Clinical Study Protocol

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: Amendment 4.0, 07 September 2021

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.

TAKEDA PHARMACEUTICALS

PROTOCOL

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

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington MA 02421		
Study Number:	TAK-071-2002		
IND Number:	146849	**EudraCT Number:**	Not Applicable
NCT Number	NCT04334317		
Compound:	TAK-071		
Date:	07 September 2021	**Version/Amendment Number:**	Amendment 4

Amendment History

Date	Amendment Number	Region
07 September 2021	Amendment 4	United States
18 January 2021	Amendment 3	United States
12 August 2020	Amendment 2	United States
06 July 2020	Amendment 1	United States
16 March 2020	Initial version	United States

1.0 ADMINISTRATIVE INFORMATION

1.1 Approval

REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation (ICH) E6 (R2) Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

[redacted] 9/8/2021

[redacted], MD PhD Date
[redacted]
or delegate

[redacted], PhD Date
[redacted]
Quantitative Clinical Pharmacology

[redacted] Date
[redacted]
Statistics and Quantitative Sciences

[redacted], MD Date
[redacted],
Neuroscience Therapeutic Area Unit

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH E6 (R2) GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the investigator (Appendix D).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix F of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

1.2 Contacts

Takeda Development Center Americas, Inc. (TDCA)–sponsored investigators will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	Contact
Serious adverse event and pregnancy reporting	Cognizant FAX: 800-963-6290
Medical Monitor (medical advice on protocol and study drug)	PPD Phone: 800-201-8725
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted], MD PhD [redacted] 95 Hayden Avenue Lexington MA 02421

1.3 Protocol Amendment 4 Summary of Changes

This section describes the changes in reference to the Protocol Incorporating Amendment No. 4.

Amendment 4 is mainly necessitated by the pharmacokinetic (PK), safety, and physiologically based PK modeling of data from the sentinel cohort completed at a designated site. Additional clarifications have been made to the excluded and allowed medications and treatments, entry criteria, and other items to avoid protocol deviations.

The primary reasons for this amendment are to:

- Allow enrollment of older subjects with Parkinson disease aged 66 to 85 years, inclusive, at a dose level of TAK-071 5 mg. Subjects aged 40 to 65 years, inclusive, will continue to receive TAK-071 at a dose level of 7.5 mg.
- Change the suggested study entry criteria for investigator assessment of fall history, cognitive impairment, prior history of stable antiparkinsonian medication, and prior history of deep brain stimulation (DBS) device implantation.
- Prohibit use of acetylcholinesterase inhibitors administration during study and modify study entry and use criteria for other medications and treatments.
- Clarify visit windows for Study Visit days.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only, and are not captured in the following table.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Section 2.0, Study Summary: Study Design / Dose Levels: Section 4.2, Benefit/Risk Profile Section 6.1, Study Design, Main Study	Allowed enrollment of older individuals aged 66 to 85 years, inclusive, at a dose level of TAK-071 5 mg. Clarified that individuals aged 40 to 65 years, inclusive, will continue to receive TAK-071 at a dose level of 7.5 mg. The TAK-071 dose level for this age group was specified as 7.5 mg (rather than ≤7.5 mg).	PK, safety, and physiologically based PK modeling of data from the completed sentinel cohort allowed for expansion of the main cohort to include participants up to 85 years of age, inclusive. The modeling also provided justification for dose level specification by age.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
2	Section 2.0, Study Summary: Subject Population Section 6.1, Study Design, Main Study Section 8.2, Study Drug Assignment and Dispensing Procedures	Removed enrollment procedures and related discussion for the sentinel cohort and for initial sentinel cohort data review and modeling.	Completion of the sentinel cohort and corresponding analysis.
3	Section 6.3.3, Dose Justification Section 7.1, Inclusion Criteria (#3) Section 8.2, Study Drug Assignment and Dispensing Procedures	Clarified upper limit of age range of study subjects, changing to 85 years, inclusive.	PK, safety, and physiologically based PK modeling of data from the completed sentinel cohort allowed for expansion of the main cohort to include participants up to 85 years of age, inclusive.
4	Section 2.0, Study Summary: Main Criteria for Inclusion Section 7.1, Inclusion Criteria (#6)	Changed suggested fall history criteria (ie, elevated risk of falls) to at least 1 fall in the last 12 months with continued elevated risk of falls per investigator judgment. Clarified that investigator judgment on fall risk may be informed by such information as, but not limited to, history, physical examination and/or a score ≥2 on item 3.10 on Movement Disorders Society–Unified Parkinson's Disease Rating Scale Part III.	Provides additional emphasis on investigator determination of fall history and provide suggested criteria. Increases study feasibility.
5	Section 2.0, Study Summary: Main Criteria for Inclusion Section 6.3.1, Subject Selection Considerations Section 7.1, Inclusion Criteria (#7)	Changed permissible Montreal Cognitive Assessment score range from 11 to 26, inclusive (rather than 17 to 24), for assessment of cognitive impairment and specify completion of cognitive assessments at screening (rather than randomization) for assessment of cognitive impairment (as specified in the study manual).	Provides additional more specific and more widely applicable criteria for assessment of cognitive impairment. Increases study feasibility.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
6	Section 2.0, Study Summary: Main Criteria for Inclusion Section 7.1, Inclusion Criteria (#10)	Clarified period for study entry assessment of stable antiparkinsonian medication as at least 30 days before randomization (rather than screening).	Clarification.
7	Section 2.0, Study Summary: Main Criteria for Exclusion Section 7.2, Exclusion Criteria (#6)	Specified period for DBS device implantation as within the past year and for stable setting as ≥2 months, if safe to do so and if the presence of DBS will not impact study assessments, and if further changes in DBS settings are not anticipated for the duration of study participation, per investigator judgment.	Provides additional context regarding criteria for prior use of DBS device for investigator. Increase study feasibility.
8	Section 7.2, Exclusion Criteria (#10)	Specified repeat screening laboratory test for inaccurate values.	Clarification.
9	Section 2.0, Study Summary: Subject Population Section 4.2, Benefit/Risk Profile Table 7.a, Excluded and Allowed Medications and Treatments	Clarified that acetylcholinesterase inhibitors, including donepezil, rivastigmine, and galantamine, are not permitted.	Risk of seizure with co-administration of TAK-071, based on data from nonclinical toxicology studies.
10	Table 7.a, Excluded and Allowed Medications and Treatments	Clarified that vaccination for coronavirus disease 2019 vaccine is allowed.	Clarification.
11	Table 7.a, Excluded and Allowed Medications and Treatments	Added exception for mirabegron among excluded anticholinergic drugs.	Allows subjects to use mirabegron.
12	Table 7.a, Excluded and Allowed Medications and Treatments	Clarified washout period for excluded antipsychotic drugs ie, at least 30 days before randomization and approval for study entry.	Clarification.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
13	Table 7.a, Excluded and Allowed Medications and Treatments	Allowed the use of antipsychotic drugs, nonbenzodiazepine hypnotics, and muscle relaxants under some circumstances. Emphasized that anticonvulsants in Table 7.b are never allowed. Clarified use of muscle relaxants under some circumstances if the total daily dose has been relatively stable from 30 days before randomization to the end of the study.	Clarification.
14	Table 7.a, Excluded and Allowed Medications and Treatments	Allowed episodic use of antidepressants, herbal remedies that are psychoactive, over-the-counter drugs, and antiparkinsonian drugs under some circumstances.	Clarification.
15	Table 7.a, Excluded and Allowed Medications and Treatments	Allowed episodic use of melatonin for subjects with REM (rapid eye movement) sleep behavior disorder and/or insomnia under described conditions.	Clarification.
16	Section 6.3.3, Dose Justification Appendix H, Sentinel Cohort (Healthy Subjects) Only	Presented justification for expanding enrollment of older participants from the sentinel cohort analysis.	Clarified by pharmacologist.
17	Section 2.0, Study Summary: Statistical Considerations	Changed the area under the concentration-time curve (AUC) PK parameter for the sentinel cohort to AUC from time 0 to 24 hours (AUC_{24}).	Clarified by pharmacologist.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
18	Appendix A, Schedule of Study Procedures, Main Study (Su.bjects With PD): Table A-1, Period 1 (footnotes a, b, c)	Clarified that screening assessments should be completed within the screening period. Clarified that assessments at Visit 2 (Period 1 baseline) may be split across 2 days and should be completed on or before Day 3. Clarified that assessments at Visit 4 (Period 1 last day of treatment period or early termination) may be split across 2 days and should occur within the visit window.	Clarification. Increase study feasibility.
19	Appendix A, Schedule of Study Procedures, Main Study (Su.bjects With PD): Table A-1, Period 1 and Table A -2, Period 2 (footnote a)	Clarified that assessments at Visit 5 (Period 2 baseline) and Visit 7 (Period 2 last day of treatment period or early termination visit) may be split across 2 days and should occur within the visit window.	Clarification. Increase study feasibility.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc. (TDCA)	**Compound:** TAK-071	
Title of Protocol: 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	**IND No.:** 146,849	**EudraCT No.:** Not Applicable
Study Number: TAK-071-2002	**Phase:** 2	

Study Design, Main Study:

This is a phase 2, randomized, double-blind, placebo-controlled, 2-period, 2-treatment crossover study to evaluate the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of TAK-071 when administered orally once daily (QD) in subjects with Parkinson disease (PD) and evidence of cognitive impairment who are at risk for falls and who are not concurrently taking acetylcholinesterase inhibitors. In parallel with the main cohort, healthy subjects will participate in the sentinel cohort portion of the study as described below.

Approximately 64 male and female subjects, aged 40 to 85 years, inclusive, will be enrolled at up to 25 sites in the United States.

The main 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.

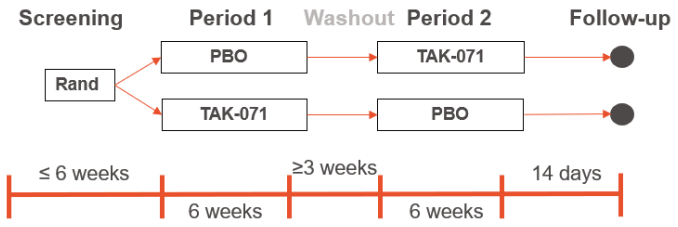
On Day 1, subjects who continue to meet inclusion and none of the exclusion criteria will be randomized 1:1 to treatment with TAK-071 or placebo.

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.

A safety follow-up call will be conducted at 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, ie, the safety follow up call.

The figure shows a schematic of the main study (all subjects with PD):



PBO: placebo; Rand: randomization.

Study Design, Sentinel Cohort:

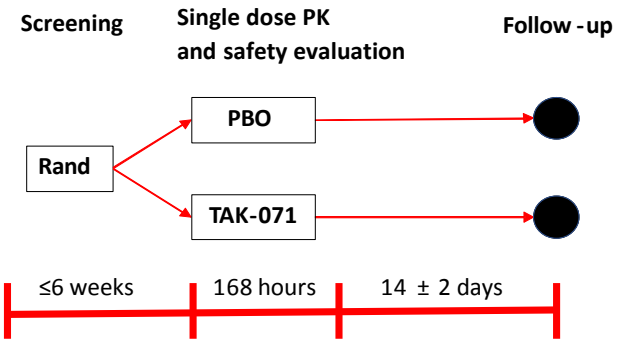
An initial sentinel cohort of healthy subjects will be enrolled at designated site(s), in parallel with enrollment of PD patients in the main cohort. Approximately 10 healthy subjects of either sex, aged 56 to 75 years, inclusive, will initially be randomized 3:1 to TAK-071 7.5 mg versus placebo. After analysis of data from these subjects, additional subjects may be enrolled, 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 in the main study. If older subjects are expected to remain below the exposure caps (potentially at a lower dose), they will also be enrolled. The maximum subject age and dose may be modified after analysis of data from the sentinel cohort. Update: At the completion of the sentinel cohort, based on PK modeling, a decision was made by the sponsor to allow enrollment of subjects aged 66 to 85 years, inclusive, at a dose of 5 mg. The dose for subjects aged 40 to 65 years, inclusive, will continue to be 7.5 mg.

The figure shows a schematic of the sentinel cohort (healthy subjects).



In unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that impact the ability to conduct study procedures according to the Schedule of Study Procedures, contingency measures may be implemented. The United States Food and Drug Administration issued guidance on the management of clinical trials during the coronavirus disease 2019 (COVID-19) pandemic (fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency. Accessed 12 June 2020). Hospital, local, state and national restrictions designed as precautions to ensure the rights, safety and wellbeing of study subjects during the COVID-19 pandemic have also been established. These restrictions may also prevent conduct of study procedures according to the Schedule of Study Procedures. Alternative approaches to study procedures and data collection for the current study are described.

Objectives for Subjects With PD

Primary Objectives

The primary objectives for subjects with PD are:

- To evaluate the efficacy of TAK-071 versus placebo on gait dysfunction, as measured by gait variability during a 2-minute walk test.
- To evaluate the safety and tolerability of TAK-071.

Secondary Objectives

The secondary objectives for subjects with PD are:

- To evaluate the efficacy of TAK-071 versus placebo on cognition globally, as determined by a cognitive profile including attention, executive functioning, and memory.
- To evaluate the PK of TAK-071.

Objectives for Healthy Subjects

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

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

Subject Population:

In the main study: Subjects diagnosed with PD who have cognitive impairment and a history of falls, aged 40 years to 85 years, inclusive. **Subjects must not be taking acetylcholinesterase inhibitors.**

In the sentinel cohort: Healthy subjects aged 56 to 75 years, inclusive, will initially be enrolled.

Number of Subjects:	**Number of Sites:**
In the main study, approximately 64 subjects with PD to ensure at least 42 completers. Each subject with PD will receive both treatments in a crossover manner: TAK-071 or placebo. **In the sentinel cohort**, initially approximately 10 subjects. Additional subjects may subsequently be enrolled. Healthy subjects will receive a single dose of TAK-071 or placebo.	Up to 25 sites in the United States.
Dose Levels: **For subjects with PD:** - Aged 40 to 65 years, inclusive: 7.5 mg TAK-071 or placebo, QD. - Aged 66 to 85 years, inclusive: 5 mg TAK-071 or placebo, QD. **For healthy subjects:** A single dose of 7.5 mg TAK-071 or placebo.	**Route of Administration:** Oral
Duration of Treatment: **For subjects with PD:** Two 6-week treatment periods. **For healthy subjects:** A single dose.	**Period of Evaluation:** **For subjects with PD:** 17 weeks, plus screening period of 1 to 42 days (23 weeks maximum total). **For healthy subjects:** 22 days plus screening period of 1 to 42 days.

Main Criteria for Inclusion:

For subjects with PD: Male and female subjects aged 40 to 85 years, inclusive. Subjects with PD (identified by MDS clinical diagnostic criteria) who have Hoehn and Yahr stage ≥2 and <4 at screening, have had at least 1 PD-related fall in the 12 months before screening, are at continued risk of falls per investigator judgment, have evidence of cognitive impairment (Montreal Cognitive Assessment [MOCA] score between 11 and 26, inclusive), can complete cognitive assessments at screening (as specified in the study manual), are able to walk without aid for 2 minutes while doing serial 3 subtraction, are on stable antiparkinsonian medication for at least 30 days before randomization and able to remain on stable dosage during study, and have a study partner involved in care of the subject at least 2 hours per day who is willing to supervise and assist the subject with medication administration and to complete fall assessments.

Subjects must not be taking acetylcholinesterase inhibitors.

Please note that subjects who have dementia with Lewy body (DLB)(ie, dementia was diagnosed before onset of

motor symptoms or up to 1 year after onset of motor symptoms) are eligible for this study consistent with the MDS clinical diagnostic criteria for PD.

For healthy subjects: Male and female subjects aged 56 to 75 years, inclusive.

Main Criteria for Exclusion:

For subjects with PD: Parkinsonism not due to primary PD; orthostatic hypotension judged to preclude safe participation in the study; prior neurosurgical intervention for PD (with the exception of deep brain stimulation [DBS] device implanted ≥1 year prior to screening with stable settings for ≥2 months and further changes in DBS settings not anticipated); dyskinesia of sufficient severity to interfere with digital gait assessments or other study aspects; excessive daytime sleepiness of sufficient severity to interfere with participation in the cognitive and gait assessments; fall-related institutionalization or hospital admission (not including emergency room visit) between screening and first baseline visit.

For subjects with PD and healthy subjects: Medical problems (other than PD) that significantly interfere with balance, gait, or completion of the study; significant risk factors for seizures; depression or other psychiatric disorder of sufficient severity to interfere with participation in the study; at risk of suicide. Additional major exclusions will include orthostatic hypotension, estimated glomerular filtration rate (eGFR) <60 mL/min (calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation; subjects not meeting the eGFR<60 mL/min or orthostasis criteria may remain eligible, conditional on agreement between sponsor and investigator); a serum total bilirubin value >1.2 × upper limit of normal (ULN); a serum ALT or AST value >1.2 × ULN. Subjects with a positive hepatitis B surface antigen test result or known or suspected active hepatitis C infection are also excluded.

Endpoints for Subjects With PD:

Primary Endpoint:

The primary endpoint for subjects with PD is the change from baseline in gait variability during a 2-minute walk on a 10-meter walkway after 6 week treatment with TAK-071 compared with placebo.

Secondary Endpoints:

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

The PK endpoints for subjects with PD are:

- Observed concentration at the end of a dosing interval (Ctrough) of TAK-071 in subjects with PD (Day 42 of Period 1 and Period 2 only).
- Maximum observed concentration (Cmax) and area under the concentration-time curve (AUC) of TAK-071 in subjects with PD.
- Time of first occurrence of Cmax (tmax).

Safety Endpoints:

The safety endpoints for subjects with PD are:

- Adverse events (AEs).
- Clinical laboratory evaluations.
- Electrocardiograms (ECGs).
- Physical examinations.
- Suicidal ideation and behavior as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS).
- Movement Disorders Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) to evaluate for worsening of motor or nonmotor symptoms.

Endpoints for Healthy Subjects:

Primary Endpoints:

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

- C_{max}.
- t_{max}.
- Area under the concentration-time curve from time 0 to 24 hours (AUC_{24}).
- Area under the concentration-time curve from time 0 to the last quantifiable concentration (AUC_{last}).
- Area under the concentration-time curve from time 0 to infinity (AUC_{inf}).

Safety Endpoints:

The safety endpoints for healthy subjects are:

- AEs.
- Clinical laboratory evaluations.
- ECGs.
- Physical examinations.
- Suicidal ideation and behavior as measured by the C-SSRS.

Statistical Considerations:

For subjects with PD, the primary outcome, the change from baseline in gait variability during a 2-minute walk test, will be analyzed using a linear mixed effect model with a random factor for subject and fixed factors for treatment, period, and sequence. Baseline covariates will be included in the model as appropriate.

The effect of treatment on the overall cognitive battery will be analyzed using a linear mixed effects model with random effects for subjects for each cognitive test, fixed factors for treatment, test, period, and sequence. The comparison of the number of falls for placebo versus TAK-071 will be analyzed using a generalized linear mixed effects model with a random factor for subjects, fixed factors for treatment, period, and sequence.

Drug effects on change from baseline for all endpoints will be assessed using 1-sided tests. In all analyses the interaction terms and covariates will be added as appropriate.

For healthy subjects, analysis will focus on PK (eg, C_{max}, t_{max}, AUC_{inf}, and AUC_{24}).

Sample Size Justification:

For subjects with PD, a sample size of 42 completers will be sufficient to detect a statistically significant ($\alpha = 0.05$, 1-sided) decrease in gait variability during walking for TAK-071 versus placebo. We expect to detect a minimum effect size of 0.32 (Cohen d) in the reduction of gait variability. For the sample size calculation, the study power was assumed to be 80%.

Given the proposed study sample size and 80% power, a minimum detectable operational effect size for the cognitive battery ($\alpha = 0.1$, 1-sided) will be 0.49. The correlations between cognitive tests are assumed to be 0.5. The minimum detectable ($\alpha = 0.1$, 1-sided) effect size in the number of falls will be approximately 0.3. For all calculations, the within-person correlation was assumed to be 0.65.

