Protocol Title:

A Randomized, Double-Blind, Placebo-Controlled Trial of IkT-148009 in Untreated Parkinson's Disease

Protocol Number: IkT-148009-201

Version 6.4

Compound: IkT-148009

Brief Title: *A Phase 2 Study of IkT-148009 in Untreated Parkinson's Disease*

Sponsor Name:
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Regulatory Agency Identifier Number(s): IND #138553

SPONSOR SIGNATURE PAGE

Protocol Number:	IkT-148009-201
Product:	IkT-148009
IND No.:	138553
Study Phase:	2
Sponsor:	Inhibikase Therapeutics, Inc.
Date of Original Protocol:	Version 3.3; 31 March 2022
Date of Current Version:	Version 6.4; 19 October 2023

Sponsor Approval

DocuSigned by:
Milton Werner
00586028F08B422...

10/19/2023

Milton H. Werner, PhD — Date

Title: President and CEO Inhibikase Therapeutics, Inc.

PROTOCOL SIGNATURE PAGE

I have received and read the Investigator's Brochure for IkT-148009. I have read the IkT-148009-201 protocol and agree to conduct the study as outlined.

The signature of the Principal Investigator constitutes an agreement that this study will be conducted according to all stipulations, clinically and administratively, as stated in the protocol, including all statements as to confidentiality. It is agreed that the conduct and results of this study will be kept confidential and that the case report forms and other pertinent data will become the property of Inhibikase Therapeutics, Inc.

It is agreed that the protocol contains all necessary information required to conduct the study as outlined in the protocol, and that the study will not be initiated without the approval of an appropriate Institutional Review Board or Ethics Review Committee.

It is agreed that all participants in this study will provide written informed consent in accordance with International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice and the requirements specified in the Code of Federal Regulations (21 CFR Parts 50, 56, 312) and/or the Declaration of Helsinki. All participants will also be informed that their medical records will be kept confidential except for review by authorized representatives of Inhibikase Therapeutics, Inc. and its associates, the U.S. Food and Drug Administration or other regulatory agencies.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Sponsor Physician	Andrew McGarry, MD	2 North Tamiami Trail, Suite 308 Sarasota, FL 34236 (732) 330-8298
Medical Monitor	Bruce Rubin, MD	Miami, Florida Mobile: (305) 299-6525 Office: (910) 442-1402

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1. Protocol Summary

1.1 Synopsis

Protocol Title:
A Randomized, Double-Blind, Placebo-Controlled Trial of IkT-148009 in Untreated Parkinson's Disease

Brief Title:
A Phase 2 study of IkT-148009 in untreated Parkinson's Disease

Rationale:
This is a Phase 2, double-blind, multi-center, randomized, placebo-controlled trial to evaluate the safety, tolerability, and exploratory efficacy of three different doses of IkT-148009 self-administered once daily (QD) with food for 12 weeks in patients with untreated Parkinson's Disease (PD).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the safety and tolerability of three IkT-148009 doses in Parkinson's Disease	• Incidence and temporal profile of treatment-emergent adverse events (TEAEs) evaluated by type/nature, severity/intensity, seriousness, and relationship to study intervention • Proportion of those randomized in each dosing cohort who discontinued the assigned regimen
Secondary	
To characterize the effects of three IkT-148009 doses on Parkinson's Disease motor features, non-motor features, measures of function, and quality of life	Change from Baseline to Week 12 in the following outcomes, arranged in hierarchical order: • Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts II + III • Patient Global Impression-Severity (PGI-S) • Clinician Global Impression of Severity (CGI-S) • MDS-UPDRS Part II

	• MDS-UPDRS Part III • MDS-UPDRS Part I • Non-Motor Symptom Scale (NMSS) • Complete Spontaneous Bowel Movement score (CSBM) • ESS (Epworth Sleepiness Scale) • Schwab and England Activities of Daily Living (SE-ADL) Scale • Parkinson's Disease Questionnaire (PDQ-39) • Patient Assessment of Upper Gastrointestinal Disorders Severity Index (PAGI-SYM) • Patient Assessment of Constipation Quality of Life (PAC-QoL) • Patient Assessment of Gastrointestinal Disorders Severity Quality of Life (PAGI-QoL)
Exploratory	
	• Analysis of phosphorylated alpha-synuclein aggregates in skin and cerebrospinal fluid(CSF)

Study Design:

This is a 12-Week, randomized, double-blind, multi-center, placebo-controlled dose-ranging clinical trial of three IkT-148009 doses in patients with untreated PD designed to assess safety, tolerability, and exploratory efficacy. It will enroll approximately 120 participants at up to 40 sites across the USusing two randomization schemas. First, participants will be randomized across the 50 mg, 100 mg or placebo groups. Once 5 people have been randomized to each of the 50 mg, 100 mg or placebo groups, additional participants will be randomized as detailed in Section 7.3 to the 50 mg, 100 mg, 200 mg or placebo groups.

After signing the informed consent form (ICF), participants will undergo screening to evaluate their eligibility. The screening period will last up to 28 days before enrollment and randomization. An Enrollment Authorization Committee (EAC) will be responsible for reviewing screening data and confirming the eligibility and suitability of participants. This process will be outlined in the EAC charter. Those selected will be enrolled and randomized to one of three active IkT-148009 arms (50, 100, or 200 mg) or a placebo arm using interactive voice/web response system (IVRS/IWRS) according to the table in section 7.3. All clinical staff, study investigators, and participants will be blinded to study assignments throughout the trial.

Enrolled participants will have eaten within 2 hours prior to reporting to the site on Day 1 (Baseline) and undergo protocol-mandated procedures. Meals should not include citrus fruits or

juice and they should not be consumed within 6 hours on either side of dosing. Each participant will self-administer the study intervention on-site at the first treatment visit and then at home, as per treatment assignment. At home, enrolled participants should eat a meal within one hour prior to dosing. Meals should not include citrus fruits or juice, and neither citrus fruits or juices should be consumed within 6 hours on either side of dosing. The treatment period consists of outpatient visits at Weeks 1, 4, 8, and 12. A safety follow-up will occur at Week 14.

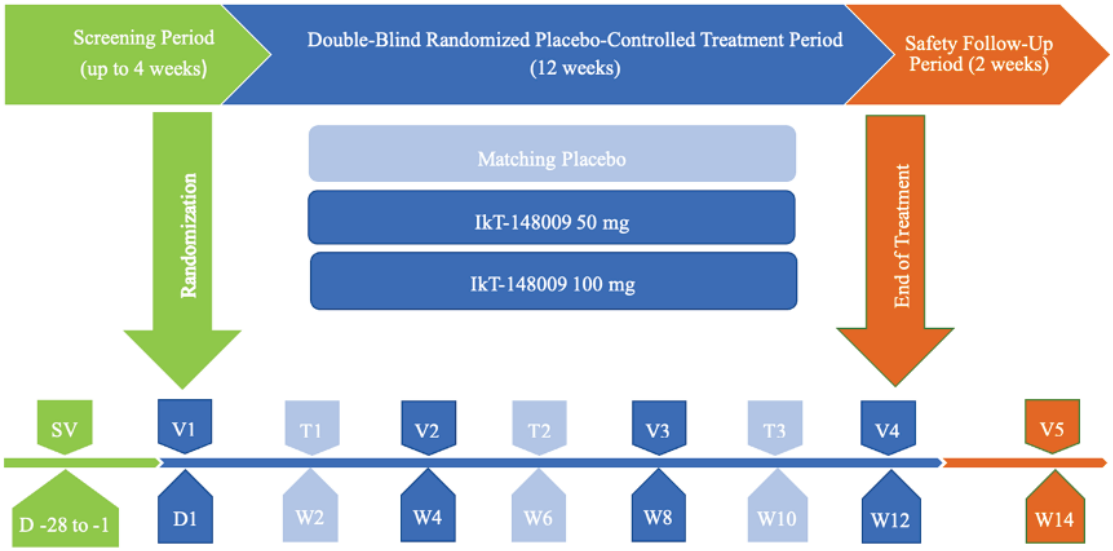
Telephone contacts at Weeks 2, 6, and 10 will occur to review and document changes in concomitant medications, assess dosing compliance, and document and/or address any AEs/SAEs.

