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

SAP Approve Date: 22 March 2018

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- Named persons or organizations associated with the study.

- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.

- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-071-1002

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

Version**:** Final

Date: 22 March 2018

Prepared by:

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PPD   Pharmaceutical Product Development

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PPD , BA
PPD , Pharmaceutical Product Development

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1.1. APPROVAL SIGNATURES

Study 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

Takeda Approvals:

PPD

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1.0 TABLE OF CONTENTS

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LIST OF APPENDICES

2.0   LIST OF ABBREVIATIONS

ADaM	Analysis Data Model
bpm	beats per minute
CV%	percent coefficient of variation
AE	adverse event
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
BMI	body mass index
C_{max}	maximum observed plasma concentration
CS	clinically significant
C-SSRS	Columbia - Suicide Severity Rating Scale
DIC	drug-in-capsule
ECG	Electrocardiogram
eCRF	electronic case report form
ET	early termination
GMLT	Groton Maze Learning Test
KSS	Karolinska Sleepiness Scale
MedDRA	Medical Dictionary for Regulatory Activities
N	number of subjects
NCS	not clinically significant
PD	pharmacodynamic
PK	Pharmacokinetic
PO	single oral
PT	preferred term
qEEG	quantitative electroencephalography
SAE	serious adverse event
SC	Subcutaneous
SD	standard deviation
SOC	system organ class
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time to first occurrence of C_{max}

3.0   OBJECTIVES

Note: Enrollment was paused in July 2017 CCI ███████████████████████████. At that time, Part 1 was complete and 12 subjects had enrolled in Part 2. The Part 2 subjects were discontinued at that time. Subsequently, in January 2018, the global product team decided not to resume enrollment in the study. Therefore, only certain safety and pharmacokinetic (PK)-related endpoints will be analyzed. The original study objectives are given below.

1.2.   PRIMARY OBJECTIVE

The primary objective of this study is as follows:
- To assess the effect of a single oral (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).

1.3.   SECONDARY OBJECTIVES

The secondary objectives of this study are as follows:
- 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 [SC]) as measured by GMLT (total number of errors).

1.4.   EXPLORATORY/ADDITIONAL OBJECTIVES

The exploratory objectives of this study are as follows:

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1.5. STUDY DESIGN

4.4.1. OVERVIEW

This study consists of 2 parts.

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

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

4.4.2. 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 are enrolled in this substudy with a minimum of 4 completers.

A schematic of Part 1, the substudy, design is provided in Figure 4.a.

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

Scopolamine is administered as a single 0.5 mg SC injection.

TAK-071 is 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 are 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 are assessed from physical examination, adverse events (AEs), clinical laboratory tests, electrocardiograms (ECGs), etc.

The planned timing of assessments and meals relative to scopolamine dosing in Part 1 is shown in Figure 4.b.

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Figure 4.b TAK-071 PK Assessments and Meal Timing Relative to Scopolamine Administration – Part 1 (Days 1 and 2)
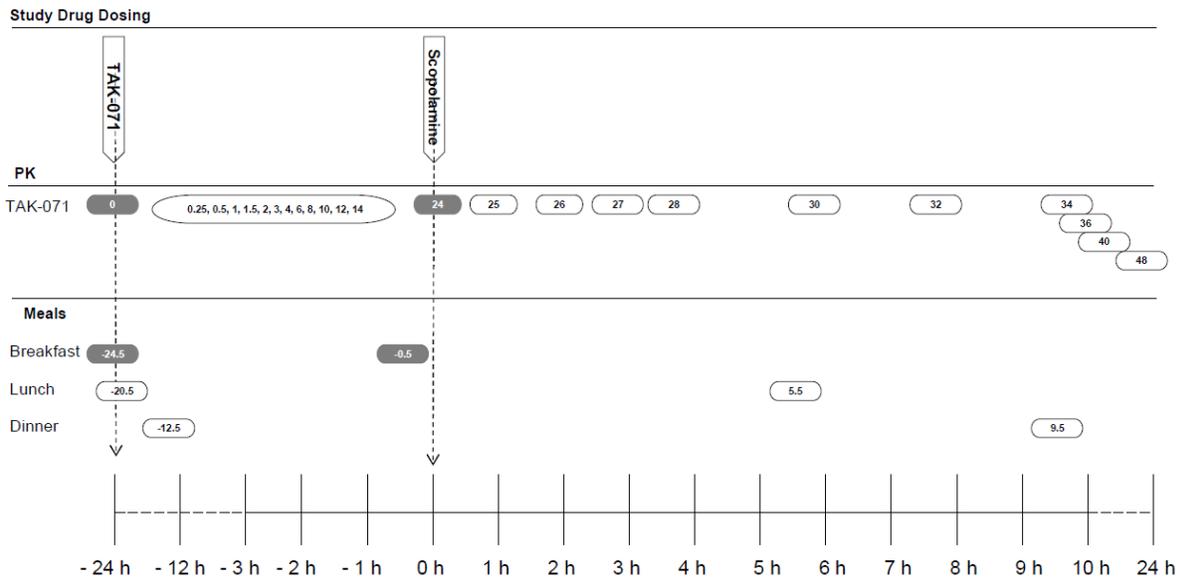
4.4.3. STUDY DESIGN – PART 2

