Title: hase 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

SAP Approve Date: 08 August 2017

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TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-071-1001

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

Version**:** Final

Date: 08 August 2017

Prepared by:

PPD

Prepared by:

PPD

1.1 Approval Signatures

Study 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

Takeda Approvals:

PPD _____ Date

PPD _____ Date

PPD _____ Date

PPD _____ Date

PPD _____ Date

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

λ_z	terminal disposition rate constant
%CV	percent coefficient of variation
AD	Alzheimer disease
ADaM	Analysis Data Model
Ae_t	amount of drug excreted in urine from time 0 to time t
AE	adverse event
ANOVA	analysis of variance
AUC	area under the plasma concentration-time curve
AUC_{12}	area under the concentration-time curve from time 0 to time 12 hours
AUC_{24}	area under the concentration-time curve from time 0 to time 24 hours
AUC_{36}	area under the concentration-time curve from time 0 to time 36 hours
AUC_{48}	area under the concentration-time curve from time 0 to time 48 hours
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_t	area under the plasma concentration-time curve from time 0 to time t
AUC_{τ}	area under the plasma concentration-time curve from time 0 to time tau
$AUEC_{12}$	Area under the effect concentration-time curve from time 0 to 12 hours
BA	bioavailability
BMI	body mass index
BSF	Bristol Stool Form
CI	confidence interval
CL_R	renal clearance
CL/F	apparent clearance after extravascular administration
CL/F_{ss}	apparent clearance after extravascular administration at steady-state
C_{max}	maximum observed concentration
CPAP	Clinical Pharmacology Analysis Plan
CSF	cerebrospinal fluid
CSR	clinic study report
DIC	drug-in-capsule
E_{max}	maximum observed effect
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalography
ET	early termination
FE	food effect
$F_{e,t}$	fraction of drug excreted in urine from time 0 to time t
HV	healthy volunteers
jHV	Japanese healthy volunteers
MAV	markedly abnormal value

MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
MRD	multiple-rising dose
N	number of subjects
NA	not applicable
PD	pharmacodynamic
PK	pharmacokinetic
PoM	proof-of-mechanism
PT	preferred term
QD	once daily
qEEG	quantitative electroencephalography
$R_{ac(AUC)}$	accumulation ratio based on AUC_{24}
$R_{ac(Cmax)}$	accumulation ratio based on C_{max}
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	International System of Units
SOC	system organ class
SRD	single-rising dose
$t_{1/2z}$	terminal disposition half-life
TEAE	treatment-emergent adverse event
t_{max}	time to first occurrence of C_{max}
TE_{max}	time from dosing to occurrence of E_{max}, taken directly from the change from Baseline data
V_z/F	volume of distribution during the terminal disposition phase after extravascular administration

4.0 OBJECTIVES

4.1 Primary Objective

The primary objectives of this study are as follows:

- To characterize the safety, tolerability, and plasma pharmacokinetic (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 mild cognitive impairment (MCI) or mild Alzheimer Disease (AD) (non-Japanese) receiving donepezil treatment for a minimum of 3 months.

4.2 Secondary Objective

The secondary objectives of this study are as follows:

- 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 cerebrospinal fluid (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.

4.3 Exploratory Objectives

The exploratory objectives of this study are as follows:

CCI

[redacted]

4.4 Study Design

4.4.1 Overview

This is a first-in-human, 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 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 2 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 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 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 CSF samples for PK analysis will be obtained in Cohort 3 (following a single dose) and Cohort 9 (at steady-state). Pharmacodynamic (PD) CCI .

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 4.a.

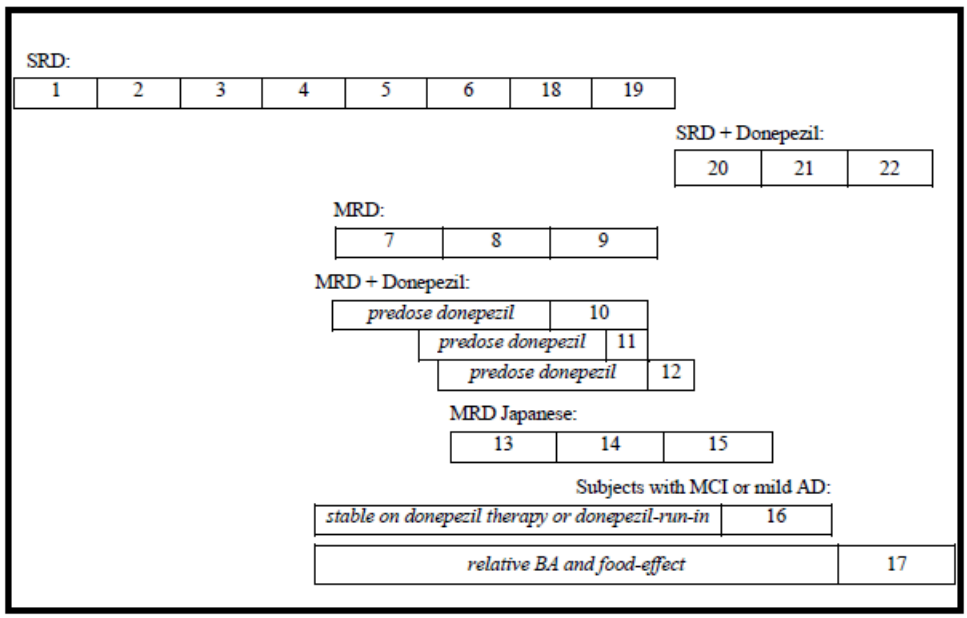
Table 4.a Overview of Treatment Cohorts

Group	Cohort	Age (years)	Type	Regimen	Number of Subjects per Cohort		
					TAK-071	Placebo	Total
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 4.a.