ESS will be assessed at Weeks 1 and 12. Gastrointestinal (GI) outcomes (PAGI-SYM, PAC-QoL, PAGI-QoL, and CSBM,) will be assessed at Baseline and Weeks 4, 8, and 12. PGI-S, CGI-S, PDQ-39, Schwab and England ADL Scale will be assessed at Baseline and Weeks 4, 8, 12 and 14. Optional exploratory skin biopsies will be obtained at Baseline and Week 4 and 12. Optional CSF collection will be obtained at Baseline and Week 12.

CSSR-S, NMSS, MDS-UPDRS, vital signs, safety laboratory data, 12-lead Electrocardiogram (ECG), concomitant medications, tolerability, and adverse events (AEs) will be obtained and documented throughout the study. The Columbia Suicide Severity Rating Scale (C-SSRS) will be assessed at each in-person visit. A safety follow-up visit will occur at two weeks after completion of the 12-week active treatment period. Data Safety Monitoring Board (DSMB) members will meet on a regular basis throughout the study to review safety data. They will have the authority to unblind upon request if deemed necessary and to stop the study if deemed appropriate, as outlined in the DSMB charter.

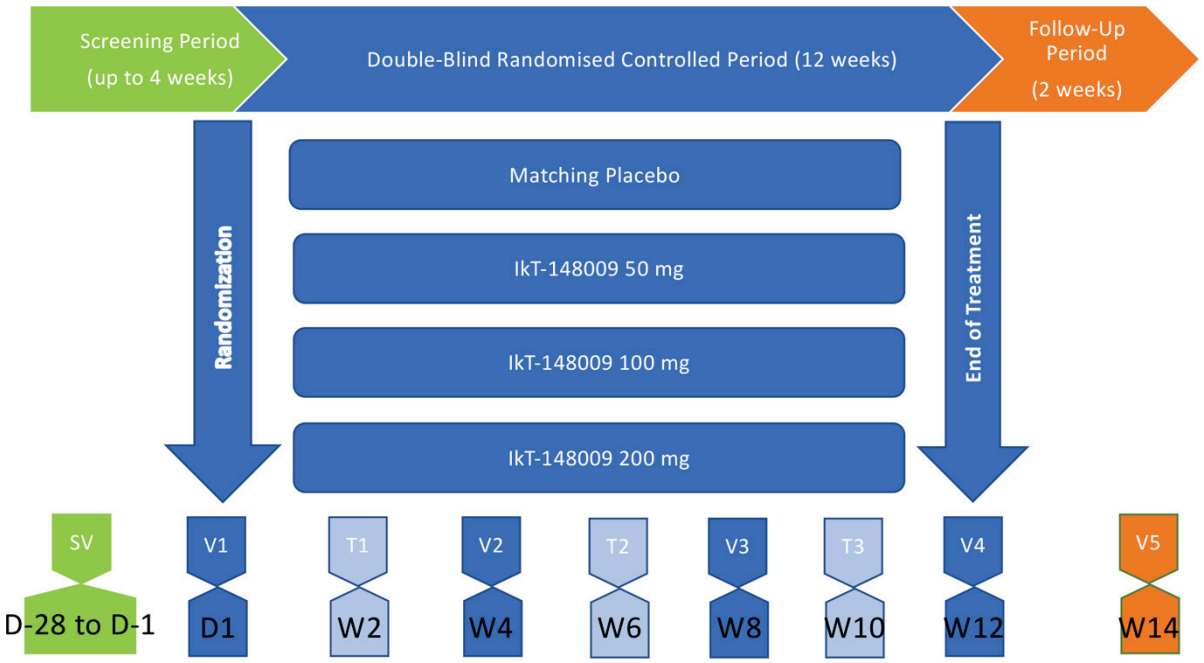
1.2 Schema

Randomization Schema 1



D=Day; SV=Screening Visit; T= Telephone Call; V= Visit; W=Week

Randomization Schema 2 ***(implemented after 5 subjects have randomized in each of the placebo, 50mg, and 100mg cohorts)***



D = day SV = screening visit V = visit T = telephone call W = week

1.3 Schedule of Activities (SoA)

Procedures	**Screening Visit**	**Baseline**	**Treatment Period (12 Weeks ± 2 days)**						**Safety Follow-up**
Study Visit	**SV**	**1**		**2**		**3**		**4 EOS/EW**	**5**
Week	**Day -28 to -1**	**Day 1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 ± 2 days**
Written informed consent	X								
Enrollment Authorization Form	X								
Outpatient visits[m]	X	X		X		X		X	X
Demographics[a]	X								
Vital signs[b]	X	X		X		X		X	X
Height and weight[c]	X	X		X		X		X	X
12-Lead ECG (triplicate)[d]	X	X		X		X		X	X
Review concomitant medications	X	X	X	X	X	X	X	X	X
Medical history	X								
Complete physical examination	X							X	X
Modified Hoehn and Yahr[e]	X								
Montreal Cognitive Assessment	X								
Telephone contact[f]	X[k]		X		X		X		
C-SSRS	X	X		X		X		X	X
Safety laboratory tests	X	X		X		X		X	X
Pharmacokinetics (Blood)[j]		X		X		X		X	
Pregnancy test[g]	X	X							X
MDS-UPDRS Parts I, II, and III	X	X		X		X		X	X

Procedures	**Screening Visit**	**Baseline**	**Treatment Period (12 Weeks ± 2 days)**						**Safety Follow-up**
Study Visit	**SV**	**1**		**2**		**3**		**4 EOS/EW**	**5**
Week	**Day -28 to -1**	**Day 1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 ± 2 days**
Epworth Sleepiness Scale (ESS)		X						X	
PAGI-SYM, PAC-QoL, PAGI-QoL		X		X		X		X	
NMSS		X		X		X		X	
SE-ADL		X		X		X		X	X
PDQ-39		X		X		X		X	X
CGI-S		X		X		X		X	X
PGI-S		X		X		X		X	X
CSBM		X[k]		X[k]		X[k]		X[k]	
Dispense/collect (unused) investigational product		X[h]		X		X		X[i]	
Review dosing compliance		X	X	X	X	X	X	X	
AEs/serious AEs	X	X	X	X	X	X	X	X	X
Skin biopsy[n]		X		X				X	
CSF Collection[n]		X						X	
Ophthalmic exams[l]	X							X	

AE=adverse event; BP=blood pressure; CGI-C=clinical global Impression of change; CSBM=Complete Spontaneous Bowel Movement Score; CSF=cerebrospinal fluid; C-SSRS=Columbia suicide severity rating scale; ECG=electrocardiogram; EOS=end of study; EW=early withdrawal; HR=heart rate; MDS-UPDRS=Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; NMSS=Non-Motor Symptom Scale; QoL=quality of life; PAC-QoL=Patient Assessment of Constipation Quality of Life; PAGI-QoL=Patient Assessment of GI Disorders Severity Quality of Life; PAGI-SYM=Patient Assessment of Upper GI Disorders Severity Index; PDQ=Parkinson's Disease Questionnaire; PGI-S=Patient Global Impression-Severity; RR=respiratory rate; SE-ADL=Schwab and England Activities of Daily Living Scale.

a. Demographics include age, race, ethnicity, and sex.
b. Vital Signs (Temperature, BP, HR, and RR) including orthostatic blood pressure measurements. At Baseline only, vital signs must be measured 3 times over the course of an hour.
c. Height measured at screening visit only.

d. 12-lead ECGs will be read locally.
e. Modified Hoehn and Yahr
f. Telephone Visits: Participants will be contacted to review concomitant medications and dosing compliance and to assess tolerability and AEs. At screening, participants will be contacted to review the stool diary completion timelines. See [k] for more information.
g. Serum testing at screening and urine testing at all other visits, for women of childbearing potential only.
h. Only dispense investigational product.
i. Only collect unused investigational product.
j. Blood will be collected just prior to dosing at baseline visit and post dose (as patients are dosing at home prior to coming into the clinic) for the subsequent blood draws
k. Patient stool diary to compute CSBM will be completed daily for the 7 days leading up to Day 1, the Week 4 visit, the Week 8 visit and the Week 12 visit. At the screening visit, participants will be given a copy of the diary. Once the EAF is approved, the site will call the participant to inform him/her what day they should begin recording in the diary. The participant will bring the diary to the site for the Day 1 visit, at which time the CSBM assessment will be completed based upon the diary entries. Prior to the Weeks 4, 8, and 12 visits, the site will call the participant to remind him/her to start recording in the diary for the 7 days leading up to the visit date. The participant will bring the completed diary to the site for these visits to be used for the CSBM assessment.
l. Ophthalmic exams include:
    1. Best corrected visual acuity
    2. Slit lamp examination of the anterior segment, particularly cornea, aqueous and lens. Slit lamp examination should determine the potential presence of dry eye, inflammatory cells in the aqueous and lens opacities.
    3. Wide-field photography
    4. Wide-field autofluorescence
    5. Wide-field fluorescein angiography (WF-FA)
    6. Spectral domain optical coherence tomography (SD-OCT)
m. Participants should be advised by study staff to avoid alcohol for 24 hours prior to any in-person visit, including screening.
n. At baseline, Skin Biospy and CSF collection must be completed prior to first dose.

