


ORIGINAL ARTICLE

Safety, pharmacokinetics and quantitative EEG modulation of TAK-071, a novel muscarinic M₁ receptor positive allosteric modulator, in healthy subjects

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Aims: TAK-071 is a muscarinic M₁ receptor positive allosteric modulator designed to have low cooperativity with acetylcholine. This was a first-in-human study to evaluate the safety, pharmacokinetics, and pharmacodynamics of TAK-071.

Methods: TAK-071 was administered as single and multiple doses in a randomized, double-blind, placebo-controlled, parallel-group design in healthy volunteers alone and in combination with donepezil. Laboratory, electrocardiogram (ECG) and electroencephalogram (EEG) evaluations were performed. Cerebrospinal fluid and blood samples were taken to evaluate the pharmacokinetics (PK), relative bioavailability and food effect.

Results: TAK-071 was safe and well tolerated, and no deaths or serious adverse events occurred. TAK-071 demonstrated a long mean (% coefficient of variation) half-life of 46.3 (25.2%) to 60.5 (51.5%) hours and excellent brain penetration following oral dosing. Coadministration with donepezil had no impact on the PK of either drug. There was no food effect on systemic exposure. Quantitative EEG analysis revealed that TAK-071 40-80 mg increased power in the 7-9 Hz range in the posterior electrode group with eyes open and 120-160 mg doses increased power in the 16-18 Hz range and reduced power in the 2-4 Hz range in central-posterior areas with eyes open and eyes closed. Functional connectivity was significantly reduced after TAK-071 at high doses and was enhanced with coadministration of donepezil under the eyes-closed condition.

Conclusions: PK and safety profiles of TAK-071 were favorable, including those exceeding expected pharmacologically active doses based on preclinical data. When administered without donepezil TAK-071 was largely free of cholinergic adverse effects. Further clinical evaluation of TAK-071 is warranted.

The authors confirm that the Primary Investigator for this study was Dr Hakop Gevorkyan and that he had direct clinical responsibility for subjects.

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KEYWORDS

Alzheimer's disease, electrophysiology, Parkinson's disease, pharmacokinetic-pharmacodynamic, phase I

1 | INTRODUCTION

Impairment of cholinergic neuronal transmission contributes to cognitive dysfunction in many neurological disorders. Postmortem studies of patients with Alzheimer's disease (AD) have confirmed significant losses in the number of basal forebrain cholinergic neurons and cortical efferents and reductions in the activity of choline acetyltransferase activity.¹ Similarly, degeneration of the cholinergic system in Parkinson's disease (PD) is extensive and contributes to cognitive and other impairments.²

Inhibition of acetylcholinesterase (AChE) by acetylcholinesterase inhibitors (AChEIs) represents a component of the current standard of care for AD and is also the mechanism of action of rivastigmine, the only drug currently approved for Parkinson's dementia in the United States. However, AChEIs have only modest efficacy in these disorders.

From a tolerability perspective, AChEIs increase the concentration of ACh at the synaptic cleft, thus nonselectively increasing activation of all subtypes of ACh receptors, leading to multiple mechanism-related side effects, most commonly diarrhea.³⁻⁵ The development of **muscarinic acetylcholine receptor 1** (M₁R) specific orthosteric agonists has been challenging because of high conservation of the orthosteric site among muscarinic receptors, and targeting an allosteric site allows for better selectivity.⁶ Research has suggested that M1 positive allosteric modulators (PAMs) with a low cooperativity (α -value) such as TAK-071 have better gastrointestinal tolerability than M1 PAMs with higher cooperativity values.⁷⁻⁹

TAK-071 (4-fluoro-2-[(3S,4S)-4-hydroxytetrahydro-2H-pyran-3-yl]-5-methyl-6-[4-(1H-pyrazol-1-yl)benzyl]-2,3-dihydro-1H-indol-1-one) is a novel M₁R PAM. M₁R is predominantly expressed in brain regions related to cognition, such as the frontal cortex and hippocampus. Based on the expression pattern of M₁R and its role in cognitive function, the selective potentiation of activation of this receptor would be expected to result in an amelioration of cognitive deficits. Indeed, in a nonclinical in vivo pharmacology study in rats, 0.3 mg kg⁻¹ TAK-071 ameliorated scopolamine-induced cognitive deficits using a novel object recognition paradigm.⁹ In a translational biomarker study for the effect of TAK-071 in cynomolgus monkeys, TAK-071 suppressed the scopolamine-induced increases in alpha, theta and delta power bands of quantitative electroencephalography (qEEG).⁷ Finally, TAK-071 demonstrated efficacy in rats with partial lesions of forebrain cholinergic neurons using 192-IgG Saporin.¹⁰

The aim of this first-in-human, phase 1 study was to determine the safety, tolerability and pharmacokinetics of single and multiple oral doses of TAK-071 administered alone or in combination with donepezil in non-Japanese and Japanese healthy subjects. Relative

What is already known about this subject

- The muscarinic M₁ receptor (M₁R) is a promising target to treat cognitive impairment associated with Alzheimer's disease and Parkinson's disease.
- TAK-071 is a novel M₁R positive allosteric modulator designed to have low cooperativity to reduce cholinergic side effects that improves cognitive function in rodents.

What this study adds

- This first-in-human study characterized the safety, tolerability and pharmacokinetics (PK) of TAK-071, as well as PK interaction with donepezil following oral dosing. Food effects and relative bioavailability of a tablet formulation and pharmacodynamic effects as determined by quantitative electroencephalography (qEEG) were also evaluated.
- The safety, tolerability, PK and exploratory pharmacodynamic effects based on this study support further clinical development of TAK-071.

bioavailability (RBA), food effects and pharmacodynamic effects on the qEEG profile were also explored.

2 | METHODS

This study was conducted at a single center in the United States (Parexel at Glendale, CA, USA) between 5 May 2016 and 8 June 2017. The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidance for Good Clinical Practice, and approved by an institutional review board (Aspire IRB LLC, Santee, CA, USA). The trial was prospectively registered on www.clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT02769065). All subjects provided written informed consent before enrolment.

2.1 | Study design

This phase 1 study was randomized, double blind and placebo controlled. Japanese subjects were included in this study to prepare for phase 2 studies.

The starting dose of 1 mg was approximately 1/192th of the no-observed-adverse-effect-level in monkeys ($10 \text{ mg kg}^{-1} \text{ day}^{-1}$), the most sensitive species in the 4-week toxicity studies.⁹ The escalating dose range was selected to cover and exceed the minimal pharmacologically active dose (approximately 3 mg).⁹

Single doses of TAK-071 were evaluated in a randomized, double-blind, placebo-controlled, parallel-group, single rising dose design. Healthy subjects were randomly assigned to TAK-071 (1, 3, 9, 20, 40, 80, 120 and 160 mg) or matching placebo in a 3:1 ratio, with eight subjects per dose cohort. Cerebrospinal fluid (CSF) samples were obtained from subjects in the 9 mg cohort. TAK-071 at 40, 60 or 80 mg (or placebo) was coadministered with donepezil 10 mg, with 12 subjects per cohort randomly assigned to TAK-071 + donepezil, donepezil or placebo in a 2:1:1 ratio (see Supporting Information Table S1).