Figure 4.a Flow of Treatment Cohorts



Schematic of the study design are included as Figure 4.b for Cohorts 1 to 6 and 18 to 22, Figure 4.c for Cohorts 7 and 8, Figure 4.d for Cohorts 9 and 13 to 15, Figure 4.e for Cohorts 10 to 12, Figure 4.f for Cohort 16, and Figure 4.g for Cohort 17.

Figure 4.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 4.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 4.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 4.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 4.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 4.g Schematic of 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 terminal disposition phase half-life [$t_{1/2z}$]). 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.

4.4.2 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 time of first occurrence of maximum observed concentration (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].

4.4.3 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.

4.4.3.1 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 maximum observed plasma concentration [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. In addition, CCI [redacted]

4.4.3.2 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 (Day 23) or Early Termination (ET). During outpatient dosing Days -18 to -11, subjects will be contacted by study site by telephone call every day to ensure treatment compliance.

Pupil size will be monitored as a biomarker of cholinomimetic effects at specified pre- and postdose time points following the penultimate dose of donepezil pretreatment and the penultimate dose of TAK-071 plus donepezil combination treatment. CCI [redacted]

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

4.4.3.3 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.

4.4.4 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: 21 days of matching placebo.

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 $t_{1/2z}$).

Pupil size will be monitored as a biomarker of cholinomimetic effects.

4.4.5 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 4.b.

Table 4.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).

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The following safety parameters will be analyzed as primary endpoints:

- Percentage of subjects who have at least 1 treatment-emergent adverse event (TEAE).
- Percentage of subjects who meet the Takeda markedly abnormal value (MAV) criteria at least once postdose for the following:
  - Clinical laboratory parameters.
  - Vital sign measurements.
  - ECG parameters.

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

- t_{max}.
- C_{max} in plasma.
- 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 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 the area under the plasma concentration-time curve (AUC) from time 0 to time tau (AUC_{τ}) ($R_{ac(AUC)}$).
- Accumulation ratio based on plasma 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 (AUC_{12}) (Cohort 3 only [Day 1]).
- Area under the CSF concentration-time curve from time 0 to 36 hours (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 AUC36 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).

5.3 Exploratory/Additional Endpoints

CCI

CCI

6.0 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).

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

This Statistical Analysis Plan (SAP) was developed based on International Conference on Harmonization E3 [1] and E9 [2] Guidelines. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the SAP was developed using the information provided in Protocol TAK-071-1001 Amendment 05, dated 15 May 2017 [3].

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

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

Data collected for subjects during the study period in which they received placebo will be pooled together in all safety summaries for each cohort and will be analyzed as one placebo group.

7.1.1 Missing Data

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

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

7.1.2 Derived Datasets and Variables

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

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

7.1.3 Definition of Study Days and Baseline

For all safety endpoints, Baseline is defined as the last non-missing measurement prior to first dose of study drug for subjects in the SRD Cohorts (Cohorts 1 to 6 and 18 to 22), non-Japanese MRD cohorts (Cohorts 7 to 12) and Japanese MRD cohorts (Cohorts 13 to 15). Baseline is defined as the last non-missing measurement prior to first dose of study drug in the respective treatment period for subjects with MCI or mild AD (Cohort 16) and subjects in relative BA and FE Cohort (Cohort 17).

For all safety endpoints in the SRD Cohorts (Cohorts 1 to 6 and 18 to 22) and non-Japanese MRD cohorts (Cohorts 7 to 12) and Japanese MRD cohorts (Cohorts 13 to 15), study day will be calculated relative to the date of first dose. Study day prior to the first dose of treatment will be calculated as: date of assessment/event – date of treatment; study day on or after the date of first dose of treatment will be calculated as: date of assessment/event – date of treatment + 1. For subjects with MCI or mild AD (Cohort 16) and relative BA and FE cohort (Cohort 17), study day will be calculated relative to the date of first TAK-071 dose in the respective treatment period. Study day prior to the first TAK-071 dose in the respective treatment period will be calculated as: date of assessment/event – date of treatment; study day on or after the first TAK-071 dose in the respective treatment period will be calculated as: date of assessment/event – date of treatment + 1.

7.2 Analysis Sets

Safety Set	The safety analysis set 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.
Pharmacokinetic 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. All subjects with valid PK parameter estimate will be included in the summaries and analyses for that parameter.
Pharmacodynamic 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 PK and PD analysis but will be presented in the subject listings.

7.3 Disposition of Subjects

The primary reason for screen failure will be summarized.

The number and percentage of subjects who complete study drug, prematurely discontinue study drug and study visits will be summarized by the pooled placebo group, each TAK-071 dose

level, TAK-071 overall, and overall total within each part (SRD cohorts, non-Japanese MRD cohorts, Japanese MRD cohorts, Cohort 16, and Cohort 17). In addition, the number and percentage of subjects will be summarized for each reason of discontinuation of study drug and study visits by the pooled placebo group, each TAK-071 dose level, TAK-071 overall, and overall total within each part (SRD cohorts, non-Japanese MRD cohorts, Japanese MRD cohorts) and by treatment sequence and overall total for Cohort 16 and Cohort 17. Subjects' study completion data, including reasons for premature termination, will be listed for each cohort by study part (SRD cohorts, non-Japanese MRD cohorts, Japanese MRD cohort, Cohort 16, and Cohort 17) for all subjects.

