Statistical Analysis Plan

NCT Number: NCT04334317

Title: A Randomized, Double-blind, Placebo-Controlled, 2-Period Crossover, Phase 2 Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Oral TAK-071 in Parkinson Disease Patients with Cognitive Impairment and an Elevated Risk of Falls

Study Number: TAK-071-2002

Document Version and Date: Final, 03 March 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-071-2002

A Randomized, Double-blind, Placebo-Controlled, 2-Period Crossover, Phase 2 Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Oral TAK-071 in Parkinson Disease Patients with Cognitive Impairment and an Elevated Risk of Falls

TAK-071 for Falls and Cognition in Parkinson Disease

PHASE 2

Version: Final

Date: 3 March 2023

Prepared by:

[redacted], Ph.D.
[redacted], Statistics, TAKEDA

Based on:

Protocol Version: Amendment 04

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AUC	area under the concentration-time curve
AUC24	area under the concentration-time curve from time 0 to 24 hours
AUCinf	area under the concentration-time curve from time 0 to infinity
AUClast	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUCτ	area under the concentration-time curve during a dosing interval
BMI	body mass index
BP	blood pressure
CGI-I	Clinician Global Impression of Improvement
CGI-S	Clinician Global Impression of Severity
CI	confidence interval
Cmax	maximum observed plasma concentration
COVID-19	coronavirus disease 2019
CRF	case report form
C-SSRS	Columbia - Suicide Severity Rating Scale
Ctrough	trough plasma concentration at steady state (observed concentration at the end of a dosing interval)
CYP	cytochrome P-450
DAMP	Data Access Management Plan
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
HR	Heart rate
IA	interim analysis
LLN	lower limit of normal
LLOQ	lower limit of quantification
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
PD	Parkinson's Disease
PGI-I	Patient Global Impression of Improvement
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
SBP	Systolic blood pressure
TEAE	treatment-emergent adverse event
t1/2 z	terminal disposition phase half-life
tmax	time to reach Cmax
ULN	upper limit of normal

4.0 OBJECTIVES

4.1 Sentinel Cohort (Healthy subjects)

4.1.1 Primary Objectives

The primary objective for healthy subjects is to evaluate the pharmacokinetics (PK) of TAK-071 in healthy subjects older than 55 years.

4.1.2 Secondary Objectives

The secondary objective for healthy subjects is to evaluate the safety and tolerability of TAK-071 in healthy subjects older than 55 years.

4.2 Main Cohort (Parkinson's Disease (PD) patients)

4.2.1 Primary Objectives

The primary objectives are:

- To evaluate the efficacy of TAK-071 versus placebo on gait dysfunction, as measured by stride time variability during a 2-minute walk test, with and without cognitive loading.
- To evaluate the safety and tolerability of TAK-071 in subjects with PD.

4.2.2 Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of TAK-071 versus placebo on cognition globally, as determined by a global cognition score including attention, executive functioning, and memory.
- To evaluate the PK of TAK-071 in subjects with PD.

4.2.3 Additional/Exploratory Objectives

The exploratory/additional objectives are:

- To evaluate the efficacy of TAK-071 versus placebo on
  - specific cognitive test scores that measure domains including attention, executive functioning, and memory;
  - fall frequency as assessed using a caregiver–reported falls diary;
  - functional mobility, as measured by time to complete the Timed Up and Go test (TUG);
  - parameters measuring postural sway with eyes open or closed;
  - gait parameters during a 2-minute, 10m walk test in the presence and absence of cognitive loading

- gait parameters during a cued 180-degree turns test;
- speech production measured via in-clinic and at-home;
- step-count as measured by a wearable pendant sensor in the home;
- fall frequency as assessed using a wearable pendant sensor in the home;
- subjective daytime sleepiness as assessed by the Epworth Sleepiness Scale (ESS);
- global improvement, as measured by the Clinical Global Impression-Improvement (CGI-I), Clinical Global Impression-Severity (CGI-S), Patient Global Impression-Improvement (PGI-I), and Patient Global Impression-Severity (PGI-S);
- motor functioning, as measured by MDS-UPDRS Part 3 and on other aspects of PD by MDS-UPDRS Parts 1, 2, and 4.

- To evaluate the relationship between specific blood-based biomarkers including neuronally derived exosomal M1 receptor and synaptic marker messenger ribonucleic acid (mRNA) expression with clinical scales of cognition, gait, balance, and MDS-UPDRS subscales as well as treatment response.
- To evaluate genomic predictors of treatment response and adverse effects to TAK-071.
- To evaluate the ratio of plasma 4-beta-hydroxycholesterol to cholesterol and the relationship to plasma TAK-071 area under the concentration-time curve (AUC).

4.3 Study Design

4.3.1 Sentinel Cohort (Healthy Subjects)

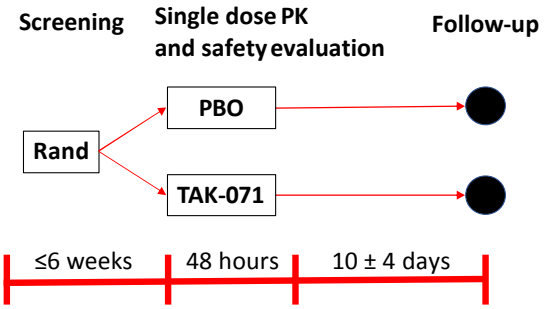
An initial sentinel cohort of up to approximately 10 healthy subjects of either sex, aged 56 to 75 years, inclusive, will be enrolled at designated site(s), in parallel with enrollment of PD patients in the main cohort. Healthy subjects will be randomized 3:1 to TAK-071 versus placebo. After analysis of data from these subjects, additional subjects may be enrolled, potentially including subjects over age 75. Enrollment of the sentinel cohort will conclude when sufficient data are available to characterize the PK in older subjects, as determined by the sponsor.

Healthy subjects will be selected on the basis of safety considerations. Of particular importance is exclusion on the basis of seizure risk factors, medical disease, and hepatic or renal impairment that may influence the PK of TAK-071.

Assessments for healthy subjects will be limited to safety, tolerability, rich PK sampling, and samples for DNA (optional) and biomarkers.

After the PK, safety, and physiologically based PK modeling data from the sentinel cohort have been assessed, a decision will be made about the dose for the remaining subjects with PD to be enrolled. If older subjects are expected to remain below the exposure caps, they will also be enrolled. The maximum subject age and dose may be modified after analysis of data from the sentinel cohort (≤7.5 or ≤5 mg QD, potentially depending on age). Figure 4.a shows a schematic of the sentinel cohort (healthy subjects).