For healthy subjects (sentinel cohort), a sample size of approximately 10 subjects at a 3:1 ratio is considered to be likely sufficient to adequately describe single-dose PK and safety.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Contract Research Organization Obligations Listing, located in the trial master file. The vendors identified in the listing for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

Abbreviation	Definition
AChEI	acetylcholinesterase inhibitor
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
$AUC_{24,ss}$	area under the concentration-time curve from time 0 to 24 hours at steady state
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the last quantifiable concentration
BMI	body mass index
CFR	Code of Federal Regulations
CGI-S/I	Clinical Global Impression-Severity/Improvement
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration at steady state
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{trough}	observed concentration at the end of a dosing interval
CYP	cytochrome P-450
DBS	deep brain stimulation
DLB	dementia with Lewy body
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
ICH	International Conference on Harmonisation
ID	identification (number)
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IWRS	interactive web response system
LBD	Lewy body dementia

Abbreviation	Definition
LFT	liver function test
MCI	mild cognitive impairment
MDS	Movement Disorders Society
MDS-UPDRS	Movement Disorders Society–Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
mRNA	messenger ribonucleic acid
NBM	nucleus basalis of Meynert
NfL	neurofilament light chain
OR	odds ratio
PAM	positive allosteric modulator
PBPK	physiologically based PK
PD	Parkinson disease
PDD	Parkinson disease dementia
PGI-S/I	Patient Global Impression-Severity/Improvement
PK	pharmacokinetic(s)
PT	Preferred Term
PTE	pretreatment event
QD	once daily
QTcF	QT interval with Fridericia correction
SAE	serious adverse event
SAP	statistical analysis plan
SAT	Sustained Attention Test
SDMT	Symbol Digit Modalities Test
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
TUG	Timed Up and Go test
ULN	upper limit of normal

4.0 INTRODUCTION

4.1 Background and Rationale

TAK-071 is a first-in-class muscarinic M_1 positive allosteric modulator (M_1 PAM) proposed for the reduction of falls and improvement of cognition in Parkinson disease (PD).

4.1.1 Falls in PD

Falls are a common cause of morbidity and mortality in patients with PD. The cause of falls is multifactorial and involves interactions between environmental, motor, and cognitive factors.

Multiple lines of evidence suggest that falls are in part a consequence of the simultaneous loss of dopaminergic and cholinergic transmission associated with PD. PD is associated with a substantial loss of cholinergic fibers, which has been demonstrated using acetylcholinesterase positron emission tomography, as well as postmortem histopathological analyses. Cortical cholinergic deficits are significant in early PD and are correlated with cognitive decline in patients with PD and are more severe than in Alzheimer disease [1]. Modelling of PD-related falls in animal models has demonstrated that loss of striatal dopamine synergizes with cholinergic neuron loss in the basal forebrain to impair gait and increase falls.

There is clinical evidence that cholinergic drugs may reduce fall risk in patients with PD. The largest published study to date (n = 130, [2] showed that rivastigmine reduced step time variability, a correlate of fall risk, and the risk of falling was lowered by approximately 50% with 6 months of treatment. A smaller study (n = 23, [3]) showed that donepezil, an acetylcholinesterase inhibitor (AChEI), also reduced the risk of falls or near falls by approximately 50%. Li et al [4] studied 176 Chinese patients with PD who were randomized to placebo or rivastigmine, another AChEI. Changes in cognition and fall incidence were compared between the 2 groups. Patients with mild cognitive impairment (MCI) (odds ratio [OR] = 2.5) or dementia (OR = 5.5) fell significantly more than patients with intact cognition. Rivastigmine improved cognition and reduced the number of falls relative to placebo (OR = 0.3). However, these studies suffer from significant methodological flaws. A recent publication [5] reported that donepezil did not improve balance in patients with PD.

Although these findings are somewhat supportive regarding AChEIs, efficacy has not been conclusively demonstrated. TAK-071 can selectively activate M_1 receptors without interfering with the temporal dynamics of ACh signaling, which plays a critical role in specific cognitive functions such as attention. AChEIs instead cause a tonic increase of ACh, with nonselective direct agonism at all muscarinic receptor subtypes while disrupting the temporal dynamics of ACh signaling, which is believed to cause adverse effects and may obscure the procognitive effects of M_1 receptor activation.

4.1.2 Cognitive Impairment in PD

Most patients with PD will develop dementia, either at least 1 year after the onset of motor symptoms (termed Parkinson disease dementia [PDD]) or less than 1 year after the onset of motor symptoms (termed dementia with Lewy body [DLB]). The term Lewy body dementia (LBD) encompasses both PDD and DLB. Currently, many experts in the field believe that there are few fundamental biological differences between these conditions and the term LBD will, therefore, be used here.

LBD has a major impact on functioning, cost of care, and quality of life. Before the development of LBD, patients initially experience MCI. In addition to the direct impact on functioning, cognitive impairment in patients with PD also significantly increases the risk for falls as described above.

Patients with PD show early and marked degeneration of the cholinergic system including a loss of cholinergic fibers from the nucleus basalis of Meynert (NBM), which mainly supplies the cortex, and the pedunculopontine nucleus, which mainly supplies the basal ganglia, thalamus, brainstem, and rostral spinal cord. The degeneration of the NBM in particular is strongly related to cognitive impairment in PD. As noted in Section 4.1.4, nonclinical data from NBM-lesioned rats is supportive of potential efficacy with respect to cognitive impairment.

TAK-071 could be valuable in the treatment of patients with PD through reducing fall risk and/or improving cognition, both unmet needs for patients. Therefore, the present study will evaluate both.

4.1.3 Impairments in Speech in PD

Speech difficulties occur in up to 90% of patients with PD over the course of the disease and significantly affect their social interactions and quality of life. Speech impairment in PD is likely the result of the combined effect of impaired motor control and cognitive deficits. In PD, a reduction in dopamine is associated with the cardinal motor symptoms of tremor, slowness of movement (bradykinesia) and muscle rigidity (stiffness). However, dopamine replacement therapy showed inconsistent effects on speech performance, suggesting the contribution of alternative neurotransmitters during speech processing. The vocal apparatus is under motor control and is therefore impacted by the loss of cholinergic projections observed in PD. Moreover, previous studies reported language processing deficits are associated with cognitive dysfunction in PD [6]. The role of the cholinergic system in cognition has been well established. Therefore, it is plausible that TAK-071, through enhancing cholinergic function, will improve both motor control and cognitive function in patients with PD, and consequentially speech function. Analysis of speech in patients with PD will provide data that are complementary to measures of walking and other complex motor tasks.

4.1.4 Nonclinical Data

Nonclinical studies suggest that TAK-071 may improve cognitive performance including working memory, recognition memory, and attention.

In Y-maze and the novel object recognition tests, TAK-071 improved working memory deficits and recognition memory, respectively, at 0.1 and 0.3 mg/kg in miR-137 Tg mice.

The neural activation pattern of TAK-071 measured by c-fos mapping in rodents was very similar to that of xanomeline, an M_1/M_4 agonist that previously showed efficacy for cognition in AD and schizophrenia but was limited by adverse events (AEs), while donepezil was not effective in this assay.

TAK-071 also significantly improved attentional function (measured by the Sustained Attention Test [SAT]) in rats with partial basal forebrain cholinergic lesions at doses as low as 0.1 mg/kg, a model where AChEIs are ineffective [7]. These findings are highly significant because the lesions in this model mirror the loss of cholinergic fibers in PD and because performance on this task is correlated with gait abnormalities and falls in a rat model of PD [8,9]. These data strongly support the potential of TAK-071 for falls and cognitive impairment in PD, as well as its differentiation from AChEIs.

Overall, these data suggest that TAK-071 is a promising therapy for cognitive impairment and falls in PD, and these data also provide important insights regarding differentiation from existing cholinergic therapies.

4.1.5 Differentiation From AChEIs and Other M_1 PAMs

There is a strong scientific basis for the notion that M_1 PAMs may be superior to AChEIs for falls and cognition. It has been established that ACh signals through slow "tonic" release as well as fast "phasic" release. Phasic ACh plays a critical role in the modulation of attention and other frontal cognitive functions that may be critical for cognitive gait control. AChEIs chronically elevate synaptic ACh levels, which may impair phasic signaling, whereas M_1 PAMs such as TAK-071 do not disrupt these temporal dynamics and support phasic signaling.

Previous nonclinical evidence has strongly supported the synergistic effect of cholinergic lesions on dopaminergic deficits in falls in a rat model of PD [7]. Rats with dual cholinergic-dopaminergic lesions have clearly shown more frequent falls than rats with either cholinergic or dopaminergic lesions. Moreover, the attention performance and falls were only correlated in these animals with dual lesions. Therefore, enhancement of cholinergic function may have a positive impact not only on cognition, but also falls in PD. Whereas AChEIs are ineffective in this dual-lesion model, TAK-071 significantly improves attentional performance, which strongly supports the prediction that TAK-071 can support phasic ACh signaling to improve cognition, and by inference cognitive control of gait.

TAK-071 has distinct pharmacology from other M_1 PAMs. For example, Merck's selective M_1 PAM MK-7622 has a higher binding cooperativity (α-value: 511, where α is the fold increase of ACh affinity for its binding site due to the effects of the PAM) than TAK-071 (α-value: 199). Higher binding cooperativity has been shown to be strongly related to poor gastrointestinal tolerability in nonclinical studies [10]. TAK-071, but not MK-7622, showed synergy with donepezil in the scopolamine-induced cognitive deficit model. Taken together with other nonclinical studies comparing these drugs, these data strongly suggest that TAK-071 affects receptor signaling differently from MK-7622 and has distinct in vivo pharmacology.

4.2 Benefit/Risk Profile

TAK-071 is a highly selective cholinergic muscarinic M_1 receptor PAM. Nonclinical data indicate that cortical cholinergic deficits are associated with cognitive decline and falls in PD models, and clinical studies suggest that cholinergic drugs may reduce fall risk in patients with PD. There is therefore a scientific rationale for exploring the potential of TAK-071 to improve cognitive function and decrease falls in patients with PD. However, clinical benefit of TAK-071 has not been established because the product has only been tested in phase 1 studies in healthy subjects.

Nonclinical toxicology studies showed convulsions in rats and monkeys and neurotoxicity in rats at high doses. Consequently, clinical doses are limited to those expected to result in plasma TAK-071 exposures of no more than 600 ng/mL and 14,000 h*ng/mL for maximum observed concentration (C_{max}) and area under the concentration-time curve from time 0 to 24 hours (AUC_{24}), respectively. This allows up to a 7.5 mg once daily (QD) clinical dose. After 7.5 mg QD doses, the projected maximum observed concentration at steady state ($C_{max,ss}$) and area under the concentration-time curve from time 0 to 24 hours at steady state ($AUC_{24,ss}$) are 549 ng/mL and 12,900 h*ng/mL, respectively, in subjects 18 to 55 years old, within the exposure limits. **In addition, TAK-071 must not be coadministered with an acetylcholinesterase inhibitor (eg, donepezil, rivastigmine, galantamine) because of the potential to cause convulsions based on data from nonclinical toxicology studies**.

In phase 1 clinical studies, a total of 139 healthy subjects 18 to 55 years old have received at least 1 dose of TAK-071. There were no SAEs or deaths reported. Review of all available clinical safety data indicates that TAK-071 is generally safe and well tolerated.

Information from the completed phase 1 studies, together with the nonclinical toxicity studies in rats and monkeys, indicates that the benefit-risk balance for TAK-071 is deemed acceptable at the proposed dose of 7.5 mg. Clinical dosing of TAK-071 with donepezil and other AChEIs is not supported.

Please see the investigator's brochure for more details regarding the safety profile of TAK-071.

Exploratory biomarker analysis, including DNA, plasma, cerebrospinal fluid, and exosome protein and nucleic acid analysis may be conducted to investigate the contribution of genetic and other biological factor variance on drug response, for example, its efficacy and safety.

5.0 STUDY OBJECTIVES AND ENDPOINTS

This section details the objectives and endpoints for the main study, ie, for subjects with PD.

For the sentinel cohort (ie, healthy subjects), please refer to Appendix H.

5.1 Objectives

5.1.1 Primary Objectives

The primary objectives for subjects with PD are:

- To evaluate the efficacy of TAK-071 versus placebo on gait dysfunction, as measured by gait variability during a 2-minute walk test.
- To evaluate the safety and tolerability of TAK-071.

5.1.2 Secondary Objectives

The secondary objectives for subjects with PD are:

- To evaluate the efficacy of TAK-071 versus placebo on cognition globally, as determined by a cognitive profile including attention, executive functioning, and memory.
- To evaluate the pharmacokinetics (PK) of TAK-071.

5.1.3 Exploratory/Additional Objectives

The exploratory/additional objectives for subjects with PD are:

- To evaluate the efficacy of TAK-071 versus placebo on specific cognitive tests that measure domains including attention, executive functioning, and memory.
- To evaluate the efficacy of TAK-071 versus placebo on gait parameters during a 2-minute walk test in the presence versus absence of cognitive loading.
- To evaluate the efficacy of TAK-071 versus placebo on gait variability and double support time during a 2-minute walk test in the presence versus absence of cognitive loading.
- To evaluate the efficacy of TAK-071 versus placebo on self-directed turns during a 2-minute walk test in the presence versus absence of cognitive loading.
- To evaluate the efficacy of TAK-071 versus placebo on cued 180-degree turns during walking.
- To evaluate the efficacy of TAK-071 versus placebo on functional mobility, as measured by time to complete the Timed Up and Go test (TUG).
- To evaluate the efficacy of TAK-071 versus placebo on postural stability, as measured by postural sway with eyes open and closed.
- To evaluate the efficacy of TAK-071 versus placebo on speech production based on in-clinic assessments.
- To evaluate the efficacy of TAK-071 versus placebo on speech production as assessed in the home.
- To evaluate the efficacy of TAK-071 versus placebo on in-home activity as measured by a wearable pendant sensor in the home.

- To evaluate the efficacy of TAK-071 versus placebo on fall frequency as assessed using a wearable pendant sensor in the home.
- To evaluate the efficacy of TAK-071 versus placebo on fall frequency as assessed using a study partner–reported falls diary.
- To evaluate the efficacy of TAK-071 versus placebo on subjective daytime sleepiness as assessed by the Epworth Sleepiness Scale (ESS).
- To evaluate the efficacy of TAK-071 versus placebo on 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).
- To evaluate the impact of TAK-071 versus placebo on 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 M_1 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 relationship of pharmacodynamic endpoints to disease characteristics.
- The ratio of plasma 4-beta-hydroxycholesterol to cholesterol and the relationship to plasma TAK-071 area under the concentration-time curve (AUC) may be analyzed.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint for subjects with PD is the change from baseline in gait variability during a 2-minute walk on a 10-meter walkway after 6-week treatment with TAK-071 compared with placebo.

5.2.2 Secondary Endpoints

The secondary efficacy endpoint for subjects with PD is the change from baseline in a global cognition profile 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, Cogstate One Card Learning Test) after 6-week treatment with TAK-071 compared with placebo.

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 AUC of TAK-071 in subjects with PD.

- t_{max}.

5.2.3 Safety Endpoints

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).
- MDS-UPDRS (to evaluate for worsening of motor or nonmotor symptoms).

5.2.4 Exploratory Endpoints

The exploratory pharmacodynamic endpoints for subjects with PD are:

- Audio recordings to verify serial subtraction performance during the 2-minute walk after 6-week treatment with TAK-071 compared with placebo.
- Change from baseline on cognitive performance on individual cognitive tests (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 compared with placebo.
- Change from baseline on gait parameters in the presence versus absence of cognitive loading during a 2-minute walk on a 10-meter walkway after 6-week treatment with TAK-071 compared with placebo.
- Change from baseline in gait variability and double support time in the presence versus absence of cognitive loading during a 2-minute walk after 6-week treatment with TAK-071 compared with placebo.
- Change from baseline in self-directed turns in the presence versus absence of cognitive loading during a 2-minute walk test after 6-week treatment with TAK-071 compared with placebo.
- Change from baseline in cued 180 degree turns after 6-week treatment with TAK-071 compared with placebo.
- Change from baseline in the completion time of the TUG after 6-week treatment with TAK-071 compared with placebo (average of 3 trials).
- Change from baseline in postural sway with eyes open and eyes closed during a 30-second balance test after 6-week treatment with TAK-071 compared with placebo.

- Change from baseline on speech performance after 3- and 6-week treatment with TAK-071 compared with placebo.
- Change from baseline in in-home activity measured by a wearable pendant sensor during 6-week treatment with TAK-071 compared with placebo.
- Change from baseline in number of falls measured by a wearable pendant sensor during 6-week treatment with TAK-071 compared with placebo.
- Change from baseline in number of falls and number of near-falls measured by a falls diary during 6-week treatment with TAK-071 compared with placebo.
- Change from baseline on the ESS after 6-week treatment with TAK-071 compared with placebo.
- Change from baseline on the CGI-S and PGI-S after 6-week treatment with TAK-071 compared with placebo.
- Values of CGI-I and PGI-I after 6-week treatment with TAK-071 compared with placebo.
- Change from baseline on MDS-UPDRS Part 3 scores (including individual motor assessments in Parts 3.1-3.18, impact of dyskinesia, and the Hoehn and Yahr scale) and on MDS-UPDRS Parts 1, 2, and 4 scores after 6-week treatment with TAK-071 compared with placebo.
- 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 will be used to assess potential variability in drug response and safety.
- Relationship of pharmacodynamic endpoints to disease characteristics.
- The relationship of the ratio of plasma 4-beta-hydroxycholesterol/cholesterol with plasma TAK-071 AUC may be analyzed.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design, Main Study

This section describes the main study (subjects with PD). For the healthy subject cohort, please see Appendix H.

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 and who are not concurrently taking acetylcholinesterase inhibitors.

Approximately 64 male and female subjects, aged 40 to 85 years, inclusive, will be enrolled at up to 25 sites in the United States.

The main 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 MDS clinical diagnostic criteria for PD, will then be given additional assessments as specified in the schedule of study procedures (Appendix A).

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.

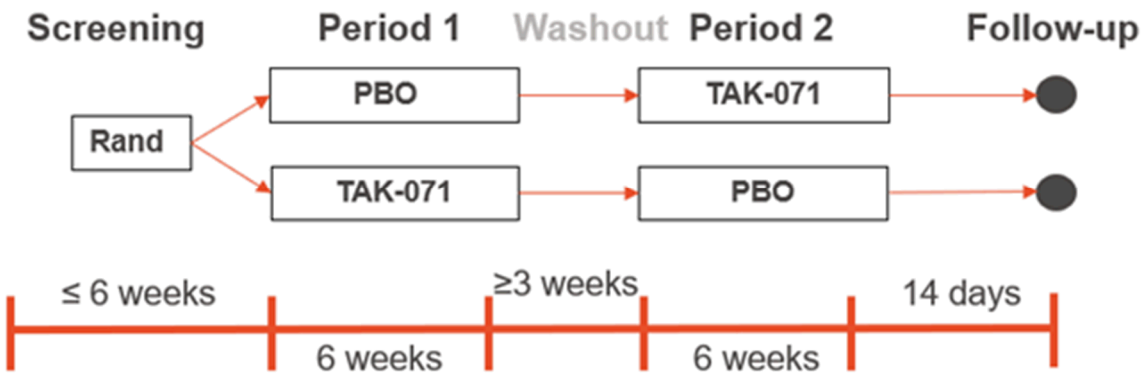
Subjects will receive TAK-071 or placebo QD from Day 1 through Day 42 of each period. Clinic visits include Day 1 and Weeks 6, 9, and 15. Clinical assessments, blood collections, and laboratory tests will be conducted at specific time points per the schedule of study procedures (Appendix A).

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, ie, the safety follow-up call.

A schematic of the main study design is included as Figure 6.a. A detailed schedule of study procedures is provided in Appendix A.

Figure 6.a Schematic of Study Design, Main Study



PBO: placebo; Rand: randomization.

While subjects with PD (initially restricted to those aged 40 to 65 years, inclusive) are being enrolled in the main study, a sentinel cohort of healthy subjects will be enrolled in parallel at designated sites (see Appendix H).

After the PK, safety, and physiologically based PK modeling data from the sentinel cohort have

been assessed, a decision will be made by the sponsor about the dose for the remaining subjects with PD to be enrolled in the main study. 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. Update: At the completion of the sentinel cohort, based on PK modeling, a decision was made by the sponsor to allow enrollment of subjects aged 66 to 85 years, inclusive, at a dose of 5 mg. The dose for subjects aged 40 to 65 years, inclusive, will continue to be 7.5 mg.

6.2 Contingency Measures Due to COVID-19 Pandemic or Other Unavoidable Circumstances

This section applies to all study subjects.

In unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that impact the ability to conduct study procedures according to the schedule of study procedures (Appendix A), contingency measures may be implemented. In March 2020, the United States Food and Drug Administration (FDA) issued guidance on the management of clinical trials during the coronavirus disease 2019 (COVID-19) pandemic (fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency. Accessed 12 June 2020). Hospital, local, state and national restrictions designed as precautions to ensure the rights, safety and wellbeing of study subjects during the COVID-19 pandemic have also been established. These restrictions may also prevent conduct of study procedures according to the Schedule of Procedures. Alternative approaches to study procedures and data collection for the current study are described in Section 9.1.24.

6.3 Justification for Study Design, Endpoints, and Dose

This section applies to the main study (subjects with PD).

6.3.1 Subject Selection Considerations

Consistent with our focus on fall prevention, we are selecting subjects with PD who are at elevated risk of falling based on a history of falls. On the other hand, subjects who are at advanced stages of PD will not be able to complete gait assessments. Subjects with Hoehn and Yahr stage ≥2 and <4 will, therefore, be selected for this study to ensure that PD severity is significant but not to the extent that the gait assessments become impossible. Furthermore, cognitive impairment is a risk factor for falls, and it is important to select subjects with sufficient cognitive impairment to avoid ceiling effects so that efficacy for cognition and improvement of gait via effects on cognition can be observed. On the other hand, very significant cognitive impairment will make following instructions and completing assessments difficult. Given these considerations, subjects who score between 11 and 26 on the Montreal Cognitive Assessment (MoCA) and who complete the cognition assessments at screening will therefore be selected.

6.3.2 Justification for Digital Endpoints

Fall risk is correlated with several aspects of gait, including gait variability measured using stride and step time variability. Stride and step time variability are variables that can be measured with high precision using digital gait assessments in the clinic and are believed to reflect cognitive gait control; gait variability is a more appropriate primary endpoint for small initial patient studies, such as the present study, than actual falls.

The wearable pendant sensor generates 2 endpoints, in-home activity and number of falls. In-home activity is measured by calculating the number of steps taken by the patient every 15 minutes throughout the day from the raw sensor data. Hourly, daily, and weekly activity is then calculated from this step count data. Number of falls is measured using a proprietary algorithm to detect a fall from the raw sensor data. If a fall is detected, the time stamp of the fall is recorded and transmitted immediately, and the raw sensor data before and after the fall is saved locally on the device for offline analysis. Daily, weekly, and monthly number of falls are then calculated on the basis of the time-stamped falls.

6.3.3 Dose Justification

TAK-071 has been tested in human phase 1 clinical studies in healthy subjects 18 to 55 years old (197 subjects total, 139 dosed with TAK-071). After single (1 to 160 mg) and multiple (3 to 15 mg QD) oral doses of TAK-071, systemic exposure (C_{max} and AUC) to TAK-071 increased in only a slightly less than dose proportional manner. TAK-071 demonstrated a long half-life of 46 to 61 hours and reasonable brain penetration after oral dose. TAK-071 was well tolerated, with no deaths or SAEs. There was 1 discontinuation due to headache and 1 severe treatment-emergent adverse event (TEAE) of syncope. Both subjects were on TAK-071 and the AEs resolved. No clinical concerns were raised by laboratory tests, ECG, physical examination, or bowel function assessment.

The simulated exposure predictions for a 7.5 mg QD dose in humans, which is the dose proposed for this study in PD, yield a C_{min} exposure (ie, 432 ng/mL) that is 6.0-fold the rat C_{max} exposure at 0.1 mg/kg (ie, 72 ng/mL), the predicted efficacious dose from the cholinergic lesion model. Therefore, there is ample margin to test the efficacy of TAK-071 in humans.

The subjects selected for this study are older than those in phase 1 clinical studies, 40 to 85 years, inclusive, versus 18 to 55 years, inclusive. The potential exposure difference was assessed through an initial preliminary physiologically based PK (PBPK) modeling of phase 1 PK data using SimCyp Simulator, and the model projection indicated an increase of less than 25% in mean exposure measures (C_{max} and AUC) for a 7.5 mg QD dose for older subjects of 40 to 75 years, inclusive, versus subjects of 18 to 55 years, inclusive. For subjects aged 40 to 75 years, inclusive, SimCyp simulations predict a geometric mean $C_{max,ss}$ of 580 ng/mL and a geometric mean $AUC_{24,ss}$ of 11,100 hr*ng/mL. Higher exposure was achieved by multiple doses of up to 15 mg in the phase 1 clinical studies and was determined to be safe and well tolerated.

To study the age effect and ensure safety for older subjects, an initial small sentinel cohort of healthy subjects aged 56 to 75 years, inclusive, was enrolled with rich PK sampling after a single dose (at designated site[s]; see Appendix H). The PBPK model developed from the sentinel cohort

data suggest that subjects 40 to 65 years can continue to receive TAK-071 7.5 mg QD. A lower dose of TAK-071 5 mg QD is recommended for subjects 66 to 85 years to keep the exposure under the exposure cap, ie, 600 ng/mL for $C_{max,ss}$ and 14,000 hr*ng/mL for $AUC_{24,ss}$. Based on these results, a decision was made to expand the main cohort to include subjects with PD aged 66 to 85 years, inclusive, at a dose of 5 mg. Of note, the PBPK modeling projections of geometric mean $C_{max,ss}$ and $AUC_{24,ss}$ are below the exposure caps. For subjects aged 40 to 65 years, inclusive, the projections of geometric mean $C_{max,ss}$ and $AUC_{24,ss}$ at a dose of 7.5 mg are 586 ng/mL and 11,663 hr*ng/mL, respectively. For subjects aged 66 to 85 years, inclusive, the projections of geometric mean $C_{max,ss}$ and $AUC_{24,ss}$ at a dose of 5 mg for TAK-071 are 556 ng/mL and 11,624 hr*ng/mL, respectively.

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.

6.4 Premature Termination or Suspension of Study or Study Site

This section applies to all subjects.

6.4.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned, unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known benefit-risk profile for TAK-071, such that the risk is no longer acceptable for subjects participating in the study.
- One or more subjects experience a seizure that in the opinion of the investigator is related to TAK-071.
- The following events occur regarding liver function:
  - Two or more subjects experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 × upper limit of normal (ULN) in the absence of a concomitant bilirubin increase.
  - One or more subjects experience ALT and/or AST elevations >3 × ULN in the presence of a total bilirubin increase >2 × ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (ie, “Hy’s Law cases”).
  - Two or more subjects experience ALT and/or AST elevations >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

6.4.2 Criteria for Premature Termination or Suspension of Study Sites

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

6.4.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

7.1 Inclusion Criteria

This section applies to the main study (subjects with PD). Criteria for the sentinel cohort (healthy subjects) are described in Appendix H.

1. The subject (or, when applicable, the subject's legally acceptable representative) signs an informed consent form indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.
2. The subject has a study partner who in the opinion of the investigator is sufficiently involved in the daily care of the subject to provide reliable information on falls, and assist the subject with at-home assessments, medication compliance, and attending study visits. Study partners who live with the subject are strongly preferred, but must spend at least 2 hours per day with the subject. The study partner must be willing to supervise and assist with medication administration and complete fall assessments on a daily basis during the study.
3. The subject is an outpatient of either sex aged between 40 and 85 years, inclusive, at the time of consent.
4. The subject has a diagnosis of PD according to MDS clinical diagnostic criteria for PD. Subjects with DLB (ie, dementia diagnosed before onset of motor symptoms or up to 1 year after onset of motor symptoms) are also eligible, consistent with MDS clinical diagnostic criteria for PD.
5. The subject has Hoehn and Yahr stage ≥2 and <4 at the screening visit (bilateral involvement without impaired balance to mild to moderate bilateral disease with some postural instability but physically independent).
6. The subject has elevated risk for falls as indicated by at least 1 fall in the last 12 months before the screening visit based on the Fall History Assessment where in the opinion of the

investigator the falls were a consequence of PD, and who are at continued elevated risk of falls per investigator judgment. Investigator judgment on fall risk may be informed by information such as, but not limited to, history, physical examination and/or a score ≥2 on item 3.10 on MDS-UPDRS Part III.

7. The subject has evidence of cognitive impairment as indicated by a MoCA score between 11 and 26, inclusive, and additionally can complete the cognitive assessments at screening (as specified in the study manual).
8. The subject has the ability to follow study instructions according to the investigator's judgement.
9. The subject can walk without aid for 2 minutes while doing serial 3 subtraction (with site staff ensuring subject safety in case of falls). Subjects who require aids for walking can be included as long as they can complete the walk test without aid.
10. The subject has been on stable antiparkinsonian medication for at least 30 days before randomization and, in the opinion of the investigator, is expected to be able to remain at a stable dosage during the study without addition of new medications during the study.
11. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential is eligible to participate if he agrees to use barrier method of contraception (ie, condom with or without spermicide) from signing of informed consent throughout the duration of the study and for 102 days after the last dose.
12. Female subjects are eligible to participate if a) not pregnant or nursing, and b) of nonchildbearing potential or agree to use highly effective contraception from signing of informed consent throughout the duration of the study and for 42 days after last dose of study drug.

7.2 Exclusion Criteria

This section applies to the main study (subjects with PD). Criteria for the sentinel cohort (healthy subjects) are described in Appendix H.

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

1. In the opinion of the investigator, the subject's parkinsonism is not due to primary PD.
2. The subject has orthostatic hypotension (defined as a decline in systolic blood pressure of 20 mm Hg or a decline in diastolic blood pressure of 10 mm Hg on standing measured within 1 minute of standing after being supine for at least 5 minutes). Subjects not meeting this criterion may be eligible if the principal investigator and the sponsor agree that the subject can safely participate in the study.
3. The subject has body mass index (BMI) less than 18 or greater than 40.
4. The patient has dyskinesia of sufficient severity to interfere with digital gait assessments during visits (as defined by MDS-UPDRS section 4.1 "Time spent with dyskinesias" and/or section 4.2 "Functional Impact of Dyskinesias" scores >2), and in the opinion of the

investigator the patient's dyskinesia is likely to interfere with the digital gait assessments or other aspects of the study.

5. In the opinion of the investigator the patient has excessive daytime sleepiness of sufficient severity to interfere with participation in the cognitive and gait assessments.
6. The subject has received neurosurgical intervention for PD (eg, pallidotomy, thalamotomy) or has had a deep brain stimulation (DBS) device placed within the past year. Individuals who had a DBS implanted ≥1 year ago and have had stable settings for ≥2 months may participate if safe to do so, if the presence of DBS will not impact study assessments, and if further changes in DBS settings are not anticipated for the duration of study participation, per investigator judgment.
7. The subject has other medical problems (neurological, visual, orthopedic, psychiatric) that in the opinion of the investigator may significantly interfere with balance or gait, or interfere with completion of the study or interpretation of study endpoints.
8. The subject has significant risk factors for seizures (a history of seizures as an adult, a history of brain injury, or other risk factors deemed relevant by the investigator).
9. The subject has significant medical disease (renal, cardiac, endocrine, pulmonary, etc) based on medical history, physical examination, ECG, or laboratory evaluations, and/or in the opinion of the investigator the subject is otherwise unlikely to be medically able to participate in the study due to any reason including having a disorder that may interfere with drug absorption, distribution, metabolism, or excretion.
10. The subject has any of the following at the screening visit: estimated glomerular filtration rate (eGFR) (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) <60 mL/min; QT interval with Fridericia correction method (QTcF) >450 msec for male subjects and >470 msec for female subjects; a serum total bilirubin value >1.2 × ULN; a serum ALT or AST value >1.2 × ULN. Subjects with a positive hepatitis B surface antigen test result or known or suspected active hepatitis C infection are also excluded. Note: Subjects with positive hepatitis C virus (HCV) serology may be enrolled if quantitative polymerase chain reaction for HCV RNA is negative, to exclude active hepatitis C infection, and the investigator agrees that the subject can safely participate in the study. Subjects with eGFR <60 mL/min may be eligible if the investigator and the sponsor agree that the subject may safely participate in the study. Any screening laboratory test may be repeated if the investigator believes that a value is inaccurate.
11. In the opinion of the investigator the patient suffers from depression or other psychiatric disorder of sufficient severity to interfere with completion of the study or interpretation of the endpoints.
12. The subject has suffered from a substance use disorder (other than tobacco-use disorder) within the past 1 year before the first dose of study medication, or in the opinion of the investigator the subject's current or past use of substances may interfere with performance on the cognitive, motor, or other assessments.

13. The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or the subject has attempted suicide within the past year before screening. Subjects who have positive answers on item number 4 or 5 on the C-SSRS (based on the past year) before randomization are excluded.
14. The subject is unwilling or unable to discontinue taking cholinesterase inhibitors and/or moderate or strong CYP 3A4 inhibitors or inducers at least 30 days before randomization.
15. The subject is taking warfarin.
16. The subject has received any investigational compound that, in the opinion of the investigator or sponsor, may not have completely washed out before the screening visit.
17. The subject has received TAK-071 in the past.
18. The subject is an immediate family member, study site employee, or in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling).
19. The subject has donated 400 mL or more of his or her blood volume within 90 days before the start of the screening visit.
20. The subject has a known hypersensitivity to any component of the formulation of TAK-071.
21. The subject has a fall-related institutionalization or hospital admission that occurs during the period between screening and the first baseline visit (not including emergency room visit).

7.3 Excluded/Allowed Medications and Treatments

This section applies to all subjects.

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

Excluded and allowed medications and treatments are shown in Table 7.a.

Table 7.a Excluded and Allowed Medications and Treatments

	Allowed Under Some Circumstances (See Comments)	Episodic Use	Comments or Exceptions
Acetylcholinesterase inhibitors	Not allowed	Not allowed	Acetylcholinesterase inhibitors are not permitted due to risk of seizure with coadministration of TAK-071. This class includes donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). Washout of at least 30 days before randomization.

Table 7.a Excluded and Allowed Medications and Treatments

	Allowed Under Some Circumstances (See Comments)	Episodic Use	Comments or Exceptions
COVID-19 vaccine (any FDA-approved manufacturer)	Allowed (see comments)	N/A	COVID-19 vaccination is allowed and recommended but should not be administered within 48 hours of any study visit, including home visits, if possible, to avoid complicating the assessment of AEs. If the vaccination cannot be scheduled at another time, a reasonable attempt should be made to reschedule the study visit. If this is not feasible, both the vaccination and the study visit should proceed as scheduled, and the investigator should notify the sponsor.
Any investigational drug	Not allowed	Not allowed	Must have completed clinical study and stopped investigational drug 90 days before screening or 5 half-lives, whichever is longer.
Anticholinergic drugs	Not allowed (exception: mirabegron is allowed)	Not allowed	Washout of at least 30 days before randomization. Although most drugs for overactive bladder have anticholinergic mechanisms of action and are excluded, mirabegron is permitted for this indication.
Stimulants	Not allowed	Not allowed	Washout of at least 30 days before randomization and approval for subject inclusion by sponsor/representative.
Antipsychotics	Allowed under some circumstances (see comments)	Not allowed	**Not allowed:** Antipsychotic drugs with significant interactions with cholinergic receptors (eg, clozapine, olanzapine) are not permitted. Washout of at least 30 days before randomization. **Allowed:** Pimavanserin (at a dose of ≤34 mg QD) and quetiapine (at a dose of ≤250 mg total daily dose) for subjects who, in the opinion of the investigator, medically require treatment with an antipsychotic drug to safely complete the study, and the dose has been stable for at least 30 days before randomization. Other antipsychotic drugs may be permitted, conditional on agreement by the investigator and sponsor that the drug will not interfere with the study. Otherwise, washout of at least 30 days before randomization.
Narcotic analgesics	Not allowed	Not allowed	Washout of at least 30 days before randomization.

Table 7.a Excluded and Allowed Medications and Treatments

	Allowed Under Some Circumstances (See Comments)	Episodic Use	Comments or Exceptions
Anticonvulsants	Allowed under some circumstances (see comments)	Not allowed	**Allowed for non-seizure indication.** **Not allowed: Subjects requiring anticonvulsants for seizure disorder or seizure risk factors are excluded from this study. Anticonvulsants listed in Table 7.b are never allowed.** **May be allowed:** Gabapentin and pregabalin at an FDA approved dose may be allowed if they are not being used for seizure disorder, the dose has been stable for at least 30 days before randomization, and, in the opinion of the investigator and sponsor, the drug is unlikely to affect the outcome measures or subject safety in this study. The use of other anticonvulsants (except those in Table 7.b, which are never allowed) for indications unrelated to seizure disorder or seizure prophylaxis may be considered if the investigator and sponsor agree that the drug is unlikely to affect the outcome measures or subject safety in this study. Otherwise, washout of at least 30 days before randomization.
Antidepressants	Allowed under some circumstances (see comments)	Allowed under some circumstances (see comments)	**Not allowed:** Bupropion is excluded in all cases and requires washout at least 30 days prior to randomization. Nefazodone is excluded as a strong CYP3A4 inhibitor under all circumstances and must be stopped at least 30 days before randomization. **Allowed:** Trazodone up to 100 mg at bedtime may also be used for insomnia, either as a stable dose or intermittently. Chronic use of other antidepressants is permitted as long as the dose is kept stable during the study.
Herbal remedies that are psychoactive (eg, kava, valerian, ginkgo biloba)	Allowed under some circumstances (see comments)	Allowed under some circumstances (see comments)	**Allowed:** Herbal remedies may be permitted conditional on approval from the investigator and sponsor if they are judged to be unlikely to affect the outcome measures and are deemed to be safe. **Not allowed:** St. John's wort is not permitted under any circumstances due to its activity as a CYP3A4 inducer and must be stopped at least 30 days before randomization. Any herbal remedies that are not permitted must be stopped at least 30 days before randomization.

Table 7.a Excluded and Allowed Medications and Treatments

	Allowed Under Some Circumstances (See Comments)	Episodic Use	Comments or Exceptions
OTC (eg, cough syrup)	Allowed under some circumstances (see comments)	Allowed under some circumstances (see comments)	**Allowed:** The OTC analgesics acetaminophen, aspirin, ibuprofen, and naproxen at approved doses are allowed at approved (per label) doses. The OTC allergy medications fexofenadine, loratadine, and cetirizine are allowed at approved (per label) doses. Other OTC remedies are permitted as long as in the opinion of the investigator and sponsor the medication will not interfere with the study or pose a risk to subjects. **Not allowed:** OTC drugs with anticholinergic properties such as diphenhydramine are excluded under all circumstances and must be stopped at least 30 days before randomization.
Melatonin	Allowed under some circumstances (see comments)	Allowed	Melatonin at doses of ≤10 mg at bedtime is permitted for subjects with REM sleep behavior disorder and/or insomnia as long as the dose is kept stable during the study and use has been relatively stable for at least 30 days before randomization. Either consistent nightly or intermittent (as needed) nightly dosing is acceptable.
Cannabis and cannabis-derived products	Allowed under some circumstances (see comments)	Not allowed	Allowed if subjects have been using cannabis and cannabis-derived products at a relatively stable level for at least 30 days before randomization. Otherwise, washout of at least 30 days before randomization. Subjects must abstain from these products for at least 24 hours before any study-related assessments.
Barbiturates	Not allowed	Not allowed	Washout at least 30 days before randomization.
Nonbenzodiazepine hypnotics (eg, zopiclone, eszopiclone, zaleplon, zolpidem, suvorexant)	Allowed under some circumstances (see comments)	Not allowed	Allowed if the total daily dose has been relatively stable from 30 days before randomization to the end of the study.
Muscle relaxants including but not limited to baclofen, tizanidine, 4-aminopyridine	Allowed under some circumstances (see comments)	Not allowed	Allowed if the total daily dose has been relatively stable from 30 days before randomization to the end of the study and, in the opinion of the investigator and sponsor, the drug is unlikely to affect the outcome measures or subject safety in this study. Otherwise, washout of at least 30 days before randomization.
Antiparkinsonian drugs	Allowed under some circumstances (see comments)	Allowed under some circumstances (see comments)	Allowed if the total daily dose has been relatively stable from 30 days before randomization to the end of the study. For medications that are occasionally taken as needed, or where the dosage is occasionally adjusted as needed, a judgment is to be made regarding the stability of dosing in collaboration with the sponsor.
Moderate/strong CYP3A inhibitor [a]	Not allowed	Not allowed	TAK-071 is primarily metabolized by CYP3A4; moderate and strong CYP3A inhibitors are excluded under all circumstances and must be stopped at least 30 days prior to randomization. Please note that subjects must not consume grapefruit or grapefruit juice, a CYP3A4 inhibitor, during the study.