2. Introduction

Parkinson's Disease (PD) is the second most prevalent neurodegenerative disorder (Savitt et al., 2006). It affects approximately 1,000,000 persons in the United States, with 60,000 new cases and 38,000 deaths annually (Savitt et al., 2006; Dauer et al., 2003). PD is an inexorably progressive disorder that is characterized clinically by bradykinesia, rigidity, rest tremor, and gait disturbances with postural instability (Savitt et al., 2006; Dauer et al., 2003). Pathologically, PD is characterized by degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc), reduction in striatal dopamine, and accumulation of protein aggregates in cell bodies and terminals known as Lewy bodies (LBs) and Lewy neurites, respectively, collectively known as Lewy pathology (Goedert et al., 2001; Goedert et al., 2013; Lee and Trojanowski, 2006). It is now appreciated that clinical and pathologic features are much more extensive than historically recognized. PD pathology affects serotonergic, cholinergic, and noradrenergic neurons and nerve cells in the olfactory system, cerebral hemisphere, brain stem, spinal cord, and peripheral autonomic nervous system in addition to SNc dopaminergic neurons (Jellinger, 2012). This non- dopaminergic pathology is associated with a variety of non-dopaminergic clinical features, none of which are adequately controlled with dopamine-replacement therapy (Schapira et al., 2014). These include falling, freezing, dysphagia, neuropsychiatric disorders, autonomic dysfunction, sensory problems, and cognitive impairment with dementia (Schapira et al., 2014). Indeed, non-dopaminergic features represent a major source of disability for PD patients. While numerous symptomatic therapies based on a dopamine replacement strategy have been developed over the past half century that provide meaningful motor benefits, non-motor therapies remain an unmet need (Schapira et al., 2014).

Over the past 20 years, a number of studies have suggested that misfolding of alpha-synuclein plays a key role in the etiopathogenesis of PD; as such, therapies directed at preventing or clearing pathologic alpha-synuclein might be neuroprotective (Winner et al., 2011; Olanow and Brundin, 2013; Polymeropoulos et al., 1997; Spillantini et al., 1997; Masliah et al., 2000; Kirik and Bjorklund, 2003; Jellinger, 2012). However, understanding of the precise toxic form of alpha-synuclein is incomplete, complicating the proper targeting of toxic alpha-synuclein for a therapeutic purpose. Recent work has provided convincing evidence that a common pathway governs initiation and progression of the disease within the central nervous system (CNS) and in the periphery (Mao et al., 2016; Brahmachari et al., 2016 and 2017). At the core of this pathway is the cellular Abelson tyrosine kinase (c-Abl) which is believed to act as as a checkpoint and play a key role in the formation and accumulation of toxic alpha-synuclein that leads to disease progression. In addition, activation of c-Abl leads to inhibition of Parkin and exacerbation of the neurodegenerative process (Werner and Olanow). Indeed, c-Abl inhibitors protect against neuronal degeneration and are associated with clinical benefits in animal models of PD (Werner and Olanow). These studies suggest that inhibition of c-Abl will be neuroprotective and blunt the rate of disease progression in PD patients.

2.1. Study Rationale

This is a Phase 2, double-blind, multi-center, randomized, placebo-controlled trial to evaluate the safety, tolerability, and exploratory efficacy of three different doses of IkT-148009 self-administered once daily (QD) with food for 12 weeks in patients with untreated PD.

2.2. Background

Despite the success of anti-parkinsonian therapies for motor features of the disease, no intervention has been discovered that adequately controls the non-dopamine features of the illness, and no therapy has been demonstrated to slow or stop clinical progression in PD. These remain major unmet medical needs.

Inhibikase Therapeutics Inc, is developing IkT-148009, a novel and potent inhibitor of the wild type c-Abl tyrosine kinase enzyme, for the treatment of PD. IkT-148009 is a chemical derivative of the anti-cancer agent imatinib (marketed as Gleevec®) with much higher potency for c-Abl kinase inhibition and greater likelihood of brain accumulation leading to effective c-Abl inhibition. IkT-148009 will be administered as powder in capsule.

A detailed description of the chemistry, pharmacology, efficacy and safety of IkT-148009 is provided in the Investigator's Brochure (IB).

3. Objectives and Endpoints

Primary Objective	Primary Endpoints
To assess the safety and tolerability of three IkT-148009 doses in Parkinson's Disease	• Incidence and temporal profile of treatment-emergent adverse events (TEAEs) evaluated by type/nature, severity/intensity, seriousness, and relationship to study intervention • Proportion of those randomized in each dosing cohort who discontinued the assigned regimen
Secondary Objectives	**Secondary Endpoints**
To evaluate the effects of three IkT-148009 doses on Parkinson's Disease motor features, non-motor features, measures of function, and quality of life	Change from Baseline to Week 12 in the following outcomes, arranged in hierarchical order: • Movement Disorder Society-sponsored revision of the Unified

	Parkinson's Disease Rating Scale (MDS-UPDRS) Parts II + III • Patient Global Impression-Severity (PGI-S) • Clinician Global Impression of Severity (CGI-S) • MDS-UPDRS Part II • MDS-UPDRS Part III • MDS-UPDRS Part I • Non-Motor Symptom Scale (NMSS) • Complete Spontaneous Bowel Movement score (CSBM) • ESS (Epworth Sleepiness Scale) • Schwab and England Activities of Daily Living (SE-ADL) Scale • Parkinson's Disease Questionnaire (PDQ-39) • Patient Assessment of Upper Gastrointestinal Disorders Severity Index (PAGI-SYM) • Patient Assessment of Constipation Quality of Life (PAC-QoL) • Patient Assessment of Gastrointestinal Disorders Severity Quality of Life (PAGI-QoL)
Exploratory	
	• Analysis of phosphorylated alpha-synuclein aggregates in skin and cerebrospinal fluid (CSF)

4. Study Design

This is a Phase 2, double-blind, multi-center, randomized, placebo-controlled trial of three IkT-148009 doses in patients with untreated PD.

4.1. Overall Design

This is a 12-Week, randomized, double-blind, multi-center, placebo-controlled dose-ranging clinical trial of three IkT-148009 doses in patients with untreated PD designed to assess safety, tolerability, and exploratory efficacy. It will enroll approximately 120 participants at up to

40 sites across the United States (US) using two randomization schemas. First, participants will be randomized across the 50 mg, 100 mg or placebo groups. Once 5 people have been randomized to each of the 50 mg, 100 mg or placebo groups, additional participants will be randomized as detailed in Section 7.3 to the 50 mg, 100 mg, 200 mg or placebo groups.

After signing the informed consent form (ICF), participants will undergo screening to evaluate their eligibility. The screening period will last up to 28 days before enrollment and randomization. An Enrollment Authorization Committee (EAC) will be responsible for reviewing screening data and confirming the eligibility and suitability of participants. This process will be outlined in the EAC charter. Those selected will be enrolled and randomized to one of two active IkT-148009 arms (50/100 mg) or a placebo arm (1:1:1) using interactive voice/web response system (IVRS/IWRS) during the first part of the study, then randomized to one of three active IkT-148009 arms or a placebo arm according to the table in section 7.3 once the 200mg dose is impletemented. All clinical staff, study investigators, and participants will be blinded to study assignments throughout the trial.

Enrolled participants will have eaten within 2 hours prior to reporting to the site on Day 1 (Baseline) and undergo protocol-mandated procedures. Meals should not include citrus fruits or juice and they should not be consumed within 6 hours on either side of dosing. Each participant will self-administer the study intervention on-site at the first treatment visit and then at home, as per treatment assignment. At home, enrolled participants should eat a meal within one hour prior to dosing. The treatment period consists of outpatient visits at Weeks 1, 4, 8, and 12. A safety follow-up will occur at Week 14.