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 M_1R 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, with a minimum of 3 completers. A schematic of the study design is provided in Figure 4.c.

Figure 4.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———→					

4.4.3.1. PRE-ENROLLMENT ENRICHMENT SCREENING – PART 2

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

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

Subjects 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 subjects unable to perform the CogState battery after training are excluded from entering Part 2, the main study.

4.4.3.2. TREATMENT SEQUENCES – PART 2

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

Subjects are randomly assigned to 1 of 10 possible treatment sequences before the first dose of study drug, each consisting of 5 treatment periods (Table 4.a).

Table 4.a Summary of Treatment Sequences in Study - Part 2

Sequence	Period 1		Period 2		Period 3		Period 4		Period 5
1	A	*Minimum 3-week washout*	B	*Minimum 3-week washout*	D	*Minimum 3-week washout*	E	*Minimum 3-week washout*	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 4.d.

Scopolamine is administered as a single 0.5 mg SC injection.

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

The dose of TAK-071 for Part 2 is selected depending on the results from Part 1 (initial substudy) and the FIH Study TAK-071-1001; however, under no circumstances does 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.

Figure 4.d PK/Pharmacodynamic (PD) Assessments and Meal Timing Relative to Scopolamine Administration – Part 2
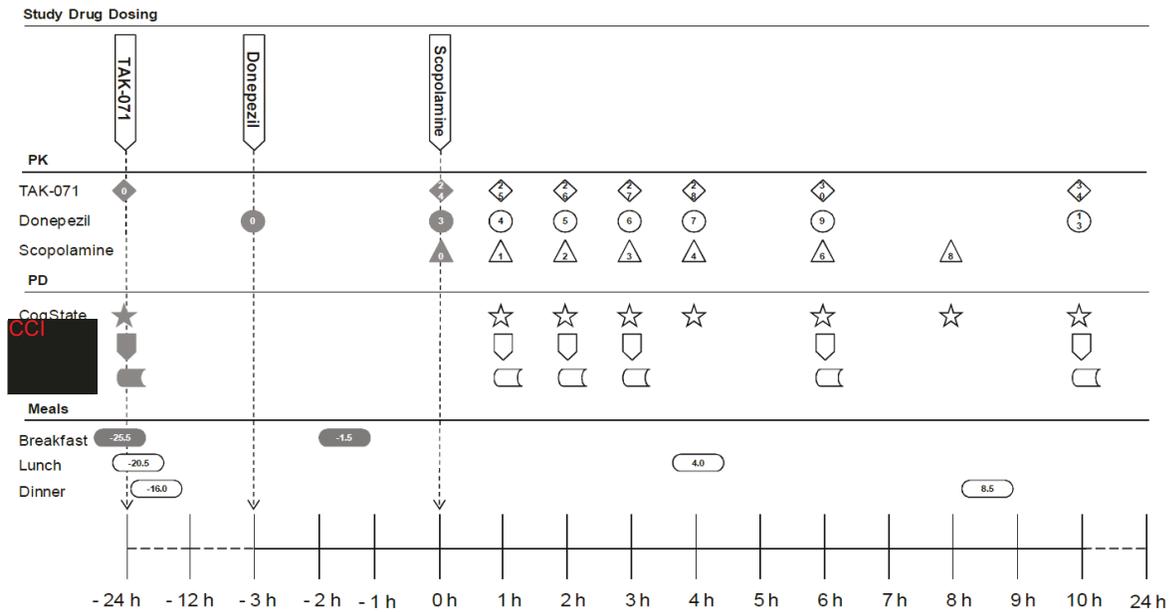
Note: Solid gray PK/PD symbols indicate predose assessments. Numbers inside symbols indicate scheduled times relative to the respective study drug dosing for the PK analyte. Shaded meal symbols indicate low-calorie, low-fat meals; all other meals are standard.