Table 7.a Excluded and Allowed Medications and Treatments

	Allowed Under Some Circumstances (See Comments)	Episodic Use	Comments or Exceptions
Moderate/strong CYP3A inducers [a]	Not allowed	Not allowed	TAK-071 is primarily metabolized by CYP3A4; moderate and strong CYP3A inducers are excluded under all circumstances and must be stopped at least 30 days prior to randomization.
Warfarin	Not allowed	Not allowed	TAK-071 is highly bound to plasma albumin, therefore warfarin is excluded. Other anticoagulants are allowed. Subjects taking warfarin must washout and start another anticoagulant at least 30 days before randomization
Benzodiazepines	Allowed under some circumstances (see comments)	Not allowed	Benzodiazepines will be allowed as long as the dose has been stable for at least 30 days before randomization, the medication is used at night for insomnia and/or REM sleep behavior disorder, or for anxiety, and investigator and sponsor agree that the drug will not interfere substantially with the study endpoints. Otherwise, benzodiazepines must be stopped at least 30 days before randomization.

CYP: cytochrome P-450; OTC: over-the-counter; QD: once daily; REM: rapid eye movement.
[a] Listed in Table 7.b.

Strong and moderate CYP3A inducers and inhibitors (Table 7.b) are excluded in all circumstances and must be stopped at least 30 days prior to randomization.

Table 7.b Strong and Moderate CYP3A Inducers and Inhibitors

Class	Specific Drugs of Concern in Class
Strong CYP3A inhibitors	
Antibiotics	Clarithromycin, telithromycin, troleandomycin
Antidepressants	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Antiprogestins	Mifepristone
Antivirals	Boceprevir, danoprevir/ritonavir, telaprevir, ombitasvir/paritaprevir/ritonavir/dasabuvir (VIEKIRA PAK)
Diuretics	Conivaptan
Food products	Grapefruit juice (double strength)
Kinase inhibitors	Ceritinib, idelalisib, ribociclib
Pharmacokinetic enhancer	Cobicistat
Protease inhibitors	Indinavir, indinavir/ritonavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, saquinavir/ritonavir, tipranavir/ritonavir
Treatments of AIDS	Elvitegravir/ritonavir

Table 7.b Strong and Moderate CYP3A Inducers and Inhibitors

Class	Specific Drugs of Concern in Class
Moderate CYP3A inhibitors	
Antiarrhythmics	Dronedarone
Antibiotics	Ciprofloxacin, erythromycin
Antiemetics	Aprepitant, casopitant, netupitant
Antifungals	Fluconazole, isavuconazole, ravuconazole
Antineoplastic agents	Imatinib
Antiparkinsonians	Istradefylline
Antivirals	Faldaprevir, letermovir
Benzodiazepines	Tofisopam
Calcium channel blockers	Diltiazem, verapamil
Food products	Grapefruit juice
H2 receptor antagonists	Cimetidine
Herbal medications	Magnolia vine (Schisandra sphenanthera)
Immunosuppressants	Cyclosporine
Kinase inhibitors	Crizotinib, duvelisib, fedratinib, nilotinib
Protease inhibitors	Amprenavir, atazanavir, atazanavir/ritonavir, darunavir, darunavir/ritonavir
Strong CYP3A inducers	
Antiandrogens	Apalutamide, enzalutamide
Antibiotics	Rifampin, rifapentine
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin
Antilipemics	Avasimibe
Antineoplastics	Mitotane
Cancer treatments	Ivosidenib
Cystic fibrosis treatments	Lumacaftor
Herbal medications	St John's wort
Moderate CYP3A inducers	
Antibiotics	Nafcillin, rifabutin
Antidiarrheals	Telotristat ethyl
Antigout and uricosuric agents	Lesinurad
Antipsychotics	Thioridazine
Antivirals	Asunaprevir, beclabuvir, daclatasvir
Endothelin receptor antagonists	Bosentan
Kinase inhibitors	Dabrafenib, lorlatinib
Nonnucleoside reverse transcriptase inhibitors	Efavirenz, etravirine, lersivirine, talviraline
Other	Elagolix
Protease inhibitors	Lopinavir, ritonavir, tipranavir
Psychostimulants	Modafinil

Source: www.druginteraction.org.

7.4 Diet, Fluid, and Activity Control

This section applies to all subjects.

The subject should abstain from alcohol consumption for 24 hours before each study visit. In addition, subjects may not consume grapefruit or grapefruit juice during the study.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

This section applies to all subjects.

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.22.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the PTE or AE.
    - Liver function test (LFT) abnormalities. Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status), if the following circumstances occur at any time during study drug treatment:
        - ALT or AST >8 × ULN, or
        - ALT or AST >5 × ULN and persists for more than 2 weeks, or
        - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or INR >1.5, or
        - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
    - Subject experiences any of the Takeda Medically Significant List events (see Section 10.1.4).
2. Significant protocol deviation. The discovery postrandomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, or continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

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

5. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.14.

6. Study termination by the sponsor.
7. Study termination by the IRB or regulatory agency.
8. Other.

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

7.6 Procedures for Discontinuation or Withdrawal of a Subject

This section applies to all subjects.

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination visit. Discontinued or withdrawn subjects may be replaced.

If a subject discontinues from the study, a replacement subject may be enrolled, if deemed appropriate by the investigator and sponsor. The study site should contact the interactive web response system (IWRS) for the replacement subject's treatment assignment and study number.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section applies to all subjects, except Section 8.1.3.

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

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Study Drug

TAK-071 drug product will be supplied as film-coated tablets containing TAK-071 active pharmaceutical ingredient or matching placebo. Other ingredients will include typical pharmaceutical excipients (mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, and magnesium stearate). The tablet coating is composed of typical pharmaceutical-grade coating components (hypromellose 2910, titanium dioxide, ferric oxide yellow, and ferric oxide red).

TAK-071 drug product or matching placebo will be supplied in white high-density polyethylene bottles with induction sealed caps. Bottle labels will bear the appropriate label text as required by

governing regulatory agencies. At a minimum, such text will include product name, product strength, number of tablets, and lot number.

8.1.1.2 Sponsor-Supplied Drug

Takeda will supply TAK-071 tablets and matching placebo.

8.1.2 Storage

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day. Refer to pharmacy manual for additional storage- and return-related instructions and information.

8.1.3 Dose and Regimen

For the subjects with PD only: subjects who meet randomization criteria on Day 1 will be randomized to 1 of 2 treatment sequences consisting of daily treatment with 7.5 mg TAK-071 or placebo. Subjects will receive 7.5 mg TAK-071 or placebo dosed QD from Day 1 through Day 42 of each period.

After the PK, safety, and physiologically based PK modeling data from the sentinel cohort (healthy subjects) have been assessed (see Appendix H), a decision will be made about the dose for the remaining subjects with PD to be enrolled in the main study. 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.

8.1.4 Overdose

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

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

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

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

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive their treatment according to the schedule allocated to each study site.

Subjects with PD aged 40 to 85 years, inclusive, will be enrolled in the main study, with 1:1 randomization to 7.5 mg TAK-071 QD versus placebo, in sequences of 4.

For the main study, subjects with PD will be randomized to 1 of 2 possible treatment sequences consisting of 2 periods and 2 treatments, alternating in a crossover fashion:

- Subjects randomized to Sequence A will receive TAK-071 in the first 6-week period and crossover to placebo in the second 6-week period.
- Subjects randomized to Sequence B will receive placebo in the first 6-week period and crossover to TAK-071 in the second 6-week period.

The investigator or the investigator's designee will access IWRS at screening to obtain the subject study number. The investigator or the investigator's designee will use the IWRS to randomize the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. The medication identification (ID) number of the study drug to be dispensed will then be provided by the IWRS. If the sponsor-supplied drug is lost or damaged, the site can request a replacement from IWRS. (Refer to IWRS manual provided separately.) The tear-off portion of the medication label will be affixed to the Dispensing Log. At subsequent drug-dispensing visits, the investigator or designee will again access IWRS to request additional study drug for a subject.

8.3 Randomization Code Creation and Storage

The IWRS system will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

The study drug blind will be maintained using the IWRS.

Since the maintenance of the blind may be compromised because of results from drug concentrations and/or pharmacodynamics assessments, such results should not be disclosed before blind breaking. In the event that results must be reported to the investigator before breaking the blind, all efforts should be made to maintain the blind (eg, as changing a medication ID number to avoid identification of subjects by the laboratory site personnel). Detailed procedures for measuring subject drug concentration levels, (including reporting results) are provided in the separately created procedure for directions on handling of biological samples for measuring drug concentrations.

8.5 Unblinding Procedure

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

For unblinding a subject, the study drug blind can be obtained by the investigator, by accessing the IWRS.

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

If any site personnel are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee for destruction. Destruction at site will be permitted if/when a Standard Operating Procedure exists after requesting and receiving sponsor's approval.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study,

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the medication ID used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- A site representative or unblinded pharmacy monitor, otherwise uninvolved with study conduct, will review the randomization schedule and subject dosing log before Day 1 dosing and after dosing to ensure all subjects received the correct dose of study drug,
- Filing all study medication documentation in the investigator's essential document file.

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

Please see the Pharmacy Manual for additional details.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. They apply to all subjects except where indicated. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The schedule of study procedures is located in Appendix A for the main study (subjects with PD) and Appendix H for the sentinel cohort (healthy subjects).

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained before the subject entering into the study, and before any protocol-directed procedures are performed.

A unique screening ID number will be generated by the IWRS and assigned to each subject after informed consent is signed and the site registers the subject in the IWRS; this ID number will be used throughout the study.

9.1.1.1 DNA Analysis Informed Consent Procedure

A separate informed consent form pertaining to collection, storage, and analysis of the sample must be obtained before collecting a blood sample for DNA analysis research for this study. The provision of consent to collect and analyze the sample for DNA analysis is independent of consent to the other aspects of the study. Providing a DNA sample is optional for this study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, and smoking status of the subject at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.10).

In addition, information on the subject's PD history including symptoms and disease characteristics and history of falls over the past 6 months will be collected.

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

9.1.3 Physical Examination Procedure

At screening and both baseline visits, a physical examination (defined as the assessment before first dose of study drug) will be conducted consisting of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) lymph nodes; and (10) other.

At the last visit of each period, (11) nervous system will be added to the examination.

All subsequent physical examinations should assess clinically significant changes from the assessment before first dose examination.

9.1.4 Neurological Examination Procedure

A separate neurological examination will be performed and collected in the eCRF. This will include testing mental status, gait, cerebellar function, cranial nerves, upper and lower extremity motor strength, reflexes, and sensation.

9.1.5 Weight, Height, and BMI

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

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

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

The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 kg/m^2. Because the BMI is used as an exclusion criterion this determination must be made after rounding.

9.1.6 Vital Sign Procedure

The investigator will review all vital signs for real-time safety monitoring purposes. Vital signs will include body temperature (oral measurement), respiratory rate, supine blood pressure (systolic and diastolic, after lying down at least 5 minutes), supine pulse (beats per minute), standing blood pressure and pulse (systolic and diastolic blood pressure and pulse, measured within 1 minute after standing after supine measurements are taken).

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

9.1.7 MoCA (Subjects With PD Only)

The MoCA is a cognitive screening examination designed to screen for MCI [11]. This 30-point test assesses 8 cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation.

9.1.8 Pharmacodynamic Measurements

In the case of subjects with PD, all in-clinic assessments are to be performed during the subject's On state after taking dopaminergic therapy. Assessments should be made within approximately the same time after a patient has taken their dopaminergic medication.

Please refer also to the study manual for the order in which gait and cognitive assessments should be performed.

Note: in unavoidable circumstances such as the COVID-19 pandemic, it may be necessary to administer clinical interviews and assessments using alternative approaches (please refer to Section 9.1.24). In some cases, audio/or video recording of subject interviews may not be possible. This will be documented in the study records.

9.1.8.1 Pharmacodynamic Measurements Related to Gait

This section applies only to the main study (subjects with PD).

9.1.8.1.1 Walk and Serial Subtraction Tests

- Serial subtraction test.
  Serial subtraction tests are commonly used to measure attention and mental concentration [12]. Subjects in this study will perform a serial subtraction 3 test while sitting in a chair. Subjects will not be corrected during this testing. The total number of correct and incorrect numbers will be recorded.
- 2-minute walk (with cognitive load).
  Subjects will be asked to walk at a self-selected comfortable pace back and forth along a 10-meter long hallway for 2 minutes while conducting a serial subtraction 3 test. Subjects will complete turns at both ends of the hallway. Verbal reminders will be provided if subjects stop counting before completing the full 2-minute walk test. The total number of correct and incorrect numbers during subtraction will be recorded.
- 2-minute walk (no cognitive load).
  Subjects will be asked to walk at a self-selected comfortable pace back and forth along a 10-meter long hallway for 2 minutes. Subjects will complete turns at both ends of the hallway.

9.1.8.1.2 Cued 180° Turns

Subjects will be asked to walk at a self-selected comfortable pace back and forth along a 10-meter-long hallway. At random times during their walk, the subjects will receive a verbal instruction to turn 180 degrees in a specific direction (left or right). After the turn, subjects will continue walking until they receive another instruction to turn. The total number of correct turns (turning in the direction instructed) will be recorded.

9.1.8.1.3 MDS-UPDRS Including Hoehn and Yahr Scale

MDS-UPDRS consists of 4 parts evaluating various aspects of PD through 65 items [13]. Part I evaluates nonmotor experiences of daily living and Part II evaluates motor experiences of daily living. Part III includes a set of motor examinations conducted by a clinician. Part IV assesses motor complications. Rater time for administrating the MDS-UPDRS is estimated to be approximately 30 minutes [14]. The Hoehn and Yahr scale is a 5-stage, descriptive ordinal scale that provides a general estimate of clinical aspects including objective signs (impairment) and functional deficits (disability) in PD [15]. Note that for this study the standard version rather than the modified version will be used.

The scale will be evaluated by a clinician. The same rater should rate a subject on each visit during the course of the study. Of note, the distinction between stages 3 and stage 4 should be made in part based on whether the subject is too disabled to live alone. Subjects who cannot live independently should be rated as stage 4 or 5 (https://www.parkinson.org/Understanding-Parkinsons/What-is-Parkinsons/Stages-of-Parkinsons).

9.1.8.1.4 Postural Sway

Subjects will be asked to stand still with feet slightly apart and hands hanging loosely at their sides for 30 seconds. The subjects will be instructed to either 1) look at a visual focal point on a wall or 2) close their eyes during the test.

9.1.8.1.5 Speech Test

Subjects will be asked to complete tasks assessing various aspects of speech and language, including speech timing, voice quality, vocal control, breath support, sentence complexity, and idea density. Details will be available in the study manual.

9.1.8.1.6 TUG

Subjects will be asked to complete the standard TUG. Subjects will begin the test sitting in a chair. Subjects will then stand up from the chair, walk 3 meters as quickly and safely as possible, cross a line marked on the floor, turn around, walk back, and sit down again in the chair. This test will be repeated 3 times (only once at screening).

9.1.8.2 Pharmacodynamic Measurements Related to Cognition

This section applies only to the main study (subjects with PD).

Please refer to the Cogstate and Operation manuals for additional details on these assessments.

9.1.8.2.1 Cogstate International Shopping List Test

The International Shopping List test is a measure of verbal learning and memory and uses a well-validated list-learning paradigm. High-frequency, high-imagery, concrete nouns (items from a shopping list) are read to the subject by the test supervisor at the rate of 1 word every 2 seconds. Once all 12 words have been read, the subject is asked to recall as many of the words as he/she can as quickly as possible. The test supervisor records the words recalled by the subject on the testing device. When the subject can recall no more words, the same list is read a second time. The test supervisor records the words recalled by the subject on this trial. This is then repeated a third time. Delayed recall condition is also available for this test. The delayed recall condition requires the subject to recall the words from the list 10 to 30 minutes later without having the list read again. The software measures the number of correct responses as recorded by the test supervisor. It takes approximately 5 minutes to complete this test.

9.1.8.2.2 Cogstate Modified Chase Test

The modified Chase test is administered prior to the first administration of the modified Groton Maze Learning test (screening visit) for additional subject familiarization. Subjects are required to "chase" a moving box around the grid for about 30 seconds, moving 1 box at a time without skipping boxes.

9.1.8.2.3 Cogstate Modified Groton Maze Learning Test

Modified Groton Maze Learning Test: The task begins with a chase task to allow subjects to become familiar with the task context. The subjects are shown a 10 × 10 grid of tiles on a computer touch screen. The subjects are instructed to 'chase' a moving tile around the grid. Once they understand the rules, they can proceed onto the timed chase test, where they must chase the target for 30 seconds. For the test, the subject is shown the same 10 × 10 grid of tiles on a computer touch screen. A 28-step pathway is hidden among these 100 possible locations. The start is indicated by the blue tile at the top left and the finish location is the tile with the red circles at the bottom right of the grid. The subjects are instructed to move 1 step from the start location and then to continue, 1 tile at a time, toward the end (bottom right). The subjects move by touching a tile next to their current location with the stylus. After each move is made, the computer indicates whether this is correct by revealing a green checkmark (ie, this is the next step in the pathway), or incorrect by revealing a red cross (ie, this is not the next step in the pathway, or the subject has broken a rule, see below). If the choice was correct, the step in the pathway remains highlighted and the subjects must locate the next step in the pathway. If a choice was incorrect (ie, a red cross is revealed), the subjects must touch the last correct location (ie, the last green checkmark revealed) and then make a different tile choice to advance toward the end. While moving through the hidden maze, the subjects are required to adhere to 2 rules. First, the subjects cannot move diagonally or touch the same tile twice in succession. Second, the subjects cannot move backwards along the pathway (eg, move back to a location that displayed a green tick, but from which they have since moved). If the subjects choose a tile that is not part of the hidden pathway, but the tile choice is within the rules, this is recorded as a different type of error (eg, not a rule break). This could be due to chance (the first time through the maze) or due to misremembering the path on subsequent attempts. The subjects learn the 28-step pathway through the maze on the basis of this trial and error feedback. Once completed, the pathway of correct responses marked on the grid is extinguished and subjects are instructed to return to the start location and find the same pathway again. The process continues until subjects have completed 5 trials in total. There are 20 well-matched alternate forms for this task, and these are selected in pseudo-random order to ensure that no subject will complete the same hidden path until all 20 have been completed.

9.1.8.2.4 Cogstate One Card Learning Test

The One Card Learning test is a measure of visual learning and uses a well-validated pattern separation paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The subject is asked whether the card displayed in the center of the screen was seen previously in this test. The subject

responds by pressing the Yes or No key. The software measures the speed and accuracy of each response. It takes approximately 6 minutes to complete this test.

9.1.8.2.5 Cogstate One Back Test

The One Back test is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The subject is asked whether the card displayed in the center of the screen is the same as the card presented immediately previously. The subject responds by pressing the Yes or No key. Because no card has been presented yet on the first trial, a correct first response is always No. The software measures the speed and accuracy of each response. It takes approximately 4 minutes to complete this test.

9.1.8.2.6 SDMT (Oral Version)

The oral version of the SDMT is administered by providing the subject with a sheet of paper at the top of which is printed the key containing (9 abstract symbols and 9 corresponding numbers). The key remains visible to the subject throughout the test. A sequence of 120 symbols (the first 10 symbols are practice items) is presented in 8 rows below the key. In each row, empty boxes are located immediately below the boxes containing the symbols. The examiner, on a copy of the test sheet, records in the empty squares the numbers that the subject associates, orally, with the symbols. In the first test phase, the subject has to make 10 trial symbol-number associations without a time limit. The examiner will correct any errors made during this phase. After this learning phase, the test proper begins. The subject has to make as many associations as possible within the 90-second time limit. If the subject is able to complete all 110 associations before the time runs out, the test is stopped. The test score is the number of correct associations made by the subject in the time allowed.

9.1.8.2.7 SAT

The SAT is a measure of sustained attention that uses a signal detection paradigm. The subject indicates whether a small gray square has been presented on screen. The subject responds by pressing the Yes key when the gray square has been presented and No when it is not presented. A distractor condition is present in some trials, where the screen background flashes at a rapid rate and thereby makes it more difficult to determine whether the gray square has been presented. Performance is measured by calculating the total correct responses. It takes approximately 11 minutes to complete the test.

