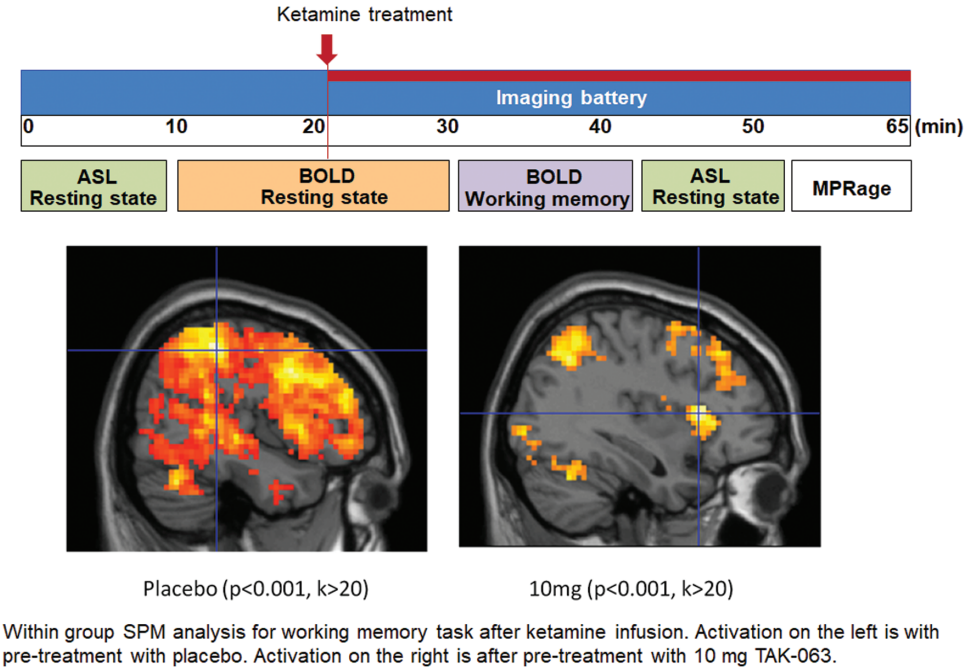
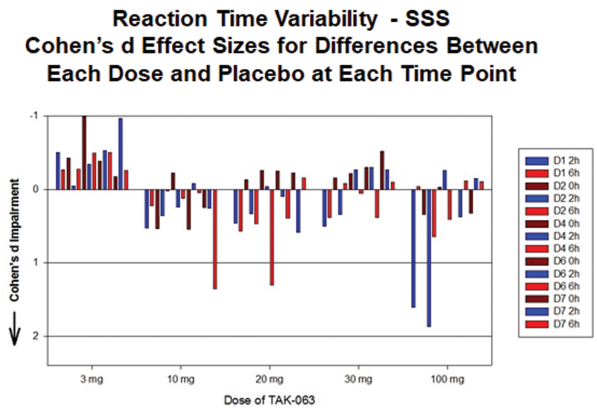


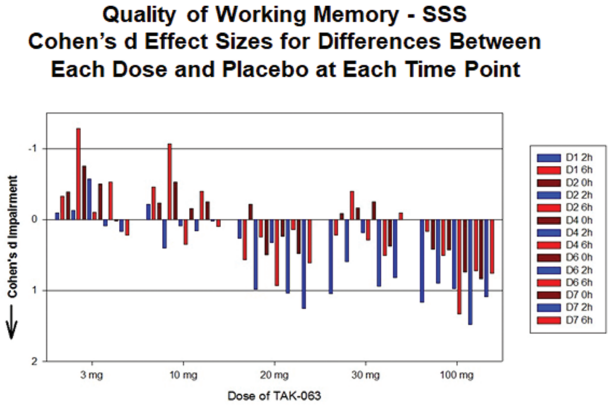
Figure 2. Attenuation of ketamine-induced changes in BOLD signal by TAK-063 in healthy human subjects. Abbreviations: ASL, arterial spin labeling; BOLD, blood oxygen level-dependent; MPRage, 3-dimension magnetization-prepared rapid gradient-echo; SPM, statistical parametric mapping.