Figure 4.a Schematic of Study Design for Subjects in the Sentinel Cohort (Healthy Subjects)



4.3.2 Main Cohort (PD Subjects)

This is a phase 2, randomized, double-blind, placebo-controlled, 2-period, 2-treatment crossover study to evaluate the efficacy, safety, tolerability, PK, and pharmacodynamics of TAK-071 when administered orally QD in subjects with PD and evidence of cognitive impairment who are at risk for falls.

Approximately 64 male and female subjects, aged 40 to ≤65 years (with potential to expand to older subjects after analysis of data from the sentinel cohort), inclusive, will be enrolled at up to 25 sites in the United States.

The study will consist of a ≤6-week screening period, two 6-week double-blind treatment periods separated by a ≥3-week washout period, at-home assessments during the third week of each 6-week treatment period, and a safety follow-up call approximately 14 days after the last dose of study drug.

At the screening visit (Visit 1), subjects who provide informed consent will proceed with screening procedures. Subjects who meet a current diagnosis of PD, as defined by Movement Disorders Society (MDS) clinical diagnostic criteria for PD, will then be given additional assessments as specified in the schedule of study procedures (Appendix A of the study protocol).

On Day 1, subjects who continue to meet inclusion and none of the exclusion criteria will be randomized 1:1 to treatment with TAK-071 or placebo.

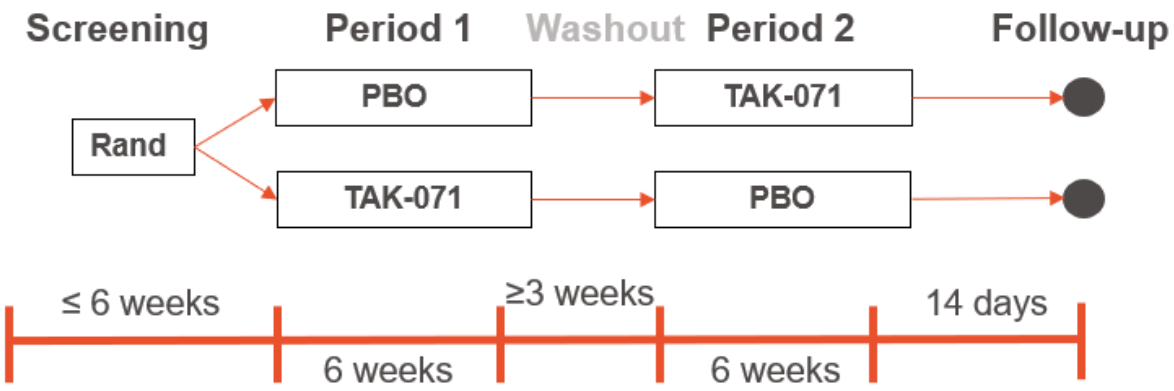
Subjects will receive TAK-071 or placebo QD from Day 1 through Day 42 of each period. Clinic visits include Day 1 and Weeks 6, 9, and 15. Clinical assessments, blood collections, and laboratory tests will be conducted at specific time points per the schedule of study procedures (Appendix A).

A safety follow-up call will be conducted on Day 21, Day 84, and 14 days after completion of the last period.

The end of the study will be the date of the last visit of the last subject for safety follow-up, i.e., the safety follow-up call.

A schematic of the study design is included as Figure 4.b. A detailed schedule of study procedures is provided in Appendix A of the study protocol.

Figure 4.b Schematic of Study Design (Main Cohort)



PBO: placebo; Rand: randomization.

5.0 ANALYSIS ENDPOINTS

5.1 Sentinel Cohort

5.1.1 Primary Endpoints

The primary endpoints for healthy subjects are the following PK parameters for TAK-071:

- C_{max}.
- t_{max}.
- AUC_{24}.
- AUC_{last}.
- AUC_{inf}.

5.1.2 Secondary Endpoints

The safety endpoints for healthy subjects are:

- AEs.
- Clinical laboratory evaluations.
- Electrocardiograms (ECGs).
- Physical examinations.

- Suicidal ideation and behavior as measured by the C-SSRS.

5.2 Main Cohort

5.2.1 Primary Endpoints

The primary efficacy endpoint for subjects with PD is the average of left and right foot stride time variability (SD) during a 2-minute walk on a 10-meter walkway, either with or without cognitive load, after 6-week treatment with either placebo or TAK-071.

The safety endpoints for subjects with PD are:

- AEs.
- Clinical laboratory evaluations.
- Electrocardiograms (ECGs).
- Physical examinations.
- Suicidal ideation and behavior as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS).

5.2.2 Secondary Endpoints

The secondary efficacy endpoint for subjects with PD is the change from baseline in a global cognition score consisting of attention (SAT, Symbol Digit Modalities Test [SDMT]), executive function (Cogstate Groton Maze Learning Test, Cogstate One Back Test), and episodic memory (Cogstate International Shopping List Test (Immediate recall and delayed recall), Cogstate One Card Learning Test) after 6-week treatment with placebo or TAK-071.

The PK endpoints for subjects with PD are:

- C_{trough} of TAK-071 in subjects with PD (Day 42 of Period 1 and Period 2 only).
- C_{max} and AUClast of TAK-071 in subjects with PD.
- t_{max}.

5.2.3 Exploratory Endpoints

The exploratory pharmacodynamic endpoints for subjects with PD are:

- Change from baseline on cognitive performance on individual cognitive test scores(SAT, SDMT, Groton Maze Learning Test, Cogstate One-Back Test, Cogstate International Shopping List Test, Cogstate One Card Learning Test) after 6 weeks of treatment with TAK-071 orplacebo.
- Change from baseline on cognitive performance on domain cognitive scores: attention (SAT, SDMT), executive function (Cogstate Groton Maze Learning Test, Cogstate One Back

Test), and episodic memory (Cogstate International Shopping List Test (Immediate recall and delayed recall), Cogstate One Card Learning Test) after 6 weeks of treatment with TAK-071 or placebo.

- Average number of falls and near-falls per month measured by a falls diary during 6-week treatment with TAK-071 or placebo.
- Change from baseline in the completion time of the TUG after 6-week treatment with TAK-071 or placebo (average of 3 trials).
- Change from baseline in the parameters measuring postural sway with eyes open and eyes closed during a 30-second balance test after 6-week treatment with TAK-071 or placebo.
- Change from baseline in step time variability and double support time during a 2-minute walk after 6-week treatment with TAK-071 or placebo.
- Change from baseline in self-directed turns during a 2-minute walk test after 6-week treatment with TAK-071 or placebo.
- Change from baseline in cued 180 degree turns after 6-week treatment with TAK-071 or placebo.
- Change from baseline in number of falls measured by a wearable pendant sensor during 6-week treatment with TAK-071 or placebo.
- Change from baseline on the ESS total score after 6-week treatment with TAK-071 or placebo.
- Values of CGI-I and PGI-I after 6-week treatment with TAK-071 or placebo.
- Change from baseline on MDS-UPDRS Part 3 scores (including individual motor assessments in Parts 3.1-3.18) and on MDS-UPDRS Parts 1, 2, and 4 scores after 6-week treatment with TAK-071 or placebo.

