Title: A Phase 1 Safety, Tolerability, and Pharmacokinetic Study of Escalating Single and Multiple Oral Doses of TAK-071 in Healthy Subjects and Subjects With Mild Cognitive Impairment/Mild Alzheimer Disease and Relative Bioavailability and Food Effect of TAK-071 in Healthy Subjects

NCT Number: NCT02769065

Protocol Approve Date: 15 May 2017

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- 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.

PROTOCOL AMENDMENT

A Phase 1 Safety, Tolerability, and Pharmacokinetic Study of Escalating Single and Multiple Oral Doses of TAK-071 in Healthy Subjects and Subjects With Mild Cognitive Impairment/Mild Alzheimer Disease and Relative Bioavailability and Food Effect of TAK-071 in Healthy Subjects

Phase 1 Single and Multiple Rising Dose Study of TAK-071 in Healthy Subjects and Subjects With Mild Cognitive Impairment/Mild Alzheimer Disease and Relative Bioavailability and Food Effect of TAK-071 in Healthy Subjects

Sponsor:	Takeda Development Center Americas, Inc. One Takeda Parkway Deerfield, IL 60015 USA		
Study Number:	TAK-071-1001		
IND Number:	128,849	**EudraCT Number:**	Not applicable
Compound:	TAK-071		
Date:	15 May 2017	**Version/Amendment Number:**	Amendment No. 05

Amendment History:

Date	Amendment Number	Region
24 March 2016	Initial version	Global
31 May 2016	01	Global
19 August 2016	02	Global
21 October 2016	03	Global
15 February 2017	04	Global
15 May 2017	05	Global

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) PPD
Medical Monitor (medical advice on protocol and compound)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	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 clinical 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 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, 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 Clinical Study Site Agreement.
- Appendix B - Responsibilities of the Investigator.

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. 05 Summary of Changes

Rationale for Amendment 05

This document describes the changes in reference to the protocol incorporating Amendment No. 05. The primary reason for this amendment is to update the study design to include an interim analysis of the single-rising dose (SRD) and multiple-rising dose (MRD) data, revise Cohort 16 inclusion criteria and screening period length, add optional run-in period for Cohort 16, and add flexible language to allow for additional SRD cohorts for TAK-071 coadministered with donepezil (10 mg). Personnel changes, inconsistencies, and minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific description of text changes and where the changes are located, see Appendix G.

Changes in Amendment 05

1. An additional SRD cohort (Cohort 22) has been added to the study and the approximate total number of subjects to be enrolled has been increased accordingly.
2. Allowing flexibility for enrollment in Cohort 16.
3. The inclusion criteria and screening period length for Cohort 16 have been revised. An optional run-in period of 49 days was added for Cohort 16.
4. An interim analysis of the SRD and MRD cohort data has been included.
5. To add no food effect statement for Cohort 16.
6. The sponsor signatories for this protocol have been updated.

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):
Takeda Development Center Americas, Inc.</td><td>Compound:
TAK-071</td></tr>
<tr><td>Title of Protocol: A Phase 1 Safety, Tolerability, and Pharmacokinetic Study of Escalating Single and Multiple Oral Doses of TAK-071 in Healthy Subjects and Subjects With Mild Cognitive Impairment/Mild Alzheimer Disease and Relative Bioavailability and Food Effect of TAK-071 in Healthy Subjects</td><td>IND No.:
128,849</td><td>EudraCT No.:
Not applicable</td></tr>
<tr><td>Study Number: TAK-071-1001</td><td colspan="2">Phase: 1</td></tr>
<tr><td colspan="3">Study Design:
This is a first-in-human, phase 1, safety, tolerability, and pharmacokinetic (PK) study of escalating single and multiple oral doses of TAK-071 in healthy adult (non-Japanese and Japanese) male and female subjects and subjects with mild cognitive impairment (MCI) or mild Alzheimer disease (AD) (non-Japanese). In addition, the relative bioavailability of a tablet formulation (test) vs the reference drug-in-capsule (DIC) formulation as well as the effect of food on the PK of the tablet formulation will be investigated in healthy subjects.
The first time TAK-071 is dosed to humans will be a single oral dose administered in Cohort 1 of the single-rising dose (SRD) part of this study. Additional cohorts (Cohorts 2 to 6, 18, and 19) will be used to study escalating single-dose levels.
Higher or lower dose cohort(s) may be added in the SRD part of the study to fully understand safety and tolerability of TAK-071. The SRD part of the study will consist of a randomized, double-blind, placebo-controlled, parallel-group ascending dose design with 8 subjects per cohort.
SRD cohorts (Cohorts 20 to 22) will explore the safety and tolerability of single doses of TAK-071 (80, 60, and 40 mg, respectively; however, actual doses administered will be determined from emerging data) when coadministered with donepezil (10 mg) in healthy subjects. These cohorts will consist of a randomized, double-blind, placebo-controlled, parallel-group ascending dose design with 12 subjects per cohort. These cohorts will establish a high well-tolerated dose of TAK-071 when coadministered with donepezil for the scopolamine challenge proof-of-mechanism (PoM) study.
Cohorts 7 to 15 will be used in the multiple-rising dose (MRD) part of this study. The MRD part of the study will thus consist of a randomized, double-blind, placebo-controlled, 9-cohort, parallel-group multiple ascending dose design with 8 subjects per cohort in Cohorts 7 to 12 and 6 subjects in Cohorts 13 to 15. Additional MRD cohorts (TAK-071 and/or TAK-071+donepezil) may be added to fully understand safety and tolerability of TAK-071. Selected MRD cohorts (Cohorts 10 to 12) will be pretreated for 3 weeks with daily oral doses of donepezil (5 mg once daily [QD]), followed by continued daily oral donepezil dosing during the TAK-071 treatment period.
Cohort 16 will include up to 8 subjects (minimum of 6) with MCI or mild AD on stable donepezil treatment or who consent to a donepezil run-in period of 5 mg dose for 28 days and titrate up to 10 mg for at least 21 days. Subjects with previous MCI/AD diagnosis who have been treated with 5 mg for at least 28 days prior to Screening may consent to a donepezil run-in period of 10 mg for at least 21 days. This cohort will be conducted in a placebo-controlled, 2-sequence, 2-period, 2-way crossover design.
Cohort 17 will include up to 12 subjects. This cohort will be conducted in an open-label 3-period, 3-sequence, 3-way crossover design. Cohorts 1 to 12 and 16 to 21 will include non-Japanese subjects. Cohorts 13 to 15 will include Japanese subjects.
Subjects in each cohort (Cohorts 1 to 16, 18, and 19) will be randomized to receive treatment with TAK-071 or matching placebo using DIC in the morning following a minimum fast of 8 hours. In Cohorts 1 to 12, 18, and 19, placebo treatments will be assigned in a 3:1 ratio (within each cohort of 8 subjects, 6 will receive active treatment and 2 will receive placebo).
Subjects in Cohorts 20 and 22 will be assigned in a 1:1:2 ratio to receive treatments (within each cohort of 12 subjects,</td></tr>
</table>

3 will receive TAK-071 placebo+donepezil placebo, 3 subjects will receive TAK-071 placebo+donepezil, and 6 subjects will receive TAK-071+donepezil).

In Cohorts 13 to 15, placebo treatments will be assigned in a 5:1 ratio (within each cohort of 6 subjects, 5 will receive active treatment and 1 will receive placebo. In Cohort 16, subjects will be assigned to 1 of 2 possible treatment sequences (AB or BA), with Treatment A being TAK-071 and Treatment B being matching placebo. In Cohort 17, subjects will be assigned to 1 of 3 possible treatments as Regimen Sequences ABC, BCA, and CAB, where, Regimen A=Fasted State and Capsule Formulation (10 mg in DIC formulation), Regimen B=Fasted State and Tablet Formulation (10 mg tablet formulation), and Regimen C=Fed State and Tablet Formulation (10 mg tablet formulation).

The safety of TAK-071 alone or in combination with donepezil or with/without food will be assessed through adverse events (AEs), clinical laboratory results, physical examination findings, electrocardiogram (ECG) findings, bowel function, vital signs, and suicidal assessments. Continuous 12-lead Holter ECG monitoring will also be performed on selected study cohorts.

The safety and tolerability of donepezil alone will be evaluated during the donepezil dosing phase (before TAK-071 is given in Cohorts 10 to 12) during the 3-week pretreatment period, and the safety and tolerability of donepezil in combination with TAK-071 (Cohorts 20 to 22) will be evaluated by assessing AEs, clinical laboratory results, physical examination findings, ECG findings, bowel function, and vital signs.

In addition to safety monitoring, TAK-071 plasma and urine PK profiles will be generated and PK parameters derived. It is planned that cerebrospinal fluid (CSF) samples for PK analysis will be obtained in Cohort 3 (following a single dose) and Cohort 9 (at steady-state). Pharmacodynamic measures will include the determination of pupil size and quantitative electroencephalography (EEG).

Approximately 186 subjects are expected to be randomized in this study.

End of study is defined as the date of last visit of the last subject for last clinical assessment.

Primary Objectives:

- To characterize the safety, tolerability, and plasma PK profile of TAK-071 when administered as single and multiple QD oral doses at escalating dose levels in healthy subjects (non-Japanese).
- To characterize the safety, tolerability, and plasma PK profile of TAK-071 when administered as single and multiple QD oral doses at escalating dose levels in healthy subjects (non-Japanese) in the presence of steady-state exposure of donepezil QD.
- To characterize the safety, tolerability, and plasma PK profile of TAK-071 when administered as single and multiple QD oral doses at escalating dose levels in healthy Japanese subjects.
- To characterize safety, tolerability, and plasma PK profile of 10 mg donepezil when administered as a single dose, and to compare it to combination of 10 mg donepezil plus TAK-071.
- To characterize the safety, tolerability, and plasma PK profile of TAK-071 when administered as multiple QD oral doses to subjects with MCI or mild AD (non-Japanese) receiving donepezil treatment for a minimum of 3 months.

Secondary Objectives:

- To assess safety of 120 mg or higher single dose of TAK-071 measured by EEG.
- To evaluate the urinary clearance of TAK-071 following single and multiple oral doses.
- To evaluate the brain penetration of TAK-071 as measured in CSF following single and multiple dosing.
- To evaluate the dose proportionality and any time dependency in TAK-071 plasma PK.
- To evaluate the effect of multiple daily doses of TAK-071 on donepezil steady-state PK.
- To evaluate the relative bioavailability (BA) of TAK-071 10 mg administered as tablet formulation compared with TAK-071 10 mg administered as DIC formulation.
- To evaluate potential effect of food on the TAK-071 plasma PK following a single oral dose of 10 mg tablet formulation.

<table>
<tr><td colspan="2">Subject Population:
Cohorts 1 to 12, 17, and 18 to 22: Healthy non-Japanese subjects aged 18 to 55 years, inclusive.
Cohorts 13 to 15: Healthy Japanese subjects aged 20 to 55 years, inclusive.
Cohort 16: Subjects aged 55 to 90 years, inclusive, with MCI or mild AD.</td></tr>
<tr><td>Number of Subjects:
Cohorts 1 to 12, 18, and 19: 8 (6 TAK-071, 2 placebo)
Cohorts 13 to 15: 6 (5 TAK-071, 1 placebo)
Cohort 16: 8 (minimum of 6 completers) (TAK-071 and placebo)
Cohort 17: 12
Cohorts 20 to 22: 12 (6 TAK-071+donepezil, 3 donepezil, 3 placebo)
Estimated total: 186 randomized</td><td>Number of Sites:
Estimated total: 1 site in the United States</td></tr>
<tr><td>Dose Levels:
TAK-071
SRD Cohorts (1 to 6, 18, and 19): first dose 1 mg TAK-071 QD, subsequent dose levels to be determined by emerging safety, tolerability, and PK data in preceding cohorts.
SRD+donepezil Cohorts (20 to 22): 80, 60, and 40 mg (the actual dose will be determined based on emerging data).
MRD Cohorts 7 to 15 and Cohort 16: doses to be determined by emerging safety, tolerability, and PK data in preceding SRD/MRD cohorts.
Note: There will be a TAK-071 exposure/dose cap, so that subjects do not exceed the observed average plasma exposures at the lowest steady-state no-observed-adverse-effect level (NOAEL) achieved in 4-week toxicology studies.
Food effect cohort (Cohort 17): 10 mg administered as a tablet or DIC. Higher or lower dose may be selected based on emerging PK data from previous cohorts.
Donepezil
Cohorts 10 to 12: donepezil 5 mg QD in the morning.
Cohort 16: donepezil 10 mg (or titrated to 10 mg in run-in period) QD in the evening (bedtime).
Cohorts 20 to 22: donepezil 10 mg as a single dose.</td><td>Route of Administration:
Oral</td></tr>
<tr><td>Duration of Treatment:
SRD Cohorts 1 to 6, 18 and 19: 1 day TAK-071
SRD+donepezil Cohorts 20 to 22: 2 days (TAK-071 on Day 1 and donepezil on Day 2).
MRD Cohorts 7 to 8: 21 days TAK-071
MRD Cohorts 9 and 13 to 15: 1 day TAK-071, followed by a 7-day washout period and 21 days of TAK-071 dosing
MRD Cohorts 10 to 12: 21 days of pretreatment with donepezil followed by 21 days of dosing with TAK-071 and donepezil.
Cohort 16: 21 days TAK-071 (Treatment A) followed by 21 days of washout and 21 days of matching placebo</td><td>Period of Evaluation:
SRD Cohorts 1 to 6, 18 and 19: approximately 40 days.
SRD+donepezil Cohorts 20 to 22: approximately 40 days.
MRD Cohorts 7 and 8: approximately 60 days.
MRD Cohorts 9 and 13 to 15: approximately 57 days.
MRD Cohorts 10 to 12: approximately 76 days.
MRD Cohort 16: approximately 130 days.
Food effect Cohort 17: approximately 82 days.</td></tr>
</table>

(Treatment B), or vice versa. A donepezil run-in period of 49 days, prior to starting Treatment A, may be included if the subject is diagnosed at Screening. Cohort 17: 1 day TAK-071 (single dose as DIC, tablet under fasting, or tablet under fed condition) in each of 3 periods with 21-day washout after Periods 1 and 2.	

Main Criteria for Inclusion:

- The subject is a man or woman who weighs at least 50 kg and has a body mass index (BMI) from 18.0 to 30.0 kg/m^2, inclusive, at Screening.
- For Cohorts 13 to 15 only: First-generation Japanese, defined as having been born in Japan of Japanese parents and Japanese grandparents and living no more than 10 years outside of Japan, with no significant change in lifestyle, including diet, while living outside of Japan.
- Cohort 16 only: Subjects with a documented previous diagnosis of MCI or mild AD, with a Mini Mental State Examination score of 18 to 30, inclusive, and no biomarker data to contradict this diagnosis. Retrospectively, subjects will have met a diagnosis of probable AD based on the National Institute of Neurological Disorders and Stroke Alzheimer's Disease and Related Disorders Association criteria or MCI diagnosis based on criteria such as subjective cognitive complaint, evidence of impairment in 1 or more cognitive domain, preservation of functions, and absence of dementia. Subjects must be receiving ongoing donepezil therapy (10 mg) for a minimum of 21 days or who consent to take donepezil dose titrated up to 10 mg as run-in treatment for at least 21 days.

Main Criteria for Exclusion:

- The subject has clinically significant (Cohorts 1 to 15, and 17 to 22) or uncontrolled (Cohort 16) neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal (GI), urologic, immunologic, endocrine, or psychiatric 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.
- A subject with a history of type 1 diabetes (Cohorts 1 to 22) or type 2 diabetes (Cohorts 1 to 15 and 17 to 22 or subject with hemoglobin A1c >6.5% at Screening. Note: subjects with controlled (hemoglobin A1c <7.0% at Screening) type 2 diabetes in Cohort 16 may participate in the study.
- 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) or has made a suicide attempt in the previous 6 months.
- Cohort 16 only: Any significant neurologic disease (other than suspected incipient or mild AD), such as Parkinson disease, stroke, transient ischemic attack, multi-infarct dementia, Huntington disease, head trauma with clinically significant cognitive sequelae, or chronic central nervous system infection.
- The subject has current or recent (within 6 months) GI disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, any surgical intervention known to impact absorption [eg, bariatric surgery or bowel resection], esophageal reflux, peptic ulcer disease, erosive esophagitis, or frequent [more than once per week] occurrence of heartburn).

Main Criteria for Evaluation and Analyses:

The primary safety endpoints are as follows:

- 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.

The primary PK parameters of TAK-071 in plasma following a single dose (Day 1) and at steady-state (after the final

dose following multiple dosing) are as follows:

- Time of first occurrence of C_{max} (t_{max}).
- Maximum observed plasma concentration (C_{max}).
- Area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24}).
- Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}) (single dose only [Day 1]).

The secondary endpoints are as follows:

Plasma and urine PK parameters of TAK-071 following a single dose (Day 1) and at steady-state (after the final dose following multiple dosing), including but not limited to the following:

- Area under the plasma concentration-time curve from time 0 to time t (AUC_t).
- Terminal disposition phase half-life ($t_{1/2z}$), as permitted by the data (single dose only [Day 1]).
- Apparent clearance after extravascular administration (CL/F).
- Apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F).
- Accumulation ratio based on AUC_{τ} ($R_{ac(AUC)}$).
- Accumulation ratio based on C_{max} ($R_{ac(Cmax)}$).
- Amount of drug excreted in urine from time 0 to time t (Ae_t).
- Fraction of administered dose of drug excreted in urine from time 0 to time t ($f_{e,t}$).
- Renal clearance (CL_R).

CSF PK of TAK-071 planned for the single-dose Cohort 3 and at steady-state in Cohort 9 (after the final dose following multiple dosing), including but not limited to the following:

- Maximum observed concentration in CSF (CSF C_{max}).
- Area under the CSF concentration-time curve from time 0 to 12 hours (CSF AUC_{12}) (Cohort 3 only [Day 1]).
- Area under the CSF concentration-time curve from time 0 to 36 hours (CSF AUC_{36}) (Cohort 9 only [Day 28]).
- The ratio of CSF AUC_{12} to the plasma AUC_{12} (CSF AUC_{12}:plasma AUC_{12}) (Cohort 3 only [Day 1]).
- The ratio of CSF AUC_{36} to the plasma AUC_{36} (CSF AUC_{36}:plasma AUC_{36}) (Cohort 9 only [Day 28]).

Plasma steady-state PK parameters of donepezil (Cohorts 10 to 12) on the last donepezil pretreatment day and after 21 daily doses of TAK-071, including but not limited to the following:

- t_{max}.
- C_{max}.
- AUC_{24}.
- Ratio of geometric mean steady-state AUC_{24} and C_{max} for donepezil after 21 daily doses of TAK-071 in reference to donepezil alone and the associated 90% confidence intervals (CIs).

Statistical Considerations:

PK Analysis

Plasma and CSF concentrations of TAK-071 and plasma concentrations of donepezil, where appropriate, will be summarized by dose or regimen over each scheduled sampling time using descriptive statistics. Individual plasma concentration data vs time will be presented in a data listing.

Plasma PK parameters and CSF PK parameters, where applicable, will be summarized separately for SRD, MRD, presence/absence of donepezil, and for Japanese subjects.

Dose proportionality for the SRD and MRD parts (separately) will be assessed using the empirical power law model. This analysis will be carried out to assess the degree of dose proportionality based on the dose-proportionality exponent (β) for the model, for both C_{max} and AUC_{∞} on Day 1 and C_{max} and AUC_{24} at steady-state.

Dose linearity will be examined in the event that dose proportionality cannot be established by using a simple linear

regression on the exposure parameter.

Trough plasma concentrations measured in the MRD part will be summarized to assess steady-state. The time to steady-state will be assessed by fitting trough concentration values to a nonlinear mixed effects model in order to predict the time to achieve 90% of the steady-state trough concentrations separately for each dose.

Time dependency will be investigated in selected MRD cohorts. The time invariance of TAK-071 will be assessed by comparing AUC_{24} for the last day of dosing to the AUC_{∞} for Day 1 using analysis of variance with a random effect for subject and a fixed effect for day.

The effect of TAK-071 on the natural log-transformed steady-state Cmax and AUC_{24} of donepezil will be assessed with a linear mixed-effects model; point estimates for geometric means and geometric mean ratios with 90% CIs will be determined.

The concentration and cumulative amount of TAK-071 excreted in urine will be summarized by dose over each scheduled collection interval and for selected time intervals, ie, 0 to 96 hours postdose, using descriptive statistics for the SRD and MRD parts.

The relative BA of the tablet formulation compared to the reference DIC formulation and the effect of food on the plasma PK of TAK-071 will be assessed using an analysis of variance (ANOVA) on the natural logarithms of Cmax and AUC_{∞}, with factors for sequence, subject nested within sequence, period, and regimen. The factor of subject nested within sequence will be random effect and others are fixed effects.

Safety Analysis

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 Bristol Stool Form scale scores will be listed. Baseline, postdose and change from Baseline to postdose laboratory data, vital signs, ECG parameters, and Bristol Stool Form scale scores will be summarized as well as percentage of subjects who meet Takeda MAV criteria.

Where applicable, within each part, for the non-Japanese and Japanese SRD and MRD cohorts separately, safety data will be summarized by placebo, each TAK-071 dose level, TAK-071 overall, and overall total. Placebo data will be pooled across cohorts for SRD and MRD parts separately.

Sample Size Justification: The sample sizes chosen for the SRD (8 subjects in Cohorts 1 to 6, 18, and 19, and 12 subjects in Cohorts 20 to 22) and MRD parts are considered to be sufficient for evaluation of safety, tolerability, and PK of each cohort but are not based on statistical power considerations. A sample size of 12 subjects (4 per sequence) was chosen for the 3-period, 3-sequence, crossover design in Cohort 17. The sample size is considered sufficient to assess the bioavailability of TAK-071 from the tablet relative to the capsule and to assess the effect of food on the bioavailability of TAK-071 from the tablet. This sample size was not based on statistical power considerations.

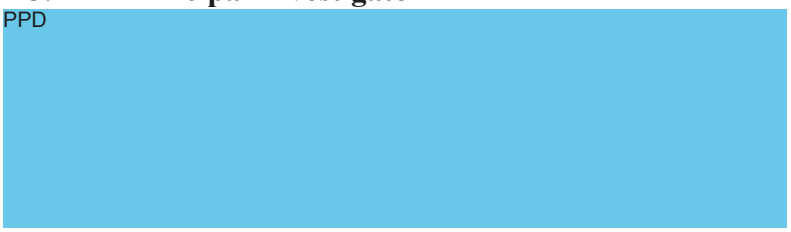
3.0 STUDY REFERENCE INFORMATION

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 identified vendors in the template 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

λ_z	terminal disposition phase rate constant
ACh	acetylcholine
AChE	acetylcholinesterase
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer disease
AE	adverse event
Ae_t	amount of drug excreted in urine from time 0 to time t.
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{12}	area under the plasma concentration-time curve from time 0 to 12 hours
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{36}	area under the plasma concentration-time curve from time 0 to 36 hours
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{τ}	area under the plasma concentration-time curve during a dosing interval
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
$AUEC_{12}$	area under the effect concentration-time curve from time 0 to 12 hours
BA	bioavailability
BMI	body mass index
bpm	beats per minute
BSF	Bristol Stool Form
CFR	Code of Federal Regulations
ChAT	choline acetyltransferase
CI	confidence interval
CL/F	apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration
CL/F_{ss}	apparent clearance after extravascular administration, at steady state, calculated using AUC_{τ}
CL_R	renal clearance
C_{max}	maximum observed concentration
CNS	central nervous system
CSF	cerebrospinal fluid
CSF AUC_{12}	Area under the CSF concentration-time curve from 0 to 12 hours
CSF AUC_{36}	Area under the CSF concentration-time curve from 0 to 36 hours
CSF C_{max}	Maximum observed CSF concentration
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
EDC	electronic data capture
EEG	electroencephalography
E_{max}	maximum observed effect
FDA	Food and Drug Administration
FE	food effect
f_e	fraction of administered dose of drug excreted in urine
$f_{e,t}$	fraction of administered dose of drug excreted in urine from time 0 to time t
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
hCG	human chorionic gonadotropin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
ICF	informed consent form
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
K_2EDTA	potassium ethylenediamine tetra-acetic acid
LFT	liver function test
M_1R	muscarinic acetylcholine receptor 1
MAV	markedly abnormal value
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
MRD	multiple-rising dose
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
OTC	over-the-counter
PAM	positive allosteric modulator
PD	pharmacodynamic
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PoM	proof-of-mechanism

PT	prothrombin time
PTE	pretreatment event
QD	once daily
qEEG	quantitative electroencephalography
$R_{ac(AUC)}$	accumulation ratio based on AUC_{τ}
$R_{ac(Cmax)}$	accumulation ratio based on C_{max}
RCF	relative centrifugal force
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
$t_{1/2z}$	terminal disposition phase half-life
TK	toxicokinetic
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration

3.4 Corporate Identification

TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
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 [1-3], 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 [4]. Of those patients diagnosed with AD, more than two-thirds will likely be categorized as having mild or moderate disease [2]. Dementia-related diseases also have a huge economic impact. Today, the total estimated worldwide cost of dementia is US $818 billion, and it will become a trillion dollar disease by 2018 [4].

Impairment of cholinergic neuronal functions leads to cognitive disturbances and memory loss, the hallmark symptoms of AD [5,6]. 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 [7]. 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 [8].

Inhibition of acetylcholinesterase (AChE), the enzyme responsible for the breakdown of ACh, represents 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 [9]. 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 [10] 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 in all subtypes of ACh muscarinic receptors (M_1-M_5R), leading to manifestation of various mechanism-related side effects, most commonly diarrhea. 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 an improved efficacy and safety profile.

TAK-071 is a novel muscarinic acetylcholine receptor 1 (M_1R) positive allosteric modulator (PAM). M_1R PAMs do not bind to the orthosteric ACh-binding site but instead act at a distinct site to potentiate activation of the receptor by its natural ligand, ACh. M_1R is predominantly expressed in brain regions related to cognition, learning, and memory, such as the frontal cortex, hippocampus, and limbic area. Based on the expression pattern of M_1R and its role in cognitive function, the selective stimulation of this receptor would be expected to result in an amelioration of cognitive deficits, with little or no worsening of the previously cited cholinergic-related side effects. Indeed, in a nonclinical in vivo pharmacology study in rats, 0.3 mg/kg TAK-071 ameliorated scopolamine-induced cognitive deficits using a novel object recognition paradigm.

TAK-071 is characterized by a high systemic bioavailability in rats and monkeys, with absolute bioavailability values of 65% and 72%, respectively. It is also a low plasma clearance compound with a low to moderate volume of distribution and brain tissue distribution in rat and monkey (total brain tissue to plasma concentration partition coefficient in these 2 species of 0.12 and 0.42, respectively). The terminal disposition phase half-life ($t_{1/2z}$) values after oral administration were 5 and 8 hours in rats and monkeys, respectively.