Multiple doses of TAK-071 were evaluated in a randomized, double-blind, placebo-controlled, parallel-group, multiple rising dose design. TAK-071 at doses of 3, 9 or 15 mg (or placebo) once a day (QD) was administered to healthy non-Japanese subjects with eight subjects per cohort (six on TAK-071, two on placebo), and to healthy Japanese subjects with five subjects on TAK-071 and one on placebo per cohort. CSF samples were obtained from subjects in the 15 mg non-Japanese cohort. Multiple doses were limited to no more than 15 mg QD due to an approximately 4-fold accumulation of drug due to the long half-life and the expectation that the corresponding exposures would cover the effective exposure range based on preclinical findings.⁹ TAK-071 at doses of 3, 9 or 15 mg (or placebo) QD was coadministered with donepezil 5 mg to non-Japanese subjects with six subjects receiving TAK-071 and two subjects receiving placebo per cohort. Subjects were pretreated for 21 days with donepezil 5 mg QD before dosing with TAK-071 and donepezil QD (see Supporting Information Table S1). Donepezil was administered at the 5 mg dose in this part of the study based on preclinical findings suggesting synergy with TAK-071.⁹

To evaluate relative bioavailability and food effect, 12 subjects were assigned to one of three possible sequential treatment regimens: ABC, BCA and CAB, where regimen A = fasted state and capsule formulation (10 mg in DIC formulation; see below for details), regimen B = fasted state and tablet formulation (10 mg tablet formulation) and regimen C = fed state and tablet formulation (10 mg tablet formulation). This was an open-label three-period, three-sequence, three-way crossover design in which each subject received all three treatments.

See **Supplemental Methods section in the Supplement** regarding sentinel dosing methods.

2.2 | Study population

Subjects were required to be healthy male or surgically sterile or postmenopausal female, age 18 to 55 years for non-Japanese and 20 to 55 years for Japanese, at least 50 kg with body mass from 18.0 to 30.0 kg m^{-2} . The Japanese subjects were required to be first generation. The subjects were required to have no clinically significant abnormality on medical history, physical examination, electrocardiogram (ECG), vital

signs and laboratory tests, and be free from any illness which could potentially confound the study results. Subjects that had a lifetime history of seizures or an electroencephalogram (EEG) abnormality at screening were excluded in the cohorts where EEG were collected. Prescription and over-the-counter medications and nutraceuticals were prohibited, other than occasional use of acetaminophen/paracetamol or other medication as approved by the sponsor on a case-by-case basis.

2.3 | Treatment

TAK-071 drug substance was manufactured by Ube Industries Limited, Yamaguchi, Japan and supplied to the clinical site and then compounded into a hard gelatin drug-in-capsule (DIC). TAK-071 tablets were manufactured by Takeda Pharmaceutical Company Limited, Osaka, Japan and supplied to the clinical site. Inactive constituents of the tablet formulation included mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate type A, magnesium stearate, hypromellose 2910, titanium dioxide, ferric oxide red and ferric oxide yellow. TAK-071 DIC placebo was a matching empty capsule. Branded or generic donepezil was sourced by the study center. Placebo for over-encapsulated donepezil was a hard gelatin capsule containing microcrystalline cellulose.

2.4 | Safety assessments

Safety measurements included adverse events (AEs), physical examinations, vital signs (body temperature, respiration, heart rate and blood pressure), clinical laboratory evaluations, pregnancy monitoring and ECG procedures.

Subjects from selected cohorts underwent safety scalp EEG during rest with eyes closed, eyes open, hyperventilation and photic stimulation, both at baseline before drug administration and after drug administration. Data collected from 30 subjects who received a single dose of either TAK-071 alone (at 120 or 160 mg, $n = 6$ per dose) or in combination with donepezil (at 40, 60 or 80 mg TAK-071 plus 10 mg donepezil, $n = 6$ per dose), and respective placebo subjects ($n = 2$ per cohort for TAK-071 alone and $n = 3$ per cohort for TAK-071 with donepezil) were analyzed (see the **Supplemental Methods section in the Supplement**). EEG records were manually reviewed by a neurologist to evaluate for abnormalities.

2.5 | Pharmacokinetic analysis

Serial blood samples for determination of plasma TAK-071 and donepezil concentrations were collected from all cohorts. CSF samples (1.25 mL per sample) for determination of TAK-071 were collected predose and at 0.5, 2, 4, 6 and 12 hours postdose in the 9 mg single dose cohort and predose and at 4, 8, 12, 24 and 36 hours post last dose in the 15 mg multiple dose cohort. See the **Supplemental Methods section in the Supplement** for further details regarding the

method of TAK-071 pharmacokinetics (PK) sample collection and concentration determination. Data were analyzed by a noncompartmental analysis using WinNonlin Professional software (Version Phoenix 6.4, Pharsight Corporation, Mountain View, CA, USA).

2.6 | EEG data collection

EEGs were recorded from 19 electrodes attached to the scalp according to the international 10-20 system (see the **Supplemental Methods section in the Supplement**). A 10-minute wake EEG recording with eyes closed for 5 minutes and eyes open for 5 minutes was performed. Predose EEGs were conducted approximately 1 hour before dosing with TAK-071. In TAK-071 dosing alone cohorts, postdose EEGs were conducted approximately 25 hours after dosing with TAK-071. In the codosing cohorts, postdose EEGs were conducted approximately 23 hours after dosing with TAK-071; following a single donepezil dose at 24 hours post TAK-071 dosing, additional EEGs were collected approximately 5 hours after dosing with donepezil (ie, approximately 29 hours after dosing with TAK-071).

2.7 | qEEG data analysis

In addition to standard power spectral analysis, preprocessed EEG data were also used to explore a possible change in brain functional connectivity and synchrony using weighted phase lag index (wPLI), which assesses the phase “lagging” or “leading” consistency between each pair of EEG electrodes.^{11,12} The data from three cohorts of 40 mg, 60 mg and 80 mg of TAK-071 were combined into the low-dose group, and those from 120 mg and 160 mg TAK-071 dosing groups combined into the high-dose group. For qEEG power statistical analysis, cluster-based permutation statistics were used across all electrodes and frequencies from 1 to 40 Hz.^{13,14} For qEEG functional connectivity statistical analysis, the recently developed method known as PeSCAR¹³ was extended to assess sensor-level connectivity. Cluster-based statistics using two-sided paired *t*-tests and 1000 permutations were used to compare postdose vs predose for each group in all frequencies within the 1-40 Hz range for all EEG electrode pairs. The output of cluster statistics is a *P* value, a cluster mask (either 0 or 1), which shows at which frequencies the cluster is significant, and cluster mass, which is the sum of the *t* values inside the cluster mask (see the **Supplemental Methods section in the Supplement** for additional detail).

