Statistical Analysis Plan

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF IKT-148009 IN UNTREATED PARKINSON'S DISEASE

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ABBREVIATIONS

Abbreviation	**Term**
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Class
BCRP	Breast cancer resistance proteing
BLQ	Below the limit of quantitation
BMI	Body Mass Index
BUN	Blood urea nitrogen
CGI-S	Clinical Global Impression of Severity
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CSF	Cerebrospinal fluid
CSBM	Complete Spontaneous Bowel Movement
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of Variation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
γ-GT	Gamma-glutamyl transferase
GI	Gastrointestinal
HbsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
ICF	Informed consent form
INR	International normalized ratio
ITT	Intent to treat
LLOQ	Lower limit of quantification
LS	Least Squares
MDR1	Multidrug resistance protein 1
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
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-SYM	Patient Assessment of Upper GI Disorders Severity Index

Abbreviation	Term
PD	Parkinson's disease
PDQ	Parkinson's Disease Questionnaire
PGI-S	Patient Global Impression-Severity
PK	Pharmacokinetic
PP	Per-Protocol
PT	Prothrombin Time
QTc	Corrected QT interval
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard deviation
SE	Standard Error
SEM	Standard Error of the Mean
SI	International System
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
WBC	White blood cell

1 INTRODUCTION

This study is being conducted for the clinical development of IkT-148009 (also known as Risvodetinib) for Parkinson's disease (PD). The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results based on Protocol IkT-148009-201 version 6.4, dated October 19, 2023.

The document may evolve over time to reflect protocol amendments, regulatory discussions, and other important changes. However, the SAP will be finalized, approved by the Sponsor, and placed on file before the database is locked and the study unblinded. In case of any differences between the SAP and the protocol, the SAP will be the final determinant. Deviations from the final approved plan will be noted in the clinical study report.

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

The primary objective for the 12-week Placebo-Controlled Study is to assess the safety and tolerability of three IkT-148009 doses in Parkinson's disease.

1.1.2 Secondary Objective

The secondary objective for the 12-week Placebo-Controlled Study is 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.

1.1.3 Exploratory Objective

Various exploratory endpoints will be examined as listed below.

1.2 STUDY ENDPOINTS

1.2.1 Primary Safety Endpoints

The primary safety endpoints are:

- Incidence of treatment-emergent adverse events (TEAEs) evaluated by severity/intensity, seriousness, and relationship to study intervention
- Proportion of those randomized in each dosing cohort who discontinued the assigned regimen

Other safety endpoints include adverse events (AEs), laboratory parameters, physical examination, vital signs, Columbia Suicide Severity Scale (C-SSRS), and 12-lead ECG measurements.

1.2.2 Primary Efficacy Endpoints

There are no primary efficacy endpoints in this study.

1.2.3 Secondary Efficacy Endpoints

Secondary efficacy endpoints include Change from baseline (CFB) to Week 12 for the following outcomes:

- The sum of Parts II + III of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
- Parkinson's Disease Questionnaire (PDQ-39) summary index
- 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) total score
- Complete Spontaneous Bowel Movement Score (CSBM)
- Epworth Sleepiness Scale (ESS) total score
- Schwab and England Activities of Daily Living (SE-ADL) Scale
- 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)

1.2.4 Exploratory Endpoints

There are two exploratory efficacy endpoints.

- Change from baseline to week 12 of the quantity of phosphorylated alpha-synuclein aggregates in the skin.
- Change from baseline to week 12 of the quantity of phosphorylated alpha-synuclein aggregates in cerebrospinal fluid (CSF).

1.3 SUMMARY OF THE STUDY DESIGN

1.3.1 General Study Design and Plan

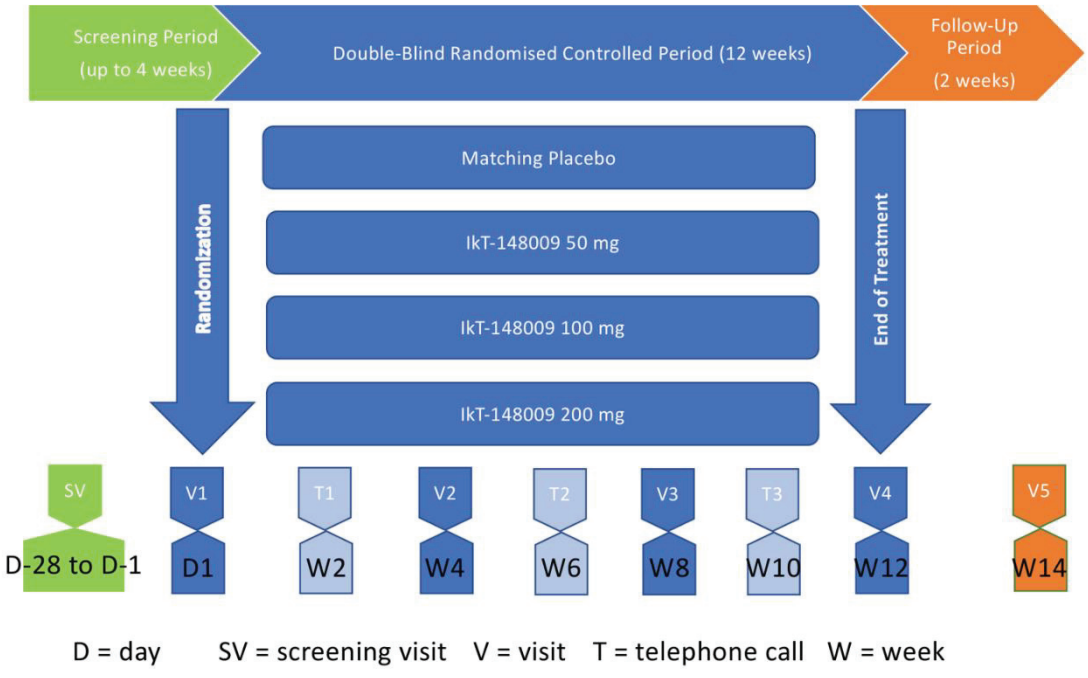
This is a 12-Week, randomized, double-blind, multi-center, placebo-controlled dose-ranging clinical trial of three IkT-148009 doses in early untreated PD designed to assess safety, tolerability, and efficacy. It was designed to enroll approximately 120 participants at up to 32 sites across the United States. In the end there were 11 participants enrolled prior to Protocol version 6.1 and 126 enrolled after Protocol version 6.1 was implemented.

The placebo-controlled period consists of in-person visits at Weeks 1, 4, 8, 12, and 14 (safety follow-up) and telephone visits at Weeks 2, 6, and 10.

After signing the informed consent form (ICF), participants will undergo screening to evaluate their eligibility. 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). Participants will first 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 to the 50 mg, 100 mg, 200 mg or placebo groups such that the final randomization scheme will be 1:1:1:1. All clinical staff, study investigators, and participants will be blinded to study assignments throughout the trial.