TAK-071 has high permeability and is not a substrate of P-glycoprotein or breast cancer resistance protein, which are highly expressed in the blood-brain barrier. In vitro plasma protein binding in mice, rats, monkeys, and humans is high (≥98.9%) and concentration independent across species (0.1 to 10 µg/mL). TAK-071 is mainly metabolized by cytochrome P-450 (CYP) 3A4 and, to a lesser extent, by CYP2D6 and/or CYP2C9. No human-specific metabolites have been identified. TAK-071 had little or no direct or time-dependent inhibitory effects on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. TAK-071 did not induce CYP1A2, but it is probably a weak inducer of CYP2B6 or CYP3A4 in vitro. Therefore, the risk of CYP-mediated drug-drug interaction between TAK-071 and donepezil is predicted to be low in humans.

TAK-071 was studied for potential toxicity in Good Laboratory Practice (GLP)-compliant repeat dosing studies in rats and monkeys for up to 28 days in duration. TAK-071 was also examined for genotoxicity in vitro and in vivo, and for phototoxicity in vitro. A toxicokinetic (TK) study was conducted in nonpregnant female rabbits to assess the tolerability and TK profile in this species after dosing with TAK-071 to support future embryo-fetal toxicity studies in this species. In the 28-day rat toxicity study, no animals died and no test article-related abnormalities were noted in body weight, food consumption, ophthalmoscopy, urinalysis parameters, hematology or clinical chemistry parameters, gross necropsy, organ weights, or histopathology. In clinical signs, loose stool was noted at 30 mg/kg/day and at 100 mg/kg/day; however, it was not considered to be toxicologically relevant because almost all findings were seen after the first dosing only. In the 28-day monkey toxicity study, no test article-related changes were noted in clinical signs, body weight, food consumption, electrocardiogram (ECG) parameters, body temperature, ophthalmoscopy, urinalysis parameters, hematology and clinical chemistry parameters, gross necropsy, organ weights, or histopathology.

Overall, the existing body of evidence suggests that TAK-071 has the potential to be of significant clinical benefit in neurodegenerative disorders associated with cognitive decline related to an impairment of ACh neurons, including AD and/or dementia with Lewy bodies. It has been shown to have adequate nonclinical pharmacologic, pharmacokinetic (PK), and toxicologic properties, supporting the initiation of clinical investigation.

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

4.2 Rationale for the Proposed Study

A broad program of nonclinical studies has already been performed to explore the pharmacology, PK, and toxicological potential of TAK-071 in animals and in vitro. Those studies indicate that TAK-071 is a selective and specific M_1R PAM, with good oral bioavailability and PK properties

as well as a toxicological profile that is not anticipated to present an unacceptable risk to humans at the proposed clinical doses.

The activation of M_1R is expected to achieve significant cognitive improvement without cholinomimetic-related side effects, including diarrhea, which is seen with donepezil and other cholinesterase inhibitors, and thus has the potential to be a treatment with an improved side effect profile for dementia with Lewy bodies and AD.

This is the first study involving dosing of TAK-071 to humans. Therefore, the main aim of this multipart single-rising dose (SRD) and multiple-rising dose (MRD) study is to explore the safety and tolerability of single and multiple doses of TAK-071 in healthy (non-Japanese) subjects. After confirmation of the acceptable safety and tolerability of TAK-071 alone, a subsequent aim of this study is to explore the safety and tolerability in combination with donepezil in healthy subjects (non-Japanese) because this is the gold standard treatment for AD, one of the key target populations of later phase TAK-071 clinical studies.

Healthy Japanese subjects will be included to investigate any ethnic differences in the safety, tolerability, and/or PK of TAK-071. This part of the study is anticipated to enable Japanese subjects to be recruited into global phase 2 and 3 clinical studies.

Following confirmation of the acceptable safety and tolerability of TAK-071 both alone and in combination with donepezil in healthy subjects, subjects with mild cognitive impairment (MCI) or mild AD (non-Japanese) will also be exposed to combination treatment with the main objective of obtaining early safety and tolerability data in the target population.

This study is intended to explore the safety and tolerability of single and multiple TAK-071 doses, some of which may exceed doses anticipated to be therapeutically effective. However, it should be noted that the study is not intended to determine the maximum tolerated dose (MTD).

In addition to the battery of tests and assessments to characterize the safety and tolerability profile of the compound, the study also includes PK assessments of TAK-071 in plasma and cerebrospinal fluid (CSF) and of donepezil in plasma. Pharmacodynamic (PD) assessments include the evaluation of the quantitative electroencephalography (qEEG) profile and pupil size measurements after TAK-071 administration in the presence and absence of donepezil for selected cohorts. These assessments will characterize the PK/PD properties of TAK-071 in humans, provide evidence of brain penetration, and probe peripheral and central cholinergic system responses.

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 drug. There may also be some discomfort from collection of blood samples and other study procedures.

This is the first study involving dosing of TAK-071 to humans. 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_1R PAMs. Therefore, data from nonclinical studies with TAK-071, together with clinical data from other

cholinomimetics, such as donepezil, are the only available guide to potential adverse reactions, which typically include side effects as a predictable consequence of its pharmacological properties, ie, diarrhea, nausea, and vomiting [11].

Based on allometric scaling of nonclinical PK data, predicated exposure in humans at the proposed starting dose of 1 mg is substantially below the corresponding exposure at the lowest no-observed-adverse-effect level (NOAEL) in toxicology (>50-fold; see Section 6.2.2.1). This dose is also lower than the human equivalent dose used in the rat safety pharmacology studies at which increased spontaneous activity was observed (3-fold) and is the lowest anticipated dose that may exert pharmacological effects on cognition.

A PK exposure cap has been instituted because the NOAEL is also the highest dose tested in the 28-day GLP toxicology studies; therefore, it is unknown if adverse events (AEs) at higher untested doses might have been reversible and/or monitorable. For this reason, stopping rules will be implemented to ensure that the maximum human exposure remains appropriately below the corresponding average exposure observed at the NOAEL in the most sensitive nonclinical species.

There is no anticipated additional risk from a potential PK interaction for cohorts coadministered TAK-071 and donepezil. Indeed, currently available in vitro data indicate that the risk of PK interaction between these 2 compounds is low. From a PD interaction point of view, it is anticipated that these 2 compounds might have synergistic effects. For this reason, in the healthy subject combination treatment cohorts, there will be 3 TAK-071 dose escalation steps, after each of which there will be a review of the safety/tolerability and available PK data. Subjects with MCI or mild AD on stable donepezil will only be dosed after review of the safety/tolerability and available PK of the combination treatment cohorts in healthy subjects.

Overall, based on the substantial exposure safety margin for the initial clinical dose and all the available preclinical pharmacology, toxicology, drug metabolism, and PK data, TAK-071 alone or in combination with donepezil is not anticipated to present unacceptable risks to healthy (non-Japanese or Japanese) subjects or to subjects with MCI or mild AD at the proposed doses and dose regimens. This study is not designed to allow the assessment of the therapeutic potential for this compound, and it is not expected that this study will result in any therapeutic benefit for the included study populations. However, data generated from this study should enable the investigation of TAK-071 in subsequent clinical proof-of-mechanism (PoM) and 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 Objectives

- To characterize the safety, tolerability, and plasma PK profile of TAK-071 when administered as single and multiple once daily (QD) oral doses at escalating dose levels in healthy subjects (non-Japanese).
- To characterize the safety, tolerability, and plasma PK profile of TAK-071 when administered as single and multiple QD oral doses at escalating dose levels in healthy subjects (non-Japanese) in the presence of steady-state exposure of donepezil QD.
- To characterize the safety, tolerability, and plasma PK profile of TAK-071 when administered as single and multiple QD oral doses at escalating dose levels in healthy Japanese subjects.
- To characterize safety, tolerability, and plasma PK profile of 10 mg donepezil when administered as a single dose, and to compare it to combination of 10 mg donepezil+TAK-071.
- To characterize the safety, tolerability, and plasma PK profile of TAK-071 when administered as multiple QD oral doses to subjects with MCI or mild AD (non-Japanese) receiving donepezil treatment for a minimum of 3 months.

5.1.2 Secondary Objectives

- To assess safety of 120 mg or higher single dose of TAK-071 measured by electroencephalography (EEG).
- To evaluate the urinary clearance of TAK-071 following single and multiple oral doses.
- To evaluate the brain penetration of TAK-071 as measured in CSF following single and multiple dosing.
- To evaluate the dose proportionality and any time dependency in TAK-071 plasma PK.
- To evaluate the effect of multiple daily doses of TAK-071 on donepezil steady-state PK.
- To evaluate the relative bioavailability (BA) of TAK-071 10 mg administered as tablet formulation compared with TAK-071 10 mg administered as drug-in-capsule (DIC) formulation.
- To evaluate potential effect of food on the TAK-071 plasma PK following a single oral dose of 10 mg tablet formulation.

5.1.3 Exploratory/Additional Objectives

- CCI

- CCI
- [redacted]
- [redacted]
- [redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

5.2.1.1 Safety

- 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.

5.2.1.2 PK

PK parameters of TAK-071 in plasma following a single dose (Day 1) and at steady-state (after the final dose following multiple dosing):

- Time of first occurrence of C_{max} (t_{max}).
- Maximum observed plasma concentration (C_{max}).
- Area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24}).
- Area under the plasma concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞}) (single dose only [Day 1]).

5.2.2 Secondary Endpoints

Plasma and urine PK parameters of TAK-071 following a single dose (Day 1) and at steady-state (after the final dose following multiple dosing), including but not limited to the following:

- Area under the plasma concentration-time curve from time 0 to time t (AUC_t).
- $t_{1/2z}$, as permitted by the data (single dose only [Day 1]).
- Apparent clearance after extravascular administration (CL/F).

- Apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F).
- Accumulation ratio based on AUC_τ ($R_{ac(AUC)}$).
- Accumulation ratio based on C_{max} ($R_{ac(Cmax)}$).
- Amount of drug excreted in urine from time 0 to time t (Ae_t).
- Fraction of administered dose of drug excreted in urine from time 0 to time t ($f_{e,t}$).
- Renal clearance (CL_R).

CSF PK parameters of TAK-071 planned for the single-dose Cohort 3 and at steady-state in Cohort 9 (after the final dose following multiple dosing), including but not limited to the following:

- CSF C_{max}.
- Area under the CSF concentration-time curve from time 0 to 12 hours (CSF AUC_{12}) (Cohort 3 only [Day 1]).
- Area under the CSF concentration-time curve from time 0 to 36 hours (CSF AUC_{36}) (Cohort 9 only [Day 28]).
- The ratio of CSF AUC_{12} to the plasma AUC_{12} (CSF AUC_{12}:plasma AUC_{12}) (Cohort 3 only [Day 1]).
- The ratio of CSF AUC_{36} to the plasma AUC_{36} (CSF AUC_{36}:plasma AUC_{36}) (Cohort 9 only [Day 28]).

Plasma steady-state PK parameters of donepezil (Cohorts 10 to 12) on the last donepezil pretreatment day and after 21 daily doses of TAK-071, including but not limited to the following:

- t_{max}.
- C_{max}.
- AUC_{24}.
- Ratio of geometric mean steady-state AUC_{24} and C_{max} for donepezil after 21 daily doses of TAK-071 in reference to donepezil alone and the associated 90% confidence intervals (CIs).

5.2.3 Exploratory/Additional Endpoints

CCI

CCI

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a first-in-human (FIH), phase 1, safety, tolerability, and PK study of escalating single and multiple oral doses of TAK-071 in healthy adult (non-Japanese and Japanese) male and female subjects and subjects with MCI or mild AD (non-Japanese). In addition, the relative bioavailability of a tablet formulation (test) vs the DIC formulation as well as the effect of food on the PK of the tablet formulation will be assessed in healthy subjects.

The first time TAK-071 is dosed to humans will be a single oral dose administered in Cohort 1 of the SRD part of this study. Additional cohorts (Cohorts 2 to 6, 18, and 19) will be used to study escalating single-dose levels.

Higher or lower dose cohort(s) may be added in the SRD part of the study to fully understand safety and tolerability of TAK-071. The SRD part of the study will consist of a randomized, double-blind, placebo-controlled, parallel-group ascending dose design with 8 subjects per cohort.

SRD cohorts (Cohorts 20 to 22) will explore the safety and tolerability of single doses of TAK-071 (80, 60 and 40 mg, respectively; however, actual doses administered will be determined from emerging data) when coadministered with donepezil (10 mg) in healthy subjects. These cohorts will consist of a randomized, double-blind, placebo-controlled, parallel-group ascending dose design with 12 subjects per cohort. These cohorts will establish a high well-tolerated dose of TAK-071 when coadministered with donepezil for the scopolamine challenge PoM study. Higher or lower dose cohort(s) may be added in the SRD part of the study to fully understand safety and tolerability of TAK-071 when coadministered with donepezil.

Cohorts 7 to 15 will be used in the MRD part of this study. The MRD will thus consist of a randomized, double-blind, placebo-controlled, 9-cohort, parallel-group multiple ascending dose design with 8 subjects in Cohorts 7 to 12 and 6 subjects in Cohorts 13 to 15. Additional MRD cohorts (TAK-071 and/or TAK-071+donepezil) may be added to fully understand safety and tolerability of TAK-071.

Selected MRD cohorts (Cohorts 10 to 12) will be pretreated for 3 weeks with daily oral doses of donepezil (5 mg QD), followed by continued daily oral donepezil dosing during the TAK-071 treatment period.

Cohort 16 will include up to 8 subjects (minimum of 6) with MCI or mild AD on stable donepezil treatment or who consent to a donepezil run-in period of 5 mg dose for 28 days and titrate up to 10 mg for at least 21 days. Subjects with previous MCI/AD diagnosis who have been treated with 5 mg for at least 28 days prior to Screening may consent to a donepezil run-in period of 10 mg for at least 21 days. This cohort will be conducted as a placebo-controlled, 2-sequence, 2-period, 2-way crossover design.

Cohort 17 will include up to 12 subjects. This cohort will be conducted in an open-label, 3-period, 3-sequence, 3-way crossover design.

Cohorts 1 to 12, and 16 to 22 will include non-Japanese subjects. Cohorts 13 to 15 will include Japanese subjects.

Subjects in each cohort (Cohorts 1 to 16, 18, and 19) will be randomized to receive treatment with TAK-071 or matching placebo using DIC in the morning following a minimum fast of 8 hours. In Cohorts 1 to 12, 18, and 19, placebo treatments will be assigned in a 3:1 ratio (within each cohort of 8 subjects, 6 will receive active treatment and 2 will receive placebo).

Subjects in Cohorts 20 to 22 will be assigned in a 1:1:2 ratio to receive treatments (within each cohort of 12 subjects, 3 will receive TAK-071 placebo+donepezil placebo, 3 subjects will receive TAK-071 placebo+donepezil, and 6 subjects will receive TAK-071+donepezil).

In Cohorts 13 to 15, placebo treatments will be assigned in a 5:1 ratio (within each cohort of 6 subjects, 5 will receive active treatment and 1 will receive placebo. In Cohort 16, subjects will be assigned to 1 of 2 possible treatment sequences (AB or BA), with Treatment A being TAK-071 and Treatment B being matching placebo. In Cohort 17, subjects will be assigned to 1 of 3 possible treatments as Regimen Sequences ABC, BCA, and CAB, where, Regimen A=Fasted State and Capsule Formulation (10 mg DIC formulation), Regimen B=Fasted State and Tablet Formulation (10 mg tablet formulation), and Regimen C=Fed State and Tablet Formulation (10 mg tablet formulation).

The safety of TAK-071 alone or in combination with donepezil will be assessed through AEs, clinical laboratory results, physical examination findings, ECG findings, bowel function, vital signs, and suicidal assessments. Continuous 12-lead Holter ECG monitoring will also be performed on selected study cohorts.

The safety and tolerability of donepezil alone will be evaluated during the donepezil dosing phase (before TAK-071 is given in Cohorts 10 to 12) during the 3-week pretreatment period, and the safety and tolerability of donepezil in combination with TAK-071 (Cohorts 20 to 22) will be evaluated by assessing AEs, clinical laboratory results, physical examination findings, ECG findings, bowel function, and vital signs.

In addition to safety monitoring, TAK-071 plasma and urine PK profiles will be generated and PK parameters derived. It is planned that CSF samples for PK analysis will be obtained in Cohort 3 (following a single dose) and Cohort 9 (at steady-state). CCI [redacted] CCI [redacted].

Approximately 186 subjects are expected to be randomized in this study.

End of study is defined as the date of last visit of the last subject for last clinical assessment.

The treatment groups and cohorts are outlined in Table 6.a.

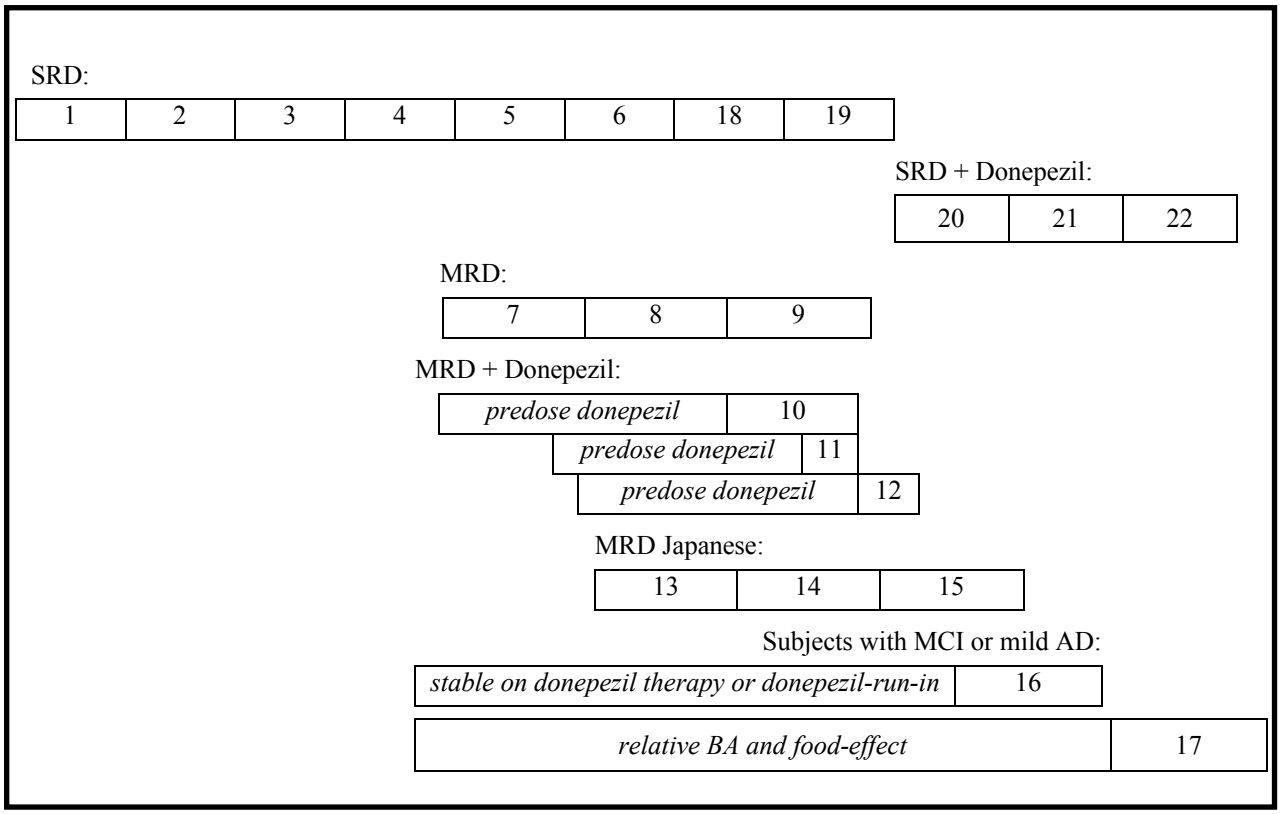
Table 6.a Overview of Treatment Cohorts

Group	Cohort	Age (years)	Type	Regimen	Number of Subjects per Cohort		Total
					TAK-071	Placebo	
SRD (a)	1 to 6, 18, and 19	18-55	HV	Single	6	2	64
SRD + donepezil post TAK-071 treatment (a, b)	20 to 22	18-55	HV	Single	6	3 (+3 donepezil)	36
MRD (a)	7, 8	18-55	HV	1 dose QD for 21 days	6	2	16
MRD (a)	9	18-55	HV	1 single dose, 7-day washout, 1 dose QD for 21 days	6	2	8
MRD + donepezil pretreatment (a, c)	10 to 12	18-55	HV	1 dose QD for 21 days	6	2	24
MRD	13 to 15	20-55	jHV	1 single dose, 7-day washout, 1 dose QD for 21 days	5	1	18
Subjects with MCI or mild AD (a)	16	55-90	MCI or mild AD (d)	21 days TAK-071 QD (Treatment A) or 21 days of matching placebo (Treatment B). Subjects will be randomized to 2 sequences (AB or BA), with 21 days washout between treatment sequences.	NA	NA	up to 8 (minimum of 6)
Relative BA and FE (e)	17	18-55	HV	Single dose in each of 3 periods with washout period of 21 days after Periods 1 and 2	12	NA	12
						Total:	186

jHV=Japanese healthy volunteers, FE=food effect, HV=healthy volunteers, NA=not applicable.
(a) Non-Japanese subjects.
(b) Donepezil (10 mg) will be given as a single dose as an over-encapsulated oral tablet, 24 hours post TAK-071 dose.
(c) Donepezil (5 mg QD) will be given as an oral tablet daily for 3 weeks prior to dosing and during the TAK-071 dosing interval.
(d) Subjects with MCI or mild AD (non-Japanese) who have been stable on 10 mg donepezil treatment for at least 21 days or who consent to donepezil run-in period.
(e) Healthy subjects. Subjects will be randomized to receive TAK-071 as a DIC formulation and a tablet formulation under fasted condition, and as a tablet formulation under fed conditions.

The flow of planned cohorts is provided in Figure 6.a.

Figure 6.a Flow of Treatment Cohorts



Schematic of study design are included as Figure 6.b for Cohorts 1 to 6 and 18 to 22, Figure 6.c for Cohorts 7 and 8, Figure 6.d for Cohorts 9 and 13 to 15, Figure 6.e for Cohorts 10 to 12, Figure 6.f for Cohort 16, and Figure 6.g for Cohort 17. Schedules of Study Procedures are listed in Appendix A.

Figure 6.b Schematic of Study Design for SRD Cohorts 1 to 6 and 18 to 22

Pretreatment Period		Treatment Period (a)		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 ——→					

(a) Subjects in Cohorts 20 to 22 will receive donepezil 10 mg or placebo as a single dose approximately 24 hours after the TAK-071 or placebo dose.

Figure 6.c Schematic of Study Design for MRD Cohorts 7 and 8

Pretreatment Period		Treatment Period		Final Visit	Follow-Up
Screening	Check-in	Multiple Dosing/PK	PK	Check-out/PK	Follow-up Telephone Call
Days -28 to -2	Day -1	Days 1 to 21	Day 22	Day 23	Day 32 (±2)
	←——Confinement ——————→				

Figure 6.d Schematic of Study Design for MRD Cohorts 9 and 13 to 15

Pretreatment Period		Treatment Period					Final Visit	Follow-Up
Screening	Check-in	Single Dose/PK	PK	Washout	Multiple Dosing/PK	PK	Check-out /PK	Follow-up Telephone Call
Days -28 to -2	Day -1	Day 1	Days 2 to 5	Days 2 to 7	Days 8 to 28	Day 29	Day 30	Day 39 (±2)
	←——Confinement ——————→							

Figure 6.e Schematic of Study Design for MRD Cohorts 10 to 12

Pretreatment Period					Treatment Period		Final Visit	Follow-Up
Screening	Check-in	Donepezil Pretreatment/ PK			TAK-071 and Donepezil Multiple Dosing/PK	PK	Check-out /PK	Follow-up Telephone Call
Days -44 to -23	Day -22	Days -21 to -19	Days -18 to -11	Days -10 to -1	Days 1 to 21	Day 22	Day 23	Day 32 (±2)
	←Confinement→		Outpatient	←——Confinement ——————→				

Figure 6.f Schematic of Study Design for Cohort 16

Pretreatment Period (a)			Treatment Period 1: TAK-071 or Placebo		Washout 21 days	Treatment Period 2: TAK-071 or Placebo		Final Visit	Follow-Up
Screening	Donepezil run-in	Check-in	Multiple Dosing/PK	PK		Check-in	Multiple Dosing/PK	Check-out /PK	Follow-up Telephone Call
Days -60 to -2	Days -49 to -1	Day -1	Days 1 to 21	Day 22		Day 41	Days 42 to 62	Day 63	Day 73 (±2)
		←———— Intermittent Confinement ————→ **Confinement on Days -1 to 2, 11, 20 to 22, 41 to 43, 52, and 61 to 63**							

(a) Subjects with MCI or mild AD on stable donepezil (10 mg) treatment or who consent to a donepezil run-in period of 5 mg dose for 28 days and titrate up to 10 mg for at least 21 days. Subjects with previous MCI/AD diagnosis who have been treated with 5 mg for at least 28 days prior to Screening may consent to a donepezil run-in period of 10 mg for at least 21 days.

Figure 6.g Schematic Study Design for Cohort 17

Pretreatment Period		**Treatment Periods 1, 2, and 3 (a)**		**Final Visit**	**Follow-Up**
Screening	Check-in	Single Dose/PK	PK		Follow-up Telephone Call
Days -28 to -2	Day -1	Day 1	Days 2 to 5 and 8	Day 8 Period 3	Day 12 (±2) Period 3
		Washout (b) Days 2 to 21 of Periods 1 and 2 only			
	←——Intermittent Confinement ——→ **Confinement on Days -1 to 4 and outpatient PK visit on Day 8**				

(a) Visit Day count shown as relative to Day 1 of each treatment period.
(b) The total washout period will be 21 days from the time of dosing.

For Cohorts 7 to 8 and 10 to 12, the dosing duration and for Cohorts 9 and 13 to 16, the dosing and/or washout duration may be adjusted if PK data from the SRD part indicate that a different period may be more appropriate (ie, 5 times the observed $t_{1/2z}$). For Cohort 17, washout period may be adjusted if PK data from previous cohorts warrants so.

The planned duration of dosing in all MRD cohorts will be of 21 days. If warranted based on emerging PK data (ie, based on the observed range of $t_{1/2z}$ values) and assuming acceptable safety and tolerability in preceding cohorts, the duration of TAK-071 dosing may be reduced to at a minimum of 14 days or extended for up to a maximum of 28 days.

