



Title: A Randomized, Double-Blind, Sponsor Unblinded, Placebo-Controlled, 5-Period Crossover, Phase 1b Study To Evaluate The Effects Of Single Oral Administration of TAK-071 On Scopolamine-Induced Cognitive Impairment In Healthy Subjects

NCT Number: NCT02918266

Protocol Approve Date: 10 March 2017

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TAKEDA PHARMACEUTICALS

PROTOCOL AMENDMENT

**A Randomized, Double-Blind, Sponsor Unblinded, Placebo-Controlled, 5-Period Crossover,
Phase 1b Study To Evaluate The Effects Of Single Oral Administration of TAK-071 On
Scopolamine-Induced Cognitive Impairment In Healthy Subjects**

Phase 1b TAK-071 Scopolamine-Induced Cognitive Impairment Study

Sponsor: Takeda Development Center Americas, Inc.
One Takeda Parkway
Deerfield, IL 60015
USA

Study Number: TAK-071-1002

IND Number: 128,849 **EudraCT Number:** Not Applicable

Compound: TAK-071

Date: 10 March 2017 **Version/Amendment Number:** Amendment No. 02

Amendment History:

Date	Amendment Number	Region
05 August 2016	Initial version	Global
02 November 2016	01	Global
10 March 2017	02	Global

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. (TDC Americas) Fax: PPD [REDACTED] Email: PPD [REDACTED]
Medical Monitor (medical advice on protocol and compound)	PPD [REDACTED], MD, PhD PPD [REDACTED] Clinical Science/CNS TDC Americas
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD [REDACTED], MD, PhD PPD [REDACTED], Clinical Science/CNS TDC Americas One Takeda Parkway Deerfield, IL 60015 USA

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Electronic signatures of the following responsible Takeda medical officer (or delegate) and other signatories are located on the last page of this document.

PPD



INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator ([Appendix B](#)).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in [Appendix D](#) of this protocol.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State)

Location of Facility (Country)

1.3 Protocol Amendment No. 02 Summary of Changes

Rationale for Amendment No. 02

This document describes the changes in reference to the protocol incorporating Amendment No. 02.

The primary reason for this amendment is to modify the main part (Part 2) of the study design to include a fifth arm and change the study to a 10-sequence, 5-period crossover study. The new study design will provide information on the combined pharmacodynamic effect of TAK-071 and donepezil.

Changes in Amendment 02

1. Modify the main part (Part 2) of the study design to include a fifth arm and change the study to a 10-sequence, 5-period crossover study.
2. Add an additional secondary objective and modify an exploratory/additional objective.
3. Change in inclusion criteria.
4. Update dietary and fluid consumption for Part 2.
5. Change in procedure for qEEG.
6. Change the order of pharmacodynamic (PD) assessments.
7. Change blood volume for Part 2.
8. Clarification on pretreatment event (PTE) collection period.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	Compound: TAK-071	
Title of Protocol: A Randomized, Double-Blind, Sponsor Unblinded, Placebo-Controlled, 5-Period Crossover, Phase 1b Study To Evaluate The Effects Of Single Oral Administration of TAK-071 On Scopolamine-Induced Cognitive Impairment In Healthy Subjects	IND No.: 128,849	EudraCT No.: Not applicable
Study Number: TAK-071-1002	Phase: 1b	
<p>Study Design:</p> <p>This study consists of 2 parts.</p> <p>Part 1 is an open-label initial substudy to explore the pharmacokinetic (PK) profile of TAK-071 in the presence of a light meal and coadministration of scopolamine to determine TAK-071 dose for Part 2, the main study.</p> <p>Part 2 is the main study to assess the effects of TAK-071 on scopolamine-induced cognitive impairment.</p> <p>Overall, a total of approximately 46 subjects (6 in Part 1 and 40 in Part 2) will be enrolled in the study.</p> <p>Part 1 is a nonrandomized, open-label, 1-treatment, 1-period, 1-sequence phase 1 study to characterize the plasma PK of TAK-071 when administered under the same conditions as in Part 2, the main study, in conjunction with scopolamine, and together with a low-calorie, low-fat breakfast in healthy adult male subjects. Approximately 6 healthy subjects will be enrolled in this substudy with a minimum of 4 completers.</p> <p>Part 2 is a randomized, double-blind, sponsor unblinded, placebo-controlled, 5-treatment, 5-period, 10-sequence crossover phase 1b proof of mechanism study to evaluate the effects of a single oral (PO) administration of TAK-071, a novel muscarinic acetylcholine receptor 1 positive allosteric modulator, on scopolamine-induced deficits in cognitive function in healthy adult male subjects. Approximately 40 subjects are expected to be randomized in this part of the study, with the total of 4 subjects per sequence with a minimum of 3 completers.</p> <p>To ensure that enrolled subjects will show cognitive impairment in the presence of scopolamine but with minimal sedation and/or fatigue, all subjects who meet Screening inclusion/exclusion criteria will be administered a subcutaneous (SC) dose of scopolamine 0.5 mg.</p> <p>Pre-enrollment enrichment procedures will be conducted as part of the Screening assessments between 56 and 2 days before Day 1, and the results will be used to accept/reject the subject for enrollment to Part 2, the main study.</p> <p>Subjects will remain under observation after scopolamine administration per principal investigator's discretion to ensure that scopolamine-induced effects have worn off and it is safe for the subjects to leave the study center.</p> <p>Any subjects unable to perform the CogState battery after training will be excluded from entering Part 2.</p> <p>In each period, subjects will check-in at the study site on Day -1 and will be confined until Day 3 (approximately 24 hours postdose of scopolamine or matching placebo).</p> <p>Blood samples for the analysis of TAK-071, scopolamine, and donepezil plasma concentrations will be obtained at specified time-points up to 24 hours after scopolamine dosing.</p> <p>Pharmacodynamic (PD) measures will include the completion of cognitive tests (ie, Groton Maze Learning Test [GMLT]) and the determination of pupil size and quantitative electroencephalography (qEEG). These tests will be performed at specified time-points up to 10 hours after scopolamine dosing. The level of sedation will be determined after the end of each set of cognitive tests using Karolinska Sleepiness Scale (KSS).</p> <p>Safety and tolerability for TAK-071 in combination with scopolamine will be obtained from treatment periods in which active TAK-071 is administered (Treatments C and D). Safety and tolerability will be obtained during Treatment A for placebo, Treatment B for scopolamine alone, and during Treatment E for donepezil in combination with scopolamine.</p>		

<p>Primary Objective:</p> <ul style="list-style-type: none"> To assess the effect of a single PO dose of TAK-071 on the attenuation of cognitive deficit induced by scopolamine (0.5 mg SC) as measured by GMLT (total number of errors). <p>Secondary Objectives:</p> <ul style="list-style-type: none"> To characterize the safety and tolerability of a single PO dose of TAK-071 when coadministered with SC scopolamine (0.5 mg) in healthy subjects. To characterize the single PO dose plasma PK profile of TAK-071 when coadministered both with scopolamine and a low-calorie, low-fat breakfast in healthy subjects. To demonstrate assay sensitivity by using donepezil 10 mg as the positive control. To assess the effect of a single PO dose of TAK-071 in combination with 10 mg donepezil on the attenuation of cognitive deficit induced by scopolamine (0.5 mg subcutaneous [SC]) as measured by Groton Maze Learning Test (GMLT) (total number of errors). 	
<p>Subject Population: Healthy male subjects who are native English speakers.</p>	
<p>Number of Subjects: <u>Part 1:</u> 6 <u>Part 2:</u> Per treatment sequence: 4, total: 40 Estimated Total: 46</p>	<p>Number of Sites: Estimated total: 1 site in the United States (US)</p>
<p>Dose Level(s): <u>Part 1:</u> TAK-071 80 mg Scopolamine hydrobromide 0.5 mg <u>Part 2:</u> TAK-071 80 mg and matching placebo. This dose might be adjusted but will not exceed highest well tolerated dose in SRD cohorts or the average maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve from 0 to 24 hours (AUC_{24}) seen at no-observed-adverse-effect level (NOAEL) in the 28-day Good Laboratory Practice (GLP) toxicology study in monkeys. Scopolamine hydrobromide 0.5 mg and matching placebo. Donepezil hydrochloride 10 mg and matching placebo.</p>	<p>Route of Administration: <u>Part 1:</u> TAK-071, PO; Scopolamine, SC <u>Part 2:</u> TAK-071 and matching placebo, PO Scopolamine and matching placebo, SC Donepezil and matching placebo, PO</p>
<p>Duration of Treatment: <u>Part 1:</u> Single dose <u>Part 2:</u> Single dose in each period; total number of dosing days: 4</p>	<p>Period of Evaluation: <u>Part 1:</u> 40 days including Screening Period, Treatment Period, and Follow-up Call/Visit. <u>Part 2:</u> Approximately 21 weeks including the Screening Period, Treatment Periods, and Follow-up Call/Visit.</p>
<p>Main Criteria for Inclusion:</p> <ul style="list-style-type: none"> The subject is a healthy male aged 18 to 55 years, inclusive. The subject weighs at least 50 kg and has a body mass index (BMI) from 18.0 to 30.0 kg/m². 	
<p>Additional Inclusion Criteria for Part 2 (Main Study):</p> <ul style="list-style-type: none"> Subject able to perform the CogState battery. Change from Baseline (average) in total GMLT errors of ≤ -5 at 2 hours postdose of scopolamine. Subjects with sleepiness score < 8 on the KSS at 2 hours postdose of scopolamine. Subject passes a hearing test with at least 80% correct responses and no more than 20% false positives. This test can be repeated once to determine eligibility. 	

Main Criteria for Exclusion:

- The subject has a known hypersensitivity to any component of the formulation of TAK-071 or placebo; or has a known hypersensitivity to donepezil (or to other biperidine derivatives), atropine, or scopolamine and/or to any component in their formulations.
- The subject has a risk of suicide or suicidal ideation with intent and plan according to the investigator's clinical judgment (affirmative answer to questions 4 and 5 of the ideation section of the Columbia-Suicide Severity Rating Scale [C-SSRS]) or has made a suicide attempt in the previous 6 months.
- The subject is a shift worker (night, late or early resulting in irregular bed times) or has crossed or will cross more than 2 time zones within 48 hours in the period from 48 hours prior to Treatment Period 1, Day 1 until the end of Treatment Period 5.
- The subject reports symptoms suggesting evidence of a current sleep disorder or history of sleep disorder, including but not limited to sleep apnea, heavy snoring, primary or chronic insomnia, narcolepsy or restless leg syndrome, as judged by medical history.

Main Criteria for Evaluation and Analyses:

Primary Endpoints:

- Change from Baseline in GMLT, as measured by the total number of errors on the GMLT at 2 hours postdose of scopolamine on Day 1 by study treatment.

Secondary Endpoints:

- Change from Baseline over time in total number of errors on the GMLT by study treatment and the derived PD parameters, as follows:
 - GMLT area under the effect curve from time 0 hours to time t ($AUEC_t$) (net area) by study treatment.
 - GMLT maximum observed effect (E_{max}) by study treatment.
 - Time to reach GMLT E_{max} by study treatment.
- Percentage of subjects who have at least 1 treatment-emergent adverse event (TEAE).
- Percentage of subjects who meet the Takeda markedly abnormal value (MAV) criteria at least once postdose for the following:
 - Clinical laboratory parameters.
 - Vital sign measurements.
 - Electrocardiogram (ECG) parameters.
- PK parameters of TAK-071 in plasma after a single dose on Day 1, as follows:
 - Maximum observed plasma concentration (C_{max}).
 - Time of first occurrence of C_{max} (t_{max}).
 - Area under the plasma concentration-time curve from time 0 to time t (AUC_t).
 - Area under the plasma concentration-time curve from time t1 to time t2 (AUC_{t1-t2}).
 - Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}), as permitted by the data.
 - Terminal disposition phase half-life ($t_{1/2z}$) in plasma, as permitted by the data.

Statistical Considerations:

PK Analysis

Plasma concentrations of TAK-071, donepezil, and scopolamine will be summarized from each treatment using descriptive statistics.

Individual plasma concentration data versus time will be presented in a data listing.

Plasma PK parameters for TAK-071, donepezil, and scopolamine will be summarized separately.

PD Analysis

To address the statistical hypotheses related to the time course of scopolamine effects, cognitive endpoints will be analyzed using a mixed analysis of variance (ANOVA) model appropriate for a 5-period crossover with fixed factors for period, sequence, treatment, hour, and treatment by hour. Additionally, the model will contain a random factor subject nested in sequence (the between-subject error) and a random residual error term (the within-subject error). A 2-sided t test ($\alpha=0.05$) using the within subject mean squared error from the mixed ANOVA model will be examined to test the primary hypothesis. Treatment differences, 2-sided 95% confidence intervals (CIs), 2-sided p-values, and effect sizes will be presented for all time points, with 2 hours post scopolamine being the time frame for the primary endpoint.

To address the statistical hypotheses related to area under the effect curve (AUEC) endpoints, cognitive endpoints will be analyzed using an ANOVA model appropriate for a 5-period crossover with fixed factors for treatment, period, and sequence. Additionally, the model will contain a random factor subject nested in sequence (the between-subject error) and a random residual error term (the within-subject error). A 2-sided t test ($\alpha=0.05$) using the within subject mean squared error from the mixed ANOVA model will be examined to test the statistical hypothesis.

For AUEC endpoints, the natural log scale treatment differences (eg, the primary treatment comparison of Treatment Y – Treatment X) will be exponentiated and reported as a mean percent change along with 95% CIs for the true mean percent change as a summary measure. The Baseline cognitive measure will be included in the model as a covariate.

Other statistical analyses will be performed as appropriate.

Safety Analysis

Adverse events (AEs) will be presented in listings, and TEAEs will be summarized in tables. Individual results of laboratory tests (hematology, chemistry, and urinalysis), vital signs, ECG parameters, and physical examination findings will be listed. Baseline, postdose and change from Baseline to postdose laboratory data, vital signs, and ECG parameters will be summarized as well as percentage of subjects who meets Takeda MAV criteria.

Sample Size Justification:

Part 1: A sample size of 6 with 4 completers is considered sufficient to guide dose selection in Part 2, the main study.

Part 2: A sample size of 26 subjects, approximately 3 subjects for each of the 10 sequences of the 5-period cross-over, will be used and is considered sufficient for evaluation of the primary cognitive endpoints for this study based on consideration of published scopolamine model literature and expert advice. Subjects who drop-out may be considered for replacement on case-by-case basis. To ensure there are enough completers a total of 40 subjects will be recruited (4 per sequence).

Using a 2-sided alpha level of 0.05, this study has a 90% power to detect an effect size of 0.67 in the GMLT (sum of 5 trials) total number of errors for the primary treatment comparison of TAK-071 + scopolamine vs placebo + scopolamine, assuming a total of 26 subjects complete the study and provide primary endpoint data.

At least 26 subjects will complete the study if 40 subjects are randomized, assuming the drop-out rate does not exceed 33%.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator

PPD



3.3 List of Abbreviations

ACh	acetylcholine
AChE	acetylcholinesterase
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer disease
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APOE	apolipoprotein E
AST	aspartate aminotransferase
AUC _∞	area under the plasma concentration-time curve from time 0 to infinity
AUC _{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC _t	area under the plasma concentration-time curve from time 0 to time t
AUC _{t1-t2}	area under the plasma concentration-time curve from time t1 to time t2
AUEC	area under the effect curve
AUEC _t	area under the effect curve from time 0 to time t
BMI	body mass index
bpm	beats per minute
CFR	Code of Federal Regulations
ChAT	choline acetyltransferase
CI	confidence interval
C _{max}	maximum observed plasma concentration
CNS	central nervous system
CRO	contract research organization
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P-450
DIC	drug-in-capsule
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalograph
E _{max}	maximum observed effect
ERP	event-related potential
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice

GGT	gamma-glutamyl transferase
GMLT	Groton Maze Learning Test
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
INR	international normalized ratio
IRB	Institutional Review Board
K ₂ EDTA	potassium ethylenediamine tetraacetic acid
KSS	Karolinska Sleepiness Scale
LFT	liver function test
M ₁ R	muscarinic acetylcholine receptor 1
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCS	not clinically significant
NOAEL	no-observed-adverse-effect level
OTC	over-the-counter
PAM	positive allosteric modulator
PD	pharmacodynamic
PGx	pharmacogenomics
PK	pharmacokinetic
PO	oral
PTE	pretreatment event
QD	once daily
qEEG	quantitative electroencephalography
RCF	relative centrifugal force
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOP	standard operating procedure
SPL	sound pressure level
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reactions
t _{1/2z}	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t _{max}	time of first occurrence of C _{max}
ULN	upper limit of normal
US	United States

WHODRUG World Health Organization Drug Dictionary

3.4 Corporate Identification

TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

Treatment of Alzheimer disease (AD) is a significant healthcare challenge [1-4], with over 46 million people living with AD or a related dementia worldwide. This number is estimated to increase to 131.5 million by 2050 [5]. Of those patients diagnosed with AD, more than two-thirds will likely be categorized as having mild or moderate disease [3]. Dementia-related diseases also have a huge economic impact. Today, the total estimated worldwide cost of dementia is United States (US) \$818 billion, and it will become a trillion dollar disease by 2018 [5].