Cognition Studies

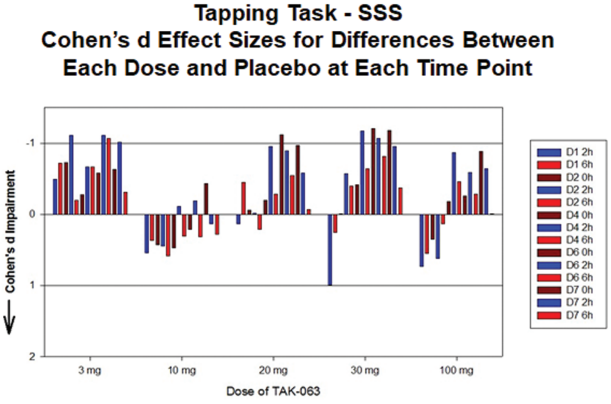
As described above, NMDA receptor antagonists, such as PCP and MK-801, have been known to cause schizophrenia-like symptoms, including cognitive deficits, in clinical and preclinical studies. We attempted to evaluate cognitive functions using animal models based on the NMDA receptor hypofunction hypothesis; however, an accurate assessment of cognitive performance in some tests was affected by NMDA receptor antagonist–induced behavioral changes, such as increased locomotor activity. Thus, in such cases we used naive animals. We focused on evaluating the effects of TAK-063 on multiple cognitive domains associated with schizophrenia, such as recognition memory, spatial working memory, attention and impulsivity,



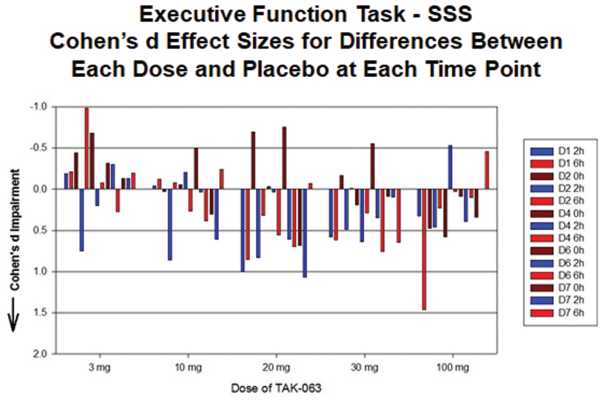
Reaction Time Variability: a composite score created from the addition of variability scores in reaction times from 3 attention tests. Reflects the ability to intently focus attention with minimal levels of fluctuation.



Quality of Working Memory: a composite score created by combining accuracy measures from 2 working memory tasks. Reflects the ability to hold articulatory and spatial information on-line, which is crucial for everyday tasks which involve executive function.



Tapping Task: The ability to press a response button as rapidly as possible for 1 min which reflects psychomotor control.



Executive Function Task: a measure which reflects the ability to rapidly switch between different processing rules.

Figure 3. Effects of TAK-063 on cognition in subjects with stable schizophrenia. Abbreviation: SSS, subjects with stable schizophrenia.

and executive function, using naive rats, PCP-treated rats and mice, and MK-801–treated rats (Shiraishi et al., 2016).

TAK-063 increased recognition memory during the novel object recognition task and increased accuracy rates while decreasing impulsive responses during a 5-choice serial reaction time task in naive rats. Of note, an increase in dopamine transmission is typically associated with increased impulsivity. Importantly, dopamine or a dopamine receptor agonist is thought to affect various neural circuits in the brain; however, PDE10A inhibition by TAK-063 increases striatal cyclic nucleotide levels in both indirect and direct pathways of striatum, which would potentially produce the effect of D2 antagonism along with D1 agonism. Thus, the pharmacological effect of PDE10A inhibition is different from that of dopamine or a dopamine receptor agonist. In PCP-treated mice and MK-801–treated rats, TAK-063 reduced spatial working memory deficits, as assessed by maze tests. An attentional set-shifting task using sub-chronic PCP-treated rats was used to assess executive function; during this task, TAK-063 reversed cognitive deficits in extradimensional shifts (Shiraishi et al., 2016). These pro-cognitive effects were observed at 0.3 mg/kg TAK-063, a dose that achieves PDE10A occupancy and exposures that are consistent with preclinical antipsychotic-like efficacy.