9.1.8.3 Other Pharmacodynamic Measures

This section applies only to the main study (subjects with PD).

9.1.8.3.1 Global Impression Scales

The CGI [17] consist of 2 subscales: CGI-S and the CGI-I. The CGI-S assesses the clinician's impression of the subject's 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 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 assessed [18]. 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.

9.1.8.3.2 ESS

ESS is a self-administered questionnaire to evaluate the level of excessive daytime sleepiness [19]. There are 8 questions measuring the subject's usual chances of dozing off or falling asleep while engaged in 8 different activities. Each item will be rated on a 4-point scale (0-3). The total ESS score is the sum of all these 8 items with the range from 0 to 24.

9.1.8.4 Biomarkers

This section applies only to the main study (subjects with PD).

Primary specimen collection is outlined in Table 9.a.

Table 9.a Primary Specimen Collection

No.	Specimen Name in Schedule of Study Procedures (Appendix A)	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
1	Plasma samples circulating biomarkers	Plasma		Biomarker measurements	Mandatory
2	Blood sample for DNA	Blood	DNA	DNA measurements	Optional
3	Plasma samples for TAK-071 PK	Plasma		PK measurements	Mandatory

PK: pharmacokinetic.

Plasma samples will be obtained for circulating biomarkers. Plasma biomarkers may include, but are not limited to, neuronally derived exosome M_1 mRNA levels, amyloid, tau, NfL, and biomarkers of synaptic integrity.

Detailed information will be provided in the laboratory manual,

Blood samples will be obtained to assay for DNA-based and other plasma-based biomarkers. These include M_1 receptor expression levels and the pharmacodynamic effects of TAK-071. Detailed information on the collection protocol and analytes will be provided in the laboratory manual.

9.1.9 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.10 Documentation of Concurrent Medical Conditions

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

9.1.11 Maximum Blood Volumes (Subjects With PD Only)

The maximum volume of blood at any single visit is approximately 27 mL and the maximum total volume of blood for the study is approximately 104 mL. See Appendix H for the sentinel cohort.

9.1.12 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be taken on the days stipulated in Appendix A. It is not necessary that the subjects fast before these blood samples are collected. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information at the investigator's discretion (eg, adding creatinine kinase isoenzymes to a serum chemistry panel that was already drawn).

Details of these procedures and required safety monitoring will be given in the laboratory manual.

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

Table 9.b Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells White blood cells with differential (absolute counts) Hemoglobin Hematocrit Platelets **Coagulation** Prothrombin time/international normalized ratio Activated partial thromboplastin time	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Total bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase γ-Glutamyl transferase Potassium Sodium Glucose Chloride Bicarbonate Calcium	pH Specific gravity Protein Glucose Blood Nitrite Microscopic analysis (only if positive dipstick results): white blood cells, red blood cells, epithelial cells, casts

Plasma
4β-Hydroxycholesterol and cholesterol Ratio of 4β-hydroxycholesterol to cholesterol

Serum	Urine/Blood
Hemoglobin A1c eGFR [a] Hepatitis B surface antigen Antibody to HCV; if positive, reflex qPCR for HCV viral RNA Female subjects: Serum human chorionic gonadotropin Female subjects, if postmenopausal and not surgically sterile: FSH [b]	Drug screen for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, alcohol, and cotinine Urine pregnancy (optional substitute for serum pregnancy at baseline visits)

eGFR: estimated glomerular filtration rate; FSH: follicle-stimulating hormone; HCV: hepatitis C virus; qPCR: quantitative PCR.

[a] Calculated using Chronic Kidney Disease Epidemiology Collaboration equation.

[b] FSH level will be obtained for female subjects at screening if they are postmenopausal (ie, continuous amenorrhea of at least 1 year) and not surgically sterile. The result must be >40 IU/L for the subject to be enrolled.

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

If subjects experience ALT or AST >3 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Refer to Sections 7.5 and 10.2.3 for the appropriate guidance on reporting abnormal LFTs.)

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

9.1.13 Contraception and Pregnancy Avoidance Procedure

9.1.13.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 102 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must not donate sperm during this period. Women of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception below.

*Women NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (eg, defined as continuous amenorrhea of at least 12 months and a follicle-stimulating hormone (FSH)>40 IU/L, confirmed before any study drug is implemented.

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

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign the consent form stating that they understand the requirements for avoidance of pregnancy during the course of the study and for 102 days after the last dose of study drug.

9.1.13.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 42 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective method of contraception (from the list in Section 9.1.13.3).

In addition they must be advised not to donate ova during this period.

9.1.13.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral oophorectomy, and tubal ligation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 years old) or women

who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

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

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are unacceptable, the acceptable methods are nonhormonal methods only:
    - Intrauterine device.
    - Bilateral tubal occlusion and bilateral tubal ligation.
    - Vasectomized partner (provided that partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of the surgical success.
    - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 42 days after last dose.
2. Unacceptable methods of contraception are:
    - Hormonal methods. Hormonal contraceptives are not considered to be highly effective contraceptives in the context of this study because the impact of TAK-071 on the metabolism of these drugs has not yet been studied. However, subjects taking these medications may continue to take them during the study as long as they are using a highly effective method of contraception listed above.
    - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
    - Spermicides only.
    - Withdrawal.
    - No method at all.
    - Use of female and male condoms together.
    - Cap/diaphragm/sponge, even if used with spermicidal jellies or creams and even with condom.
3. Subjects will be provided with information on highly effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

4. During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
    a) Contraceptive requirements of the study.
    b) Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
    c) Assessment of subject compliance through questions such as:
        i. Have you used the contraception consistently and correctly since the last visit?
        ii. Have you forgotten to use contraception since the last visit?
        iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes").
        iv. Is there a chance you could be pregnant?
5. In addition to a negative serum hCG pregnancy test at screening, female subjects of childbearing potential must also have a negative urine dipstick hCG pregnancy test 1 day or the same day before receiving any dose of study medication.

9.1.14 Pregnancy

If any subject is found to be pregnant during administration of active study drug, for example, after baseline/Day 1 or within 42 days of the last dose of active study drug, she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. The pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.2.

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

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

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

9.1.15 ECG Procedure

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

For both screening and safety ECGs, a standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, QT interval with Fridericia correction, and QT interval with Bazett correction.

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

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

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

9.1.16 Assessment of Suicidal Ideation and Behavior

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

9.1.17 Sample Collection for DNA Analysis

This section applies only to the main study (subjects with PD).

When optional sampling of whole blood for DNA analysis occurs, the subject must sign a special informed consent for the DNA sample.

DNA forms the basis for the genes that make the body produce proteins such as enzymes, drug transporters, or drug targets, and may be evaluated for the genetic contribution to how the drug is broken down or how the drug affects the body. Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to TAK-071.
- Determining how TAK-071 affects the primary and secondary endpoints.

- Generating information needed for research, development, and regulatory approval of tests to predict response to TAK-071.

See the laboratory manual for detailed instructions on collecting, handling, storing, and shipping DNA samples.

9.1.18 Plasma Sample for Circulating Biomarkers

This section applies only to the main study (subjects with PD).

Whole blood samples will be collected in the study and processed into plasma for analysis of circulating biomarkers. The plasma will be aliquoted into 2 samples.

All cells in the body release small extracellular vesicles called exosomes, and the cellular origin can be determined by enriching the exosomes using markers on their surface. Neuronally derived exosomes will be enriched from the plasma and used to explore muscarinic receptor M_1 expression and other transcripts related to cholinergic tone. See the laboratory manual for detailed instructions on collecting, handling, storing, and shipping of plasma samples for circulating biomarkers.

9.1.19 Blood Samples for PK Analysis

Blood samples for PK analysis of plasma TAK-071 will be collected into chilled vacutainers containing anticoagulant K_2EDTA according to the schedules in Appendix A and Appendix C.

9.1.20 Bioanalytical Methods

Plasma concentrations of TAK-071 will be measured by a validated method using high-performance liquid chromatography with tandem mass spectrometry.

9.1.21 PK Parameters

In the main study (subjects with PD), the plasma C_{max}, observed concentration at the end of a dosing interval (C_{trough}), and t_{max} of TAK-071 will be determined. See Appendix H for the sentinel cohort.

Actual sampling times, rather than scheduled sampling times, will be used in all data presentations.

9.1.22 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is withdrawn at the screening visit, the investigator should complete the eCRF. The IWRS should be contacted as a notification of screen failure.

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

- PTE/AE.
- Did not meet entrance criteria (specify reason).
- Significant protocol deviation.

- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination by sponsor.
- Study termination by IRB or regulatory agency.
- Other specify reason.

Screening ID numbers assigned to subjects who fail screening should not be reused.

Subjects who fail screening can be rescreened, with approval of the sponsor. They should be assigned a new screening ID number.

9.1.23 Documentation of Randomization

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

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

9.1.24 Alternative Approaches to Study Procedures and Data Collection Due to COVID-19 or Other Unavoidable Circumstances

In unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that impact the ability to conduct study procedures according to the Schedule of Procedures (Appendix A), contingency measures may be implemented. In acknowledgement of FDA guidance (fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency. Accessed 12 June 2020), as well as study site, hospital, local, state, and national restrictions established during these kinds of circumstances, the following measures are being taken for the current study:

- Other than the final visit, alternative methods for conducting subject visits (eg, telephone visits, video conferencing, or in-home study visits conducted by site personnel contingent upon local regulations) may be used per approval by the sponsor or designee.
  - Approval may be granted to omit collection of certain study assessments and visit windows may be extended.
  - When approval is given for a subject to miss an in-person study visit, a study site physician will speak directly with the subject by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status.
  - At minimum, the study site physician or other qualified site personnel should conduct the following assessments within specified-visit window timeframes: AE assessments, documentation of concomitant medication, administration of C-SSRS, and an assessment of clinical symptoms.

  - Other study assessments may be collected using an alternative method as feasible, and may involve audio or video recording where allowed by local regulation. In some cases, audio and/or video recording of subject interviews may not be possible. This will be documented in the study records.
  - Sites may seek approval to extend a visit window in order to conduct an on-site visit. Assessments that cannot be completed during the protocol-specified window will be considered missing data and such departures will be recorded in the study records.
  - The maximum interval between successive study visits may be no longer than 8 weeks.
- The final visit should be performed in person. When it is not possible for the subject to come to the study site, the preferred alternative for the final visit is for qualified study site personnel to go to the subject's residence and conduct the protocol-specified procedures in that location. Assessments collected at a subject's residence should comply with applicable local regulations.

All subject discontinuations and alternative approaches to study procedures (ie, procedures not conducted per the Schedule of Procedures) due to the COVID-19 pandemic must be documented in the study records as related to COVID-19. Data collected using alternative methods may be handled differently in the final data analyses. This will be documented in the statistical analysis plan (SAP).

9.2 Monitoring Subject Treatment Compliance

This section applies only to the main study (subjects with PD). An electronic drug diary will be implemented in this study. Further details regarding this diary are provided in the study reference manual. Subjects also will be required to bring study drug packaging to each clinic visit, regardless of whether the study drug packaging is empty.

Noncompliance with study drug includes subjects who are <75% compliant between visits (including noncompliance as assessed via the electronic drug diary). If these criteria for noncompliance are met on more than 1 occasion during the study, the subject will be considered significantly out of compliance and the site investigator will need to discuss the subject's continuation in the study with the sponsor (or designee). On the basis of the assessment of the investigator and sponsor (or designee), an out-of-compliance subject may be withdrawn from the study.

9.3 Schedule of Observations and Procedures

The detailed schedule for all study-related procedures for all evaluations in the main study (subjects with PD) is shown in Appendix A. Assessments should be completed at the designated visit/time points.

A brief overview of the study schedule is presented in Table 9.c.

Table 9.c Overview of Main Study Schedule (Subjects With PD)

	Screening	6-Week Double-blind Treatment Period (Periods 1 and 2)			Washout	Follow-up Safety Phone Call
		Baseline	At-Home Assessment	Last Day of Treatment Period or Early Termination		(Week 17)
Period 1 Study Visit Number	1	2	3	4		
(Study Day)	(Day -42 up to Day -1)	(Day 1)	(Day 21 ±2)	(Day 42 ±2)	(Day 43 to Day 63) [a]	
Period 2 Study Visit Number		5	6	7		8
(Study Day)		(Day 64 ±2)	(Day 84 ±2)	(Day 105 ±2)		(Day 119)

[a] At least 3 weeks for washout.

The study schedule and specific visits for the sentinel cohort (healthy subjects) are described in Appendix H.

9.3.1 Screening

Subjects will be screened within 1 to 42 days before baseline/randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.22 for procedures for documenting screen failures.

Procedures to be completed at screening are listed in Appendix A.

Subjects who fail screening can be rescreened, with approval of the sponsor. They should be assigned a new screening ID number.

9.3.2 Treatment Period

The 6-week treatment period begins with baseline/randomization, continues with 6 weeks of study medication, and ends on the last day of study medication (or early termination).

This is followed by a 3-week washout period, after which the treatment period is repeated.

9.3.2.1 Baseline/Randomization

Baseline/randomization will take place on study Day 1.

Procedures to be completed at baseline are listed in Appendix A.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IWRS, as described in Section 8.2.

Subjects will be instructed on when to take the first dose of study drug as described in Section 6.1. The procedure for documenting randomization failures is provided in Section 9.1.23.

9.3.2.2 Treatment and Washout Periods

Procedures to be completed during each of the 2 treatment periods and the intervening washout period are listed in Appendix A.

9.3.3 Final Visit or Early Termination

The final visit will occur on the last day of treatment in treatment period 2 (or early termination).

Procedures to be completed at this visit are listed in Appendix A.

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

9.3.4 Follow-up

The follow-up phone call occurs 14 days after the final visit or early termination.

9.3.5 Post Study Care

Study drug will not be available on completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

9.4 Biological Sample Retention and Destruction

Please refer to the sample management plan.

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

Subjects who consented and provided a sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time. The sponsor will be notified of consent withdrawal.

When a subject requests disposal of a stored sample during the retention period, the site will ask the vendor to destroy the sample via the sponsor according to the procedure. the vendor will destroy the sample in accordance with the procedure, and notify the site and sponsor. However, a sample may be retained if documentation (including medical records) identifying the subject donor has been destroyed and it is impossible to link the sample to any given subject.

Even if the sample can be linked to the subject, when DNA analysis has been conducted, the remaining samples will be destroyed and the results of DNA analysis of anonymized subject will be retained by the sponsor.

The sponsor has put into place a system to protect the subject's personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

This section applies to all subjects.

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

Changes in intensity of AEs/serious PTEs:

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

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

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

Overdose:

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

10.1.4 SAEs

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

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

Table 10.a Takeda Medically Significant AE List

Blood and lymphatic system disorders	**Pregnancy, puerperium, and perinatal conditions**
Agranulocytosis	Spontaneous abortion
Aplastic anaemia	Stillbirth and fetal death
Cardiac disorders	**Renal and urinary disorders**
Torsade de pointes	Acute renal failure
Ventricular fibrillation	**Respiratory, thoracic, and mediastinal disorders**
Ventricular tachycardia	Acute respiratory distress syndrome
Hepatobiliary disorders	Acute respiratory failure
Acute liver failure	Pulmonary fibrosis
Hepatic necrosis	Pulmonary hypertension
Immune system disorders	**Skin and subcutaneous tissue disorders**
Anaphylactic shock	Stevens-Johnson syndrome
Infections and infestations	Toxic epidermal necrolysis
Confirmed or suspected endotoxin shock	**Vascular disorders**
Confirmed or suspected transmission of infectious agent by a medicinal product	Malignant hypertension
COVID-19	
COVID-19 pneumonia	
Nervous system disorders	
Convulsive seizure	
Malignant hyperthermia	
Neuroleptic malignant syndrome	

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

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

10.1.5 Intensity of PTEs and AEs

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

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

10.1.6 Causality of AEs

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

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

10.1.7 Relationship to Study Procedures

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

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

10.1.8 Start Date

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

10.1.9 Stop Date

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

10.1.10 Frequency

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

10.1.11 Action Concerning Study Drug

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

10.1.12 Outcome

- Recovered/resolved: subject returned to first assessment status with respect to the AE/PTE.

- Recovering/resolving: the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved: there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae: the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal: the AEs/PTEs which are considered as the cause of death.
- Unknown: the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug baseline/Day 1) or until screen failure. For subjects who discontinue before study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug baseline/Day 1). Routine collection of AEs will continue until the follow-up safety phone call (≥14 days after the last dose).

10.2.1.1 PTE and AE Reporting

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

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not

the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.2 Collection, Reporting, and Acknowledgment of SAEs

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

The preferred method of reporting SAEs is via the SAE eCRF page in the electronic data capture (EDC) system. If access to EDC is not feasible within 24 hours of receiving the event, a paper SAE form should be submitted via fax (see Section 1.2 for fax number).

If fax is used, site personnel need to confirm successful transmission of all pages and include an email address on the fax cover sheet so that an acknowledgment of receipt can be returned via email within 1 business day.

Email submission of SAE forms with a PDF attachment should only be used in the case where fax is not possible and EDC is not feasible within 24 hours of receiving the event,

In case of email, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day,

If SAEs are reported via fax or by email, the EDC must be updated as soon as possible with the appropriate information,

The SAE information should be completed as fully as possible but contain, at a minimum:

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

- Causality assessment.

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

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

10.2.3 Reporting of Abnormal LFTs

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

If a subject is noted to have ALT or AST >3 × ULN and total bilirubin >2 × ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported per Section 10.2.2. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.11 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should update the SAE form in the eCRF and provide other written documentation within 24 hours of receipt. However, as a back-up, if required, the SAE paper form should be completed, signed by the investigator, and transmitted within 24 hours to the attention of the contact listed in Section 1.2. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the attention of the contact listed in Section 1.2, if requested.

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

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

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

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study. Data will be reviewed by the sponsor only.

12.0 DATA HANDLING AND RECORDKEEPING

This section applies to all subjects.

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

12.1 eCRFs

This study will use eCRFs.

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

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

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

Corrections eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should also be included.

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 (R2) Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (R2) (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 (R2) Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

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

13.0 STATISTICAL METHODS

This section applies to all subjects unless otherwise indicated.

13.1 Statistical and Analytical Plans

A SAP will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Safety and PK analyses of the sentinel cohort will be conducted as described in a separate Internal Review Charter prior to that.

A blinded data review will be conducted before database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

13.1.1.1 Safety Analysis Set

The safety analysis set will include all subjects who were randomized and received at least 1 dose of the study drug. Subjects in this analysis set will be used for demographics, baseline characteristics, and safety summaries.

13.1.1.2 PK Analysis Set

The PK analysis set will consist of subjects who receive at least 1 dose of study drug and who have at least 1 measurable plasma concentration of TAK-071.

13.1.1.3 Pharmacodynamic Analysis Set

The pharmacodynamic analysis set will consist of subjects who receive at least 1 dose of study drug and who have at least 1 evaluable postdose pharmacodynamic measure. All TAK-071 dose groups will be combined.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be listed and summarized by each sequence group and overall using the safety analysis set.

13.1.3 Pharmacodynamic Analysis (Subjects With PD)

Summary statistics will be provided for the observed values of the efficacy measures at baseline and each of the postdose visits by treatment groups. Change from baseline will also be summarized with descriptive statistics by treatment groups.

The primary outcome, the change from baseline in gait variability during a 2-minute walk test, will be analyzed using a linear mixed effect model with a random factor for subject and fixed factors for treatment, period, and sequence. Baseline covariates will be included in the model as appropriate.

The effect of treatment on the overall cognitive battery will be analyzed using a linear mixed effects model with random effects for subjects for each cognitive test, fixed factors for treatment, test, period, and sequence. The comparison of the number of falls for placebo versus TAK-071 will be analyzed using a generalized linear mixed effects model with a random factor for subjects and fixed factors for treatment, period, and sequence.

To address the exploratory outcomes, the continuous endpoints will be analyzed using linear mixed effects models with a random factor for subject and fixed factors for treatment, period, and sequence.

Drug effects on change from baseline for all endpoints will be assessed using 1-sided tests. In all analyses the interaction terms and covariates will be added as appropriate. If the outcomes are positively skewed, a logarithmic transformation may be applied. All other statistical analyses of pharmacodynamic endpoints will be described in the SAP.