Impairment of cholinergic neuronal functions leads to cognitive disturbances and memory loss, the hallmark symptoms of AD [6,7]. A reduction in cholinergic neurotransmission has been observed in very early stages of AD and is also considered to be associated with the cognitive decline associated with dementia with Lewy bodies and Parkinson disease [8]. Postmortem studies of patients with AD have confirmed significant losses in the number of basal forebrain cholinergic neurons and cortical efferents and reductions in the activity of choline acetyltransferase (ChAT) activity, the enzyme that converts choline to acetylcholine (ACh) in presynaptic nerve terminals. Reductions in ChAT activity were significant in the medial frontal cortex, inferior parietal cortex, and hippocampus and were consistent with clinical symptoms [9].

Inhibition of acetylcholinesterase (AChE), the enzyme responsible for the breakdown of ACh, is the current standard of care for AD. This therapeutic strategy results in the generalized preservation of endogenous ACh and aims to compensate for its disease-related decline. These treatments have only modest effects in the treatment of AD [10]. The combination of AChE inhibitors (AChEIs) with the *N*-methyl-D-aspartate antagonist memantine has a weak effect in the treatment of mild to moderate AD [11] with transient clinical benefit.

From a safety and tolerability perspective, AChEIs, such as donepezil, galantamine, and rivastigmine, increase the concentration of ACh at the synaptic cleft, thus nonselectively increasing ACh concentration at all subtypes of ACh muscarinic receptors (M₁-M₅R). At high concentrations, this can lead to manifestation of various mechanism-related side effects, most commonly vomiting, diarrhea, and muscle cramps. Therefore, given the paucity of treatment options as well as the tolerability profile of current standard of care, there exists an unmet medical need for a new, more selective treatment for patients with AD with improved efficacy and safety profiles.

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For full details on all the relevant nonclinical studies, please refer to the Investigator Brochure.

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4.2 Rationale for the Proposed Study

Scopolamine is a muscarinic M_{1-5} receptor antagonist, and due to its anticholinergic activity, scopolamine produces transitory impairments of attention, memory, and executive functions.

Cognitive impairments in AD and in some other neurodegenerative disorders are associated with impaired cholinergic transmission in the central nervous system (CNS): impairments in mesial temporal and basal forebrain cholinergic memory circuits lead to cognitive deficits, such as storage and retrieval of new learning, and these brain areas also have important roles in other aspects of cognition, such as information processing speed. AD disrupts this neurotransmission, and it is marked by a substantial neuron loss in the nucleus basalis of Meynert, which results in diminished production and availability of ACh.

A scopolamine challenge paradigm has been used in both nonclinical models and human trials to confirm procognitive effects of cholinomimetic drugs (such as the cholinesterase inhibitor donepezil) by transiently simulating a cholinergic deficit similar to that seen in AD [12-16].

4.3 Benefit/Risk Profile

There is no expected clinical benefit for subjects entering this study. The risks of participation are primarily those associated with adverse reactions to the study drugs. There may also be some discomfort from collection of blood samples and other study procedures.

While extensive clinical safety and efficacy data are available from other cholinomimetic agents, such as donepezil, there are currently no safety data from clinical studies in the public domain for other M_1 R PAMs. The safety data from nonclinical studies with TAK-071 and clinical data from other cholinomimetics, such as donepezil, include side effects such as diarrhea, nausea, and vomiting secondary to the pharmacologic activity of the compound [17]. At the time of start of this study, safety, tolerability, and PK data will be available from all SRD study cohorts from the first-in human (FIH) study. This proof of mechanism study may therefore only start after completion and review of the SRD cohorts and confirmation of the acceptable single-dose safety, tolerability, and PK of TAK-071.

Scopolamine may cause drowsiness, dizziness or blurred vision [18]. Therefore, to minimize the risk to subjects (ie, due to driving or operating dangerous machinery), subjects will be kept at the study center for at least 8 hours and will only be allowed to leave the study center earlier than 8 hours upon confirmation by the investigator or designee that scopolamine effects have worn off.

The most common adverse events (AEs) for donepezil are diarrhea, muscle cramps, fatigue, nausea, vomiting, dry mouth, and insomnia [17]. Donepezil has been previously administered to healthy subjects in the context of multiple phase 1 clinical trials, including bioequivalence trials [19,20] as well as in other scopolamine challenge studies ([21,22] and [Study ROF-ALZ_102]), indicating that single doses of 10 mg are safe and well tolerated in this population.

It is not expected that this study will result in any therapeutic benefit for the included study population. However, data generated from this study should enable the investigation of TAK-071 in subsequent clinical efficacy studies of longer duration in the relevant subject populations (ie, phase 2).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

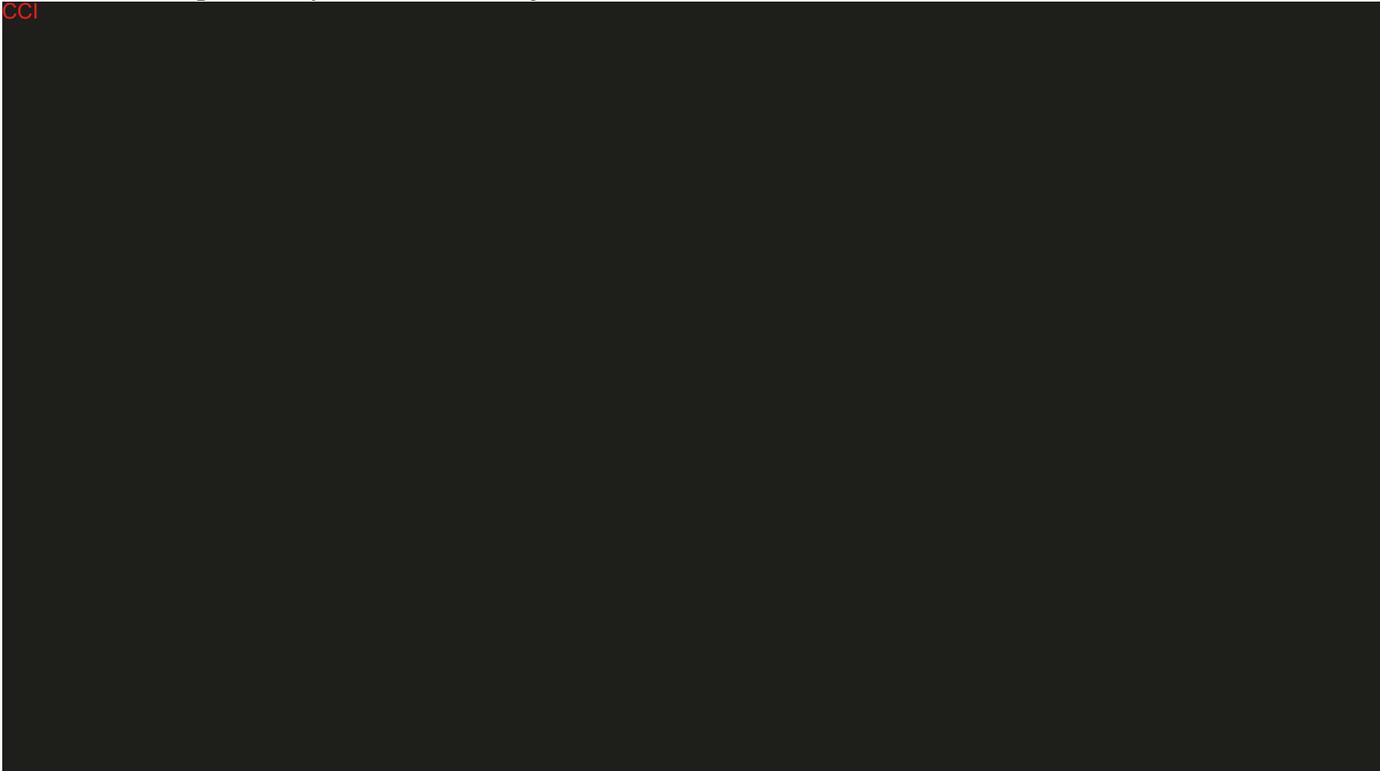
- To assess the effect of a single PO dose of TAK-071 on the attenuation of cognitive deficit induced by scopolamine (0.5 mg subcutaneous [SC]) as measured by Groton Maze Learning Test (GMLT) (total number of errors).

5.1.2 Secondary Objectives

- To characterize the safety and tolerability of a single PO dose of TAK-071 when co-administered with SC scopolamine (0.5 mg) in healthy subjects.
- To characterize the single PO dose plasma PK profile of TAK-071 when co-administered both with scopolamine and a low-calorie, low-fat breakfast in healthy subjects.
- To demonstrate assay sensitivity by using donepezil 10 mg as the positive control.
- To assess the effect of a single PO dose of TAK-071 in combination with 10 mg donepezil on the attenuation of cognitive deficit induced by scopolamine (0.5 mg subcutaneous [SC]) as measured by Groton Maze Learning Test (GMLT) (total number of errors).

5.1.3 Exploratory/Additional Objectives

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5.2 Endpoints

5.2.1 Primary Endpoint

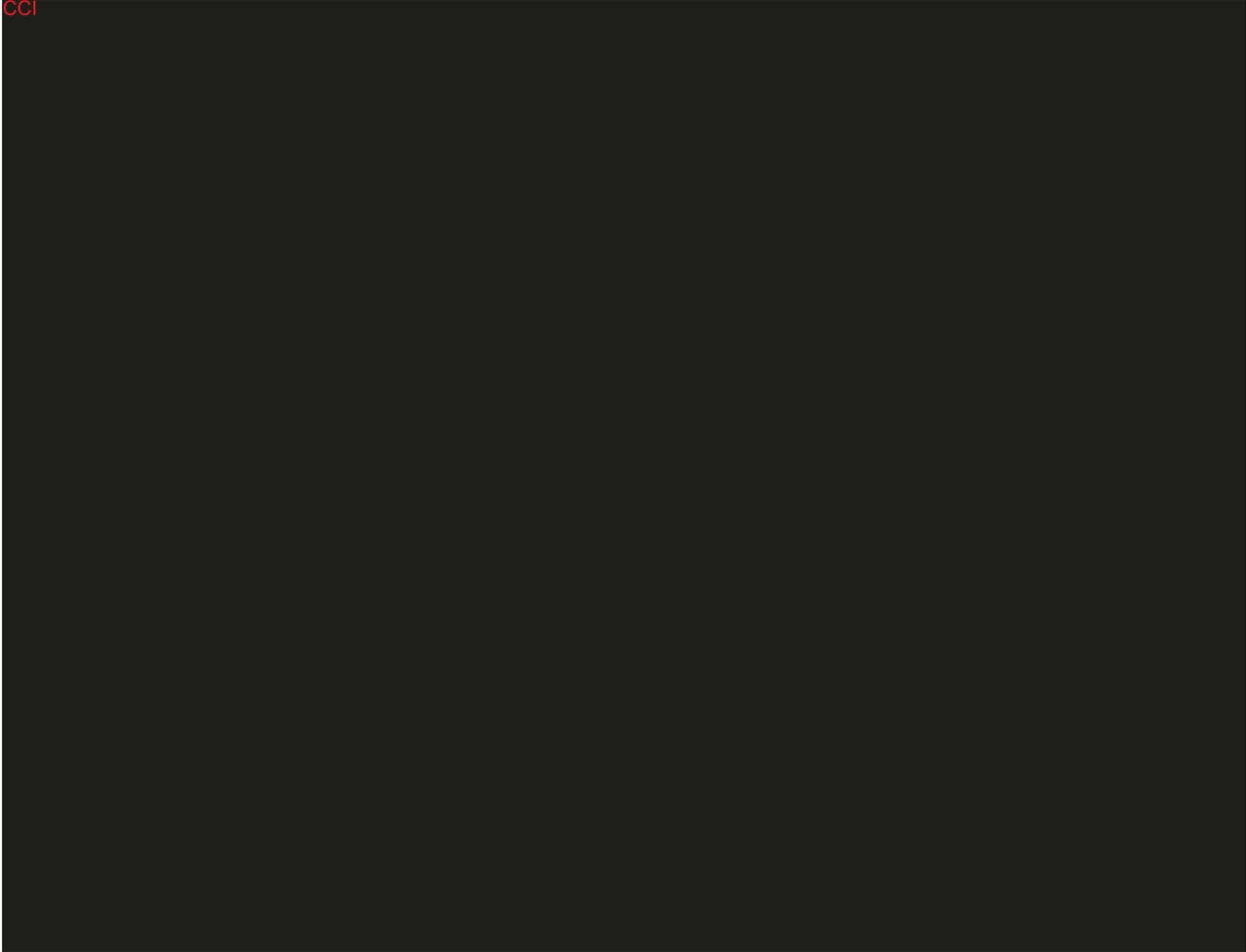
- Change from Baseline in GMLT, as measured by the total number of errors on the GMLT at 2 hours postdose of scopolamine on Day 1 by study treatment.

5.2.2 Secondary Endpoints

- Change from Baseline over time in total number of errors on the GMLT by study treatment and the derived pharmacodynamic (PD) parameters, as follows:
 - GMLT area under the effect curve from time 0 hours to time t ($AUEC_t$) (net area) by study treatment.
 - GMLT maximum observed effect (E_{max}) by study treatment.
 - Time to reach GMLT E_{max} by study treatment.
- Percentage of subjects who have at least 1 treatment-emergent adverse event (TEAE).
- Percentage of subjects who meet the Takeda markedly abnormal value (MAV) criteria at least once postdose for the following:
 - Clinical laboratory parameters.
 - Vital sign measurements.
 - ECG parameters.
- PK parameters of TAK-071 in plasma after a single dose on Day 1, as follows:
 - Maximum observed plasma concentration (C_{max}).
 - Time of first occurrence of C_{max} (t_{max}).
 - Area under the plasma concentration-time curve from time 0 to time t (AUC_t).
 - Area under the plasma concentration-time curve from time t1 to time t2 (AUC_{t1-t2}).
 - Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}), as permitted by the data.
 - $t_{1/2z}$ in plasma, as permitted by the data.

5.2.3 Additional Endpoints

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6.0 STUDY DESIGN AND DESCRIPTION

This study consists of 2 parts.

Part 1 is an open label initial substudy to explore PK profile of TAK-071 in the presence of light meal and coadministration of scopolamine to determine TAK-071 dose for Part 2, the main study.

Part 2 is the main the study to assess the effects of TAK-071 on scopolamine-induced cognitive impairment.

6.1 Study Design – Part 1

This is a nonrandomized, open-label, 1-treatment, 1-period, 1-sequence phase 1 study to characterize the plasma PK of TAK-071 when administered under the same conditions as in Part 2, the main study, this is in conjunction with scopolamine, and together with a low-calorie, low-fat breakfast in healthy adult male subjects. Approximately 6 healthy subjects will be enrolled in this substudy with a minimum of 4 completers.

A schematic of Part 1, the substudy, design is provided in [Figure 6.a](#).

Figure 6.a Schematic of Study Design – Part 1

Pretreatment Period		Treatment Period		Final Visit	PK Follow-Up	Follow-up
Screening	Check-in	Single Dose/PK	PK	Check-out/PK	PK	Follow-up Telephone Call
Days -28 to -2	Day -1	Day 1	Days 2-4	Day 5	Day 8	Day 12 (±2)
		←—Confinement—→				

Subjects will check-in at the study site on Day -1 and will be confined until the completion of assessments on Day 4. A follow-up PK assessment will be performed on Day 8 and a final follow-up will occur of Day 12 (±2).

Scopolamine will be administered as a single 0.5 mg SC injection.