Telephone contacts at Weeks 2, 6, and 10 will occur to review and document changes in concomitant medications, assess dosing compliance, tolerability, and document/address any adverse events.

ESS will be assessed at Weeks 1 and 12. Gastrointestinal (GI) outcomes (PAGI-SYM, PAC-QoL, PAGI-QoL, and CSBM) will be assessed at Baseline and Weeks 4, 8, and 12. PGI-S, CGI-S, PDQ-39, Schwab and England ADL Scale will be assessed at Baseline and Weeks 4, 8, 12 and 14. Optional exploratory skin biopsies will be obtained at Baseline and Week 4 and 12. Optional CSF collection will be obtained at Baseline and Week 12.

CSSR-S, NMSS, MDS-UPDRS, vital signs, safety laboratory data, 12-lead Electrocardiogram (ECG), concomitant medications, tolerability, and adverse events (AEs) will be obtained and documented throughout the study. The Columbia Suicide Severity Rating Scale (C-SSRS) will be assessed at each in-person visit. A safety follow-up visit will occur at two weeks after completion of the 12-week active treatment period. Data Safety Monitoring Board (DSMB) members will meet on a regular basis throughout the study to review safety data. They will have the authority to unblind upon request if deemed necessary and to stop the study if deemed appropriate, as outlined in the DSMB charter.

A participant will be considered to have completed the study if he/she completes all study periods followed by the safety follow-up visit in accordance with the schedule of activities (SoA, Section 1.3), or when end of study is declared.

See the SOA (Section 1.3) for the full list of study assessments and timings.

4.2. Justification for Dose

Based on the objectives to identify a minimum safe dose, maximum safe tolerated dose, and evaluate efficacy, the following three IkT-148009 doses are proposed for the study along with placebo: 50 mg QD, 100 mg QD and 200 mg QD IkT-148009. Data from the validated animal studies and clinical pharmacokinetics from prior trials were used to define the doses for this study.

4.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study globally.

A participant is considered to have completed the study if he/she completes all visits in accordance with the SoA (Section 1.3).

5. Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

5.1. Statistical Hypotheses

The safety and tolerability of different dose levels of IkT-148009 will be assessed as an overall evaluation of all safety endpoints. No formal statistical hypothesis will be tested.

5.2 Multiplicity Adjustment

The safety and tolerability of different dose levels of IkT-148009 will be assessed as an overall evaluation of all safety endpoints. No formal statistical hypothesis will be tested.

The efficacy endpoints will be tested in hierarchical order by endpoint and within each endpoint by dose. First, the primary endpoint will be compared to placebo for the primary endpoint. If the difference for the high dose is statistically significant, the middle dose will be compared to placebo for the primary endpoint. If the difference in both high and middle doses are statistically significant, the low dose will be compared to placebo for the primary endpoint.

Next, if there is a statistically significant difference in all dose levels for the primary endpoint, the testing will continue by comparison of high dose vs placebo for the secondary endpoint ranked highest, followed by comparisons of the same endpoint for the middle and low dose, as long as all previous comparisons have been statistically significant. The procedure will continue similarly for all remaining secondary endpoints.

In case not all endpoints are compared as a part of the hierarchical testing procedure, the statistical tests will be reported for descriptive purposes and interpreted in an exploratory manner.

The steps in the hierarchical testing procedure are as follows:

1. MDS-UPDRS Parts II + III
2. Patient Global Impression-Severity (PGI-S)
3. Clinician Global Impression of Severity (CGI-S)
4. MDS-UPDRS Part II
5. MDS-UPDRS Part III
6. MDS-UPDRS Part I
7. Non-Motor Symptom Scale (NMSS)
8. Complete Spontaneous Bowel Movement score (CSBM)
9. ESS (Epworth Sleepiness Scale)
10. SE-ADL Scale
11. PDQ-39
12. PAGI-SYM
13. PAC-QoL
14. PAGI-QoL

5.3 Analysis Sets

There are three analysis sets:

Analysis Set	Description
Modified Intent to Treat (mITT)	The mITT will include all participants who have been randomized, received at least one dose of study drug, and have at least one post-baseline evaluation of the primary efficacy endpoints. Participants will be included in the analyses according to the intervention they were randomized to (intended to receive). This set will be used to analyze efficacy endpoints.
Safety analysis set	The Safety set will include all participants who are randomized and received at least one dose or study intervention. Participants will be included in the analyses according to the intervention that they received (actually received).
Per-protocol Set (PP)	Includes all participants who complete the study without a major protocol deviation.

5.4. Statistical Analyses

5.4.1. General Considerations

The below mentioned general principles will be followed throughout the study:

A detailed description of the analysis methods to be performed in the study will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized and approved prior to unblinding and database lock. Descriptions in the SAP will predominate over protocol in case of any differences and any major change to the SAP will be reflected in a protocol amendment.

Unless otherwise noted, the baseline value is defined as the last value observed prior to the first administration of study intervention on Day 1.

Unless otherwise noted, missing data will not be imputed but will be analyzed as missing.

Descriptive statistics will include the number of non-missing patients (n), mean, standard deviation (SD), median, minimum, and maximum values for continuous variables, and for categorical variables, the frequencies and percentages of patients will be presented.

The number of Below the limit of quantitation (BLQ) values i.e., the n below lower limit of quantification (LLOQ) will be reported for each time point.

All study data will be included in study data listings. In general, all data will be listed by time point within participants. All summary tables will present descriptive statistics for the parameters being analyzed.

SAS® version 9.4 or higher will be used for all analyses.

5.4.2. Primary Endpoint Analysis

The primary objective is to assess the safety and tolerability of IkT-148009.

The safety and tolerability will be assessed descriptively based on an overall evaluation of the following endpoints:

- Incidence and temporal profile of TEAEs, evaluated by type/nature, severity/intensity, seriousness, and relationship to study intervention
- Incidence of related TEAEs (including possibly- and probably-related TEAEs) of moderate or severe intensity

- Incidence of TEAEs leading to withdrawal of study drug
- Incidence of serious adverse events (SAEs), including suicidality as measured by the C-SSRS
- Changes in physical examination, vital signs (blood pressure, heart rate, respiratory rate, and temperature), 12-lead ECG, and laboratory data (hematology and blood chemistry)
- Safety analysis is described further in Section 5.4.3. Safety endpoints will be summarized with descriptive statistics.
- Proportion of those randomized in each dosing cohort who discontinue the assigned regimen

5.4.3 Secondary Endpoint Analysis (Efficacy)

The efficacy endpoints (as changes from Baseline at Week 12) will be evaluated in hierarchical order (by endpoint and within each endpoint, by dose). The order of testing is defined in Section 9.1.1. The following endpoints will be evaluated:

- MDS-UPDRS Parts II + III
- PGI-S (proportion of patients who improved from baseline)
- Clinician Global Impression of Severity (CGI-S) (proportion of patients who improved from baseline)
- MDS-UPDRS Part II
- MDS-UPDRS Part III
- MDS-UPDRS Part I
- Non-Motor Symptom Scale (NMSS)
- Complete Spontaneous Bowel Movement score (CSBM)
- ESS (Epworth Sleepiness Scale)
- SE-ADL Scale
- PDQ-39
- PAGI-SYM
- PAC-QoL
- PAGI-QoL

Descriptive statistics for each continuous endpoint will be presented as Change from Baseline by treatment group and visit. Furthermore, the differences between the dose levels versus placebo at Week 12 in the continuous secondary endpoints will be estimated using a Mixed Model for Repeated Measures (MMRM) using the mITT Set. The MMRM will include the observed changes from baseline from all post-baseline visits as the response values and the treatment group, visit and the interaction between the treatment group and visit as fixed factors. The baseline value will be used as a covariate in the model.

An unstructured covariance structure will be applied for MMRM. In case the model will not converge with the unstructured covariance structure, Heterogeneous Autoregressive (1) (ARH[1]), Heterogeneous Compound Symmetry (CSH), Autoregressive(1) (AR[1]) or Compound Symmetry (CS) covariance structure will be used instead in this order. The denominator degrees of freedom will be computed using the Kenward-Roger method.