The precise dosing time of TAK-071 relative to scopolamine is 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.

The precise dosing time of TAK-071 relative to scopolamine is 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 is 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 are obtained at specified time-points up to 10 hours after scopolamine dosing.
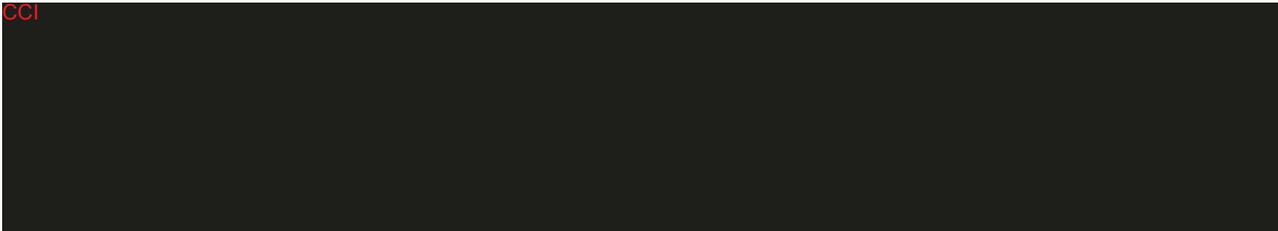
Information on the safety and tolerability of TAK-071 in combination with scopolamine and/or donepezil is obtained from treatment periods in which active TAK-071 is administered (Treatments C and D). Safety and tolerability are obtained during Treatment A for placebo, Treatment B for scopolamine alone, and during Treatment E for donepezil in combination with scopolamine.

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4.0 ANALYSIS ENDPOINTS

Note: Some of the planned endpoints have been removed or modified due to the early study termination. See Section 7.10.17.13 for details.

5.1 PRIMARY ENDPOINT

No longer applicable.

5.2 SECONDARY ENDPOINTS

- 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, for Part 1 only, 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 of last quantifiable concentration (AUC_{last}).
    - Area under the plasma concentration-time curve from time 0 to time t (AUCt).
    - 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.

5.3 EXPLORATORY/ADDITIONAL ENDPOINTS

No longer applicable

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5.0   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, is 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 are not replaced, therefore to ensure there are enough completers a total of 40 subjects are recruited (4 per sequence).

In particular, this sample-size calculation was based on a consideration of effect sizes seen in a similar study [5]. 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%.

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6.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 GENERAL PRINCIPLES

This Statistical Analysis Plan (SAP) was developed based on International Conference on Harmonization E3 [6] and E9 [7] Guidelines. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the SAP was developed using the information provided in Protocol TAK-071-1002 Amendment 02, dated 10 March 2017 [8].

All study-related raw data, including derived data, will be presented in data listings. Continuous data will be summarized using: number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, coefficient of variation (CV%) and geometric mean will also be included in the summary of continuous data. Categorical data will be summarized using the number and percentage of subjects for each category where appropriate.

All statistical tests will be 2-tailed at α=0.05 level for significance unless otherwise stated. The p-values less than or equal to α (when rounded to three digits) are reported as "significant". The phrase "no significant difference" indicates that all p-values for the tests are greater than α. All computations will be performed prior to rounding.

Due to the timing of the early study termination, no subjects began Period 2 and only 12 subjects were enrolled in Part 2. Therefore all data for Part 2 will be summarized by treatment, but not by sequence.

7.1.1. MISSING DATA

There will be no imputation of incomplete or missing data. Decisions regarding inclusion or exclusion of data from an analysis for subjects who are noncompliant with the dose schedule, or who have incomplete data, will be made on a case-by-case basis, but the data will be presented in data listings regardless.