2.8 | Statistical analysis

Baseline, postdose and change from baseline to postdose laboratory data (hematology, chemistry and urinalysis), vital signs, ECG parameters and Bristol Stool Form scale scores were summarized by trial cohorts as well as percentage of subjects who meet internal markedly abnormal value criteria.

PK parameters were summarized using descriptive statistics. Dose proportionality was assessed using the empirical power law model. Dose linearity was examined in the event that dose proportionality cannot be established by using a simple linear regression on the exposure parameter. The time to steady state was assessed by fitting trough concentration values to a nonlinear mixed effects model to predict the time to achieve 90% of the steady-state trough concentrations separately for each dose. Time invariance of TAK-071 was assessed by comparing AUC₂₄ for the last day of dosing to the AUC_∞ for day 1 using analysis of variance with a random effect for subject and a fixed effect for day.

The effect of TAK-071 on the natural log-transformed steady-state C_{max} and AUC₂₄ of donepezil was assessed with a linear mixed-effects model; point estimates for geometric means and geometric mean ratios with 90% confidence intervals were determined.

The relative bioavailability of the tablet formulation compared to the reference drug in capsule formulation and the effect of food on the plasma PK of TAK-071 were assessed using ANOVA on the natural logarithms of C_{max} and AUC_∞, with a random factor for subject nested within sequence and fixed factors for sequence, period and regimen.

2.9 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.¹⁵

3 | RESULTS

3.1 | Subject demographic characteristics

A total of 177 subjects were randomized and received at least one dose of study drug (the safety set). See Supporting Information Table S1. Only one subject discontinued.

All analyses are based on the safety set. The demographic and baseline characteristics were generally similar across treatment groups (Table 1).

3.2 | Safety and tolerability

No deaths or serious AEs were reported. Most treatment emergent adverse effects (TEAEs) were mild or moderate. One subject in the RBA/food effect cohort had a TEAE of syncope during regimen A (TAK-071 10 mg capsule, fasting), which was rated as severe by the investigator and resolved without treatment. One subject who received multiple doses of TAK-071 15 mg discontinued due to mild headache, which resolved.

TABLE 1 Summary of demographic and baseline characteristics: all cohorts

	Cohort type					
	SRD without DPZ n = 64	SRD with DPZ n = 35	Non-Japanese MRD n = 24	Japanese MRD n = 18	MRD with DPZ n = 24	RBA/food effect n = 12
Age (yr)						
Mean (SD)	34.4 (8.38)	36.4 (9.36)	35.3 (7.70)	36.6 (7.71)	36.8 (7.10)	33.5 (7.15)
Min, max	18, 55	25, 55	20, 49	27, 51	23, 52	27, 50
Gender (n [%])						
Male	59 (92.2)	29 (82.9)	24 (100.0)	18 (100.0)	24 (100.0)	12 (100.0)
Female	5 (7.8)	6 (17.1)	0	0	0	0
Ethnicity (n [%])						
Hispanic or Latino	16 (25.0)	12 (34.3)	6 (25.0)	0	5 (20.8)	2 (16.7)
Not Hispanic or Latino	48 (75.0)	23 (65.7)	18 (75.0)	18 (100.0)	19 (79.2)	10 (83.3)
Race (n [%])						
Asian	5 (7.8)	2 (5.7)	0	18 (100.0)	2 (8.3)	0
Black	17 (26.6)	8 (22.9)	7 (29.2)	0	9 (37.5)	3 (25.0)
Native Hawaiian or other Pacific islander	3 (4.7)	1 (2.9)	0	0	0	0
White	36 (56.3)	23 (65.7)	15 (62.5)	0	12 (50.0)	8 (66.7)
Multiracial	3 (4.7)	1 (2.9)	2 (8.3)	0	1 (4.2)	1 (8.3)
Height (cm)						
Mean (SD)	175.1 (6.86)	174.5 (9.64)	174.8 (7.17)	173.8 (7.01)	174.1 (7.63)	176.6 (6.17)
Weight (kg)						
Mean (SD)	79.29 (10.187)	77.09 (10.857)	78.58 (11.437)	70.48 (11.354)	77.86 (9.150)	79.70 (9.275)
BMI (kg/m ²)						
Mean (SD)	25.81 (2.643)	25.30 (2.351)	25.66 (2.984)	23.26 (2.774)	25.67 (2.451)	25.55 (2.665)
Min, max	18.4, 30.0	19.2, 29.9	18.1, 30.0	19.0, 28.9	20.2, 29.8	19.8, 29.6

Abbreviations: BMI, body mass index; DPZ, donepezil; MRD, multiple-rising dose; RBA, relative bioavailability; SRD, single-rising dose.

As shown in Table 2, in the single rising dose (SRD) cohorts without donepezil, the most common TEAEs among subjects receiving any dose of TAK-071 were headache and AEs related to lumbar puncture. In the multiple rising dose (MRD) cohorts without donepezil, the most common TEAE among subjects receiving any dose of TAK-071 was headache. Cholinergic AEs were notably absent in these subjects. In contrast, cholinergic AEs were observed with donepezil and TAK-071 in combination with donepezil.

In the RBA/food effect cohort, TEAEs of syncope, toothache, insomnia and abnormal dreams were each reported by one of 12 subjects (8.3%).

Markedly abnormal values for laboratory parameters were few in number; they were either noted before the administration of study drug or resolved by the next study visit. There were no concerning trends regarding the subjects' QT values in any of the dose groups. There were no clinically significant changes observed on physical examination or on stool frequency or consistency.

Clinical EEG was performed for subjects receiving single doses of TAK-071120 and 160 mg and for subjects receiving single doses

of 10 mg donepezil plus TAK-071 40, 60 or 80 mg. A total of 54 subjects were evaluated. The only EEG abnormality that was noted after but not before the administration of TAK-071 was generalized slowing in the theta range. Two subjects that received 160 mg TAK-071 and one subject in the same cohort who received placebo demonstrated this finding, which was not considered to be of clinical significance. Although one subject showed spikes and sharp waves at screening and was excluded, there were no other instances of this abnormality before or after administration of TAK-071, donepezil or TAK-071 and donepezil.