6.1.1 SRD Part (Cohorts 1 to 6 and 18 to 22)

The SRD part of the study is a randomized, double-blind, placebo-controlled, parallel-group, ascending dose design involving single-dose escalation through 7 (or more, if needed) cohorts. Subjects will be confined throughout the Treatment Period (from Day -1 to Day 5), with a follow-up assessment on Day 12 (±2) days. Based on emerging preliminary PK data following Cohort 1, an additional visit for PK collection will be done on Day 8. For Cohorts 1 to 6, 18, and 19, healthy subjects will be randomly assigned to TAK-071 or matching placebo in a 3:1 ratio.

For Cohorts 20 to 22, healthy subjects will be randomly assigned to TAK-071+donepezil, donepezil, and placebo in a 2:1:1 ratio so that after completion of each cohort, 6 subjects had received TAK-071+donepezil, 3 subjects had received donepezil+TAK-071 placebo, and 3 subjects had received donepezil placebo+TAK-071 placebo.

Sentinel dosing will be used for Cohort 1 (1 subject to receive TAK-071 and 1 subject to receive placebo) to provide safety and tolerability evaluations prior to administering TAK-071 to the remainder of subjects within the cohort. After reviewing 24-hour postdose safety and tolerability data from the sentinel group, the remaining 6 subjects of the cohort may be dosed provided that the AE profile of TAK-071 in the first 2 subjects is considered acceptable. For subsequent cohorts (2, 4 to 6, 18, and 19), the intent is to stagger dosing between the first 2 subjects (1 TAK-071 and 1 placebo) and subsequent subjects dosed, starting no earlier than the median t_{max} observed in

earlier cohorts (providing that there are no issues arising in the previous cohort). Depending on the observed length of t_{max}, this could involve dosing the next day.

Sentinel dosing will be used for Cohorts 20 to 22 (1 subject to receive donepezil placebo+TAK-071 placebo, 1 subject to receive donepezil+TAK-071 placebo, and 1 subject to receive donepezil+TAK-071). After reviewing 24-hour postdose safety and tolerability data from the sentinel group, the remaining 9 subjects of the cohort may be dosed provided that the AE profile of TAK-071 in the first 3 subjects is considered acceptable.

For Cohort 3, subjects will be staggered across multiple days to facilitate CSF collection.

For Cohort 3, CSF samples will be obtained at 5 selected time points after the dose on Day 1 via an indwelling cannula to provide an indication of brain penetration for TAK-071 and the concentration relative to circulating plasma concentrations. If measured CSF concentrations are deemed to be low, ie, most time points are below the limit of quantification of the assay, TAK-071 CSF concentrations may also be determined in subsequent SRD cohorts until acceptable concentrations are attained.

CCI [redacted].

6.1.2 MRD Part (Cohorts 7 to 15)

Each of the healthy subject MRD cohorts, including TAK-071 alone in non-Japanese subjects (Cohorts 7 to 9), TAK-071 in combination with donepezil in non-Japanese subjects (Cohorts 10 to 12), and TAK-071 alone in Japanese subjects (Cohorts 13 to 15), will be a randomized, double-blind, placebo-controlled, 9-cohort, parallel-group, multiple ascending dose design with 8 subjects per cohort (6 active and 2 placebo) for Cohorts 7 to 12 and 6 subjects per cohort (5 active and 1 placebo) for Cohort 13 to 15.

Dosing will be staggered in Cohorts 7 and 8 and 10 to 11 between the first 2 subjects (1 TAK-071 and 1 placebo) and subsequent subjects dosed, starting no earlier than the median t_{max}. Depending on the observed length of t_{max}, this could involve dosing the next day. For Cohort 9, subjects will be staggered across multiple days to facilitate CSF collection. CCI [redacted] Japanese Cohorts 13 to 15 will not require staggering since doses will be equal or lower than those in the corresponding non-Japanese Cohorts 7 to 9, thus effectively acting as front runner groups.

Additional MRD cohorts may be added to fully understand safety and tolerability of TAK-071.

6.1.2.1 Non-Japanese Subjects (Cohorts 7 to 9)

Dose escalation will progress through 3 cohorts. Subjects will be confined during the Treatment Period from Day -1 to Day 22 (Cohorts 7 and 8) or Day 29 (Cohort 9).

For Cohorts 7 and 8, healthy subjects will be randomized to receive multiple doses (21 oral doses QD) of TAK-071 or matching placebo in a 3:1 ratio.

For Cohort 9, TAK-071 or placebo will be administered as a single oral dose, followed by a 7-day washout period and then daily dosing for 21 days or matching placebo in a 3:1 ratio. The 7-day

washout period in Cohort 9 is intended to provide sufficient time to characterize the TAK-071 terminal disposition phase, but it is not expected to result in complete disappearance of TAK-071 from plasma prior to starting repeat dosing on Day 8. Nonetheless, Day 8 trough concentrations are expected to be very low (ie, <5% steady state C_{max}).

For Cohort 9, the potential for time dependency in PK will be evaluated. CSF samples will also be obtained at 5 selected time points after the dose on Day 28 via an indwelling cannula to provide an indication of brain penetration and the concentration relative to circulating plasma concentrations at steady-state of TAK-071. CCI [redacted]

6.1.2.2 Non-Japanese Subjects Pretreated With Donepezil (Cohorts 10 to 12)

Cohorts 10 to 12 will be conducted in a double-blind manner with respect to TAK-071 but not for donepezil. Therefore, healthy subjects will be randomized to receive 21 QD oral doses of either TAK-071 or matching placebo in a 3:1 ratio. In addition, subjects will be pretreated for 3 weeks with daily oral doses of donepezil (5 mg), followed by continued daily oral donepezil QD dosing during the 21-day TAK-071 treatment period. Subjects will be confined from Day -22 to Day -19. Subjects will be discharged from the clinic on Day -19 and will continue donepezil dosing at home on Days -18 to -11. Subjects will return to clinic on Day -10 and remain confined until the Study Exit visit (Day 23) or Early Termination. During outpatient dosing (Days -18 to -11), subjects will be contacted by study site by telephone call every day to ensure treatment compliance.

CCI [redacted]

Additional MRD cohorts may be added to fully understand safety and tolerability of TAK-071 in subjects pretreated with donepezil.

6.1.2.3 Japanese Subjects (Cohorts 13 to 15)

The MRD part in Japanese subjects will involve dose escalation through 3 cohorts. Subjects will be confined throughout the Treatment Period from Day -1 to Day 29. Healthy Japanese subjects will be randomized to receive a single dose of TAK-071 or matching placebo in a 5:1 ratio, followed by a 7-day washout period and multiple doses (21 oral doses QD) of TAK-071 or placebo. The 7-day washout period in Cohorts 13 to 15 is intended to provide sufficient time to characterize the TAK-071 terminal disposition phase, but it is not expected to result in complete disappearance of TAK-071 from plasma prior to starting repeat dosing on Day 8. Nonetheless, Day 8 trough concentrations are expected to be very low (ie, <5% steady state C_{max}).

PK parameters will include a determination of time to steady-state, potential for accumulation, and time dependency in PK. In addition, data will be compared with data generated in non-Japanese subjects to determine if there are any ethnic differences in human PK.

6.1.3 Subjects With MCI or Mild AD (Cohort 16)

Cohort 16 will have a placebo-controlled, randomized, 2-sequence, 2-period, crossover study design to investigate the safety, tolerability, and PK in 1 of the intended target populations for TAK-071 treatment (subjects with MCI or mild AD). Up to 8 subjects (minimum of 6) previously diagnosed with MCI or mild AD and receiving ongoing donepezil (10 mg) therapy or who consent to a donepezil run-in period of 5 mg dose for 28 days and titrate up to 10 mg for at least 21 days. Subjects with previous MCI/AD diagnosis who have been treated with 5 mg for at least 28 days prior to Screening may consent to a donepezil run-in period of 10 mg for at least 21 days will be enrolled in Cohort 16. Subjects will continue with their donepezil therapy during the TAK-071 Treatment Period.

Subjects will be randomized to 1 of 2 possible treatment sequences (AB or BA) before the first dose of study drug. In each period, subjects will receive 1 of 2 possible treatments as follows:

- Treatment A: TAK-071 QD for 21 days, or
- Treatment B: matching placebo QD for 21 days.

There will be a washout period of at least 21 days between the treatment sequences. The washout and/or dosing duration may be adjusted with additional day(s) if PK data from the SRD/MRD parts indicate that a longer washout may be more appropriate (ie, 5 times the observed $t_{1/2z}$).

CCI [redacted].

6.1.4 Relative BA and FE Cohort (Cohort 17)

Cohort 17 will be administered in 3 single-dose regimens in a 3-way crossover design to 12 male and female subjects using 10 mg oral dose treatments. Subjects will receive a TAK-071 10 mg single oral regimen on Day 1 of each period. TAK-071 tablet or DIC will be administered with 240 mL of water.

Regimen A – Fasted State and Capsule Formulation (10 mg in DIC formulation)

Subjects will be fasted overnight for at least 8 hours. Treatment will be administered orally with 240 mL of water. No food should be allowed for at least 4 hours postdose. Water can be allowed after 2 hours postdose.

Regimen B – Fasted State and Tablet Formulation (10 mg [2× 5 mg] tablet formulation)

Subjects will be fasted overnight for at least 8 hours. Treatment will be administered orally with 240 mL of water. No food should be allowed for at least 4 hours postdose. Water can be allowed as desired after 2 hours postdose.

Regimen C – Fed State and Tablet Formulation (10 mg [2× 5 mg] tablet formulation)

Subjects will be fasted overnight for at least 8 hours. After this time, subjects should start the standard high fat meal (~50% fats) 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 25 minutes or less. Drug product should be dosed 30 minutes after

the start of the meal with 240 mL of water. No food should be allowed for at least 4 hours postdose. Water can be allowed as desired after 2 hours postdose.

Four subjects will be randomly assigned to 1 of 3 sequence groups and receive the regimens in the order shown in Table 6.b.

Table 6.b Sequence Groups and Regimen Assignment for Cohort 17

Sequence Group	Number of Subjects	Period 1 Day 1	Period 2 Day 1	Period 3 Day 1
1	4	**A**	**B**	**C**
2	4	**B**	**C**	**A**
3	4	**C**	**A**	**B**

Regimen A: Fasted State and Capsule Formulation (10 mg in DIC formulation).
Regimen B: Fasted State and Tablet Formulation (10 mg tablet formulation).
Regimen C: Fed State and Tablet Formulation (10 mg tablet formulation).

6.1.5 Dose Escalation

All decisions concerning dose escalation will be made by the Takeda clinical science representative and the principal investigator.

Additionally, the Takeda clinical science physician and the principal investigator may jointly decide to not escalate the dose for a particular cohort but rather administer the same or a lower dose level to the next cohort.

After dosing in Cohort 2, there will be a minimum period of 4 days between each dose escalation to allow for review of safety and tolerability data and any available PK data. For Cohorts 1, 3, 4, 5, and 6, dose escalation to the next cohort will also be conditional to a review of preliminary 24-hour PK data after the last administered dose. For Cohort 3, it is planned that preliminary 12-hour CSF PK data will also be required prior to dose escalation. For further details on dose escalation justification and requirements, see Section 6.2.2.2. In the event that higher dose SRD cohorts are required, dose escalation to the next cohort will also be conditional to a review of preliminary 24-hour PK data after the last administered dose from the preceding cohort.

For each dose level administered/completed cohort, the principal investigator and Takeda clinical science physician will carefully review the available blinded 24-hour safety, tolerability, and available PK data and determine whether dosing should stop or continue (and, if continue, at what dose, including whether to repeat the previous dose), whether to review PK data on the last administered dose in additional cohorts, and whether the blind should be broken to identify whether the subjects received TAK-071 or placebo.

All AEs reported during the Treatment Period, both within and across cohorts will be evaluated to assess the need for subject and/or study termination in accordance with the prespecified criteria for discontinuation/termination (Section 6.3.1).

Following assessment of the AE data and predefined criteria for study termination, dose escalation may be interrupted/stopped and the blind broken for further analysis. Based on review of

unblinded data, Takeda in consultation with the principal investigator will decide if and how it is appropriate for the study to proceed.

If agreement regarding a dose escalation decision cannot be reached between the principal investigator and Takeda, the study will be stopped.

Other criteria to consider discontinuation of cohort entry are as follows.

1. If a serious adverse event (SAE) whose relationship to the study drug cannot be denied is observed.
2. At the onset of an AE for which relationship to the study drug cannot be denied and for which it is considered difficult to give medications continuously.

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Study Design

This phase 1 study is randomized, double blind, and placebo controlled to avoid subjective bias in the assessment of safety and tolerability and pharmacological effects of the study drug. Placebo will be administered as a control in order to establish the frequency or magnitude of changes in clinical endpoints that may occur in the absence of active treatment.

The study will be initiated as an SRD (Cohorts 1 to 6, 18, and 19) so that each enrolled subject will only receive a single exposure to study drug to minimize the potential for adverse effects from repeated drug exposure. The SRD TAK-071+donepezil cohorts (Cohorts 20 to 22) will establish a high well-tolerated dose of TAK-071 when coadministered with donepezil, and will help to determine the dose in the scopolamine PoM study.

Cohorts 18 and 19 (and additional cohorts, if needed) with dose(s) of 120 mg or higher dose are to explore the safety and tolerability of TAK-071 in single dose(s) of at least 120 mg, with a special focus on safety EEG. CCI [redacted]

Optional cohorts have been included to allow the opportunity to explore higher exposures in the event that neither the NOAEL plasma exposure threshold nor the MTD are attained. Identifying a single TAK-071 dose that, while remaining appropriately below the 28-Day monkey NOAEL threshold, provides a high plasma exposure that is deemed to be of importance for the purposes of an upcoming PoM scopolamine challenge study (TAK-071-1002) in healthy subjects. This is because a high TAK-071 dose is expected to maximize the potential for observing a significant reversal of scopolamine-induced cognitive impairment.

The MRD (Cohorts 7 to 9) will allow for the characterization of the safety/tolerability and PK of repeated TAK-071 daily exposures over a limited duration of time, as well as the characterization of any time dependency in the PK in Cohort 9 (the highest dose). Subjects in the first MRD cohort (Cohorts 7) will only be dosed after confirmation of acceptable safety and tolerability and evaluation of the 24-hour plasma PK and 12-hour CSF PK data from Cohort 3. The

safety/tolerability and PK of repeated TAK-071 doses in combination with donepezil will be investigated in MRD Cohorts 10 to 12 in healthy subjects.

Japanese subjects have been included in this study in order to facilitate study in this ethnic group as part of phase 2 studies (Cohorts 13 to 15). Consequently, it is important to assess the safety, tolerability, and PK in this population at the earliest opportunity.

Clinical trials with cholinomimetic drugs show differential tolerability in healthy young adults and the target population of patients with AD [12]. Therefore, the strategy in this study is to include an MCI/mild AD cohort (Cohort 16) to act as a bridge to determine the safety and tolerability of TAK-071 in combination with a cholinesterase inhibitor in the target population (subjects with MCI or mild AD). This cohort, together with the experience of the combined TAK-071 and donepezil treatment in healthy subjects, will help guide selection of appropriate doses for later-stage efficacy studies [13].

A preliminary assessment of the effect of food and a tablet formulation on TAK-071 PK is included (Cohort 17) to expedite the further development of TAK-071. A crossover design is planned to enable each subject to provide their own control reference point (fasted DIC/tablet delivery). Subjects will be randomly assigned to 1 of 3 sequence groups to avoid bias. A 21-day washout interval between treatments is planned to ensure that there is no drug carryover effect. Discontinued or withdrawn subjects may be replaced to ensure that a minimum of 10 subjects complete all 3 regimens.

A total of up to 186 subjects are required for this design, and numbers required per cohort are deemed to be the lowest required for satisfying the overall aims of the study.

6.2.2 Dose Selection

6.2.2.1 TAK-071 Starting Dose (Cohort 1)

The starting dose for this FIH study was determined taking into consideration the results of the definitive 4-week repeat-dose toxicity studies in rats and monkeys, the results from the safety pharmacology studies in rats and human PK predictions (based on allometric scaling) together with the observed minimal effective dose and exposure in animal models.

In the rat, the NOAELs were 100 and 30 mg/kg/day in males and females, respectively, with associated Day 28 average exposures of 105,000 and 146,000 ng·hr/mL, respectively. Based on body surface area, 30 mg/kg/day in the rat equates to 180 mg/m^2, with a human dose equivalent of 4.8 mg/kg/day×60 kg=288 mg/day.

In the monkey, the NOAEL in both sexes was 10 mg/kg/day, with associated Day 28 mean exposures of 48,000 and 49,100 ng·hr/mL in males and females, respectively. Based on body surface area, 10 mg/kg/day equates to 120 mg/m^2, with a human dose equivalent of 3.2 mg/kg/day×60 kg=192 mg/day.

Given the lower NOAEL and associated exposures in monkeys, the FIH dose will be based on this species rather than the rat. Therefore, considering the regulatory guidelines for setting the maximum recommended starting dose (MRSD) based on the Food and Drug Administration

(FDA) Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers [14] and the imposition of a 10-fold safety margin, the MRSD for this FIH study is 19.2 mg/day.

In safety pharmacology studies in rats, doses ≥10 mg/kg were associated with increases in activity, with no effects observed at 3 mg/kg. Based on allometric scaling of the 3 mg/kg dose, the human equivalent dose would be approximately 29 mg, and imposing a 10-fold margin would result in a human equivalent dose of 2.9 mg/day.

Additionally, nonclinical studies (data on file) have also suggested (based on efficacy in animal models and allometric scaling) that the human minimum effective dose could be in the range of 1 to 10 mg. As shown in Table 6.c, the human plasma exposure for TAK-071 at the lowest anticipated minimum effective dose of 1 mg, obtained based on allometric scaling and monkey PK data, is predicted to be substantially below the corresponding exposure at the lowest NOAEL level in the most sensitive species (>50-fold).

Table 6.c Exposure to TAK-071 at the NOAEL in Rats and Monkeys (28-day GLP data) at Steady-State and Human Predicted Mean Exposure After a Single 1 mg TAK-071 Dose

Nonclinical Toxicity Study	NOAEL (mg/kg/day)	C_{max} (ng/mL)	AUC_{24} (ng·hr/mL)
28-day GLP repeat-dose rat	100/30	7220/8940	105,000/146,000
28-day GLP repeat-dose monkey	10	3320/3190	48,000/49,100
Human Predicted 1 mg TAK-071	NA	37.7	951 (a)

Note: Results reported as male/female.
NA=not applicable.
(a) Predicted human AUC_{∞}.

Overall, a TAK-071 dose of 1 mg is an appropriate starting dose for this FIH study because of the following:

- It is significantly lower (19-fold) than the regulatory requirements for an MRSD based on the NOAEL from the monkey 4-week repeat-dose toxicity study [15].
- It has an ample predicted exposure-based safety margin (50-fold).
- It is lower (3-fold) than the estimated human equivalent dose base on safety pharmacology studies.
- It is the lowest dose anticipated to have a potential for cognitive improvement effects in humans.

6.2.2.2 Dose Escalations and Maximum TAK-071 Dose to be Administered

The study is intended to explore the safety and tolerability of single and multiple TAK-071 doses, some of which may exceed doses anticipated to be therapeutically effective. However, it should be noted that the study is not intended to determine the MTD.

For Cohort 2, the actual choice of the subsequent dose level will occur after a review of the blinded 24-hour safety, tolerability, and PK data from Cohort 1. Dose escalation to this cohort will be limited to an escalated dose that is expected to give no greater than an average approximately 3-fold increase in either C_{max} or AUC_{24} based on experience in the preceding cohort. In the event that the majority of plasma concentrations of TAK-071 are below the limit of detection, or exposures are significantly lower than predicted based on animal data, the dose will be escalated up to 5-fold with respect to the starting dose, if safety and tolerability of the initial dose are found to be acceptable.

The dose escalation decision after dosing in Cohort 2 will be based primarily on a review of the blinded 24-hour safety and tolerability data. PK data (0 to 24 hours postdose) will be generated after each cohort (but not available prior to the next cohort) and will not inform dose escalation decisions for these cohorts unless emerging information from the preceding cohorts indicates that PK data are needed between cohorts.

Dose escalation decisions following dosing in Cohort 3 will be based on a review of the blinded 24-hour safety, tolerability, and preliminary plasma PK and 12-hour CSF PK data.

For Cohorts 5, 6, 18, and 19, the actual choice of dose level will occur after a review of the blinded 24-hour safety, tolerability, and preliminary plasma PK data from Cohorts 4, 5, and 6, respectively. Based on extrapolation, using a power-law model, of currently available preliminary plasma PK parameters (C_{max} and AUC_{24}), the planned dose (120 mg) in Cohort 18 is not expected to result in individual subjects exceeding the lowest average NOAEL plasma exposure achieved in 4-week GLP animal toxicology studies.

For any additional cohorts, the actual choice of dose level will occur after a review of the blinded 24-hour safety, tolerability, and preliminary plasma PK data from the preceding cohort. The dose used will not be expected to exceed the lowest NOAEL plasma exposure achieved in 4-week GLP animal toxicology studies.

It is planned that Cohort 2 plasma samples (post-24 hours) will be analyzed separately and will not comprise part of the dose escalation PK datasets.

For illustration purposes, and based on human PK predictions using animal data, the planned dose escalation in the SRD is as follows: 1, 3, 9, 20, 40, and 50 mg. However, based on emerging safety and PK data from Cohort 1 through 6, 18, and 19, doses of 80, 60, and 40 mg are planned for Cohorts 20 to 22 to understand safety and tolerability of TAK-071+donepezil (10 mg). The TAK-071 plasma exposure following an 80 mg TAK-071 + 10 mg donepezil dose is predicted to be approximately equivalent to 15 mg TAK-071 + 5 mg donepezil in chronic administration in the MRD study, and this dose was well-tolerated in Cohort 12. A dose of 160 mg TAK-071 + 10 mg donepezil will provide an approximate 1.5-fold increase in TAK-071 exposure compared to the 80 mg TAK-071 + 10 mg donepezil dose. The dose selected for Cohort 21 will be not higher than 160 mg and will be based on the safety data from TAK-071 120 mg dose.

It is planned that the MRD cohorts will start no sooner than after all subjects in the SRD Cohort 4 have been dosed. The starting dose of the MRD cohorts will then be decided following a review of the blinded 24-hour safety (AEs, vital signs, ECG, clinical laboratory results) and tolerability from

Cohort 4 and the 24-hour preliminary plasma PK and 12-hour CSF PK data from Cohort 3. Under no circumstances will the starting dose for MRD Cohort 7 exceed that of the immediately preceding cohort for which blinded 24-hour safety and tolerability data have been evaluated and deemed to be acceptable. For example, safety and tolerability data from Cohort 4 would enable a maximum starting MRD dose analogous to Cohort 3. In the unlikely event that CSF concentrations are found to be low, ie, the majority of time points are below the limit of quantification, the MRD start may be postponed until a single dose that provides acceptable CSF concentrations is identified.

For subsequent MRD cohorts, doses will be selected after review of the blinded safety, tolerability, and available PK data arising from the ongoing SRD part and previous MRD cohort. Selected doses will include exposures that have the potential to be in the range required for therapeutic efficacy and can be chosen to provide either higher or lower exposure. Higher exposure can be greater than approximately 3-fold increments in exposure compared with the previous MRD cohort provided that overall, these do not exceed the highest dose administered in the SRD at that time and/or the NOAEL exposure (either after the first dose or upon attainment of steady-state).

Safety pharmacology studies in monkeys are in progress to examine the effects of donepezil and TAK-071 when dosed alone and in combination on the central nervous system (CNS), and on cardiovascular and respiratory function; the PK of the compounds will also be determined. The data from this study will be used for guiding TAK-071 dose selection and for determining the TAK-071 exposure caps for Cohorts 10 to 12 and 16.

The starting TAK-071 dose for MRD Cohort 10 will be that used in MRD Cohort 7, if supported by the preliminary safety and tolerability data. Cohort 10 will start no sooner than after the last dose in MRD Cohort 8 has been given and after the 24-hour postdose blinded safety, tolerability, and available PK data have been evaluated. It is intended that in Cohorts 10 to 12, the same doses will be used as for Cohorts 7 to 9 and, in particular, that the dose for CCI [redacted] However, if warranted after review of the blinded safety, tolerability, and available PK data arising from the ongoing MRD part and previous SRD cohorts, planned doses might be altered. In that event, TAK-071 doses would then be selected to include exposures in the range believed to be required for therapeutic efficacy in combination with donepezil and could be chosen to provide either higher or lower exposure but under no circumstances would exceed the highest TAK-071 dose administered in MRD Cohorts 7 to 9.

Cohort 13 can start after the last dose of Cohort 7 has been completed, providing there are no safety concerns arising from Cohort 7 following evaluation of the 24-hour postdose blinded safety, tolerability, and available PK data. The oral doses of TAK-071 for Cohorts 13 to 15 will be those used for Cohorts 7 to 9, respectively. This will facilitate a direct comparison of exposure in Japanese and non-Japanese subjects. If TAK-071 is not tolerated at a particular dose level in Japanese subjects, alternative doses may be selected for Cohorts 13 to 15. However, under no circumstances will doses in Japanese subjects exceed those of Cohorts 7 to 9.

Cohort 16, consisting of subjects with MCI or mild AD, may start after Cohorts 10 to 12 have been completed and their preliminary safety, tolerability, and available PK data have been evaluated.

The selected TAK-071 doses in subjects with MCI or mild AD will not exceed the highest TAK-071 dose tested in the healthy subject donepezil combination treatment Cohorts 10 to 12.

The TAK-071 dosing frequency in the healthy subject MRD Cohorts 7 to 15 and patient Cohort 16 will be QD. The dosing duration in all MRD cohorts is planned to be 21 days, as it is expected that the majority subjects will attain steady state prior to the last dosing day. If warranted based on emerging PK data from the SRD (ie, several subjects present $t_{1/2z}$ >140 hours) with acceptable safety and tolerability in preceding cohorts, the duration of TAK-071 dosing may be extended for up to a maximum of 28 days. The maximal duration of dosing in the MRD cohorts of 28 days has been set based on the FDA 'Guidance for Industry - M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals' and the available 28-day GLP toxicology studies. Under no circumstances a subject will receive >28 TAK-071 doses in total through the course of their participation in this study. If the majority of subjects present with shorter $t_{1/2z}$ values (ie, <65 hours), TAK-071 dosing duration may be shortened to a minimum of 14 days.

Cohort 17, the relative BA and food effect cohorts, a 10 mg single dose will be administered as a DIC or a tablet formulation under fasted condition and tablet formulation in fed state. A dose of 10 mg has been selected because, based on nonclinical and ongoing clinical data, this is the highest anticipated dose likely to be used in future clinical studies.