The number and percentage of subjects who comprised each analysis set will be summarized by the pooled placebo group, each TAK-071 dose level, TAK-071 overall, and overall total for all subjects in each part of the study and by treatment sequence and overall total for Cohort 16 and Cohort 17.

7.4 Protocol Deviations

The protocol deviations will be provided in a data listing and summarized by the pooled placebo group, each TAK-071 dose level, TAK-071 overall, and overall total within each part (SRD cohorts, non-Japanese MRD cohorts, Japanese MRD cohorts) and by treatment sequence and overall total for Cohort 16 and Cohort 17.

7.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by the pooled placebo group, each TAK-071 dose level, TAK-071 overall, and overall total within each part (SRD cohorts, non-Japanese MRD cohorts, Japanese MRD cohorts) and by treatment sequence and overall total for Cohort 16 and Cohort 17. Summary statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous variables (eg, age, height, weight, and BMI), and the number and percentage of subjects within each category will be presented for categorical variables (eg, gender, race, ethnicity, caffeine consumption, alcohol use, reproductive status, and smoking status).

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

7.6 Medical History and Concurrent Medical Conditions

Medical history obtained includes any significant conditions or diseases that stopped at or prior to signing of informed consent. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent.

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

Medical history and concurrent medical condition verbatim reported terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version to be delineated in the clinical study report (CSR). No summaries for medical history and concurrent medical conditions will be provided. All medical history and concurrent medical conditions will be listed.

7.7 Medication History and Concomitant Medications

Medication history information obtained includes any medication stopped at or within 28 days prior to signing of informed consent. Medications used from signing of informed consent through the end of study will be considered as concomitant medications.

Medication history and concomitant medications will be coded using World Health Organization Drug Dictionary, version to be delineated in the CSR. No summaries for medication history and concomitant medications will be provided. All medication history and concomitant medications data will be listed.

7.8 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in the data listing for all subjects. Summaries of PK and PD data will be provided by placebo (as applicable) and TAK-071 dose level in each part of the study. No other summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

7.9 Efficacy Analysis

Not applicable.

7.10 Pharmacokinetic Analysis

7.10.1 Plasma Pharmacokinetic Concentrations

Collection of Blood Samples for Pharmacokinetic Analysis 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 Cohorts 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

Collection of Blood Samples for Pharmacokinetic Analysis 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

Collection of Blood Samples for Pharmacokinetic Analysis 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.

Collection of Blood Samples for Pharmacokinetic Analysis 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

Collection of Blood Samples for Pharmacokinetic Analysis 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)

Collection of Blood Samples for Pharmacokinetic Analysis 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 of TAK-071

Collection of Blood Samples for Pharmacokinetic Analysis Cohort 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, 72, 96 and 168 hours post TAK-071 dose
Donepezil	Plasma	2	Predose (within 30 minutes before dosing) and 1, 2, 3, 4, 6, 8, 12, 16, 24, 32, 36, 40, 48, 56, 72, and 144 post donepezil dose

The concentration of TAK-071 will be summarized by TAK-071 dose level, treatment, or regimen, as applicable, over each scheduled sampling time using descriptive statistics (including N, arithmetic mean, SD, %CV, median, minimum, maximum, geometric mean and %CV of the geometric mean), separately for the TAK-071 SRD part (TAK-071 alone [Cohort 1 to 6, 18, and 19]) or in presence of donepezil [Cohorts 20 to 22] for non-Japanese subjects), the MRD part (TAK-071 alone for non-Japanese subjects [Cohorts 7 to 9], TAK-071 alone for Japanese subjects [Cohorts 13 to 15], or TAK-071 in the presence of donepezil [Cohorts 10 to 12] for non-Japanese subjects), subjects with MCI or Mild AD (Cohort 16), and the relative BA/FE cohort (Cohort 17).

Similarly, the concentration of donepezil will be summarized separately for the SRD part ([Cohorts 20 to 22] for non-Japanese subjects) and the MRD part ([Cohorts 10 to 12] for non-Japanese subjects). Plasma PK parameters for donepezil will also be listed and summarized for subjects with MCI or Mild AD (Cohort 16).

Individual plasma concentration data versus time will be presented similarly in data listings. Additionally, graphical plots of individual and mean plasma concentration vs time profiles by treatment will be presented.

7.10.2 Plasma Pharmacokinetic Parameters

The PK parameters of plasma TAK-071 will be determined from the concentration-time profiles for all evaluable subjects according to standard noncompartmental analysis methods by Takeda or its designee. 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 using the equation: $AUC_\infty=AUC_{last}+C_{last}/\lambda z$
AUC_{last}	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{24}	Area under the concentration-time curve from time 0 to time 24 hours. $AUC_{24} = AUC_\tau$ at steady-state.
AUC_t	Area under the concentration-time curve from time 0 to time t
C_{max}	Maximum observed concentration.
CL/F	Apparent clearance after extravascular administration, calculated as $=Dose/AUC_\infty$.
CL/F_{ss}	Apparent clearance after extravascular administration at steady-state, calculated as $=Dose/AUC_{24}$.
λ_z	Terminal disposition rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase.
$R_{ac(AUC)}$	Accumulation ratio based on AUC_{24}, calculated as AUC_{24} (steady-state)/ AUC_∞ (Day 1)
$R_{ac(Cmax)}$	Accumulation ratio based on C_{max}, calculated as C_{max} (steady-state)/ C_{max} (Day 1)
$t_{1/2z}$	Terminal disposition half-life, calculated as $\ln(2)/\lambda z$.
t_{max}	Time to 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 using the equation: $(CL/F)/\lambda_z$.