Plasma concentrations that are below the limit of quantification will be treated as zero in the summarizing of concentration values and deriving of PK parameters. These values will be flagged in the data listings, and deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

7.1.2. DERIVED DATASETS AND VARIABLES

Derived datasets will be generated according to CDISC guidance documents: Analysis Data Model (ADaM) Implementation Guide, Version 1.0 (17 Dec 2009); ADaM Data Structure for Adverse Event Analysis, Version 1.0 (10 May 2012).

Body mass index (BMI) will be calculated as weight (kg)/(height (m))^2 and will be presented to 1 decimal place. BMI will be calculated for Screening.

7.1.3. DEFINITION OF STUDY DAYS AND BASELINE

For all safety endpoints, Baseline is defined as the last non-missing measurement prior to first dose of study drug for subjects in Part 1. Baseline is defined as the last non-missing

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measurement prior to first dose of study drug in the respective treatment period for subjects in Part 2, unless otherwise specified.

For all safety endpoints in Part 2, study day will be calculated relative to the date of first dose in the respective treatment period. Study day prior to the first dose of treatment in the respective treatment period will be calculated as: date of assessment/event – date of treatment; study day on or after the first dose of treatment in the respective treatment period will be calculated as: date of assessment/event – date of treatment + 1.

7.2   ANALYSIS SETS

Safety Set The safety analysis set consists of all subjects who are enrolled and received 1 dose of study drug. Subjects in this analysis set are used for demographic, baseline characteristics, and safety summaries.

Pharmacokinetic Set The PK set consists of all subjects who receive study drug and have at least 1 measurable plasma concentration. All subjects with valid PK parameter estimate will be included in the summaries and analyses for that parameter.

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 PK analysis but will be presented in the subject listings.

7.3   DISPOSITION OF SUBJECTS

The primary reason for screen failure will be summarized.

The number and percentage of subjects who complete study drug, prematurely discontinue study drug, and do not complete all study visits will be summarized overall for Part 1, and by treatment and overall for Part 2. In addition, the number and percentage of subjects will be summarized for each reason of discontinuation of study drug and study visits. Subjects' study completion data, including reasons for premature termination, will be listed by study part for all subjects.

The number and percentage of subjects who comprised each analysis set will be summarized for Part 1 by overall and for Part 2 by treatment and overall total for all subjects.

7.4   PROTOCOL DEVIATIONS

The significant protocol deviations will be provided in a data listing and summarized by treatment (Part 2 only) and overall total.

7.5   DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized for all randomized subjects by treatment sequence (Part 2 only) and overall total. Summary statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous variables (i.e., age, height, weight, and BMI, and years of full-time education), and the number and percentage of subjects within

each category will be presented for categorical variables (i.e. gender, race, ethnicity, caffeine consumption, alcohol use, academic qualifications, and smoking status).

Demographic variables of screen failure subjects and reasons for screen failures will be summarized for all subjects who are screened but not enrolled in the study. Individual demographic characteristics, date of informed consent, any available safety data and reason for screen failure will also be presented in the data listing.

7.6 MEDICAL HISTORY AND CONCURRENT MEDICAL CONDITIONS

Medical history obtained includes determining whether the subjects 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.

Medical history and concurrent medical condition verbatim reported terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). No summaries for medical history and concurrent medical conditions will be provided. All medical history and concurrent medical conditions will be listed.

7.7 MEDICATION HISTORY AND CONCOMITANT MEDICATIONS

Medication history information obtained includes any medication relevant to eligibility criteria stopped at or within 30 days prior to signing of informed consent. Medications used from signing of informed consent through the end of study will be considered as concomitant medications.

Medication history and concomitant medications will be coded using World Health Organization Drug Dictionary. No summaries for medication history and concomitant medications will be provided. All medication history and concomitant medications data will be listed.

7.8 STUDY DRUG EXPOSURE AND COMPLIANCE

The date and time of each dose for each subject will be reported in the data listing for all subjects. Summaries of PK data will be provided by treatment. No other summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

7.9 EFFICACY ANALYSIS

Not applicable.