3.3 | Pharmacokinetics

Following single (1 to 160 mg) and multiple (3 to 15 mg QD) oral doses of TAK-071, systemic exposure (C_{max} and AUC) to TAK-071 increased slightly less than dose proportionally, as the point estimates for slopes in the empirical power law model were 0.784 to 0.904. Mean (% coefficient of variation) TAK-071 $t_{1/2z}$ was long, ranging

TABLE 2 Most commonly observed AEs in the SRD and MRD cohorts

Cohorts	Treatment	N	Any TEAEs	Headache	Back pain	Post LP syndrome	Neck pain	Abdominal pain	Nausea	Vomiting	Diarrhea	Dizziness
SRD	Pooled placebo	16	4	0	0	1	0	0	0	0	0	0
	1 mg TAK	6	2	1	0	0	0	0	0	0	0	0
	3 mg TAK	6	0	0	0	0	0	0	0	0	0	0
	9 mg TAK	6	4	3	2	2	2	0	0	0	0	0
	20 mg TAK	6	2	0	0	0	0	0	0	0	0	0
	40 mg TAK	6	0	0	0	0	0	0	0	0	0	0
	80 mg TAK	6	1	0	0	0	0	0	0	0	0	0
	120 mg TAK	6	0	0	0	0	0	0	0	0	0	0
	160 mg TAK	6	2	0	1	0	0	0	0	0	0	0
		Pooled placebo	6	3	2	0	0	0	0	0	0	0
MRD	3 mg TAK	6	1	1	0	0	0	0	0	0	0	0
	9 mg TAK	6	1	0	0	0	0	0	0	0	0	0
	15 mg TAK	6	3	2	0	0	0	0	0	0	0	0
		Pooled placebo	6	2	0	0	0	0	0	0	0	0
MRD + DON	3 mg TAK + DON	6	2	2	0	0	0	0	0	0	0	0
	9 mg TAK + DON	6	3	1	0	0	0	2	0	0	0	0
	15 mg TAK + DON	6	3	1	0	0	0	1	0	0	0	0
		Pooled placebo	3	2	0	0	0	0	0	0	0	0
MRD (Japanese)	3 mg TAK	5	2	0	0	0	0	0	0	0	0	0
	9 mg TAK	5	2	1	0	0	0	0	0	0	0	0
	15 mg TAK	5	3	2	0	0	0	0	0	0	0	0
		Placebo + placebo	9	4	0	0	0	0	0	0	0	1
SRD + DON	Placebo + DON	9	5	0	0	0	0	0	3	0	1	0
	40 mg TAK + DON	5	4	0	0	0	0	0	2	0	1	2
	60 mg TAK + DON	5	6	0	0	0	0	0	6	4	0	0
		80 mg TAK + DON	5	5	0	0	0	0	4	3	2	0

Abbreviations: DON, donepezil; TAK, TAK-071; LP, lumbar puncture.

from 46.3 (25.2%) to 60.5 (51.5%) hours. The mean steady-state plasma concentration-time profiles of TAK-071 are provided in Figure 1.

Multiple-dose PK parameters (t_{max} , C_{max} , AUC_{τ} and accumulation ratios) were similar between non-Japanese and Japanese subjects (Table 3). Using a nonlinear mixed-effect approach to model TAK-071 trough concentrations, steady-state TAK-071 plasma concentrations were reached after approximately 14 and 9 days of QD dosing for non-Japanese and Japanese subjects, respectively. The ANOVA analysis suggested a slight time dependency for the PK of TAK-071, especially at higher doses. The ratios of TAK-071 AUC_{τ} at steady state to AUC_{∞} after a single dose were 0.777 to 0.958, with the lowest ratio (0.777) observed at the highest dose (15 mg).

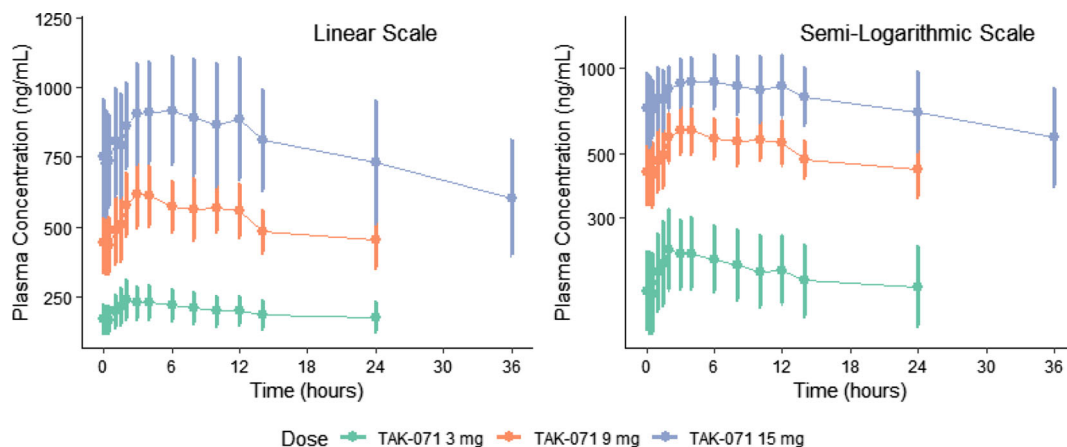
Donepezil 5 mg QD for 21 days did not change the PK of TAK-071 following multiple-dose treatment of 3-15 mg QD. Treatment with TAK-071 40-80 mg (single dose) or 3-15 mg QD had little effect on the plasma PK of donepezil (Table 4).

Single doses of TAK-071 9 mg and multiple doses of TAK-071 15 mg QD resulted in mean AUC_{12} and AUC_{36} in CSF of 13.7 and 361 $h \cdot ng \cdot mL^{-1}$, respectively. These values were 0.91% and 1.14% of the corresponding AUC values in plasma. Because TAK-071 is highly bound to plasma proteins (99.6%), the AUC values in CSF were approximately 2.3- to 2.9-fold greater than the corresponding free TAK-071 AUC values in plasma, indicating excellent brain penetration of TAK-071 following oral administration.

Minimal urinary excretion of TAK-071 (<1%) was observed after both single- and multiple-dose TAK-071 with a mean CL_R ranging between 0.00194 and 0.00543 L/h for non-Japanese subjects and 0.00249 and 0.00343 L/h for Japanese subjects.

TAK-071 systemic exposures for the tablet and capsule formulation were not significantly different. The ratios of the least squares geometric means of TAK-071 C_{max} and AUC_{∞} between tablet and capsule formulations under fasted conditions were approximately 1.15 and 0.95, respectively; the 90% CIs of the ratios were contained within the equivalence limits of 0.80 to 1.25.