6.0 DETERMINATION OF SAMPLE SIZE

Sentinel Cohort:

The sample size for an initial sentinel cohort will be approximately 10 subjects initially (with potential replacement for dropouts at sponsor's discretion) at designated sites. Additional (including, potentially older) subjects may be enrolled after analysis of the resulting data from subjects aged 56 to 75 years, inclusive. This sample size is not based on statistical power considerations and considered to be sufficient for evaluation of safety, tolerability, and PK modeling to define safe dose for people 65 years and older.

Main Cohort:

A sample size of 44 completers will be sufficient to detect a statistically significant ($\alpha = 0.05$, 1-sided, 80% power) decrease in stride time variability in 2-minute walk either with or without cognitive load for TAK-071 versus placebo. We expect to detect an effect size of at least 0.32 (Cohen d) in the reduction of stride time variability, 33% higher than what was observed in Henderson et al. (2016) [2]. Assuming the within-subject correlation of 0.65 [3], the true effect size for the two-period cross-over design is 0.382. The sample size calculation is done with nQuery v9.2 (Statsols, San Diego, CA, USA).

It is expected that approximately 64 subjects will be randomized to ensure at least 44 completers, assuming a 31% drop-out rate.

Given the proposed study sample size and 80% power, a detectable operational effect size [4] for the global cognition score ($\alpha = 0.1$, 1-sided) will be at least 0.324. For all primary and secondary outcomes, the within-subject correlation was assumed to be 0.65 [3].

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Unless otherwise described, general principles, definitions, and summaries described in Section 7.1 to 7.8 will be applied to each part of the study.

Randomized subjects are the subjects who are enrolled and received a randomization number.

All study-related raw data, including derived data, will be presented in data listings. Continuous data will be summarized using the following descriptive statistics: number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, the geometric mean will also be included in the summary of continuous data. Categorical data will be summarized using the number and percent of subjects for each category, where appropriate. When presenting summary statistics by treatment groups, the treatment groups include placebo and TAK-071.

All p-values will be rounded to 3 decimal points (e.g., 0.123) and two-sided.

Unless otherwise stated, baseline value is defined as the last observed value before the first dose of study medication. In addition, period 2 baseline assessments need to be at least 19 days after the end of period 1 treatment (main cohort only).

All data analyses and figures will be generated using SAS System® Version 9.4 or higher and PK analysis will be done using Phoenix® WinNonlin® software version 8.0 or higher (Certara, Princeton, NJ, USA).

7.2 Definition of Study Days and Study Visit Windows

For main cohort subjects, study day will be calculated relative to the date of the first dose of the study drug for each period. For sentinel cohort subjects, study day will be calculated relative to the date of the first dose of the study drug. Study days prior to the first dose of study drug will be

calculated as: {date of assessment/event – date of first dose of study drug of the subject}. Study days on or after the first dose of study drug will be calculated as: {date of assessment/event – date of first dose of study drug of the subject + 1}.

The study visit schedules are presented in Table 7.a for the Sentinel Cohort, Table 7.b and Table 7.c for the Main Cohort.

For main cohort subjects, a visit window for week 6 visit (day 42 visit for period 1 or day 105 visit for period 2) will be a visit occurred between study day 23 to 63 within that period, but no later than 3 days after the treatment end date of that period.

The value used in analysis for by-visit summaries is the value within the specified window that is the closest to the scheduled study day. If two observations are equidistant from the scheduled visit date, the observation with a later date will be used.

If the date of first dose of double-blind study drug collected in the eCRF is missing, then for summary purposes the day after the first dispense date will be used as an estimate for the date of first dose. However, if all dispensed study drug is returned, then the subject is assumed to have not taken any study drug, and the first dose date will not be imputed.

If the date of last double-blind study drug dose collected in the eCRF is missing, then the latest of the following dates will be used for the last dose date for analysis and summary purposes: date of last visit (recorded in the eCRF)and the last double-blind study drug dispense date (following the last drug return date) + 42 days (i.e., the longest double-blind study drug dispensing interval).

Table 7.a Visit (Days/Hours) for Scheduled Visits/Samples of Healthy Subjects from Sentinel Cohort

	Screening	Baseline					Last Day of Treatment Period or Early Termination
Study Day	**Day -42 up to Day -1**	**Day 1**	**Day 2** (**Day 2**+24 hr)	**Day 3** (**Day 2**+48 hr)	**Day 4** (**Day 2**+72 hr)	**Day 5** (**Day 2**+96 hr)	**Day 8** (**Day 2** +68 hr)

Table 7.b Visit Windows (Days) for Scheduled Visits of PD Subjects During the Treatment Period 1

	Screening	6-Week Double-blind Treatment Period (Period 1)			Washout
		Baseline	At-home Assessment	Last Day of Treatment Period or Early Termination	
Study Day	**Day -42 up to Day -1**	**Day 1**	**Day 21 ±2**	**Day 42 ±2**	**Day 43 to Day 63**[a]

[a] Washout is ≥3 weeks.

Table 7.c Visit Windows (Days) for Scheduled Visits of PD Subjects During the Treatment Period 2

	6-Week Double-blind Treatment Period (Period 2)			Follow-up Safety Phone Call
	Baseline	At-home Assessment	Last Day of Treatment Period or Early Termination	(Week 17)
Study Day	Day 64 ±2	Day 84 ±2	Day 105 ±2	Day 119

For all efficacy and safety data, data that are obtained more than 3 days after the last dose of study medication (start date – last dose date >3) will be listed but excluded from summaries and analyses. Adverse events that start more than 22 days after the last dose of study medication for sentinel cohort subjects or AEs that start more than 22 days after the last dose of the study medication for each period of the main cohort subjects (start date – last dose date >22) will be listed but excluded from the summaries and analyses.