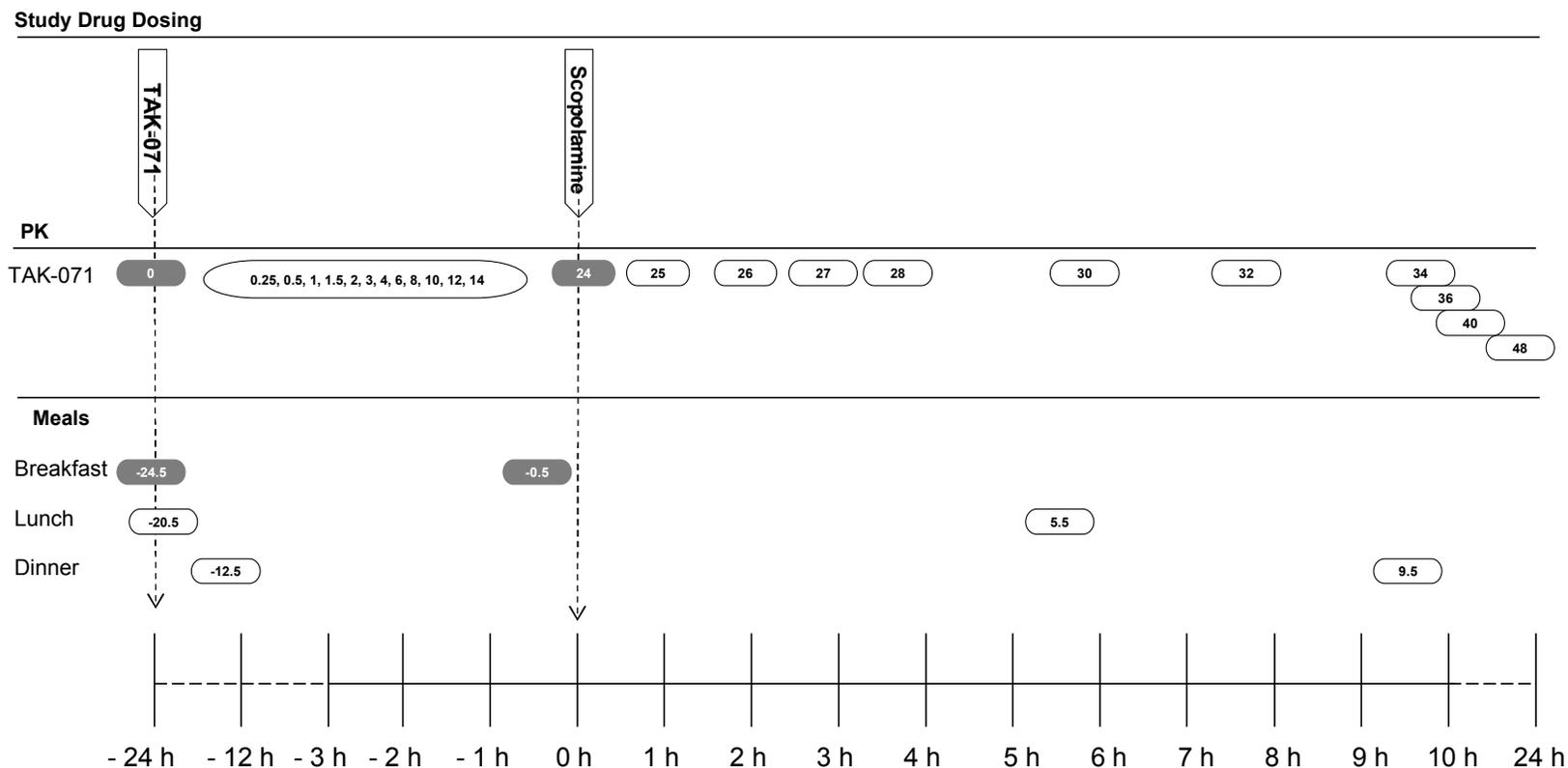
TAK-071 will be administered as a single PO dose (as drug-in-capsule [DIC]) 24 hours before scopolamine administration.

Blood samples for the analysis of TAK-071 plasma concentrations will be obtained at specified time-points up to 168 hours after TAK-071 dosing (144 hours after scopolamine dosing).

Safety and tolerability of TAK-071 in combination with scopolamine will be assessed from physical examination, AEs, clinical laboratory tests, ECGs, etc.

The planned timing of assessments and meals relative to scopolamine dosing in Part 1 is shown in [Figure 6.b](#).

Figure 6.b TAK-071 PK Assessments and Meal Timing Relative to Scopolamine Administration – Part 1 (Days 1 and 2)



6.2 Study Design – Part 2

This is a randomized, double-blind, sponsor unblinded, placebo-controlled, 5-treatment, 5-period, 10-sequence crossover phase 1b proof of mechanism study to evaluate the effects of a single PO administration of TAK-071, a novel M₁R PAM, on scopolamine-induced deficits in cognitive function in healthy adult male subjects.

Approximately 40 subjects are expected to be randomized in this study, with the total of 4 subjects per sequence and with a minimum of 3 completers. A schematic of the study design is provided in [Figure 6.c](#).

Figure 6.c Schematic of Study Design – Part 2

Screening Period	Treatment Periods 1 to 5				Wash-Out Periods 1 to 4	Follow-Up
Screening and Pre-Enrollment Enrichment	Check-in	Baseline PD	Single Dose PK/PD	PK/PD		Follow-up Telephone Call/Visit
Days -56 to -2	Day -1	Day 1	Day 2	Day 3	Days 4 to 20	Day 9 (±2) Period 5
	←—Confinement—→					

6.2.1 Pre-Enrollment Enrichment Screening – Part 2

To ensure that enrolled subjects will show cognitive impairment in the presence of scopolamine but with minimal sedation and/or fatigue, all subjects who meet Screening inclusion/exclusion criteria will be administered an SC dose of scopolamine 0.5 mg.

Pre-enrollment enrichment procedures will be conducted as part of the Screening assessments between 56 and 2 days before Day 1, and the results will be used to accept/reject the subject for enrollment to Part 2, the main study.

Subjects will remain under observation post-scopolamine administration per principal investigator's discretion to ensure that scopolamine-induced effects have worn off and it is safe for the subjects to leave the study center.

Any subject unable to perform the CogState battery after training will be excluded from entering Part 2, the main study.

6.2.2 Treatment Sequences – Part 2

In each period, subjects will check-in at the study site on Day -1 and will be confined until Day 3 (approximately 24 hours postdose of scopolamine or matching placebo).

Subjects will be randomly assigned to 1 of 10 possible treatment sequences (described in [Section 8.1.3](#)) before the first dose of study drug, each consisting of 5 treatment periods ([Table 6.a](#)).

Table 6.a Summary of Treatment Sequences in Study - Part 2

Sequence	Period 1		Period 2		Period 3		Period 4		Period 5
1	A	<i>Minimum 3-week washout</i>	B	<i>Minimum 3-week washout</i>	D	<i>Minimum 3-week washout</i>	E	<i>Minimum 3-week washout</i>	C
2	B		C		E		A		D
3	C		D		A		B		E
4	D		E		B		C		A
5	E		A		C		D		B
6	A		C		B		E		D
7	B		D		C		A		E
8	C		E		D		B		A
9	D		A		E		C		B
10	E		B		A		D		C

A=scopolamine matching placebo SC + TAK-071 matching placebo PO + donepezil matching placebo PO.

B=scopolamine 0.5 mg SC + TAK-071 matching placebo PO + donepezil matching placebo PO.

C=scopolamine 0.5 mg SC + TAK-071 PO + donepezil matching placebo PO.

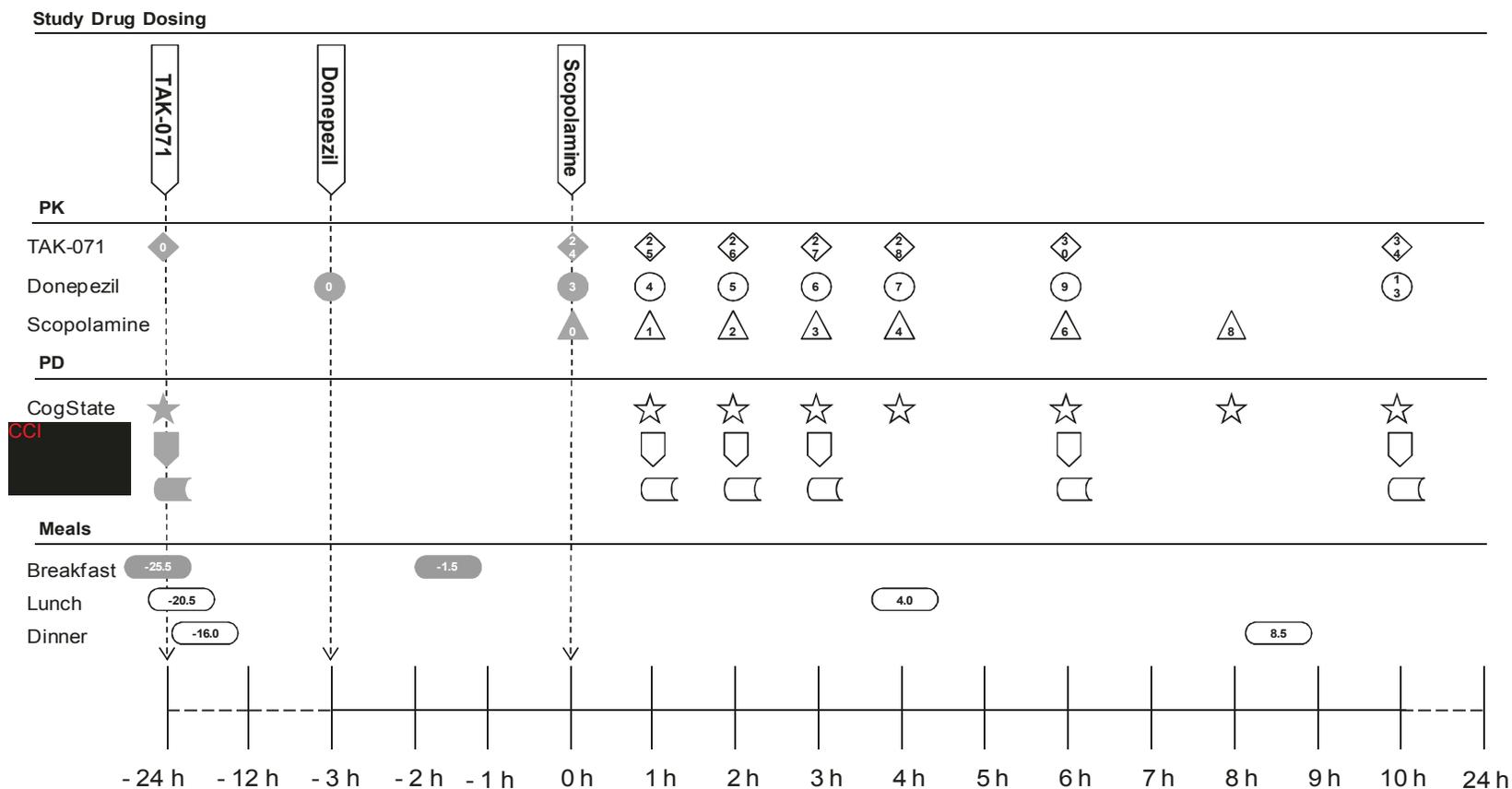
D=scopolamine 0.5 mg SC + TAK-071 PO + donepezil 10 mg PO.

E=scopolamine 0.5 mg SC + TAK-071 matching placebo PO + donepezil 10 mg PO.

A 3-week (21-day) washout between treatment periods is required because of the long $t_{1/2z}$ of donepezil to minimize the potential for carryover effects.

The planned timing of assessments and meals relative to scopolamine dosing is shown in [Figure 6.d](#).

Figure 6.d PK/PD Assessments and Meal Timing Relative to Scopolamine Administration – Part 2



Note: Solid gray PK/PD symbols indicate predose assessments. Numbers inside symbols indicate scheduled times relative to the respective study drug dosing for the PK analyte. Shaded meal symbols indicate low-calorie, low-fat meals; all other meals are standard.

Scopolamine (0.5 mg) or matching placebo will be administered as a single SC injection.

TAK-071 or matching placebo will be administered as a single PO dose (as DIC) 24 hours before scopolamine administration.

The dose of TAK-071 for Part 2 will be selected depending on the results from Part 1 (initial substudy) and the FIH Study TAK-071-1001; however, under no circumstances will the selected TAK-071 dose exceed the maximum tolerated dose (MTD), or if the MTD is not attained, the highest dose tested in the SRD part of the FIH study.

The precise dosing time of TAK-071 relative to scopolamine will be selected to ensure that both drugs reach their anticipated peak effects at approximately the same time to maximize the potential to observe TAK-071 procognitive effects.

Donepezil (10 mg) tablet (overencapsulated) or matching placebo will be administered as a single capsule PO 3 hours before injecting scopolamine to maximize the chances of observing a reversal of the scopolamine-induced cognitive impairment.

Blood samples for the analysis of TAK-071, scopolamine, and donepezil plasma concentrations will be obtained at specified time-points up to 10 hours after scopolamine dosing.

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Information on the safety and tolerability of TAK-071 in combination with scopolamine and/or donepezil will be obtained from treatment periods in which active TAK-071 is administered (Treatments C and D). Safety and tolerability will be obtained during Treatment A for placebo, Treatment B for scopolamine alone, and during Treatment E for donepezil in combination with scopolamine.

6.3 Justification for Study Design, Dose, and Endpoints

6.3.1 Justification for Design for Part 1

An initial substudy (Part 1) has been included since to date TAK-071 has only been administered as a single agent under fasted conditions in Study TAK-071-1001. In the present study, TAK-071 administration will occur 24 hours prior to scopolamine and together with a low-calorie, low-fat breakfast.

Scopolamine has the potential of PK drug-drug interaction as antimuscarinics can inhibit gastrointestinal motility, delay gastric emptying, and prolong gastrointestinal transit time [27,28].

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6.3.2 Justification for Design for Part 2

This is a randomized, double-blind, sponsor-unblinded, placebo-controlled, 5-treatment, 5-period, 10-sequence crossover phase 1b proof of mechanism study to evaluate the effects of single PO administration of TAK-071, a novel M₁ PAM, on scopolamine-induced deficits in cognitive function in healthy adult male subjects.

The study is being conducted as double-blind and placebo-controlled to avoid subjective bias in the assessment of response. The crossover design was selected to reduce the sample size needed and to minimize intersubject variability.

Scopolamine was selected because it has long been used for the induction of deficits in psychomotor and cognitive function, and the impairments resemble those seen in Alzheimer disease. It is therefore expected that in this study, scopolamine will induce the desired cognitive impairment for the cognitive assessments within a short time with minimal sedation and/or fatigue. To ensure this, pre-enrollment enrichment Screening will be performed for all study subjects who meet Screening inclusion/exclusion criteria after administration of scopolamine 0.5 mg SC. Only subjects who display an acceptable decline in cognitive function with minimal sedation will be allowed to enter the main study.

Donepezil has been selected as the positive control for this study because it is the most frequently used medication for the symptomatic treatment of mild to moderately severe Alzheimer disease at the therapeutic dose of 10 mg once daily (QD).

Combination of donepezil and TAK-071 will provide information about PD effect of an acetylcholinesterase inhibitor in combination with M1PAM measured by amelioration of scopolamine induced cognitive and EEG effects.

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The SC administration of scopolamine has a $t_{1/2z}$ of 3 to 4 hours and reaches C_{max} within 10 to 30 minutes. The cognitive impairment induced by SC administration of scopolamine appears to be maximal approximately 1 to 2 hours after administration and disappears after 6 to 8 hours postinjection, allowing for a minimal but sufficient period of subject supervision before subjects are discharged safely on Day 3. The minimum 21-day washout between the last dose in a period and the first dose in the subsequent period will be sufficient to ensure no drug carryover effect.

TAK-071 and donepezil will be administered 24 and 3 hours, respectively, prior to administration of scopolamine so that the t_{max} of TAK-071 (26 hours in plasma after an 80 mg dose) and donepezil (approximately 3 to 4 hours in plasma) occur at approximately the same time as the maximal scopolamine-induced cognitive impairment effects (approximately 1 to 2 hours after SC administration). The time of administration of TAK-071 relative to scopolamine may be adjusted upon review of emerging PK data from the FIH study.

6.3.3 Justification for Dose

6.3.3.1 *TAK-071*

A high TAK-071 dose will be used in this study to maximize the potential for observing a significant reversal of scopolamine-induced cognitive impairment. The dose of TAK-071 will be selected depending on the results from the FIH Study TAK-071-1001; however, under no circumstances will the selected TAK-071 dose exceed the MTD, or if the MTD is not attained, the highest dose tested in the SRD part of the FIH study. At present, it is planned that the dose for the initial substudy (Part 1) and main study (Part 2) will be 80 mg, this the highest dose tested in an SRD setting to date.

If following a review of the preliminary PK results of Part 1 (initial substudy) reveals that there is an effect of scopolamine and/or food on the plasma exposure of TAK-071 (increase or decrease), the selected TAK-071 dose for Part 2 may be adjusted to ensure that exposures remain on target; and below the lowest no-observed-adverse-effect level (NOAEL) plasma exposure achieved in 4-week GLP animal toxicology studies.

The dosing time of TAK-071 relative to scopolamine will be selected to ensure that both drugs attain their anticipated peak effects at approximately the same time to maximize the potential to observe TAK-071 procognitive effects. Based on preliminary TAK-071 plasma concentration data following a dose of 80 mg indicating that peak concentrations occur at median time of 26 hours postdose, it is planned that dosing of TAK-071 should occur 24 hours prior to scopolamine administration. The precise timing of TAK-071 dosing may be adjusted if warranted based on emerging data.