Non-Japanese subjects



Japanese subjects

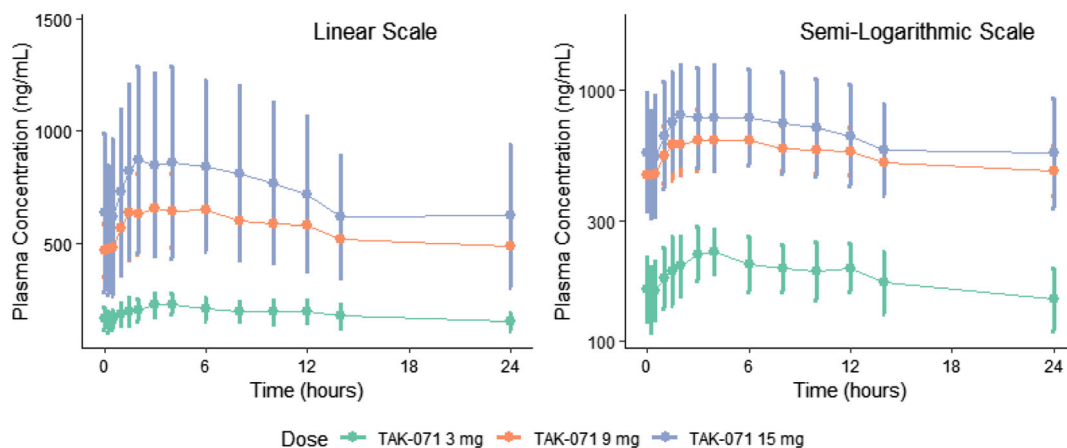


FIGURE 1 Mean plasma steady-state concentration-time curves of TAK-071 (linear [left panels] and semi-log [right panels]) following multiple oral administration of TAK-071 3, 9 or 15 mg to healthy non-Japanese subjects or Japanese subjects. Cohort number is indicated in the figure legend

TABLE 3 Summary of plasma PK parameter estimates of TAK-071 following multiple oral administration of TAK-071 3, 9 or 15 mg QD to healthy non-Japanese or Japanese subjects

TAK-071 dose (mg QD) [n]		t_{\max} (h)	C_{\max} (ng mL ⁻¹)	$C_{\text{av,ss}}$ (ng mL ⁻¹)	AUC_{τ} (h*ng mL ⁻¹)	$R_{\text{ac}(C_{\max})}$	$R_{\text{ac}(AUC)}$
TAK-071 MRD treatment, non-Japanese subjects							
3 [6]	Mean ^a	2.50	245	199	4783	3.30	3.57
	SD ^b	2.00-6.00	66.16	52.42	1258.0	0.5916	0.7177
	CV%	...	27.1	26.3	26.3	17.9	20.1
9 [6]	Mean ^a	4.00	647	522	12 520	3.58	3.71
	SD ^b	2.00-12.05	95.03	88.86	2132.7	1.296	1.192
	CV%	...	14.7	17.0	17.0	36.2	32.1
15 [5]	Mean ^a	3.00	936	830	19 920	3.54	3.78
	SD ^b	1.00-12.00	174.0	190.2	4563.7	0.8632	1.263
	CV%	...	18.6	22.9	22.9	24.4	33.4
TAK-071 MRD treatment, Japanese subjects							
3 [5]	Mean ^a	4.00	236	185	4439	2.96	2.97
	SD ^b	3.00-4.00	49.24	47.32	1135.6	0.2618	0.3875
	CV%	...	20.9	25.6	25.6	8.8	13.0
9 [5]	Mean ^a	3.00	680	561	13 450	3.33	3.24
	SD ^b	1.50-6.05	182.0	126.0	3024.3	0.7483	0.5661
	CV%	...	26.8	22.5	22.5	22.5	17.5
15 [5]	Mean ^a	3.00	895	714	17 120	3.29	3.10
	SD ^b	1.50-6.00	420.1	337.0	8088.8	1.541	1.421
	CV%	...	46.9	47.2	47.2	46.9	45.9

Abbreviations: %CV, percent coefficient of variation; AUC_{τ} , area under the plasma concentration-time curve during a dosing interval; $C_{\text{av,ss}}$, average plasma concentration at steady state; C_{\max} , maximum observed plasma concentration; MRD, multiple-rising dose; PK, pharmacokinetic; QD, once daily; $R_{\text{ac}(AUC)}$, accumulation ratio (based on AUC); $R_{\text{ac}(C_{\max})}$, accumulation ratio (based on C_{\max}); t_{\max} , time of first occurrence of C_{\max} .

^aMedian is presented for t_{\max} .

^bMin-max is presented for t_{\max} .

TABLE 4 Assessment of the effect of TAK-071 on steady-state PK parameters of donepezil

TAK-071 dose	Parameter (unit)	Day 21 n	Day -1 n	LS mean estimates on logarithmic scale		Comparison (day 21/day -1)	
				Day 21	Day -1	Point estimate	90% CI
3	C_{\max} (ng mL ⁻¹)	8	8	3.276	3.128	1.160	(1.072, 1.256)
	AUC_{τ} (h*ng mL ⁻¹)	8	8	6.156	6.012	1.155	(1.059, 1.260)
9	C_{\max} (ng mL ⁻¹)	8	8	3.386	3.418	0.969	(0.914, 1.028)
	AUC_{τ} (h*ng mL ⁻¹)	8	8	6.317	6.264	1.055	(0.989, 1.126)
15	C_{\max} (ng mL ⁻¹)	8	8	3.235	3.120	1.121	(1.027, 1.224)
	AUC_{τ} (h*ng mL ⁻¹)	8	8	6.071	5.970	1.106	(1.014, 1.207)

Abbreviations: AUC_{τ} , area under the plasma concentration-time curve during a dosing interval; C_{\max} , maximum observed plasma concentration; PK, pharmacokinetic. A linear mixed-effect model on the natural log (ln)-transformed parameters was performed with day as a fixed effect and subject as a random effect. The least squares means and difference of least squared means for the ln-transformed parameters was exponentiated to obtain the geometric means and ratios of geometric means on the original scale.

No food effect was observed on TAK-071 systemic exposure for the tablet formulation of TAK-071. The ratios of the least squares geometric means of TAK-071 C_{\max} and AUC_{∞} under fasted and fed conditions (fed/fasted) were approximately 0.97 and 1.09,

respectively; the 90% CIs of the ratios were contained within the equivalence limits of 0.80 to 1.25. However, median t_{\max} was significantly ($P < .05$) delayed for the TAK-071 tablet administered under fed conditions versus fasted conditions (6 and 2 hours, respectively).

3.4 | Pharmacodynamics

3.4.1 | qEEG power

Under both eyes-open and eyes-closed conditions, placebo and placebo + donepezil did not influence predose vs postdose qEEG power. Under the eyes-open condition, low single doses of TAK-071 (40, 60 and 80 mg) significantly increased power in the 7-9 Hz range in the posterior electrode group ($P = .04$; Figure 2A). This effect was enhanced in the low-dose TAK-071 + donepezil eyes-open condition ($P = .01$ in the 7-9 Hz range, postero-central electrodes; $P = .01$ in the 16-18 Hz range central electrodes; Figure 2B). Conversely,

low-dose TAK-071 + donepezil decreased power in the 1-3 Hz range in central-posterior areas in the eyes-open condition (Figure 2D). In the eyes-closed condition, low-dose TAK-071 alone was not significant (Figure 2F), however, low-dose TAK-071 + donepezil increased global power in the 7-9 Hz range (Figure 2G), showing similar effects to the eyes-open condition (Figure 2B). Consistently, high single doses (120 and 160 mg) of TAK-071 alone increased global power in the 16-18 Hz range and reduced power in the 2-4 Hz range in central-posterior areas in both eyes-open (Figure 2C,E) and eyes-closed (Figure 2H,I) conditions.