The study design is depicted in Figure 1 below. The Schedule of Activities (SoA) can be found in the Protocol Section 1.1, Table 1.

Figure 1 Randomization Schema 1



1.3.2 Randomization and Blinding

Participants will initially be randomly assigned in a 1:1:1 ratio to one of two doses of active IkT-148009 or placebo by the IVRS/IWRS system. Once 5 participants have been randomized to each of the 50mg, 100mg, or placebo groups, participants will be randomized at the ratio presented in the Protocol section 7.3 to ensure that each arm (50mg, 100mg, 200mg, or placebo) is fully enrolled at the same time in a 1:1:1:1 ratio. All clinical staff, study investigators, and participants will be blinded to study assignments throughout the trial. The sponsor and analysis team will be unblinded after the study is complete.

1.3.3 Sample Size and Statistical Power Considerations

A group size of 30 participants per dose was deemed sufficient to evaluate the potential safety and tolerability of IkT-148009. A sample size of 30 per group would provide > 80% power to detect a 5 point difference in the change from baseline UPDRS II + III between groups with a standard deviation of 6 points, a drop-out rate of 10%, and alpha = 0.05. Secondary measures will use appropriate descriptive statistics to assess study outcomes.

2 STATISTICAL CONSIDERATIONS

2.1 GENERAL CONSIDERATIONS

SAS® 9.4 or higher will be used to perform all analyses.

All descriptive statistics for continuous variables will be reported using the number of non-missing participants (n), mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number and percentage of participants.

The default significance level will be 0.05. p-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as “<0.001”. A p-value greater than 0.999 will be reported as “>0.999”.

Minimum and maximum values will be rounded to the precision of the original value. Means and medians will be rounded to one decimal place greater than the precision of the original value. SD and Confidence Intervals (CI) will be rounded to two decimal places greater than the precision of the original value. Percentages for summarizing categorical data will be rounded to one decimal place.

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.

2.2 DEFINITIONS OF ANALYSIS SETS

The number of participants who signed the Informed Consent Form (ICF), the number and the percentage of participants included in each analysis set, and the number and the percentage of participants excluded from each analysis set will be presented by dose group and overall. Reasons for exclusion from each analysis set will also be summarized. Reasons for exclusion from the mITT analysis of efficacy include:

- Did not have a valid baseline MDS-UPDRS score
- Did not receive at least one dose of study drug
- Did not have at least one valid post-baseline evaluation of the MDS-UPDRS score
- Randomized prior to Protocol version 6.1

Reasons for exclusion from the Safety analysis set include:

- Did not receive at least one dose of study drug

There are four analysis sets:

Analysis Set	***Description***
Modified Intent to Treat (mITT)	The mITT population will include all randomized participants who have a valid baseline MDS-UPDRS, received at least one dose of study drug, and have at least one post-baseline evaluation of the MDS-UPDRS assessment. Participants randomized prior to Protocol version 6.1 will be excluded. Participants will be analyzed according to their assigned intervention. This set will be used to analyze efficacy endpoints.
Safety	The Safety analysis set will include all participants eceived at least one dose or study drug. in the Safety analysis set will be analyzed according to the intervention that they actually received.
Per-protocol Set (PP)	Includes all participants in the mITT analysis set who complete the study without a major protocol deviation deemed as impacting the secondary efficacy endpoints.
Full Analysis Set (FAS)	The FAS will include all randomized participants who have a valid baseline MDS-UPDRS, received at least one dose of study drug, and have at least one post-baseline evaluation of the MDS-UPDRS assessment. Participants randomized prior to Protocol version 6.1 will be included. Participants will be analyzed according to their assigned intervention. This set will be used for sensitivity analysis.

Protocol deviations will be identified programmatically as well as based on protocol deviations collected by the study monitors. After the last participant exits the trial and prior to database lock, protocol deviations will be reviewed to determine which participants fall into these categories.

2.3 Definitions and Conventions for Data Handling

2.3.1 Baseline Definition

Unless otherwise noted, the last value observed prior to the first administration of study intervention on Day 1 will be the baseline value. If there is no value prior to the study intervention, then the baseline value will not be imputed, and will be set to missing.

2.3.2 Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date (Day 1) is defined as the day of first administration of study intervention.

- Study Day = (date of event – reference start date +1) if the event date is on or later than reference start date
- Study Day = (date of event – reference start date) if the event date is earlier than reference start date

There is no Study Day 0. In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

2.3.3 End of Study

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

2.3.4 Analysis Visit Windows

The analysis time point assigned for the post-baseline visits will be assigned based on the analysis windows described in Table 2-1:

Table 2-1 Analysis visit windows for measurements

Adjusted Defined Windows Visit	*Scheduled Study Day*	*Maximum Windows*
Baseline (Day 1)	1	Study Day =1
Week 4	29	2 ≤ Study Day≤ 43
Week 8	57	44 ≤ Study Day≤ 71

Adjusted Defined Windows Visit	*Scheduled Study Day*	*Maximum Windows*
Week 12	85	72 ≤ Study Day≤ 91
Safety follow-up	99	92 ≤ Study Day

Applying the above visit window rules will be done after identifying treatment visits by CRF visit labels.

2.3.5 Missing Data Handling Rules

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

Any participant with a missing Week 12 visit is defined as a non-completer.

Some individual scales or subscales have their own guidelines for missing items, which will be described in Section 3.2 along with the scale. Unless otherwise specified, if ≤ 20% of the total number of items are missing, then the mean score of the non-missing items for that scale or subscale will be calculated, rounded up to the nearest integer, and imputed to the missing item(s). Otherwise, the assessment score will be set to missing.

Handling of partial or missing dates for adverse events (AEs), concomitant medication start or end dates, and death dates are described in Appendix 8.1. Missing AE severity or relationship will be reported as missing.

2.3.6 Other Data Points Definition

A screen failure is defined as a participant who consents to participate in the clinical study but is subsequently not entered into the study.

2.4 MULTIPLE COMPARISONS/MULTIPLICITY

The safety and tolerability of different dose levels of IkT-148009 will be assessed as an overall evaluation of all safety endpoints. A formal statistical hypothesis of safety endpoints will not be tested. The efficacy endpoints will be tested in hierarchical order by endpoint within dose group. First, the change in MDS-UPDRS Parts II + III endpoint for the high dose will be compared to placebo. Next, if there is a statistically significant difference in the high dose levels for the MDS-UPDRS Parts II + III endpoint, the testing will continue by comparison of high dose vs placebo for the next endpoint in the hierarchy. The procedure will continue similarly for all remaining secondary endpoints. If all efficacy endpoints are significant for the high dose group, then testing will proceed for the middle dose group, then the low dose group.