13.1.4 PK Analysis

Descriptive statistics will be used to summarize plasma concentrations over collection time. Individual plasma concentration data will be presented in data listings.

Descriptive statistics will also be used to summarize plasma PK parameters. Individual plasma PK parameters will be presented in data listings.

13.1.5 Other Analyses (Subjects With PD)

Disease characteristics may be used as covariates in the statistical analyses of primary, secondary, and exploratory outcomes.

Other analyses may include, but are not limited to, the analysis of digital device data, such as wearable pendant sensor and/or digital gait assessment data; plasma biomarkers including neuronally derived exosome M_1 mRNA levels, amyloid, tau, NfL, and biomarkers of synaptic integrity; and DNA-based biomarkers.

The statistical analyses of in-home activity and number of falls, collected by the wearable pendant sensor, will be described in detail in the SAP.

The analyses listed in this section will be performed if useful and appropriate. The corresponding data and the analyses results may not be included in the clinical study report.

13.1.6 Safety Analysis

AEs will be summarized using the safety analysis set.

All AEs will be coded using MedDRA. Data will be summarized using Preferred Term (PT) and primary System Organ Class (SOC).

TEAEs will be summarized by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to study drug (related versus not related), severity of AEs, and related AEs.

Data listings will be provided for all AEs including TEAEs, AEs leading to study drug discontinuation, and SAEs.

Clinical laboratory variables, vital signs, and ECG parameters will be summarized with descriptive statistics for baseline, postdose, and change from baseline to postdose values.

Individual results of vital sign and ECG parameters that meet Takeda's markedly abnormal criteria will be summarized and provided in the data listings. All vital sign data and all ECG data will be provided in the data listings.

13.2 Interim Analysis, Sentinel Analysis, and Criteria for Early Termination

No formal interim analysis is planned. The safety and PK review of the sentinel cohort will be described in detail in the Internal Review Charter. Stopping rules are described in Section 6.4.

13.3 Determination of Sample Size (Subjects With PD)

A sample size of 42 completers with PD will be sufficient to detect a statistically significant (α = 0.05, 1-sided) decrease in gait variability during walking for TAK-071 versus placebo. We expect to detect a minimum effects size of 0.32 (Cohen d) in the reduction of gait variability, similar to that observed in [2]. For the sample size calculation, the study power was assumed to be 80%.

Given the proposed study sample size and 80% power, a minimum detectable operational effect size [20] for the cognitive battery (α = 0.1, 1-sided) will be 0.49. The correlations between

cognitive tests are assumed to be 0.5. The minimum detectable ($\alpha = 0.1$, 1-sided) effect size in the number of falls will be approximately 0.3, similar to the effect size for the number of falls observed in the literature [2,3]. For all calculations, the within-person correlation for the primary and secondary outcomes was assumed to be 0.65 [3].

It is expected that approximately 64 subjects will be randomized to ensure at least 42 completers. During the study, blinded monitoring of the data will take place to evaluate assumptions regarding the distribution of key study variables. If necessary up to 70 subjects may be randomized. Details will be provided in the SAP.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

This section applies to all subjects.

14.1 Study-Site Monitoring Visits

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

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

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, such as the COVID-19 pandemic, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

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

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

This section applies to all subjects.

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

15.1 IRB

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

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

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

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

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

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

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by

law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

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Appendix A Schedule of Study Procedures, Main Study (Su.bjects With PD)

Table A-1 Period 1

	Screening [a]	6-Week Double-blind Treatment Period (Period 1)			Washout
		Baseline [b]	At-home Assessment	Last Day of Treatment Period or Early Termination [c]	
Study Visit Number	**1**	**2**	**3**	**4**	
(Study Day)	**(Day -42 up to Day -1)**	**(Day 1)**	**(Day 21 ±2)**	**(Day 42 ±2)**	**(Day 43 to Day 63) [d]**
Administrative Procedures					
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographics	X				
Education and handedness		X			
Medical history	X				
Disease characteristics	X				
Medication history	X				
Concomitant medications	X	X	X	X	
Fall history assessment	X				
Clinical Procedures/Assessments					
Vital signs, weight, and BMI	X	X		X	
Height	X				
MoCA	X				
MDS UPDRS including Hoehn and Yahr scale	X	X		X	
PTE/AE assessment	X	X	X	X	
12-lead ECG	X	X		X	
Physical examination without nervous system	X	X			
Physical examination with nervous system				X	
Neurological examination	X	X			
C-SSRS	X	X	X	X	
Serial subtraction test, seated	X	X		X	
2-minute walk with no cognitive load		X		X	

Table A-1 Period 1

	Screening [a]	6-Week Double-blind Treatment Period (Period 1)			Washout
		Baseline [b]	At-home Assessment	Last Day of Treatment Period or Early Termination [c]	
Study Visit Number	**1**	**2**	**3**	**4**	
(Study Day)	**(Day -42 up to Day -1)**	**(Day 1)**	**(Day 21 ±2)**	**(Day 42 ±2)**	**(Day 43 to Day 63) [d]**
2-minute walk-under serial subtraction condition with audio recording to verify cognitive performance	X [e]	X		X	
Cognition assessment [f]	X	X		X	
Cued 180° turns		X		X	
TUG [g]	X	X		X	
Postural sway with eyes open and closed		X		X	
Speech test (in clinic)	X	X		X	
Speech test (at home)			See schedule in Appendix B for speech test		
ESS		X		X	
CGI-I/PGI-I				X	
CGI-S/PGI-S		X		X	
Compliance Procedures					
Randomization		X			
Dispense study drug		X			
Confirm study drug compliance [h]		X	X	X	
Collect remaining study drug				X	
Provide wearable pendant sensor, electronic drug diary, and falls diary for at-home daily use		X			
Confirm in-home wearable pendant sensor and electronic drug diary compliance		X	X	X	
Collect wearable pendant sensor, electronic drug diary device, and falls diary				X (Only at early termination)	

Table A-1 Period 1

	Screening [a]	6-Week Double-blind Treatment Period (Period 1)			Washout
		Baseline [b]	At-home Assessment	Last Day of Treatment Period or Early Termination [c]	
Study Visit Number	**1**	**2**	**3**	**4**	
(Study Day)	**(Day -42 up to Day -1)**	**(Day 1)**	**(Day 21 ±2)**	**(Day 42 ±2)**	**(Day 43 to Day 63) [d]**
Laboratory Procedures/Assessments					
Clinical laboratory evaluations, including 4β-hydroxycholesterol and cholesterol	X	X		X	
Urine drug and alcohol screen	X	X		X	
Serum pregnancy test (hCG) [i]	X	X		X	
HBsAg and anti-HCV	X				
Plasma samples for circulating biomarkers [j,k]		X		X [k]	
Blood sample for DNA (optional) [j]		X			
Plasma samples for TAK-071 PK [j,l]		X		X	

AE: adverse event; anti-HCV: antibody to hepatitis C virus; BMI: body mass index; C-SSRS: Columbia Suicide Severity Rating Scale; CGI-I/PGI-I: Clinical/Patient Global Impression-Improvement; ECG: electrocardiogram; ESS: Epworth Sleepiness Scale; HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; MoCA: Montreal Cognitive Assessment; MDS UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale; PD: Parkinson disease; PGI-S/CGI-S: Patient/Clinical Global Impression-Severity; PK: pharmacokinetic; PTE: pretreatment event; TUG: Timed Up and Go test.

[a] Screening assessments should be completed within the screening period.

[b] Assessments at Visit 2 (Period 1 baseline) may be split across 2 days and should be completed on or before Day 3.

[c] Assessments at Visit 4 (Period 1 last day of treatment period or early termination) may be split across 2 days and should occur within the visit window.

[d] Washout is ≥3 weeks.

[e] The 2-minute walk at screening is done without audio recording.

[f] Assessments include Symbol Digit Modalities Test, Cogstate International Shopping List Test, Cogstate Modified Chase Test (only administered at screening visit), Cogstate Modified Groton Maze Learning Test, Cogstate One Card Learning Test, Cogstate One Back Test, Cogstate International Shopping List Test—Recall, and Sustained Attention Task.

[g] TUG: 1 trial at screening, 3 trials at each baseline and last/early termination visit.

[h] Drug compliance will be evaluated with an electronic drug diary.

[i] Pregnancy test is administered when applicable based on subject sex. For Baseline (Visit 2), urine pregnancy test may be used instead of serum pregnancy.

[j] See Appendix C for timing of samples.

[k] Biomarker sample to be collected at Visit 4, but not early termination.

[l] Additional samples can be collected as needed.

Table A-2 Period 2

	6-Week Double-blind Treatment Period (Period 2)			Follow-up Safety Phone Call
	Baseline [a]	At-home Assessment	Last Day of Treatment Period or Early Termination [a]	(Week 17)
Study Visit Number	5 [a]	6	7 [a]	8
(Study Day)	(Day 64 ±2)	(Day 84 ±2)	(Day 105 ±2)	(Day 119)
Administrative Procedures				
Informed consent				
Inclusion/exclusion criteria	X			
Demographics				
Medical history				
Disease characteristics				
Medication history				
Concomitant medications	X	X	X	X
Fall history assessment				
Clinical Procedures/Assessments				
Vital signs, weight, and BMI	X		X	
Height				
MoCA				
MDS UPDRS including Hoehn and Yahr scale	X		X	
PTE/AE assessment	X	X	X	X
12-lead ECG	X		X	
Physical examination without nervous system	X			
Physical examination with nervous system			X	
Neurological examination	X			
C-SSRS	X	X	X	
Serial subtraction test, seated	X		X	
2-minute walk with no cognitive load	X		X	
2-minute walk under serial subtraction condition with audio recording to verify cognitive performance	X		X	
Cognition assessment [b]	X		X	
Cued 180° turns	X		X	
TUG [c]	X		X	
Postural sway with eyes open and closed	X		X	
Speech test (in clinic)	X		X	

Table A-2 Period 2

	6-Week Double-blind Treatment Period (Period 2)			Follow-up Safety Phone Call
	Baseline [a]	At-home Assessment	Last Day of Treatment Period or Early Termination [a]	(Week 17)
Study Visit Number	5 [a]	6	7 [a]	8
(Study Day)	(Day 64 ±2)	(Day 84 ±2)	(Day 105 ±2)	(Day 119)
Speech test (at home)		See schedule in Appendix B for speech test		
ESS	X		X	
CGI-I/PGI-I			X	
CGI-S/PGI-S	X		X	
Compliance Procedures				
Randomization	X			
Dispense study drug	X			
Confirm study drug compliance [d]	X	X	X	
Collect remaining study drug			X	
Provide wearable pendant sensor, electronic drug diary, and falls diary for at-home daily use	X			
Confirm in-home wearable pendant sensor and electronic drug diary compliance	X	X	X	
Collect wearable pendant sensor, electronic drug diary device, and falls diary, (Visit 7 only)			X	
Laboratory Procedures/Assessments				
Clinical laboratory evaluations, including 4β-hydroxycholesterol and cholesterol	X		X	
Urine drug and alcohol screen	X		X	
Serum pregnancy test (hCG) [e]	X		X	
HBsAg and anti-HCV				
Plasma samples for circulating biomarkers [f,g]	X		X [g]	
Blood sample for DNA (optional) [f]				
Plasma sample for TAK-071 PK [f,h]	X		X	

AE: adverse event; anti-HCV: antibody to hepatitis C virus; BMI: body mass index; C-SSRS: Columbia Suicide Severity Rating Scale; CGI-I/PGI-I: Clinical/Patient Global Impression-Improvement; ECG: electrocardiogram; ESS: Epworth Sleepiness Scale; HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; MoCA: Montreal Cognitive Assessment; MDS UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale; PD: Parkinson disease; PGI-S/CGI-S: Patient/Clinical Global Impression-Severity; PK: pharmacokinetic; PTE: pretreatment event; TUG: Timed Up and Go test.

[a] Assessments at Visit 5 (Period 2 baseline) and Visit 7 (Period 2 last day of treatment period or early termination visit) may be split across 2 days and should occur within the visit window.

Table A-2 Period 2

	6-Week Double-blind Treatment Period (Period 2)			Follow-up Safety Phone Call
	Baseline [a]	At-home Assessment	Last Day of Treatment Period or Early Termination [a]	(Week 17)
Study Visit Number	5 [a]	6	7 [a]	8
(Study Day)	(Day 64 ±2)	(Day 84 ±2)	(Day 105 ±2)	(Day 119)

[b] Assessments include Symbol Digit Modalities Test, Cogstate International Shopping List Test, Cogstate Modified Chase Test (only administered at screening visit), Cogstate Modified Groton Maze Learning Test, Cogstate One Card Learning Test, Cogstate One Back Test, Cogstate International Shopping List Test—Recall, and Sustained Attention Task.

[c] TUG: 1 trial at screening, 3 trials at each baseline and last/early termination visit.

[d] Drug compliance will be evaluated with an electronic drug diary.

[e] Pregnancy test is administered when applicable based on subject sex. For study visit 5 (Day 64), a urine pregnancy test may be used instead of serum pregnancy.

[f] See Appendix C for timing of samples.

[g] Biomarker sample to be collected at Visit 7, but not early termination.

[h] Additional samples can be collected as needed.

Appendix B Schedule of At-Home Speech Tests (Subjects With PD)

Period	Study Days for Morning Notification and At-Home Speech Assessment	Window for At-Home Speech Assessments
First	Days 19, 21, 23	Days 19-24
Second	Days 82, 84, 86	Days 82-87

No more than 1 assessment per day.

Notifications will be provided the morning of the assessment day. If the assessment is not done at that time, a second notification will be sent 1 hour later. The next morning, if the assessment is still not done, a third notification will be sent at same time of day as the first notification.

Appendix C Schedule of Samples Across Both Periods, Main Study

Subjects With PD						
Visit	**Visit 1 (Screening)**	**Visit 2**	**Visit 4**	**Visit 5**	**Visit 7**	**Early Termination Visit**
Day(s)	**-42 to -1**	**1**	**42 (±2)**	**64 (±2)**	**105 (±2)**	
Clinical laboratory samples	X	X	X	X	X	X
Plasma samples for circulating biomarkers		Predose	2 hours	Predose	2 hours	
Blood sample for DNA (optional)		Predose				
Plasma sample for TAK-071 PK [a]		Predose; 1 hour, 2 hours	Predose; 1 hour, 2 hours, 3 hours	Predose; 1 hour, 2 hours	Predose; 1 hour, 2 hours, 3 hours	X

PD: Parkinson disease; PK: pharmacokinetic.

Appendix D Responsibilities of the Investigator

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

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

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

10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix E Elements of the Subject Informed Consent

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

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

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

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

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from screening throughout the duration of the study, and for 42 days after the last dose. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during the study, the study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use barrier or highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for 102 days after the last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix F Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix G Amendment History

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
07 September 2021	Amendment 4	Not applicable	United States
18 January 2021	Amendment 3	Not applicable	United States
12 August 2020	Amendment 2	Not applicable	United States
06 July 2020	Amendment 1	Not applicable	United States
16 March 2020	Initial version	Not applicable	United States

Protocol Amendment 3

The primary reasons for this amendment are to:

- Add healthy subjects at the beginning of the study as a sentinel cohort for rich pharmacokinetic (PK) sampling, to be conducted at designated sites. Remove subjects with Parkinson disease (PD) from the sentinel cohort. To clarify procedures that are specific to each cohort, move information specific to the sentinel cohort to an appendix and remove sentinel cohort information from main text.
- Allow initial subjects with PD to enroll in main study in parallel to when the sentinel cohort is running. These subjects must be ≤65 years old. Older subjects with PD may be enrolled pending the results of the sentinel cohort PK.
- Remove cognitive load from the primary objective and endpoint. Add an exploratory/additional objective and endpoint around evaluation of gait parameters, and clarify that exploratory endpoints for change from baseline on gait parameters, gait variability, double support time, and self-directed turns are in the presence versus absence of cognitive loading.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only, and are not captured in the following table.

Protocol Amendment 3			
Summary of Changes Since Amendment 2			
Description of Each Change and Rationale			**Sections Affected by Change**
No.	**Description**	**Rationale**	**Location**
1	Lower dose may be used depending on pharmacokinetic (PK) results.	Clarify that proposed TAK-071 dose is ≤7.5 mg and that the maximum subject age and dose may be modified after analysis of data from the sentinel cohort.	Section 4.2, Benefit/Risk Profile Section 6.1, Study Design, Main Study Section 8.1.3, Dose and Regimen Section 8.2, Study Drug Assignment and Dispensing Procedures

Protocol Amendment 3			
Summary of Changes Since Amendment 2			
	Description of Each Change and Rationale		**Sections Affected by Change**
No.	**Description**	**Rationale**	**Location**
2	Given the inclusion criteria, some subjects may not be able to complete the task required to measure the original primary endpoint (2-minute walk with cognitive loading).	Remove cognitive load from primary objective and endpoint.	Section 2.0, Study Summary: Study Design 5.1.1, Primary Objectives 5.2.1, Primary Endpoint 13.1.3, Pharmacodynamic Analysis (Subjects With PD)
3	Examine the interaction of cognitive loading and treatment, which was removed from primary objectives and endpoint. Clarify that exploratory endpoints for change from baseline on gait parameters, gait variability, double support time, and self-directed terms are in the presence versus absence of cognitive loading and treatment.	Add an exploratory/additional objective and endpoint around evaluation of gait parameters in presence versus absence of cognitive loading. Change "presence and absence" of cognitive loading to "presence versus absence" in the exploratory objectives and endpoints.	5.1.3, Exploratory/Additional Objectives 5.2.4, Exploratory Endpoints
4	Separation of main study and sentinel cohort, where elements differ, makes protocol easier to follow. Study sites enrolling only subjects with PD do not need to see instructions specific to healthy subjects. Single PK site for healthy subjects, appendix will clarify procedures for them.	Remove sentinel cohort from main text. Move sentinel cohort to new Appendix H with elements specific to sentinel cohort (healthy subjects).	Section 2.0, Study Summary Section 5.2.2, Secondary Endpoints Section 6.1, Study Design, Main Study Section 6.3.3, Dose Justification Section 8.2, Study Drug Assignment and Dispensing Procedures Section 9.1.21, PK Parameters Section 9.3 Schedule of Observations and Procedures Appendix A, Schedule of Study Procedures, Main Study (Subjects With PD): Table A-1, Period 1 Appendix C, Schedule of Samples Across Both Periods, Main Study Appendix H, Sentinel Cohort (Healthy Subjects) Only
5	Make age descriptions consistent.	Express all age ranges as "inclusive".	Section 2.0, Study Summary Section 6.1, Study Design, Main Study

Protocol Amendment 3			
Summary of Changes Since Amendment 2			
Description of Each Change and Rationale			**Sections Affected by Change**
No.	**Description**	**Rationale**	**Location**
6	Data from healthy older subjects will be sufficient to extend the PK profile established in younger healthy adult subjects. Designated site(s) will conduct the sentinel cohort, with rich PK sampling.	Add healthy subjects at the beginning of the study as a sentinel cohort for rich PK sampling, at designated site(s). Remove subjects with PD from the sentinel cohort.	Section 2.0, Study Summary Section 6.1, Study Design, Main Study Appendix A, Schedule of Study Procedures, Main Study (Subjects With PD)
7	Sentinel cohort data is needed before enrollment of older PD subjects can begin; there is no restriction on enrollment of PD subjects aged ≤65 years.	Allow initial subjects with PD to enroll in main study in parallel to when the sentinel cohort is running. These subjects must be aged ≤65 years. Older subjects with PD may be enrolled pending the results of the sentinel cohort PK.	Section 2.0, Study Summary Section 6.1, Study Design, Main Study Section 6.3.3, Dose Justification Section 8.1.3, Dose and Regimen
8	PK results from sentinel cohort and later subjects with PD may allow older subjects.	Remove age 85 years as upper limit.	Section 2.0, Study Summary Section 6.1, Study Design, Main Study Section 6.3.3, Dose Justification Section 7.1, Inclusion Criteria (#3) Section 8.1.3, Dose and Regimen Section 8.2, Study Drug Assignment and Dispensing Procedures
9	Consistent with Movement Disorders Society clinical diagnostic criteria for PD.	Clarify that subjects with DLB are permitted.	Section 6.3.1, Subject Selection Considerations 7.1, Inclusion Criteria (#4)
10	Increase study feasibility.	Change the criteria for cognitive impairment to MOCA score of 17 (rather than 18) to 24, inclusive.	Section 6.3.1, Subject Selection Considerations Section 7.1, Inclusion Criteria (#7)
11	Does not intend capacity in the legal sense.	Clarify ability, rather than capacity, to follow instructions.	Section 7.1, Inclusion Criteria (#8)
12	Enable recruitment of some subjects with orthostasis who may still safely participate in study.	Modify exclusion on the basis of orthostatic hypotension.	Section 7.2, Exclusion Criteria (#2)
13	Clarifies that both criteria defining dyskinesia severity must be met to exclude subject. Expands investigator opinion to interference with more than digital gait assessments.	Change "scores >2), **or** in the opinion" to "scores >2), **and** in the opinion". Dyskinesia exclusion extended to interference with other aspects of study.	Section 7.2, Exclusion Criteria (#4)