6.3.3.2 *Donepezil*

Donepezil is the most frequently used medication for the symptomatic treatment of mild to moderately severe Alzheimer disease. Donepezil, administered at the therapeutic dose of 10 mg QD, will serve as a positive control in this study. Donepezil has been previously administered to healthy subjects in the context of multiple phase 1 clinical trials, indicating that single doses of 10 mg are safe and well tolerated in this population [19-22]. In particular, donepezil doses of both 5 and 10 mg have been employed in published [21,22] and unpublished (Study ROF-ALZ_102) scopolamine challenge studies. The higher 10 mg dose is therefore expected to maximize the chances of a successful positive control in the present study.

6.3.3.3 *Scopolamine*

The SC dose of 0.5 mg is a safe and efficacious dose for the purpose of this study's endpoints. This dose has been previously found to result in maximal cognitive impairment with minimal associated sedation and/or fatigue [29]. SC administration will provide the advantage of better reproducibility, or lower variability, in the dynamic changes in the cognitive impairment profile over time. This is important to ensure that most subjects will attain maximal cognitive impairment at approximately the same time (approximately 2 hours postdose).

6.3.4 **Justification for Endpoints**

The CogState GMLT will serve as the primary outcome measure in this study. From a psychometric perspective, the GMLT can be repeated often in an experimental setting and with little or no practice effect. From a construct validity aspect, the GMLT measures a variety of cognitive functions (immediate and short-term memory for visuospatial information), and it is sensitive to the detection of subclinical perseverative errors and slowed information-processing speed.

6.4 **Premature Termination or Suspension of Study or Study Site**

6.4.1 **Criteria for Premature Termination or Suspension of the Study**

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- Study discontinuation due to non-safety reasons such as:
 - A finding (eg, PK, PD, efficacy, biologic targets, etc) from another nonclinical or clinical trial using the trial treatment(s) that results in the trial being stopped for a non-safety related reason.
 - Data from comparator(s), drug(s) of the same class, or methodology(ies) used in this trial become available and results in the trial(s) being stopped for a non-safety related reason.
 - The study is stopped due to non-scientific and non-safety reasons, such as slow enrollment.
- Study discontinuation due to safety reasons:
 - Early trial termination due to unanticipated safety concerns arising from clinical or nonclinical trials with the trial treatment(s), comparator(s), drug(s) of the same class or methodology(ies) used in this trial.
 - New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for subjects participating in the study.

6.4.2 **Criteria for Premature Termination or Suspension of Study Sites**

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement,

is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.4.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB), or a regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures including requesting that a subject fast for any laboratory evaluations.
3. The subject is male and aged 18 to 55 years, inclusive, at the time of informed consent and first study drug dose.
4. The subject weighs at least 50 kg and has a body mass index (BMI) from 18.0 to 30.0 kg/m², inclusive at Screening.
5. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use barrier method of contraception (eg, condom with or without spermicide)* from signing of informed consent throughout the duration of the study and for 70 days after the last dose of study drug.

* Definitions and highly effective methods of contraception are defined in Section 9.1.9 and reporting responsibilities are defined in Section 9.1.10.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 30 days prior to the first dose of study drug.
2. The subject has received TAK-071 in a previous clinical study.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate or potentially confound the study results.
5. The subject has a known hypersensitivity to any component of the formulation of TAK-071 or placebo; or has a known hypersensitivity to donepezil (or to other biperidine derivatives), atropine, or scopolamine and/or to any component in their formulations.
6. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use) at Screening or Check-in (Day -1) of Period 1.

7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as regular consumption of 4 or more units per day) within 1 year prior to the Screening visit or is unwilling to agree to abstain from alcohol and drugs throughout the study. One unit is equivalent to a half-pint of beer or 1 measure of spirits or 1 glass of wine.
8. Subject has taken any excluded medication, supplements, or food products during the time periods listed in the Excluded Medications and Dietary Products table listed in Section 7.4.
9. Subject intends to donate sperm during the course of this study or for 70 days after the last dose of study drug.
10. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking TAK-071, donepezil, scopolamine, or a similar drug in the same class, or that might interfere with the conduct of the study.
11. Subject has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention).
12. Subject has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Day 1 of Period 1.
13. Subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody at Screening or a known history of human immunodeficiency virus infection.
14. Subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 28 days prior to Check-in Day -1 of Period 1. Cotinine test is positive at Screening or Check-in (Day -1) of Period 1.
15. The subject has poor peripheral venous access.
16. Subject has donated or lost 450 mL or more of his blood volume (including plasmapheresis), or had a transfusion of any blood product within 30 days prior to Day 1 of Period 1.
17. The subject has a risk of suicide or suicidal ideation with intent and plan according to the investigator's clinical judgment (affirmative answer to questions 4 and 5 of the ideation section of the Columbia-Suicide Severity Rating Scale [C-SSRS]) or has made a suicide attempt in the previous 6 months.
18. The subject is a shift worker (night, late, or early resulting in irregular bed times) or has crossed or will cross more than 2 time zones within 48 hours in the period from 48 hours prior to Treatment Period 1, Day 1 until the end of Treatment Period 5.
19. The subject reports symptoms suggesting evidence of a current sleep disorder or history of sleep disorder, including but not limited to sleep apnea, heavy snoring, primary or chronic insomnia, narcolepsy or restless leg syndrome, as judged by medical history.

20. The subject has a Fridericia-corrected QT interval >450 ms or PR interval outside the range of 120 to 220 ms, confirmed on repeat testing within a maximum of 30 minutes, at Screening or Check-in.
21. Subject has abnormal Screening or Check-in (Day -1) of Period 1 laboratory values that suggest a clinically significant underlying disease, confirmed upon repeat testing.

7.3 Additional Inclusion Criteria for Part 2 After Pre-Enrollment Enrichment Screening

1. Subject able to perform the CogState battery.
2. Change from Baseline (average) in total GMLT errors of ≤ -5 at 2 hours postdose of scopolamine.
3. Subjects with sleepiness score <8 on the KSS at 2 hours postdose of scopolamine.
4. Subject passes a hearing test with at least 80% correct responses and no more than 20% false positives. This test can be repeated once to determine eligibility.

7.4 Excluded Medications, Supplements, Dietary Products

Use of the agents in [Table 7.a](#) is prohibited from the time points specified until subject completes PK assessment on Day 8 in Part 1, the initial substudy, or is discharged from the unit in Period 5 in Part 2, the main study.

Table 7.a Prohibited Medications, Supplements, Dietary Products

28 Days Prior to Check-in (Day -1) of Period 1	7 Days Prior to Check-in (Day -1) of Period 1	72 Hours Prior to Check-in (Day -1) of Period 1
Prescription medications (other than donepezil, where applicable)	OTC medications (a)	Products containing caffeine
Nutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements	poppy seeds
Intake of known OTC inhibitors/inducers of CYPs 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1, and 2A6 (b) Intake of the following drug classes: anti-emetics; antidiarrhetics, anticholinergics, cholinergic agonists and laxatives	Foods or beverages containing grapefruit or Seville-type (sour) oranges and marmalade, apple, orange, or pineapple juices, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	
Nicotine-containing products	Alcohol containing products	
Immunization/vaccines		

OTC=over-the-counter.

(a) Occasional use of acetaminophen/paracetamol (≤ 1 g/day) or other medication as approved by Takeda on a case-by-case basis is allowed, but is prohibited on dosing and sample collection days. Prohibition and approval on a case-by-case basis may both be acceptable terms.

(b) For a list of moderate/strong CYP3A4, 2D6, or 2C9 inducers/inhibitors, see [Appendix F](#).

Subjects must be instructed not to take any medications including OTC products, without first consulting with the investigator.

7.5 Diet, Fluid, and Activity Control

7.5.1 Part 1

Subjects will be confined to the clinic for the duration of the treatment period (Day -1 through Day 4).

During the confinement period, subjects will receive 3 meals and an evening snack. The breakfast on Day 1 will be a low-fat, low-calorie, defined as <300 calories and <20% fat content. The 2 meals will have approximately 30% fat (relative to the total calories). The study menu should be recorded and submitted to the study file with a copy provided to the sponsor prior to the start of the study. The start and end time of meals and percentage of meals consumed on Days 1 to 2 will be recorded in the electronic case report form (eCRF).

7.5.2 Part 2

Subjects will be confined to the clinic for the duration of each treatment period (Day -1 through Day 3).

During the confinement in each treatment period, subjects will receive 3 meals and an evening snack. The breakfast on Day 1 of each treatment period will be a low-fat low-calorie, defined as <300 calories and <20% fat content. The 2 meals will have approximately 30% fat (relative to the total calories). The meals served on the day of dosing should be identical (same items offered) for each period in the study. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor prior to the start of the study. The start and end time of meals and percentage of meals consumed on Days 1 and 2 will be recorded in the eCRF.

TAK-071 or matching placebo will be administered with approximately 240 mL of water after a fast of at least 8 hours as a single PO dose (DIC) 24 hours before scopolamine dosing and approximately 1.5 hours following a low-calorie, low-fat breakfast. No additional food will be permitted for up to 4 hours after TAK-071 dosing. Donepezil will be administered with approximately 240 mL of water after a fast of at least 8 hours as a single PO dose 3 hours before scopolamine dosing. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after TAK-071, donepezil, or placebo administration. Meal timings, as well as their caloric and fat content, may be changed in the event of adjustments to the TAK-071 administration time.

Subjects will remain upright (seated, standing, or ambulatory) for 1 hour following the dose administration, except as necessitated by the occurrence of an AE or study procedures (eg, obtaining 12-lead ECG). Subjects will refrain from strenuous and/or unaccustomed exercise throughout the entire course of the study.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.18.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

- Liver function test (LFT) abnormalities

Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/Baseline status, see Section 9.1.8), if the following circumstances occur at any time during study drug treatment:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8× upper limit of normal (ULN), or
- ALT or AST >5× ULN and persists for more than 2 weeks, or
- ALT or AST >3× ULN in conjunction with elevated total bilirubin >2× ULN or international normalized ratio (INR) >1.5, or

- ALT or AST $>3 \times$ ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($>5\%$).
- 2. Significant protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
- 3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documentation.
- 4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

- 5. Study termination. The sponsor, IRB, independent ethics committee (IEC), or regulatory agency terminates the study.
- 6. Other.

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Drug

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term “study drug” refers to all or any of the drugs defined below.

- TAK-071 and matching placebo.
- Scopolamine and matching placebo.
- Donepezil and matching placebo.

8.1.1.1 *Investigational Study Drug*

TAK-071 Drug Substance

TAK-071 drug substance will be manufactured by Ube Industries Limited, Yamaguchi, Japan and supplied to the clinical site and then compounded into a hard capsule.

TAK-071 DIC and Matching Placebo

The TAK-071 DIC will be prepared at the clinical site by feeding TAK-071 drug substance into a hard gelatin capsule (color: Swedish orange opaque). The range of TAK-071 drug substance loaded will be 1 to 30 mg per capsule. Compounding and blinding instructions will be provided to the clinical site using the compounding worksheet or a similar document. The matching placebo will be an empty capsule and will also be prepared at the site.

The composition of the TAK-071 DIC and matching placebo is provided in [Table 8.a](#).

Table 8.a Composition of TAK-071 for DIC and Matching Placebo

Components	TAK-071 DIC	Matching Placebo
TAK-071	1-30 mg	0 mg
Hard gelatin capsule (Size: 00, Color: Swedish orange opaque)		

8.1.1.2 *Donepezil and Matching Placebo*

Donepezil 10 mg tablet manufactured by Eisai Inc. will be overencapsulated, labeled in a blinded fashion with third-party dispensing, and delivered as a PO capsule. The composition of the overencapsulated donepezil and matching placebo is provided in [Table 8.b](#).

Table 8.b Composition of Overencapsulated Donepezil and Matching Placebo

Components	Aricept OE	Matching Placebo
Donepezil 10 mg tablet, United States Pharmacopeia	1 tablet	-
Microcrystalline cellulose, National Formulary	qs	qs
Hard gelatin capsule (Color: Swedish orange opaque)		

OE=overencapsulated.

qs=quantity sufficient.

8.1.1.3 *Scopolamine and Matching Placebo*

Scopolamine, under generic name hyoscine hydrobromide, manufactured by Martindale Pharmaceuticals Ltd. will be delivered as a 0.5 mg SC injection.

The placebo for scopolamine will be the equivalent volume of saline delivered as SC injection.

8.1.1.4 *Sponsor-Supplied Drug*

TAK-071 drug substance is manufactured by Ube Industries Limited, Yamaguchi, Japan and supplied to the clinical site by Takeda Development Center Americas, Inc. (TDC Americas).

Scopolamine will be sourced from the United Kingdom as hyoscine hydrobromide 600 µg/mL ampoules and supplied to the clinical site by TDC Americas.

Branded Aricept (as donepezil) will be sourced locally and overencapsulated by the clinical site.

8.1.2 **Storage**

Based upon the recent stability study data, the recommended storage conditions for the TAK-071 DIC are 20°C to 25°C (68°F to 77°F), with excursion permitted within 15°C to 30°C (59°F to 86°F). Any excursions from the labeled storage conditions must be reported to Takeda immediately.

Overencapsulated donepezil must be stored according to the label.

Scopolamine must be stored according to the commercial label.

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction.

All study drugs must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 **Dose and Regimen**

8.1.3.1 *Part 1*

TAK-071 80 mg on Day 1 (24 hours prior to scopolamine administration) administered as DIC PO and scopolamine 0.5 mg SC on Day 2.

8.1.3.2 Part 2

TAK-071 dose will be selected based on the SRD part of the study TAK-071-1001 and part 1 of this study.

- Treatment A=scopolamine matching placebo SC + TAK-071 matching placebo PO + donepezil matching placebo PO.
- Treatment B=scopolamine 0.5 mg SC + TAK-071 matching placebo PO + donepezil matching placebo PO.
- Treatment C=scopolamine 0.5 mg SC + TAK-071 PO + donepezil matching placebo PO.
- Treatment D=scopolamine 0.5 mg SC + TAK-071 PO + donepezil 10 mg PO.
- Treatment E=scopolamine 0.5 mg SC + TAK-071 matching placebo PO + donepezil 10 mg PO.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Study Drug Assignment and Dispensing Procedures

8.2.1 Part 1

Subjects will be assigned, in the order they are enrolled to receive treatment. Subjects will be assigned a 4-digit enrollment number by the clinic site personnel in sequential order beginning with 1001 and ending with 1006.

8.2.2 Part 2

Subjects will be assigned, in the order in which they are randomized into the study, to receive their treatment according to the randomization schedule allocated to the site.

Subjects will be assigned a 4-digit randomization number. The number will be assigned by the clinic site personnel in sequential order beginning with 2001 and ending with 2040. This 4-digit number will be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections. This 4-digit number should only be used

for the purposes described in this section. It does not replace the 3-digit subject number which is assigned at the time the informed consent is obtained and which is used for all other procedures to identify the subjects throughout the study.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule and will provide it to the site pharmacist prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

For Part 1 (initial substudy), drug will be administered open-label.

For Part 2 (main study), the investigational drug blind is maintained through a randomization schedule held by the dispensing pharmacist. The site-designated study personnel will maintain the investigational drug blind information. The study subjects, Principle Investigator, as well as all other clinical research site staff, will remain blinded to treatment throughout the conduct of the study. Sponsor staff will be unblinded, and will ensure that the blind is not accidentally broken.

8.5 Unblinding Procedure

This is applicable only to Part 2 (main study). The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. All study assessments and causality should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the study drug blind is broken to discuss the need for unblinding.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, the site should contact the sponsor to determine if study drug should be stopped or if the subject should be withdrawn from the study.

No change should be made to any assessment of the subject after unblinding.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (TAK-071 drug substance, DIC, donepezil, scopolamine, and matching placebos), the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee or destruction at the site according to local procedures following sponsor approval.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee

should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs (TAK-071 drug substance, DIC, donepezil, scopolamine, and matching placebos) received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- A site representative or unblinded pharmacy monitor, otherwise uninvolved with study conduct, will review the randomization table/schedule and subject dosing log prior to Day 1 dosing and following dosing to ensure all subjects received the correct dose of study drug.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all sponsor-supplied drugs (TAK-071 drug substance, DIC, donepezil, scopolamine, and matching placebos) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date, date and amount dispensed, including initials, seal, or signature of the person dispensing the drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in [Appendix A](#).

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section [15.2](#).

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed, including requesting that a subject fast for laboratory evaluations.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.1.1 *Pharmacogenomic Informed Consent Procedure*

Pharmacogenomics (PGx) informed consent is a component of the overall study informed consent. The requirements are described in Section [15.2](#).