Lastly, within the low-dose TAK-071 cohorts, we attempted to identify the minimum dose that would significantly affect qEEG

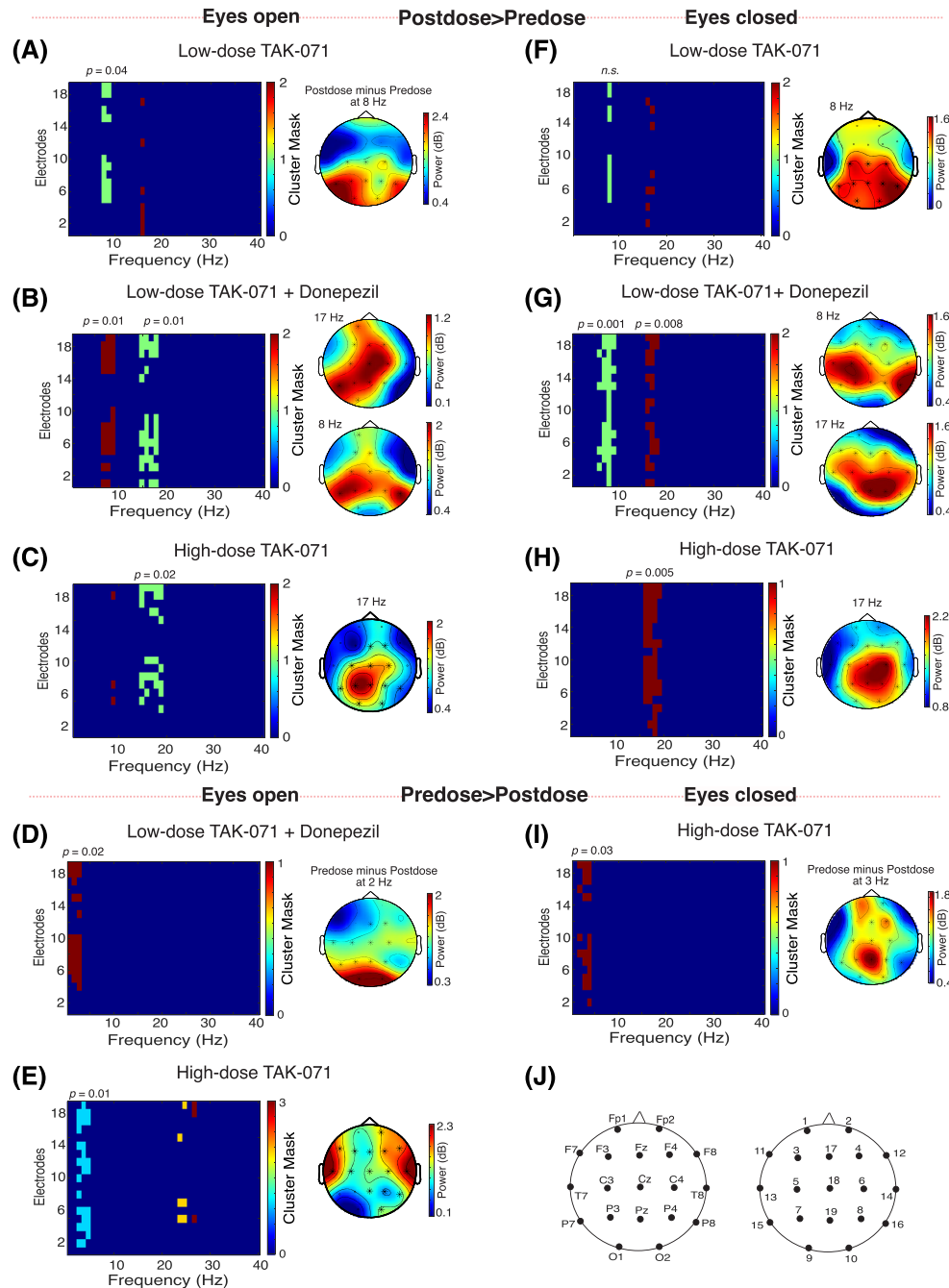


FIGURE 2 Cluster masks and power topography of significant differences between predose and postdose qEEG data under eyes-open (left column) and eyes-closed conditions (right column). Postdose > predose results are shown in panels A-C and F-H, and predose > postdose results are shown in panels D-E and I. (A, F) low-dose (40-80 mg) TAK-071, (B, G) low-dose TAK-071 + donepezil, (C, H) high-dose (160-180 mg) TAK-071. The results from A-C under eyes-open and F-H under eyes-closed conditions show increased power in postdose compared to predose, and the topography was estimated via postdose minus predose at certain frequency bands within the significant cluster mask. (D-E) Increased power in predose compared to postdose under eyes-open and (I) high-dose TAK-071 under the eyes-closed condition. (J) Electrode names and their locations number used in the y axis of the cluster masks in A-I

power. To this end, the power values within the first cluster mask in the eyes-open condition in Figure 2A and eyes-closed condition in Figure 2F were extracted. Power values in predose data were subtracted from postdose data for each electrode and frequency bin within the corresponding cluster mask and then averaged. Despite the small sample size and relatively high variation, one-sided tests for mean power values for each dose under two different conditions (eyes-open and eyes-closed) were statistically significantly greater than predose (or baseline) after the correction for multiple comparisons for both the 60 mg (eyes-closed) and 80 mg (eyes-open and eyes-closed) doses (Figure 3A). In addition, we pooled both eyes-open and eyes-closed data together and used a linear mixed model with dose level and condition as fixed factors and subject as a random effect. We found statistically significant differences from predose for the 60 and 80 mg doses ($P = .0005$ and 0.0002 , respectively; Figure 3B). The linear effect of dose as estimated from the mixed effect model was close to significant ($P = .0577$).