7.2.1 Conventions for Missing Adverse Event Dates

Adverse events with start dates that are completely or partially missing will be imputed as follows:

- If month and year are known but day is missing.
  - If month and year are the same as month and year of first dose date, then impute to first dose date;
  - If month and year are not the same as of the first dose, impute first day of the month.
- If year is known but day and month are missing.
  - If year is same as year of 1st dose date, then 1st dose date will be used instead.
  - If year is different than year of 1st dose date, then 1st of January of the year will be used.
- If year and day are known but month is missing.
  - If year and day are the same as year and day of first dose date, then impute to first dose month;
  - If year is the same but the day is different from the first dose date then if day is after the first dose date impute first dose month, otherwise, impute month next after the first dose month.
  - If year is different, then impute January as a month.
- If year, month, and day are unknown then impute date of the first dose.

Imputing missing AE start date is mandatory. After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date.

Adverse events with stop dates that are completely or partially missing will be imputed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed.
- If year is known, but day and month are missing.
  - If YYYY ≤ year of last dose, then 31st of December will be imputed.
  - If YYYY > year of last dose, then the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).
- If all are missing, no imputation is necessary. The event will be considered "ongoing."

If an AE is ongoing, AE stop date could be missing. Otherwise, AE stop date could be imputed per above rules. If a subject dies during the study and AE stop date is missing, then the death date will be used for AE stop date. After the imputation, all the imputed stop dates are compared with the start dates to ensure the stop date does not occur before the start date. If the imputed stop date occurs prior to the start date, then the imputed stop date will be the same as the start date.

The imputed dates will not be populated on the data listing, they are used for derivation purpose only. The actual and incomplete date will be on the data listing.

7.2.2 Conventions for Missing Concomitant Medication Dates

Concomitant medications with start date that are completely or partially missing will be analyzed as follows:

- If month and year are known, but day is missing, then impute day to first of the month.
- If year is known, but day and month are missing, then 1st of January of the year will be imputed.
- If year and day are known, but month is missing, then January will be imputed.

Concomitant medications with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed.
- If year is known, but day and month are missing then 31st of December will be imputed.
- If year and day are known, but month is missing then December will be imputed.

- If all are missing, no imputation is necessary. Concomitant medication will be considered as "ongoing".

If a concomitant medication is ongoing, the stop date could be missing. Otherwise, concomitant medications stop date could be imputed per above rules. If a subject dies during the study and the concomitant medication stop date is missing, then the death date will be used for the stop date. After the imputation, all the imputed stop dates are compared with the start dates to ensure the stop date does not occur before the start date. If the imputed stop date occurs prior to the start date, then the imputed stop date will be the same as the start date.

The imputed dates will not be populated on the data listing, they are used for derivation purpose only. The actual and incomplete date will be on the data listing.

7.2.3 Conventions for Missing PK Data

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero in the summarization of concentration values and derivation of PK parameters, with the exception of BLQ values observed between 2 quantifiable concentrations which will be set to missing. Missing concentrations will be excluded from summaries and PK parameter calculations and will be treated as excluded with a corresponding footnote to explain the reason. 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.

7.2.4 Conventions for Missing Efficacy Data

The pharmacodynamic analyses will be performed according to ITT principle. The subjects will be analyzed according to the treatment that they are randomized to. To evaluate the impact of missing data, last observation carried forward (LOCF) imputation will be performed for selected endpoints in the Main Cohort only.

7.3 Analysis Sets

Safety Set

The safety set will consist of all subjects who are randomized and receive at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries. In summaries and analysis using the Safety Set, subjects will be analyzed by the treatment which they received.

PK Set

The PK analysis set will consist of all subjects who receive at least 1 dose of TAK-071 and have at least 1 measurable plasma concentration. If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis but will be presented in the subject listings. In summaries and analysis using the PK Set, subjects will be analyzed by the treatment which they received.

Pharmacodynamic Set (Main Cohort only)

The Pharmacodynamic analysis set will consist of all subjects who receive at least 1 dose of study drug and have at least 1 evaluable Pharmacodynamic endpoint. In summaries and analysis using the Pharmacodynamic Set, subjects will be analyzed by the treatment to which they are randomized.

7.4 Disposition of Subjects

All summaries in this section will be performed for Sentinel and Main cohorts respectively.

Disposition of all screened subjects will be tabulated (count and percent); there will be no inferential analysis of subject disposition data.

- All subjects who signed informed consent form.
- All subjects who were randomized.
- All subjects who were not randomized.

The primary reasons for subjects who were not randomized will be summarized.

Disposition of randomized subjects will be tabulated as below by corresponding treatment groups and overall:

- All subjects who randomized but did not receive any study drug.
- All subjects who received at least one dose of study drug (Main cohort only).
- Subjects who completed the study drug.
- Subjects who prematurely discontinued study drug (Main cohort only).
- Subjects who completed all study visits.
- Subjects who prematurely discontinued study visits.

Primary reasons for discontinuation of study drug/visits, as entered on the electronic case report form (eCRF), will be tabulated. The primary reasons for premature discontinuation of study drug/study visit will be presented for each subject in listings. The primary reason for premature discontinuation of study drug is applicable to the main cohort only.

Significant protocol deviations will be listed using the Safety Set by corresponding treatment groups and overall.

7.5 Demographic and Other Baseline Characteristics

All summaries in this section will be performed for Sentinel and Main cohorts respectively.

Demographics of the screening failures collected on the eCRF will be summarized.

For subjects in the Safety Set, demographics and other baseline characteristics will be summarized by treatment groups (Sentinel cohort) or by treatment sequence (Main cohort) and overall. Descriptive statistics will be used to summarize data for continuous variables like age

and weight (number of subjects [N], mean, median, SD, minimum, and maximum) and for categorical variables like sex, ethnicity, and race. Baseline disease characteristic table and listing are applicable to the main cohort subjects only.

All individual demographic and baseline characteristics will be listed by treatment (Sentinel cohort) or by treatment sequences (Main cohort), study center and subject number. The demographic data listing will include subject identifier, treatment sequence, age at date of informed consent, sex, race, height, baseline weight and baseline BMI and other demographic and baseline information collected in the eCRF.

7.6 Medical History and Concurrent Medical Conditions

Medical history includes any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Concurrent medical conditions are those significant ongoing conditions or diseases present at signing of informed consent. Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, version 23 or higher) coding system.

All medical history and concurrent medical condition data will be listed by subject for the sentinel and main cohorts separately. The listing will contain subject identifier, treatment, system organ class (SOC), preferred term (PT), whether there was any medical history or concurrent condition, and, if yes, a detail of the medical history or concurrent condition.

7.7 Prior 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.

No summary statistics for prior and concomitant medications will be provided. All medication history and concomitant medications data will be listed by subject. Study part and/or cohorts will be included in the listing.

7.8 Study Drug Exposure and Compliance

All summaries in this section will be performed for the main cohort only.