PGx sample collection is mandatory.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, caffeine consumption, alcohol use, and smoking status of the subject at Screening. The following data will also be collected: years of full-time education and academic qualifications.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section [9.1.7](#)).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 30 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A Baseline physical examination (defined as the assessment prior to first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as not clinically significant (NCS) or clinically significant (CS) by the investigator and recorded in the

source document and eCRF. All CS findings/changes will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0 or Section 9.1.7.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the study drug must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF described in Section 10.0.

9.1.4 Weight, Height and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Height is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as:

$$\text{Metric:} \quad \text{BMI} = \text{weight (kg)/height (m)}^2$$

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then $\text{BMI} = 79.2 / 1.76^2 = 25.56818 \text{ kg/m}^2$

The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 kg/m². However, if the BMI is used as entry criteria, then this determination must be made after rounding.

9.1.5 Vital Sign Procedure

Vital signs will include body temperature (oral), respiratory rate, supine blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (beats per minute [bpm]).

All measurements will be recorded on the source documents and in the eCRF.

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject OTC. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at Screening examination, according to the judgment of the investigator. The condition (ie, diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. During the treatment period, laboratory samples will be taken following a minimum 8 hour overnight fast on the days stipulated in the Schedule of Study Procedures (Appendix A).

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells	ALT	pH
White blood cells with differential (absolute counts)	Albumin	Specific gravity
Hemoglobin	Alkaline phosphatase	Protein
Hematocrit	AST	Glucose
Platelets	Total bilirubin	Blood
	Direct bilirubin	Nitrite
	Total protein	
Coagulation	Creatinine	Microscopic analysis (only if positive dipstick results):
PT/INR	Blood urea nitrogen	white blood cells, red blood cells, epithelial cells, casts
aPTT	Creatine kinase	
	GGT	
	Potassium	
	Sodium	
	Glucose	
	Chloride	
	Bicarbonate	
	Calcium	
	Lactate dehydrogenase	
	Glutamate dehydrogenase	

Diagnostic Screening:	
Serum	Urine
Hepatitis panel, including HBsAg and anti-HCV	Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine

aPTT=activated partial thromboplastin time, GGT= gamma-glutamyl transferase, PT=prothrombin time.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3× ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a

maximum of 7 days and preferably within 48-72 hours after the abnormality is noted. (Refer to Section 7.6 and Section 10.2.3 for the appropriate guidance on reporting abnormal LFTs.)

If the ALT or AST remains elevated $>3 \times$ ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 for reporting requirements).

The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the principal investigator or sub investigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose will require clear and complete documentation in the source documents as to the investigator's assessment of NCS before proceeding with enrollment/randomization.

All CS laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A CS laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.9 Contraception and Pregnancy Avoidance Procedure

9.1.9.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 70 days after the last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential *must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

9.1.9.2 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchiectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as “those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are excluded, the only acceptable methods of contraception are:
 - Intrauterine device.
 - Bilateral tubal occlusion.
2. Unacceptable methods of contraception are:
 - Hormonal methods.
 - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
 - Spermicides only.
 - Withdrawal.
 - No method at all.
 - Use of female and male condoms together.
 - Cap/diaphragm/sponge without spermicide and without condom.
 - Sexual abstinence is NOT an acceptable method of contraception.
3. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of sperm during the course of the study.

9.1.9.3 General Guidance With Respect to the Avoidance of Pregnancy

During the course of the study all subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
- Assessment of subject compliance through questions such as:
 - Have you used the contraception consistently and correctly since the last visit?
 - Have you forgotten to use contraception since the last visit?

9.1.10 Pregnancy

Women of childbearing potential will not be included in this study.

Any pregnancies in the partner of a male subject during the study or for 70 days after the last dose should be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study drug, eg, after Day 1 of Period 1 or within 70 days after the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.1.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject's partner of their right to receive treatment information. If the subject or subject's partner chooses to receive unblinded treatment information, the individual blind should be broken by the investigator.

If the female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All reported pregnancies, in female partners of male subjects, will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using one of the following categories: within normal limits, abnormal but NCS, or abnormal and CS. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, QT interval with Fridericia correction, and QT interval with Bazett correction.

One copy of the 12-lead ECG with the investigator's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. If the original ECG is printed on thermal paper, the ECG report must be photocopied and certified. The photocopy will be filed with the original ECG in the source.

If an ECG is scheduled at the same time as blood draws or vital signs, the ECG will be obtained within 0.5 hours before the scheduled blood draw/vital sign assessment. Predose ECGs may be done within 1 hour prior to dosing. If an ECG coincides with a meal, the ECG will take precedence followed by the meal.

9.1.12 PGx Sample Collection

PGx sample collection is mandatory.

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) form the basis for the genes that make the body produce proteins such as enzymes, drug transporters, or drug targets, and may be evaluated for the genetic contribution of how the drug is broken down, or how the drug affects the body. This is called a “Pharmacogenomics research study.” Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to TAK-071.
- Finding out more information about how TAK-071 works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to TAK-071.
- Identifying variations in genes related to the biological target of TAK-071.

This information may be used, for example, to develop a better understanding of the safety and efficacy of TAK-071 and other study drugs, to increase understanding of the disease/condition being studied, and for improving the efficiency, design, and study methods of future research studies.

9.1.12.1 DNA Sample Collection

Parts 1 and 2

One 6-mL whole blood sample for DNA isolation will be collected before dosing on Day 1 from each subject in the study into plastic potassium ethylenediamine-tetraacetic acid (K₂EDTA) spray-coated tubes, and stored under frozen conditions.

Part 2

One 6-mL whole blood sample for DNA sample will be used to explore the relationship between cognitive response to scopolamine and the apolipoprotein E (APOE) status of the subject. This sample will be collected from individuals during Screening at the pre-enrollment enrichment Screening Visit.

If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible. In addition, if the DNA sample is not collected at the designated time point described in the protocol, it can be collected at a later time point.

In addition, because pharmacogenomics is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response or diseases, which may lead to additional hypothesis-generating exploratory research on stored samples.

9.1.12.2 RNA Sample Collection

Part 1

Two whole blood samples (2.5 mL per sample) will be collected at each time point for RNA analysis from each subject into a PAXgene tube.

Part 2

Two whole blood samples (2.5 mL per sample) will be collected at each time point for RNA analysis from each subject in each of the 5 Treatment Periods into a PAXgene tube.

Each PGx sample for a study subject should be identifiable on the requisition form with an 8-digit subject identification (ID), the 5-digit site number plus the 3-digit subject number.

The samples will be stored for no longer than 15 years after completion of the TAK-071 study and/or until the drug development of TAK-071 is no longer actively pursued by Takeda or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda.

Detailed instructions for storing, handling, and shipping samples are provided in the Laboratory Manual.

9.1.13 PK Sample Collection

9.1.13.1 Collection of Blood for PK Sampling

Instructions for sample collection, processing, and shipment are provided in [Appendix E](#).

In Part 1, the substudy, serial blood samples for determination of TAK-071 will be collected according to [Table 9.b](#).

Table 9.b Collection of Blood Samples for PK Analysis – Part 1

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Plasma	1	Predose (within 30 minutes before TAK-071 dosing) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 25, 26, 27, 28, 30, 32, 34, 36, 40, 48, 56, 64, 72, 96, and 168 hours post TAK-071 dose

In Part 2, the main study, serial blood samples for determination of TAK-071, scopolamine, and donepezil will be collected during each period according to [Table 9.c](#).

Table 9.c Collection of Blood Samples for PK Analysis – Part 2

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Plasma	1	-24 hours (predose of TAK-071) and 0 (predose of scopolamine), 1, 2, 3, 4, 6, and 10 hours postdose relative to scopolamine dosing.
Scopolamine	Plasma	2	Predose (predose of scopolamine) and 1, 2, 3, 4, 6, and 8 hours postdose relative to scopolamine dosing.
Donepezil	Plasma	2	-3 hours (predose of donepezil) and 0 (predose of scopolamine), 1, 2, 3, 4, 6, and 10 hours postdose relative to scopolamine dosing.

Note: Time points relative to each study drug administration, as shown in [Figure 6.d](#), are as follows: (a) TAK-071: predose (approximately 30 minutes before dosing) and 24, 25, 26, 27, 28, 30, and 34 hours postdose relative to TAK-071 dosing, (b) Donepezil: predose (within 30 minutes before dosing) and 3, 4, 5, 6, 7, 9, and 13 hours postdose relative to donepezil dosing, and (c) Scopolamine: predose (predose of scopolamine) and 1, 2, 3, 4, 6, and 8 hours postdose relative to scopolamine dosing.

The actual time of sample collection will be recorded on the source document and eCRF.

Sampling time points may be adjusted based on the preliminary emerging PK data from the FIH study, but the total number of samples collected per subject should not exceed the planned number.

Placebo samples will not be analyzed by the bioanalytical laboratory except 2 samples per subject receiving placebo, 1 predose and the other around the t_{max} to ensure from a safety perspective that no additional subjects could have been on active treatment.

9.1.13.2 Bioanalytical Methods

Plasma concentrations of TAK-071, donepezil, and scopolamine will be measured by separate methods using high-performance liquid chromatography with tandem mass spectrometry.

9.1.14 PK Parameters

The PK parameters of TAK-071 and its metabolites, donepezil, and scopolamine will be determined from the concentration-time profiles for all evaluable subjects according to standard noncompartmental analysis methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated for plasma concentration values of TAK-071 and its metabolites:

Symbol/Term	Definition
Plasma	
$AUC_{t_1-t_2}$	Area under the plasma concentration-time curve from time t_1 to time t_2
AUC_t	Area under the plasma concentration-time curve from time 0 to time t
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity
C_{max}	Maximum observed plasma concentration
$t_{1/2z}$	Terminal disposition phase half-life
t_{max}	Time of first occurrence of C_{max}

In general, if AUC_{∞} cannot be accurately estimated in a sufficient number of subjects, area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}) will be reported instead. Additional plasma PK parameters may be derived and/or reported as appropriate.

In addition to the above, other PK analysis methodologies may be employed to further characterize the PK behavior of TAK-071 in healthy subjects, including conventional compartmental analyses and nonlinear mixed-effect modeling using TAK-071 pooled data across studies.

9.1.15 PD Assessments (Only for Part 2)

9.1.15.1 Cognitive Testing

CCI



Table 9.d CogState Cognitive Test Battery

Task Name	Time to Complete (mins)	Unit of Measurement	Cognitive Domain
CCI	5	Total number of errors	Executive function, problem solving, reasoning, episodic memory
	2	Log ₁₀ milliseconds	Psychomotor function/information processing
	3	Log ₁₀ milliseconds	Attention
	6	Arcsine proportion correct	Visual learning
	2	Arcsine proportion correct	Working memory

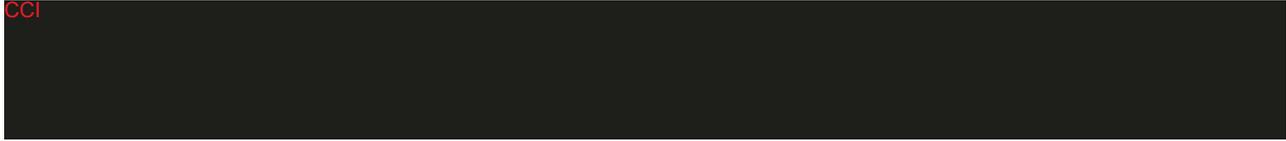
9.1.15.2

CCI

CCI



CCI



9.1.15.3

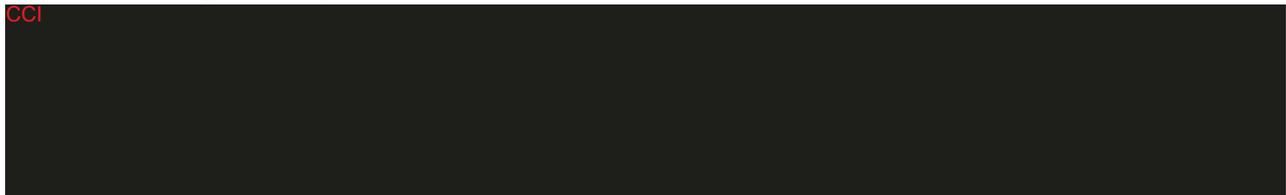
CCI

CCI



9.1.15.4 *Pupillometry*

CCI



9.1.16 PD Parameters (Only for Part 2)

CCI

The PD parameters will include the following:

Symbol/Term	Definition
AUEC _t	Area under the effect curve from time 0 to time t
E _{max}	Maximum observed effect
Time to E _{max}	Time from scopolamine dosing to occurrence of E _{max}

Additional PD parameters may be estimated and/or reported, as appropriate.

CCI

9.1.17 PK/PD Assessment Order (Only for Part 2)

For PD Baseline on Day 1 and predose to scopolamine the following order should be followed:

- Low-calorie low-fat breakfast: Approximately 2.5 hour prior to study drug dosing.
- qEEG and ERP: Approximately 120 minutes prior to study drug dosing.
- Pupillometry: Approximately 100 minutes prior to study drug dosing.
- Cognitive test: Immediately after pupillometry and approximately 90 minutes prior to study drug dosing.
- Sleepiness monitoring: Immediately after cognitive testing and approximately 70 minutes prior to study drug dosing.
- PK blood draw: To be taken approximately within 30 minutes of the scheduled time point.

PK/PD assessments that coincide at the same scheduled time point will be performed in the following order:

- qEEG: Approximately 40 minutes prior to scheduled time point.
- Pupillometry: Immediately after qEEG and approximately 5 minutes prior to scheduled time point.
- PK blood draw: To be taken approximately at the scheduled time.
- Cognitive test: Immediately after PK blood draw.

- Sleepiness monitoring: Immediately after cognitive testing.

9.1.18 Assessment of Suicidal Ideation and Behavior

The C-SSRS was developed by researchers at Columbia University as a tool to systematically assess suicidal ideation and behavior in subjects during participation in a clinical trial of centrally-acting drugs. The C-SSRS is composed of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with subquestions assessing the severity. The tool is administered via interview with the subject.

9.1.19 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If a subject is withdrawn at the Screening visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria <specify reason>.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Subject identification numbers assigned to subjects who fail Screening should not be reused. If a subject fails Screening, but is later successfully rescreened, the data for the subject will be entered as if these were two separate subjects. Therefore the data should be entered as follows:

1. The screen failure data should be entered as a screen failure subject.
2. Rescreened subjects should be assigned a new subject number and treated as a stand-alone subject.

9.1.20 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study drug, appropriate mouth and/or hand checks will be

performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study drug supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations in Part 1, the initial substudy, and Part 2, the main study, are shown in [Appendix A](#). Assessments should be completed at the designated visit/time points.

9.3.1 Study Exit

For Part 1, subjects will be discharged from the clinic on Day 5; for Part 2, subjects will be discharged from clinic on Day 3 of Period 5.

For all subjects receiving study drug, the investigator must complete the End of Study eCRF page.

9.3.2 Early Termination

The reason for discontinuation must be documented in the source document and eCRF.

PK samples should be collected at the Early Termination Visit, if possible and relatively close to a protocol-specified time point. The site may seek guidance. For example, collect samples if early withdrawal is due to an AE and/or if several hours elapsed since last blood draw.

For all subjects receiving study drug, the investigator must complete the End of Study eCRF page.

9.3.3 Follow-up Visit/Telephone Call

For Part 1, a Follow-up Visit for PK will occur on Day 8 and a final Follow-up Visit will occur on Day 12 (± 2).

For Part 2, the Follow-up Visit will occur on Day 9 (± 2 days) of Period 5 and will be considered the subject's last visit.

If abnormal CS findings are observed at discharge, subjects must visit the clinic for re-evaluation per investigator's discretion. If no abnormal CS findings are observed at study exit, follow-up will be conducted via a telephone call.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12. The genetic material will be preserved and retained at **PPD** for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The samples will be sent to a central laboratory that processes the blood samples and serves as a secure storage facility. The samples will be initially stored at PPD. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

When subjects request disposal of a stored sample during the retention period, the site will ask PPD to destroy the sample via the sponsor according to the procedure. PPD will destroy the sample in accordance with the procedure, and notify the site and sponsor.

The sample will be labeled with a unique sample identifier as in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers; the samples are stripped of all personal identifying information but a key linking the samples to clinical analysis data exists. This link means that the subject may be identified but only indirectly. The code number sample identifier will be kept secure by or on behalf of the sponsor.

Subjects who consented and provided a PGx sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

9.5 Blood Volume

Total blood sampling volume for an individual subject for Part 1 and Part 2 are shown in Table 9.e and Table 9.f, respectively.

Table 9.e Approximate Blood Volume for Part 1

Sample Type	Sample Volume (mL)	Number of Samples							Total Volume (mL)
		Screening and Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	
Clinical laboratory tests	20 mL	2 (a)	1	1	1	1	2	1	180
Serology test	8.5 mL	1	0	0	0	0	0	0	8.5
PGx DNA sample collection	6 mL	0	1	0	0	0	0	0	6
PGx RNA sample collection	2.5 mL	0	2	0	2	0	0	0	10
TAK-071 PK blood collection	3 mL	0	13	10	3	1	1	1	87
Total Approximate Blood Sampling Volume									291.5

(a) 1 each at Screening and at Check-in.