The least square (LS) means for each treatment group, SEM, and LS mean difference between different dose levels and placebo along with the 95% confidence intervals will be provided. The P-value for the hypothesis testing will also be provided.

The categorical secondary endpoints (PGI-S and CGI-S) will be analyzed using the GLIMMIX procedure for binomial data with logic link. The model will include the observed binomial values from all post-baseline visits as the response values and the treatment group, visit and the interaction between the treatment group and visit as fixed factors. The baseline value will be used as a covariate in the model.

5.4.4 Exploratory Endpoint Analysis

Exploratory endpoints include the proportion of phosphorylated alpha-synuclein in skin and CSF.

Descriptive statistics will be provided for each of the exploratory outcomes.

5.4.5 Safety Analyses

Safety assessments will include TEAEs tabulated by cohort; descriptive statistics for continuous variables and frequency counts for discrete variables. No inferential statistical analysis is planned for safety data.

The number and percentage of subjects reporting TEAEs will be tabulated for the safety analyses set by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class (SOC) with a breakdown by treatment, and further by relationship to study drug, as well as by maximum severity. Listings of deaths, SAEs, and TEAEs that lead to discontinuation of a subject will be presented.

For laboratory data, a treatment-emergent abnormal value is an abnormality that was not present before dosing, but was present after dosing, or one that represents an exacerbation of a pre-existing abnormal value.

All clinical laboratory data will be listed by subject for the safety analysis set, with abnormal lab results presented by subject in another listing. Descriptive statistics will be provided for baseline, end of study and for other times during the study if appropriate.

Vital signs will be listed at each time point for all subjects in the safety analysis set. Clinically significant findings on Safety ECG will be recorded as TEAEs, coded, listed and tabulated. Physical examination findings including neurological examination findings will be listed for all subjects in the safety analysis set. Clinically significant findings will be included as TEAEs.

No imputation of values for missing data will be performed. Standard clinical monitoring and data management practices will be used to ensure the integrity of data.

For all safety analyses, the placebo dose group will be pooled across cohorts. AEs will be coded using MedDRA with the version used specified in the clinical study report. The overall incidence of AEs will be displayed by System Organ Class (SOC), preferred term, and dose group, as well as incidence of TEAEs:

1. by maximum severity
2. by relationship to study drug
3. by seriousness
4. related TEAEs of moderate or severe intensity
5. Leading to withdrawal of study drug
6. SAE
7. Suicidality as measured by the C-SSRS

Data from the physical exam, vital signs, clinical laboratory measures, and ECGs will be summarized using descriptive statistics by dose group and time point, where applicable. Continuous endpoints will be summarized with n, mean, SD, median, minimum and maximum. In addition, change from baseline values will be calculated at each time point and will be summarized using descriptive statistics. Out-of-range safety endpoints may be categorized as low or high, where applicable. For all categorical endpoints, summaries will include counts and percentages. Shift tables will be provided for clinical laboratory results.

Changes in the physical examination involving new findings or aggravated existing abnormalities judged clinically significant by the investigator will be reported as an AE.

5.4.6 Other Analyses

Subgroup analyses of the primary endpoint will be made to assess consistency of the intervention effect across the following subgroups:

- Above and below median UPDRS part III at baseline
- Age group: < 65 vs ≥ 65 years
- Sex: female vs male

If the number of participants is too small (less than 10%) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. Further details on the statistical analysis will be provided in the SAP.

5.5. Interim Analysis

No interim analysis is planned for this study.

5.6. Sample Size Determination

A group size of 30 patients per dose was deemed sufficient to evaluate the potential safety and tolerability of IkT-148009. Secondary measures will use appropriate descriptive statistics to assess study outcomes.

6. Study Population

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Men and women ≥ 30 and ≤ 80 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

1. Participants who are diagnosed with PD consistent with UK Brain Bank criteria and MDS Research Criteria; must include bradykinesia with sequence effect and motor asymmetry.
2. Receiving no anti-parkinsonian therapy
3. Modified Hoehn/Yahr Stage < 3.0
4. Montreal Cognitive Assessment ≥ 24
5. Patient expected to be able to participate in trial without need for additional anti-parkinsonian therapy

Sex and Contraceptive/Barrier Requirements

Male participants:

1. Male participants must agree to practice an acceptable method of highly effective birth control from the screening visit, while on study and for 30 days after receiving the last dose of study drug. Highly effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with their partner's highly effective method.

Female participants:

1. Female participants of childbearing potential and male participants with female partners of childbearing potential must agree to either remain abstinent or use adequate and reliable contraception throughout the study and at least 30 days after the last dose of study drug has been taken.

Informed Consent

1. Capable of giving signed ICF as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other Inclusions

1. Approved as an appropriate and suitable candidate by the EAC.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Diagnosis/suspicion of secondary or atypical parkinsonism
2. Previous procedure or surgery for PD, or anticipation of these during the study
3. High likelihood of needing anti-parkinsonian treatment over the study period, in the opinion of the investigator
4. Clinically significant orthostatic hypotension
5. Clinically significant hallucinations requiring antipsychotic use in the 12 months prior to Screening
6. Clinically significant medical, surgical, psychiatric, or laboratory abnormalities in the judgement of the treating investigator or the EAC

Prior/Concomitant Therapy

1. Past treatment with levodopa, dopaminergic agonists, monoamine oxidase-B inhibitors, supplements containing levodopa (i.e. *Mucana pruriens*)or A2A antagonists for more than 28 days, or treatment with any of these medications or supplements within 28 days prior to screening
2. Past treatment with irreversible monoamine oxidase-B inhibitors (e.g., selegiline) for more than 28 days; must be discontinued for at least 90 days before screening
3. Currently receiving moderate or strong Cytochrome P450 (CYP) 3A4/5 inducers or CYP3A4/5 inhibitors (except for topical administration)

4. Currently receiving any antipsychotic, metoclopramide, reserpine, or amphetamine.

Prior/Concurrent Clinical Study Experience

1. Current participation in another investigational clinical trial and/or receipt of any investigational medication within 90 days prior to screening
2. Previous randomization into this or another IkT-148009 study

Diagnostic Assessments

1. Active suicidal ideation within one year prior to screening visit, as determined by the Columbia Suicide Rating Scale (answer of "yes" on question 4 or 5)
2. Current diagnosis or history of substance abuse (excluding nicotine or caffeine) by Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria
3. Medical or recreational use of marijuana in the 3 months prior to the screening visit
4. Any social or behavioral reason that would preclude completion of the study, in the judgement of the investigator
5. Any skin condition that would interfere with obtaining adequate samples
6. Evidence of advanced, age-related macular degeneration (neovascular or geographic atrophy) or intermediate macular degeneration as defined by Beckman classification (Large drusen > 125 um and/or any AMD pigmentary abnormalities). Evidence of retina/choroid neovascularization from any cause. Evidence of central serous retinopathy.
7. Abnormal amylase and/or lipase at screening (may be repeated during screening period)
8. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 2.5 times the upper limit of normal (ULN)
9. Significant renal impairment as determined by the following criteria:

- Creatinine clearance (CrCL) less than or equal to 60 mL/min for subjects < 65 years of age
- Creatinine clearance (CrCL) less than 55 mL/min or the presence of other evidence of chronic kidney disease such as proteinuria for subjects ≥ 65 years of age

10. Currently lactating, pregnant or planning on becoming pregnant during the study

6.3 Stopping Rules

1. Any participant that develops clinical abnormalities in the macula, retina, choroid or fundus that was not pre-existing must stop dosing unless it is clearly unrelated to the study medication.

2. If two participants develop clinical abnormalities in the macula, retina, choroid or fundus that was not pre-existing, all participants at that dose must stop dosing unless it is clearly unrelated to the study medication.

Sponsor must be alerted to these findings within 24 hours.

6.4. Screen Failures

A screen failure occurs when a participant who voluntarily consented to participate in the clinical study is subsequently not entered into the study. A minimal set of screen failure information is required to ensure transparent reporting on screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Laboratory test results that do not meet eligibility requirements may be repeated once within the 28-day screening period prior to designating the individual as a screen failure. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should sign a new ICF and be assigned a new participant number if the repeat screening visit falls outside of the 28-day screening period.

7. Study Intervention(s) and Concomitant Therapy

7.1. Study Intervention(s) Administered

Three different doses (50/100/200 mg) of IkT-148009 or placebo capsules will be self-administered with food by the enrolled participants in this clinical trial.