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 calculated if necessary, in accordance with the Clinical Pharmacology Analysis Plan (CPAP).

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}. Additional donepezil plasma PK parameters may be derived and/or reported as appropriate, in accordance with the CPAP.

Plasma PK parameters for TAK-071 will be listed and summarized separately for the TAK-071 SRD part (TAK-071 alone [Cohorts 1 to 6, 18, and 19]) or in presence of donepezil [Cohorts 20

to 22] for non-Japanese subjects), the MRD part (TAK-071 alone for non-Japanese subjects [Cohorts 7 to 9], TAK-071 alone for Japanese subjects [Cohorts 13 to 15], or TAK-071 in the presence of donepezil [Cohorts 10 to 12] for non-Japanese subjects), subjects with MCI or Mild AD (Cohort 16), and the relative BA/FE cohort (Cohort 17).

Plasma PK parameters for donepezil will be listed and summarized separately for the SRD part ([Cohorts 20 to 22] for non-Japanese subjects) and the MRD part ([Cohorts 10 to 12] for non-Japanese subjects). Plasma PK parameters for donepezil will also be listed and summarized for subjects with MCI or Mild AD (Cohort 16).

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

Dose proportionality for the SRD and MRD parts will be assessed (separately) using the empirical power law model [4]. 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 (SRD) and for C_{max} and AUC_{24} at steady-state (Day 21 or 28 for MRD).

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 parts (separately for Japanese and non-Japanese subjects) 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 average time to achieve 90% of the steady-state trough concentrations separately for Japanese and non-Japanese subjects. Should data be insufficient to perform the nonlinear model, a linear mixed model approach will be used.

Time dependency will be investigated in MRD parts (separately for Japanese [Cohorts 7 to 9] and non-Japanese [Cohorts 13 to 15] subjects). The time invariance of TAK-071 will be assessed by comparing AUC_{24} for the last day of dosing (Day 21 for Cohorts 7 and 8 and Day 28 for Cohorts 9 and 13 to 15) to the AUC_{∞} for Day 1 using analysis of variance with a random effect for subject and dose level, day, and interaction of dose level by day as fixed effects. If AUC_{∞} cannot be robustly estimated in a sufficient number of subjects, then the AUC_{last} will be used instead in statistical analyses. This analysis will also be performed similarly using TAK-071 C_{max}.

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

$$yijk=\mu + \tau j + si + \varepsilon ij \ (i=1, \ldots N; j=A, B),$$

where μ is a general mean of a logarithmically transformed primary variable, si is the random effect of subject i, τj is the fixed effect of treatment (TAK-071 plus donepezil vs donepezil alone) j, εij is the random error of the observation yij, 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.

In addition, the ratio of geometric mean AUC_{24} and C_{max} for donepezil after 21 daily doses of TAK-071 (Day 28) in reference to donepezil after a single dose at steady-state (Day -1) and the associated 90% CIs will be estimated.

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.

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

7.10.3 Urine Pharmacokinetic Concentrations

Collection of Urine Samples for Pharmacokinetic Analysis 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

Collection of Urine Samples for Pharmacokinetic Analysis 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.

Collection of Urine Samples for Pharmacokinetic Analysis 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.

Collection of Urine Samples for Pharmacokinetic Analysis 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 Day 21 and 61.

Urine samples will not be collected from Cohorts 10 to 12, 17, 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).

The amount of TAK-071 in urine will be summarized by TAK-071 dose level over each scheduled collection interval using descriptive statistics (N, arithmetic mean, SD, median, minimum, and maximum), separately for the TAK-071 SRD part ([Cohort 1 to 6, 18, and 19]) for non-Japanese subjects), the MRD part (TAK-071 alone for non-Japanese subjects [Cohorts 7 to 9] and for Japanese subjects [Cohorts 13 to 15]), and subjects with MCI or Mild AD (Cohort 16). Individual urine concentration and amount data versus time interval along with urine volume will be presented in a data listing.

7.10.4 Urine Pharmacokinetic Parameters

The urine PK parameters of TAK-071 will be determined from the concentration-time profiles for all evaluable subjects by Takeda or its designee. Scheduled sampling times will be used in all computations involving urine collection times.

The following urine PK parameters of TAK-071 will be estimated:

Symbol/Term	Definition
Ae_t	Amount of drug excreted in urine from time 0 to time t for each interval and cumulative
$f_{e,t}$	Fraction of administered dose of drug excreted in urine from time 0 to time t for each interval and cumulative
CL_R	Renal clearance, calculated as Ae_t/AUC_t for Day 1and Ae_t/AUC_{24} at steady-state

Additional urine PK parameters may be derived and/or reported as appropriate, in accordance with the CPAP.

Descriptive statistics (including N, arithmetic mean, SD, CV%, median, minimum and maximum) will be used to summarize the urine PK parameters for TAK-071 by TAK-071 dose level, separately for the TAK-071 SRD part ([Cohort 1 to 6, 18, and 19]) for non-Japanese subjects), the MRD part (TAK-071 alone for non-Japanese subjects [Cohorts 7 to 9] and for Japanese subjects [Cohorts 13 to 15]), and subjects with MCI or Mild AD (Cohort 16). Individual urine PK parameters will be presented in a data listing. Plots of individual and mean cumulative amounts excreted in urine vs time profiles will be produced.