Table 9.f Approximate Blood Volume for Part 2

Sample Type	Sample Volume (mL)	Number of Samples					Total Volume (mL)	
		Screening	Period 1 (Day -1 to 3)	Period 2 (Day -1 to 3)	Period 3 (Day -1 to 3)	Period 4 (Day -1 to 3)		Period 5 (Day -1 to 3)
Clinical laboratory tests	20 mL	2	1	1	1	1	2	160
Serology test	8.5 mL	1	0	0	0	0	0	8.5
PGx DNA sample collection	6 mL	1	1	0	0	0	0	12
PGx RNA sample collection	2.5 mL	0	4	4	4	4	4	50
TAK-071 PK blood collection	3 mL	0	8	8	8	8	8	120
Scopolamine PK blood collection	4 mL	0	7	7	7	7	7	140
Donepezil PK blood collection	4 mL	0	8	8	8	8	8	160
Total Approximate Blood Sampling Volume								650.5

The maximum volume of blood for Part 1 at any single day is approximately 70 mL, and the approximate total volume of blood for the study is 291.5 mL.

The maximum volume of blood for Part 2 at any single day is approximately 120 mL, and the approximate total volume of blood for the study is 650.5 mL.

Direct venipuncture is the preferred method of blood collection; however, a catheter with a single saline flush may be used.

A catheter with a normal saline flush may be used; however, the total blood volume does not include discarded blood from predraws (assuming minimally the catheter dead volume plus 1 mL of blood is discarded each time a sample is collected from a catheter). Should a catheter be used, the total blood volume taken during the study must not exceed 650.5 mL.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be CS (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG retest and/or continued monitoring of an abnormal value or findings are not considered an

intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, “worsening of...”).
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious, or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg “worsening of...”).
- If a subject has a pre-existing degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of...”).

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of...”).
- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of...”).

Changes in intensity of AEs/Serious PTEs:

- If the subject experiences changes in intensity of an AE/serious PTE, the event should be captured once with the maximum intensity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the

worsening of the condition should be recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing conditions and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
 - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
 - May require intervention to prevent items 1 through 5 above.
 - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
 - Includes any event or synonym described in the Takeda Medically Significant AE List ([Table 10.a](#)).

Table 10.a Takeda Medically Significant AE List

	Term
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product Neuroleptic malignant syndrome / malignant hyperthermia Spontaneous abortion / stillbirth and fetal death

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as “Important Medical Events” satisfying SAE reporting requirements.

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Intensity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

- Mild: The event is transient and easily tolerated by the subject.
- Moderate: The event causes the subject discomfort and interrupts the subject’s usual activities.
- Severe: The event causes considerable interference with the subject’s usual activities.

10.1.6 Relationship of AEs to Study Drug(s)

The relationship (causality) of each AE to study drug(s) will be assessed using the following categories:

- Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
- Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining “Not recovered/not resolved”.

- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject’s participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug on Day 1 for Part 1, or Pre-enrollment Enrichment Visit for Part 2, or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug (Day 1 of Period 1). Routine collection of AEs will continue until the Follow-up Visit/Call or Early Termination.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.

5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated $>3 \times$ ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST $>3 \times$ ULN and total bilirubin $>2 \times$ ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory

tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. If the subject was hospitalized, copies of any relevant data from the hospital records (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of the study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary (WHODRUG).

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and date.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to

retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

13.1.1.1 Safety Set

The Safety Analysis Set will consist of all subjects who are enrolled and received 1 dose of study drug. Subjects in this analysis set will be used for demographics, Baseline characteristics, and safety summaries.

13.1.1.2 PK Set

The PK Set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration or amount of drug in the urine.

If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis, but the data will be presented in the subject listings.

13.1.1.3 PD Set

The PD Set will consist of all subjects who receive study drug and have at least 1 postdose PD measurement.

If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis but will be presented in the subject listings.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and Baseline characteristics will be summarized for all randomized subjects. For continuous variables (eg, age, height, weight, and BMI), the summary will consist of descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). For categorical variables (eg, ethnicity and race), the summary will consist of number and percentage of subjects in each category.

13.1.3 PK Analysis

Plasma concentrations of TAK-071, donepezil, and scopolamine will be summarized from each treatment using descriptive statistics.

Individual plasma concentration data versus time will be presented in a data listing.

Plasma PK parameters for TAK-071, donepezil, and scopolamine will be summarized separately.

A more detailed analysis will be presented in the SAP. The relationship between PK and PD may be explored and detailed in a separate plan. Additional analyses may also be considered.

13.1.4 PD Analysis

13.1.4.1 Cognitive Testing Analysis

To address the statistical hypotheses related to the time course of scopolamine effects, cognitive endpoints will be analyzed using a mixed analysis of variance (ANOVA) model appropriate for a 5-period crossover with fixed factors for period, sequence, treatment, hour, and treatment by hour. Additionally, the model will contain a random factor subject nested in sequence (the between-subject error) and a random residual error term (the within-subject error). A 2-sided t-test ($\alpha=0.05$) using the within subject mean squared error from the mixed ANOVA model will be examined to test the primary hypothesis. Treatment differences, 2-sided 95% CIs, 2-sided p-values, and effect sizes will be presented for all time points, with 2 hours post scopolamine being the time frame for the primary endpoint.

To address the statistical hypotheses related to area under the effect curve (AUEC) endpoints, cognitive endpoints will be analyzed using an ANOVA model appropriate for a 5-period crossover with fixed factors for treatment, period, and sequence. Additionally, the model will contain a random factor subject nested in sequence (the between-subject error) and a random residual error term (the within-subject error). A 2-sided t test ($\alpha=0.05$) using the within subject mean squared error from the mixed ANOVA model will be examined to test the statistical hypothesis.

For AUEC endpoints, the natural log scale treatment differences (eg, the primary treatment comparison of Treatment Y – Treatment X) will be exponentiated and reported as a mean percent change along with 95% CIs for the true mean percent change as a summary measure. Other statistical treatments (such as multivariate analysis of covariance [ANCOVA]) will be outlined in the SAP.

The Baseline cognitive measure will be included in the model as a covariate.

Other statistical analyses will be performed as appropriate.

13.1.4.2

CCI

CCI

13.1.5 Safety Analysis

The safety of TAK-071 in combination with scopolamine will be assessed through AEs, clinical laboratory results, physical examination findings, ECG findings, vital signs, and suicidal assessments.

Summary tables will include the number and percent of subjects in each treatment experiencing at least 1 TEAE by system organ class and preferred term. If a subject has more than 1 AE that codes to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than 1 AE within a system organ class category, the subject will be counted only once for that system organ class.

TEAEs possibly or probably related to study medication will be tabulated in the same manner. TEAEs will also be summarized by maximum intensity. All AEs will be listed.

AEs will be summarized using the safety analysis set. All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class.

Clinical laboratory tests (hematology, chemistry, and urinalysis), vital signs, and ECG parameters will be listed. The results that meet TDC markedly abnormal criteria will be flagged in the listing.

The percentage of subjects who meet TDC markedly abnormal criteria at least once postdose will be summarized.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

For Part 1, a sample size of 6 enrolled and 4 completers is considered sufficient for providing guidance on the TAK-071 dose selection for Part 2, the main study. This is not based on any statistical power.

For Part 2, a sample size of 26 subjects, approximately 3 subjects for each of the 10 sequences of the 5-period cross-over, will be used and is considered sufficient for evaluation of the primary cognitive endpoints for this study based on consideration of published scopolamine model literature and expert advice. Subjects who drop-out will not be replaced, therefore to ensure there are enough completers a total of 40 subjects will be recruited (4 per sequence).

In particular, this sample-size calculation was based on a consideration of effect sizes seen in a similar study [21]. Using a 2-sided alpha level of 0.05, this study has a 90% power to detect an effect size of 0.67 in the GMLT (sum of 5 trials) total number of errors for the primary treatment comparison of TAK-071+scopolamine vs placebo+scopolamine, assuming a total of 26 subjects complete the study and provide primary endpoint data.

At least 26 subjects will complete the study if 40 subjects are randomized, assuming the drop-out rate does not exceed 33%.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the sponsor or its designee (contract research organization [CRO]) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation eCRF should be completed by the site and acknowledged by the sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. [Table 14.a](#) defines the windows allowed for sample collections.

However, blood samples not collected within the interval specified for the scheduled sample time should be documented as deviations in the site source document.

Table 14.a Windows for PK Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 30 minutes predose	0 hour
±5	postdose to <24 hours
±30 minutes	>24 to ≤96 hours
±24 hours	>96 hours

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section [14.1](#).

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the “Responsibilities of the Investigator” that are listed in [Appendix B](#). The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB

IRBs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol’s review and approval. This protocol, the Investigator’s Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific Screening activity). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification no protocol activities, including Screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports, and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator’s final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a PGx sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with

this section and the study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on www.ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state, country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on www.ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

Part 1

Day	Screening	Check-in	Treatment				Final Visit	PK Follow-Up	Follow-Up (a)
	-28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	(Day 5)/ ET	Day 8	Day 12 (±2)
Informed consent	X								
Demographics and medical history	X								
Medication history	X								
HBsAg and anti-HCV	X								
Inclusion/exclusion criteria	X	X							
Height, weight and BMI (b)	X	X							
Pregnancy avoidance counseling	X	X					X	X	
Physical exam	X	X					X		(X)
Urine drug and urine alcohol screen	X	X							
Clinical laboratory evaluations (c)	X	X	X	X	X	X	X	X	(X)
Vital signs (d)	X	X	X	X	X	X	X	X	(X)
Concomitant medications (e)	X	X	X	X	X	X	X	X	X
12-lead ECG (f)	X	X	X	X	X	X	X	X	(X)
Confinement		X	X	X	X	X			
TAK-071 dosing (g)			X						
Scopolamine dosing (h)				X					
PGx DNA collection (i)			X						
PGx RNA collection (i)			X		X				
TAK-071 PK (j)			X	X	X	X	X (k)	X	
Food intake (l)			X	X					
CSSRS (m)	X	X					X		(X)
AE assessment (n)	X	X	X	X	X	X	X	X	X

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

ET=Early Termination Visit, h=hours.

- (a) Follow-up will occur by telephone on Day 12 (± 2) unless abnormal clinically significant findings are observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion. Assessments indicated in parentheses (X) are only to be performed in case of attendance to study site.
- (b) Height and BMI will be collected at Screening only.
- (c) Blood samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected upon rising after a minimum 8-hour overnight fast.
- (d) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained as indicated.
- (e) All ongoing medications will be recorded from Screening and throughout the study.
- (f) A standard 12-lead ECG will be recorded at Screening and at Check-in (Day -1), Day 1 (predose [within 60 minutes prior to dosing]), and upon rising on Days 2, 3, 4 and 5, final visit and follow-up visit (Day 8).
- (g) TAK-071 DIC will be administered on Day 1 (-24.0 hours relative to scopolamine dose).
- (h) Scopolamine will be administered on Day 2.
- (i) Blood samples for PGx analysis will be collected as follows: 6 mL for DNA on Day 1; 2 \times 2.5 mL for RNA predose on Day 1, and 24 hours post scopolamine dose.
- (j) Blood samples (one 3-mL sample per scheduled time) for PK analysis of plasma TAK-071 will be collected into chilled vacutainers (containing anticoagulant K₂EDTA) for plasma measurement of TAK-071 predose (within 30 minutes prior to dosing) and the specified time points (see [Table 9.b](#)).
- (k) A PK blood sample should be collected at the ET Visit if possible.
- (l) Food intake will be recorded on Days 1 and 2. On Day 1, breakfast will be served at 30 minutes prior to TAK-071 dose, lunch will be served at approximately 3.5 hours post TAK-071 dose, and dinner will be served at 11.5 hours post TAK-071 dose. On Day 2, breakfast will be served at 30 minutes prior to scopolamine dose, lunch will be served at approximately 5.5 hours post scopolamine dose, and dinner will be served at 9.5 hours post scopolamine dose.
- (m) C-SSRS will be determined as indicated. If clinically significant at Final Visit, C-SSRS will also be determined as part of the Follow-up Visit.
- (n) PTEs will be collected from signing of informed consent to predose of study drug on Day 1. Any events that occur after dosing with study drug on Day 1 will be captured as an AE.

Appendix A Schedule of Study Procedures (continued)

Part 2

Day	Screening	Periods 1, 2, 3, 4 and 5											Study Exit (a)	Follow-up (b)	
	Days -56 to -2	Check-in Day -1	Day 1			Day 2					Day 3 (Periods 1 to 4)	(Day 3 of Period 5)/ ET	Day 9 (±2) of Period 5		
Scheduled Time Relative to Scopolamine Dosing (c)			-26 h	-25 h	-24 h	-3 h	0 h	1, 2, and 3 h	4 h	6 h	8 h	10 h	24 h		
Informed consent	X														
Demographics and medical history	X														
Medication history	X														
HBsAg and anti-HCV	X														
Inclusion/exclusion criteria	X	X (d)													
Vital signs (e)	X	X	X										X	X	(X)
Height, weight and BMI (f)	X	X (d)													
Concomitant medications (g)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy avoidance counseling	X	X											X	X	
Physical exam	X	X											X	X	(X)
Urine drug and urine alcohol screen	X	X													
Randomization		X (d)													
Clinical laboratory evaluations (h)	X	X												X	(X)

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

Day	Screening	Check-in Day -1	Periods 1, 2, 3, 4 and 5											Study Exit (a)	Follow-up (b)
	Days -56 to -2		Day 1			Day 2						Day 3 (Periods 1 to 4)	(Day 3 of Period 5)/ ET	Day 9 (±2) of Period 5	
			-26 h	-25 h	-24 h	-3 h	0 h	1, 2, and 3 h	4 h	6 h	8 h				10 h
Scheduled Time Relative to Scopolamine Dosing (c)															
12-lead ECG (i)	X	X	X										X	X	(X)
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	
TAK-071 dosing (c) (j)				X											
Donepezil dosing					X										
Scopolamine dosing	X (k)					X									
PGx DNA collection (l)	X		X (d)												
PGx RNA collection (l)			X									X	X		
TAK-071 PK (c) (m)				X#		X	X	X	X			X		X (a)	
Donepezil PK (n)						X^	X	X	X	X		X		X (a)	
Scopolamine PK (o)							X*	X	X	X	X			X (a)	
CogState battery tests	X (k) (p)	X (q)		X (r)				X	X	X	X	X			
Sedation assessment (s)	X (k)			X				X	X	X	X	X			
CCI															
P300 ERP (t)				X				X		X		X			
CCI															
C-SSRS (v)	X	X											X	X	(X)
AE assessment (w)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

ET=Early Termination Visit, h=hours.

* Predose of scopolamine; # Predose of TAK-071; ^Predose of donepezil.

- (a) A PK blood sample should be collected at the ET Visit if possible.
- (b) Follow-up will occur by telephone on Day 9 (± 2) of Period 5 unless abnormal clinically significant findings are observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion. Assessments indicated in parentheses (X) are only to be performed in case of attendance to study site.
- (c) TAK-071 dosing time relative to scopolamine dosing and nominal times for scheduled assessments in Days 1 to 3 of each treatment period will be confirmed once actual TAK-071 clinical PK data becomes available. The times at which the assessments occur relative to scopolamine dosing may be changed and assessment time points might be removed, but the number of assessments will not be increased over the planned total number.
- (d) Period 1 only.
- (e) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained as indicated.
- (f) Height and BMI will be collected at Screening only.
- (g) All ongoing medications will be recorded from Screening and throughout the study.
- (h) Blood samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected upon rising after a minimum 8-hour overnight fast.
- (i) A standard 12-lead ECG will be recorded at Screening and at Check-in (Day -1), Day 1 (predose [within 60 minutes prior to dosing]), and Day 3 of each treatment period.
- (j) DIC will be dispensed for treatment.
- (k) Pre-enrollment enrichment procedures are to be performed after all other Screening assessments have been performed and deemed to be in compliance with study requirements. The GMLT will be performed at Baseline (after sufficient practice) and 1, 2, and 3 hours postdose. Baseline assessment will be done on 2 occasions (separated by 30 minutes) prior to administration of scopolamine, and the average will be derived.
- (l) Blood samples for PGx analysis will be collected as follows: 6 mL for APOE at pre-enrollment enrichment Screening Visit, 6 mL for DNA on Day 1 of Period 1 only; 2 \times 2.5 mL for RNA predose on Day 1, and 24 hours post scopolamine dose of each period.
- (m) Blood samples (one 3-mL sample per scheduled time) for PK analysis of plasma TAK-071 will be collected into chilled Vacutainers (containing anticoagulant K₂EDTA) for plasma measurement of TAK-071 predose (within 30 minutes prior to dosing) and the specified time points (See [Table 9.c](#)).
- (n) Blood samples (one 4-mL sample per scheduled time) for PK analysis of plasma donepezil will be collected into chilled Vacutainers containing anticoagulant sodium heparin (See [Table 9.c](#)).
- (o) Blood samples (one 4-mL sample per scheduled time) for PK analysis of plasma scopolamine will be collected into chilled Vacutainers containing anticoagulant K₂EDTA (See [Table 9.c](#)).
- (p) GMLT (only) will be undertaken at Baseline and at 1, 2 and 3 hours postdose of scopolamine (other CogState Battery tests will not be performed at this visit). Baseline assessment will be done on 2 occasions, separated by 30 minutes, prior to administration of scopolamine.
- (q) Subjects will be required to practice the cognitive test battery on up to 3 occasions, at investigator discretion.
- (r) Baseline assessment will be done on 2 occasions, separated by 30 minutes.
- (s) Level of sedation will be assessed after each cognitive test.
- (t) qEEG and P300 ERP will be measured at the time points outlined.
- (u) **CCI** [REDACTED].
- (v) C-SSRS will be determined as indicated. If clinically significant at Final Visit, C-SSRS will also be determined as part of the Follow-up Visit.
- (w) PTEs will be collected from signing of informed consent to pre-dosing of study drug on Day 1. Any events that occur after dosing with study drug on Day 1 will be captured as an AE.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the “Statement of Investigator” (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures; including study specific (nonroutine/nonstandard panel) Screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject’s medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject’s personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject’s legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's

legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
 - a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
 - b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
 - c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
 - d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
 - e) that the subject's identity will remain confidential in the event that study results are published.

25. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 70 days after the last dose of study drug after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as www.ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

Instructions for Processing of Plasma Samples for PK Analysis of TAK-071

1. Collect 3 mL of venous blood into a chilled Becton-Dickinson Vacutainer. All TAK-071 blood samples should be collected into Vacutainers containing K₂EDTA.
2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 (relative centrifugal force [RCF]) at 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots using 1.5 to 3.5 mL polypropylene cryotubes. A minimum of approximately 0.5 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-071-1002), analyte (TAK-071), sample matrix (ie, plasma) randomization number, period, profile day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C or lower until shipment to PPD. No more than 45-60 minutes will elapse between blood collection and freezing the plasma sample.

Instructions for Processing of Plasma Samples for PK Analysis of Donepezil

1. Collect 4 mL of venous blood into a chilled Becton-Dickinson Vacutainer. All donepezil blood samples should be collected into Vacutainers containing sodium heparin.
2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 RCF at 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots using 1.5 to 3.5 mL polypropylene cryotubes. A minimum of approximately 0.8 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-071-1002), analyte (donepezil), sample matrix (ie, plasma) randomization number, period, profile day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C or lower until shipment to PPD. No more than 45-60 minutes will elapse between blood collection and freezing the plasma sample.

Instructions for Processing of Plasma Samples for PK Analysis of Scopolamine

1. Collect 4 mL of venous blood into a chilled Becton-Dickinson Vacutainer. All scopolamine blood samples should be collected into Vacutainers containing K₂EDTA.
2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 RCF at 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots using 1.5 to 3.5 mL polypropylene cryotubes. A minimum of approximately 0.8 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-071-1002), analyte (scopolamine), sample matrix (ie, plasma) randomization number, period, profile day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C or lower until shipment to PPD. No more than 45-60 minutes will elapse between blood collection and freezing the plasma sample.

Shipping of Plasma Samples

The following instructions are recommended unless they differ from the site's standard operating procedures (SOPs) for labeling, packaging, or shipping of PK samples.

1. Biological samples (ie, plasma) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.
2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
3. Separate the duplicate SET 2 samples from the SET 1 samples.
4. Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc) containing additional absorbent material.
5. Using a permanent marker, write the 4-digit randomization sequence number, sample matrix (plasma) number of samples, and "SET 1" on each self-sealing bag.
6. Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 3 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."

7. An inventory of individual samples should accompany each shipment and should include the sponsor's name (Takeda), study drug (TAK-071), protocol number (TAK-071-1002), investigator's name, sample type (plasma), subject randomization number, Period, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.
8. For sample packing, utilize dry ice generously (eg, 20-25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a Styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
9. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the Styrofoam container. Place the lid on the Styrofoam container and seal completely with strapping tape. Place the Styrofoam container in a cardboard shipping carton and seal securely with strapping tape.
10. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
11. Affix an address label to each shipping carton. Complete the address label with the following information:

Plasma Samples for TAK-071 and Donepezil

PPD
PP
D

Phone: PPD

Fax: PPD

email: PPD

Plasma Samples for Scopolamine

PPD

Attn: PPD

2701 Kent Ave.

West Lafayette, IN 47906

Phone: PPD

email: PPD

12. Affix a carbon dioxide label on each carton, specifically:
 - Carbon Dioxide Solid UN-1845
 - Class 9 PKG GR III
 - Quantity _____
 - (fill in weight to nearest lb/kg and specify unit of measure used)
13. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark **KEEP FROZEN** on each carton. Specify a return address and contact person on the carton.
14. Obtain the airway bill number and a receipt of shipment from the carrier.
15. After shipping of the TAK-071 and donepezil samples, **please email PPD [REDACTED] at PPD [REDACTED]** to notify him of next day delivery. After shipping of the scopolamine samples, **please email PPD [REDACTED] at PPD [REDACTED]** to notify him of next day delivery. When calling, provide the following information:
 - Name of courier or transport company
 - Time and date the shipment left the clinical site
 - Airway bill number

Appendix F Moderate and Strong CYP3A4, 2D6, or 2C9 Inducers/Inhibitors

Please note that this is not an exhaustive list. The medication for each subject will have to be individually reviewed to identify potential CYP3A, 2D6, or 2C9 strong/moderate inhibitory medications or foods.

CYP Isoform	Strong Inhibitors	Moderate Inhibitors
CYP3A4	indinavir nelfinavir lopinavir /ritonavir ritonavir clarithromycin erythromycin itraconazole ketoconazole nefazodone saquinavir saquinavir/ritonavir telithromycin boceprevir conivaptan grapefruit /grapefruit juice mibefradil posaconazole telaprevir voriconazole	aprepitant atazanavir atazanavir/ritonavir fluconazole verapamil diltiazem amprenavir atazanavir ciprofloxacin darunavir/ritonavir fosamprenavir grapefruit/grapefruit juice imatinib cimetidine cyclosporin fluvoxamine posaconazole
CYP2C9	NA	amiodarone fluconazole miconazole oxandrolone
CYP2D6	Bupropion, fluoxetine, paroxetine, quinidine	cinacalcet, duloxetine, sertraline, terbinafine
	Strong Inducers	Moderate Inducers
CYP3A4	avasimibe phenobarbital carbamazepine phenytoin rifampicin rifabutin st. john's wort troglitazone	bosentan efavirenz etravirine modafinil nafcillin
CYP2C9	rifampicin secobarbital	NA
CYP2D6	dexamethasone, rifampin	NA

Other food products to be avoided

Star fruit/star fruit juice, pomegranates/pomegranate juice, papaya/papaya juice, Séville oranges/Séville orange juice

Sources: Polasek et al. [30], <http://medicine.iupui.edu/clinpharm/ddis/main-table/>,
<http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm>
 NA=not applicable.

Appendix G Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment No. 02 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Modify the main part (Part 2) of the study design to include a fifth arm and change the study to a 10-sequence, 5-period crossover study.

The primary change is described in Sections [6.2 Study Design – Part 2](#).

Initial wording: This is a randomized, double-blind, sponsor unblinded, placebo-controlled, 4-treatment, 4-period, 4-sequence crossover phase 1b proof of mechanism study to evaluate the effects of a single PO administration of TAK-071, a novel M₁R PAM, on scopolamine-induced deficits in cognitive function in healthy adult male subjects.

Approximately 32 subjects are expected to be randomized in this study, with the total of 8 subjects per sequence, with a minimum of 6 completers. A schematic of the study design is provided in Figure 6.c.

[Original Figure 6.c Schematic of Study Design – Part 2]

6.2.1 Pre-Enrollment Enrichment Screening – Part 2

...

Subjects will remain under observation for a minimum of 8 hours post-scopolamine administration to ensure that scopolamine-induced effects have worn off and it is safe for the subjects to leave the study center.

Any subjects unable to perform the CogState battery after training will be excluded from entering Part 2, the main study.

6.2.2 Treatment Sequences – Part 2

In each period, subjects will check-in at the study site on Day -1 and will be confined until Day 3 (approximately 24 hours postdose of scopolamine).

Subjects will be randomly assigned to 1 of 4 possible treatment sequences (described in Section 8.1.3) before the first dose of study drug, each consisting of 4 treatment periods (Table 6.a).

[Original Table 6.a Summary of Treatment Sequences in Study - Part 2]

...

Scopolamine will be administered as a single 0.5 mg SC injection.

...

Donepezil will be administered as a single 10 mg capsule PO 3 hours before injecting scopolamine to maximize the chances of observing a reversal of the

scopolamine-induced cognitive impairment.

...

Information on the safety and tolerability of TAK-071 in combination with scopolamine will be obtained from treatment periods in which active TAK-071 is administered (Treatment B). Safety and tolerability will be obtained during Treatment A for scopolamine alone and during Treatment C for donepezil in combination with scopolamine.

Amended or new wording This is a randomized, double-blind, sponsor unblinded, placebo-controlled, 4-5-treatment, 4-5-period, 4-10-sequence crossover phase 1b proof of mechanism study to evaluate the effects of a single PO administration of TAK-071, a novel M₁R PAM, on scopolamine-induced deficits in cognitive function in healthy adult male subjects.

Approximately 32-40 subjects are expected to be randomized in this study, with the total of 8-4 subjects per sequence, with a minimum of 6-3 completers. A schematic of the study design is provided in Figure 6.c.

[Revised Figure 6.c Schematic of Study Design – Part 2]

[Figure 6.c revisions:

- “Treatment Periods 1-4” column revised to “Treatment Periods 1 to 5”.
- Column added for “Wash out Periods 1 to 4” with “Days 4 to 20”.
- “Follow-Up” column; days revised from “Day 72 (±2)” to “Day 9 (±2) Period 5”.]

6.2.1 Pre-Enrollment Enrichment Screening – Part 2

...

Subjects will remain under observation for a minimum of 8 hours post-scopolamine **post-scopolamine** administration **per principal investigator’s discretion** to ensure that scopolamine-induced effects have worn off and it is safe for the subjects to leave the study center.

Any subjects **subject** unable to perform the CogState battery after training will be excluded from entering Part 2, the main study.

6.2.2 Treatment Sequences – Part 2

In each period, subjects will check-in at the study site on Day -1 and will be confined until Day 3 (approximately 24 hours postdose of scopolamine **or matching placebo**).

Subjects will be randomly assigned to 1 of 4-10 possible treatment sequences (described in Section 8.1.3) before the first dose of study drug, each consisting of 4-5 treatment periods (Table 6.a).

Table 6.a Summary of Treatment Sequences in Study - Part 2

Sequence	Period 1		Period 2		Period 3		Period 4		Period 5
1	A	<i>Minimum 3-week washout</i>	B	<i>Minimum 3-week washout</i>	D	<i>Minimum 3-week washout</i>	C -E	<i>Minimum 3-week washout</i>	C
2	B		C		A -E		D		
3	C		D		B -A		A		
4	D		A -E		C -B		B -C		
5	E		A		C		D		
6	A		C		B		E		
7	B		D		C		A		
8	C		E		D		B		
9	D		A		E		C		
10	E		B		A		D		

A=scopolamine + matching placebo for placebo SC + TAK-071 and matching placebo PO + donepezil; matching placebo PO.

B=TAK-071, scopolamine, and 0.5 mg SC + TAK-071 matching placebo for PO + donepezil; matching placebo PO.

C=donepezil, scopolamine, and 0.5 mg SC + TAK-071 PO + donepezil matching placebo for TAK-071; PO.

D=all placebo scopolamine 0.5 mg SC + TAK-071 PO + donepezil 10 mg PO.

E=scopolamine 0.5 mg SC + TAK-071 matching placebo PO + donepezil 10 mg PO.

Scopolamine (0.5 mg) or matching placebo will be administered as a single 0.5 mg SC injection.

TAK-071 or matching placebo will be administered as a single PO dose (as DIC) 24 hours before scopolamine administration.

...

Donepezil (10 mg) tablet (overencapsulated) or matching placebo will be administered as a single 10 mg capsule PO 3 hours before injecting scopolamine to maximize the chances of observing a reversal of the scopolamine-induced cognitive impairment.

...

Information on the safety and tolerability of TAK-071 in combination with scopolamine and/or donepezil will be obtained from treatment periods in which active TAK-071 is administered (Treatment B-Treatments C and D). Safety and tolerability will be obtained during Treatment A for placebo, Treatment B for scopolamine alone, and during Treatment ~~C~~-E for donepezil in combination with scopolamine.

Rationale for Change:

The new study design will provide information on the combined pharmacodynamic effect of TAK-071 and donepezil.

The following sections also contain this change:

- Title Page.
- Section 2.0 STUDY SUMMARY.
- Section 6.3.2 Justification for Design for Part 2.
- Section 7.5.2 Part 2.
- Section 8.1.3.2 Part 2.
- Section 8.2.2 Part 2.
- Section 8.6 Accountability and Destruction of Sponsor-Supplied Drugs.
- Section 9.1.12.2 RNA Sample Collection Part 2.
- Section 9.3.1 Study Exit.
- Section 9.3.3 Follow-up Visit/Telephone Call.
- Section 13.1.4.1 Cognitive Testing Analysis.
- Section 13.3 Determination of Sample Size.
- Appendix A Schedule of Study Procedures Part 2.

Change 2: Add an additional secondary objective and modify an exploratory/additional objective.

The primary change is described in Sections 5.1.2 and 5.1.3:

Initial wording

5.1.2 Secondary Objectives

- To characterize the safety and tolerability of a single PO dose of TAK-071 when co-administered with SC scopolamine (0.5 mg) in healthy subjects.
- To characterize the single PO dose plasma PK profile of TAK-071 when co-administered both with scopolamine and a low-calorie, low-fat breakfast in healthy subjects.
- To demonstrate assay sensitivity by using donepezil 10 mg as the positive control.