The endpoints outlined in Section 6.2.3 are those which will allow an appropriate assessment of safety, tolerability, and PK of TAK-071, effect of food on the PK of TAK-71 and relative BA for a tablet versus DIC formulation.

Enrolled participants who withdraw from the study for reasons other than safety may be replaced to ensure adequate numbers of evaluable subjects. The decision to replace a withdrawn subject will be made at the discretion of Takeda and the investigator.

6.2.2.3 Dose selection for the Food Effect/Relative BA Cohort 17

Based on nonclinical and preliminary clinical data, the doses for chronic treatment likely to be effective in the clinic are anticipated to be in the range of 3 to 10 mg QD. Tablets of 1 and 5 mg have been developed because it is thought these strengths will provide the flexibility to cover doses within the cited effective range in future clinical studies. The planned dose for the BA/FE Cohort 17 will therefore be 10 mg, administered as either a single 10 mg DIC formulation (Reference) or as 2 x 5 mg tablet formulation (Test) with or without a high-fat high-calorie meal. The choice of 10 mg has been made for practical reasons and because it is expected to have the greatest potential (as compared to lower doses) for a food effect. A higher or lower dose may be tested for Cohort 17 if warranted based on emerging preclinical or clinical data; however, under no circumstances will the selected TAK-071 dose exceed 20 mg, thus ensuring there is an approximately 10-fold safety margin with respect to single dose exposures in humans versus those observed at the NOAEL in the 28-Day GLP monkeys toxicology study. An approximately 10-fold safety margin is thought to be ample enough to provide exposure coverage in the event of an increase in plasma TAK-071 concentrations due to either a formulation and/or food effect.

6.2.2.4 Donepezil Dose Selection

Donepezil is a marketed drug and has been widely used in the human population at a 5 mg oral dose, which is the lowest dose level used in the treatment of AD. In addition, nonclinical studies show that TAK-071 has the potential to be efficacious in a scopolamine-induced cognitive deficit model in the presence of low/suboptimal donepezil doses due to synergistic effects. TAK-071 will likely be used as add-on therapy in subsequent clinical studies; consequently, it is relevant to study the lower standard dose of donepezil. Due to the plasma half-life of donepezil (>70 hours), it is necessary to pretreat subjects with donepezil for 3 weeks to ensure that steady-state concentrations have been reached prior to dosing with TAK-071. Although donepezil is available at higher strengths (10 and 23 mg), there is an increased incidence of side effects, including nausea, vomiting, and diarrhea, at these dose levels. Consequently, it is not suitable to provide a loading dose to facilitate reaching the desired plasma concentrations in a shorter time interval.

A dose of 5 mg QD has been selected for the healthy subject cohorts (10 to 12) because the target population of patients with AD is known to better tolerate cholinomimetic treatments as compared with healthy young adults [12]; thus, a dose of 5 mg is thought to be appropriate for the purposes of an initial evaluation of the safety, tolerability, and PK of the donepezil plus TAK-071 combination. Because PK sampling for donepezil plasma concentrations will be performed in these cohorts, for practical purposes and to avoid PK sampling overnight, donepezil dosing will occur in the morning simultaneously with TAK-071. This will also provide an opportunity to evaluate the potential for a drug-drug interaction of TAK-071 on donepezil while at steady-state. For this reason, the exact dosing time of donepezil relative to TAK-071 will be selected so as to ensure that both drugs attain their peak concentrations at approximately the same time to maximize the potential for interaction. Donepezil is reported to have a t_{max} of 3 to 4 hours, and preliminary TAK-071 PK data from SRD Cohorts 1 to 4 indicates that maximum, or near maximum, plasma concentrations are attained approximately 4 hours postdose; thus, donepezil should be dosed approximately 1 hour after TAK-071; however, the definitive dosing time of donepezil relative to TAK-071 will be confirmed following evaluation of all preliminary PK data from the SRD part of the FIH study.

According to the donepezil (Aricept) product label, the recommended starting dosage of donepezil is 5 mg administered once per day in the evening, just prior to retiring. The maximum recommended dosage in patients with mild-to-moderate AD is 10 mg per day. A dose of 10 mg should not be administered until patients have been on a daily dose of 5 mg for 4 to 6 weeks. Because the majority of patients with mild AD are prescribed donepezil 10 mg QD, 10 mg has been selected as the donepezil dose for Cohort 16. To minimize variability, subjects who are regularly taking this dose in the evening, as recommended in the product labeling [11], will be recruited into the study. This will also provide safety and tolerability data for the combination treatment in the intended target population under realistic dosing regimen conditions and will also provide data at a higher donepezil dose than that tested in the preceding healthy subject cohorts.

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 Cohorts 20 to 22.

6.2.3 Endpoints

The SRD/MRD cohorts (Cohorts 1 to 15, and 18 to 22) will be conducted in healthy subjects to collect safety and tolerability information that will not be biased by any comorbidity and other intrinsic/extrinsic factors. The safety and tolerability will then be investigated in subjects with MCI or mild AD (Cohort 16) at doses with an acceptable safety profile in the healthy subject cohorts. The safety endpoints include AEs, vital signs, weight, ECG findings, and laboratory test results. In addition, bowel function will be assessed (eg, BSF scale) to further investigate the potential cholinomimetic effects on the gastrointestinal (GI) tract.

The plasma concentration of TAK-071 will be examined to characterize the PK of TAK-071 following single and multiple doses. Determination of TAK-071 PK in this study will also enable the evaluation of the effect of ethnicity on PK as well as exploration of the comparability of PK between the target population (patients with AD) and healthy subjects.

Currently available in vitro data indicate there is a low potential for PK drug-drug interaction of TAK-071 on donepezil via CYP enzymes. The determination of donepezil plasma concentrations will enable the investigation of any effect of TAK-071 on donepezil PK via any other unaccounted for mechanisms prior to dosing subjects with MCI or mild AD. The effect of donepezil on TAK-071 PK will also be explored.

The investigation of CSF concentrations of TAK-071 is intended to establish some understanding of the approximate level of brain penetration relative to plasma for TAK-071 itself, which will be helpful for guiding dose selection within the present study and for the interpretation of future studies.

The M3 receptor, rather than M1, is the most abundant postjunctional receptor and is thought to be the most important muscarinic receptor subtype for mediating pupil contraction. Because TAK-071 selectively modulates M1 activity, changes in pupil size following TAK-071 treatment are not expected [16]. However, this evaluation will allow confirmation of the lack of engagement with other muscarinic receptors in a clinical setting.

CCI [redacted]

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 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.

- 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.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Study-specific criteria for terminating the study (eg, study meets predefined rule for futility or benefit, study meets predefined stopping rules within or between cohorts per Section 6.1.5).

1. Dose escalation will be stopped if it is predicted that further dose escalation will not result in a further increase in plasma exposure (ie, an exposure ceiling is reached).
2. Dose escalation will be stopped at a dose level (ie, 1 escalation step) below the dose that is predicted to give a TAK-071 AUC or C_{max} that exceeds that of the 28-day monkey toxicology study NOAEL.
3. Two or more subjects in any single cohort or across more than 1 cohort experience any of the Takeda Medically Significant List events (as outlined in Table 10.a).*
4. Two or more subjects in any single cohort or across more than 1 cohort experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5× upper limit of normal (ULN) in the absence of a concomitant bilirubin increase [see point 5 below].*
5. One or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations >3× ULN in the presence of a total bilirubin increase >2× ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (ie, “Hy’s Law cases”).
6. Two or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).*

   * Please note that the study may be terminated early prior to full attainment of these criteria (eg, if just 1 subject experiences 1 of these events) if warranted by safety data from the other subjects dosed in the study to date.
7. Two or more subjects in any single dose cohort show a shift in safety EEG electroclinical assessment from rating (grading) 0 to 2, or any of the subjects shows clinical signs of clinically manifest convulsive or non-convulsive seizure activity.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

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

In the event that the sponsor, an institutional review board (IRB), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational 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. For Cohorts 10 to 12, check-in occurs on Day -22 for all eligibility criteria.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

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 (ICF) 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 a healthy man or woman. Subjects should be aged 18 to 55 years, inclusive (nonelderly at the time of informed consent and first study drug dose) for Cohorts 1 to 12, and 17 to 22; 20 to 55 years, inclusive, for Cohorts 13 to 15; and 55 to 90 years, inclusive, for Cohort 16.
4. The subject weighs at least 50 kg and has a body mass index (BMI) from 18.0 to 30.0 kg/m^2, inclusive, at Screening.
5. For Cohorts 13 to 15 only: First-generation Japanese, defined as having been born in Japan of Japanese parents and Japanese grandparents and living no more than 10 years outside of Japan, with no significant change in lifestyle, including diet, while living outside of Japan.
6. Cohort 16 only:
   a) Subjects with a documented previous diagnosis of MCI or mild AD or current diagnosis of AD criteria met at Screening Visit.
   b) Mini Mental State Examination (MMSE) score of 18 to 30, inclusive for subjects with existing diagnosis of MCI or mild AD or 18 to 26 inclusive for subjects diagnosed with mild AD at Screening and no biomarker data to contradict this diagnosis.
   c) Retrospectively, or at Screening Visit, subjects will have met a diagnosis of probable AD based on the National Institute of Neurological Disorders and Stroke Alzheimer's Disease and Related Disorders Association criteria [17] or retrospective clinical diagnosis of MCI based on criteria such as subjective cognitive complaint, evidence of impairment in 1 or more cognitive domain, preservation of functions, and absence of dementia [18]. (Note: treatment can be initiated ONLY based on Mild AD Diagnosis at Screening Visit.)
   d) Subjects must be receiving ongoing donepezil therapy (10 mg) in the evening for a minimum of 21 days prior to Check-in (Day -1).
7. A female subject with no childbearing potential, defined as subjects who have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal

(defined as continuous amenorrhea of at least 2 years and follicle-stimulating hormone [FSH] >40 IU/L).

8. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 30 days after last dose.

*Definitions and acceptable methods of contraception are defined in Section 9.1.10 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.11 Pregnancy.

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 is an immediate family member, study site employee, or 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.
3. If female, the subject is of childbearing potential (eg, premenopausal, not sterilized).
4. The subject has clinically significant (Cohorts 1 to 15 and 17 to 22) or uncontrolled (Cohort 16) neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, GI, urologic, immunologic, endocrine, or psychiatric 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. A subject with a history of type 1 diabetes (Cohorts 1 to 22) or type 2 diabetes (Cohorts 1 to 15 and 17 to 22) or subject with hemoglobin A1c >6.5% at Screening. Note: subjects with controlled (hemoglobin A1c <7.0% at Screening) type 2 diabetes in Cohort 16 may participate in the study.
6. A subject with evidence or history of a significant hepatic disorder that may either compromise subject safety or interfere with the safety and/or outcome evaluation of the study drug. Subjects with acute hepatitis (including but not limited to hepatitis B or hepatitis C) or subjects with the following results will be excluded:
   a) Total bilirubin >1.5× ULN or
   b) ALT or AST >2× ULN and total bilirubin >1.3 mg/dL.
7. A subject with a creatinine clearance <60 mL/min (as determined by the Cockcroft-Gault formula), confirmed on repeat testing.
8. The subject has a known hypersensitivity to any component of the formulation of TAK-071 or placebo. For Cohorts 10 to 12, 16, and 20 to 22, subject has a known hypersensitivity to any component of the formulation of donepezil.

9. The subject has a sustained supine blood pressure outside the ranges of 90 to 140 mm Hg for systolic and 60 to 90 mm Hg for diastolic, confirmed on repeat testing within a maximum of 30 minutes, at Screening or Check-in.
10. The subject has a sustained resting vital signs heart rate outside the range 50 to 100 beats per minute (bpm), confirmed on repeat testing within a maximum of 30 minutes, at Screening or Check-in.
11. The subject has a history of hereditary short QT syndrome.
12. The subject has a Fridericia-corrected QT interval >450 ms or PR interval outside the range 120 to 220 ms, confirmed on repeat testing within a maximum of 30 minutes, at Screening or Check-in.
13. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use) at Screening or Check-in.
14. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the Screening Visit; or regularly drinks more than 21 units of alcohol per week in men (or more than 4 units per day) and 14 units in women (or more than 3 units per day); or is unwilling to agree to abstain from alcohol and drugs throughout the study. One unit is equivalent to a half pint of beer, 1 measure of spirits, or 1 glass of wine.
15. 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 (or donepezil for Cohorts 10 to 12, 16, and 20 to 22) or a similar drug in the same class or that might interfere with the conduct of the study.
16. 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.
17. The 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 7.3).
18. The subject has evidence of current cardiovascular, CNS, GI condition, seizure, or any other neurological condition that increases the risk of seizure.
19. Cohort 16 only: Any significant neurologic disease (other than suspected incipient or mild AD), such as Parkinson disease, stroke, transient ischemic attack, multi-infarct dementia, Huntington disease, head trauma with clinically significant cognitive sequelae, or chronic CNS infection, per investigator discretion.
20. Cohorts 9, 10 to 12, and 18 to 22 only: Subjects with a history of eye diseases/ocular pathology (eg, eye injury, cataract surgery, glaucoma).
21. The subject has current or recent (within 6 months) GI disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, any surgical intervention known to impact absorption [eg, bariatric surgery or bowel resection], esophageal reflux,

peptic ulcer disease, erosive esophagitis, or frequent [more than once per week] occurrence of heartburn).

22. The subject has a history of cancer, except basal cell carcinoma that has been in remission for at least 5 years prior to Check-in.
23. A subject with a known history of human immunodeficiency virus infection at Screening.
24. The subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, electronic cigarettes, chewing tobacco, nicotine patch, or nicotine gum) within 28 days prior to Check-in or has a positive cotinine test at Screening or Check-in.
25. The subject has poor peripheral venous access.
26. The subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis) or had a transfusion of any blood product within 45 days prior to the first dose of study drug.
27. The subject has a clinically significant abnormal ECG at Screening or Check-in. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, justified, and documented by signature of the principal investigator or medically qualified investigator.
28. The subject has abnormal Screening or Check-in laboratory values that suggest a clinically significant underlying disease, confirmed on repeat testing.

7.2.1 Additional Exclusion Criteria for Cohorts With CSF Collection

1. The subject has had CSF collection performed within 30 days prior to Check-in.
2. The subject has a known hypersensitivity to the anesthetic or its derivatives used during CSF collection or any medication used to prepare the area of lumbar puncture.
3. The subject has significant vertebral deformities (scoliosis or kyphosis) that, in the opinion of the investigator, may interfere with the lumbar puncture procedure.
4. The subject has a history of clinically significant back pain and/or injury in the opinion of the investigator.
5. The subject has local infection at the puncture site.
6. The subject has thrombocytopenia or other suspected bleeding tendencies noted before the procedure.
7. The subject has developed signs and symptoms of spinal radiculopathy, including lower extremity pain and paresthesias.
8. The subject has any focal neurological deficit that might suggest an increase in intracranial pressure.
9. The subject has any abnormal findings on ophthalmological assessment/funduscopy suggestive of raised intracranial pressure (ie, optic disc swelling/edema; or [uncontrolled] hypertensive retinopathy).

10. The subject suffers regularly from moderate-to-severe headaches requiring analgesics.

7.2.2 Additional Exclusion Criteria for Cohorts 18 to 22

1. Subjects with lifetime history of seizures, including but not limited to childhood febrile seizure.
2. Subjects with EEG abnormality at Screening of Category 2, exclusionary criteria defined in the EEG manual. Categories: 0 (within normal limits), 1 (mildly abnormal, not exclusionary) and 2 (abnormal, exclusionary).

7.3 Excluded Medications, Dietary Products, Procedures, and Treatments

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

Table 7.a Prohibited Medications and Dietary Products

28 Days Prior to Check-in	7 Days Prior to Check-in	72 Hours Prior to Check-in
Cohorts 1 to 15, 17 to 22 (and higher dose cohort, if needed): Prescription medications (other than donepezil, where applicable)	OTC medications (a)	Products containing caffeine or xanthine
Nutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements	Poppy seeds
Immunization/vaccines	Foods or beverages containing grapefruit or Seville-type (sour) oranges and marmalade, apple, orange, pineapple, 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	
Cohorts 1 to 15: Intake of known OTC inhibitors/inducers of CYPs 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1, and 2A6	Intake of the following drug classes: antacids and proton pump inhibitors.	
Cohort 16: Intake of known OTC or prescription drugs that are moderate or strong inhibitors of CYP3A4 (eg, azole antifungals), 2D6 (eg, fluoxetine), or 2C9 (b) (c)		
Intake of the following drug classes: anti-emetics; antidiarrhetics, anticholinergics, cholinergic agonists and laxatives		

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) In Cohort 16, Takeda may review and approve concomitant medications on a case-by-case basis.
(c) For a list of moderate/strong CYP3A4, 2D6, or 2C9 inducers/inhibitors [19-21], see Appendix F.

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

7.4 Diet, Fluid, and Activity Control

Subjects will be confined to the clinic for the duration of each Treatment Period. During confinement, subjects will be given 3 meals and an evening snack, each containing approximately 30% fat (relative to the total calories). The meals served on the day of dosing should be similar in composition and caloric content for each cohort 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.

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence followed by the study procedure and then the meal.

7.4.1 Fasting Cohorts (1 to 15 and 17 to 22)

TAK-071 and placebo will be administered with approximately 240 mL of water after a fast of at least 8 hours. Subjects will continue to fast for an additional 4 hours after dosing. If a subject is unable to continue fasting for 4 hours postdose, a light snack may be provided no earlier than 2 hour postdose on nonintense PK collection days. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration.

While subjects should aim to swallow all the study drug medication in quick succession with approximately 240 mL of water, if the combined total number of capsules/tablets required for delivering the dose for a cohort (ie, Cohort 6) exceeds 2 dosage units, subjects will be allowed to have a small amount of additional water (up to approximately 120 mL) to complete the study drug administration, and the administered approximate total volume should be recorded in the electronic case report form (eCRF).

For Cohorts 20 to 22, on Day 1, TAK-071 administration, diet, fluid, and activity control will be same as above. On Day 2, donepezil will be administered with approximately 240 mL of water after a fast of at least 8 hours. A low-fat, low-calorie breakfast, defined as <300 calories and <20% fat content, will be given at approximately 1.5 hours after donepezil administration. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration. The study menu should be recorded and submitted to the study file. The start and end time of meals and percentage of meals consumed on Day 1 and Day 2 will be recorded in the eCRF.

Subjects will remain upright (seated, standing, or ambulatory) for 4 hours 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.

For cohorts with CSF sampling, subjects need to remain recumbent due to CSF sampling.

For relative BA of tablet formulation (compared to DIC) and the FE cohort (Cohort 17), TAK-071 will be administered as DIC and tablet formulations in a cross-over design as 3 regimens (Regimens A, B, and C). For all 3 regimens study drug will be administered after an overnight fast of at least 8 hours on each dosing day. Subjects randomized to Regimens A and B will remain fasted prior to dosing; however, subjects assigned to Regimen C should start the standard high fat meal (~ 50% fats) 30 minutes prior to administration of the drug product and finish the meal within 25 minutes. On dosing days, the source documentation and the eCRF will record whether the subjects consumed 100% of their breakfast (or the approximate percentage of the meal consumed: 0%, 25%, 50%, or 75%) during the fed regimen (Regimen C). Subjects in all 3 regimens will fast for an additional 4 hours after dosing. Water will be allowed ad libitum after 2 hours postdose.

Subjects in Regimen C, randomized to receive drug administration with food, will consume a high-fat (approximately 50% of the total caloric content of the meal), high-calorie (approximately 1000 calories) breakfast beginning 30 minutes prior to study drug administration, consume the

meal within 25 minutes and receive study drug 30 minutes after the start of the meal. Subjects will then fast from food until approximately 4 hours postdose at which time a standard lunch will be served. Water will be allowed ad libitum after 2 hours postdose. The content of a sample high-fat breakfast is listed in Table 7.b.

Table 7.b Content of a Standard, High-Fat Breakfast

2 fried or scrambled eggs
2 strips bacon
2 slices of toast with 2 pats of butter
4 oz (113 g) hash browns (fried potato)
240 mL whole milk

7.4.2 Cohort 16

Based on the preliminary results from cohort 17, food did not appear to affect the systemic exposure to TAK-071. Therefore, TAK-071 and donepezil can be given with or without food. However, on the days of blood draws for clinical laboratory tests, TAK-071 and placebo will be administered with approximately 240 mL of water after a fast of at least 8 hours.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of a subject from the study or study drug should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.19.

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 medication 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 9.1.9), if any 1 of the following circumstances occur at any time during study drug treatment:

      – ALT or AST >8×ULN.

      – ALT or AST >5×ULN and persists for more than 2 weeks.

      – ALT or AST >3×ULN in conjunction with elevated total bilirubin >2×ULN or INR>1.5.

      – ALT or AST >3×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 postrandomization 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.
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. Withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category.
5. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
6. If, in spite of preventive measures, the PK exposure (C_{max} and AUC_{24} for steady-state) in an individual unexpectedly exceeds, or is predicted to exceed upon repeat dosing, the corresponding average steady-state exposure at the NOAEL in the 28-day monkey toxicology study.
7. Other.

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

7.6 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 7.5. 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.

Enrolled participants who withdraw from the study for reasons other than safety may be replaced to ensure adequate numbers of evaluable subjects. The decision to replace a withdrawn subject will be made at the discretion of Takeda and the investigator.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication 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 clinical trial material.

8.1 Study Medication and Materials

Study drug refers to TAK-071, matching placebo, and donepezil. TAK-071 drug substance will be compounded into a hard capsule (DIC) or formulated as a tablet, which will be labeled in a blinded fashion with third-party dispensing. Donepezil will be packed and labeled in an unblinded fashion at the study site. An unblinded pharmacist will manage and prepare doses as needed throughout the study.

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.

8.1.1.1 Investigational 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 can be found 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 to 30 mg	0 mg
Hard gelatin capsule (Size: 00, Color: Swedish orange opaque)		

TAK-071 Tablet

The TAK-071 tablet will be available in 2 strengths (1 and 5 mg). In addition to TAK-071, the inactive constituents of the tablet formulation include mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate type A, magnesium stearate, hypromellose 2910, titanium dioxide, ferric oxide red, and ferric oxide yellow.

8.1.1.2 Companion Medication

Donepezil is delivered orally as a 5 mg oral tablet QD in Cohorts 10 to 12 and a 10 mg (or 5 mg followed by 10 mg in run-in period) oral tablet QD in Cohort 16. In Cohorts 20 to 22, donepezil 10 mg tablet manufactured by Eisai Inc. will be over-encapsulated, labeled in a blinded fashion with third-party dispensing, and delivered as an oral capsule. The composition of the over-encapsulated donepezil and matching placebo is provided in Table 8.b.

Table 8.b Composition of Over-Encapsulated Donepezil and Matching Placebo

Components	Aricept OE	Matching Placebo
Donepezil 10 mg tablet, United States Pharmacopeia	1 tablet	-
Microcrystalline cellulose, National Formulary	Approximately 100 mg	Approximately 150 mg
Hard gelatin capsule (Size: AA, Color: Swedish orange opaque)		

OE=over-encapsulated.

8.1.1.3 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).

TAK-071 tablets are manufactured by Takeda Pharmaceutical Company Limited, Osaka, Japan and supplied to the clinical site.

Either branded Aricept or generic donepezil (5 and 10 mg tablets) will be selected based on study design and sourced locally by the clinical site. For Cohorts 20 to 22, however, branded Aricept will be selected and over-encapsulated since stability data in the over-encapsulated condition is available only for branded Aricept.

8.1.2 Storage

Based upon the recent stability study data, the recommended storage conditions for the TAK-071 DIC and tablets are 20°C to 25°C (68°F to 77°F) with temporary excursions permitted 15°C to 30°C (59°F to 86°F). Any excursions from the labeled storage conditions must be reported to Takeda immediately. Donepezil tablet must be stored according to the commercial label. Over-encapsulated donepezil must be stored according to the 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 drug 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

The investigator or investigator's designee will instruct the subject on dosing procedures. All dosing will occur while subjects are in the clinic under the supervision of the principal investigator

or designee (except Days -18 to -11 during Cohorts 10 to 12 where the subject will self-administer donepezil and Days 3 to 10, 12 to 19, 43 to 50, and 52 to 59 during Cohort 16 where the subject will self-administer TAK-071 or placebo each morning at home). The doses taken in the clinic will be administered to the subjects by the investigator or investigator's designee. The exact time of dose will be recorded in the source documents and on the appropriate eCRF.

The planned initial dose of TAK-071 or matching placebo for Cohort 1 is 1 mg. TAK-071 is dosed on the morning of Day 1 after fasting for at least 8 hours. Cohorts 2 through 6, 18, and 19 will escalate through the SRD levels and Cohorts 7 through 9 through the MRD dose levels. Additionally, Cohorts 10 to 12 will be pretreated for 3 weeks with 5 mg donepezil orally continuing through Day 21. In healthy subjects in Cohorts 10 to 12, donepezil will be administered in the morning, shortly before or after TAK-071; the precise relative timing will be confirmed once TAK-071 PK data are available. Cohorts 9 and 13 through 15 will have 1 dose of TAK-071 on Day 1 followed by a 7-day washout period before administration of 21 daily doses of TAK-071. Subjects in Cohorts 20 to 22 will be administered as a single dose of TAK-071 or placebo on Day 1, and a single dose of donepezil or placebo approximately 24 hours later on Day 2.

In Cohort 16, subjects with MCI or mild AD who are stable on donepezil will be randomized to 1 of 2 possible treatment sequences consisting of 2 periods and 2 treatments, alternating in a crossover fashion. In each period, subjects will receive 1 of the following treatments: TAK-071 QD for 21 days (Treatment A) or 21 days of matching placebo (Treatment B). Background 10 mg QD donepezil treatment will be administered in the evening just before bedtime.

In Cohort 17 (Relative BA and FE), TAK-071 DIC or tablet will be administered as a single dose (Regimen A, B, and C) in a cross-over design over 3 periods, with a 21-day washout after each treatment. The planned dose is 10 mg in each of the 3 periods. Diet assigned to each regimen is described in Section 7.4.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational 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, PTEs and AEs.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

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

8.2 Investigational Drug Assignment and Dispensing Procedures

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. The Randomization Sequence Number will be entered onto the eCRF.

For each dosing cohort in SRD, MRD, and BA/FE parts, randomized subjects will be assigned a 5-digit randomization number in the order which they are enrolled. Randomization sequence numbers will be XYY01 to XYY08 (Cohorts 7 to 12) or XYY06 (Cohorts 13 to 15), where X refers to SRD (Part 1) or MRD (Part 2) and Y refers to cohort number.