Protocol Amendment 3			
Summary of Changes Since Amendment 2			
	Description of Each Change and Rationale		**Sections Affected by Change**
No.	**Description**	**Rationale**	**Location**
14	Enable recruitment of subjects who may still safely participate in study.	Modify exclusion on the basis of eGFR, QTcF, and HCV status.	Section 7.2, Exclusion Criteria (#10)
15	Other psychiatric disorders of sufficient severity could interfere with completion of the study or interpretation of the endpoints.	Expand exclusion from depression to depression or other psychiatric disorder.	Section 7.2, Exclusion Criteria (#11)
16	Substance use disorders with the exception of tobacco use disorder are an exclusion, as the later is not expected to interfere with the study.	Clarify that substance use disorders do not include tobacco-use disorder for purposes of exclusion.	Section 7.2, Exclusion Criteria (#12)
17	Subjects with emergency room visit due to fall may be safe to continue in the study.	Clarify that fall-related institutionalization or hospital admission does not include emergency room visit.	Section 7.2, Exclusion Criteria (#21)
18	Add and clarify timing of vaccination.	Clarify that vaccination for COVID-19 is allowed provided it is not within 48 hours of a study visit.	Table 7.a, Excluded and Allowed Medications and Treatments
19	Allow subjects to use trazodone for insomnia.	Change antidepressant criterion in Table 7.a regarding trazodone.	Table 7.a, Excluded and Allowed Medications and Treatments
20	Allow if investigator and sponsor agree the drug will not interfere with the study.	Allow the use of antipsychotic drugs (aside from pimavanserin and quetiapine, which are already permitted) under some circumstances.	Table 7.a, Excluded and Allowed Medications and Treatments
21	Broaden conditions where anticonvulsants are acceptable.	Allow the use of anticonvulsants if not used for seizure disorder.	Table 7.a, Excluded and Allowed Medications and Treatments
22	Allow use of stable dose for insomnia, rapid eye movement sleep disorder, and anxiety.	Allow use of benzodiazepines under some circumstances.	Table 7.a, Excluded and Allowed Medications and Treatments
23	Clarify that nonbenzodiazepine hypnotics may be used if dose is relatively stable from 30 days before randomization to the end of the study, rather than requiring washout.	Allow the use of nonbenzodiazepine hypnotics under some circumstances.	Table 7.a, Excluded and Allowed Medications and Treatments
24	Clarify relationship of scale to independent living criterion.	Provide web reference for Hoehn and Yahr scale.	Section 9.1.8.1.3, MDS-UPDRS Including Hoehn and Yahr Scale
25	Match updates to schedule of assessments.	Update blood volume estimate.	Section 9.1.11, Maximum Blood Volumes (Subjects With PD Only)

Protocol Amendment 3			
Summary of Changes Since Amendment 2			
Description of Each Change and Rationale			**Sections Affected by Change**
No.	**Description**	**Rationale**	**Location**
26	Clarifies that these are 2 separate tests.	Clarify that samples for 4β-hydroxycholesterol **and** cholesterol will be collected.	Table 9.b, Clinical Laboratory Tests
27	Make criteria for female partners of male subjects consistent with criteria for female subjects.	Clarify that amenorrhea must be at least 12 months to determine if a female subject is not of childbearing potential.	Section 9.1.13.1, Male Subjects and Their Female Partners
28	Correct inadvertent omission.	Add tubal ligation to definitions and procedures of pregnancy avoidance.	Section 9.1.13.3, Definitions and Procedures for Contraception and Pregnancy Avoidance
29	Results of serum human chorionic gonadotropin test may not be available before dosing. female subjects could be perimenopausal and having irregular periods.	Rule out pregnancy with urine dipstick the previous or same day before receiving any dose of study medication. Remove requirement to confirm menses in month before first dose.	Table 9.b, Clinical Laboratory Tests Section 9.1.13.3, Definitions and Procedures for Contraception and Pregnancy Avoidance Appendix A, Schedule of Study Procedures, Main Study (Subjects With PD): Table A-1, Period 1 and Table A -2, Period 2
30	Paper CRFs do not exist for study.	Omit mention of paper CRFs.	Section 12.1, eCRFs
31	Clarified by statistician.	Change Blinded Data Review Manual to Internal Review Charter.	Section 13.1, Statistical and Analytical Plans
32	Clarification.	Delete assumption of 5% type I error for exploratory outcomes.	Section 13.1.3 Pharmacodynamic Analysis (Subjects With PD)
33	Consistent with contingency measures due to coronavirus disease 2019.	Clarify that site monitoring visits can be onsite or remote.	Section 14.1, Study-Site Monitoring Visits
34	Education and handedness will/may be used as covariates for analyses of pharmacodynamic measures.	Collect education and handedness at baseline (subjects with PD).	Appendix A, Schedule of Study Procedures, Main Study (Subjects With PD): Table A-1, Period 1
35	No audio recording will be used at screening walk test.	Clarify walk test at screening.	Appendix A, Schedule of Study Procedures, Main Study (Subjects With PD): Table A-1, Period 1
36	Clarify footnotes.	Correct footnotes in Appendices A and C.	Appendix A, Schedule of Study Procedures, Main Study (Subjects With PD): Table A-1, Period 1 and Table A -2, Period 2 Appendix C, Schedule of Samples Across Both Periods, Main Study

Protocol Amendment 3			
Summary of Changes Since Amendment 2			
Description of Each Change and Rationale			Sections Affected by Change
No.	Description	Rationale	Location
	Clarify subject populations.	Throughout clarify that certain sections apply to sentinel, main, or all.	Global change.

Protocol Amendment 2

The primary reasons for this amendment were to:

- Remove Amendment Type from Amendment History table on cover page.
- Change maximum subject age to ≤65 years, with the option of increasing age limit later.
- Allow up to 25 study sites.
- Clarify that subjects who drop out of the sentinel cohort may be replaced, at sponsor's discretion.
- Replace modified Hoehn and Yahr scale with original Hoehn and Yahr scale.
- Remove description of speech tasks.
- Revise table of excluded medications.
- Revise estimates of total blood volume.
- Correct tests for 4β-hydroxycholesterol, cholesterol, and ratio of 4β-hydroxycholesterol to cholesterol to be plasma samples, not serum.
- Correct sample collection information for plasma biomarkers.

Protocol Amendment 2		
Summary of Changes Since Amendment 1		
Description of Each Change and Rationale		Sections Affected by Change
Description	Rationale	Location
Remove Amendment Type from Amendment History table on cover page	Not applicable to US study.	Cover page.
Change maximum subject age to ≤65 years, with the option of increasing the age limit later if pharmacokinetic and safety data permit.	FDA guidance.	Section 2.0, Study Summary: Study Design, Number of Sites Section 6.1, Study Design
Allow up to 25 study sites.	Flexibility to add more sites.	Section 2.0, Study Summary: Study Design, Subject Population, Main Criteria for Inclusion Section 6.1, Study Design

Protocol Amendment 2		
Summary of Changes Since Amendment 1		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	**Rationale**	**Location**
Clarify that subjects who drop out of the sentinel cohort may be replaced, at sponsor's discretion.	Replacement is not necessary in all cases.	Section 2.0, Study Summary: Study Design Section 6.1, Study Design Section 8.2, Study Drug Assignment and Dispensing Procedures Section 13.3, Determination of Sample Size
Revise table of excluded medications to standardize all washout periods to 30 days.	Simplify for sites.	Table 7.a, Excluded and Allowed Medications and Treatments
Require antipsychotics pimavanserin and quetiapine to be at a steady dose 30 days before randomization.	Clarified requirements.	Table 7.a, Excluded and Allowed Medications and Treatments
Allow gabapentin when it is used for neuropathic pain and the dose has been stable for at least 30 days before randomization. Allow use of anticonvulsants for other indications such as migraine headache if the investigator and sponsor agree that the drug is unlikely to affect the outcome measures.	Clarify permitted exceptions to exclusion of anticonvulsants. Standardize prior dose requirements to 30 days before randomization.	Table 7.a, Excluded and Allowed Medications and Treatments
Permit antidepressants (except bupropion and nefazodone) if dose is kept stable during study and has been a stable dose for 30 days before randomization.	Standardize prior dose requirements to 30 days before randomization.	Table 7.a, Excluded and Allowed Medications and Treatments
Remove St John's Wort from allowed herbal products. Allow herbal remedies, conditional on approval from the investigator and sponsor.	As a cytochrome P-450 inhibitor, St John's wort is excluded. Allowed if judged unlikely to affect the outcome measures and are deemed safe.	Table 7.a, Excluded and Allowed Medications and Treatments
Permit use of over-the-counter (OTC) medications not otherwise listed under certain circumstances.	Investigator and sponsor judge the medication will not interfere with the study or pose a risk to subjects.	Table 7.a, Excluded and Allowed Medications and Treatments
Allow exceptions to melatonin use for certain conditions if use has been relatively stable for 30 days before randomization.	Standardize prior dose requirements to 30 days before randomization.	Table 7.a, Excluded and Allowed Medications and Treatments

Protocol Amendment 2		
Summary of Changes Since Amendment 1		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	**Rationale**	**Location**
Clarify circumstances where use of cannabis and derived products is allowed; exclude episodic use.	Allows if subjects have been using cannabis and cannabis-derived products at a relatively stable dose and frequency for at least 30 days before randomization.	Table 7.a, Excluded and Allowed Medications and Treatments
Clarify that subjects taking warfarin must wash out and start another anticoagulant at least 30 days before randomization.	Subject safety.	Table 7.a, Excluded and Allowed Medications and Treatments
Clarify that benzodiazepines, when excluded, must be stopped at least 30 days before randomization.	Clarifies washout requirements when excluded.	Table 7.a, Excluded and Allowed Medications and Treatments
Replace modified Hoehn and Yahr scale with original Hoehn and Yahr scale.	The standard Hoehn and Yahr was selected by the Movement Disorders Society to include in the Movement Disorders Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Use of the modified Hoehn and Yahr with the MDS-UPDRS could cause confusion at sites and lead to the wrong version being used.	Section 9.1.8.1.3, MDS-UPDRS Including Hoehn and Yahr Scale
Remove detailed table of speech tasks.	Table included errors. Material will be presented in study manual.	Section 9.1.8.1.5, Speech Test
Revise estimates of total blood volume.	Site advice.	Section 9.1.11, Procedures for Clinical Laboratory Samples
Correct tests for 4β-hydroxycholesterol, cholesterol, and ratio of 4β-hydroxycholesterol to cholesterol.	Corrected to be plasma samples, not serum.	Table 9.b, Clinical Laboratory Tests
Update references.	Remove references that occurred in prior (Amendment 1) Summary of changes. Removed reference to modified Hoehn and Yahr scale.	Section 16.0, REFERENCES
Correct sample collection information for plasma biomarkers.	Remove collection at early termination visit.	Appendix A, Schedule of Study Procedures Appendix C, Schedule of Samples Across Both Periods
Add appendix of amendment history.	Takeda process requires history of prior amendments.	Appendix G, Amendment History

Protocol Amendment 1:

The primary reasons for this amendment were to:

- Describe a sentinel cohort for age effects on PK, in which initial subjects enrolled have rich PK sampling. The results of single-dose and steady-state PK analyses from these subjects will be used to decide the dose, up to 7.5 mg, for the remaining subjects to be enrolled. Subjects up to age 85 could possibly be included in the future, based on these PK analyses.
- Moved evaluation of PK from exploratory to secondary objectives.
- Add sentinel cohort PK endpoints to the secondary endpoints.
- Add evaluation of the ratio of plasma 4-beta-hydroxycholesterol to cholesterol and the relationship to plasma TAK-071 area under the concentration-time curve (AUC) as an exploratory objective, and add the relationship of the ratio of plasma 4-beta-hydroxycholesterol/cholesterol with plasma TAK-071 AUC as an exploratory endpoint.
- Clarify inclusion criteria, exclusion criteria, and dose justification.
- Clarify requirements in the excluded medications table, add a table of strong and moderate cytochrome P-450 (CYP)3A inhibitors and inducers, and exclude consumption of grapefruit and grapefruit juice.
- Add orthostatic hypotension to vital sign procedures.
- Add neurological examination.
- Clarify descriptions of modified Hoehn and Yahr scale and cognitive assessments, add Cogstate Modified Chase Test, and include Symbol Digit Modalities Test (SDMT) in screening procedures.
- Clarify that fasting before sample collection is not necessary and remove lactate dehydrogenase and glutamate dehydrogenase from serum chemistry tests. Add 4β-hydroxycholesterol, cholesterol, and their ratio at baseline to the serum chemistry tests.
- Modify serum chemistry tests with more conservative criteria regarding renal and hepatic function.
- Increase stringency of contraceptive requirements for women of childbearing potential.
- Add section on sample collection for circulating biomarkers.
- Allow rescreening of subjects who fail screening, with sponsor permission.
- Update Takeda Medically Significant Adverse Events list.
- Provide for blinded safety and PK reviews.
- Provide flexibility for subjects and investigators if procedures for data collection need to be modified due to the coronavirus disease 2019 (COVID-19) pandemic.

- Reorganize Schedule of Study Procedures. Add an appendix with a schedule for at-home speech assessments. Update schedule of samples. Removed appendix on Preferred Gait and Cognitive Measurement Procedure Sequence. Renumbered appendices accordingly.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only, and are not captured in the following table.

Protocol Amendment 1		
Summary of Changes Since Original Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	**Rationale**	**Location**
Moved evaluation of pharmacokinetic (**PK**) from exploratory to **secondary objectives**.	Emphasize importance of PK in establishing dose.	Section 2.0, Study Summary: Secondary Objectives Section 5.1.3, Exploratory/Additional Objectives Section 5.1.2, Secondary Objectives
Add sentinel cohort PK endpoints to the **secondary endpoints**.	Clarify PK endpoints for sentinel cohort versus all other subjects.	Section 2.0, Study Summary: Study Design Section 5.2.3, Secondary Endpoints
Describe a sentinel cohort for **age effects on PK**. The results of single-dose and steady-state PK analyses from these subjects will be used **to decide the dose, 7.5 mg or lower, for the remaining subjects to be enrolled.**	The results of single-dose and steady-state PK analyses from these subjects will be used to decide the dose, 7.5 mg or lower, for the remaining subjects to be enrolled. Depending on the sentinel cohort PK results, age-specific dosing may be used. At a later date, after sufficient PK data are available, whether subjects up to age 85 years are expected to remain below the exposure caps will be determined. If so, subjects up to age ≤85 years may be enrolled.	Section 2.0, Study Summary: Study Design Section 6.1, Study Design Section 6.3.3, Dose Justification Section 8.1.3, Dose and Regimen Section 8.2, Study Drug Assignment and Dispensing Procedures Section 9.1.20, PK Parameters Section 13.1.4, PK Analysis Appendix A, Schedule of Study Procedures Appendix C, Schedule of Samples Across Both Periods
Allow for **possible inclusion of subjects up to age 85 years** at a future date, based on PK results in sentinel cohort.	To allow a greater age range of subjects.	Section 2.0, Study Summary: Study Design; Subject Population; Main Criteria for Inclusion Section 6.1, Study Design Section 6.3.3, Dose Justification Section 7.1, Inclusion Criteria, criterion #3

Protocol Amendment 1		
Summary of Changes Since Original Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	**Rationale**	**Location**
Provide potential modifications to **account for the COVID-19 pandemic.**	To allow flexibility for subjects and investigative sites in data collection.	Section 2.0, Study Summary: Study Design Section 6.2, Contingency Measures Due to COVID-19 Pandemic or Other Unavoidable Circumstances, Section 9.1.8, Pharmacodynamic Measurements Section 9.1.23, Alternative Approaches to Study Procedures and Data Collection Due to COVID-19 or Other Unavoidable Circumstances Section 14.2, Protocol Deviations Section 16.0, REFERENCES
Add to Study Summary, subjects are able to walk without aid for 2 minutes **while doing serial 3 subtraction**.	Makes summary consistent with inclusion criteria in Section 7.1, criterion #9.	Section 2.0, Study Summary: Main Criteria for Inclusion
Inclusion criterion #10, subjects stable on antiparkinsonian medication for **30 days** (rather than 4 weeks).	Standardize medication exclusions from 4 weeks to 30 days.	Section 2.0, Study Summary: Main Criteria for Inclusion Section 7.1, Inclusion Criteria
Exclusion criterion #10, replace **aspartate aminotransferase (AST) and alanine aminotransferase (ALT)** > 2 × upper limit of normal (ULN) with **>1.2 × ULN** and replace serum creatinine >1.5 × ULN with **estimated glomerular filtration rate** (eGFR) (calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) **<60 mL/min**.	These values are more conservative than the original cutoff criteria.	Section 2.0, Study Summary: Main Criteria for Exclusion Section 7.2, Exclusion Criteria, criterion #10
Add evaluation of **the ratio of plasma 4-beta-hydroxycholesterol to cholesterol and the relationship to plasma TAK-071** area under the concentration-time curve (AUC) as an exploratory objective, and add the relationship of the ratio of plasma 4-beta-hydroxycholesterol/cholesterol with plasma TAK-071 AUC as an exploratory endpoint.	To evaluate the relationship of these parameters to TAK-071 exposure.	Section 5.1.3, Exploratory/Additional Objectives Section 5.2.4, Exploratory Endpoints

Protocol Amendment 1		
Summary of Changes Since Original Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	**Rationale**	**Location**
Clarify language about age in **dose justification**.	Change made to ensure subject safety.	Section 6.3.3, Dose Justification
Inclusion criterion #12, female subjects of childbearing potential must use **highly effective contraception** (rather than effective).	Highly effective is a more conservative requirement.	Section 7.1, Inclusion Criteria, criterion #12 Section 9.1.12, Contraception and Pregnancy Avoidance Procedure
Exclusion criterion #2, orthostatic hypotension definition reduces time after standing to **1 minute**.	Juraschek et al [1] suggest that the 1-minute time point is actually more predictive of adverse outcomes (including falls, which is of concern here). Juraschek et al added to references.	Section 7.2, Exclusion Criteria, criterion #2 Section 9.1.6 Vital Sign Procedure Section 16.0, REFERENCES
Exclusion criterion #8, add other risk factors deemed relevant by the investigator to the **definition of risk factors for seizures**.	Clarify risk definition to allow investigator judgment.	Section 7.2, Exclusion Criteria, criterion #8
Remove use of Geriatric Depression Scale (GDS). Replace with exclusion criterion #11, **in the opinion of the investigator the patient suffers from depression** of sufficient severity to interfere with completion of the study or interpretation of the endpoints.	Investigator advice and literature [2]. Lopez et al added to references. Yesavage et al deleted from references.	Section 7.2, Exclusion Criteria, criterion #11 Deletion of GDS (Short Form) from former Section 9.1.6.1 Deleted GDS from Appendix A, Table A-1, Period 1 Section 16.0, REFERENCES
Exclusion criterion #12, revise to replace history of drug abuse or alcohol dependences with substance use disorder, and also exclude subjects whose **current or past use of substances** may interfere with performance on the cognitive, motor, or other assessments.	Broadens exclusion to activities that might interfere with assessments.	Section 7.2, Exclusion Criteria, criterion #12
Exclusion criterion #14, exclude subjects who cannot discontinue **cholinesterase inhibitor and/or moderate or strong cytochrome P-450 3A4 inhibitor** at least 30 days before **randomization** (rather than baseline visit).	These drugs will interfere with the metabolism of TAK-071 and must be excluded to ensure safety of subjects.	Section 7.2, Exclusion Criteria, criterion #14
Exclusion criterion #16, change **washout period for prior investigational compounds** from 90 days to investigator judgement.	Allows exclusion of entities that may not have washed out in 90 days, such as monoclonal antibodies.	Section 7.2, Exclusion Criteria, criterion #16