3.5 | qEEG functional connectivity

We next examined brain network alteration induced by TAK-071 to assess changes in the strength of connections between cortical and subcortical areas, based in part on previous findings of reduced functional connectivity after donepezil administration.¹⁶

The results of functional connectivity under eyes-open are presented in Supporting Information Figure S3. Under the eyes-closed condition, the qEEG placebo group did not show a change in postdose vs predose qEEG functional connectivity (Figure 4A). However, the

placebo + donepezil group showed marginal significance of reduced functional connectivity (Figure 4B) that mostly involved beta band synchronization. This effect was increased following low-dose TAK-071 ($P = .02$; Figure 4C) in the beta band, with a peak around 23 Hz. Postdose vs predose differences were most pronounced under the low-dose TAK-071 + donepezil condition ($P = .01$; Figure 4D) in the alpha band near 12 Hz and the beta band near 23 Hz. Under the eyes-closed condition, high-dose TAK-071 did not influence functional connectivity. This lack of effect was most likely the result of a strong power difference in the predose vs postdose conditions that confounded the wPLI analysis.¹⁷

To summarize the drug effect on functional connectivity, the values within the cluster mask (left panel, Figure 4) and significant electrode pairs (right panel, Figure 4) were extracted. Functional connectivity values of predose were subtracted from postdose within each electrode pair and across frequencies inside the cluster mask and then averaged within each subject. Using a one-sample *t*-test we tested whether the mean is different from zero for various drug combinations as shown in Figure 5. Reduced functional connectivity was observed with donepezil alone ($P = .04$), low-dose TAK-071 alone ($P = .02$) and the combination had more pronounced effects than either drug alone ($P = .01$).

4 | DISCUSSION

This was a single-center first-in-human Phase I study that sought to determine the safety, tolerability, PK and central pharmacodynamic effects of TAK-071 in healthy subjects. Overall, TAK-071 was safe

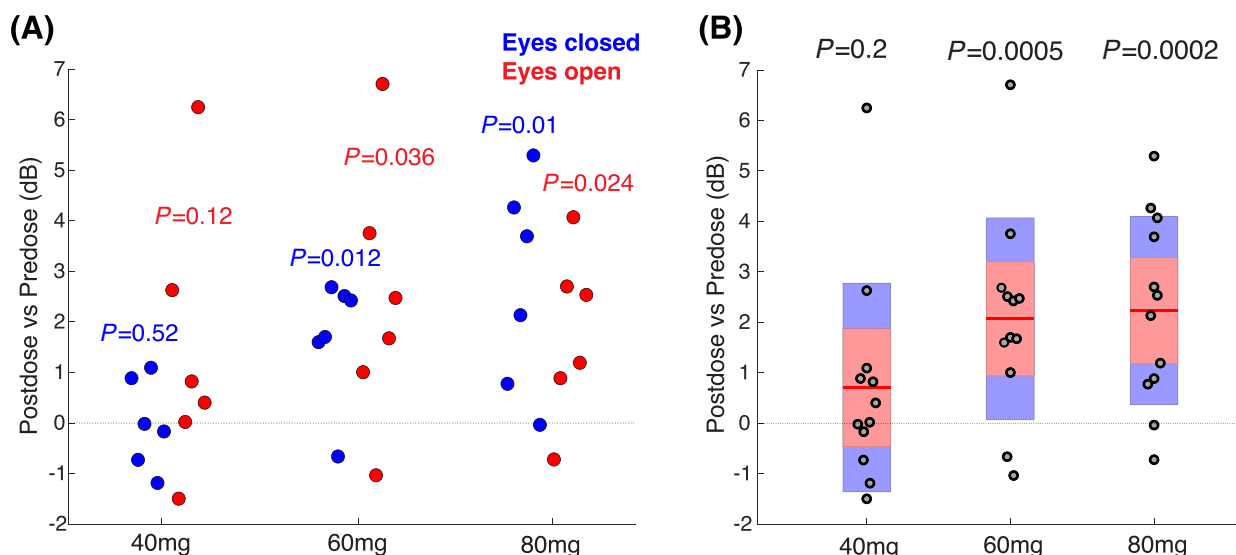


FIGURE 3 Predose data was subtracted from postdose within the cluster mask and then averaged, giving one value for each subject. (A) Individual subject data from both eyes open and eyes closed marked with different colors for each dose group with corresponding uncorrected *P* value. (B) The same data from (A) but showing eyes open and eyes closed data pooled together. Corresponding *P* value from linear mixed model is shown for each dose group separately. The red line in each box plot is the mean, the shaded red area is the 95% confidence interval and the blue shaded area is one standard deviation

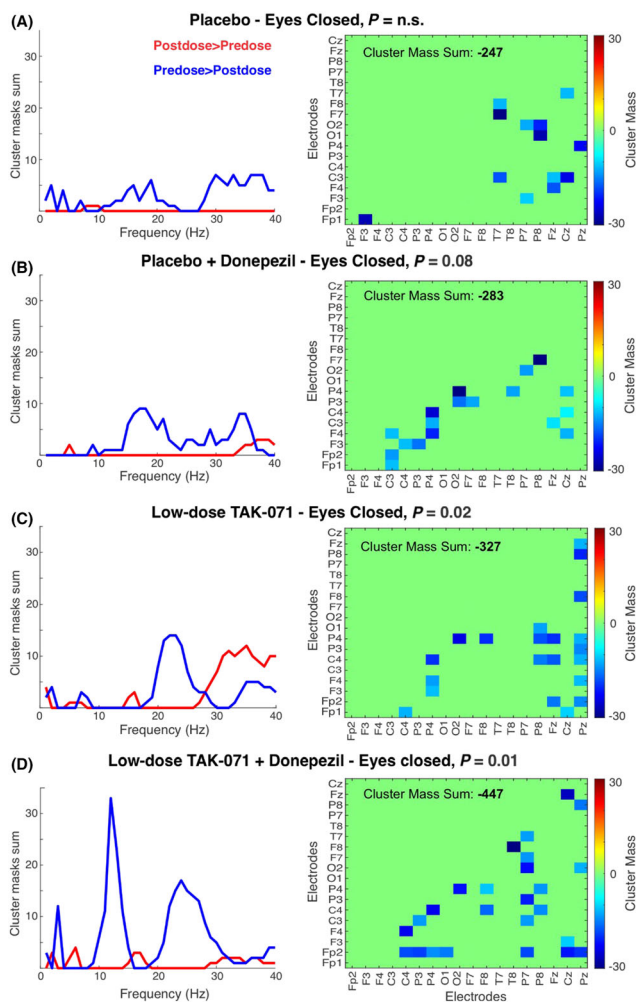


FIGURE 4 Cluster masks sum and connectivity matrix of significant differences between postdose and predose qEEG data under eyes-closed conditions for (A) placebo, (B) placebo + donepezil, (C) low-dose (40, 60 and 80 mg) TAK-071 and (D) low-dose (40, 60 and 80 mg) TAK-071 + donepezil. Note that in each plot the blue color means functional connectivity is reduced in postdose compared to predose

and well tolerated at the doses tested. There were no serious AEs or deaths. The doses in the MRD cohorts and the 20-160 mg SRD cohorts yielded exposures that were equal to or greater than the pharmacologically active exposures tested in previous non-clinical pharmacological studies in mouse and rat models of cognitive dysfunction.^{9,10}