7.10.5 CSF Pharmacokinetic Concentrations

Collection of CSF Samples for Pharmacokinetic Analysis Cohorts 3 and 9.

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-071	CSF	1	Cohort 3: Predose (within 30 minutes before dosing) and at 0.5, 2, 4, 6, and 12 hours postdose
		28	Cohort 9: Predose (within 30 minutes before dosing) and at 4, 8, 12, 24 and 36 hours post last dose

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.

The concentration of TAK-071 in CSF will be summarized by TAK-071 dose level over each scheduled sampling time using descriptive statistics (including N, arithmetic mean, SD, %CV, median, minimum, maximum, geometric mean and %CV of the geometric mean). Individual plasma concentration data versus time will be presented in a data listing. Additionally, graphical plots of individual and mean CSF concentration vs time profiles by treatment will be presented.

7.10.6 CSF Pharmacokinetic Parameters

The CSF PK parameters of TAK-071 will be determined from the CSF concentration-time profiles for all evaluable subjects according to standard noncompartmental analysis methods by Takeda or its designee. 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) (Cohort 3 only) and CSF AUC_{36} at steady-state (after final dose following multiple dosing) (Cohort 9 only), 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 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.

Additional CSF PK parameters may be derived and/or reported as appropriate, in accordance with the CPAP.

CSF PK parameters for TAK-071 will be listed and summarized using descriptive statistics (including N, arithmetic mean, SD, %CV, median, minimum, maximum, geometric mean and %CV of the geometric mean). Geometric mean and geometric %CV will be presented for AUC and C_{max} only.

7.10.7 Pharmacodynamic Measurements

CCI [redacted].

7.11 Other Outcomes

Not applicable.

7.12 Safety Analysis

Within each part (SRD cohorts, MRD cohorts, Cohort 16, and Cohort 17), for the non-Japanese and Japanese SRD and MRD cohorts separately, all safety summary tables will be presented by the pooled placebo group, each TAK-071 dose level, TAK-071 overall, and overall total within each part (SRD cohorts, non-Japanese MRD cohorts, Japanese MRD cohorts, Cohort 16, and Cohort 17) in the Safety Set. Safety data collected after administration of study drug under fed conditions will be summarized separately from data collected during administration of the same dose level under fasted conditions.

7.12.1 Adverse Events

A PTE will be 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 or placebo) administration or increase in dose/start of donepezil prior to TAK-071 dose. A TEAE will be defined as an AE or a serious AE (SAE) that occurs or gets worse after receiving the first dose of study drug and within 30 days (onset date – last date of dose + 1 $\leq$30) after the last dose of study drug. A TEAE may also be a pretreatment AE or a concurrent medical condition diagnosed prior to the date of first dose of study drug that increases in severity after the start of dosing. AE data with onset occurring more than 30 days after last dose of study drug (AE start date – last dose date >30) will be listed, but not included in the summary tables.

AE verbatim reported terms will be coded by system organ class, high-level term and preferred term using MedDRA, version to be delineated in the CSR.

TEAE summary tables will include numbers and percentages of subjects experiencing at least one AE by system organ class (SOC) and preferred term (PT) and will be tabulated for SRD

cohorts, non-Japanese MRD cohorts, Japanese MRD cohorts, Cohort 16, and Cohort 17. TEAEs will be summarized according to the treatment most recently received prior to the onset of the event. The TEAE summaries for SRD cohorts, non-Japanese MRD cohorts, Japanese MRD cohorts will also include a treatment group for TAK-071 overall, including all TEAEs summarized for any dose level of TAK-071.

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

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

A subject with 2 or more different AEs within the same level of the MedDRA term and TAK-071 dose level and pooled placebo will be counted only once in that level using the most extreme incident for the intensity tables, and related events to study drug for the causality tables.

Most frequent TEAEs are defined as the AEs occurring in at least 2 subjects in any treatment (ie, pooled placebo or individual dose level).

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

7.12.2 Clinical Laboratory Evaluations

For SRD Cohorts 1 to 6 and 18 to 22, blood samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected at Screening, at Check-in (Day -1), on Days 1 through 5 (Final Visit)/ ET, Day 8, and at the Follow-up Visit. On Day 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, samples will be taken upon rising in the morning under fasted condition. Laboratory sample collection on Day 8 does not require fasting conditions.

For MRD healthy volunteer Cohorts 7 and 8, blood samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected at Screening, at

Check-in (Day -1), on Days 1, 2, 5, 8, 14, 20, 21, 22, 23 (Final Visit)/ ET and at the Follow-up Visit. 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, samples will be taken predose upon rising in the morning under fasted condition.

For MRD healthy volunteer Cohort 9, blood samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected at Screening, at Check-in (Day -1), on Days 1, 2, 3, 8, 9 10, 15, 20, 27, 28, 29, 30 (Final Visit)/ ET and at the Follow-up Visit. 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, samples will be taken predose upon rising in the morning under fasted condition.

For MRD + Donepezil pretreatment healthy volunteer Cohorts 10 to 12, blood samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected at Screening, at Check-in (Day -22), on Days -21, -10, -1, 1, 2, 5, 8, 11, 14, 20, 21, 23 (Final Visit)/ ET and at the Follow-up Visit. 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, samples will be taken predose upon rising in the morning under fasted condition.