7.10 PHARMACOKINETIC ANALYSIS

7.10.1 PLASMA PHARMACOKINETIC CONCENTRATIONS

Collection of Blood Samples for Pharmacokinetic 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

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Collection of Blood Samples for Pharmacokinetic 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	1	Predose (predose of scopolamine) and 1, 2, 3, 4, 6, and 8 hours postdose relative to scopolamine dosing.
Donepezil	Plasma	1	-3 hours (predose of donepezil) and 0 (predose of scopolamine), 1, 2, 3, 4, 6, and 10 hours postdose relative to scopolamine dosing.

Note: For Part 2 time points relative to each study drug administration are as follows:
TAK-071: predose (approximately 30 minutes before dosing) and 24, 25, 26, 27, 28, 30, and 34 hours postdose relative to TAK-071 dosing;
Donepezil: predose (within 30 minutes before dosing) and 3, 4, 5, 6, 7, 9, and 13 hours postdose relative to donepezil dosing;
Scopolamine: predose (predose of scopolamine) and 1, 2, 3, 4, 6, and 8 hours postdose relative to scopolamine dosing.

The concentration of TAK-071 and donepezil will be summarized separately by treatment, as applicable, over each scheduled sampling time using descriptive statistics (including N, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and CV% of the geometric mean).

Individual plasma concentration data versus time will be presented similarly in data listings. Additionally, graphical plots of individual and mean plasma concentration vs time profiles will be presented for Part 1 (TAK-071) only.

No listings or summaries from the scopolamine concentration data will be presented.

7.10.2   PLASMA PHARMACOKINETIC PARAMETERS

Since Part 2 of the study was terminated early, the following parameters will only be computed for Part 1. The PK parameters of plasma TAK-071 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.

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The following PK parameters will be calculated for plasma concentration values of TAK-071:

Symbol/Term	Definition
Plasma	
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration.
AUC_∞	Area under the plasma concentration-time curve from time 0 to infinity, as permitted by the data.
C_{max}	Maximum observed plasma concentration.
$t_{1/2z}$	Terminal disposition phase half-life.
t_{max}	Time to first occurrence of C_{max}, as permitted by the data.

Additional plasma PK parameters may be calculated if necessary, in accordance with the Clinical Pharmacology Analysis Plan.

Plasma PK parameters for TAK-071 will be listed and summarized separately by treatment. Descriptive statistics (including N, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and CV% of the geometric mean) will be used as appropriate. Geometric mean and CV% of the geometric mean will be reported for AUCs and C_{max} only. All subjects with a valid PK parameter estimate will be included in the summaries and analyses for that parameter.

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.

7.10.3 PHARMACODYNAMIC PARAMETERS

Since Part 2 was terminated early, these endpoints will not be listed or summarized.

7.11 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. All safety summary tables are presented by treatment group within Part 1 and Part 2.

7.11.1 ADVERSE EVENTS

A TEAE is defined as an adverse event or a serious adverse event (SAE) that occurs or gets worse after receiving the first dose of study drug (the dose administered on Day 1 for Part 1 and on Day 1 of Period 1 for Part 2; run-in scopolamine is considered study drug) until the Follow-up Visit/Call or Early Termination. A TEAE may also be a pretreatment adverse event or a concurrent medical condition diagnosed prior to the date of first dose of study drug that increases in severity after the start of dosing.

Adverse event verbatim reported terms will be coded by system organ class, high-level term and preferred term using MedDRA.

TEAE summary tables will include numbers and percentages of subjects experiencing at least one AE by system organ class (SOC) and preferred term (PT) and will be tabulated by treatment group within Part 1 and Part 2. TEAEs will be summarized according to the treatment most recently received prior to the onset of the event.

The following is a list of AE summary tables to be generated:

- − Overview of TEAEs.
- − TEAEs by SOC and PT at subject and event level.
- − Subject Mappings for TEAEs.
- − TEAEs by PT.
- − Most Frequent TEAEs by PT.
- − Most Frequent Non-Serious TEAEs by PT.
- − Relationship of TEAEs to Study Drug by SOC and PT.
- − Drug-Related TEAEs by SOC and PT.
- − Intensity of TEAEs by SOC and PT.
- − Intensity of Drug-Related TEAEs by SOC and PT.
- − Pretreatment Events by SOC and PT.

If a subject has more than one AE that codes to the same PT, the subject will be counted only once for that PT. If a subject has more than one AE within an SOC category, the subject will be counted only once for that SOC. TEAEs possibly or probably related to study medication will be tabulated in the same manner. TEAEs will also be summarized by maximum intensity.