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

The order of hierarchical testing will be as follows:

1. MDS-UPDRS Parts II + III

2. PDQ-39
3. Patient Global Impression-Severity (PGI-S)
4. Clinician Global Impression of Severity (CGI-S)
5. MDS-UPDRS Part II
6. MDS-UPDRS Part III
7. MDS-UPDRS Part I
8. Non-Motor Symptom Scale (NMSS)
9. Complete Spontaneous Bowel Movement score (CSBM)
10. ESS (Epworth Sleepiness Scale)
11. Schwab and England ADL Scale
12. Patient Assessment of Upper GI Disorders Severity Index (PAGI-SYM)
13. Patient Assessment of Constipation Quality of Life (PAC-QoL)
14. Patient Assessment of GI Disorders Severity Quality of Life (PAGI-QoL)

2.5 EXAMINATION OF SUBGROUPS

Subgroup analysis of the proportion of participants who discontinue treatment up to Week 12 will be made to assess consistency of the intervention effect across the subgroups:

- Above and below median baseline UPDRS part III
- Age group < 65 vs ≥ 65
- Sex: female vs male
- Baseline CSBM ≤ 3 vs CSBM > 3

If the number of participants is too small (< 10% in a subgroup), then the subgroup categories may be redefined prior to unblinding the study. Descriptive statistics will be presented.

2.6 POOLING OF CENTERS

This study is a multicenter study with approximately 32 sites planned across the United States. Decisions regarding pooling of data across sites that had low enrollment will be made and documented prior to treatment unblinding.

3 PRIMARY, SECONDARY AND OTHER VARIABLES

3.1 PRIMARY EFFICACY ENDPOINT

There are no primary efficacy variables in this study. The primary tolerability endpoint is the proportion of participants who discontinue treatment up to Week 12.

Safety endpoints will be reported descriptively (see Section 3.4).

3.2 SECONDARY EFFICACY ENDPOINTS

The Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-

UPDRS) is used for several of the endpoints below. It is a four-part scale, with each item in the scale rated as 0-4, where 0=normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

Change from baseline is calculated for each endpoint as *Value at Visit X - Value at baseline*.

3.2.1 MDS-UPDRS Parts II + III

This endpoint combines the results from Part II (Motor Aspects of Experiences of Daily Living), which has 13 items, and Part III (Motor Examination), which has 33 items. Part II and Part III scores are totaled, then added together, with a range of 0 – 184.

Change from baseline (CFB) will be calculated for Visits 2 (Week 4), 3 (Week 8), 4 (Week 12), and 5 (Safety follow-up). A negative CFB reflects improvement.

3.2.2 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).

Each item is scored as one of 5 ordered response categories. Each dimension score is summed then divided by the number of items and multiplied by 100 to get a percentage score ranging from 0 to 100, with lower scores indicating better health and higher scores more severe symptoms. The PDQ-39 is scored by taking the sum of the 8 scale scores, divided by the number of dimensions (8), which yields a score between 0 and 100 (Hagell 2009).

CFB will be calculated for Visits 2 (Week 4), 3 (Week 8), 4 (Week 12), and 5 (Safety follow-up). A negative CFB reflects improvement.

3.2.3 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, and very severe).

CFB will be calculated for Visits 2 (Week 4), 3 (Week 8), 4 (Week 12), and 5 (Safety follow-up). A negative CFB reflects improvement.

3.2.4 Clinical 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 participant's 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 (severely ill), and 7 (among the most extremely ill).

CFB will be calculated for Visits 2 (Week 4), 3 (Week 8), 4 (Week 12), and 5 (Safety follow-up). A negative CFB reflects improvement.

3.2.5 MDS-UPDRS Part II

This endpoint uses the results from MDS-UPDRS Part II (Motor Aspects of Experiences of Daily Living), which has 13 items. Item scores are totaled with a range from 0-52.

CFB will be calculated for Visits 2 (Week 4), 3 (Week 8), 4 (Week 12), and 5 (Safety follow-up). A negative CFB reflects improvement.

A total Part II score can be calculated if up to 2 items are missing, assuming that items are missing at random across participants (Goetz et al, 2015). The total score is calculated as the [(sum of non-missing scores) × (total number items)] / (number of non-missing scores).

3.2.6 MDS-UPDRS Part III

This endpoint uses the results from MDS-UPDRS Part III (Motor Examination), which has 33 items. Item scores are totaled with a range of 0-132.

CFB will be calculated for Visits 2 (Week 4), 3 (Week 8), 4 (Week 12), and 5 (Safety follow-up). A negative CFB reflects improvement.

A total Part III score can be calculated if up to and including 7 items are missing, assuming that items are missing at random across participants (Goetz et al, 2015). The total score is calculated as the [(sum of non-missing scores) × (total number items)] / (number of non-missing scores).

3.2.7 MDS-UPDRS Part I

This endpoint uses the results from MDS-UPDRS Part I (Non-Motor Aspects of Experiences of Daily Living), which has 13 items. Item scores are totaled with a range from 0-52.

CFB will be calculated for Visits 2 (Week 4), 3 (Week 8), 4 (Week 12), and 5 (Safety follow-up). A negative CFB reflects improvement.

If a single item is missing for a participant, a total Part I score can be calculated (Goetz et al, 2015), assuming that items are missing at random across participants. The total score is calculated as the [(sum of non-missing scores) × (total number items)] / (number of non-missing scores).

3.2.8 Non-Motor Symptom Scale (NMSS)

The NMSS is a 30-item scale divided into 9 domains as specified in Table 3-1:

Table 3-1 Domains of the NMSS

Domain	*Number of items*	*Question numbers*
Cardiovascular/falls	2	1-2
Sleep/fatigue	4	3-6
Mood/cognition	6	7-12
Perceptual problems/hallucinations	3	13-15
Attention/memory	3	16-18
Gastrointestinal	3	19-21
Urinary	3	22-24
Sexual function	2	25-26
Miscellaneous	4	27-30

Each item is rated for frequency (1=rarely, 2=often, 3=frequent, 4=very frequent) and severity (0=none, 1=mild, 2=moderate, 3=severe) of symptoms (Van Wamelen et al, 2020). The item score for each item is calculated as frequency × severity. Item scores within a domain are added for a total domain score, and the domain scores are added to get the total score. The total score has a range of 0 to 360, with higher scores reflecting higher symptomatic burden.

CFB will be calculated for Visits 2 (Week 4), 3 (Week 8), and 4 (Week 12). A negative CFB reflects improvement.

3.2.9 Complete Spontaneous Bowel Movement Score (CSBM)

The mean number of complete spontaneous bowel movements (CSBM) during the previous week will be assessed at baseline and at each Visit. 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.

Constipation is defined by the Rome IV criteria for constipation as less than or equal to 3 spontaneous bowel movements per week.

CFB will be calculated as the sum of unassisted diary values for Visits 2 (Week 4), 3 (Week 8), and 4 (Week 12). An increase (positive value) reflects improvement.

3.2.10 Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) assesses sleepiness over time (Johns 1991). Patients and caregivers are asked to rate their likelihood of falling asleep during 8 daily activities, including reading, watching television, sitting in different situations, and driving.

Each item is scored as 0 (would never doze), 1 (slight chance of dozing), 2 (moderate chance of dozing), or 3 (high chance of dozing). Items are added for a total score ranging from 0 to 24. A high score reflects more severe sleep disorder.