For example:

- Subjects in SRD Cohort 1 will have randomization sequence numbers 10101 to 10108, and subjects in SRD Cohort 2 will have numbers 10201 to 10208.
- Subjects in MRD Cohort 7 will have randomization sequence numbers 20701 to 20708, and subjects in MRD Cohort 11 will have numbers 21101 to 21108.
- Subjects in MRD Cohort 13 will have randomization sequence numbers 21301 to 21306.
- Subjects in BA/FE Cohort 17 will have randomization sequence numbers 21701 to 21712.
- Subjects in Cohort 20 will have randomization sequence numbers 12001 to 12012.

If a subject needs to be replaced, the replacement subject will receive the same treatment or treatment sequence of the subject being replaced. The replacement randomization number will be 50 larger than the randomization number of the subject who is being replaced. For example, randomization number 10251 will be used for the subject who replaces the subject who had randomization number 10201, using the same treatment or treatment sequence in Cohort 2.

This 5-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 and/or PD sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory and will be used by the laboratory to report the subject data results. This 5-digit number should only be used for the purposes described in this section. It does not replace the 3-digit subject number that is assigned at the time the informed consent is obtained and used for all other procedures to identify the subjects throughout the study.

Study drugs will be dispensed in the clinic under the supervision of the investigator or designee.

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. A revised randomization schedule for Cohorts 13 to 15 will be provided to the site pharmacist. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Drug Blind Maintenance

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.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational 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 investigational drug blind is broken to discuss the need for unblinding.

The sponsor must be notified as soon as possible if the investigational 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, investigational drug must be stopped immediately and the subject withdrawn from the study.

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

8.5.1 Sponsor PD Unblinding

A Takeda representative outside the main study team will receive the randomization schedule to analyze the PD data for interim analysis. This team member will not be involved in the conduct of the study or interpretation of any safety or PK data.

8.5.2 Sponsor Interim Analysis Unblinding

The main Takeda study team will be unblinded to Cohorts 1 to 15 and 17 to 22 data during the interim analysis and Cohort 16 will remain blinded.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or before being destroyed at the site following local site procedures with sponsor approval.

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, and donepezil), 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 following local procedures with 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 that

the medication is in good condition. If the quantity and conditions are acceptable, the investigator or designee should acknowledge the receipt of the shipment by signing the bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list and 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, and donepezil) received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to, the following:

- 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, otherwise uninvolved with study conduct, will review the randomization 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, and donepezil) 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, 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.

All study drug not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

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.

The timing of planned procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests) currently outlined in the protocol may be modified during the study based on newly available safety, tolerability, PK, or PD data (eg, to obtain data closer to the time of peak plasma concentrations). These changes may increase the number of study procedures for a given subject during his/her participation in the entire study.

If additional days of dosing or confinement are required based on emerging data, the following at a minimum would be collected daily; AE assessment, concomitant medication assessment, vital signs, Bristol stool scale, and ECG.

If additional safety laboratory or PK samples are obtained, the total blood volume should not exceed a total blood volume of 550 mL.

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 Pharmacogenomics 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, reproductive status (including last menstrual period), and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8).

For subjects in Cohort 16, the following medical history will be collected: diagnosis, date of diagnosis, MMSE score, date of onset of donepezil treatment, and dose and timing of administration of donepezil (evening [bedtime] required).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes (see more details in Section 9.1.3.1); (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) GI 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 or clinically significant by the investigator and recorded in the source document and eCRF. All clinically significant 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 9.1.8.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the investigational drug must be assessed as not clinically significant or clinically significant by the investigator and recorded in the source document and eCRF. Any clinically significant change or new diagnosis as a result of a clinically significant 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.

9.1.3.1 Funduscopy (Cohorts With CSF Sampling Only)

A Baseline ophthalmological assessment of the retina (funduscopy) will be performed at Screening for subjects enrolled in cohorts for CSF sampling. Funduscopy will be performed by a trained person (optometrist, ophthalmologist, or neurologist) after dilatation of the pupil in both eyes by administration of tropicamide 0.5% eye drop. After pupil dilatation, subjects will be advised to wear sunglasses for the next 4 to 6 hours and avoid operating a car.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms with 1 decimal place.

BMI should be derived as follows: BMI=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 BMI=79.2/1.76^2=25.56818 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/m^2. However, if the BMI is used to satisfy the entry criteria, then this determination must be made after rounding.

9.1.5 MMSE

The MMSE is an 11-question tool that tests 5 areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30, with lower scores indicating more cognitive impairment [22]. The MMSE will be administered at Screening to subjects in Cohort 16 only by trained site personnel.

9.1.6 Vital Sign Procedure

In subjects who are not undergoing CSF collection (Cohorts 2, 4 to 8, and 10 to 22), vital signs will include body temperature (oral), respiratory rate, and orthostatic blood pressure and pulse (bpm).

In subjects who have completed enrollment for Cohort 1 at the time of this amendment and in subjects who are undergoing CSF collection (Cohorts 3 and 9), vital signs include body temperature (oral), respiratory rate, supine blood pressure (resting more than 5 minutes), and pulse (bpm).

Vital signs should be collected daily, predose and upon morning rising on days during confinement. In addition, vital signs should be collected in Cohorts 3 and 9 at approximately 5 hour postdose on Day 1 and Day 8 (Cohort 9 only). Vital signs may be repeated. 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 the scheduled blood draw.

For BA/FE Cohort 17, for the fed regimen, if vital signs coincide with a meal, vital signs will take precedence followed by the meal.

For Cohorts 2, 4 to 8, and 10 to 22, orthostatic blood pressure and pulse will be measured at predose and at 2, 4, 6, 8, and 12 hours postdose in the first 24 hours after the initial dose of TAK-071 (Day 1) and then afterwards on days while subjects are in the phase 1 unit. Orthostatic blood pressure will be measured as follows [23]:

1. Have the patient lie down for 5 minutes.
2. Measure blood pressure and pulse rate.
3. Have the patient stand.
4. Repeat blood pressure and pulse rate measurements after standing 1 and 3 minutes.

A drop in bp of ≥20 mm Hg, or in diastolic bp of ≥10 mm Hg, or experiencing lightheadedness or dizziness is considered abnormal [23].

9.1.7 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 Takeda. 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 Follow-up Call/Visit), 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.

9.1.8 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 the Screening/Baseline examination. The condition (ie, diagnosis) should be described.

9.1.9 Procedures for Clinical Laboratory Samples

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

Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information at the investigator's discretion (eg, adding creatinine kinase isoenzymes to a serum chemistry panel that was already drawn).

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

Diagnostic Screening:	
Serum	**Urine/Blood**
Hemoglobin A1c Creatinine clearance (a) HBsAg and anti-HCV Female subjects: serum hCG (b) Female subjects, if postmenopausal and not surgically sterile: FSH (d)	Drug screen for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine (c).

aPTT=activated partial thromboplastin time, HBsAg=hepatitis B surface antigen, hCG=human chorionic gonadotropin, HCV=hepatitis C virus, PT=prothrombin time.
(a) Calculated using the Cockcroft-Gault formula.
(b) Serum hCG pregnancy test will be done at Screening, Check-in, Final Visit/Early Termination and at the Follow-up Visit if the subject is brought back to the clinic for re-evaluation (Cohorts 1 to 15 only). For Cohort 17 (BA/FE) additional serum hCG pregnancy tests will be done in each period at check-in.
(c) To be performed at Screening and as indicated in the Schedule of Assessments.
(d) FSH level will be obtained for female subjects at Screening if they are postmenopausal (ie, continuous amenorrhea of at least 2 years) and not surgically sterile. The result must be >40 IU/L for the subject to be enrolled.

The local laboratory will perform laboratory tests for hematology, coagulation, 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, γ-glutamyl transferase, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

If the ALT or AST remains elevated >3×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 Reporting of Abnormal Liver Function Tests for reporting requirements).

Please refer to Section 7.5 for discontinuation criteria and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3×ULN in conjunction with total bilirubin >2×ULN.

Laboratory reports must be signed and dated by the principal investigator or subinvestigator 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 not clinically significant before proceeding with enrollment/randomization.

All clinically significant laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A clinically significant 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.

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

9.1.10 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 30 days after 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 spermicidal cream or jelly).

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (eg, defined as continuous amenorrhea of at least 2 years and an FSH>40 IU/L, confirmed before any study drug is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

Subjects will be provided with information on acceptable 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 during the course of the study and for 30 days after the last dose of study drug.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are excluded, the only acceptable methods of contraception are as follows:

Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.

Intrauterine devices (IUDs):

- Copper T PLUS condom or spermicide.

During the course of the study, regular serum hCG pregnancy tests will be performed for female subjects (Cohorts 1 to 15 and 17 to 22) and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A). In addition to a negative serum hCG pregnancy test at Screening, female subjects must have a negative serum hCG pregnancy test at Check-in prior to receiving any dose of study medication.

9.1.11 Pregnancy

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

However, if any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 30 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, within 30 days of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

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 subject was participating in a clinical study at the time the female partner of a male subject became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies 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.

9.1.12 ECG Procedure

The investigator will review all vital signs and 12-lead ECG data, including estimates of ECG intervals, for real-time safety monitoring purposes, and an assessment of normality/abnormality will be recorded in the eCRF.

Holter recordings will be stored by Takeda and will be sent to a central ECG analysis laboratory for retrospective expert review and estimation of ECG intervals at an appropriate time for the TAK-071 program during or after completion of the present study.

9.1.12.1 Screening and Safety ECGs

A standard 12-lead ECG will be recorded as indicated in the Schedules of Assessments (Appendix A). 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, or abnormal and clinically significant. 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, QT interval with Bazett correction, and T and U wave morphology.

All stationary 12-lead ECG machines will be supplied by the site. Subjects should be in a supine position following an approximate 10-minute rest period for ECG recordings. Should technical difficulties occur during recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

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. If an ECG coincides with a meal, the ECG will take precedence followed by the meal.

9.1.12.2 Holter

To help ensure high-quality data recording, prior to electrode placement, the anatomical sites must be prepared to allow for proper skin/electrode interface. Any hair on the electrode sites must be shaven. Any oils, lotions, or dead skin should be removed from the electrode sites using an abrasive, alcohol prep pad designed for this purpose. An indelible skin marker must be used to mark the exact electrode placement site so that the electrode positions will remain constant throughout each treatment period. The electrodes should always be attached to the Holter connecting cable prior to skin placement.

All Holter recordings will be obtained on 1000 sps flash cards using a 12-lead Holter recorder. The flash cards will be couriered to the central cardiac core laboratory. Alternatively, Holter recordings will be digitally transmitted to the central cardiac core laboratory, as appropriate.

Each 12-lead Holter ECG acquisition window will be approximately 10 minutes in duration, from which cardiac data analysis laboratory will extract 10-second ECGs in triplicate. This window will be preceded by 10 minutes of quiet supine rest. The timing of continuous 12-lead Holter ECG monitoring is provided in Table 9.b.

Table 9.b Timing of Holter ECG Monitoring

Cohort	Scheduled Time
2, 4, 6, 18, 19	2 hours predose until 48 hours postdose
7 to 8	2 hours predose until 24 hours postdose on Day 1 and 1 hour predose until 48 hours postdose on Day 21
9	2 hours predose until 48 hours postdose on Day 1 and 1 hour predose until 48 hours postdose on Day 28

ECG extraction time points (triplicates) will occur at 1.5, 1, and 0.5 hours predose on Day 1 (Cohorts 2, 4, 6 to 9, and 18 to 19) for estimation of Baseline and immediately prior (within 15 minutes) to the predose PK blood draw on the last TAK-071 dosing day (Cohorts 7 to 9). In addition, postdose triplicate ECG extractions will occur immediately prior (within 15 minutes) to each PK blood draw, starting with the 0.5 postdose collection (see Section 9.1.15 for PK sampling time points).

Triplicate parameter estimates will be derived from the ECG traces at each nominal time point, including heart rate, RR interval, PR interval, QT interval, QRS interval, QT interval with Fridericia correction, QT interval with Bazett correction, and T and U wave morphology, as appropriate. Other time points may also be retrospectively assessed if clinical observations or findings require further investigation.

Subjects will be supervised while remaining at rest, quiet, awake, and in a supine position from at least 10 minutes prior to the beginning of each ECG extraction time point and will remain quiet, awake, motionless, and supine for at least 10 minutes after the beginning of each ECG extraction time point.

ECGs derived from Holter monitoring are not intended to be analyzed for real-time safety monitoring but will be used for future retrospective ECG analyses, unless an earlier analysis is warranted by emerging safety information.

9.1.13 Bowel Function

Subjects will be provided with a bowel function diary card during Screening to record their Baseline bowel function using the BSF scale for stool consistency rating.

From Check-in through Final Visit, subjects will use the bowel function diary card to assess the time of each bowel movement during the dosing period (and until Check-out/Final Visit), stool consistency (pictorial BSF score), and completeness of evacuation for an exploratory comparison of the clinical effects of TAK-071.

Stool frequency is defined as the number of episodes of defecation recorded per day in the bowel function card; stool consistency is defined by the 7-point pictorial BSF scale, which ranges from unformed/watery to hard pellets; ease of passage is defined by the 7-point adjectival scale, which

ranges from incontinence to requiring manual disimpaction; and sense of complete evacuation is defined by a yes-or-no answer to the question "Did you feel like you completely emptied your bowels?" [24].

9.1.14 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 how the drug is broken down or how the drug affects the body. This is called a "PGx research study." Specific purposes of this study include the following:

- Identifying genetic reasons why certain people respond differently to TAK-071
- Finding out more information about the mechanism of action of TAK-071.
- 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 and for improving the efficiency, design, and study methods of future research studies.

Since PGx is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

DNA Collection (SRD Cohorts 1 to 6 and 18 to 22, MRD Cohorts 7 to 9 and 13 to 16

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 (K_2EDTA) spray-coated tubes and stored under frozen conditions.

DNA Collection (MRD Cohorts 10 to 12)

One 6-mL whole blood sample for DNA isolation will be collected before dosing on Day -21 from each subject in the study into plastic K_2EDTA spray-coated tubes and stored under frozen conditions.

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.

RNA Collection (SRD Cohorts 1 to 6 and 18 to 22)

Two whole blood samples (2.5 mL per sample) will be collected predose on Day 1, 12 hours postdose on Days 1 and 5 for RNA analysis from each subject in the study into a PAXgene tube.

RNA Collection (MRD Cohorts 7 and 8)

Two whole blood samples (2.5 mL per sample) will be collected predose on Day 1 and 12 hours postdose on Days 1 and 21 for RNA analysis from each subject in the study into a PAXgene tube.

RNA Collection (MRD Cohorts 9 and 13 to 15)

Two whole blood samples (2.5 mL per sample) will be collected predose on Day 1, predose on Day 8, and 12 hours postdose on Day 28 for RNA analysis from each subject in the study into a PAXgene tube.

RNA Collection (MRD Cohorts 10 to 12)

Two whole blood samples (2.5 mL per sample) will be collected predose donepezil on Day -21, predose TAK-071 on Day 1, and 12 hours postdose on Day 21 for RNA analysis from each subject in the study into a PAXgene tube.

RNA Collection (Cohort 16)

Two whole blood samples (2.5 mL per sample) will be collected predose on Days 1 and 42 and 12 hours postdose on Days 21 and 62 for RNA analysis from each subject in the study into a PAXgene tube.

Each PGx sample should be identifiable on the requisition form with an 8-digit subject identification number (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 the handling and shipping of samples will be provided in the Laboratory Manual.

No DNA or RNA samples will be collected in Cohort 17.

9.1.15 PK Sample Collection

9.1.15.1 Collection of Blood for PK Sampling

Blood samples (one 3-mL sample per scheduled time) for PK analysis of plasma TAK-071 will be collected into chilled vacutainers containing anticoagulant K_2EDTA according to the schedule in Appendix A. Blood samples (one 4-mL sample per scheduled time for Cohorts 10 to 12 and 20 to 21) for PK analysis of plasma donepezil will be collected into chilled vacutainers containing anticoagulant sodium heparin according to the schedule in Appendix A. Instructions for sample processing and shipment are provided in Appendix E.

Serial blood samples for determination of TAK-071 (and donepezil, where stated) will be collected according to Table 9.c for Cohorts 1 to 6, 18, and 19; Table 9.d for Cohorts 7 and 8; Table 9.e for Cohorts 9 and 13 to 15; Table 9.f for Cohorts 10 to 12; Table 9.g for Cohort 16, and Table 9.h for Cohort 17, and Table 9.i for Cohorts 20 to 22.

Table 9.c Collection of Blood Samples for PK Analysis for Cohorts 1 to 6, 18, and 19

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Plasma	1	Cohorts 1 to 6: Predose (within 30 minutes before dosing) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 48, 72, 96, and 168 hours postdose Cohort 18 and 19: Predose (within 30 minutes before dosing) and 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 32, 40, 48, 56, 64, 72, 96, and 168 hours postdose

Table 9.d Collection of Blood Samples for PK Analysis for Cohorts 7 and 8

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Plasma	1	Predose (within 30 minutes before dosing) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours postdose
TAK-071	Plasma	8, 14, 19, and 20	Predose (within 30 minutes before dosing)
TAK-071	Plasma	21	Predose (within 30 minutes before dosing) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours postdose

Table 9.e Collection of Blood Samples for PK Analysis for Cohorts 9 and 13 to 15

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Plasma	1	Predose (within 30 minutes before dosing) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 48, 72, and 96 hours postdose
TAK-071	Plasma	8	Predose (within 30 minutes before dosing) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours postdose
TAK-071	Plasma	15, 20, 26, and 27	Predose (within 30 minutes before dosing of TAK-071)
TAK-071	Plasma	28	Predose (within 30 minutes before dosing) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours postdose. For Cohort 9 only, an additional sample at 36 hours postdose

Table 9.f Collection of Blood Samples for PK Analysis for Cohorts 10 to 12

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Plasma	1	Predose (within 30 minutes before dosing) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours postdose of TAK-071
TAK-071	Plasma	8, 14, 19, and 20	Predose (within 30 minutes before dosing of TAK-071)
TAK-071	Plasma	21	Predose (within 30 minutes before dosing) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours postdose of TAK-071
Donepezil	Plasma	-7, -3, and -2	Predose (within 30 minutes before dosing of donepezil)
Donepezil	Plasma	-1	Predose (within 30 minutes before dosing) and 1, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours postdose of donepezil
Donepezil	Plasma	8, 14, and 20	Predose (within 30 minutes before dosing of donepezil)
Donepezil	Plasma	21	Predose (within 30 minutes before dosing) and 1, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours postdose of donepezil

Table 9.g Collection of Blood Sample for PK Analysis of Cohort 16

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Plasma	1, 21, 42, and 62	Predose (within 30 minutes before dosing) and 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose of TAK-071
Donepezil	Plasma	1, 21, 42, and 62	Predose (within 30 minutes before dosing of donepezil)

Table 9.h Collection of Blood Sample for PK Analysis of Cohort 17

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Plasma	1 (each of 3 periods)	Predose (within 30 minutes before dosing) and 0. 5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 32, 40, 48, 72, 96, and 168 hours postdose

Table 9.i Collection of Blood Sample for PK Analysis of Cohorts 20 to 22

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Plasma	1	Predose (within 30 minutes before dosing) and 2, 4, 8, 12, 16, 24, 25, 26, 27, 28, 30, 32, 36, 40, 48, 56, 64, 72, 96, and 168 hours post TAK-071 dose
Donepezil	Plasma	2	Predose (within 30 minutes before donepezil dosing) and 1, 2, 3, 4, 6, 8, 12, 16, 24, 32, 40, 48, 72, 144 hours post donepezil dose

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 collected from prior cohort(s), 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 expected time at which C_{max} occurred (as emerging from the actual measurement of the samples of the first dose group) to ensure from a safety perspective that no additional subjects could have been on active treatment.

9.1.15.2 Collection of Urine for PK Sampling

Serial urine samples for determination of TAK-071 will be collected according to Table 9.j for Cohorts 1 to 6 and 18 (and higher dose cohorts, if needed), Table 9.k for Cohorts 7 and 8, Table 9.l for Cohorts 9 and 13 to 15, and Table 9.m for Cohort 16.

Table 9.j Collection of Urine Samples for PK Analysis for Cohorts 1 to 6, 18 and 19

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Urine	1	Predose urine void within approximately 1 hour of dosing and (0 to 6), (6 to 12), (12 to 24), (24 to 48), (48 to 72), and (72 to 96) hours postdose

Table 9.k Collection of Urine Samples for PK Analysis for Cohorts 7 and 8

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Urine	1	Predose urine void within approximately 1 hour of dosing and (0 to 6), (6 to 12), and (12 to 24) hours postdose
TAK-071	Urine	21	(0 to 6), (6 to 12), and (12 to 24) hours after the last dose

Note: Subjects should void urine prior to dosing on Day 21.

Table 9.l Collection of Urine Samples for PK Analysis for Cohorts 9 and 13 to 15

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Urine	1	Predose urine void within approximately 1 hour of dosing and (0 to 6), (6 to 12), (12 to 24), (24 to 48), (48 to 72), and (72 to 96) hours postdose
TAK-071	Urine	28	(0 to 6), (6 to 12), and (12 to 24) hours postdose

Note: Subjects should void urine prior to dosing on Day 28.

Table 9.m Collection of Urine Samples for PK Analysis for Cohort 16

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	Urine	1 and 42	Predose urine void within approximately 1 hour of dosing and (0 to 6), (6 to 12), and (12 to 24) hours postdose
TAK-071	Urine	21 and 62	(0 to 6), (6 to 12), and (12 to 24) hours postdose

Note: Subjects should void urine prior to dosing on Days 21 and 61.

Urine samples will not be collected from Cohorts 10 to 12, 17 and 20 to 22.

The timing of the urine collection intervals may be adjusted based on the preliminary emerging PK data collected from prior cohort(s).

Instructions for PK sample processing and shipment are provided in Appendix E.

Urine samples for subjects randomized to placebo will not be analyzed.

9.1.15.3 Collection of CSF for PK Sampling

It is planned that CSF samples (1.25 mL per sample) for determination of TAK-071 will be collected predose (within 30 minutes before dosing) and at 0.5, 2, 4, 6, and 12 hours postdose in Cohort 3 and predose (within 30 minutes before dosing) and at 4, 8, 12, 24, and 36 hours post last dose in Cohort 9.

The procedure will be performed by an experienced anesthetist using local anesthetic (used to numb the skin and tissues) injected into the skin and disc space between the lumbar vertebrae to prevent discomfort during the procedure. An indwelling spinal catheter will be inserted into the subarachnoid space at the level of the L2 to L3 or L3 to L4 intervertebral space by trained personnel at the site. The procedure will be performed under sterile conditions, and the subject will be closely observed and monitored during the CSF collection.

Instructions for CSF collection and lumbar x-ray are provided in the Study Manual.

If measured concentrations in Cohort 3 are excessively low, ie, most time points are below the limit of quantification of the assay, TAK-071 CSF concentrations may also be determined in subsequent SRD cohorts until a dose deemed to provide adequate brain penetration is identified (eg, a dose that provides CSF concentrations analogous to the efficacious free [estimated] plasma concentrations observed in preclinical animal models). A different criterion might be applied.

CSF sampling time points may be adjusted based on the preliminary emerging PK data; the total number of CSF samples collected per subject will not exceed the planned number.

9.1.15.4 Bioanalytical Methods

Plasma, urine, and CSF concentrations of TAK-071 will be measured by high-performance liquid chromatography with tandem mass spectrometry.

Part of the archival plasma and urine samples will be sent to Drug Metabolism and Pharmacokinetics Research Laboratories at Shonan Research Center for potential analysis of unknown metabolite characterization, if appropriate.

9.1.16 PK Parameters

The plasma PK parameters of TAK-071 will be determined from the plasma 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:

Symbol/Term	Definition
Plasma	
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{24}	Area under the plasma concentration-time curve from time 0 to time 24 hours
AUC_t	Area under the plasma concentration-time curve from time 0 to time t
C_{max}	Maximum observed concentration.
CL/F	Apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration
CL/F_{ss}	Apparent clearance after extravascular administration, at steady state, calculated using AUC_{τ}
λ_z	Terminal disposition phase rate constant
$R_{ac(AUC)}$	Accumulation ratio based on AUC_{τ}
$R_{ac(Cmax)}$	Accumulation ratio based on C_{max}
$t_{1/2z}$	Terminal disposition phase half-life
t_{max}	Time of first occurrence of C_{max}
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration

For Cohort 17 the key PK parameters C_{max}, t_{max}, and AUC_{∞} will be determined.

In general, if AUC_{∞} cannot be accurately estimated in a sufficient number of subjects, AUC_{last} will be used for statistical analysis instead. Additional plasma PK parameters may be derived and/or reported as appropriate.

The urine PK parameters of TAK-071 will be determined from the concentration-time profiles for all evaluable subjects according to standard noncompartmental analysis methods. Scheduled sampling times will be used in all computations involving urine collection times. The following urine PK parameters of TAK-071 will be estimated:

Urine	
Ae_t	Amount of drug excreted in urine from time 0 to time t
$f_{e,t}$	Fraction of administered dose of drug excreted in urine from time 0 to time t
CL_R	Renal clearance

Additional urine PK parameters may be derived and/or reported as appropriate.

The CSF PK parameters of TAK-071 (planned for Cohorts 3 and 9) will be determined from the CSF 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: CSF C_{max} following a single dose (Day 1) and at steady-state (after final dose following multiple dosing), CSF AUC_{12} following a single dose (Day 1) and CSF AUC_{36} at

steady-state (after final dose following multiple dosing), and the ratio of CSF AUC_{12} to the plasma AUC_{12} (CSF AUC_{12}:plasma AUC_{12}) following a single dose (Cohort 3) and the ratio of CSF AUC_{36} to the plasma AUC_{36} (CSF AUC_{36}:plasma AUC_{36}) at steady-state (Cohort 9). In the event that CSF sampling time points are adjusted in Cohort 9 following review of PK data from previous cohorts, ie, continuous sampling is extended to 48 hours postdose and then the corresponding AUC for the investigated time interval (ie, AUC_{48}) will be used instead of AUC_{36}. Additional CSF PK parameters may be derived and/or reported as appropriate.

The plasma PK parameters of donepezil 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: t_{max}, C_{max}, and AUC_{24}. In addition, the ratio of geometric mean AUC_{24} and C_{max} for donepezil after 21 daily doses of TAK-071 in reference to donepezil alone and the associated 90% CIs will be estimated. Additional donepezil 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.

9.1.17 PD Assessments

9.1.17.1 CCI

qEEGs will be collected for subjects in Cohorts 9, 12, and 18 to 22.