Consistent with the findings in rats, improvements in cognition were observed in subjects with schizophrenia in the phase 1 multiple-rising dose study (Figure 3; Macek et al., 2016c). Improvements over placebo were observed in the 3 mg TAK-063 group in measures of attention-reaction time variability and in the tapping task in the 3 and 30 mg groups. Improvements in the quality of working memory were observed in the 3 and 10 mg groups, and improvements in executive function were observed in the 3 mg TAK-063 group. These findings were consistent with the Go criteria for the compound.

Discussion

The translational strategy for TAK-063 was designed to guide the development of the compound, despite the lack of validated nonclinical models for evaluating PDE10A inhibition in schizophrenia. The main objective was to demonstrate that the effects of TAK-063 were consistent in nonclinical and clinical studies, and the decision to move into phase 2 development

was contingent on consistency between phase 1 results and critical preclinical data. The findings with TAK-063 generally were consistent, with analogous pharmacodynamic effects in nonclinical models and human subjects across studies of EEG, fMRI BOLD, and cognition. TAK-063 also exhibited pharmacokinetics in humans that were supportive of our targeted daily dosing profile. Based on the concordance between nonclinical and clinical studies, the achievement of pharmacologically active exposures, and favorable safety and tolerability profiles in the single- and multiple-rising dose studies, a 20 mg TAK-063 dose was selected for a phase 2 study. Some impairments in cognition were noted in both healthy subjects and subjects with schizophrenia (Macek et al., 2016c; Tsai et al. 2016), which may have been due to the somnolent effects of TAK-063; these effects appeared to decrease over time (Macek et al., 2016c). Interestingly, correlations between improvements in cognition and EEG measures were observed in patients with schizophrenia who received TAK-063 (Macek et al., 2017a). TAK-063 increased gamma power in the EEG (in frontal, central, and parietal regions) and improved cognitive domains, such as reaction time variability, quality of working memory, and tapping tasks, in SSS (data not shown). In our phase 1 program, PET occupancy and ketamine-challenge fMRI BOLD studies were only conducted in healthy male subjects. Thus, based on currently available data, any relation between sex differences and pharmacological effects is not understood and further studies for the investigation of any sex-specific differences are needed.

There remains a need for rigorous translational development strategies to evaluate the pharmacodynamic effects observed in humans relative to those observed in nonclinical models in the development of antipsychotics. Many animal models used to evaluate antipsychotics were not prospectively developed to recapitulate the psychosis observed in humans. Commonly used models, such as the PCP- or methamphetamine-induced inhibition of hyperlocomotion by dopamine antagonists, are considered valid because the dopamine antagonists used clinically to treat schizophrenia exert pharmacological effects in these models.

The relevance of nonclinical models of cognition to the specific cognitive impairments observed in schizophrenia is poorly defined, and using these models to characterize the cognitive effects of drugs represents a challenge. Because of the limitations in models for developing antipsychotic and other central nervous system–related therapies, it is imperative to conduct human studies to demonstrate consistency between these data and those generated in nonclinical experiments.

The comprehensive translational strategy used for TAK-063 effectively guided clinical development, and findings in clinical studies were generally consistent with nonclinical findings. Therefore, TAK-063 was advanced into a phase 2, proof-of-concept study of 20 mg TAK-063 versus placebo in patients with an acute exacerbation of psychotic symptoms. The 20 mg dose was chosen based on the signals detected in nonclinical studies and phase 1 data, and was considered to be the highest dose that was well tolerated and that had demonstrated pharmacodynamic effects consistent with potential antipsychotic effects (Macek et al., 2017b). In conclusion, our approach to the TAK-063 development program provides a framework for the evaluation of new therapeutic approaches, even when relevant nonclinical models are not available.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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Statement of Interest

KS and HK are employees of Takeda Pharmaceutical Company Limited, Fujisawa, Japan. TAM and KA were employees of Takeda Development Center Americas, Inc., Deerfield, IL, at the time of this study.

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