Protocol Amendment 1		
Summary of Changes Since Original Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	**Rationale**	**Location**
Allow **benzodiazepines** for subjects with REM sleep disorder.	Benzodiazepines are sometimes used by PD patients for this indication and may need to continue to take these medications during the study.	Table 7.a, Excluded and Allowed Medications and Treatments
Allow **melatonin** for subjects with rapid eye movement (REM) behavior disorder and/or insomnia.	Melatonin has efficacy for REM behavior disorder and insomnia and is often used by Parkinson disease patients for these reasons.	Table 7.a, Excluded and Allowed Medications and Treatments
Allow the antipsychotics pimavanserin (at a dose of ≤34 mg once daily **and quetiapine** (at a dose of ≤250 mg total daily dose).	Allowed for subjects who in the opinion of the investigator medically require treatment with an antipsychotic drug to safely complete the study.	Table 7.a, Excluded and Allowed Medications and Treatments
Change **sedatives/hypnotics** to 2 categories, **barbiturates and nonbenzodiazepine hypnotics.**	Provide more refined guidelines on allowed drug classes to improve clarity.	Table 7.a, Excluded and Allowed Medications and Treatments
Clarify **anticholinergic** exclusion to state that for overactive bladder, subjects may be treated with mirabegron, which works by a different mechanism.	Although most drugs for overactive bladder have anticholinergic mechanisms of action and are excluded, mirabegron does not and is permitted for this indication.	Table 7.a, Excluded and Allowed Medications and Treatments
Clarify which **antidepressants** are allowed and excluded.	Bupropion is excluded in all cases. Nefazodone is excluded as a strong CYP3A4 inhibitor under all circumstances and must be stopped at least 30 days before randomization. Chronic use of other antidepressants is permitted as long as the dose is kept stable during the study and the dose has been stable for at least 8 weeks before randomization.	Table 7.a, Excluded and Allowed Medications and Treatments
Exclude consumption of **grapefruit and grapefruit juice**.	Grapefruit is a CYP3A4 inhibitor.	Table 7.a, Excluded and Allowed Medications and Treatments Section 7.4, Diet, Fluid, and Activity Control
Make **over-the-counter (OTC) drugs** a separate category and clarify when they are allowed and excluded.	Rationale is to provide more refined guidelines on allowed drug classes. OTC drugs will be allowed if the investigator agrees on a case by case basis.	Table 7.a, Excluded and Allowed Medications and Treatments

Protocol Amendment 1		
Summary of Changes Since Original Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	**Rationale**	**Location**
Various drug categories: **stable dose or washout** requirements of 4 weeks modified to **30 days**; washout criteria before screening changed to **before randomization**.	Criteria changed to be as uniform as possible across drug classes to minimize errors.	Table 7.a, Excluded and Allowed Medications and Treatments
Add **table of strong and moderate CYP3A inducers and inhibitors**.	Identifies these classes of drugs, which must be excluded in all circumstances and stopped at least 30 days before randomization.	Table 7.b, Strong and Moderate CYP3A Inducers and Inhibitors
Add **neurological examination** with physical examination.	A focused neurological examination is needed to evaluate for potential exclusions and to ensure subject safety.	Section 9.1.3, Physical Examination Procedure Section 9.1.4, Neurological Examination Procedure Appendix A, Schedule of Study Procedures
Add **orthostatic blood** pressure to vital sign procedures.	Make consistent with exclusion criteria.	Section 9.1.6, Vital Sign Procedure
Clarify that **Timed Up and Go test** at screening is only done once.	Distinguish screening from other visits.	Section 9.1.8.1, Pharmacodynamic Measurements Related to Gait Appendix A, Schedule of Study Procedures
Clarify description of **modified Hoehn and Yahr scale**.	Describe scores of modified scale. Add Bayés and Counihan [16] to reference list.	Section 9.1.8.1.3, MDS-UPDRS Including Hoehn and Yahr Scale Section 16.0, REFERENCES
Define the stages of the **modified Hoehn and Yahr Scale**.	Clarify categories.	Section 9.1.8.1.3, MDS-UPDRS Including Hoehn and Yahr Scale
Add description of **Cogstate Modified Chase Test**; add to schedule of procedures.	Test added to screening visit for practice.	Section 9.1.8.2, Pharmacodynamic Measurements Related to Cognition Appendix A, Schedule of Study Procedures
Clarify description of **Cogstate International Shopping List Test**.	Add delayed recall condition.	Section 9.1.8.2, Pharmacodynamic Measurements Related to Cognition
Clarify description of **Symbol Digit Modalities Test**; add to schedule of procedures.	First 10 of 120 symbols in sequence are practice items.	Section 9.1.8.2, Pharmacodynamic Measurements Related to Cognition Appendix A, Schedule of Study Procedures
Clarify description of **Patient Global Impression** (PGI) scales.	PGI-Improvement is rated on 7-point scale and PGI-Severity is rated on 6-point scale.	Section 9.1.8.3.1 Global Impression Scales
Add that **fasting** before sample collection is not necessary.	Fasting not necessary.	Section 9.1.11, Procedures for Clinical Laboratory Samples

Protocol Amendment 1		
Summary of Changes Since Original Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	**Rationale**	**Location**
Revise estimate of **maximum blood volumes** to include separate estimate for subjects in sentinel cohort.	Sentinel cohort will have more PK samples taken.	Section 9.1.11, Procedures for Clinical Laboratory Samples
Add **plasma 4β-hydroxycholesterol, cholesterol, and their ratio** to the laboratory tests at baseline	These tests may be used in the future if they prove useful in predicting TAK-071 PK.	Table 9.c, Clinical Laboratory Tests
Remove lactate dehydrogenase and glutamate dehydrogenase from serum chemistry tests.	Tests not necessary.	Table 9.c, Clinical Laboratory Tests
Replace serum creatinine clearance test with **eGFR**.	More conservative indicator of renal function.	Table 9.c, Clinical Laboratory Tests
Add abstinence as acceptable **contraception**.	True abstinence (defined in section) is highly effective contraception.	Section 9.1.12.3, Definitions and Procedures for Contraception and Pregnancy Avoidance
Add section on sample collection for **circulating biomarkers.**	Distinguishes this sample from the optional sample for DNA.	Section 9.1.17, Plasma Sample for Circulating Biomarkers
Allow rescreening of subjects who have failed original screening, with sponsor permission.	Allows subjects who may have been mildly ill at original screening to be enrolled later.	Section 9.1.21, Documentation of Screen Failure Section 9.3.1, Screening
Update Takeda **Medically Significant AE** List.	Company-wide list has been updated to include COVID-19 and other conditions.	Table 10.a, Takeda Medically Significant AE List
Add blinded **safety analysis to evaluation of sentinel cohort**.	Change made to ensure subject safety.	Section 13.1, Statistical and Analytical Plans
Clarify that no formal interim analysis is planned and that **blinded safety and available PK review of the sentinel cohort** will be described in a manual.	Clarify intentions for review of data.	Section 13.2, Interim Analysis, Sentinel Analysis, and Criteria for Early Termination
Reorganize Appendix A to separate treatment Periods 1 and 2, add visits specific to sentinel cohort.	Clarify visits and procedures.	Appendix A, Schedule of Study Procedures
Correct **window for Day 21, Day 84 procedures** from ±4 to ±2 days.	Make window consistent with other visits.	Appendix A, Schedule of Study Procedures
Add a **new Appendix B for timing of at-home speech assessments**; reordered appendices overall.	Clarify procedures.	Appendix B, Schedule of At-Home Speech Tests
Add separate row in Appendix C for **plasma PK samples for the sentinel cohort**.	The sentinel cohort will have rich PK sampling in Period 1	Appendix C, Schedule of Samples Across Both Periods

Protocol Amendment 1		
Summary of Changes Since Original Protocol		
Description of Each Change and Rationale		**Sections Affected by Change**
Description	**Rationale**	**Location**
Remove Appendix D, Preferred Gait and Cognitive Measurement Procedure Sequence.	This material will be provided in a study manual.	Appendices.

Appendix H Sentinel Cohort (Healthy Subjects) Only

H.1 Objectives and Endpoints for Healthy Subjects

H.1.1 Objectives

H.1.1.1 Primary Objective

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

H.1.1.2 Secondary Objective

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

H.1.2 Endpoints

H.1.2.1 Primary Endpoints

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

- C_{max}.
- t_{max}.
- AUC_{24}.
- Area under the concentration-time curve from time 0 to the last quantifiable concentration (AUC_{last}).
- AUC_{inf}.

H.1.2.2 Safety Endpoints

The safety endpoints for healthy subjects are:

- AEs.
- Clinical laboratory evaluations.
- ECG.
- Physical examinations.
- Suicidal ideation and behavior as measured by the C-SSRS.

H.2 STUDY DESIGN FOR SENTINEL COHORT (HEALTHY SUBJECTS)

An initial sentinel cohort of healthy subjects will be enrolled at designated site(s), in parallel with enrollment of PD patients in the main cohort. Approximately 10 healthy subjects of either sex, aged 56 to 75 years, inclusive, 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. Enrollment of the sentinel cohort will conclude when sufficient data are available to characterize the PK in older subjects, as determined by the sponsor.

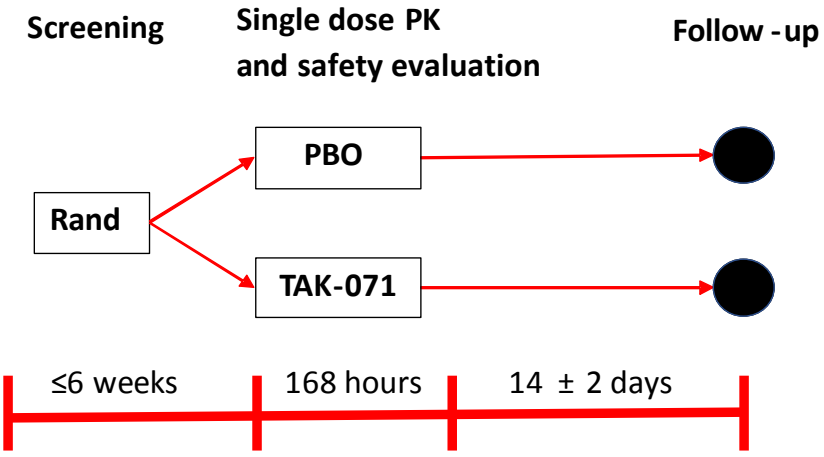
Healthy subjects will be selected on the basis of safety considerations. Of particular importance is exclusion on the basis of seizure risk factors, medical disease, and hepatic or renal impairment that may influence the PK of TAK-071.

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.

Figure H-2 shows a schematic of the sentinel cohort (healthy subjects).

Figure H-2 Schematic of Study Design for Subjects in the Sentinel Cohort (Healthy Subjects)



H.3 ENTRY CRITERIA

H.3.1 Inclusion Criteria for Healthy Subjects

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

13. The subject signs an informed consent form indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.

14. The subject is a healthy individual of either sex aged between 56 and 75 years, inclusive (for initial set of subjects in the sentinel cohort) at the time of consent. Older subjects may be enrolled after analysis of data from subjects aged 56 to 75 years, inclusive.
15. The subject has the ability to follow study instructions according to the investigator's judgement.
16. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential is eligible to participate if he agrees to use barrier method of contraception (ie, condom with or without spermicide) from signing of informed consent throughout the duration of the study and for 102 days after the last dose.
17. Female subjects are eligible to participate if a) not pregnant or nursing, and b) of nonchildbearing potential or agree to use highly effective contraception from signing of informed consent throughout the duration of the study and for 42 days after last dose of study drug.

H.3.2 Exclusion Criteria for Healthy Subjects

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

22. The subject has BMI less than 18 or greater than 40.
23. The subject has other medical problems (neurological, visual, orthopedic, psychiatric) that in the opinion of the investigator may significantly interfere with completion of the study or interpretation of study endpoints.
24. The subject has significant risk factors for seizures (a history of seizures as an adult, a history of brain injury, or other risk factors deemed relevant by the investigator).
25. The subject has significant medical disease (renal, cardiac, endocrine, pulmonary, etc) based on medical history, physical examination, ECG, or laboratory evaluations, and/or in the opinion of the investigator the subject is otherwise unlikely to be medically able to participate in the study due to any reason including having a disorder that may interfere with drug absorption, distribution, metabolism, or excretion.
26. The subject has any of the following at the screening visit: estimated eGFR (CKD-EPI) <60 mL/min; QTcF >450 msec for male subjects and >470 msec for female subjects; a serum total bilirubin value >1.2 × ULN; a serum ALT or AST value >1.2 × ULN. Subjects with a positive hepatitis B surface antigen test result or known or suspected active hepatitis C infection are also excluded. Note: Subjects with positive HCV serology may be enrolled if quantitative polymerase chain reaction for HCV RNA is negative, to exclude active hepatitis C infection, and the investigator agrees that the subject can safely participate in the study. Subjects with eGFR <60 mL/min may be eligible if the investigator and the sponsor agree that the subject may safely participate in the study.

27. In the opinion of the investigator the patient suffers from depression or other psychiatric disorder of sufficient severity to interfere with completion of the study or interpretation of the endpoints.
28. The subject has suffered from a substance use disorder (other than tobacco-use disorder) within the past 1 year before the first dose of study medication, or in the opinion of the investigator the subject's current or past use of substances may interfere with completion of the study.
29. The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or the subject has attempted suicide within the past year before screening. Subjects who have positive answers on item number 4 or 5 on the C-SSRS (based on the past year) before randomization are excluded.
30. The subject is unwilling or unable to discontinue taking cholinesterase inhibitors and/or moderate or strong CYP 3A4 inhibitors or inducers at least 30 days before randomization.
31. The subject is taking warfarin.
32. The subject has received any investigational compound that, in the opinion of the investigator or sponsor, may not have completely washed out before the screening visit.
33. The subject has received TAK-071 in the past.
34. The subject is an immediate family member, study site employee, or in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling).
35. The subject has donated 400 mL or more of his or her blood volume within 90 days before the start of the screening visit.
36. The subject has a known hypersensitivity to any component of the formulation of TAK-071.

H.4 Study Drug

Dose and regimen. Healthy subjects who meet randomization criteria on Day 1 will be randomized to a single dose of ≤7.5 mg TAK-071 or placebo.

Study Drug Assignment and Dispensing Procedures. The randomization will be to sequences in blocks of 3. Subjects will be assigned to receive their treatment according to the schedule allocated to each study site. Healthy subjects will be randomized 3:1 to a single dose of ≤7.5 mg QD TAK-071 or placebo, respectively (see Section 8.2).

H.5 PK Parameters.

In the sentinel cohort, single-dose t_{max}, C_{max}, AUC_{inf}, and area under the concentration-time curve from time 0 to 24 hours (AUC_{24}) will be determined. Actual sampling times, rather than scheduled sampling times, will be used in all data presentations.

H.6 Study Procedures

The schedule of study procedures for the sentinel cohort is shown in Table H-6.

Table H-6 Schedule of Study Procedures, Sentinel Cohort (Healthy Subjects)

	Screening	Baseline					Last Day of Treatment Period or Early Termination	Follow-up Safety Phone Call
Study Visit Number	**1**	**2**	**2+24 hr**	**2+48 hr**	**2+72 hr**	**2+96 hr**	**2+168 hr**	
(Study Day)	**(Day -42 up to Day -1)**	**(Day 1)**	**(Day2)**	**(Day 3)**	**(Day 4)**	**(Day 5)**	**(Day 8)**	**(Day 22±2)**
Confinement [a]	X	X	X	X	X	X	X	
Informed consent	X							
Inclusion/exclusion criteria	X	X[b]						
Demographics	X							
Medical history	X							
Medication history	X							
Concomitant medications	X	X[b]					X	X
Vital signs, weight, and BMI	X	X[b]	X	X	X	X	X	
Height	X							
PTE/AE assessment	X	X[b]	X	X	X	X	X	X
12-lead ECG	X	X					X	
Physical examination without nervous system							X	
Physical examination with nervous system	X	X[c]						
C-SSRS	X	X[c]					X	
Randomization		X						
Administer study drug		X						

Table H-6 Schedule of Study Procedures, Sentinel Cohort (Healthy Subjects)

	Screening	Baseline					Last Day of Treatment Period or Early Termination	Follow-up Safety Phone Call
Study Visit Number	**1**	**2**	**2+24 hr**	**2+48 hr**	**2+72 hr**	**2+96 hr**	**2+168 hr**	
(Study Day)	**(Day -42 up to Day -1)**	**(Day 1)**	**(Day2)**	**(Day 3)**	**(Day 4)**	**(Day 5)**	**(Day 8)**	**(Day 22±2)**
Clinical laboratory evaluations, including 4β-hydroxycholesterol and cholesterol [d]	X	X[c]					X	
Urine drug and alcohol screen	X	X[c]					X	
Serum pregnancy test (hCG) [e]	X	X[c]					X	
HBsAg and anti-HCV	X							
Plasma samples for TAK-071 PK [d,f]		X	X	X	X	X	X	

AE: adverse event; anti-HCV: antibody to hepatitis C virus; BMI: body mass index; C-SSRS: Columbia Suicide Severity Rating Scale; ECG: electrocardiogram; HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; PK: pharmacokinetic; PTE: pretreatment event.

[a] Confinement to the study site after screening is optional. Confinement from 0 to 48 hr is required. Confinement, or lodging outside the unit, is optional after 48 hr.

[b] If subject is confined on Day -1, test should be performed on Day -1 as well as Day 1. Weight and BMI do not need to be repeated.

[c] If subject is confined on Day -1, test may be performed on Day -1 instead of Day 1.

[d] See Table H.8 for timing of samples.

[e] Pregnancy test is administered when applicable based on subject sex. For Visit 2 (Day 1), a dipstick urine pregnancy test may be used instead of serum pregnancy test.

[f] Additional samples can be collected as needed.

H.6.1 Screening

H.6.2 Baseline/Randomization

Procedures to be completed at baseline are listed in Table H-6.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized. The randomization system for healthy subjects will be described in a study manual. The procedure for documenting randomization failures is provided in Section 9.1.23.

H.6.3 Treatment Period

Subjects will be administered a single oral dose of TAK-071 under observation in the clinic. PK sampling and other procedures will be performed over the subsequent 48 hours according to Table H-6. and Table H-8.

H.6.4 Final Visit or Early Termination

The final visit will occur on Day 8 (or early termination).

Procedures to be completed at this visit are listed in Table H-6.

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

H.6.5 Follow-up

The follow-up phone call occurs 14 days after the final visit or early termination.

H.6.6 Poststudy Care

Study drug will not be available on completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

H.7 Cholesterol Determination

A plasma sample will be taken and may be analyzed to determine the levels of 4β-hydroxycholesterol and cholesterol, and to calculate their ratio.

H.8 Sampling and Blood Volumes

For the sentinel cohort, the maximum volume of blood at any single visit is approximately 41 mL and the maximum total volume of blood for the study is approximately 72 mL.

The schedule of samples in the sentinel cohort is shown in Table H-8.

Table H-8 Schedule of Samples, Sentinel Cohort (Healthy Subjects)

	Screening	Baseline					Last Day of Treatment Period or Early Termination
Study Visit Number	**1**	**2**	**2+24 hr**	**2+48 hr**	**2+72 hr**	**2+96 hr**	**2+168 hr**
(Study Day)	**(Day -42 up to Day -1)**	**(Day 1)**	**(Day2)**	**(Day 3)**	**(Day 4)**	**(Day 5)**	**(Day 8)**
Clinical laboratory samples	X	X					X
Plasma sample for TAK-071 PK [a]		Predose; 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 14 hours following the dose	24 hours after dose	48 hours after dose	72 hours after dose	96 hours after dose	168 hours after dose

PK: pharmacokinetics.

[a] Additional samples can be collected as needed.

X denotes a single sample at any time during the visit.

H.9 Statistics

The sample size for an initial sentinel cohort will be approximately 10 subjects initially (with potential replacement of 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 is not based on statistical power considerations and considered to be sufficient for evaluation of safety, tolerability, and PK modeling to define a safe dose for people 65 years and older.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Pharmacology Approval	14-Sep-2021 15:36 UTC
[redacted]	Clinical Approval	14-Sep-2021 16:09 UTC
[redacted]	Biostatistics Approval	14-Sep-2021 21:01 UTC
[redacted]	Clinical Approval	15-Sep-2021 12:52 UTC