For MRD Japanese healthy volunteer Cohorts 13 to 15, blood samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected at Screening, at Check-in (Day -1), on Days 1, 2, 3, 8, 9, 10, 15, 20, 27, 28, 29, 30 (Final Visit)/ ET and at the Follow-up Visit. 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, samples will be taken predose upon rising in the morning under fasted condition.

For Cohort 16 in subjects with MCI or Mild AD, blood samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected at Screening, at Run-in Period (Day -21), at Check-in (Day -1), on Days 1, 2, 11, 20, 21, 22, 41, 42, 43, 52, 61, 62, 63 (Final Visit)/ ET and at the Follow-up Visit. On Days 1 and 41, 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 all other days, samples will be taken predose upon rising in the morning under fasted condition.

For BA/FE Cohort 17, blood samples for clinical laboratory tests (hematology, coagulation, serum chemistry, urinalysis) will be collected at Screening and in each period at Check-in (Day -1), 30 minutes postdose on Day 1, upon rising on Days 2 and 5 and, at PK visit on Day 8 (Day 8 of Period 3 is the final visit), at ET, if occurs, and Follow-up Visit (Day 12 [±2]) of Period 3, as appropriate.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of clinical safety laboratory variables will be summarized by the pooled placebo group, each TAK-071 dose level, TAK-071 overall, and overall total within each part (SRD cohorts, MRD cohorts, Cohort 16, and Cohort 17) for baseline, each postdose time point, and change from period baseline to postdose

time points in International System of Units (SI). Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

Individual results for hematology, chemistry, and coagulation laboratory tests will be evaluated against the Takeda predefined laboratory MAV criteria (Appendix A) using the result and criteria in SI units. All subjects with results that meet the MAV criteria will be presented in a data listing. The number and percentage of subjects with at least one postdose markedly abnormal laboratory test result will be summarized. The mapping of the subjects who meet the MAV criteria for postdose lab results will be listed as a table. All postdose clinical lab results, including scheduled and unscheduled measurements will be included in the MAV summaries.

All clinical laboratory data will be presented in both SI and conventional units in data listings.

7.12.3 Vital Signs

In subjects who are not undergoing CSF collection (Cohorts 2, 4 to 8, and 10 to 18), vital signs will include body temperature (oral), respiratory rate, and orthostatic blood pressure and pulse (bpm). For orthostatic blood pressure, a drop in systolic blood pressure of ≥20 mm Hg, or in diastolic blood pressure of ≥10 mm Hg, or experiencing lightheadedness or dizziness is considered abnormal.

In subjects who have completed enrollment for Cohort 1 at the time of the protocol amendment 03 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).

For SRD Cohorts 1 to 6 and 18 to 22, vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, at Check-in (Day -1), on Days 1 through 5 (Final Visit)/ ET and at the Follow-up Visit. 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.

For MRD healthy volunteer Cohorts 7 and 8, vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, at Check-in (Day -1), on Days 1 through 23 (Final Visit)/ ET and at the Follow-up Visit. 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.

For MRD healthy volunteer Cohort 9, vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, at Check-in (Day -1), on Days 1 through 30 (Final Visit)/ ET and at the Follow-up Visit.

For MRD + Donepezil pretreatment healthy volunteer Cohorts 10 to 12, vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, at Check-in (Day -22), on Days -21 through -19, Days -10 through -1, Days 1 through 23 (Final Visit)/ ET and at the Follow-up Visit. 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.

For MRD Japanese healthy volunteer Cohorts 13 to 15, vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, at Check-in (Day -1), on Days 1 through 30 (Final Visit)/ ET and at the Follow-up Visit. 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.

For Cohort 16 in subjects with MCI or Mild AD, vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, at Run-in Period (Day -49 and Day -21), at Check-in (Day -1), on Days 1, 2, 11, 20, 21, 22, 41, 42, 43, 52, 61, 62, and 63 (Final Visit)/ ET and at the Follow-up Visit. 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, 40 to 42, 51, and 60 to 62 (upon morning rising)/ ET.

For BA/FE Cohort 17, vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening and in each period at Check-in (Day -1), Day 1 (predose [within 45 minutes prior to dosing], and at 1, 3, and 12 hours postdose), and Days 2 through 5 (upon rising), Day 8 PK visit, Study Exit ([Day 8 of Period 3]/ ET and Follow-up Visit (Day 12 [±2]) of Period 3, as appropriate.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of these vital signs will be summarized by the pooled placebo group, each TAK-071 dose level, TAK-071 overall, and overall total within each part (SRD cohorts, MRD cohorts, Cohort 16, and Cohort 17) for baseline, each postdose time point, and change from period baseline to postdose time points. Only the vital signs collected at the scheduled visits or time points will be included in the summary. No statistical tests will be performed for the observed vital signs.

All individual vital signs that meet Takeda's predefined criteria for markedly abnormal values (Appendix B) will be listed. The number and percentage of subjects with at least one postdose markedly abnormal vital sign measurement will be summarized. The mapping of the subjects who meet the MAV criteria for postdose vital sign parameters will be listed as a table. All postdose vital signs, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

7.12.4 12-Lead ECGs

For SRD Cohorts 1 to 6 and 18 to 22, 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), Days 2 through 5 (upon morning rising)/ ET and at the Follow-up Visit. Single ECGs will be taken at all visits. 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.

For MRD healthy volunteer Cohorts 7 and 8, 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)/ ET and at the Follow-up Visit. Single ECGs will be taken at all visits. 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.

For MRD healthy volunteer Cohort 9, 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/ ET, and at the Follow-up Visit. Single ECGs will be taken at all visits. 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.