CCI

CCI

[redacted]

CCI

[redacted]

9.1.17.2 CCI [redacted]

CCI

[redacted]

CCI

[redacted]

9.1.18 PD Parameters

CCI

[redacted]

The PD parameters will include the following:

Symbol/Term	
$AUEC_{12}$	Area under the effect concentration-time curve from time 0 to 12 hours; calculated as the area under the effect concentration-time curve that is above the Baseline minus the area that is below the Baseline and above the effect concentration-time curve (net area).
E_{max}	Maximum observed effect, taken directly from change from Baseline data.
Time to E_{max}	Time from dosing to occurrence of E_{max}, taken directly from the change from Baseline data.

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

9.1.19 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be not eligible at this 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.
- Failure to 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 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 2 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 a subject is found to be ineligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.1.21 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.

9.2 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 is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening

Subjects in Cohorts 1 to 9, 13 to 15, and 17 to 22 will be screened within 28 days prior to randomization, subjects in Cohorts 10 to 12 will be screened within 44 days prior to randomization, and Cohort 16 will be screened within 60 days prior to randomization in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.19 for procedures for documenting screening failures.

9.3.2 Study Randomization

Study randomization will take place on Day 1 for Cohorts 1 to 9, 13 to 15, and 17 to 22. Study randomization will take place on Day -21 for Cohorts 10 to 12.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized as described in Section 8.2. Subjects will be administered the first dose of study drug in the unit under the supervision of the investigator or designee, as described in Section 8.2. The procedure for documenting Screening failures is provided in Section 9.1.19.

9.3.3 Treatment Phase/Washout Phase

For Cohorts 1 to 6 and 18 to 22, the Treatment Phase will consist of a single dose of study drug (for Cohorts 20 to 22 donepezil will be administered approximately 24 hours after the TAK-071 dose). For Cohorts 7, 8, and 10 to 12, the Treatment Phase will consist of 21 QD doses of study drug. For

Cohorts 9 and 13 to 15, the Treatment Phase will consist of a single dose of study drug, followed by a washout period of 7 days and 21 QD doses of study drug.

For Cohorts 9 and 13 to 15, the washout and/or dosing duration may be adjusted with additional day(s) if PK data from the SRD part indicate that a longer duration may be more appropriate.

For Cohort 16 the treatment duration will consist of 21 QD doses of Treatment A (TAK-071) or B (placebo) in Period 1, a 21-day washout, and then 21 daily doses of Treatment A or B in Period 2. Treatment assignments will be switched between Period 1 and 2. A donepezil run-in period of 49 days, prior to starting Treatment A, may be included if the subject is diagnosed at Screening.

For Cohort 17, the treatment duration will consist of a single dose of study drug in each of 3 periods. Washout period of 21 days will follow Periods 1 and 2.

The washout and/or dosing duration may be adjusted with additional day(s) if PK data from the SRD part indicate that a longer washout may be more appropriate.

9.3.4 Final Visit

Subjects will be released from the clinic on Day 5 for Cohorts 1 to 6 and 18 to 22; Day 23 for Cohorts 7, 8, and 10 to 12; Day 30 for Cohorts 9 and 13 to 15; Day 63 for Cohort 16, and Day 8 of Period 3 for Cohort 17.

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

9.3.5 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.

9.3.6 Follow-up Visit/Telephone Call

The Follow-up Visit will occur by phone on Day 12 (±2 days) for Cohorts 1 to 6 and 18 to 22; Day 32 (±2 days) for Cohorts 7, 8, and 10 to 12; Day 39 (±2 days) for Cohorts 9 and 13 to 15; Day 73 (±2 days) for Cohort 16; and Day 12 (±2 days) of Period 3 for Cohort 17 and will be considered the subject's last visit unless abnormal clinically significant findings are observed at discharge. If abnormal clinically significant findings are observed, subjects must visit the clinic for re-evaluation per investigator's discretion. If no abnormal clinically significant findings are observed, follow-up will occur 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 9.1.14. The genetic material will be preserved and retained at Covance 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 sample and serves as a secure storage facility. The samples will be initially stored at Covance Central Laboratory Services. 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.

The sample will be labeled with a unique sample identifier similar to labeling 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 numbers 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. The investigator must notify the sponsor of consent withdrawal.

9.5 Blood Volume

Total blood sampling volume for an individual subject is shown in Table 9.q for Cohorts 1 to 6, 18, and 19; Table 9.r for Cohorts 7 and 8; Table 9.s for Cohorts 9 and 13 to 15; Table 9.t for Cohorts 10 to 12; Table 9.u for Cohort 16, and Table 9.v for Cohort 17, and Table 9.w for Cohorts 20 to 22.

Table 9.q Approximate Blood Volume for Cohorts 1 to 6, 18, and 19

		Number of Samples								
Sample Type	**Sample Volume (mL)**	**Screening**	**Day -1**	**Day 1 (a)**	**Day 2**	**Day 3**	**Day 4**	**Final Visit Day 5**	**PK Follow-Up Day 8**	**Total Volume (mL)**
Clinical laboratory tests	20	1	1	1	1	1	1	1	1	160
Serology tests	8.5	1	0	0	0	0	0	0	0	8.5
PGx DNA sample collection	6	0	0	1	0	0	0	0	0	6
PGx RNA sample collection	2.5	0	0	4	0	0	0	2	0	15
PK blood collection (b)	3	0	0	13	1	1	1	1	1	54
		Total Approximate Blood Sampling Volume								**243.5**

(a) TAK-071 dose.
(b) For Cohorts 18 and 19, PK blood samples were as follows: Day 1: 9, Day 2: 3, Day 3: 1: Day 4: 1, Day 5:1, and Day 8:1 (Total volume 54 mL).

Table 9.r Approximate Blood Volume for Cohorts 7 and 8

Sample Type	Sample Volume (mL)	Number of Samples									Total Volume (mL)
		Screening	Day -1	Day 1 (a)	Day 2	Days 4-5	Days 8-20	Day 21 (b)	Day 22	Final Visit Day 23	
Clinical laboratory tests	20	1	1	1	1	1 (c)	3 (d)	1	1	1	**220**
Serology tests	8.5	1	0	0	0	0	0	0	0	0	**8.5**
PGx DNA sample collection	6	0	0	1	0	0	0	0	0	0	**6**
PGx RNA sample collection	2.5	0	0	4	0	0	0	2	0	0	**15**
PK blood collection	3	0	0	13	1	0	4 (e)	13	1	0	**96**
										Total Approximate Blood Sampling Volume	**345.5**

(a) First dose of multiple daily TAK-071.
(b) Last dose of multiple daily TAK-071.
(c) Blood sample on Day 5.
(d) Blood samples on Days 8, 14, and 20.
(e) Blood samples on Days 8, 14, 19, and 20.

Table 9.s Approximate Blood Volume for Cohorts 9 and 13 to 15 (Japanese)

Sample Type	Sample Volume (mL)	Number of Samples											Total Volume (mL)
		Screening	Day -1	Day 1 (a)	Day 2	Days 3-7	Day 8 (b)	Days 9-17	Days 18-27	Day 28 (c)	Day 29	Final Visit Day 30	
Clinical laboratory tests	20	1	1	1	1	1 (d)	1	3 (e)	2 (f)	1	1	1	**280**
Serology test	8.5	1	0	0	0	0	0	0	0	0	0	0	**8.5**
PGx DNA sample collection	6	0	0	1	0	0	0	0	0	0	0	0	**6**
PGx RNA sample collection	2.5	0	0	2	0	0	2	0	0	2	0	0	**15**
PK blood collection	3	0	0	13	1	3 (g)	13	3 (h)	3 (i)	13	2 (j)	0	**147**
								Total Approximate Blood Sampling Volume					**456.5**

Note: There is a 7-day washout between the single dose of TAK-071 and the first dose of multiple-dose TAK-071.
(a) First single dose of TAK-071.
(b) First dose of multiple daily TAK-071.
(c) Last dose of multiple daily TAK-071.
(d) Blood sample on Day 3.
(e) Blood sample on Days 9, 10, and 15.
(f) Blood samples on Days 20 and 27.
(g) Blood samples on Days 3, 4, and 5.
(h) Blood sample on Day 15.
(i) Blood sample on Days 20, 26, and 27.
(j) Blood sample at 24 hours post last dose for all 3 cohorts and an additional sample for only Cohort 9 at 36 hours post last dose.

Table 9.t Approximate Blood Volume for Cohorts 10 to 12

		Number of Samples												
Sample Type	**Sample Volume (mL)**	**Screening**	**Day -22**	**Day -21 (a)**	**Days -10 to -2**	**Day -1**	**Day 1 (b)**	**Day 2**	**Days 3-8**	**Day 11**	**Days 12-20**	**Day 21 (c)**	**Day 22**	**Final Visit Day 23**	**Total Volume (mL)**
Clinical laboratory tests	20	1	1	1	1 (d)	1	1	1	2 (e)	1	2	1	0	1	**280**
Serology test	8.5	1	0	0	0	0	0	0	0	0	0	0	0	0	**8.5**
PGx DNA sample collection	6	0	0	1	0	0	0	0	0	0	0	0	0	0	**6**
PGx RNA sample collection	2.5	0	0	2	0	0	2	0	0	0	0	2	0	0	**15**
PK blood collection for TAK-071	3	0	0	0	0	0	13	1	1(f)	0	3 (g)	13	1	0	**96**
PK blood collection for donepezil	4	0	0	0	3 (h)	10	1	0	1(f)	0	2 (g)	10	1	0	**112**
														Total Approximate Blood Sampling Volume	**517.5**

(a) First dose of donepezil.
(b) First dose of multiple daily TAK-071.
(c) Last dose of multiple daily TAK-071.
(d) A blood sample for clinical laboratory tests will be collected on Day -10.
(e) Blood samples on Days 5, 8.
(f) Blood sample will be collected on Day 8.
(g) Blood samples will be collected on Days 14, 19 (TAK-071 only), and 20.
(h) Blood samples will be collected for PK analysis of donepezil on Days -7, -3, and -2.

Table 9.u Approximate Blood Volume for Cohort 16

Sample Type	Sample Volume (mL)	Number of Samples														Total Volume (mL)
		Screening	Day -1	Day 1 (a)	Day 2	Day 11	Day 20	Day 21 (b)	Day 22	Day 41	Day 42 (c)	Day 43	Day 52	Day 61	Day 62 (d)	Final Visit Day 63	
Clinical laboratory tests	20	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**300**
Serology test	8.5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**8.5**
PGx DNA sample collection	6	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	**6**
PGx RNA sample collection	2.5	0	0	2	0	0	0	2	0	0	2	0	0	0	2	0	**20**
PK blood collection TAK-071	3	0	0	9	1	0	0	9	1	0	9	1	0	0	9	1	**120**
PK blood collection donepezil	4	0	0	1	0	0	0	1	0	0	1	0	0	0	1	0	**16**
																Total Approximate Blood Sampling Volume	**470.5**

(a) First dose of study drug in Period 1.
(b) Last dose of study drug in Period 1.
(c) First dose of study drug in Period 2.
(d) Last dose of study drug in Period 2.

Table 9.v Approximate Blood Volume for Cohort 17

Sample Type	Sample Volume (mL)	Number of Samples													Total Volume (mL)
		Screening	Day -1	Day 1 (a)	Days 2 to 5	Day 8	Day -1	Day 1 (b)	Days 2 to 5	Day 8	Day -1	Day 1 (c)	Days 2 to 5	Final Visit Day 8	
			Period 1				Period 2				Period 3				
Clinical laboratory tests	20	1	1	1	2 (d)	1	1	1	2 (d)	1	1	1	2 (d)	1	**320**
Serology test	8.5	1	0	0	0	0	0	0	0	0	0	0	0	0	**8.5**
PK blood collection TAK-071	3	0	0	11	6 (e)	1	0	11	6 (e)	1	0	11	6 (e)	1	**162**
														Total Approximate Blood Sampling Volume	**490.5**

(a) Single dose of study drug in Period 1.
(b) Single dose of study drug in Period 2.
(c) Single dose of study drug in Period 3.
(d) Days 2 and 5.
(e) Three samples on Day 2 and 1 sample each on Days 3, 4, and 5.

Table 9.w Approximate Blood Volume for Cohorts 20 to 22

Sample Type	Sample Volume (mL)	Number of Samples								Total Volume (mL)
		Screening	Day -1	Day 1 (a)	Day 2	Day 3	Day 4	Final Visit Day 5	PK Follow-Up Day 8	
Clinical laboratory tests	20	1	1	1	1	1	1	1	1	160
Serology tests	8.5	1	0	0	0	0	0	0	0	8.5
PGx DNA sample collection	6	0	0	1	0	0	0	0	0	6
PGx RNA sample collection	2.5	0	0	4	0	0	0	2	0	15
PK blood collection TAK-071	3	0	0	6	9	3	1	1	1	63
PK blood collection donepezil	4	0	0	0	9	3	1	1	1	60
							Total Approximate Blood Sampling Volume			**312.5**

(a) TAK-071 dose only. Donepezil will be administered approximately 24 hours after the TAK-071 dose.

The maximum volume of blood at any single day is approximately 75 mL for Cohorts 1 to 8, and 18 to 22; 70 mL for Cohorts 9 and 13 to 15; 80 mL for Cohorts 10 to 12; 61 mL for Cohort 16; 53 mL for Cohort 17.

The approximate total volume of blood for the study is 243.5 mL for Cohorts 1 to 6, 18, and 19; 345.5 mL for Cohorts 7 and 8; 453.5 mL for Cohorts 9 and 13 to 15; 517.5 mL for Cohorts 10 to 12; 470.5 mL for Cohort 16; 490.5 mL for Cohort 17; and 312.5 mL for Cohorts 20 to 22.

Direct venipuncture is the preferred method of blood collection; however, a catheter with a single saline flush may be used. If a catheter with a normal saline flush is used, 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). If a catheter is used, the total blood volume taken during the study must not exceed 550 mL for healthy subjects and 480 mL for subjects with MCI or mild AD.

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 study drug (TAK-071) administration or increase in dose/start of donepezil prior to TAK-071 dose; 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 finding), 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 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 parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (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 re-test and/or continued monitoring of an abnormal value 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) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent 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 condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, 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 starting administration of the study drug, the worsening or complication should be recorded appropriately 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 severity of AEs/serious PTEs:

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

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

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 Severity 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 Causality of AEs

The relationship 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 drugs 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 drugs, 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 physician.

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 for reasons other than the event, dosing with study drug was already stopped before the onset of the 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 one 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 (TAK-071) (Day 1 for Cohorts 1 to 9, 13 to 15, and 17 to 22; Day -21 for Cohorts 10 to 12; and Day 1 [if on stable 10 mg dose at Screening] or Day -21 [if donepezil dose increased to 10 mg in subjects already on donepezil 5 mg], or Day -49 [if donepezil initiated as 5 mg dose]) 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 for Cohorts 1 to 9, 13 to 15, and 17 to 22; Day -21 for Cohorts 10 to 12; and Day 1, Day -21, or Day -49 as the case may be [see above]). Routine collection of AEs will continue until the Follow-up Telephone Call/Visit (Day 12 for Cohorts 1 to 6 and 18 to 21, Day 32 for Cohorts 7 to 8 and 10 to 12, Day 39 for Cohorts 9 and 13 to 15, Day 72 for Cohort 16, and Day 28 for Cohort 17).

For subjects in Cohort 16 who receive donepezil during the run-in period, they will be followed-up for PTEs/AEs via weekly phone calls during the run-in period.

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. Nonserious 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. Severity.

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 (eCRF SAE form in electronic data capture [EDC]) must be completed, in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. A paper SAE form should only be used if EDC is not available. 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×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×ULN and total bilirubin >2×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 9.1.9 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 that is not available at the time of the first report becomes available at a later date, the investigator should update the SAE form in the eCRF and provide other written documentation within 24 hours of receipt. However, as a back-up, if required, the SAE paper form should be completed, signed by the investigator, and transmitted within 24 hours to the attention of the contact listed in Section 1.1. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the attention of the contact listed in Section 1.1, 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 an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No independent data safety monitoring board/data monitoring committee is required for this study.

The Takeda clinical science representative and the principal investigator will review the safety and tolerability data and available PK data (if applicable) for each cohort prior to dosing any additional cohort. The decision for the next subsequent dose must be agreed by the Takeda clinical science lead and the principal investigator. If any one person has concerns regarding subsequent dosing then this acts as veto and the decision not to proceed with an additional cohort escalated to Takeda management.

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 conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 CRFs (Electronic and Paper)

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

The sponsor or its designee will supply investigative 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.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date 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 clinical 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 and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. 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 ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), 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 Clinical Study Site Agreement between the investigator and sponsor.

Refer to the phase 1 Site Specifications document 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 unblinding of a subject's treatment assignment. 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

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 demographic, Baseline characteristics, and safety summaries.

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.

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

For each part of the study, descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and Baseline characteristics variables (age, height, weight, and BMI) for the pooled placebo group, each TAK-071 dose level, TAK-071 overall, and overall total, as applicable (ie, by sequence and overall only for the cross-over portions of the study, cohorts 16 and 17). For each part, the number and percentage of subjects in each class of the categorical demographic variables and Baseline characteristics variables (sex, ethnicity, and race) will be tabulated for the pooled placebo group, each TAK-071 dose level, TAK-071 overall, and overall total. Placebo data will be pooled across the cohorts within each part.

For each part, demographic variables of screen failure subjects and reasons for screen failures will be summarized overall for subjects who are screened but not enrolled in the study. Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

13.1.3 PK Analysis

Plasma and CSF concentrations of TAK-071 and donepezil, where appropriate, will be summarized by dose or regimen over each scheduled sampling time using descriptive statistics (including arithmetic mean, SD, median, minimum and maximum, geometric mean, and percent coefficient of variation of the geometric mean). Individual plasma concentration data vs time will be presented in a data listing, along with graphical plots of individual and mean plasma concentration vs time profiles by treatment.

Plasma PK parameters and CSF PK parameters, where applicable, will be summarized separately for SRD, MRD, presence/absence of donepezil, and for subjects with MCI or mild AD and Japanese subjects. Descriptive statistics (including arithmetic mean, SD, median, minimum and maximum, geometric mean, and percent coefficient of variation of the geometric mean) will be used as appropriate.

Dose proportionality for the SRD and MRD parts (separately) will be assessed using the empirical power law model [25]. This analysis will be carried out to assess the degree of dose proportionality based on the dose proportionality exponent (β) for the model for both C_{max} and AUC_{∞} on Day 1 and for C_{max} and AUC_{24} at steady-state.

Dose linearity will be examined in the event that dose proportionality cannot be established by using a simple linear regression on the exposure parameter.

Trough plasma concentrations measured in the MRD part will be summarized to assess steady-state. The time to steady-state will be assessed by fitting trough concentration values to a nonlinear mixed effects model in order to predict the time to achieve 90% of the steady-state trough concentrations separately for each dose.

Time dependency will be investigated in selected MRD cohorts. The time invariance of TAK-071 will be assessed by comparing AUC_{24} for the last day of dosing to the AUC_{∞} for Day 1 using analysis of variance with a random effect for subject and a fixed effect for day. If AUC_{∞} cannot be robustly estimated in a sufficient number of subjects, then the AUC_{last} will be used instead in statistical analyses.

In Cohorts 10 to 12, a linear mixed model will be used to evaluate the effect of TAK-071 on the steady-state PK parameters (C_{max} and AUC_{24}) of donepezil:

$$yijk=\mu + \tau j + \pi k + si + \varepsilon ijk \ (i=1, \ldots N; j=A, B, C; k=1, 2, 3),$$

where μ is a general mean of a logarithmically transformed primary variable, si is the random effect of subject i, πk is the fixed effect of period k, τj is the fixed effect of treatment j, εijk is the random error of the observation yijk, and N is the number of subjects included in the analysis.

The model will be used to estimate 90% CIs together with their corresponding geometric mean ratios for the PK parameters obtained from the comparisons between the treatments. The comparison of interest is TAK-071 plus donepezil vs donepezil alone.

Other exploratory comparisons, including the PK of Japanese subjects or subjects with MCI or mild AD vs healthy subjects and the effect of donepezil on the PK of TAK-071, will be performed

by using side-by-side tabular summaries of exposure-related PK parameters and by graphical comparisons of concentration-time profiles, as appropriate.

For the BA/FE cohort, PK parameters of TAK-071 will be summarized by regimen. A mixed effects analysis of variance (ANOVA) will be performed on natural logarithms of TAK-071 C_{max} and AUCs with sequence, period, and regimen as fixed effects and subject nested within sequence as a random effect. Within the framework of ANOVA, comparisons will be performed for tablet versus capsule and for fed versus fasting dosing condition to assess the relative bioavailability of TAK-071.

The ratios and the 90% CIs for the central values of each test regimen relative to the reference regimen will be provided. Wilcoxon signed-rank test will be used to compare t_{max} between the test and reference regimens.

The concentration and cumulative amounts of TAK-071 excreted in urine will be summarized by dose over each scheduled collection interval and for selected time intervals, ie, 0 to 96 hours postdose, using descriptive statistics for SRD and MRD. Individual urine TAK-071 data vs time will be presented in a data listing, along with plots of individual and mean cumulative amounts excreted in urine vs time profiles will be produced.

A more detailed description of the analyses will be presented in the SAP.

13.1.4 PD Analysis

For PD variables at each assessment time point, corresponding changes from Baseline and derived PD parameters (eg, E_{max} and $AUEC_{12}$) will be listed by subject and summarized using descriptive summary statistics (including arithmetic mean, SD, median, minimum and maximum, geometric mean, and percent coefficient of variation of the geometric mean) as appropriate. Graphical plots of individual and mean absolute and change from Baseline vs time profiles will also be produced for each treatment group, along with plots showing derived parameters by dose.

CCI [redacted] (Cohorts 9, 12, and 18 to 22 [and higher dose SRD cohorts, if needed]) with respect to the steady-state presence of TAK-071 alone (Day 27, Cohort 9), the steady-state presence of donepezil alone (Day -2, Cohort 12), and the steady-state presence of donepezil and TAK-071 (Day 20, Cohort 12). Baseline is defined as the predose time point prior to donepezil or TAK-071 dosing, as appropriate.

Change from Baseline in pupil size diameter will be estimated (Cohorts 9, 10 to 12, 16, and 18 to 22 [and higher dose SRD cohorts, if needed]) with respect to the steady-state presence of TAK-071 alone (Day 27, Cohort 9), the steady-state presence of donepezil alone (Day -2, Cohorts 10 to 12), and the steady-state presence of donepezil and TAK-071 (Day 27, Cohorts 10 to 12 or Day 20 or 40, Cohort 16). Baseline is defined as the predose time point prior to donepezil or TAK-071 dosing, as appropriate.

Mixed model analysis using the same analysis of variance model as described in Section 13.1.3 section might be used to evaluate differences in the change from Baseline $AUEC_{12}$ and E_{max} parameters between the TAK-071 treatments and placebo.

Additional details will be provided in the SAP.

13.1.5 Safety Analysis

All safety data will be presented in listings. Where applicable, within each part, for the non-Japanese and Japanese SRD and MRD cohorts separately, safety data will be summarized by placebo, each TAK-071 dose level, TAK-071 overall, and overall total, as applicable (ie, by sequence and overall only for the cross-over portions of the study, cohorts 16 and 17). Placebo data will be pooled across cohorts for the SRD and MRD parts separately.

13.1.5.1 AEs

All AEs will be coded by system organ class (SOC) and preferred term using MedDRA. TEAEs with onset occurring within 30 days (onset date – last date of dose +1≤30) after study drug administration will be listed and included in the summary tables. TEAEs will be summarized by SOC and preferred term. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to study drug (related vs not-related), severity of AEs, and related AEs. AEs leading to study drug discontinuation and SAEs will be listed. Data listings will be provided for all AEs, including PTEs, TEAEs, AEs leading to study drug discontinuation, and SAEs.

13.1.5.2 Clinical Laboratory Evaluation

Individual results of laboratory tests from hematology, chemistry, and urinalysis that meet Takeda's MAV criteria to be defined in the SAP will be listed and summarized. Baseline, postdose, and change from Baseline to postdose laboratory data will be summarized. All clinical laboratory data will be listed.

13.1.5.3 Vital Signs

Individual results of vital signs that meet Takeda's MAV criteria to be defined in the SAP will be listed and summarized. Observed values and changes from Baseline in vital sign measurements (systolic and diastolic blood pressure, heart and respiratory rate, and oral temperature) will be summarized. All vital signs data will be provided in the data listings.

13.1.5.4 ECGs

Individual results of ECG parameters that meet Takeda's MAV criteria to be defined in the SAP will be listed and summarized. Observed values and changes from Baseline in ECG parameters will be summarized. All ECG data will be provided in the data listings.

Shift tables will be generated for the investigator's ECG interpretations. All ECG data will be provided in the data listings.

13.1.5.5 Bowel Function

Data describing stool frequency, time to first stool after dosing, stool consistency, and ease of passage will be assessed using descriptive statistics as appropriate. In addition, diary components

(ie, the daily stool counts and BSF scores) will be examined graphically by subjects and by dose group to assess the time course of drug effect over time.

Descriptive statistics by visit will be presented for the percentage of subjects with BSF scale scores ≥6 vs <6 post Baseline compared with BSF scale scores ≥6 vs <6 at Baseline and for the percentage of subjects with a change from Baseline in BSF scale score of ≥2.

13.2 Interim Analysis and Criteria for Early Termination

Section 6.1.5 describes the blinded safety and available PK review that will take place after completion of each cohort and prior to the next dose escalation stage in the study.

13.2.1 Interim Analysis of Cohorts 1 to 15 and 17 to 22 Data

Interim analysis of all data (except Cohort 16) will be completed to enable the planning of phase 2 studies, while Cohort 16 enrollment is ongoing. The interim analysis will be initiated once all SRD and MRD cohorts have completed the study.

The main Takeda study team will be unblinded to the data in order to provide interim results to support phase 2 protocol development.

13.2.2 Interim Analysis of PD Data

CCI [redacted] A Takeda representative, outside of the main Takeda study team, will analyze unblinded data and provide summary results by treatment group to the main study team.

13.2.2.1 Pupillometry Data

For Cohorts 18 and 19, an unblinded interim analysis will be performed for pupillometry data to obtain information about target engagement measured by changes in dilatation and contraction velocity, initial and final diameter of the pupil, and P75 from Baseline to postdose.

Pupillometry data for Cohort 9, 12, 20, and 22 may be analyzed to further explore the PD interaction of TAK-071 and donepezil.

13.2.2.2 CCI [redacted]

CCI [redacted]

13.3 Determination of Sample Size

The sample sizes chosen for the SRD and MRD parts are considered to be sufficient for evaluation of safety, tolerability, and PK of each cohort but are not based on statistical power considerations.

A sample size of 12 subjects (4 per sequence) was chosen for the 3-period, 3-sequence, crossover design in Cohort 17. The sample size is considered sufficient to assess the bioavailability of TAK-071 from the tablet relative to the capsule and to assess the effect of food on the bioavailability of TAK-071 from the tablet. This sample size was not based on statistical power considerations.