Following single and multiple doses, the systemic exposure to TAK-071 (C_{max} and AUC) increased slightly less than dose proportionally within the tested dose range. Mean TAK-071 $t_{1/2z}$ was long, ranging from 46.3 to 60.5 hours, and steady-state TAK-071 plasma concentrations were reached within 14 days of QD dosing. TAK-071 exhibited a wide range of T_{max} values (1-12 hours) in non-Japanese subjects during multiple dosing, likely due to low aqueous solubility of TAK-071 leading to variability in oral absorption. The ratios of AUC in

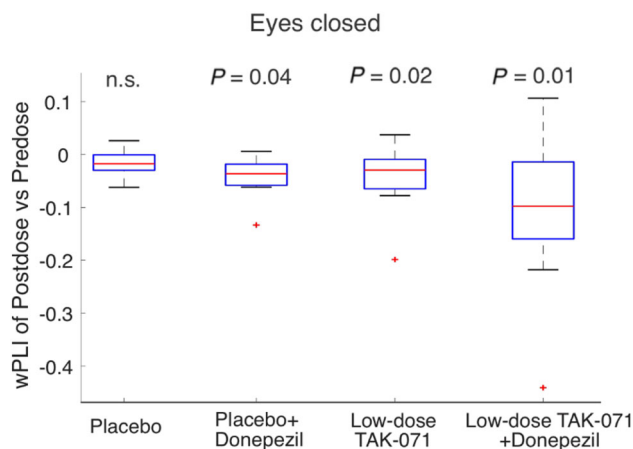


FIGURE 5 Comparison of the weighted phase lag index (wPLI) difference in postdose vs predose averaged across subjects under different drug doses for the eyes-closed condition. The boxplot shows the median and the 25th and 75th percentiles of the data

CSF over the corresponding free plasma AUC were 2.3- to 2.9-fold, indicating excellent brain penetration of TAK-071. The brain penetration of TAK-071 is similar to or better than available medications that treat the symptoms of Alzheimer's disease, ie, donepezil, galantamine, rivastigmine and memantine.¹⁸⁻²¹ To reach the site of action in the brain, these treatments attained CSF to free plasma exposure ratio of approximately 0.4 to 3.7 following oral administration. Urinary excretion of TAK-071 was minimal (<1%) after single- and multiple-dose TAK-071.

There were no PK interactions between TAK-071 and donepezil. The PK parameters of TAK-071 were similar between cohorts with and without donepezil; treatment with TAK-071 had little effect on the plasma PK parameters of donepezil. The PK parameters were similar between non-Japanese and Japanese populations, supporting justification of the same doses for Japanese and non-Japanese populations in future clinical trials.

TAK-071 systemic exposure (C_{max} and AUC_{∞}) for the tablet and capsule formulation was not significantly different (90% CI of the ratios contained within 0.80 to 1.25), demonstrating the bioequivalence of these two formulations. No food effect was observed on TAK-071 systemic exposure (C_{max} and AUC_{∞}) for the tablet formulation of TAK-071, suggesting no restriction of meal times relative to TAK-071 dosing in future patient trials.

Effects of TAK-071 on qEEG power were observed under eyes-open and eyes-closed conditions, which were enhanced when low-dose TAK-071 was coadministered with donepezil. In addition, a significant difference in wPLI was observed following administration of TAK-071 with donepezil. Donepezil increases cholinergic tone indiscriminately, whereas an M1 PAM such as TAK-071 should selectively increase postsynaptic response to acetylcholine where M1 receptors are expressed. Given that previous EEG-fMRI data have shown reduced functional connectivity between brain areas following

application of donepezil,¹⁶ our findings that TAK-071 enhanced this effect is consistent. Previous studies have consistently found that AD patients present with increased resting state cortical theta power and decreased alpha-beta power.^{22–25} Furthermore, increased cortical theta power is associated with drowsiness.²⁶ Here, we demonstrate that during a brief period of resting state, TAK-071 reduced theta power and enhanced alpha-beta power in healthy subjects (Figure 2), which may suggest a beneficial impact in AD and perhaps increasing wakefulness. Numerous studies have also suggested an association between increased beta power/coherence and top-down processing (eg, attentional control) (see Fries²⁷ for review). Considering this hypothesis, increased power in beta suggests that TAK-071 may enhance higher-order cognitive processing, but future studies including patients and cognitive tasks are needed to confirm these interpretations.

TAK-071 was designed to maximize gastrointestinal tolerability by minimizing cooperativity.⁵ Allosteric modulators like TAK-071 bind to a receptor site that is distinct from the orthosteric ligand binding site and potentiate the actions of the orthosteric ligand. Allosteric modulator binding increases the affinity of the orthosteric ligand for the orthosteric site (binding cooperativity factor, α).⁶ TAK-071 was designed to minimize α to maximize tolerability. TAK-071 was found to have a low tendency to cause cholinergic side effects in rodents,⁹ and the safety and tolerability results reported here suggest that TAK-071 is also safe and well tolerated in humans. Notably, gastrointestinal AEs that are commonly observed with cholinergic agents such as nausea, vomiting and diarrhea were uncommon with TAK-071 alone and were primarily observed with donepezil or donepezil in combination with TAK-071. These results support further development of TAK-071 for indications involving dysfunction of cholinergic signaling.

5 | CONCLUSIONS

TAK-071 was safe and well tolerated, and no deaths or serious AEs occurred at all doses, including those exceeding expected pharmacologically active doses based on preclinical data. TAK-071 demonstrated excellent brain penetration and central effects on qEEG following oral dose. The safety, tolerability, PK and exploratory PD profiles support further clinical evaluation of TAK-071.

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COMPETING INTERESTS

W.Y., D.L.B., P.K., D.V., L.R. and A.A.S. are employees of Takeda Pharmaceuticals. F.M. was a paid consultant to Takeda through Signal

Insight, LLC, and was an employee of Massachusetts General Hospital, Harvard Medical School, Boston, MA.

CONTRIBUTORS

W.Y. analyzed the pharmacokinetic data and contributed to authoring the manuscript. F.M., D.B., P.K. and D.V. analyzed the EEG data and contributed to authoring the manuscript. F.M. designed the study and contributed to authoring the manuscript. H.G. was responsible for the clinical conduct of the study and reviewed the manuscript. L.R. oversaw the design of the study and contributed to authoring the manuscript. A.S. was responsible for conceptualization of the manuscript and contributed to authoring the manuscript.

PATIENT CONSENT

All subjects included in this study provided fully informed written consent before participating in this study.

CLINICAL TRIAL REGISTRATION

This study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov) as NCT02769065.

DATA AVAILABILITY STATEMENT

Research data are not shared due to commercial restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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