The date and time of each dose for each subject will be reported in the data listing. Listings and summary statistics for TAK-071 plasma concentrations and pharmacokinetic parameters will also be provided.

The summary of study drug exposure and compliance will be based on the Safety Set. Duration of exposure to study medication for each subject is defined as (date of last dose – date of first dose +1). The date of the first dose and date of the last dose in each treatment period for the main cohort is determined by the corresponding in-clinic visit dates. If the date of last dose is missing, the last dose date will be estimated as the later date between the last drug dispense date plus the number of days in the dosing interval and the last study visit day for analysis and summary purposes.

Treatment duration (days) will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) for each treatment (placebo or TAK-071).

Percent of study drug compliance at each period will be calculated in two ways:

1) Compliance by tablet counts as {(number of tablets dispensed – number of tablets returned)/(date of last dose – date of first dose +1)} *100%. If the number of returned tablets is missing, then 100% compliance will be assigned for that treatment period.
2) Compliance by days as the number of days when the drug was taken (as reported by subject or caregiver in the medication diary)/ total number of days in which the compliance was reported in the medication diary between the date of the first dose and the date of last dose, inclusive in that treatment period*100%.

For each treatment(Placebo or TAK-071), study medication compliance will be summarized as the number of subjects and the frequency in each compliance category (<50%, 50 to 70%, and ≥70%) for both options above. Study medication compliance summarized as a continuous variable using descriptive statistics (n, mean, SD, median, minimum, and maximum) for each treatment group.

All study drug administration and accountability data will be listed by subject ID, age/gender, period, treatment, first and last dose dates, medication identification number, date dispensed and returned, number of tablets dispensed and returned, and compliance percentages by tablet counts, number of days in which compliance was reported in the diary (diary compliance) and compliance percentages by days.

7.9 Efficacy Analysis (Main cohort)

The efficacy analysis will be based on the Pharmacodynamic Set. For all efficacy analyses, baseline value is defined as the last observed value at or before the date that the first dose of study medication was taken for each treatment period. In addition, period 2 baseline assessments need to occur at least 19 days after the end of period 1 treatment. Separately, a flag will be derived to indicate whether a baseline assessment occurred at the same day of the first dose but after the actual treatment start time.

7.9.1 Primary objective: Stride Time Variability Analysis

The primary objective is to evaluate the efficacy of TAK-071 versus placebo on gait dysfunction, as measured by stride time variability during a 2-minute walk test.

We will calculate stride time variability as the average of the right and left leg's stride time variability (measured as SD) and referred to as STV.

STV values from 2-minute walk without cognitive load will be analyzed using a linear mixed effect model of the log-transformed STV for each period, with treatment, period, and log-transformed baseline STV as predictors. The inference is on the ratio of the geometric mean STV of TAK-071 period to the geometric mean STV of placebo period, adjusted for period and log-transformed baseline STV.

Similar analysis will be done for the STV values from 2-minute walk with cognitive load. The following schematic code is an example of SAS code for STV assessment:

```
proc mixed data=data;
  class Period Treatment (ref ="Placebo")  Subjid;
  model LogSTV = Period Treatment LogBaseSTV / ddfm=KR solution;
  repeated Period/ subject=Subjid type=un;
  lsmeans Treatment / diff cl exp;
run;
```

The SAS procedure above assumes an unstructured covariance matrix that may cause a problem with model convergency. In a case the procedure does not converge, we would use a compound symmetry (cs) structure. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

We will present the adjusted Least Squares Means (LSMs) and the associated SEs for log STV in TAK-071 and Placebo for 2-minute walks. The adjusted difference between the expected means for log(TAK-071)-log(Placebo) will be exponentiated to provide estimates of the ratio of adjusted geometric means and will be presented with corresponding two-sided 95% CIs for the ratios and p-values.

To address the potential bias due to missing data, we will run sensitivity analyses using the LOCF option mentioned in Section 7.2.4, using the most recent assessment performed prior to week 6 within the same period. The models will be the same one as described above using the observed data supplemented with the imputed values.

7.9.2 Cognition Analysis

The secondary outcome is a change from baseline in a global cognition score consisting of attention (SAT, Symbol Digit Modalities Test [SDMT]), executive function (Cogstate Groton Maze Learning Test, Cogstate One Back Test), and memory (Cogstate International Shopping List Test(immediate recall and delayed recall), Cogstate One Card Learning Test) after 6-week treatment with TAK-071 compared with placebo. Please refer to the Protocol Amendment 3 Section 9.1.8.2 or Cogstate and Operation manuals for additional details on these cognitive tests.

The change from baseline in the global cognition score will be analyzed using a linear mixed effect model, with treatment, period and baseline global cognition score modeled as fixed effects and subject as the random effect. The inference is on the difference between the mean change from baseline on global cognition score from the TAK-071 period and the placebo period, adjusted for period and baseline global score.

The following schematic code is an example of SAS code for overall cognition analysis:

```
proc mixed data=data;
class Period Treatment (ref ="Placebo")  Subjid;
model CFB(GlobalScore) = Period Treatment Base / ddfm=KR solution;
repeated Period/ sub=Subjid type=un;
lsmeans Treatment / diff cl;
run;
```

The adjusted means (Least Squares Means) and their two-sided 95% confidence intervals (CIs) and difference between the expected means for TAK-071-Placebo with corresponding two-sided 95% CI and p-value will be estimated for the global cognition score.

Similar analysis will be done for each individual cognitive test scores as well as each of the three domain(attention, executive function, and memory) scores.

To address the potential bias due to missing data, we will run sensitivity analyses for the week 6 global cognition score using the LOCF option mentioned in Section 7.2.4. The LOCF will be applied to each missing individual test score in order to calculate the imputed global cognition score, using the most recent assessment performed prior to week 6 within the same period. The models will be the same one as described above using the observed data supplemented with the imputed values.

7.9.3 Fall Data Analysis

Subjects will complete a daily ePRO diary to record falls and near falls.

Monthly fall rate (MFR) for each treatment period based on study schedule will be calculated as below:

$$MFR\ from\ diary = \left(\frac{Total\ number\ of\ falls\ over\ the\ non-missing\ diary\ days\ for\ a\ given\ period}{number\ of\ non-missing\ diary\ days\ in\ that\ period}\right) * 30.4375$$

If a diary for a given day reports ≥0 fall, the day will be counted as a non-missing diary day. If a diary for a given day does not report any information about fall (including 0), the day will be counted as a missing diary day for the fall.

MFR will be summarized by treatment period. PD set will be used.

Monthly near fall rate will be calculated similarly as MFR.