Most frequent TEAEs are defined as the AEs occurring in at least 2 subjects in any treatment (ie, Treatment A).

Data listings will be provided for all AEs (including pretreatment events for enrolled subjects), AEs leading to study drug discontinuation, SAEs, and AEs resulting in death.

7.11.2   CLINICAL LABORATORY EVALUATIONS

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

For Part 1, blood samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) are collected at Screening, at Check-in (Day -1), on Days 1 through 5 (Final Visit)/ Early Termination (ET), Day 8, and at the Follow-up Visit.

For Part 2, blood samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) are collected at Screening and in each period at Check-in (Day -1), at Study Exit (on Day 3 of Period 5/ET), and Follow-up (on Day 9 [±2] of Period 5), as appropriate.

Individual results for hematology, chemistry, and coagulation laboratory tests are evaluated against the Takeda predefined laboratory markedly abnormal value (MAV) criteria (Appendix A) using the result and criteria in SI units.

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Clinical laboratory tests (hematology, chemistry, and urinalysis) will be listed. The results that meet MAV criteria will be flagged in the listing. For Part 1 only, baseline, postdose and change from Baseline to postdose laboratory data will be summarized. Baseline is defined as the last non-missing measurement prior to first dose of study drug.

The percentage of subjects who meet MAV criteria at least once postdose will be summarized by overall total for Part 1 and by treatment and overall total for Part 2..

7.11.3 VITAL SIGNS

Vital signs 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 are recorded on the source documents and in the eCRF.

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

For Part 1, vital signs (oral temperature, respiration, pulse, and blood pressure) are obtained at Screening, at Check-in (Day -1), on Days 1 through 5 (Final Visit)/ ET, Day 8, and at the Follow-up Visit (on Day 12).

For Part 2, vital signs (oral temperature, respiration, pulse, and blood pressure) are obtained at Screening and in each period at Check-in (Day -1), Day 1 (-26 hours predose), and Day 3 (period 1 to 4), Study Exit ([Day 3 of Period 5]/ ET), and Follow-up (Day 9 [±2]) of Period 5, as appropriate.

Individual vital signs are evaluated against Takeda's predefined criteria for MAV (Appendix B). All vital signs will be listed. The results that meet MAV criteria will be flagged in the listing. Baseline, postdose and change from Baseline to postdose vital signs parameters will be summarized. Baseline is defined as the last non-missing measurement prior to first dose of study drug for subjects in Part 1. Baseline is defined as the last non-missing measurement prior to first dose of study drug in the respective treatment period for subjects in Part 2

The percentage of subjects who meet MAV criteria of vital signs at least once postdose will be summarized by overall total for Part 1 and by treatment and overall total for Part 2.

7.11.4 12-LEAD ECGS

A standard 12-lead ECG is recorded. The investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant (NCS), or abnormal and clinically significant (CS). The following parameters will be recorded from the subject's ECG trace: heart rate, RR interval, PR interval, QRS interval, and QTcF (QT interval with Fridericia correction method) and QTcB (QT interval with Bazett correction method) interval.

If an ECG is scheduled at the same time as blood draws or vital signs, the ECG is 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 takes precedence followed by the meal.

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For Part 1, a standard 12-lead ECG is recorded at Screening, Check-in (Day -1), Day 1 (predose [within 60 minutes prior to dosing]), on Days 2 through 5 (upon morning rising)/ ET, Day 8, and at the Follow-up (on Day 12[±2]).

For Part 2, a standard 12-lead ECG is recorded at Screening, and in each period at Check-in (Day -1), Day 1 (predose [within 60 minutes prior to dosing], Day 3 (Period 1 to 4), Study Exit (Day 8 of Period 5)/ ET, and Follow-up (Day 9 [±2] of Period 5), as appropriate.

Individual ECGs are evaluated against Takeda's predefined criteria for MAV (Appendix C). All ECGs will be listed. The results that meet MAV criteria will be flagged in the listing. Baseline, postdose and change from Baseline to postdose ECG parameters will be summarized. Baseline is defined as the last non-missing measurement prior to first dose of study drug for subjects in Part 1. Baseline is defined as the last non-missing measurement prior to first dose of study drug in the respective treatment period for subjects in Part 2

The percentage of subjects who meet MAV criteria of ECGs at least once postdose will be summarized by overall total.