For MRD + Donepezil pretreatment healthy volunteer Cohorts 10 to 12, 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)/ ET and at the Follow-up Visit. Single ECGs will be taken at all visits.

For MRD Japanese healthy volunteer Cohorts 13 to 15, 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)/ ET and at the Follow-up Visit. Single ECGs will be taken at all visits.

For Cohort 16 in subjects with MCI or Mild AD, a standard 12-lead ECG will be recorded at Screening, Check-in (Day -1), Days 1, 21, 41, and 61 (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, 40 to 42, 51, and 60 to 62 (upon morning rising)/ ET and at the Follow-up Visit. Single ECGs will be taken at all visits.

For BA/FE Cohort 17, a standard 12-lead ECG 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)/ ET, and Follow-up Visit Day 12 (±2), as appropriate.

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 NCS, or abnormal and CS. The following parameters will be recorded from the subject's ECG trace: heart rate, RR interval, PR interval, QRS interval, and QTcF (QT interval with Fridericia correction method) and QTcB (QT interval with Bazett correction method) interval.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of the quantitative ECG results will be presented. The changes of ECG results from baseline results will be summarized by the pooled placebo group, each TAK-071 dose level, TAK-071 overall, and overall total within each part (SRD cohorts, MRD cohorts, Cohort 16, and Cohort 17).

All individual ECGs that meet Takeda's predefined criteria for MAV (Appendix C) will be listed. The number and percentage of subjects with at least one postdose markedly abnormal ECG measurement will be summarized. Subjects who meet the MAV criteria for postdose ECG will be mapped to their respective qualifying ECG result. All postdose MAV ECGs, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

For ECG interpretation data, shift tables will be provided by visit for the number of subjects with each interpretation by the interpretation at baseline.

All other ECG data will be presented in data listings.

Dates and times for the start and stop of continuous 12-lead Holter ECG monitoring will be presented in a data listing. The Holter ECG recordings will be stored, and no data will be extracted for summary and analysis during the conduct of this study.

7.12.5 Other Observations Related to Safety

7.12.5.1 Physical Examination

For SRD Cohorts 1 to 6 and 18 to 22, physical examinations will be performed at Screening, at Check-in (Day -1), Day 5 (Final Visit)/ ET and at the Follow-up Visit.

For MRD healthy volunteer Cohorts 7 and 8, physical examinations will be performed at Screening, at Check-in (Day -1), Day 23 (Final Visit)/ ET and at the Follow-up Visit.

For MRD healthy volunteer Cohort 9, physical examinations will be performed at Screening, at Check-in (Day -1), Day 30 (Final Visit)/ ET and at the Follow-up Visit.

For MRD + Donepezil pretreatment healthy volunteer Cohorts 10 to 12, physical examinations will be performed at Screening, at Check-in (Day -22), Day 23 (Final Visit)/ ET and at the Follow-up Visit.

For MRD Japanese healthy volunteer Cohorts 13 to 15, physical examinations will be performed at Screening, at Check-in (Day -1), Day 30 (Final Visit)/ ET and at the Follow-up Visit.

For Cohort 16 in subjects with MCI or Mild AD, physical examinations will be performed at Screening, at Check-in (Day -1), Day 63 (Final Visit)/ ET and at the Follow-up Visit.

For BA/FE Cohort 17, physical examinations will be performed at Screening, at Check-in (Day -1), and at the Follow-up Visit.

A full physical examination will be conducted at Screening. All other physical examinations will be abbreviated/event driven. A Baseline ophthalmological assessment of the retina (fundoscopy) will be performed at Screening for subjects enrolled in cohorts for CSF sampling.

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

The fundoscopy examination results will be presented in a data listing. No summary tables will be provided.

7.12.5.2 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 96 hours after the last dose), 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; 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?"

For SRD Cohorts 1 to 6 and 18 to 22, at Screening, BSF scale will be obtained at Screening, at Check-in (Day -1), on Days 1 through 5 (Final Visit)/ ET.

For MRD healthy volunteer Cohorts 7 and 8, BSF scale will be obtained at Screening, at Check-in (Day -1), on Days 1 through 23 (Final Visit)/ ET.

For MRD healthy volunteer Cohort 9, BSF scale will be obtained at Screening, at Check-in (Day -1), on Days 1 through 30 (Final Visit)/ ET.

For MRD + Donepezil pretreatment healthy volunteer Cohorts 10 to 12, BSF scale will be obtained at Screening, at Check-in (Day -22), on Days -21 through -1, Days 1 through 23 (Final Visit)/ ET.

For MRD Japanese healthy volunteer Cohorts 13 to 15, BSF scale will be obtained at Screening, at Check-in (Day -1), on Days 1 through 30 (Final Visit)/ ET.

For Cohort 16 in subjects with MCI or Mild AD, BSF scale will be obtained at Screening, at Run-in Period (Day -49 and Day -21), at Check-in (Day -1), on Days 1 through 63 (Final Visit)/ ET.

Descriptive statistics by visit will be presented for the percentage of subjects with BSF scale scores ≥6 vs <6 postbaseline 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. Mean change from Baseline in BSF score and stool frequency will also be presented. Summary statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous variables (eg, time to first stool after dosing and stool frequency), and the number and percentage of subjects within each category will be presented for categorical variables (eg, stool consistency).

The results will be summarized by the pooled placebo group, each TAK-071 dose level, TAK-071 overall, and overall total within each part (SRD cohorts, MRD cohorts, and Cohort 16).