Enrolled participants who withdraw from the study for reasons other than safety may be replaced to ensure adequate numbers of evaluable subjects. The decision to replace a withdrawn subject will be made at the discretion of Takeda and the investigator.

In addition, in the event of a nonsafety-related critical procedure study interpretation (ie, CSF collection) where a subject is not withdrawn and remains in the study for the completion of all other assessments, that subject may be replaced on a case-by-case basis to ensure evaluability of that particular endpoint (ie, CSF, PK).

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 institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or 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 ICFs), and 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, 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 the primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

The investigator should document all protocol deviations.

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/Hours	Nominal Sampling Time
no more than 30 minutes predose	0 hour
±5 minutes	immediately postdose to ≤6 hours
±10 minutes	>6 hours to ≤12 hours postdose
±15 minutes	>12 hours 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 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 Approval

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, ICF) reviewed; and state the approval date. The sponsor will 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 notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the ICF, 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 ICF, 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 ICF 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 ICF 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 approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB and the sponsor prior to use.

The ICF, 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 ICF, 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. 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 ICF 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 ICF and subject authorization (if applicable) at the time of consent and prior to the 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 ICF, 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 ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs 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 ICF.

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. The sponsor must be notified 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 study database or documentation via a unique 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 its monitor or designee's monitor, 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 clinical 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 Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical 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 interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing. For some registries, Takeda will assist callers in locating trial 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 Takeda providing this information to callers must provide Takeda 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 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 clinical study subjects. Refer to the Clinical 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

SRD Cohorts 1 to 6, 18, and 19

	Screening Days -28 to -2	Check-in Day -1	Day 1	Day 2	Day 3	Day 4	Final Visit Day 5	PK Follow-Up Day 8	ET (a)	Follow-up Day 12 (±2) (b)
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Demographics and medical history	X									
Medication history and concurrent medical conditions	X									
Physical examination	X	X					X		X	(X)
Vital signs (c)	X	X	X	X	X	X	X		X	(X)
Height, weight, and BMI (d)	X	X					X		X	
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X
Clinical laboratory evaluations (f)	X	X	X	X	X	X	X	X	X	(X)
Serum hCG (g)	X	X					X		X	(X)
FSH (h)	X									
12-lead ECG (i)	X	X	X	X	X	X	X		X	(X)
Continuous 12-lead Holter ECG (j)			X	X	X					
Urine drug and alcohol screen	X	X								
HBsAg and anti-HCV	X									
Hemoglobin A1c	X									
Creatinine clearance	X									
Confinement		X	X	X	X	X				
PGx DNA collection (k)			X							
PGx RNA collection (k)			X				X			

Footnotes are on last table page.

SRD Cohorts 1 to 6, 18 and 19 (continued)

	Screening Days -28 to -2	Check-in Day -1	Day 1	Day 2	Day 3	Day 4	Final Visit Day 5	PK Follow-Up Day 8	ET (a)	Follow-up Day 12 (±2) (b)
PK blood collection (l)			X	X	X	X	X	X	X	
PK urine collection (m)			X	X	X	X	X			
CSF (n)			X							
Lumbar x-ray (n)	X									
Funduscopy (o)	X									
TAK-071 dosing (p)			X							
PTE assessment (q)	X	X	X							
AE assessment (r)			X	X	X	X	X	X	X	X
Bowel function (s)	X	X	X	X	X	X	X		X	
C-SSRS (t)	X	X					X		X	(X)
CCI [redacted]										
Pupillometry (v)		X	X	X						

Footnotes are on the following page.

ET=Early Termination Visit, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus.
(a) A PK blood sample should be collected at the Early Termination Visit, if possible.
(b) 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.
(c) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained as indicated. In Cohort 3, vital signs will be collected at approximately 5 hours postdose. In addition, orthostatic blood pressure will be measured in all cohorts except Cohort 3, at predose and at 2, 4, 6, 8, and 12 hours postdose in the first 24 hours after the initial dose of TAK-071 and then daily afterwards while subjects are confined in the phase 1 unit as detailed in Section 9.1.6.
(d) Height and BMI will be collected at Screening only.
(e) All ongoing medications will be recorded from Screening and throughout the study.
(f) Blood and urine samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected as indicated. On Day 1, the urine sample for urinalysis will be taken predose (within 2 hours prior to dosing) and the blood sample will be taken 1 hour postdose. On subsequent days, blood and urine samples will be taken upon rising in the morning under fasted condition. Laboratory sample collection on Day 8 does not require fasting conditions.
(g) During the course of the study, regular serum hCG pregnancy tests will be performed for female subjects and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. In addition to a negative serum hCG pregnancy test at Screening, female subjects must have a negative serum hCG pregnancy test at Check-in prior to receiving the first dose of study drug.
(h) FSH concentration will be obtained from postmenopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(i) A standard 12-lead ECG will be recorded at Screening, Check-in (Day -1), Day 1 (predose [within 60 minutes prior to dosing], and at 0.5, 1, 2, 4, and 8 hours postdose), and Days 2 through 5 (upon morning rising) or ET. Single ECGs will be taken at all visits.
(j) Continuous 12-lead Holter ECG monitoring will be conducted from 2 hours predose until 48 hours postdose in Cohorts 2, 4, 6, 18, and 19 only.
(k) Blood samples for PGx analysis will be collected as follows: 6 mL for DNA on Day 1; 2×2.5 mL for RNA analysis on Day 1 (predose and 12 hours postdose) and Day 5.
(l) Blood samples (up to 3 mL/sample collected into K_2EDTA-coated tubes) for plasma measurement of TAK-071 will be collected predose (within 30 minutes prior to dosing) and at specified time points outlined in Section 9.1.15.
(m) Urine samples for PK analyses will be collected predose within approximately 1 hour of dosing and at specified intervals outlined in Section 9.1.15.
(n) CSF (up to 1.25 mL/sample) will be obtained predose (within 30 minutes before dosing) and at 0.5, 2, 4, 6, and 12 hours post dose in Cohort 3 only. If not performed within the last 12 months prior to Screening, a lumbar x-ray will be performed at Screening in Cohort 3 subjects to ensure that there are no deformities that could interfere with insertion of an indwelling cannula for the subsequent collection of CSF.
(o) Funduscopy will be performed in Cohort 3 only.
(p) DIC will be dispensed for treatment.
(q) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(r) Any event after dosing on Day 1 will be captured as an AE.
(s) Bowel function will be assessed using the BSF scale and daily stool count.
(t) 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.
(u) CCI [redacted] CCI
(v) Pupillometry will be performed only in Cohort 18 (and higher dose SRD cohorts, if needed) at check-in (Day -1), predose on Day 1, approximately 25 hours postdose (Day 2).

SRD+Donepezil Cohorts 20 to 22

	Screening Days -28 to -2	Check-in Day -1	Day 1	Day 2	Day 3	Day 4	Final Visit Day 5	PK Follow-Up Day 8	ET (a)	Follow-up Day 12 (±2) (b)
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Demographics and medical history	X									
Medication history and concurrent medical conditions	X									
Physical examination	X	X					X		X	(X)
Vital signs (c)	X	X	X	X	X	X	X		X	(X)
Height, weight, and BMI (d)	X	X					X		X	
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X
Clinical laboratory evaluations (f)	X	X	X	X	X	X	X	X	X	(X)
Serum hCG (g)	X	X					X		X	(X)
FSH (h)	X									
12-lead ECG (i)	X	X	X	X	X	X	X		X	(X)
Urine drug and alcohol screen	X	X								
HBsAg and anti-HCV	X									
Hemoglobin A1c	X									
Creatinine clearance	X									
Confinement		X	X	X	X	X				
PGx DNA collection (j)			X							
PGx RNA collection (j)			X				X			

Footnotes are on last table page.

SRD (Pretreated with Donepezil) Cohorts 20 to 22 (continued)

	Screening Days -28 to -2	Check-in Day -1	Day 1	Day 2	Day 3	Day 4	Final Visit Day 5	PK Follow-Up Day 8	ET (a)	Follow-up Day 12 (±2) (b)
Donepezil dosing (k)				X						
TAK-071 dosing (k)			X							
TAK-071 PK blood collection (l)			X	X	X	X	X	X	X	
Donepezil PK blood collection (m)				X	X	X	X	X	X	
PTE assessment (n)	X	X	X							
AE assessment (o)			X	X	X	X	X	X	X	X
Bowel function (p)	X	X	X	X	X	X	X		X	
C-SSRS (q)	X	X					X		X	(X)
CCI										
Pupillometry (s)		X	X	X						

Footnotes are on the following page.

ET=Early Termination Visit, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus.
(a) A PK blood sample should be collected at the Early Termination Visit, if possible.
(b) 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.
(c) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained as indicated. In addition, orthostatic blood pressure will be measured at predose and at 2, 4, 6, 8, and 12 hours postdose in the first 24 hours after the initial dose of TAK-071 and then daily afterwards while subjects are confined in the phase 1 unit as detailed in Section 9.1.6.
(d) Height and BMI will be collected at Screening only.
(e) All ongoing medications will be recorded from Screening and throughout the study.
(f) Blood and urine samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected as indicated. On Day 1, the urine sample for urinalysis will be taken predose (within 2 hours prior to dosing) and the blood sample will be taken 1 hour postdose. On subsequent days, blood and urine samples will be taken upon rising in the morning under fasted condition.
(g) During the course of the study, regular serum hCG pregnancy tests will be performed for female subjects and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. In addition to a negative serum hCG pregnancy test at Screening, female subjects must have a negative serum hCG pregnancy test at Check-in prior to receiving the first dose of study drug.
(h) FSH concentration will be obtained from postmenopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(i) A standard 12-lead ECG will be recorded at Screening, Check-in (Day -1), Day 1 (predose [within 60 minutes prior to dosing], and at 0.5, 1, 2, 4, and 8 hours postdose), and Days 2 through 5 (upon morning rising) or ET. Single ECGs will be taken at all visits.
(j) Blood samples for PGx analysis will be collected as follows: 6 mL for DNA on Day 1; 2×2.5 mL for RNA analysis on Day 1 (predose and 12 hours postdose) and Day 5.
(k) TAK-071 as DIC will be dispensed for treatment. Donepezil 10 mg will be administered approximately 24 hours after TAK-071 dose.
(l) Blood samples for TAK-071 PK (up to 3 mL/sample collected into K_2EDTA-coated tubes) for plasma measurement of TAK-071 will be collected predose (within 30 minutes prior to dosing) and at specified time points outlined in Section 9.1.15.
(m) Blood samples for donepezil PK (up to 4 mL/sample collected into sodium heparin tubes) for plasma measurement of donepezil will be collected predose (within 30 minutes prior to dosing) and at specified time points outlined in Section 9.1.15.
(n) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(o) Any event after dosing on Day 1 will be captured as an AE.
(p) Bowel function will be assessed using the BSF scale and daily stool count.
(q) 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.
(r) CCI [redacted] CCI
(s) Pupillometry will be performed at check-in on Day -1 (approximately 25 hours predose), Day 1 (1 hour predose), and Day 2 (approximately 23 hours post TAK-071 dose) and 5 hours post donepezil dose.

MRD Healthy Volunteer Cohorts 7 and 8

	Screening Days -28 to -2	Check-in Day -1	Day(s) 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Final Visit Day 23	ET (a)	Follow-up Day 32 (±2) (b)
Informed consent	X																										
Inclusion/exclusion criteria	X	X																									
Demographics and medical history	X																										
Medication history and concurrent medical conditions	X																										
Physical examination	X	X																							X	X	(X)
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Height, weight and BMI (d)	X	X																							X	X	
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory evaluations (f)	X	X	X	X			X			X						X						X	X	X	X	X	(X)
Serum hCG (g)	X	X																							X	X	X
FSH (h)	X																										
12-lead ECG (i)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Continuous 12-lead Holter ECG (j)			X	X																			X	X	X		
Urine drug and alcohol screen	X	X																									
HBsAg and anti-HCV	X																										
Hemoglobin A1c	X																										
Creatinine clearance	X																										
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
TAK-071 dosing (k)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
PGx DNA collection (l)			X																								
PGx RNA collection (l)			X																				X				
PK blood collection (m)			X	X						X						X					X	X	X	X		X	
PK urine collection (n)			X	X																			X	X			
PTE assessment (o)	X	X	X																								
AE assessment (p)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bowel function (q)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS (r)	X	X																							X	X	(X)

Footnotes are on the following page.

ET=Early Termination Visit, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus.
(a) A PK blood sample should be collected at the Early Termination Visit if possible.
(b) Follow-up will occur by telephone on Day 32 (±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.
(c) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained as indicated. In addition, orthostatic blood pressure will be measured at predose and at 2, 4, 6, 8, and 12 hours postdose in the first 24 hours after the initial dose of TAK-071 and then daily afterwards while subjects are confined in the phase 1 unit as detailed in Section 9.1.6.
(d) Height and BMI will be collected at Screening only.
(e) All ongoing medications will be recorded from Screening and throughout the study.
(f) Blood and urine samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected as indicated. On Day 1, the urine sample for urinalysis will be taken predose (within 2 hours prior to dosing) and the blood sample for these tests will be taken 1 hour postdose. On subsequent days, blood and urine samples will be taken predose upon rising in the morning under fasted condition.
(g) During the course of the study, regular serum hCG pregnancy tests will be performed for female subjects and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. In addition to a negative serum hCG pregnancy test at Screening, female subjects must have a negative serum hCG pregnancy test at Check-in prior to receiving the first dose of study drug.
(h) FSH concentration will be obtained from postmenopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(i) A standard 12-lead ECG will be recorded at Screening, Check-in (Day -1), Day 1 (TAK-071 predose [within 60 minutes prior to dosing] and at 0.5, 1, 2, 4, and 8 hours postdose), Days 2 through 21 (predose), Days 22 and 23 (upon morning rising) or ET. Single ECGs will be taken at all visits.
(j) Continuous 12-lead Holter ECG monitoring will be conducted from 2 hours predose until 24 hours postdose TAK-071 on Day 1 and from 1 hour predose until 48 hours postdose TAK-071 on Day 21.
(k) DIC will be dispensed for treatment
(l) Blood samples for PGx analysis will be collected as follows: 6 mL for DNA on Day 1; 2×2.5 mL for RNA on Day 1 (predose and 12 hours postdose) and 12 hours postdose on Day 21.
(m) Blood samples (3 mL/sample) for plasma measurement of TAK-071will be collected predose (within 30 minutes prior to dosing) and specified time points outlined in Section 9.1.15.1.
(n) Urine samples for PK analyses will be collected predose within approximately 1 hour of dosing and specified time points outlined in Section 9.1.15.2.
(o) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(p) Any event after dosing on Day 1 will be captured as an AE.
(q) Bowel function will be assessed using the BSF scale and daily stool count.
(r) 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.

MRD Healthy Volunteer Cohort 9

	Day(s)																			Final Visit Day 30	ET (a)	Follow-up Day 39±2 (b)
	Screening -28 to -2	Check-in -1	1	2	3	4	5	6 to 7	8	9	10	11 to 14	15	16 to 19	20	21 to 26	27	28	29			
Informed consent	X																					
Inclusion/exclusion criteria	X	X																				
Demographics and medical history	X																					
Medication history and concurrent medical conditions	X																					
Physical examination	X	X																		X	X	(X)
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Height, weight and BMI (d)	X	X																		X	X	
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory evaluations (f)	X	X	X	X	X				X	X	X		X		X		X	X	X	X	X	(X)
Serum hCG (g)	X	X																		X	X	(X)
FSH (h)	X																					
12-lead ECG (i)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Continuous 12-lead Holter ECG (j)			X	X	X													X	X	X		
Urine drug and alcohol screen	X	X																				
HBsAg and anti-HCV	X																					
Hemoglobin A1c	X																					
Creatinine clearance	X																					
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
TAK-071 dosing (k)			X						X	X	X	X	X	X	X	X	X	X				
PGx DNA collection (l)			X																			
PGx RNA collection (l)			X						X									X				
PK blood collection (m)			X	X	X	X	X		X	X			X		X	X	X	X	X		X	
PK urine collection (n)			X	X	X	X												X	X			
CCI																						
CSF (o)																		X	X			
Lumbar x-ray (o)	X																					
Funduscopy	X																					
PTE assessment (p)	X	X	X																			
AE assessment (q)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bowel function (r)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS (s)	X	X																		X	X	(X)
Pupil size (t)			X														X					

Footnotes are on the following page.

ET=Early Termination Visit, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus.
(a) A PK blood sample should be collected at the Early Termination Visit if possible.
(b) Follow-up will occur by telephone on Day 39 (±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.
(c) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained as indicated.
(d) Height and BMI will be collected at Screening only.
(e) All ongoing medications will be recorded from Screening and throughout the study.
(f) Blood and urine samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected as indicated. On Day 1, the urine sample for urinalysis will be taken at predose (within 2 hours prior to dosing) and the blood sample for these tests will be taken 1 hour postdose. On subsequent days, samples will be taken predose upon rising in the morning under fasted condition.
(g) During the course of the study, regular serum hCG pregnancy tests will be performed for female subjects and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. In addition to a negative serum hCG pregnancy test at Screening, female subjects must have a negative serum hCG pregnancy test at Check-in prior to receiving the first dose of study drug.
(h) FSH concentration will be obtained from postmenopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(i) A standard 12-lead ECG will be recorded at Screening, Check-in (Day -1), Days 1 and 8 (TAK-071 predose [within 60 minutes prior to dosing] and at 0.5, 1, 2, 4, and 8 hours postdose), and Days 2 to 7 and 9 to 30 upon morning rising, or ET. Single ECGs will be taken at all visits.
(j) Continuous 12-lead Holter ECG monitoring will be conducted 2 hours predose until 48 hours postdose on Day 1 and 1 hour predose until 48 hours postdose on Day 28.
(k) DIC will be dispensed for treatment.
(l) Blood samples for PGx analysis will be collected as follows: 6 mL for DNA on Day 1; 2×2.5 mL for RNA predose TAK-071 on Day 1, predose TAK-071 on Day 8, and 12 hours postdose on Day 28.
(m) Blood samples (3 mL/sample into EDTA coated tubes) for plasma measurement of TAK-071 will be collected predose (within 30 minutes prior to dosing) and specified time points outlined in Section 9.1.15.1.
(n) Urine samples for PK analyses will be collected predose within approximately 1 hour of dosing and specified time points outlined in Section 9.1.15.2.
(o) CSF (up to 1.25 mL/sample) will be obtained Day 28 at predose (within 30 minutes before dosing) and at 4, 8, 12, 24, and 36 hours post last dose. If not performed within the last 12 months prior to Screening, a lumbar x-ray will be performed at Screening in to ensure that there are no deformities that could interfere with insertion of an indwelling cannula for the subsequent collection of CSF.
(p) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(q) Any event after dosing on Day 1 will be captured as an AE.
(r) Bowel function will be assessed using the BSF scale and daily stool count.
(s) 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.
(t) Pupil size will be measured at the time points outlined in Section 9.1.17.2.

MRD + Donepezil Pretreatment Healthy Volunteer Cohorts 10 to 12

	Screening -44 to -23	Day																					Final Visit Day 23	ET (a)	Follow-up Day 32 (±2) (b)
		Check- in -22	-21 to -19	-18 to -11	-10 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 to 19	20	21	22			
Informed consent	X																								
Inclusion/exclusion criteria	X	X																							
Demographics and medical history	X																								
Medication history and concurrent medical conditions	X																								
Physical examination	X	X																					X	X	(X)
Vital signs (c)	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Height, weight and BMI (d)	X	X																					X	X	
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory evaluations (f)	X	X	X		X	X	X			X			X			X			X		X	X		X	X	(X)
Urine drug and alcohol screen	X	X																							
Serum hCG (g)	X	X			X																		X	X	(X)
FSH (h)	X																								
12-lead ECG (i)	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
HBsAg and anti-HCV	X																								
Hemoglobin A1c	X																								
Creatinine clearance	X																								
Confinement		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
TAK-071 dosing (j)						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Donepezil dosing (k)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Subject Call Dosing Reminder (l)				X																					
PGx DNA collection (m)			X																						
PGx RNA collection (m)			X			X																X			
PK blood collection (n,o)					X	X	X						X						X	X	X	X	X		X	
CCI																										
PTE assessment (q)	X	X	X																						
AE assessment (r)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bowel function (s)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS (t)	X	X			X																		X	X	(X)
Pupil size measurement (u)			X		X	X															X					

Footnotes are on the following page.

ET=Early Termination Visit, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus.
(a) A PK blood sample should be collected at the ET Visit if possible.
(b) Follow-up will occur by telephone on Day 32 (±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.
(c) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained as indicated. In addition, orthostatic blood pressure will be measured at predose and at 2, 4, 6, 8, and 12 hours postdose in the first 24 hours after the initial dose of TAK-071 and then daily afterwards while subjects are confined in the phase 1 unit as detailed in Section 9.1.6.
(d) Height and BMI will be collected at Screening only.
(e) All ongoing medications will be recorded from Screening and throughout the study.
(f) Blood and urine samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected as indicated. On Days -21 to -1, blood and urine samples will be collected on Days -21, -10 and -1. On Day 1, the urine sample for urinalysis will be taken at predose (within 2 hours prior to dosing) and the blood sample for these tests will be taken 1 hour postdose. On subsequent days, blood and urine samples will be taken predose upon rising in the morning under fasted condition.
(g) During the course of the study, regular serum hCG pregnancy tests will be performed for female subjects and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. In addition to a negative serum hCG pregnancy test at Screening, female subjects must have a negative serum hCG pregnancy test at Check-in (Day -10) prior to receiving the first dose of study drug.
(h) FSH concentration will be obtained from postmenopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(i) A standard 12-lead ECG will be recorded at Screening, Check-in (Day -22) (donepezil predose [within 60 minutes prior to dosing]), Day -1, Day 1 (TAK-071 predose [within 60 minutes prior to dosing] and at 0.5, 1, 2, 4, and 8 hours postdose), Days 2 to 21 (predose), and Days 22 to 23 (upon morning rising) or ET. Single ECGs will be taken at all visits.
(j) DIC will be dispensed for treatment
(k) Donepezil will be given as an oral daily 5 mg tablet in the morning. Subjects will administer donepezil in the morning at home on Days -18 to -11.
(l) Subjects should be called each outpatient day with a reminder to take their study medication in the morning daily on Days -18 to -11.
(m) Blood samples for PGx analysis will be collected as follows: 6 mL for DNA predose donepezil on Day -21; 2×2.5 mL for RNA predose donepezil on Day -21, predose TAK-071 on Day 1, and 12 hours postdose on Day 21.
(n) Blood samples (3 mL/sample collected into EDTA-coated tubes) for plasma measurement of TAK-071 will be collected predose (within 30 minutes prior to dosing) and specified time points outlined in Section 9.1.15.1.
(o) Blood samples (4 mL/sample collected into sodium heparin tubes) for the measurement of donepezil will be collected predose (within 30 minutes prior to TAK-071 dosing) and specified time points outlined in Section 9.1.15.1.
(p) CCI [redacted] CCI

(r) Any event after the first dose of donepezil on Day -21 will be captured as an AE.
(s) Bowel function will be assessed using the BSF scale and daily stool count.
(t) C-SSRS will be determined as indicated. On Days -10 to -1, C-SSRS will be done on Day -1 only. If clinically significant at Final Visit, C-SSRS will also be determined as part of the Follow-up Visit.
(u) Pupil size will be measured at the time points outlined in Section 9.1.17.2.

MRD Japanese Healthy Volunteer Cohorts 13 to 15

	Day(s)																			Final Visit Day 30	ET (a)	Follow-up Day 39±2 (b)
	Screening -28 to -2	Check-in -1	1	2	3	4	5	6 to 7	8	9	10	11 to 14	15	16 to 19	20	21 to 26	27	28	29			
Informed consent	X																					
Inclusion/exclusion criteria	X	X																				
Demographics and medical history	X																					
Medication history and concurrent medical conditions	X																					
Physical examination	X	X																		X	X	(X)
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Height, weight and BMI (d)	X	X																		X	X	
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory evaluations (f)	X	X	X	X	X				X	X	X		X		X		X	X	X	X	X	(X)
Serum hCG (g)	X	X																		X	X	(X)
FSH (h)	X																					
12-lead ECG (i)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Urine drug and alcohol screen	X	X																				
HBsAg and anti-HCV	X																					
Hemoglobin A1c	X																					
Creatinine clearance	X																					
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
TAK-071 dosing (j)			X						X	X	X	X	X	X	X	X	X	X				
PGx DNA collection (k)			X																			
PGx RNA collection (k)			X						X									X				
PK blood collection (l)			X	X	X	X	X		X	X			X		X	X	X	X	X		X	
PK urine collection (m)			X	X	X	X												X	X			
PTE assessment (n)	X	X	X																			
AE assessment (o)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bowel function (p)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS (q)	X	X																		X	X	(X)

Footnotes are on the following page.

ET=Early Termination Visit, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus.
(a) A PK blood sample should be collected at the Early Termination Visit if possible.
(b) Follow-up will occur by telephone on Day 39 (±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.
(c) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained as indicated. In addition, orthostatic blood pressure will be measured at predose and at 2, 4, 6, 8, and 12 hours postdose in the first 24 hours after the initial dose of TAK-071 and then daily afterwards (upon morning rising) while subjects are confined in the phase 1 unit as detailed in Section 9.1.6.
(d) Height and BMI will be collected at Screening only.
(e) All ongoing medications will be recorded from Screening and throughout the study.
(f) Blood and urine samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected as indicated. On Day 1, the urine sample for urinalysis will be taken at predose (within 2 hours prior to dosing) and the blood sample for these tests will be taken 1 hour postdose. On subsequent days, blood and urine samples will be taken predose upon rising in the morning under fasted condition.
(g) During the course of the study, regular serum hCG pregnancy tests will be performed for female subjects and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. In addition to a negative serum hCG pregnancy test at Screening, female subjects must have a negative serum hCG pregnancy test at Check-in prior to receiving the first dose of study drug.
(h) FSH concentration will be obtained from postmenopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(i) A standard 12-lead ECG will be recorded at Screening, Check-in (Day -1), Days 1 and 8 (TAK-071 predose [within 60 minutes prior to dosing] and at 0.5, 1, 2, 4, and 8 hours postdose). On the remaining days during confinement 12-lead ECG be recorded (upon morning rising), or ET. Single ECGs will be taken at all visits.
(j) DIC will be dispensed for treatment.
(k) Blood samples for PGx analysis will be collected as follows: 6 mL for DNA on Day 1; 2×2.5 mL for RNA predose TAK-071 on Day 1, predose TAK-071 on Day 8, and 12 hours postdose on Day 28.
(l) Blood samples (3 mL/sample into EDTA coated tubes) for plasma measurement of TAK-071 will be collected predose (within 30 minutes prior to dosing) and specified time points outlined in Section 9.1.15.1.
(m) Urine samples for PK analyses will be collected predose within approximately 1 hour of dosing and specified time points outlined in Section 9.1.15.2.
(n) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(o) Any event after dosing on Day 1 will be captured as an AE.
(p) Bowel function will be assessed using the BSF scale and daily stool count.
(q) 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.