If one or more items are missing, then the ESS is set to missing.

ESS will be obtained during Visit 1 (baseline) and Visit 4 (Week 12). Change from baseline will be calculated. A negative CFB reflects improvement.

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

The SE-ADL is a single item that assesses the difficulty that a participant 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, …). CFB will be calculated for Visits 2 (Week 4), 3 (Week 8), 4 (Week 12), and 5 (Safety follow-up). The participant value will be recorded. A positive value of CFB reflects improvement.

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

The Patient Assessment of Upper GI Disorders Severity Index (PAGI-SYM) measures symptom severity in patients with upper GI disorders. The participant is asked to rate the severity of symptoms over the last 2 weeks. There are 20 items in 6 subscales: heartburn/regurgitation, postprandial fullness/early satiation, bloating, nausea/vomiting, lower abdominal pain, and upper abdominal pain. Each item is rated from 0 (none) to 5 (very severe).

Each subscale is calculated as the mean of each non-missing item in the subscale. The PAGI-SYM score is calculated by taking the mean of all subscale scores (Sebaratnam et al, 2021). If > 50% of items in a subscale are missing, the subscale score and total score are defined as missing (Tiegland et al, 2018).

CFB will be calculated for Visits 2 (Week 4), 3 (Week 8), and 4 (Week 12). A negative CFB reflects improvement.

3.2.13 Patient Assessment of Constipation Quality of Life (PAC-QoL)

The Patient Assessment of Constipation Quality of Life (PAC-QoL) assesses the effect that constipation has on daily life over the past 2 weeks. There are 28 items in 4 domains: physical discomfort (4 items), psychosocial discomfort (8 items), treatment satisfaction (5 items), and worries and discomfort (11 items). Each item is rated from 0 (not at all/never) to 4 (extremely/always). Items 25, 26, 27, and 28 should be scored reversed (Marquis, et al, 2005).

Each domain is calculated as the mean of the items in the domain. The total score is calculated as the mean of the 4 mean domain scores.

CFB will be calculated for Visits 2 (Week 4), 3 (Week 8), and 4 (Week 12). A negative CFB reflects improvement.

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

The Patient Assessment of GI Disorders Severity Quality of Life (PAGI-QoL) assesses the effect that GI problems have on daily life over the past 2 weeks. There are 30 items in 5 dimensions: daily activities (10 items, Q1-10), clothing (2 items, Q11-12), diet and food habits (7 items, Q13-20), relationship (3 items, Q20-22), and psychological well-being and distress (8 items, Q23-30). Each item is rated from 0 (none of the time) to 5 (all the time) (De La Loge et al, 2004).

Individual items are rated such that a higher score represents a worse outcome. However, each subscale score is taken as the mean of the items in each subscale, when all item responses are reverse-coded such that a higher score represents a better disease-specific quality of life. The PAGI-QOL summary score is calculated as the mean of all subscales (Sebaratnam et al. 2021).

In case of missing data, the subscale score is calculated when 50% or less of the items are missing for that scale. If >50% of items in a subscale are missing, the score is set to missing. If a subscale score is set to missing then the total score is also set to missing.

CFB will be calculated for Visits 2 (Week 4), 3 (Week 8), and 4 (Week 12). A negative CFB reflects improvement.

3.3 EXPLORATORY ENDPOINTS

3.3.1 Phosphorylated alpha-synuclien aggregates

Skin biopsy will be collected at Visit 1 (baseline), Visit 2 (Week 4), and Visit 4 (Week 12) from participants at select sites. CSF samples will be collected at Visit 1 (baseline) and Visit 4 (Week 12). No statistical assessment will be done for these measures.

3.4 SAFETY ENDPOINTS

The primary objective of the study is to assess safety and tolerability of three doses of IkT-148009 in participants with PD, as described in Section 3.4.2.2.

Tolerability is defined as the proportion of participants who discontinue the assigned regimen, and will be reported for the Safety Set.

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

- Incidence and of TEAEs, evaluated by 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)
- Proportion of those randomized in each dosing cohort who discontinue the assigned regimen

Safety analysis is described further in Section 4.3. Safety endpoints will be summarized with descriptive statistics.

3.4.1 Extent of Exposure

Time on treatment in days will be derived from the following formula:

Time on treatment (days) = (date of last dose) – (date of first dose) + 1.

This calculation does not consider any gaps in exposure caused by the participant missing one or more scheduled doses.

Extent of exposure will be reported for the Safety Set using date of first dose of active treatment.

3.4.2 Adverse events

The adverse event verbatim descriptions (investigator terms from the CRF) will be classified into medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to primary System Organ Class (SOC) and preferred term (PT) using MedDRA, Version 26.0 or newer.

A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date, or a worsening in severity from baseline (pre-treatment), on or after the first dose of study intervention up to the Safety follow-up visit or Early Termination Visit following study drug discontinuation.

An AE will be considered treatment related if the investigator considers that there is a reasonable possibility that the event may have been caused by the investigation product. If a causal relationship to study intervention is missing for an AE that started on or after the date of first dose of study intervention, causality will not be imputed and a category of "missing" will be included as necessary in incidence summaries. An event with missing onset date will be imputed as treatment-emergent, unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study intervention start date).

An AE will be considered serious (SAE) if it meets the definition of SAE given in the protocol Appendix 10.3.2, as recorded on the AE form of the CRF.

If AE have missing or incomplete start or end dates, they will be imputed as described in Appendix 8.1.

The SOCs will be presented in alphabetical order and the PTs will be presented in frequency order for the highest dose of active treatment within each SOC. A participant who reports more than 1 AE in different SOCs will counted once in the overall total. A participant who reports AEs in different PTs in the same SOC will be counted only once in the SOC total. A participant reporting more than 1 AE in a given PT will be counted only once for that term. In severity and relatedness tables, the most severe or related AE will be counted.

3.4.3 Clinical Laboratory Variables

Laboratory safety assessments will be performed in a central laboratory at each Visit. The hematology, clinical chemistry, urinalysis, and other parameters are outlined in Appendix 2 of the protocol. Laboratory data are to be reported in SI units, except for the blood eosinophils counts which will be reported in conventional units.

For values recorded with a leading greater than or less than ('>', '<') symbol, the reported numeric value will be used for analysis and the value with the symbol will be included in the listings, unless otherwise specified. For example, a value of <0.01 will be analyzed as 0.01 and listed as <0.01.

Absolute values will be compared to the relevant reference range and classified as LNH (low (below normal limit), normal (within normal limits) or high (above normal limit)). The central laboratory ranges will be used for laboratory variables. All absolute values falling outside the reference ranges will be flagged as L (low) or H (high).

3.4.4 Vital Signs, Physical Examination Findings, and ECG

3.4.4.1 Vital Signs

Predose vital signs (body temperature, blood pressure (BP), heart rate, and respiration rate) will be obtained at each Visit (Week 0 (baseline), 4, 8, 12, and 14). Blood pressure and heart rate will be measured both supine and standing.