Dosage form: Capsule

Strength: 50 mg/capsule

Dosage frequency: Once daily

Quantity: 4 capsules per day

The double-blind dosing for the three treatment arms will be achieved using a blister pack configuration. Each participant will take a combination of active and placebo capsules once daily based on which group they are randomized to, to ensure the double blind is maintained.

7.2. Preparation, Handling, Storage, and Accountability

The composition and pharmaceutical quality of the investigational product will be maintained according to the current Good Manufacturing Practice (GMP) and Good clinical practice (GCP) guidelines and are available for review in the study intervention documentation.

Upon receipt of the medication, the investigator or designee will inspect the medication and complete and return the Acknowledgment of Receipt Form enclosed with the parcel. A copy of the signed receipt will be kept in the study files.

The study intervention must be carefully stored at 25°C (77°F); excursions permitted between 15-30°C (59-86°F) [see United States Pharmacopeia Controlled Room Temperature]. It should be protected from moisture.

The study intervention may not be used for any purpose other than the present study. After the study is completed, all unused study intervention must be retained, returned as directed or destroyed on site per the sponsor's instructions.

The investigator or designee will be responsible for ensuring appropriate storage, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory must be available for inspection by the designated representatives of the sponsor or the sponsor's representatives on request, and must include the information below:

- the identification of the participant to whom the drug was dispensed;
- the date(s) and quantity of the drug dispensed to the participant;

A copy of the inventory record and a record of any clinical supplies that have been destroyed must be documented as directed. This documentation must include at least the information below or as agreed with the sponsor:

- the number of unused units;
- the number of units destroyed at the end of each outpatient study.

7.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

Study intervention will be dispensed at the study visits as summarized in the SoA (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

This is a double-blind study in which participants/care providers/investigators/outcomes assessors, etc. are blinded to study intervention. The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator should consult with the medical monitor (if/when possible) prior to unblinding. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is

unblinded, sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

The study will begin with 50 mg, 100 mg and placebo groups. The 200 mg dose will be added at one of the defined enrollment timepoints defined in the table below:

Randomization Schema	# placebo subjects enrolled	# 50 mg subjects enrolled	# 100 mg subjects enrolled	# 200 mg subjects enrolled	Randomization
Schema 1	5	5	5	0	1:1:1:0
Schema 2	25	25	25	30	5:5:5:6
Schema 1	10	10	10	0	1:1:1:0
Schema 2	20	20	20	30	2:2:2:3
Schema 1	15	15	15	0	1:1:1:0
Schema 2	15	15	15	30	1:1:1:2
Schema 1	20	20	20	0	1:1:1:0
Schema 2	10	10	10	30	1:1:1:3

If appropriate, the DSMB may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

7.4. Study Intervention Compliance

Participants will self-administer the study intervention, as directed on a daily basis for the duration of the study, taken no more than one hour after a consumed meal. On the first dosing day, the meal will be consumed no more than two hours prior to taking the first dose.

Dosing compliance will be assessed by direct questioning and counting returned capsules during the site visits and documented in the source documents and relevant forms. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of IkT-148009 capsules dispensed to and administered by each participant must be maintained. Intervention start and stop dates, including dates for intervention delays will also be recorded.

7.5. Dose Modification and Continued Access to Study Intervention After the End of the Study

After completion of study period, no access will be provided to the study interventions.

7.6. Concomitant Therapy

Any medication, including over the counter or prescription medicines, recreational drugs, vitamins, herbal supplements, or other substances intended for therapeutic or beneficial purposes that the participant is receiving at the time of enrollment or receives during the study must be documented. For each, the following must be recorded:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor will review concomitant therapies for each patient in accordance with the Medical Monitoring Plan and the Medical Data Review Plan and document this review. Any findings or concerns will be discussed/reviewed and decisions documented.

All participants will be questioned by the PI or research personnel about concomitant treatment at each telephone and clinic visit.

The use of marijuana is not permitted from 3 months prior to screening through the end of the double-blind treatment period. For symptomatic treatment of nausea and/or emesis, the use of an anti-emetic may be considered.

7.6.1. Initiation of Dopaminergic Therapy

If medically necessary, participants may need to begin medications to treat the motor symptoms of PD during the study. This is not actively encouraged, but is permitted in the judgment of the participant, investigator, and in consultation with the medical monitor. Participants who start PD medication are encouraged to remain in the study and complete study activities as best as possible.

8. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 1.

8.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. If the study intervention is permanently discontinued, efforts will be made to encourage the participant to remain in the study for evaluation according to planned study procedures per SoA. See the SoA for data to be collected at the time of follow-up and for any further evaluations that need to be completed.

8.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study intervention and the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

8.3. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- Safety/laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be outlined in the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

9.1.1. Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS is a well-established tool for characterizing the signs and symptoms of PD (Goetz et al, 2008). The three parts used in this study are: Part I (Non-Motor Aspect of

Experiences of Daily Living), Part II (Motor Aspects of Experiences of Daily Living), and Part III (Motor Examination). Items in each domain are rated from 0-4, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

9.1.2. Patient Global Impression – Severity (PGI-S)

The PGI-S is a single-item tool used to determine how severe a person feels their symptoms are at the time of questioning. It is based on a 5-point scale (None, mild, moderate, severe, very severe).

9.1.3. Clinician Global Impression of Severity (CGI-S)

The CGI-S is a 7-point scale used to indicate how the clinician views the severity of the patients illness at the time of questioning (Guy, 1976). The range includes 1 (“normal”), 2 (“borderline ill, not ill at all”), 3 (“mildly ill”), 4 (“moderately ill”), 5 (“markedly ill”), 6 (“severily ill”), and 7 (“among the most extremely ill patients”).

9.1.4. Parkinson’s Disease Questionnaire (PDQ– 39)

The PDQ-39 is a self-administered questionnaire that assesses how often people affected by PD experience difficulties across 8 dimensions of daily living, including mobility (10 items), activities of daily living (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognition (4 items), communication (3 items), and bodily discomfort (3 items). (Peto et al 1995). It also assesses the impact of PD on specific dimensions of functioning and well-being. The PDQ-39 is scored on a scale of 0 to 100, with lower scores indicating better health and higher scores more severe symptoms.

9.1.5. Schwab and England Activities of Daily Living Scale (SE-ADL)

The SE-ADL is a single item that assesses the difficulty that a patient has in completing daily activities. It ranges from 0% (bedridden) to 100% (completely independent). Scores are coded in increments of 10 (i.e., 100, 90, 80, 70, …). The rater column does not need to be completed.

9.1.6. Non-Motor Symptom Scale (NMSS)

The NMSS is a 30-item scale divided into 9 domains (cardiovascular, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, GI, urinary, sexual function, miscellaneous) (Chaudhuri et al 2007). Each item is rated for frequency (rarely/often/frequent/very frequent) and severity (none/mild/moderate/severe) of symptoms.

9.1.7. Complete Spontaneous Bowel Movement Score (CSBM)

The total number of spontaneous bowel movements and the stool types will be assessed at baseline, week 4, week 8, and week 12. A patient diary will be provided to record all bowel movements in the 7 days leading up to these timepoints. A spontaneous bowel movement is a stool not induced by rescue medication such as laxative, enema, or suppository use during the previous 24 hour period. “Complete” refers to the sensation of complete evacuation of the stool (Lacy et al, 2012).

9.1.8. Patient Assessment of Upper GI Disorders Severity Index (PAGI-SYM)

The PAGI-SYM measures symptom severity in patients with upper GI disorders. The patient is asked to rate the severity of symptoms over the last 2 weeks. There are 20 items which are rated from 0 (none) to 5 (very severe).

9.1.9. Patient Assessment of Constipation Quality of Life (PAC-QoL)

The PAC-QoL assesses the effect that constipation has on daily life over the past 2 weeks. There are 28 items which are rated from 0 (not at all) to 4 (extremely).

9.1.10. Patient Assessment of GI Disorders Severity Quality of Life (PAGI-QoL)

The PAGI-QoL assesses the effect that GI problems have on daily life over the past 2 weeks. There are 30 items which are rated from 0 (none of the time) to 5 (all the time).

9.1.11. Epworth Sleepiness Scale (ESS)

The ESS assesses sleepiness over time. Patients and Caregivers are asked to rate (on a scale of 0 to 3) their likelihood of falling asleep during 8 daily activities, including reading, watching television, and driving.