7.11.5 OTHER OBSERVATIONS RELATED TO SAFETY

7.11.5.1 PHYSICAL EXAMINATION

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 NCS or 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.

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.

For Part 1, physical examinations are performed at Screening, at Check-in (Day -1), Final Visit (Day 5/ET), and at the Follow-up (on Day 12[±2]).

For Part 2, physical examinations are performed at Screening, in each period at Check-in (Day -1), Day 3 (Period 1 to 4), Study Exit (Day 3 of Period 5/ET), and at the Follow-up (on Day 9[±2] of Period 5).

The physical examination findings will be presented in a data listing. No summary tables will be provided.

7.11.5.2 COLUMBIA - SUICIDE SEVERITY RATING SCALE (C-SSRS)

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.

For Part 1, the C-SSRS is performed at Screening, at Check-in (Day -1), and Final Visit (Day 5 / ET). If clinically significant at Final Visit, C-SSRS will also be determined as part of the Follow-up (on Day 12[±2]).

For Part 2, the C-SSRS is performed at Screening, in each period at Check-in (Day -1), Day 3 (Period 1 to 4), and Study Exit (Day 5 of Period 5/ ET). If clinically significant at Final Visit, C-SSRS will also be determined as part of the Follow-up (on Day 9[±2] of Period 5).

C-SSRS data will be presented in data listings. No summary tables will be provided.

7.12 INTERIM ANALYSIS

Not applicable.

7.13 CHANGES IN THE STATISTICAL ANALYSIS PLAN

CCI

One derived PK endpoint, area under the plasma concentration-time curve from time t1 to time t2, has been removed from Part 1.

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Appendix A   Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	$< 0.8 \times$ LLN	$> 1.2 \times$ ULN
Hematocrit	Both	$< 0.8 \times$ LLN	$> 1.2 \times$ ULN
RBC count	Both	$< 0.8 \times$ LLN	$> 1.2 \times$ ULN
WBC count	Both	$<0.5 \times$ LLN	$>1.5 \times$ ULN
Platelet count	Conventional	$<75 \times 10^3/\mu L$	$>600 \times 10^3/\mu L$
	SI	$<75 \times 10^9/L$	$>600 \times 10^9/L$

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Coagulation—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
prothrombin time/international normalized ratio	Both		$>1.5 \times$ ULN
activated partial thromboplastin time	Both		$>1.5 \times$ ULN

LLN=lower limit of normal, ULN=upper limit of normal.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	$>3 \times$ ULN
AST	Both	--	$>3 \times$ ULN
GGT	Both	--	$>3 \times$ ULN
Alkaline phosphatase	Both	--	$>3 \times$ ULN
Chloride	Conventional	<75 mEq/L	>126 mEq/L
	SI	<75 mmol/L	>126 mmol/L
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 μmol/L
Direct bilirubin	Both	--	>2 ULN
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	$<0.8 \times$ LLN	$>1.2 \times$ ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI	--	>177 μmol/L
Blood urea nitrogen	Conventional	--	>30 mg/dL
	SI	--	>10.7 mmol/L
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>6.0 mEq/L
	SI	<3.0 mmol/L	>6.0 mmol/L

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Glucose	Conventional	<50 mg/dL	>350 mg/dL
	SI	<2.8 mmol/L	>19.4 mmol/L
Bicarbonate	Conventional	<8.0 mEq/L	
	SI	<8.0 mmol/L	
Creatine kinase	Conventional	--	>5 × ULN
	SI	--	>5 × ULN
Calcium	Conventional	<7.0 mg/dL	>11.5 mg/dL
	SI	<1.75 mmol/L	>2.88 mmol/L

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B   Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	^{o}C	< 35.6	>37.7

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Appendix C   Criteria for Markedly Abnormal Values for Electrocardiograms

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	< 50	> 120
QT Interval	msec	≤ 50	≥ 460
QTcB Interval	msec	≤ 50	≥ 500 OR ≥ 30 change from baseline and ≥ 450
QTcF Interval	msec	≤ 50	≥ 500 OR ≥ 30 change from baseline and ≥ 450