Absolute values will be compared to the relevant reference ranges and classified as LNH as defined in Section 3.4.3.

Body mass index (BMI) will be calculated from the height and weight as follows:

$$BMI\ (kg/m2) = weight\ (kg)/(height\ (m))^{2}$$

3.4.4.2 Physical Examination

Complete physical examinations will be performed at Screening only. Each component of

the baseline physical examination will be recorded as normal, abnormal-not clinically significant, or abnormal- clinically significant. Significant changes will be reported as AEs.

3.4.4.3 ECG

ECG assessments are performed at each visit using a triplicate 12-lead ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

Clinically significant findings will be listed and summarized for the Safety Analysis Set.

3.4.5 Other Safety Variables

All women of childbearing potential will take serum/urine pregnancy tests at baseline and Week 14.

Opthalmic exams will consist of spectral domain optical coherence tomography (SD-OCT) and will evaluate changes to the choroid and to evaluate the fundus. Significant findings will be reported as AEs.

Participants will be observed for suicidal ideation and behavior (SIB) and will take the C-SSRS suicidality assessment at every Visit. Participants with suicidal ideation will be presented in a listing.

4 ANALYSIS METHODS

4.1 PARTICIPANT INFORMATION

4.1.1 Disposition of Participants

The number of participants screened and the number and percentage of participants who failed screening and the reasons for screen failure will be summarized for all participants based on data reported on the Screen Failure CRFs. The distribution of the number of randomized participants enrolled by each site will be summarized for each randomized treatment group and overall.

Study Completion: The number and percentage of randomized and treated participants who completed the study and who discontinued from the study will be summarized according to the reason for discontinuation for the mITT, based on data reported on the End of Study CRF.

Completion of Study Treatment: The number and percentage of randomized and treated participants who completed study treatment and who discontinued from study treatment will be summarized according to the reason for discontinuation for the mITT, based on data reported on the End of Treatment CRF.

Reasons for study or treatment discontinuation include:

- Adverse event

- Death
- Pregnancy
- Non-compliance with study drug
- Participant withdrew consent
- Protocol deviation
- Study terminated by Sponsor
- Site terminated by Sponsor
- Lost to follow-up
- Investigator/Physician decision, specify
- Other, specify

4.1.2 Protocol Deviations

Major and minor protocol deviations will be assessed by sponsor personnel following the Protocol Deviation Management Plan. A protocol deviation will be classified as major if there is a potential to significantly impact the completeness, accuracy, and/or reliability of the study data, or affect a participant's rights, safety, or well-being. All protocol deviations will be identified and finalized prior to database lock and treatment unblinding.

The number and percentage of participants with protocol deviations in the mITT Population will be summarized by treatment group and overall. A similar summary will be provided for major PDs due to the COVID-19 pandemic.

A listing of these cases will be provided with the tables, and a listing of all collected protocol deviations will be presented in an appendix listing.

4.1.3 Demographics and baseline characteristics

Demographic and baseline characteristics for the Safety analysis set will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, height, weight, and BMI; categorical variables include sex, age group (< 65 vs ≥ 65), race, and ethnicity.

The status of Parkinson's disease at screening will be summarized according to the categorical variable Modified Hoehn and Yahr stage, and the Montreal Cognitive Assessment total score.

Baseline scores for efficacy assessments will be summarized in the mITT as in Table 4-1:

Table 4-1 Baseline scores for efficacy assessments

Assessment	*Variable type*	*Subscales/domains*
MDS-UPDRS	Continuous	Part II+III
PDQ-39	Continuous	Total score Mobility Activities of daily living Emotional well-being

		Stigma Social support Cognition Communication Bodily discomfort
PGI-S	Categorical	
CGI-S	Categorical	
MDS-UPDRS	Continuous	Part II Part III Part I
NMSS	Continuous	Total score Cardiovascular Sleep/fatigue Mood/cognition Perceptual problems/hallucinations Attention/memory GI Urinary Sexual function Miscellaneous
CSBM	Continuous	
ESS	Continuous	
SE-ADL	Continuous	
PAGI-SYM	Continuous	Total score Heartburn/regurgitation Postprandial fullness/early satiation Bloating Nausea/vomiting Lower abdominal pain Upper abdominal pain
PAC-QoL	Continuous	Total score Physical discomfort Psychosocial discomfort Treatment satisfaction Worries and discomfort
PAGI-QoL	Continuous	

4.1.4 Medical History

The Medical History will be coded by MedDRA (26.0) or higher version. A participant data listing of medical and surgical history will be provided.

4.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced, March 2018 or newer. The number and percentage of participants who took prior and concomitant medications will be summarized for the Safety population by treatment, Anatomical Therapeutic Chemical (ATC) Classification and WHO Drug preferred term. Prior medications will be defined as medications that stopped prior to the first dose of study drug. Concomitant medications will be defined as medications that (1) with a start date before the first dose of study drug and an end date after the first dose of study drug or ongoing, or (2) with a start date on or after the date of the first dose of study drug up to 14 days following the last dose.

Common PD therapies are listed in Table 4-2. All ATC2 codes of 'N04' will be included as anti-Parkinson medication.

Table 4-2 Common PD therapies.

Drug class	***Medication***
Levodopa	Carbidopa-levodopa Levodopa Duodopa
Dopamine agonists	Pramipexole Rotigotine Apomorphine Ropinirole Stalevo
MAO B inhibitors	Selegiline Rasagiline Safinamide
COMT inhibitors	Entacapone Opicapone Tolcapone
Anticholinergics	Benzatropine Trihexyphenidyl
Mixed mechanism	Amantadine
Adenosine A2A receptor antagonist	Istradefylline

COMT= Catechol-O-methyltransferase; MAO= monoamine oxidase.

Summary tables will be provided for prior PD therapies and prior and concomitant general medications along with supportive listings. Listings will include indication, start date, stop date (or ongoing), and dosage information.

Medications known to be Cytochrome P450 (CYP) 3 A4/5 inhibitors or inducers and those known to be MDR1 or BCRP inhibitors will be listed separately and marked as prior or concomitant (see https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers for the list of drugs in this category).

4.1.6 Treatment Compliance

At each study visit, the participant will be instructed to bring their pill bottles with them and the number of remaining pills will be counted and recorded. Treatment compliance will be defined as actual number of pills taken divided by the expected number of pills × 100. In order to allow for subjects who discontinue IP early in the compliance calculation, the number of expected dosing occasions will be calculated as the number of scheduled dosing occasions up to and including the last available dosing occasion for that subject.

Mean treatment compliance will be listed and summarized for the Safety set, as well as the number and percent of those taking greater than or equal to 85% of the assigned study drug doses. A participant's dosing compliance will be calculated as the percentage of visits for which dosing compliance was met.

4.2 EFFICACY ANALYSES

4.2.1 Summary of efficacy analyses

Efficacy analysis will be performed at the end of the 12-week study during Final Analysis.