9.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

9.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, lymphatic, musculoskeletal, GI, and neurological systems as well as assessment of general appearance, abdomen, skin, and extremities. Height and weight will also be measured and recorded.

9.2.2. Vital Signs

Vital signs (VS) for blood pressure and pulse are to be measured after subjects remain supine for 5 min and after 2 min standing. Baseline VS will be measured 3 times at baseline over the course of an hour. Respiratory rate, pulse oximetry and temperature will also be collected. Vital signs measurements outside of the normal range (as per the CRU SOP) should be repeated. All time points are relative to the time of dosing.

9.2.3. Electrocardiograms

Standard (triplicate) 12-lead ECG(s) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Corrected QT interval should be done by Fredericia (QTcF).

9.2.4. Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor should be notified.

- All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

9.2.5. Pregnancy Testing

All women of childbearing potential will take serum/urine pregnancy tests, per SoA (Section 1.3).

9.2.6. Ophthalmic Exams

Ophthalmic exams include:

- Best corrected visual acuity
- Slit lamp examination of the anterior segment, particularly cornea, aqueous and lens. Slit lamp examination should determine the potential presence of dry eye, inflammatory cells in the aqueous and lens opacities.
- Wide-field photography
- Wide-field autofluorescence
- Wide-field fluorescein angiography (WF-FA)
- Spectral domain optical coherence tomography (SD-OCT)

Opthalmic exams are performed at screening and at 12 weeks. All images will be uploaded to a secure portal with patient-identifying information redacted. Exam reports are required for all ophthalmic exams at screening and at 12 weeks. The exam reports at 12 weeks must compare observations at 12 weeks to what was observed at screening to determine if any changes occured.

9.2.7. Pharmacokinetics

Blood samples will be drawn either *pre-dose (at baseline) or either pre-dose or post-dose* on the subsequent visit days (see SoA) to analyze steady-state pharmacokinetics for IkT-148009 and its primary metabolites.

9.2.8. Suicidal Ideation and Behavior Risk Monitoring

Patients with PD may occasionally develop suicidal ideation or behavior.

Participants being treated with IkT-148009 should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior throughout the study. Participants who experience signs of SIB should undergo a risk assessment.

All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

During the informed consent process, families and caregivers of participants being treated with IkT-148009 should be alerted about the need to monitor participants for the emergence of SIB and to report such symptoms immediately to the study investigator.

Baseline assessment of SIB/intervention-emergent SIB will be monitored throughout the study period using the C-SSRS. The C-SSRS will be assessed by trained personnel only. The scale consists of 4 categories: suicidal ideation, intensity of suicidal ideation, suicidal behavior, and actual/potential lethality which can be answered by Yes or No. At the screening visit the questionnaire for the past 6 months will be used, and for all other visits the version "Since the last visit" will be administered.

At each suicidality assessment, participants thought to have significant suicidal ideation with actual plan and intent or suicidal behavior must be evaluated by a clinician or mental health professional skilled in the evaluation of suicidality, who will determine if it is safe for the participant to continue in the trial. Specific criteria that indicate a need for further assessment include:

- Suicidal ideation associated with actual intent and/or plan in the past 6 months; (a "YES" answer to C-SSRS questions 4 "some intent to act without specific plan" or 5 "specific plan and intent").
- Previous history of suicide behaviors in the past 5 years (a "YES" answer to any of the suicidal behavior items of the C-SSRS with the behavior occurring in the past 5 years).
- The investigator's judgment that a risk assessment is warranted.

Participants who respond "Yes" to items 4 or 5, or to any behavioral question of the C-SSRS on more than one occasion during the trial may be discontinued from the trial.

9.3. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative [LAR]).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention/study.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

9.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the timepoints specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF until the follow-up visit at the timepoints specified in the SoA (Section 1.3).

During the screening period baseline abnormalities (any sign or symptom present, such as abnormal screening laboratory value) will be assessed for clinical significance and captured in medical history as ongoing. Any baseline abnormality that increases in severity or frequency should be captured as an adverse event if determined clinically significant by the investigator. All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

9.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

9.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

9.3.5. Pregnancy

The risks of using the study drug during pregnancy are not known. It is possible that this study drug may cause harm to an unborn baby. This includes death, birth defects or other unforeseen health problems for the baby.

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the time period for postintervention contraception as determined in Section 6.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy of the female participant or female partner of male participant (after obtaining the necessary signed ICF from the female partner).

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the sponsor.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 9.3.5. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partners, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention and will be withdrawn from the study.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Good clinical practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), investigator's brochure (IB), and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC,

European regulation 536/2014 for clinical studies and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their LAR and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their LARs will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their LAR.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Exploratory research could include measurement of protein levels in vescicles that originated in the brain and are isolated from blood and/or plasma and/or urine. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Enrollment Authorization Committee and Data Safety Monitoring Board

Enrollment Authorization Committee is an independent group of medical experts responsible for ensuring that only those patients who met all eligibility criteria, as outlined in the final approved protocol, are suitable and appropriate for inclusion in the study.

Participant safety will be continuously monitored by the sponsor's external Data Safety Monitoring Board (DSMB), which monitors the safety and scientific integrity of a human research intervention and makes recommendations to the sponsor regarding the stopping of a study for harms.

The DSMB is a group of independent scientists (at least two expert clinicians who are treating PD patients and a biostatistician).

DSMB may request for unblinding of an individual participant or group of participants treatment, if the study intervention details plays a significant role in making certain decisions in participant's best interest.

10.1.6. Dissemination of Clinical Study Data

Every research study involving human patients must be registered in a publicly accessible database before recruitment of the first patient.

Researchers, authors, sponsors, editors, and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human patients and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of

interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic case report forms (eCRFs) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Guidance on completion of eCRFs will be provided in electronic CRF completion guideline (eCCG).

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for two years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data, and its origin can be found in e.g., source data acknowledgment or monitoring guidelines.

The investigator must maintain accurate documentation (source data) that supports the information entered in the source documents and an eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment:

The trial start date is the date on which the clinical study will be open for recruitment of participants. The first site open is considered as the first act of recruitment.

Study/Site Termination:

The sponsor or designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any contract research organization(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the central laboratory/local laboratory.

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Laboratory Tests	Parameters			
Hematology	Hemoglobin Hematocrit Red blood cell (RBC) count Platelet count PT (in seconds)-International normalized ratio (INR)	RBC indices: Reticulocyte count	White blood cell (WBC) count with differential: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils	
Clinical chemistry	Blood urea nitrogen (BUN) Sodium, triglycerides Urea and uric acid Bicarbonate	Potassium Albumin Cholesterol Sodium Calcium	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT)	Total and direct bilirubin (should be differentiated only when total bilirubin is above 1.5 X ULN)
	Creatinine Creatinine clearance Creatinine kinase	Lactate dehydrogenase (LDH) inorganic phosphorus lipase	Alkaline phosphatase[2] Gamma-glutamyl transferase (γ-GT)	Total protein Amylase Potassium Magnesium Glucose (non-fasting) Lipase
Pregnancy testing	Highly sensitive [serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)			
Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick Microscopic examination (if blood or protein is abnormal)			
Other screening tests	Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only), thyroid stimulating hormone (TSH), Luteinizing hormone (LH), Total Testosterone, and Inhibin B			

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Definition of Unsolicited and Solicited AE
• An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant/participant's parent(s)/ LAR(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants/participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/participant's parent(s)/LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/participant's parent(s)/LAR(s) will be collected during an interview with the participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., Electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease) • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study

• Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
Results in death
Is life threatening • The term life threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Is a suspected transmission of any infectious agent via an authorized medicinal product

Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- There may be instances when copies of medical records for certain cases are requested by sponsor/sponsor designee/local health authorities. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor/sponsor designee/local health authorities.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to sponsor/local health authorities. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor/local health authorities.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor/sponsor designee/local health authorities to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide his/her detailed report with a copy of any postmortem findings.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to sponsor/sponsor designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to sponsor/sponsor designee via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to sponsor or sponsor's designee will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the sponsor or sponsor's designee/SAE coordinator by telephone. • Contacts for SAE reporting will be provided

10.4. Appendix 4: Contraceptive and Barrier Guidance

Study specific contraception requirements for women of childbearing potential are outlined in Section 10.4.2.