Monthly fall/near fall rate derived from the wearable device will be calculated similarly as:

$$MFR\ from\ device = \left(\frac{Total\ number\ of\ falls\ or\ near\ falls\ over\ the\ non-missing\ days\ for\ a\ given\ period}{number\ of\ non-missing\ days\ in\ that\ period}\right) * 30.4375$$

A generalized estimating equation negative binomial regression model will be used to evaluate the drug effect on the monthly fall/near fall rate from either diary or wearable device. The response variable will be the number of falls recorded in the placebo and TAK-071 period. The model will include treatment and period. The log(number of days) will be used as an offset variable. An unstructured variance-covariance structure will be used initially in these models. Other variance-covariance structures will be evaluated if there are convergence issues with the model. The estimated incident rate ratio (IRR) of MFR comparing treatment period to placebo period, and the associated 95% CIs, and p-values will be estimated from the model.

The following schematic code is an example of SAS code for monthly fall rate analysis:

```
proc genmod data=data;
class subjid treatment(ref="Placebo") period;
model number_of_fall = treatment period / dist=negbin link=log offset=log(number of day);
repeated subject = subjid(period) / Type=UN;
lsmeans treatment /diff cl exp;
run;
```

7.9.4 MDS-UPDRS and Other Gait Parameters Analysis

From 2-minute walk test with and without cognitive load we will analyze

- Step Time Variability
- Stride length variability
- Double support time
- Foot strike angle
- Range of motion (G/T-Coronal, G/T Sagittal, G/T Transverse, Arm)
- Swing velocity
- Turn velocity

In addition, we will consider

- MDS-UPDRS Part III sum scores (including individual motor assessments in Parts 3.1-3.18) impact of dyskinesia, and the Hoehn and Yahr scale
- MDS-UPDRS Parts I, II, and IV sum scores
- Completion time of the TUG
- Postural sway with eyes open and eyes closed during a 30-second balance test, measured by average frequency dispersion, mean velocity, average Acc-RMS Sway, average sway area, average ang-sway area.

The detailed description of these tests can be found in the Protocol Amendment 3 Section 9.1.8.1. The total scores from MDS-UPDRS Part I, Part II, Part III, Part IV as well as the

combined total scores from Part I-III will be analyzed. If there are missing item scores in any of the MRS-UPDRS Part, the part summary score is not calculated. All analyses will be done using linear mixed models with random effect for subject, fixed effects for treatment, period, and with baseline value as covariates, similarly to what was described in section 7.9.1.

7.10 Epworth Sleepiness Scale (ESS) Total Score Analysis

ESS [5] will be measured at baseline and last day of treatment period or early termination (Days 1, 42, 64 and 105), and the total scores will be derived and summarized for each visit. Change from baseline in the ESS total scores to the end of each period will be derived and summarized. ESS data will be presented in the listing. Summary statistics by treatment will be provided for observed ESS total score at baseline and post dose days, as well as for the change from baseline. In addition, number, and percent of subjects with a total ESS score <10 will be summarized at each visit by treatment groups. Shift tables will be presented.

Similar to the analysis of the primary efficacy endpoint, linear mixed effect model will be used to evaluate the effect of TAK-071 on the change from baseline in the ESS total score. Baseline total ESS score will be included as the covariate in the model. Treatment, period will be included as fixed effect and subject as a random effect. The least squares mean of change from baseline in total ESS score for each treatment and the associated SE and 95% CI will be calculated for TAK-071 and placebo, along with difference between TAK-071 and placebo and associated SEs, 95% CIs, and p-values.

7.11 PGI and CGI Analysis

The CGI scales consist of 2 subscales: the CGI-Severity (CGI-S) and the CGI-Improvement (CGI-I). The CGI-S assesses the clinician's impression of the subject's current clinical condition. Both the CGI-I and CGI-S will be rated with respect to stability (gait, balance, falls) and cognition in separate assessments. The clinician should use his/her total clinical experience with this subject population and rate the current severity of the subject's illness on a 7-point scale ranging from 1) "Normal, not at all ill" to 7) "Among the most extremely ill patients". This rating is based on observed and reported symptoms, behavior, and function in the past 7 days and should reflect the average severity level across the 7 days. The CGI-I assesses the subject's improvement (or worsening) on a 7-point scale ranging from 1) Very much improved since the initiation of treatment to 7) Very much worse since the initiation of treatment. Each time the subject is seen after treatment has been initiated, the clinician compares the subject's overall clinical condition to the 1-week period just before the initiation of medication use (baseline). The CGI-S score obtained at the baseline visit (Day 1/Day 64) serves as a basis for making this assessment. In all cases, the assessment should be made independent of whether the clinician believes the improvement is drug-related or not.

Patient-reported global impression of severity and improvement (PGI-S and PGI-I, respectively) will be also assessed. PGI-I will be rated on a 7-point scale and PGI-S will be rated on a 6-point scale. Both the PGI-I and PGI-S will be rated with respect to stability (gait, balance, falls) and cognition in separate assessments.

Summary statistics for CGI-S, PGI-S, CGI-I and PGI-I will be provided by treatment at baseline and end of period..

For the linear model for analysis of the change from baseline for the CGI score, CGI-S will be used as the baseline and CGI-I will be the measure of the change from baseline. The CGI-S responses will be mapped to 1 to 7, starting with 1 = Normal and continuing in order. The CGI-I responses will be mapped to two categories: "Improved" and "Not improved". Responses of "Very much improved" and "Much improved" will be mapped to "Improved"; all other non-missing responses will be mapped to "Not Improved". In this case, the summary of observed values and change from baseline for the CGI-I scales will include the number and percent of subjects "Improved" or "Not Improved" at each time point. A GEE logistic regression model will be used to analyze the two-category CGI-I score. The model will include treatment, and period and baseline CGI-S as covariates. The odds ratio of improvement for active versus placebo will be extracted, as well as two-sided 95% CIs, and p-values.

The analysis for PGI-S/PGI-I will follow the same approach described above for CGI-S/CGI-I.

7.12 Exploratory Pharmacodynamic Analysis

Plasma biomarkers including neuronally derived exosomal M_1 receptor mRNA, amyloid, tau, neurofilament light chain (NfL), biomarkers of synaptic integrity, and potentially additional blood-based biomarkers, DNA samples and data from wearable digital devices and speech performance will be exploratory in nature and will help in the design of future studies. In addition, we are going to explore the relationship of pharmacodynamic endpoints to disease characteristics, subgroup and mediation analyses. These analyses are not related to the main study objectives concerning the safety, tolerability and PK, will not be available during the dosing periods of the study, will not be used for clinical decision making during the study, and will not be included in the Clinical Study Report. Thus, analysis of these data will be described and performed independently of this document by Takeda or its designee.