Table 4-3 Summary of estimands for efficacy analyses

Endpoint (mITT)	*Population Level Summary (Analysis)*	*Section*
Change from baseline to Week 12:		
MDS-UPDRS Sum of Part II+III	Mean difference between treatment groups (MMRM)	4.2.3
PDQ-39	Mean difference between treatment groups (MMRM)	4.2.3
PGI-S	proportion of participant s who improved from baseline (GLIMMIX)	4.2.3
CGI-S	proportion of participant s who improved from baseline (GLIMMIX)	4.2.3
MDS-UPDRS Part II	Mean difference between treatment groups (MMRM)	
MDS-UPDRS Part III	Mean difference between treatment groups (MMRM)	4.2.3
MDS-UPDRS Part I	Mean difference between treatment groups (MMRM)	4.2.3
NMSS	Mean difference between treatment groups (MMRM)	4.2.3
CSBM	Mean difference between treatment groups (MMRM)	4.2.3
ESS	Mean difference between treatment groups (MMRM)	4.2.3
Schwab and England ADL Scale	Mean difference between treatment groups (MMRM)	4.2.3
PAGI-SYM	Mean difference between treatment groups (MMRM)	4.2.3
PAC-QoL	Mean difference between treatment groups (MMRM)	4.2.3
PAGI-QoL	Mean difference between treatment groups (MMRM)	4.2.3

4.2.2 Primary Analysis

4.2.2.1 Primary Analysis

There is no primary efficacy endpoint. The primary tolerability endpoint is the proportion of participants in the Safety Set who discontinue treatment up to Week 12 and will be reported with the Safety Analysis.

The other primary safety analyses are described in Section 4.3.2.

4.2.3 Secondary Efficacy Analyses

The efficacy endpoints (as changes from baseline at Week 12) will be evaluated in hierarchical order as described in Section 2.4. The following endpoints will be evaluated:

- Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts II + III
- Parkinson's Disease Questionnaire (PDQ-39) summary index
- 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) total score
- Complete Spontaneous Bowel Movement Score (CSBM)
- Epworth Sleepiness Scale (ESS) total score
- Schwab and England Activities of Daily Living (SE-ADL) Scale
- 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)

The estimand for the key efficacy endpoint is defined as follows:

A. Population: Participants with Parkinson's Disease as defined by inclusion/exclusion criteria and in the modified Intent-to-Treat (mITT) population.

B. Variable: Change from baseline to Week 12 in the MDS-UPDRS Parts II + III score.

C. Intercurrent Events:

   a. Premature Discontinuation of Study Treatment

   b. Initiation of PD Medication for Treatment of Motor Features

D. Summary: Treatment differences of the least-squared mean (LSM) change from baseline at Week 12 in the MDS-UPDRS Parts II + III summary index between 50, 100, or 200 mg IkT-148009 vs placebo.

For data that are missing due to premature discontinuation of study treatment or initiation of PD medication, no specific imputation will be done. If possible, the collection of data will be continued and used according to the treatment policy strategy. Descriptive statistics for each endpoint will be presented as change from baseline by treatment group and visit.

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.

For each endpoint and treatment group, the null hypothesis will be $H_0: \delta = 0$ and the alternative hypothesis will be $H_0: \delta \neq 0$, where δ = treatment difference = $(\bar{x} - \mu)$.

For participants $i=1, \ldots, I$ and repeated observations $j=1,\ldots,J$, the MMRM model can be parameterized as

$$\mathbf{Y}_i = X_i\boldsymbol{\beta} + Z_i\mathbf{b}_i + \boldsymbol{\varepsilon}_i$$

Where $\mathbf{Y}_i$ = a J_i dimensional vector of outcome measurements for the i^{th} participant,

$\boldsymbol{\beta}$ = a p dimensional vector containing the fixed effects (baseline, treatment effect, time),

X_i, Z_i = $(J_i \times p)$ and $(J_i \times q)$ dimensional design matrices of known covariates,

$\mathbf{b}_i$ = q dimensional vector containing the random effects ($\mathbf{b}_i \sim N(0, D)$) and

$\boldsymbol{\varepsilon}_i$ = J_i dimensional vector of residual components ($\boldsymbol{\varepsilon}_i \sim N(0, \Sigma_i)$).

The MMRM will include the observed change from baseline from Week 4, Week 8, and Week 12 as the response values, baseline value as a covariate, and treatment group, visit, and treatment group × visit interaction term as fixed factors. An unstructured covariance structure will be assumed first. If this model does not converge, Heterogeneous Autoregressive (1) (ARH[1]), Heterogeneous Compound Symmety (CSH), Autoregressive (1) (AR[1]) or Compound Symmetry (CS) covariance structure will be used (in this order). The denominator degrees of freedom will be computed using the Kenward-Roger method.

The least square (LS) means estimate for each treatment group, SEM, and LS mean difference between different dose levels and placebo will be provided, along with the 95% confidence intervals (CI) and *p*-value, for each assessment. Only the LS means for Week 12 will be used for statistical comparison.

Categorical endpoints (PGI-S, CGI-S) will be analyzed using the GLIMMIX procedure for binomial data with the logit 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. "Improved" is defined as at least a whole number decrease in score for PGI-S and CGI-S. Response values will be the proportion who improved since baseline at each post-baseline visit. The proportion who improved at each assessment will be presented, along with the odds ratio, 95% CI and *p*-value. Only the proportion who improved at Week 12 will be used for statistical comparison.

Endpoints will be tested in the order presented in Section 2.4 with 2-sided α=0.05. Endpoints not compared as part of the hierarchical testing procedure will be reported for descriptive purposes only.

Each of the secondary efficacy endpoints is described in Section 3.2.

4.2.4 Other Efficacy Analyses

The exploratory endpoints are:

- Phosphorylated alpha-synuclein aggregates in skin and
- Phosphorylated alpha-synuclein aggregates in CSF

4.2.5 Sensitivity Analyses

As a sensitivity analysis for the MDS-UPDRS Parts II + III, the MMRM will be repeated as described in Section 4.2.3 using the FAS.

Any efficacy endpoints that reach statistical significance may also be further explored on a post hoc basis using sensitivity analysis in which the Hypothetical Scenario is applied to Intercurrent Events, using the assumptions of Missing at Random (MAR) and Missing Not at Random (MNAR), respectively, to perform Multiple Imputation (MI) to impute data after the first occurrence of PD medication use. For MI using MNAR, copy-reference (placebo) will be used.

4.2.6 Pharmacokinetic Analysis

Pharmacokinetic samples will be drawn predose at baseline and postdose at Weeks 4, 8, and 12.

IkT-148009 concentration will be listed and descriptively analyzed by treatment group for the PK analysis set. Descriptive statistics include N, mean, geometric mean, SD, SEM, median, %CV, minimum and maximum. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the determination of summary statistics and will be treated as missing for the calculation of the geometric means.

Mean (+/- SD) of plasma IkT-148009 concentrations will be plotted by treatment at each time point.