Female participants of childbearing potential must receive pregnancy prevention counseling and be advised of the risk of the fetus if they become pregnant during treatment and for 30 days after the last dose of study intervention.

10.4.1. Definition

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Note: Site staff documentation from the sources like participant's medical records, medical examination, or medical history is acceptable.

- Premenarchal female

- Postmenopausal female

    - 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 may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trail enrollment.

10.4.2. Contraception Guidance

Contraception Methods for Female Participants

Acceptable methods of effective contraception include:

- Combined (estrogen and progestogen containing) or progestogen-only hormonal methods given oral, intravaginal, transdermal, injectable, or implantable route
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female participant of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success).
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associate with the study interventions; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant)
- Male or female condom with or without spermicide
- Cap, Diaphragm or sponge with spermicide
- Double barrier method: the male uses a condom, and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both parents use a condom)

10.5. Appendix 5: Concomitant Medications

All trial participants during the clinical trial period will be allowed to use concomitant medications, as needed. Particular scrutiny will be given to medications which are known to be Cytochrome P450 (CYP) 3A4/5 inhibitors and inducers and medications known to be MDR1 or BCRP inhibitors. These concomitant medications will be noted and evaluated in accordance with the Medical Monitoring Plan and the Medical Data Review Plan to determine if any exclusions are warranted.

For the list of drugs falling under the CYP3A4/5, MDR1 and BCRP categories refer https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

10.6. Appendix 6: Abbreviations and Definitions

Abbreviation/Term	
ADL	Activities of Daily Living
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BLQ	Below the limit of quantitation
BUN	Blood urea nitrogen
c-Abl	cellular Abelson tyrosine kinase
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CrCL	Creatinine clearance
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CSBM	Complete Spontaneous Bowel Movement Score
CYP	Cytochrome P450
eCCG	electronic CRF completion guideline
ECG	Electrocardiogram
eCRF	electronic case report form
FSH	Follicle Stimulating Hormone
GCP	Good clinical practice
GI	Gastrointestinal
GMP	Good manufacturing practice
HbsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HIV	Human immunodeficiency virus

HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IUD	Intrauterine device
IUS	Intrauterine hormonal-releasing system
IVRS	interactive voice response system
IWRS	interactive web response system
LAR	legally authorized representative
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LLOQ	Lower limit of quantification
MDS-	Movement Disorder Society-sponsored revision of the Unified
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
NMSS	Non-Motor Symptom Scale
PAC-QoL	Patient Assessment of Constipation Quality of Life
PAGI-QoL	Patient Assessment of GI Disorders Severity Quality of Life
PAGI-	Patient Assessment of Upper GI Disorders Severity Index
PD	Parkinson's Disease
PDQ	Parkinson's Disease Questionnaire
PGI-S	Patient Global Impression-Severity
PK	Pharmacokinetics
PT	Prothrombin time
QD	once daily
QoL	Quality of life
QTc	Corrected QT interval
RBC	Red blood cell
SD	Standard deviation

SD-OCT	Spectral domain optical coherence tomography
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SE-ADL	Schwab and England Activities of Daily Living Scale
SIB	suicidal ideation and behavior
SoA	Schedule of Activities
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell count
WF-FA	Wide-field fluorescein angiography

10.7. Appendix 7: Protocol Amendment History

Changes from protocol version 3.3:

- Section 1.3 (SoA) Fluorescein dye angiography of the eye added as an additional assessment at baseline and end of study.
- Section 9.1.2 (PGI-S) Description of assessment corrected as an error was identified in the text.
- Section 9.1.3 (CGI-S) Description of assessment corrected as an error was identified in the text.
- Section 9.1.5 (SE-ADL) Corrected error in description of scoring.
- Section 9.1.8 (CSBM) Incorrect timepoints identified in description corrected.
- Section 9.2.7 (Fluorescein dye angiography of the eye) Added to explain the rational for addition of this assessment.

Changes from protocol version 4.0

- Section 1.3 (SoA) Fluorescein dye angiography of the eye removed as an additional assessment at baseline as it was included in error.

Changes from protocol version 4.1

- Section 1.3 (SoA) Footnote J added to define timing of blood draws for Pharmacokinetic assessments
- Section 4.1 (Overall Design) Added details regarding eating pre-dose
- Section 7.4 (Study Intervention Compliance) Added details regarding eating pre-dose
- Section 7.6 (Concomitant Therapy) Added more detailed information regarding review of concomitant medications by medical monitor
- Section 9.1.7 (Whole Gut Transit Time) Added that this assessment will not be conducted at all sites, but is required for patients at sites selected
- Section 9.2.8 (Pharmacokinetics) Section added to explain the purpose and timing of blood sample draws for pharmacokinetic measures.
- 10.5 (Appendix 5: Concomitant Medications) Additional detail added to describe concomitant medications that require additional medical review and monitoring

Changes from protocol version 4.2

- Section 1.3 (SoA) Addition of SmartPill assessments and clarification of instructions
- Section 4.1 (Overall Design) Clarification on the consumption of citrus fruits or juice with regards to dosing
- Section 9.1.5 (SE-ADL) Clarification that rater column does not need to be completed
- 9.1.7 (Whole Gut Transit Time) Additional information and clarification added to provide sites with clear instructions regarding SmartPill dosing and assessment
- 9.2.3 (Electrocardiograms) Clarification to ensure triplicate ECGs are performed at all timepoints

Changes from protocol version 5.0

- Section 1.3 (SoA) Removal of Smartpill assessments throughout protocol and changes to definition of ophthalmic exams and the type of exams to be performed.
- Section 1. (Protocol Summary) Change in number of dosing groups from 3 (50/100/200) to 2 (50/100) plus placebo throughout protocol
- Section 6.2 (Exclusion Criteria) Added exclusion criteria to diagnostic assessments for age-related macular degeneration
- Section 6.3 (Stopping Rules) Added stopping rules for participants
- Section 9.2.6 (Opthalmic exams) definition of these exams updated along with instructions for comparative analysis at 12 weeks.
- Section 9.2.7 (Fluorescein Angiography) is eliminated and incorporated into the new section 9.2.6.

Changes from protocol version 6.0

- Section 10.1.3. (Informed Consent Process) Added more detail about potential exploratory research

Changes from protocol version 6.1

- Change in number of dosing groups from 2 (50/100) to 3 (50/100/200) plus placebo throughout protocol
- Section 1.3 (SoA) addition of footnote advising patients to avoid alcohol prior to visits.

Changes from protocol version 6.2

- Updated section 6.1 to modify age range for inclusion from ≥ 30 and ≤ 75 to ≥ 30 and ≤ 80
- Updated section 6.1 to modify the Montreal Cognitive Assessment inclusion criteria from ≥ 26 to ≥ 24
- Updated section 6.2 to modify the creatinine clearance exclusion criteria from < 60 mL/min for all participants to the following criteria:
    - Creatinine clearance (CrCL) less than or equal to 60 mL/min for subjects < 65 years of age
    - Creatine clearance (CrCL) greater than or equal to 55 mL/min and the absence of proteinuria or hematuria for subjects ≥ 65 years of age
- Updated section 6.2 to clarify that supplements containing levodopa like *Mucuna pruriens* are not permitted
- Updated section 6.4 to clarify procedures regarding screen failures and rescreening activities

Changes from protocol version 6.3

- Fixed typographical error in section 6.2 Exclusion 9 language:
    - Corrected language: Creatinine clearance (CrCL) ~~greater than or equal to~~ less than 55 mL/min ~~and the absence of proteinuria or hematuria~~ or the presence of other evidence of chronic kidney disease such as proteinuria for subjects ≥ 65 years of age
- Updated language in section 9.3.1
    - Removed: Medical occurrences that begin before the start of study intervention but after obtaining ICF will be recorded as medical history/current medical conditions, not as AEs.
    - Added: During the screening period baseline abnormalities (any sign or symptom present, such as abnormal screening laboratory value) will be assessed for clinical significance and captured in medical history as ongoing. Any baseline abnormality that increases in severity or frequency should be captured as an adverse event if determined clinically significant by the investigator
- Provided clarifying language regarding the QTcF calculation to section 9.2.3
- Updated foot notes in SOA to clarify the following points:
    - Footnote b: At Baseline only, vital signs must be measured 3 times over the course of an hour.
    - Footnote n: At baseline, Skin Biospy and CSF collection must be completed prior to first dose.

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