A plot of mean (±SD) bowel movement by study day by treatment will be presented.

All BSF data will be presented in a data listing.

7.12.5.3 Columbia - Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an instrument designed to systematically assess and track suicidal behavior and suicidal ideation throughout the trial. The C-SSRS has 4 domains, Suicidal Ideation, Ideation Intensity, Suicidal Behavior and Actual Suicide Attempts.

For SRD Cohorts 1 to 6 and 18 to 22, the C-SSRS will be performed at Screening, at Check-in (Day -1), Day 5 (Final Visit)/ ET. If clinically significant at Final Visit, C-SSRS will also be determined as part of the Follow-up Visit.

For MRD healthy volunteer Cohorts 7 and 8, the C-SSRS will be performed at Screening, at Check-in (Day -1), Day 23 (Final Visit)/ ET. If clinically significant at Final Visit, C-SSRS will also be determined as part of the Follow-up Visit.

For MRD healthy volunteer Cohort 9, the C-SSRS will be performed at Screening, at Check-in (Day -1), Day 30 (Final Visit)/ ET. If clinically significant at Final Visit, C-SSRS will also be determined as part of the Follow-up Visit.

For MRD + Donepezil pretreatment healthy volunteer Cohorts 10 to 12, the C-SSRS will be performed at Screening, at Check-in (Day -22), Day -1, Day 23 (Final Visit)/ ET. If clinically significant at Final Visit, C-SSRS will also be determined as part of the Follow-up Visit.

For MRD Japanese healthy volunteer Cohorts 13 to 15, the C-SSRS will be performed at Screening, at Check-in (Day -1), Day 30 (Final Visit)/ ET. If clinically significant at Final Visit, C-SSRS will also be determined as part of the Follow-up Visit.

For Cohort 16 in subjects with MCI or Mild AD, the C-SSRS will be performed at Screening, at Check-in (Day -1), Day 63 (Final Visit)/ ET. If clinically significant at Final Visit, C-SSRS will also be determined as part of the Follow-up Visit.

For BA/FE Cohort 17, 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)/ ET, and Follow-up Visit [Period 3 Day 12 (±2)] (as appropriate, if clinically significant at Study Exit).

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

7.12.5.4 Mini Mental State Examination

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. The MMSE will be administered at Screening to subjects in Cohort 16 only by trained site personnel.

The MMSE results will be presented in data listings. No summary tables will be provided.

7.12.5.5 Lumbar X-Ray

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

A lumbar x-ray will be performed at Screening in Cohort 3 and Cohort 9 subjects.

Lumbar x-ray data will be presented in data listings. No summary tables will be provided.

7.13 Interim Analysis

7.13.1 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.

7.13.2 Interim Analysis of PD Data

CCI

[redacted]

7.14 Changes in the Statistical Analysis Plan

Only Cohorts 1 to15 and 17 to 22 will be unblinded after the clinical database freezes. Cohort 16 will remain blinded and be analyzed later.

8.0 REFERENCES

1. Guideline on Structure and Content of Clinical Study Reports, International Conference on Harmonisation, Section ICH E3, 1996.
2. Guideline on Statistical Principles for Clinical Trials, International Conference on Harmonisation, Section ICH E9, 1998.
3. Protocol Amendment 5: 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. 15 MAY 2017.
4. Gough K, Hutchison M, Keene O, Byrom B, Ellis S, Lacey L, et al. Assessment of dose proportionality: report from the statisticians in the pharmaceutical industry/pharmacokinetics UK joint working party. Drug Inform J 1995; 29: 1039-48.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

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

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

Coagulation—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Prothrombin time/international normalized ratio	Both		>1.5 × ULN
Activated partial thromboplastin time	Both		>1.5 × ULN

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

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3 × ULN
AST	Both	--	>3 × ULN
GGT	Both	--	>3 × ULN
Alkaline phosphatase	Both	--	>3 × ULN
Chloride	Conventional	<75 mEq/L	>126 mEq/L
	SI	<75 mmol/L	>126 mmol/L
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 μmol/L
Direct bilirubin	Both	--	>2 ULN
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8 × LLN	>1.2 × ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI	--	>177 μmol/L
Blood urea nitrogen	Conventional	--	>30 mg/dL
	SI	--	>10.7 mmol/L
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>6.0 mEq/L
	SI	<3.0 mmol/L	>6.0 mmol/L
Glucose	Conventional	<50 mg/dL	>350 mg/dL
	SI	<2.8 mmol/L	>19.4 mmol/L
Bicarbonate	Conventional	<8.0 mEq/L	
	SI	<8.0 mmol/L	
Creatine kinase	Conventional	--	>5 × ULN
	SI	--	>5 × ULN
Calcium	Conventional	<7.0 mg/dL	>11.5 mg/dL
	SI	<1.75 mmol/L	>2.88 mmol/L

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

Appendix B Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	°C	<35.6	>37.7
Orthostatic systolic blood pressure	mm Hg	CHG <= -20	
Orthostatic diastolic blood pressure	mm Hg	CHG <= -10	
Orthostatic pulse	bpm		CHG >10

Appendix C Criteria for Markedly Abnormal Values for Electrocardiograms

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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	10-Aug-2017 14:33 UTC
	Clinical VP Approval	10-Aug-2017 16:27 UTC
	Biostatistics Approval	10-Aug-2017 16:37 UTC
	Safety Approval	10-Aug-2017 17:02 UTC
	Clinical Pharmacology Approval	10-Aug-2017 17:15 UTC