4.3 SAFETY ANALYSIS

All safety assessments will be performed on the Safety Analysis. Safety data presented by treatment group will be summarized on an ‘as treated’ basis. Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, ophthalmic exams, suicidality, and extent of exposure. Study Day 1 for all safety analyses is defined as the date of the first dose of study drug. Safety and tolerability endpoints will be assessed at Week 12. Tolerability will be assessed by

comparing percentages of premature drug and study discontinuations in the treatment.

4.3.1 Extent of Exposure

Time on treatment will be defined as the *date of last dose – date of first dose + 1*. Total dose will be defined as the *time on treatment* × *actual dose level*. Temporary interruptions in dosing or missed doses will not be considered. Time on treatment and total dose will be summarized by dose group for the safety analysis set.

4.3.2 Adverse Events

Treatment emergent adverse events (TEAEs) are defined as those that start or worsen after the first dose of study intervention until the Safety follow-up visit is completed. Safety assessments will include TEAEs tabulated by treatment group; descriptive statistics for continuous variables and frequency counts for discrete variables. No inferential statistical analysis is planned for safety data.

TEAEs will be summarized by treatment group. The incidence of TEAEs will be reported as the number (percent) of participants with TEAEs within system organ class (SOC) and preferred term (PT). Participants will be counted only once within a SOC and PT, even if the participant experienced more than one TEAE within a specific SOC and PT.

TEAEs will also be summarized by dose group, SOC and PT for the following:

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. Serious Adverse Events (SAE)
7. Suicidality as measured by the C-SSRSSafety and tolerability endpoints will be summarized for the end of the week-12 placebo-controlled study.

Supportive listings will be provided for each summary table. The AE listing will include day of onset and end day.

4.3.3 Deaths

All deaths will be reported as AEs. The cause of death will be defined as the Preferred Term for the AE with an outcome of “fatal”, and the date of death will be defined as the end date of that AE. A participant data listing of all deaths will be provided, including which AE led to death.

4.3.4 Clinical Laboratory Data

Clinical laboratory tests (hematology and clinical chemistry) and their central reference ranges are listed in Table 4-4 and Table 4-5.

Table 4-4 Hematology tests and reference ranges

Laboratory test	***Lower limit of normal***	***Upper limit of normal***	***Units***
WBC	Over 16 yr: 4.1	12.3	$X_{10}E_3$/uL
Hemoglobin	Female 12-65 yr: 11.6	Female 12-65 yr: 16.2	g/dL
	Female 66-110 yr: 11.0	Female 66-110 yr: 16.1	
	Male 18-65 yr: 13.0	Male 18-65 yr: 17.5	
	Male 66-110 yr: 13.0	Male 66-110 yr: 17.7	
Hematocrit	Female 12-65 yr: 35.0	Female 12-65 yr: 47.0	%
	Female 66-110 yr: 33.0	Female 66-110 yr: 46.0	
	Male 18-65 yr: 40.0	Male 18-65 yr: 52.0	
	Male 66-110 yr: 37.0	Male 66-110 yr: 50.0	
RBC count	Female 12-65 yr: 3.8	Female 12-65 yr: 5.5	$X_{10}E_6$/uL
	Female 66-110 yr: 3.8	Female 66-110 yr: 5.40	
	Male 18-65 yr: 4.1	Male 18-65 yr: 5.9	
	Male 66-110 yr: 4.0	Male 66-110 yr: 5.8	
MCV	Female: 79	98	fL
	Male: 79	97	
MCH	26	34	Pg/cell
MCHC	31	37	g/dL
RDW	11.6	14.8	%
Platelet count	140	450	$X_{10}E_3$/uL
Neutrophils	40.9	77.0	%
Lymphocytes	15.5	16.6	%
Monocytes	3.1	12.5	%
Eosinophils	0.0	6.0	%
Basophils	0.0	2.4	%
Blasts	0	0	%
Promyelocytes	0	0	%
Myelocytes	0	0	%
Metamyelocytes	0	0	%
Bands	0.0	5.0	%
Prolymphocytes	0	0	%
Atypical lymphocytes	0	3	%
Neutrophils Absolute	2.03	8.36	$x_{10}E_3$/uL
Lymphocytes Absolute	1.02	3.36	$x_{10}E_3$/uL
Monocytes Absolute	0.18	0.90	$x_{10}E_3$/uL
Eosinophils Absolute	0.00	0.56	$x_{10}E_3$/uL
Basophils Absolute	0.00	0.17	$x_{10}E_3$/uL
Blasts Absolute	0.00	0.00	$x_{10}E_3$/uL
Promyelocytes Abs	0.00	0.00	$x_{10}E_3$/uL
Myelocytes Absolute	0.00	0.00	$x_{10}E_3$/uL
Metamyelocytes Absolute	0.00	0.00	$x_{10}E_3$/uL
Bands Absolute	0.00	0.50	$x_{10}E_3$/uL
Prolymphocytes Absolute	0.00	0.00	$x_{10}E_3$/uL
Atypical lymphocytes Absolute	0.00	0.30	$x_{10}E_3$/uL
Nucleated RBC	0	0	/100WBC
Plasma cells Absolute	0.00	0.00	$x_{10}E_3$/uL
Plasma cells	0	0	%
Reticulocytes	0.3	2.8	%
Reticulocytes Absolute	13.5	123.0	$x_{10}E_3$/uL
MCV = mean corpuscular volume; MCH= mean corpuscular hemoglobin; RBC = red blood cell; RDW = red cell distrubtion width; WBC = white blood cell.			

Table 4-5 Clinical chemistry tests and reference ranges

Laboratory test	*Lower limit of normal*	*Upper limit of normal*	*Units*
Sodium	135	147	mEq/L
Potassium	3.3	5.1	mEq/L
Bicarbonate	19	29	mEq/L
BUN/Urea	18-60 yr: 6	20	mg/dL
	61-110 yr: 8	23	
Creatinine	Female: 0.51	0.95	mg/dL
	Male: 0.67	1.17	
Creatinine Clearance			
Glucose (non-fasting)	16-59 yr: 74	106	mg/dL
	60-90 yr: 82	115	
	91-109 yr: 75	121	
Lipase	Over 16yr: 13	60	U/L
Calcium	12-65 yr: 8.4	10.3	mg/dL
	66-90 yr: 8.8	10.2	
	91-109 yr: 8.2	9.6	
Phosphorus	2.5	4.5	mg/dL
Magnesium	1.3	2.1	mEq/L
Protein Total	6.0	8.0	g/dL
Albumin	3.5	5.2	g/dL
Bilirubin Total	≤ 1.2		mg/dL
Bilirubin Direct	≤ 0.3		mg/dL
ALT	Female: ≤33		U/L
	Male: ≤41		
AST	Female: ≤31		U/L
	Male: ≤37		
GGT	Female: 5	36	U/L
	Male: 8	61	
Alkaline phosphatase	Female: 35	104	U/L
	Male: 40	129	
LDH	≤250		U/L
CK	Female: 26	192	U/L
	Male: 39	308	
Uric acid	Female: 2.4	5.7	mg/dL
	Male: 3.4	7.0	
Amylase total	28	100	U/L
eGFR/1.73m2 CKD-EPI		≥60	mL/min
LIPID PANEL			
Cholesterol	<200		mg/dL
Triglycerides	<150		mg/dL
URINALYSIS			
Urine dipstick appearance	CLEAR		
Urine dipstick bilirubin	NEGATIVE		
Urine dipstick blood	NEGATIVE		
Urine dipstick color	YELLOW		
Urine dipstick glucose	NEGATIVE		
Urine dipstick ketones	NEGATIVE		
Urine dipstick leukocyte esterase	NEGATIVE		