7.13 Pharmacokinetic Analysis

7.13.1 Plasma Concentration

Blood samples for the determination of plasma concentrations of TAK-071 will be collected at the following time points for PK assessment:

Sentinel Cohort:

Predose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 14 hours postdose on Day 1; 24 hours postdose (Day 2); 48 hours postdose (Day 3); 72 hours postdose (Day 4); 96 hours postdose (Day 5) and 168 hours postdose (Day 8).

Main Cohort:

Day 1 (Period 1): Predose and 1 and 2 hours postdose

Day 42 (Period 1): Predose and 1, 2, and 3 hours postdose

Day 64 (Day 1 Period 2): Predose and 1 and 2 hours postdose

Day 105 (Day 42 Period 2): Predose and 1, 2, and 3 hours postdose

TAK-071 plasma concentrations will be tabulated and summarized at each scheduled time point using descriptive statistics (including number of observations (n), mean, median, SD, percent coefficient of variation [%CV], minimum, and maximum) for each dose level (if needed), and separately for each cohort (Sentinel and Main Study). Actual sampling times postdose will be considered to be deviations where the actual sample collection time deviated from nominal collection time by more than ±5 minutes up to 4 hours postdose, ±15 minutes between 6 and 96 hours, ±1 day on Day 8, ±2 days between Days 42 and 64, and ±3 days on Day 105. Samples collected outside these windows will be flagged in data listings and excluded from summaries and mean figures.

Individual subject plasma concentration data and actual sampling times will be listed separately for each cohort (Sentinel and Main).

7.13.2 Plasma Pharmacokinetic Parameters

The plasma PK parameters of TAK-071 will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated if feasible using non-compartmental analysis using Phoenix WinNonLin (version 8.0 or higher (Certara, Princeton, NJ, USA)): AUC_{24} (sentinel cohort only), AUC_{last}, AUC_{τ} (sentinel cohort only), AUC_{inf} (sentinel cohort only), C_{max}, C_{trough} (main cohort only), t_{max}, and $t_{1/2z}$(sentinel cohort only). Additional PK parameters may be calculated if necessary.

The plasma PK parameter estimates will be tabulated and summarized by using descriptive statistics (n, mean, median, SD, %CV, minimum, and maximum) for each dose level (if needed), and separately for each cohort (Sentinel and Main). In addition, geometric means and geometric %CVs will be calculated for C_{max}, AUCs and C_{trough}. Individual PK parameters will be presented in a data listing for each subject, separately for each cohort (Sentinel and Main).

The individual plasma concentration of TAK-071 will be plotted by actual time on linear and semi-logarithmic scales, separately for each cohort (Sentinel and Main). Mean (±SD) plasma concentrations will be plotted by scheduled time for each day (as applicable) on linear and semi-logarithmic scales, separately for each cohort (Sentinel and Main).

All PK summaries and analyses will be based on the PK set by dose levels (if needed) and within each cohort (Sentinel and Main).

Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

The following PK parameters will be calculated from plasma concentrations of TAK-071, as data permit:

Table 7.d Plasma PK Parameters Definition

Symbol/Term	Definition
Plasma	
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval (168 h), calculated using the linear trapezoidal rule. (Sentinel only)
AUC_{24}	Area under the concentration-time curve from time 0 to time 24 hours, calculated using the linear trapezoidal rule. (Sentinel only)
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration, calculated using the linear trapezoidal rule.
AUC_{inf}	Area under the concentration-time curve from time 0 to infinity, calculated as $[AUC_{last} + C_{last} / \lambda_z]$, where C_{last} is the last observed quantifiable concentration, calculated using the linear trapezoidal rule. (Sentinel only)
C_{max}	Maximum observed concentration
C_{trough}	Trough plasma concentration at steady state (observed concentration at the end of a dosing interval) (Main only; Day 42 of Periods 1 and 2 only)
$t_{1/2z}$	Terminal disposition phase half-life (Sentinel only)
t_{max}	Time to reach C_{max}

Additional PK parameters and the relationship of the ratio of plasma 4-beta-hydroxycholesterol/cholesterol with plasma TAK-071 AUC may be analyzed. Details will be documented in the clinical pharmacology analysis plan (CPAP).

For the main cohort of PD subjects, a population PK approach will be used to derive the PK parameters and the population PK analysis will be reported separately.

7.14 Safety Analysis

Summaries of safety data will be presented by Cohort (Sentinel and PD subjects) and treatment group.

7.14.1 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA.

The Treatment-Emergent Adverse Events (TEAE) are defined as those AEs that occurred after the start of the treatment and up to 22 days after the end of treatment (for each period for the Main cohort subjects). TEAE summary tables will include numbers and percentages of subjects experiencing at least one TEAE by SOC and PT and will be tabulated by treatment. The TEAEs will also be summarized for all subjects in the overview assessment. The following is a list of TEAE summary tables to be generated:

- Overview of Treatment-Emergent Adverse Events.

- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Treatment-Emergent Adverse Events by Preferred Term.
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Most Frequent (≥2 subjects or ≥5% based on total number of safety set subjects in any treatment group, whichever larger) Treatment-Emergent Adverse Events by Preferred Term.
- Most Frequent (≥2 subjects or ≥5% based on total number of safety set subjects in any treatment group, whichever larger) Non-Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Relationship of Treatment-Emergent Adverse Events to Study Drug by System Organ Class and Preferred Term.
- Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Drug-Related Treatment-Emergent Adverse Events by Preferred Term.
- Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

In addition, data listings will be provided for all AEs including: TEAEs, TEAEs leading to death, TEAEs leading to study drug discontinuation, and SAEs.

7.14.2 Clinical Laboratory Evaluations

Clinical safety laboratory tests include clinical chemistry, hematology, and urinalysis. A list of all the clinical laboratory evaluations can be found in Protocol Section 9.1.12.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of clinical laboratory variables will be summarized for baseline and post-dose values, as well as change from baseline to post dose values by study visits and treatment. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

Individual results for clinical laboratory tests will be evaluated against the Takeda predefined laboratory markedly abnormal values (MAV) criteria (Appendix A) using the result and criteria in SI units. All subjects with at least 1 post-dose laboratory result that meets the MAV criteria will be presented in a data listing.

The number and percentage of subjects with at least one post-dose markedly abnormal laboratory test result will also be summarized by treatment. Subjects who meet the MAV criteria will be mapped to their respective qualifying laboratory result. All pre- and post-dose clinical lab MAV results, including scheduled and unscheduled measurements, will be included in the MAV summaries.