Subjects With MCI or Mild AD Cohort 16

	Day																							
	Screening -60 to -2	Run-in Period (a) -49	Run-in Period (a) -21	Check-in -1	1	2	3 to 10	11	12 to 19	20	21	22	23 to 40	41	42	43	44 to 51	52	53 to 60	61	62	Final Visit Day 63	ET (b)	Follow-up Day 73±2 (c)
Informed consent	X																							
Inclusion/exclusion criteria	X			X																				
Demographics and medical history	X																							
Medication history and concurrent medical conditions	X																							
Physical examination	X			X																		X	X	(X)
MMSE	X																							
Diagnosis of AD/MCI	X																							
Vital signs (d)	X	X	X	X	X	X		X		X	X	X		X	X	X		X		X	X	X	X	(X)
Height, weight and BMI (e)	X			X																		X	X	
Concomitant medications (f)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory evaluations (g)	X		X	X	X	X		X		X	X	X		X	X	X		X		X	X	X	X	(X)
FSH (h)	X																							
12-lead ECG (i)	X			X	X	X		X		X	X	X		X	X	X		X		X	X	X	X	(X)
Urine drug and alcohol screen	X																							
HBsAg and anti-HCV	X																							
Hemoglobin A1c	X																							
Creatinine clearance	X																							
Confinement				X	X	X		X		X	X	X		X	X	X		X		X	X			
TAK-071 dosing or placebo (j)					X	X	X	X	X	X	X				X	X	X	X	X	X	X			
Donepezil dosing (k)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
PGx DNA collection (l)					X																			
PGx RNA collection (l)					X						X				X						X			
PK blood collection (m,n)					X	X					X	X			X	X					X	X	X	
PK urine collection (o)					X	X					X	X			X	X					X	X		
PTE assessment (p)	X																							
AE assessment (q)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bowel function (r)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS (s)	X			X																		X	X	(X)
Pupil size measured (t)					X					X					X					X				

Footnotes are on the following page.

ET=Early Termination Visit, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus.
(a) Only subjects in donepezil run-in period will have these assessments.
(b) A PK blood sample should be collected at the Early Termination Visit if possible.
(c) Follow-up will occur by telephone on Day 73 (±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.
(d) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained as indicated. In addition, orthostatic blood pressure will be measured at predose and at 2, 4, 6, 8, and 12 hours postdose in the first 24 hours after the initial dose of TAK-071 and then afterwards on Days 2, 11, 20 to 22, 41 to 43, 52, and 61 to 63 (upon morning rising or arrival for outpatient visit) or ET as detailed in Section 9.1.6.
(e) Height and BMI will be collected at Screening only.
(f) All ongoing medications will be recorded from Screening and throughout the study.
(g) Blood and urine samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected as indicated. On Days 1 and 42, the urine sample for urinalysis will be taken at predose (within 2 hours prior to dosing) and the blood sample for these tests will be taken 1 hour postdose. On all other days, when the subjects are confined at the phase 1 unit, blood and urine samples will be taken predose upon rising in the morning under fasted condition.
(h) FSH concentration will be obtained from postmenopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile). The result must be >40 IU/L for the subject to be enrolled.
(i) A standard 12-lead ECG will be recorded at Screening, Check-in (Day -1), Days 1, 21, 42, and 62 (TAK-071 predose [within 60 minutes prior to dosing] and at 0.5, 1, 2, 4, and 8 hours postdose), Days 2, 11, 20 to 22, 41 to 43, 52, and 61 to 63 (upon morning rising or arrival for outpatient visit) or ET. Single ECGs will be taken at all visits.
(j) DIC will be dispensed for treatment.
(k) Subjects must be receiving ongoing donepezil therapy (10 mg) in the evening for a minimum of 21 days prior to Check-in and during the study (if subjects were receiving 5 mg dose at Screening, it should be up-titrated to 10 mg on Day -21). Alternatively, subjects may be diagnosed at Screening and start donepezil run-in for 49 days prior to Day -1, and on stable 10 mg dose of donepezil 21 days prior to Day -1. Subjects will continue with their donepezil therapy during the TAK-071 Treatment Period.
(l) Blood samples for PGx analysis will be collected as follows: 6 mL for DNA on Day 1; 2×2.5 mL for RNA predose TAK-071 on Days 1 and 42 and 12 hours postdose on Days 21 and 62.
(m) Blood samples (3 mL/sample into EDTA coated tubes) for plasma measurement of TAK-071 will be collected predose (within 30 minutes prior to dosing) and specified time points outlined in Section 9.1.15.1.
(n) Blood samples (4 mL/sample collected into sodium heparin tubes) for the measurement of donepezil will be collected predose (within 30 minutes prior to TAK-071 dosing) and specified time points outlined in Section 9.1.15.1.
(o) Urine samples for PK analyses will be collected predose within approximately 1 hour of dosing and specified time points outlined in Section 9.1.15.2.
(p) PTEs will be collected from signing of informed consent up until dosing on Day 1 or prior to the first dose of donepezil during the run-in period.
(q) Any event after TAK-071 dose on Day 1 or after the first dose of donepezil in newly diagnosed subjects or first day the dose of donepezil is increased in subjects who are receiving lower donepezil dose during the run-in period will be captured as an AE. During the run-in period, weekly telephone calls will be made for AE assessment.
(r) Bowel function will be assessed using the BSF scale and daily stool count.
(s) 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.
(t) Pupil size will be measured at the time points outlined in Section 9.1.17.2.

BA/FE Cohort 17

	Screening	Check-in	Periods 1, 2, 3						Final Visit	Early Termination	Follow up
	Day										
Study Day:	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**8 (Periods 1 and 2)**	**8 (Period 3)**	**(a)**	**12±2 days post Period 3 dosing (b)**
Informed consent	X										
Confinement		X	X	X	X	X	X				
Inclusion/exclusion criteria	X	X									
Demographics and medical history	X										
Medication history	X										
Physical examination	X	X								X	(X)
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	(X)
Weight, height, and BMI (d)	X	X								X	(X)
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X									
Clinical laboratory tests (f)	X	X	X	X			X	X	X	X	(X)
Hepatitis panel	X										
Hemoglobin A1c	X										
FSH (g)	X										
Pregnancy test (hCG)	X	X							X	X	(X)
Urine drug screen	X	X									
ECG (h)	X	X	X	X	X	X	X	X	X	X	(X)
PK blood collection (i)			X	X	X	X	X	X	X	X	
Study Drug Dosing (j)			X								
PTE assessment (k)	X	X	X								
AE assessment (l)		X	X	X	X	X	X	X	X	X	X
C-SSRS (m)	X	X							X	X	(X)

Footnotes are on the following page.

NOTE: Study exit will occur on Day 8 of Period 3 when all scheduled assessments have been completed.
(a) A PK blood sample should be collected at the Early Termination Visit if possible.
(b) Follow-up will occur by telephone on Day 12±2 of Period 3 unless abnormal clinical significant findings were observed upon discharge. In these cases subjects must then be brought back to the clinic for re-evaluation per investigators discretion.
(c) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be recorded at Screening and in each period at Check-in (Day -1), Orthostatic vitals should be collected on Day 1 (predose [within 45 minutes prior to dosing] and at 2, 4, 6, 8, and 12 hours postdose), and Days 2 through 5 (upon rising), Day 8 PK visit, Study Exit ([Day 8 of Period 3] or Early Termination and Follow-up Visit (Day 12 [±2]) of Period 3, as appropriate.
(d) Height and BMI will be collected at Screening only and if early terminated.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening and in each period at Check-in (Day -1), on Day 1 urine will be collected predose and blood will be collected 1 hour post dose, upon rising on Days 2 and 5 and, at PK visit on Day 8 (Day 8 of Period 3 is the final visit), at Early Termination, if occurs, and Follow-up Visit (Day 12 [±2]) of Period 3, as appropriate.
(g) A FSH level will be obtained on postmenopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile). The result must be >40 IU/L for the subject to be enrolled.
(h) Standard 12-lead ECGs will be recorded at Screening, and in each period at Check-in (Day -1), Day 1 (predose [within 45 minutes prior to dosing], and at 0.5, 1, 2, 4, and 8 hours postdose), Days 2 through 5 (upon morning rising), and Day 8 of Period 1 and 2, Study Exit (Day 8 of Period 3) or Early Termination, and Follow-up Visit Day 12 (±2), as appropriate.
(i) Blood samples (~3 mL/sample) for PK analyses will be collected at Predose (within 30 minutes prior to dosing) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 32, 40, 48, 72, 96, and 168 hours postdose in each period.
(j) For fasted regimens, there will be an overnight fast with a minimum period of 8 hours prior to dosing and for the fed regimen, after an overnight of fast of approximately 8 hours followed by consuming a high-fat meal before dosing. The high-fat meal is to be finished within 25 minutes. Dosing commences 30 minutes after the start of the meal.
(k) PTEs will be collected from signing of informed consent up until dosing on Day 1 of Period 1.
(l) Any event after dosing on Day 1 of Period 1 will be captured as an AE.
(m) C-SSRS: Columbia-Suicide Severity Rating Scale. The Screening/Baseline C-SSRS will be administered at Screening and the Since Last Visit C-SSRS will be administered at Day -1 Period 1, at Study Exit (Day 8 Period 3) or Early Termination, and Follow-up Visit [Period 3 Day 12 (±2)] (as appropriate, if clinically significant at Study Exit).

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 that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB 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, 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. 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 is 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, 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 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 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;
    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. All female subjects must be of non-childbearing potential.

26. Male subjects must use adequate contraception (as defined in the informed consent) from Screening, throughout the duration of the study, and for 30 days after the last dose of study drug. 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.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as 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.

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 K_2EDTA.
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. A minimum of 0.5 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-071-1001), sample matrix (ie, plasma) randomization/enrollment 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, Middleton, WI. 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. A minimum of 0.8 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-071-1001), sample matrix (ie, plasma) randomization/enrollment 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, Middleton, WI. No more than 45-60 minutes will elapse between blood collection and freezing the plasma sample.

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

1. Collect urine into polypropylene containers. During the collection interval, the urine will be stored at approximately 4°C. The urine collection will require the use 2% (w/v) Tween80 to prevent compound absorption to collection/storage containers.
2. At the end of each void (no more than 30 minutes postvoid), mix the urine, transfer to a graduated cylinder, measure and record the volume. For the urine sample in the graduated cylinder intended for bioanalysis, measure "X" amount of 2% Tween80 solution (2% Tween80 by weight in water) into a separate graduated cylinder (where "X" equals 1 part in 10 of the urine volume in the cylinder).
3. Pour ¾ of the "X" amount of the 2% Tween80 solution into the graduated cylinder containing the subject's urine. Mix and transfer to the bioanalysis sample jug for the time period.
4. With the remaining 2% Tween80 solution, rinse the original collection jug and combine with the sample in the bioanalysis sample jug for the time period.
5. Store the collection jug at approximately 4°C during the collection period. Record the final volume of the urine fortified with the 2% Tween80 solution.
6. Mix well and measure the urine volume within 2 hours of the end of the collection period.
7. Transfer approximately 5.0 mL aliquots of urine in duplicate into appropriate polypropylene containers. Container should be filled to approximately 50% of the nominal volume. Labeling should include protocol number (TAK-071-1001), 4-digit randomization number, period, nominal day and time, and either "SET 1" (for original sample), or "SET 2" (for duplicate sample).
8. Freeze the urine samples immediately and store frozen at approximately -80°C or lower. Keep samples frozen at approximately -80°C or lower until shipment to PPD. 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.

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

1. Using the peristaltic pump collect approximately 1.25 mL of CSF into a polypropylene tube. Note: the tubing may need to be flushed with the appropriate amount of CSF prior to initiation of collection of subsequent samples.
2. Immediately after collection, within 5 minutes, volumetrically remove a 1.0 mL aliquot of the collected sample to a properly labeled polypropylene cryo tube, the remaining sample after the 1.0 mL is removed can be discarded. Add 100 µL of 2% Tween 80 solution, cap the tube and vortex gently for approximately 2 seconds. Labeling should include protocol number (TAK-071-1001), matrix (CSF), 5-digit randomization number, period, nominal day and time.
3. Freeze the CSF samples immediately and store frozen at approximately -80 C or lower until shipment to PPD.

Shipping of Plasma, CSF and Urine 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, urine, or CSF) 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. Please note that there are only SET 1 samples for CSF.
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 5-digit randomization sequence number, sample matrix (ie, plasma, CSF, or urine), 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-071-1001), investigator's name, sample type (ie, plasma, CSF, or urine), subject randomization/enrollment 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, CSF, and Urine Samples for TAK-071
    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 samples, **please email** PPD **at** PPD to notify him of next day delivery. When calling, provide the

    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.

CYP450 Isoform	Strong Inhibitors	Moderate Inhibitors
CYP3A4	indinavir nelfinavir lopinavir /ritonavir ritonavir clarithromycin erythromycin itraconazole ketoconazole nefazodone saquinavir saquinavir/ritonavir telithromycin boceprevir conivaptan mibefradil posaconazole telaprevir voriconazole	aprepitant atazanavir atazanavir/ritonavir fluconazole verapamil diltiazem amprenavir atazanavir ciprofloxacin darunavir/ritonavir fosamprenavir imatinib cimetidine cyclosporin fluvoxamine posaconazole
CYP2C9	n/a	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	n/a
CYP2D6	Dexamethasone, rifampin	n/a

NA=not applicable.

(a) Polasek TM, Lin FP, Miners JO, Doogue MP. Perpetrators of pharmacokinetic drug-drug interactions arising from altered cytochrome P450 activity: a criteria-based assessment. Br J Clin Pharmacol 2011;71(5):727-36.
(b) Indiana University Department of Medicine. P450 Drug Interaction Table. Indiana University, Division of Clinical Pharmacology. Updated 25 January 2012. Accessed 03 April 2013. Available at: http://medicine.iupui.edu/clinpharm/ddis/table.aspx.
(c) FDA. Drug development and drug interactions: table of substrates, inhibitors and inducers. U.S. Food and Drug Administration. Updated 27 October 2014. Accessed 04 June 2015. Available at: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.

Appendix G Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment No. 05 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: An additional SRD cohort (Cohort 22) has been added to the study and the approximate total number of subjects to be enrolled has been increased accordingly.

The primary change occurs in Section 6.1 Study Design:

Initial wording:	SRD cohorts (Cohorts 20 and 21) will explore the safety and tolerability of single doses of TAK-071 (planned 80 and 160 mg, respectively; however, actual doses administered will be determined from emerging data) when coadministered with donepezil (10 mg) in healthy subjects. These cohorts will consist of a randomized, double-blind, placebo-controlled, parallel-group ascending dose design with 12 subjects per cohort. These 2 cohorts will establish a high well-tolerated dose of TAK-071 when coadministered with donepezil for the scopolamine challenge PoM study. … Cohort 16 will include up to 8 subjects (minimum of 6) with MCI or mild AD on stable donepezil treatment. This cohort will be conducted as a placebo-controlled, 2-sequence, 2-period, 2-way crossover design. .... Cohorts 1 to 12, and 16 to 21 will include non-Japanese subjects. Cohorts 13 to 15 will include Japanese subjects. … Subjects in Cohorts 20 and 21 will be assigned in a 1:1:2 ratio to receive treatments (within each cohort of 12 subjects, 3 will receive TAK-071 placebo+donepezil placebo, 3 subjects will receive TAK-071 placebo+donepezil, and 6 subjects will receive TAK-071+donepezil). … The safety and tolerability of donepezil alone will be evaluated during the donepezil dosing phase (before TAK-071 is given in Cohorts 10 to 12) during the 3-week pretreatment period, and the safety and tolerability of donepezil in combination with TAK-071 (Cohorts 20 and 21) will be evaluated by assessing AEs, clinical laboratory results, physical examination findings, ECG findings, bowel function, and vital signs. … Approximately 174 subjects are expected to be randomized in this study.

	…
	Schematic of study design are included as Figure 6.b for Cohorts 1 to 6 and 18 to 21, Figure 6.c for Cohorts 7 and 8, Figure 6.d for Cohorts 9 and 13 to 15, Figure 6.e for Cohorts 10 to 12, Figure 6.f for Cohort 16, and Figure 6.g for Cohort 17. Schedules of Study Procedures are listed in Appendix A
Amended or new wording:	SRD cohorts (Cohorts 20 ~~and 21~~**to 22**) will explore the safety and tolerability of single doses of TAK-071 (~~planned~~ 80~~and 160~~**, 60 and 40** mg, respectively; however, actual doses administered will be determined from emerging data) when coadministered with donepezil (10 mg) in healthy subjects. These cohorts will consist of a randomized, double-blind, placebo-controlled, parallel-group ascending dose design with 12 subjects per cohort. These ~~2~~ cohorts will establish a high well-tolerated dose of TAK-071 when coadministered with donepezil for the scopolamine challenge PoM study. **Higher or lower dose cohort(s) may be added in the SRD part of the study to fully understand safety and tolerability of TAK-071 when coadministered with donepezil.** .... Cohorts 1 to 12 and 16 to ~~21~~**22** will include non-Japanese subjects. Cohorts 13 to 15 will include Japanese subjects. … Subjects in Cohorts 20~~and 21~~ **to 22** will be assigned in a 1:1:2 ratio to receive treatments (within each cohort of 12 subjects, 3 will receive TAK-071 placebo+donepezil placebo, 3 subjects will receive TAK-071 placebo+donepezil, and 6 subjects will receive TAK-071+donepezil). … The safety and tolerability of donepezil alone will be evaluated during the donepezil dosing phase (before TAK-071 is given in Cohorts 10 to 12) during the 3-week pretreatment period, and the safety and tolerability of donepezil in combination with TAK-071 (Cohorts 20~~and 21~~ **to 22**) will be evaluated by assessing AEs, clinical laboratory results, physical examination findings, ECG findings, bowel function, and vital signs. … Approximately ~~174~~**186** subjects are expected to be randomized in this study. … Schematic of study design are included as Figure 6.b for Cohorts 1 to 6 and 18 to ~~21~~**22**, Figure 6.c for Cohorts 7 and 8, Figure 6.d for Cohorts 9 and 13 to 15, Figure 6.e for Cohorts 10 to 12, Figure 6.f for Cohort 16, and Figure 6.g for Cohort 17. Schedules of Study Procedures are listed in Appendix A.

Rationale for Change:

To further evaluate the safety and tolerability of TAK-071 when coadministered with donepezil.

The following sections also contain this change:

- Section 2.0 Study Summary.
- Section 5.2.3 Exploratory/Additional Endpoints.
- Table 6.a Overview of Treatment Cohorts.
- Figure 6.a Flow of Treatment Cohorts.
- Figure 6.b Schematic of Study Design for SRD Cohorts 1 to 6 and 18 to 22.
- Section 6.1.1 SRD Part (Cohorts 1 to 6 and 18 to 22).
- Section 6.2.1 Study Design.
- Section 6.2.2 Dose Selection.
- Section 6.2.3 Endpoints.
- Section 7.1 Inclusion Criteria.
- Section 7.2 Exclusion Criteria.
- Section 7.2.2 Additional Exclusion Criteria for Cohorts 18 to 22.
- Table 7.a Prohibited Medications and Dietary Products.
- Section 7.4 Diet, Fluid, and Activity Control.
- Section 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling.
- Section 8.1.3 Dose and Regimen.
- Section 9.1.6 Vital Sign Procedure.
- Section 9.1.10 Contraception and Pregnancy Avoidance Procedure
- Section 9.1.14 PGx Sample Collection.
- Section 9.1.15 PK Sample Collection.
- Table 9.i Collection of Blood Sample for PK Analysis of Cohorts 20 to 22.
- Section 9.1.17 PD Assessments.
- Table 9.n Collection of [redacted]
- Table 9.o Collection of Safety [redacted]
- Table 9.p Pupillometry Collection.

- Section 9.3.1 Screening.
- Section 9.3.2 Study Randomization.
- Section 9.3.3 Treatment Phase/Washout Phase.
- Section 9.3.4 Final Visit.
- Section 9.3.6 Follow-up Visit/Telephone Call.
- Section 9.5 Blood Volume.
- Table 9.w Approximate Blood Volume for Cohorts 20 to 22.
- Section 10.2.1 Collection and Reporting of AEs.
- Section 13.1.4 PD Analysis.
- Section 13.2 Interim Analysis and Criteria for Early Termination.
- Appendix A Schedule of Study Procedures.

Change 2: Allowing flexibility for enrollment in Cohort 16.

The primary change occurs in Section 6.1.3 Subjects With MCI or Mild AD (Cohort 16):

Initial wording:	Cohort 16 will have a placebo-controlled, randomized, 2-sequence, 2-period, crossover study design to investigate the safety, tolerability, and PK in 1 of the intended target populations for TAK-071 treatment (subjects with MCI or mild AD). Up to 8 subjects (minimum of 6) previously diagnosed with MCI or mild AD and receiving ongoing donepezil (10 mg) therapy will be enrolled in Cohort 16. Subjects will continue with their donepezil therapy during the TAK-071 Treatment Period.
Amended or new wording:	Cohort 16 will include up to 8 subjects (minimum of 6) with MCI or mild AD on stable donepezil treatment **or who consent to a donepezil run-in period of 5 mg dose for 28 days and titrate up to 10 mg for at least 21 days. Subjects with previous MCI/AD diagnosis who have been treated with 5 mg for at least 28 days prior to Screening may consent to a donepezil run-in period of 10 mg for at least 21 days**. This cohort will be conducted as a placebo-controlled, 2-sequence, 2-period, 2-way crossover design.

Rationale for Change:

To facilitate improved enrollment, added flexibility to include subjects who have previous diagnosis, but are on a lower donepezil dose and subjects who are currently diagnosed and are to participate in a donepezil step-up dose run-in period for Cohort 16.

The following sections also contain this change:

- Section 2.0 Study Summary.
- Table 6.a Overview of Treatment Cohorts.
- Figure 6.a Flow of Treatment Cohorts.
- Figure 6.f Schematic of Study Design for Cohort 16
- Section 6.1.3 Subjects With MCI or Mild AD (Cohort 16)
- Section 6.2.2 Dose Selection.
- Section 7.1 Inclusion Criteria.
- Section 7.4 Diet, Fluid, and Activity Control.
- Section 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling.
- Section 9.3.3 Treatment Phase/Washout Phase.
- Appendix A Schedule of Study Procedures.

Change 3: The inclusion criteria and screening period length for Cohort 16 have been revised. An optional run-in period of 49 days was added for Cohort 16.

The primary change occurs in 7.1 Inclusion Criteria:

Initial wording:

3. The subject is a healthy man or woman. Subjects should be aged 18 to 55 years, inclusive (nonelderly at the time of informed consent and first study drug dose) for Cohorts 1 to 12, and 17 to 21; 20 to 55 years, inclusive, for Cohorts 13 to 15; and 60 to 80 years, inclusive, for Cohort 16.

…

6. Cohort 16 only:
   a) Subjects with a documented previous diagnosis of MCI or mild AD.
   b) Mini Mental State Examination (MMSE) score of 20 to 30, inclusive, at Screening and no biomarker data to contradict this diagnosis.

Amended or new wording:

3. The subject is a healthy man or woman. Subjects should be aged 18 to 55 years, inclusive (nonelderly at the time of informed consent and first study drug dose) for Cohorts 1 to 12, and 17 to ~~21~~**22**; 20 to 55 years, inclusive, for Cohorts 13 to 15; and ~~60~~**55** to ~~80~~**90** years, inclusive, for Cohort 16.

…

6. Cohort 16 only:
   a) Subjects with a documented previous diagnosis of MCI or mild AD **or current diagnosis of AD criteria met at Screening Visit.**
   b) Mini Mental State Examination (MMSE) score of ~~20~~**18** to 30, inclusive, at Screening and no biomarker data to contradict this diagnosis.

Rationale for Change:

To improve enrollment, subjects who are diagnosed with MCI or mild at during Screening and enrollment age range are allowed.

The following sections also contain this change:

- Section 2.0 Study Summary.
- Table 6.a Overview of Treatment Cohorts.
- Section 10.0 Pretreatment Events and Adverse Events.
- Appendix A Schedule of Study Procedures.

Change 4: An interim analysis of the SRD and MRD cohort data has been included.

The primary change occurs in 13.2 Interim Analysis and Criteria for Early Termination:

Initial wording: No formal interim analysis of safety and PK data is planned. Section 6.1.5 describes the blinded safety and available PK review that will take place after completion of each cohort and prior to the next dose escalation stage in the study.

Amended or new wording: Section 6.1.5 describes the blinded safety and available PK review that will take place after completion of each cohort and prior to the next dose escalation stage in the study.

13.2.1 Interim Analysis of Cohorts 1 to 15 and 17 to 22 Data

Interim analysis of all data (except Cohort 16) will be completed to enable the planning of phase 2 studies, while Cohort 16 enrollment is ongoing. The interim analysis will be initiated once all SRD and MRD cohorts have completed the study.

The main Takeda study team will be unblinded to the data in order to provide interim results to support phase 2 protocol development.

Rationale for Change:

To provide interim results to support phase 2 protocol development.

The following section also contain this change:

Section 8.5.2 Sponsor PD Unblinding

Change 5: To add no food effect statement for Cohort 16.

The primary change occurs in Section 7.4 Diet, Fluid, and Activity Control:

Amended or new wording:

16.1.1 Cohort 16

Based on the preliminary results from cohort 17, food did not appear to affect the systemic exposure to TAK-071. Therefore, TAK-071 and donepezil can be given with or without food. However on the days of blood draws for clinical laboratory tests, TAK-071 and placebo will be administered with approximately 240 mL of water after a fast of at least 8 hours.

Rationale for Change:

To reflect change in dose administration based on preliminary PK data.

Change 6: The sponsor signatories for this protocol have been updated.

The primary change occurs in Section 1.2 Approval:

Initial wording:

SIGNATURES

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

Amended or new wording:

SIGNATURES

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

PPD

Rationale for Change:

To reflect personnel changes at the sponsor.

Amendment 05 to A Phase 1 Safety, Tolerability, and Pharmacokinetic Study of Escalating Single and Multiple Oral Doses of TAK-071 in Healthy Subjects and Subjects With Mild Cognitive Impairment/Mild Alzheimer Disease and Relative Bioavailability and Food Effect of TAK-071 in Healthy Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	15-May-2017 18:54 UTC
	Clinical Approval	15-May-2017 19:02 UTC
	Clinical Pharmacology Approval	15-May-2017 20:23 UTC