5.1.3 Exploratory/Additional Objectives

CCI



CCI



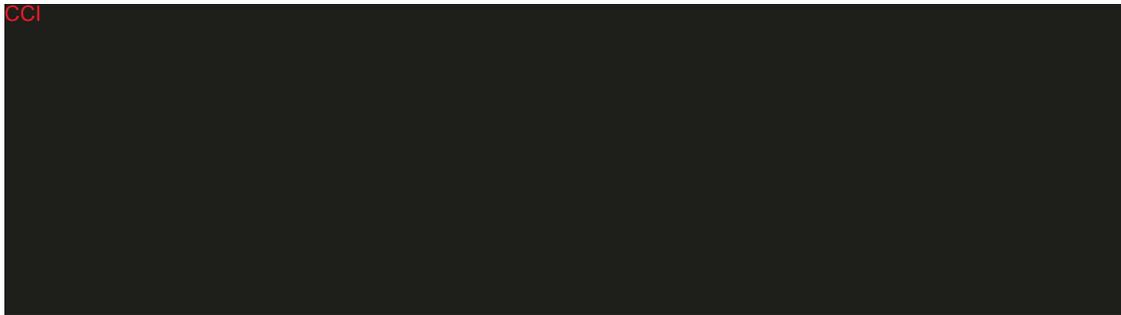
Amended **5.1.2 Secondary Objectives**

or new text

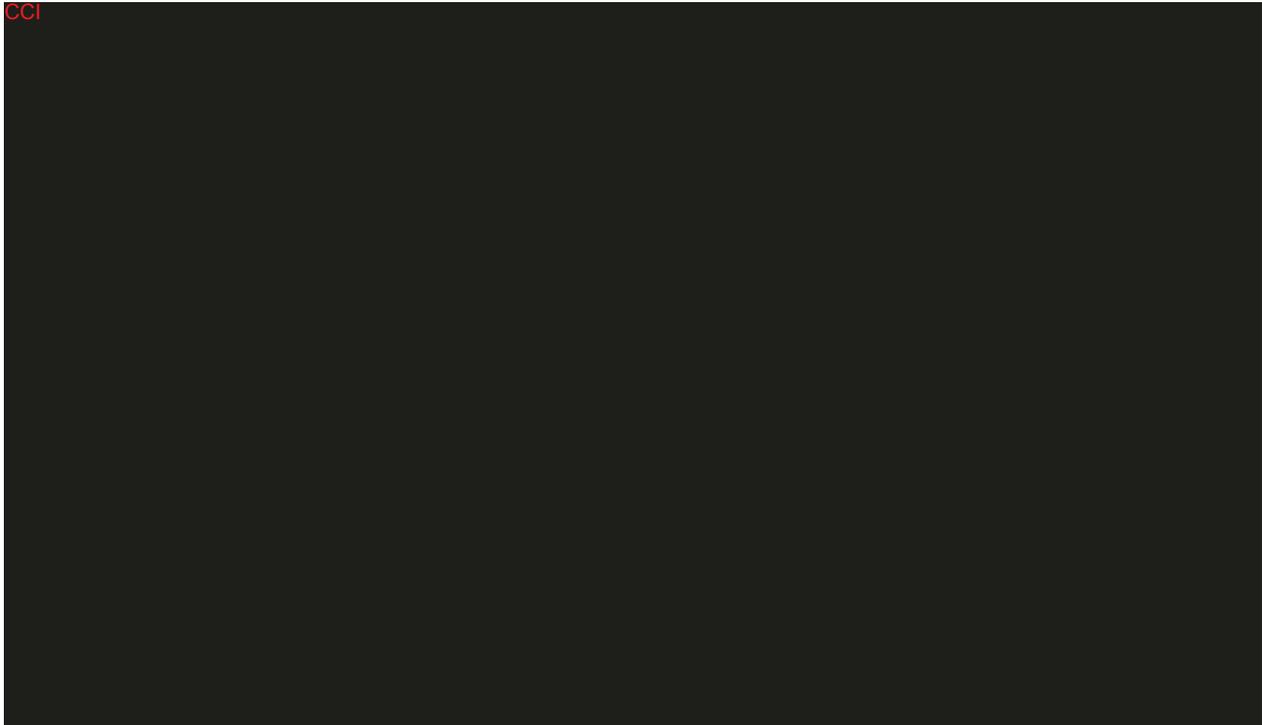
- To characterize the safety and tolerability of a single PO dose of TAK-071 when co-administered with SC scopolamine (0.5 mg) in healthy subjects.
- To characterize the single PO dose plasma PK profile of TAK-071 when co-administered both with scopolamine and a low-calorie, low-fat breakfast in healthy subjects.
- To demonstrate assay sensitivity by using donepezil 10 mg as the positive control.
- **To assess the effect of a single PO dose of TAK-071 in combination with 10 mg donepezil on the attenuation of cognitive deficit induced by scopolamine (0.5 mg subcutaneous [SC]) as measured by Groton Maze Learning Test (GMLT) (total number of errors).**

5.1.3 Exploratory/Additional Objectives

CCI



CCI



Rationale for Change:

To include additional objective(s) for the updated study design.

The following sections also contain this change:

- Section 2.0 [STUDY SUMMARY](#).
- [Appendix A Schedule of Study Procedures Part 2](#).

Change 3: Change in inclusion criteria.

The primary change is described in Section 7.3:

Initial wording	7.3 Additional Inclusion Criteria for Part 2 After Pre-Enrollment Enrichment Screening <ol style="list-style-type: none">1. Subject able to perform the CogState battery.2. Change from Baseline (average) in total GMLT errors of ≤ -5 at 2 hours postdose of scopolamine.3. Subjects with sleepiness score < 8 on the KSS at 2 hours postdose of scopolamine.4. Subject passes a hearing test with at least 90% correct responses and no more than 10% false positives. This test can be repeated once to determine eligibility.
-----------------	--

Amended or new text **7.3 Additional Inclusion Criteria for Part 2 After Pre-Enrollment Enrichment Screening**

1. Subject able to perform the CogState battery.
2. Change from Baseline (average) in total GMLT errors of ≤ -5 at 2 hours postdose of scopolamine.
3. Subjects with sleepiness score < 8 on the KSS at 2 hours postdose of scopolamine.
4. Subject passes a hearing test with at least ~~90~~**80**% correct responses and no more than ~~10~~**20**% false positives. This test can be repeated once to determine eligibility.

Rationale for Change:

Revision in the criteria.

The following section also contain this change:

- Section [2.0 STUDY SUMMARY](#).

Change 4: [Update dietary and fluid consumption for Part 2.](#)

The primary change is described in Section [7.5.2 Part 2](#):

Initial wording TAK-071 will be administered as a single PO dose (DIC) 24 hours before scopolamine dosing approximately 1.5 hours following a low-calorie, low-fat breakfast. No additional food will be permitted for up to 4 hours after TAK-071 dosing. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after TAK-071 drug administration. Meal timings, as well as their caloric and fat content, may be changed in the event of adjustments to the TAK-071 administration time.

Amended or new text TAK-071 **or matching placebo** will be administered **with approximately 240 mL of water after a fast of at least 8 hours** as a single PO dose (DIC) 24 hours before scopolamine dosing **and** approximately 1.5 hours following a low-calorie, low-fat breakfast. No additional food will be permitted for up to 4 hours after TAK-071 dosing. **Donepezil will be administered with approximately 240 mL of water after a fast of at least 8 hours as a single PO dose 3 hours before scopolamine dosing.** Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after TAK-071 ~~drug~~, **donepezil, or placebo** administration. Meal timings, as well as their caloric and fat content, may be changed in the event of adjustments to the TAK-071 administration time.

Rationale for Change:

To include additional treatments and provide further clarifications.

Change 5: Change in procedure for qEEG.

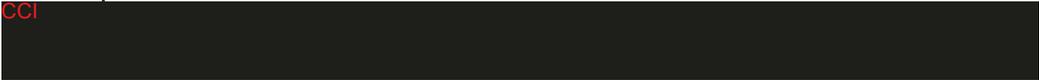
The primary change is described in Section 9.1.15.3 qEEG:

Initial wording The electroencephalographs (EEGs) will be acquired using the Brain Atlas Bio-logic system; and signal will be recorded from 20 electrodes attached to the scalp according to the international 10-20 system. A 10-minute EEG recording will be made for each subject while they rest with their eyes closed; minimum of 60 seconds artifact-free epochs are going to be subsequently selected for processing. Frequency domains will be obtained from the corresponding frequency bands by using the Fourier transform and the following: δ (1-3.5 Hz), θ (4-7.5 Hz), α_1 (8-9.5 Hz), α_2 (10-11.5 Hz), β_1 (12-20.5 Hz), β_2 (21-30.5 Hz) and γ (30-50 Hz) frequency bands.

Baseline assessment for qEEG will be done on 2 occasions approximately 24 hours apart. The average of the 2 Baseline assessments will be used for any calculations involving Baseline (ie, estimation of change from Baseline).

An additional assessment may be made at another suitable time point if it is judged that this will add additional learning/information given the observations at the earlier time points.

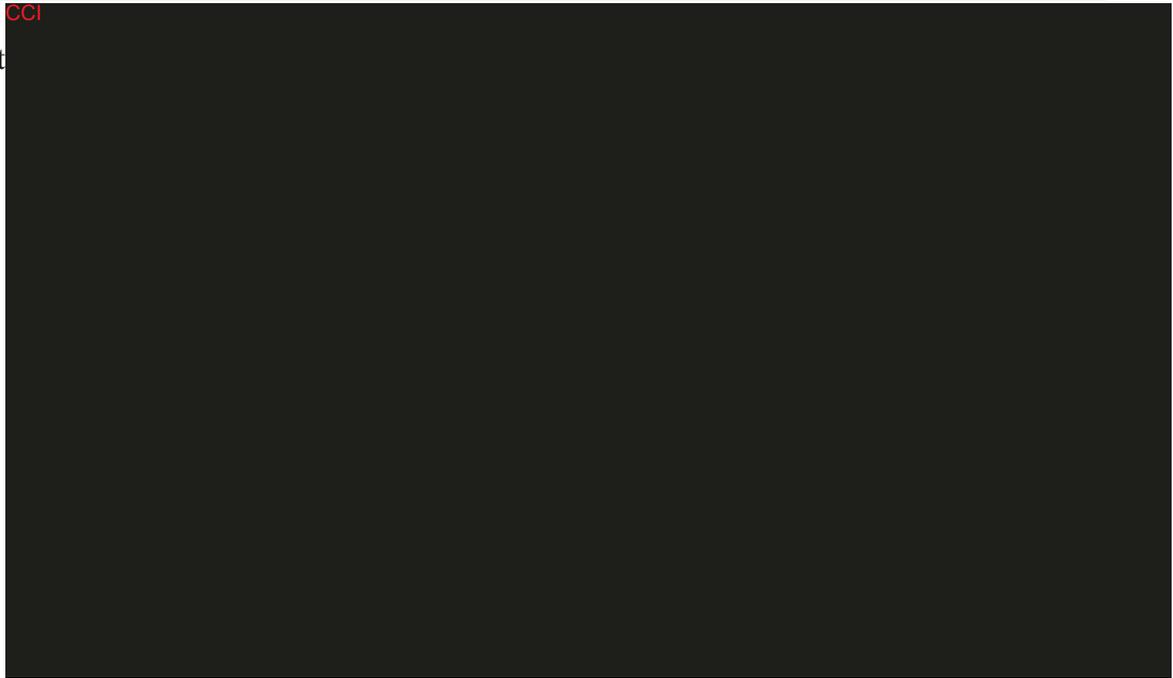
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A brief hearing test will be performed for the purpose of documenting that subjects have adequate hearing to participate in the auditory ERP procedure. A series of 60 tones between 1 and 3 seconds apart are presented at 70 dB SPL. If the subject presses a key within 500 ms after the presentation of the tone, a CORRECT response is recorded. If the subject presses a key more than 1000 ms after the presentation of the tone (but before the next tone), a FALSE_POSITIVE is recorded. Subjects who pass with at least 90% correct responses and no more than 10% false positives will be eligible to participate in the auditory ERP procedure.

A score sheet that includes subject ID, date, percent correct, and percent of false positives will be created for each subject. A Pass/Fail determination will be provided as well. If the 90 percent/10 percent criteria is not met, the procedure can be repeated once. No additional data will be transferred to sponsor.

Amended
or new text



A brief hearing test will be performed for the purpose of documenting that subjects have adequate hearing to participate in the auditory ERP procedure. ~~A series of 60 tones between 1 and 3 seconds apart are presented at 70 dB SPL. If the subject presses a key within 500 ms after the presentation of the tone, a CORRECT response is recorded. If the subject presses a key more than 1000 ms after the presentation of the tone (but before the next tone), a FALSE_POSITIVE is recorded. Subjects who pass with at least 90% correct responses and no more than 10% false positives will be eligible to participate in the auditory ERP procedure.~~ **(Three-Stimulus Auditory Oddball Task). The test will present three types of stimulus tones for a total of 100 stimuli: Standard Tones (70%), Target Tones (15%), and Distractor Tones (15%).**

All three tones are brief 75ms binaural sound stimuli, which differ in pitch but no in loudness (70dB sound pressure level [SPL]). Subjects attend to the tones which occur every 1.2 seconds and respond when a tone is heard. Subjects who pass with at least 80% correct responses (hits) and no more than 20% incorrect responses (false alarms) will be eligible to participate in the auditory ERP procedure.

A **paper** score sheet that includes subject ID, date, percent correct, and percent of false positives **alarms** will be created for each subject. ~~A~~ **and a** Pass/Fail determination will be provided as well. If the ~~90~~**80** percent/~~10~~**20** percent criteria is not met, the procedure can be repeated once. No additional data will be transferred to sponsor.

Rationale for Change:

Amended to capture recent procedural change.

Change 6: Change the order of pharmacodynamic (PD) assessments.

The primary change is described in Section 9.1.17 PK/PD Assessment Order (Only for Part 2):

Initial wording For PD Baseline on Day 1 and predose to Scopolamine the following order should be followed:

- Low-calorie low-fat breakfast: Approximately 2 hour prior to study drug dosing.
- Pupillometry: Approximately 90 minutes prior to study drug dosing.
- qEEG and ERP: Immediately after pupillometry and approximately 85 minutes prior to study drug dosing.
- Cognitive test: Immediately after qEEG and approximately 60 minutes prior to study drug dosing.
- Sleepiness monitoring: Immediately after cognitive testing and approximately 45 minutes prior to study drug dosing.
- PK blood draw: To be taken approximately within 30 minutes of the scheduled time point.

PK/PD assessments that coincide at the same scheduled time point will be performed in the following order:

- Pupillometry: Approximately 20 minutes prior to scheduled time point.
 - qEEG: Immediately after pupillometry and approximately 15 minutes prior to scheduled time point.
 - PK blood draw: To be taken approximately at the scheduled time.
 - Cognitive test: Immediately after PK blood draw.
 - Sleepiness monitoring: Immediately after cognitive testing.
-

Amended For PD Baseline on Day 1 and predose to scopolamine the following order should be or new text followed:

- Low-calorie low-fat breakfast: Approximately 2.5 hours prior to study drug dosing.
- **qEEG and ERP: Approximately 120 minutes prior to study drug dosing.**
- Pupillometry: Approximately ~~90 minutes prior to study drug dosing.~~
- ~~qEEG and ERP: Immediately after pupillometry and approximately 85~~**100** minutes prior to study drug dosing.
- Cognitive test: Immediately after ~~qEEG~~**pupillometry** and approximately ~~60~~**90** minutes prior to study drug dosing.
- Sleepiness monitoring: Immediately after cognitive testing and approximately ~~45~~**70** minutes prior to study drug dosing.
- PK blood draw: To be taken approximately within 30 minutes of the scheduled time point.

PK/PD assessments that coincide at the same scheduled time point will be performed in the following order:

- ~~Pupillometry~~**qEEG**: Approximately ~~20~~**40** minutes prior to scheduled time point.
- ~~qEEG~~**Pupillometry**: Immediately after ~~pupillometry~~**qEEG** and approximately ~~15~~**5** minutes prior to scheduled time point.
- PK blood draw: To be taken approximately at the scheduled time.
- Cognitive test: Immediately after PK blood draw.
- Sleepiness monitoring: Immediately after cognitive testing.

The following sections also contain one or more of these changes:

- Section [9.1.15.4](#)

Rationale for Change:

To obtain accurate PD assessments.

Change 7: Change blood volume for Part 2.

The primary change is described in Section 9.5 Blood Volume.

Initial wording: **[Original Table 9.f Approximate Blood Volume for Par 2]**
 ...

The maximum volume of blood for Part 2 at any single day is approximately 120 mL, and the approximate total volume of blood for the study is 536.5 mL.

...

A catheter with a normal saline flush may be used; however, the total blood volume does not include discarded blood from predraws (assuming minimally the catheter dead volume plus 1 mL of blood is discarded each time a sample is collected from a catheter). Should a catheter be used, the total blood volume taken during the study must not exceed 550 mL.

Amended or new wording:

Table 9.f Approximate Blood Volume for Part 2

Sample Type	Sample Volume (mL)	Number of Samples						Total Volume (mL)
		Screening	Period 1 (Day -1 to 3)	Period 2 (Day -1 to 3)	Period 3 (Day -1 to 3)	Period 4 (Day -1 to 3)	Period 5 (Day -1 to 3)	
Clinical laboratory tests	20 mL	2	1	1	1	1	2	140 160
Serology test	8.5 mL	1	0	0	0	0	0	8.5
PGx DNA sample collection	6 mL	1	1	0	0	0	0	12
PGx RNA sample collection	2.5 mL	0	4	4	4	4	4	40 50
TAK-071 PK blood collection	3 mL	0	8	8	8	8	8	96 120
Scopolamine PK blood collection	4 mL	0	7	7	7	7	7	112 140
Donepezil PK blood collection	4 mL	0	8	8	8	8	8	128 160
Total Approximate Blood Sampling Volume								536.5 650.5

...

The maximum volume of blood for Part 2 at any single day is approximately 120 mL, and the approximate total volume of blood for the study is ~~536~~650.5 mL.

....

A catheter with a normal saline flush may be used; however, the total blood volume does not include discarded blood from predraws (assuming minimally the catheter dead volume plus 1 mL of blood is discarded each time a sample is collected from a catheter). Should a catheter be used, the total blood volume taken during the study must not exceed ~~550~~650.5 mL.

Rationale for Change:

To account for samples in the additional period.

Change 8: Clarification on pretreatment event (PTE) collection period.

The primary change is described in Section [10.2.1.1 PTE and AE Collection Period](#):

Initial wording	Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Day 1 of Period 1) or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.
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Amended or new text	Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (on Day 1 for of Period Part 1), or Pre-enrollment Enrichment Visit for Part 2 , or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.
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Rationale for Change:

To make correction.

Amendment 2 – A Randomized, Double-Blind, Sponsor Unblinded, Placebo-Controlled, 5-Period Crossover, Phase 1b Study To Evaluate The Effects Of Single Oral Administration of TAK-071 On Scopolamine-Induced Cognitive Impairment In Healthy Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	13-Mar-2017 13:24 UTC
PPD	Biostatistics Approval	13-Mar-2017 13:49 UTC
PPD	Clinical Science Approval	14-Mar-2017 13:03 UTC