Listings of all clinical safety laboratory data will be provided in the listings and will be presented in both SI and conventional units (and CV units, if available). Laboratory data outside of the normal reference range will be indicated in the listings.

7.14.3 Vital Signs

Vital sign measurements include blood pressure (SBP and DBP), pulse, respiratory rate, and body temperature.

SBP, DBP and pulse will be summarized (N, mean, SD, median, minimum, and maximum) for baseline, post-dose, and change from baseline (or change from time-matched baseline to post-dose, if appropriate) by treatment. Only the scheduled measurements will be included in the summary.

Respiratory rate and temperature will be summarized for baseline, post-dose, and change from baseline at each time point by treatment. Only the scheduled measurements will be included in the summary.

All individual vital signs that meet Takeda's predefined criteria for MAVs (Appendix B) will be listed. The number and percentage of subjects with at least one post-dose markedly abnormal vital sign measurement will be summarized by treatment. Subjects who meet the MAV criteria will be mapped to their respective qualifying vital sign result. All pre- and post-dose MAV vital signs, including both scheduled and unscheduled measurements, will be included in the MAV summaries. Listings of all vital signs data will be provided in the listings, and vital sign MAVs will be flagged.

7.14.4 12-Lead ECGs

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will manually interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

The following parameters will be calculated automatically by the ECG machine: heart rate, PR interval, RR interval, QT interval, QRS interval, and QT interval with Fridericia correction method (QTcF) and QTcB.

Descriptive statistics of the continuous ECG parameters will be summarized for baseline, post-dose, and change from baseline at each post-dose time point by treatment and time. Only the ECGs collected at the scheduled visits or time points will be included in the summary. No statistical tests will be performed for the observed ECG parameters.

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

Individual subject ECGs will be presented in a data listing.

7.14.5 Other Observations

Physical examination findings and C-SSRS data results will be presented in the data listings. C-SSRS listings will include data from "at screening" questionnaire for the screening visit and "since last visit" questionnaire for any post-screening visits.

7.15 PK/Pharmacodynamic and PK/Safety Analysis

The relationships between TAK-071 plasma concentrations and selected Pharmacodynamic and safety measures will be explored graphically as data permit.

A scatterplot of TAK-071 plasma concentration (x-axis) versus the observed post treatment STV from a 2-minute walk with and without cognitive load (y-axis) will be produced. TAK-071 plasma concentrations for placebo data will be included in the plot with a concentration of 0. Only measurements from time points common to both STV and PK assessments will be used. Data from all doses of TAK-071 (if they vary) will be displayed together in the plot. A similar scatterplot of TAK-071 plasma concentration (x-axis) versus change from baseline in HR, SBP and DBP will be produced. TAK-071 plasma concentrations for placebo data will be included in the plot with a concentration of 0. Only measurements from time points common to both vital signs and PK assessments will be used. Data from all doses of TAK-071 will be displayed together in the plot.

In addition, graphical description of the relationship between PK parameters (CL/F, AUC, Cmax and $t_{1/2z}$) and subjects characteristics such as age, sex, liver function (such as AST, ALT, albumin, and bilirubin) and kidney function (estimated GFR) will be presented.

7.16 Unblinded Data Reviews and Interim Analysis

7.16.1 Unblinded Data Reviews

Unblinded data safety review of the Sentinel cohort will be performed by Takeda team and the process is described in detail in the Data Access Management Plan (DAMP).

7.16.2 Interim Analysis

Not applicable.

7.17 Changes from the Analysis Specified in the Protocol

1. The variable "sequence" is deleted from the list of linear mixed effect model covariates.
2. Cognitive test is analyzed for each test separately, as well as by separate models for the domain scores and the global cognitive score.
3. The analysis of the fall rate is analyzed using generalized estimating equations with a negative binomial distribution.
4. All P-values are reported as 2-sided.

8.0 REFERENCES

1. A Randomized, Double-blind, Placebo-Controlled, 2-Period Crossover, Phase 2 Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Oral TAK-071 in Parkinson Disease Patients With Cognitive Impairment and an Elevated Risk of Falls Takeda Development Center, Ltd., Protocol Amendment 03, TAK-071-2002, dated 19 January, 2021.
2. Henderson EJ, Lord SR, Brodie MA, Gaunt DM, Lawrence AD, Close JC, et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomized, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol 2016;15(3):249-58.
3. Chung KA, Lobb BM, Nutt JG, Horak FB. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease. Neurology. 2010 Oct 5;75(14):1263-9.
4. Dallow NS, Leonov SL, Roger JH. Practical usage of O'Brien's OLS and GLS statistics in clinical trials. Pharm Stat 2008;7(1):53-68.
5. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(6):540-5.
6. Ratitch, B., Lipkovich, I. & O'Kelly, M. 2013. Combining Analysis Results from Multiply Imputed Categorical Data - PharmaSUG Paper SP03.

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 x LLN	>1.5 x ULN
Platelet count	Conventional	<75 x 10^3/μL	>600 x 10^3/μL
	SI	<75 x 10^9/L	>600 x 10^9/L

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

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3x ULN
AST	Both	--	>3x ULN
GGT	Both	--	>3x ULN
Alkaline phosphatase	Both	--	>3x ULN
Total bilirubin	Conventional	--	>1.5x ULN
	SI	--	>1.5x ULN
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional	--	>1.5x ULN
	SI		>1.5x ULN
Blood urea nitrogen	Conventional		>40 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	>5.3 mEq/L
	SI	<3.0 mmol/L	>5.3 mmol/L
CPK	Both	--	>3x ULN
Glucose	Conventional	<50 mg/dL	>300 mg/dL
	SI	<2.8 mmol/L	>19.4 mmol/L
Calcium	Conventional	<7.7 mg/dL	>11.1 mg/dL
	SI	<1.92 mmol/L	>2.77 mmol/L

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CPK=creatine phosphokinase, 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	<40	>115
Systolic blood pressure	mm Hg	<90	≥160
Diastolic blood pressure	mm Hg	<50	≥100
Systolic blood pressure change	mm Hg		>20, >30
Diastolic blood pressure change	mm Hg		>20, >30
Body temperature	oC		>38.5
Respiratory Rate	Breath/min		>21

Appendix C Criteria for Markedly Abnormal Values for Electrocardiograms

Parameter	Lower Criteria	Upper Criteria
Heart rate	<40 beats per minute	>115 beats per minute
PR	≤80 milliseconds	≥200 milliseconds
QTcF Interval	≤300 milliseconds	>500 milliseconds OR ≥30 milliseconds change from baseline and >450 milliseconds
QRS	≤80 milliseconds	≥180 milliseconds