Urine dipstick nitrite	NEGATIVE		
Urine dipstick pH	5.0	8.0	
Urine dipstick protein	NEGATIVE		
Urine dipstick specific gravity	1.001	1.035	
Urine dipstick urobilinogen	NORMAL/TRACE		
Urine dipstick microscopy	NORMAL		
Urinalysis RBC	Male: 0	5	HPF
	Female: 0	8	
Urinalysis WBC	Male: 0	3	HPF
	Female: 0	12	
COAGULATION			
Prothrombin time	Over 1 yr: 10.0	14.3	sec
INR	0.8	1.2	
ENDOCRINOLOGY			
B-hCG	NEGATIVE		
FSH			mIU/mL
LH	Male 18-49yr: 1.5	9.3	mIU/mL
Testosterone Total	Male 18-49yr: 123.06	813.86	ng/dL
	Male ≥50yr: 86.98	780.10	
THYROID PANEL			
TSH	0.55	4.78	uIU/mL
TESTED at QD Nichols Institute			
Inhibin B	Male: 47	308	pg/mL
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate; GGT = gamma glutamyl transferase; LDH = lactate dehydrogenase; RBC = red blood cells.			

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 based on baseline.

Laboratory values that are non-missing and reported as 'below the detectable limit' of an assay will be replaced by the detectable limit in the summary tables. Laboratory results will be summarized using International System (SI) units.

Baseline, observed value for each time point, and changes in hematology and clinical chemistry variables for each time point will be summarized using descriptive statistics for the Safety analysis set by treatment group.

Each laboratory parameter will have shift tables presented that compare the baseline LNH classification to the LNH classification at each post-baseline visit and at the end of treatment.

All laboratory values will be listed by participant for the safety analysis set.

4.3.5 Vital Signs, Physical Examination Findings, and ECG

4.3.5.1 Vital Signs

Descriptive statistics for vital signs parameters and changes from baseline will be presented by visit and treatment group. Orthostatic hypotension will be defined as either

- (Supine systolic BP – standing systolic BP) > 20 mmHg
- (Supine diastolic BP – standing diastolic BP) > 10 mmHg

A listing will be presented at each time point for all participants in the safety analysis set.

4.3.5.2 Physical Examinations

Physical examination findings, including neurological examination findings, will be listed for all participants in the safety analysis set as "Normal", "Abnormal-Clinically Significant", and "Abnormal-Non-Clinically Signifiant". Clinically significant findings will be included as TEAEs.

4.3.5.3 ECG

Descriptive statistics for ECG parameters will be listed and summarized by treatment group.

ECG interpretation will be categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant. Clinically significant findings for ECG will be recorded as TEAEs, listed, and tabulated.

4.3.6 Other Safety Analyses

Positive pregnancy tests will be presented in a listing.

Ophthalmic exam and C-SSRS findings will be listed.

4.4 OTHER EXPLORATORY ANALYSIS

A subgroup analysis of the proportion of participants who discontinue treatment up to Week 12 will be made to assess consistency of the intervention effect across the subgroups:

- Above and below median UPDRS part III at baseline
- Age group: < 65 vs ≥ 65 years
- Sex: female vs male
- Baseline CSBM ≤ 3 vs CSBM > 3

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.

5 INTERIM ANALYSIS AND DATA MONITORING COMMITTEE

5.1 INTERIM ANALYSIS

An interim analysis will not be conducted. Final analysis will be performed at the end of the 12-week placebo-controlled study and will include all safety and efficacy endpoints. The study team will be unblinded for the Final analysis.

5.2 DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) will meet on a regular basis to review safety data, as outlined in the DSMB charter. The DSMB will consist of at least two expert clinicians who are actively treating PD participants, and a biostatistician.

6 SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

The definition of mITT was changed to exclude those who were randomized prior to Protocol version 6.1. A Full Analysis Set (FAS) was defined to include everyone who meets the other requirements for inclusion in the mITT, including those randomized prior to Protocol version 6.1 The FAS will be used to perform a sensitivity analysis on the MDS-UPDRS Parts II+III.

The order of hierarchical testing for statistical significance was changed to test all endpoints in the highest dose first (200 mg), then the 100 mg dose, then the 50 mg dose. Testing order of the endpoints was changed.

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8 APPENDICES

8.1 PARTIAL DATES FOR ADVERSE EVENTS AND PRIOR/CONCOMITANT MEDICATION

Dates missing the day or both the day and month of the year will adhere to the following conventions in order to classify treatment-emergent AEs and to classify prior/concomitant medications:

Adverse Events

- The missing day of onset of an AE will be set to:
  - First day of the month that the event occurred, if the onset YYYY-MM is after the YYYY-MM of first study treatment

  - The day of the first study treatment, if the onset YYYY-MM is the same as YYYY-MM of the first study treatment
  - The date of informed consent, if the onset YYYY-MM is before the YYYY-MM of the first treatment.

- The missing day of resolution of an AE will be set to:
  - The last day of the month of the occurrence. If the participant died in the same month, then set the imputed date as the death date.
- If the onset date of an AE is missing both the day and month, the onset date will be set to:
  - January 1 of the year of onset, if the onset year is after the year of the first study treatment
  - The date of the first treatment, if the onset year is the same as the year of the first study treatment
  - The date of informed consent, if the onset year is before the year of the first treatment
- If the resolution date of an AE or end date of an IP is missing both the day and month, the date will be set to:
  - December 31 of the year of occurrence. If the participant died in the same year, then set the imputed date as the death date.

Prior/concomitant medication

- The missing day of start date of a therapy will be set to the first day of the month that the event occurred.
- The missing day of end date of a therapy will be set to the last day of the month of the occurrence.
- If the start date of a therapy is missing both the day and month, the onset date will be set to January 1 of the year of onset.
- If the end date of a therapy is missing both the day and month, the date will be set to December 31 of the year of occurrence.
- If the start date of a therapy is null and the end date is not a complete date then the start date will be set to the earlier of the imputed partial end date and the date of the first study visit.

- If the start date of a therapy is null and the end date is a complete date
  - and the end date is after the date of the first study visit then the start date will be set to the date of the first study visit.
  - otherwise the start date will be set to the end date of the therapy.
- If the end date of a therapy is null and the start date is not a complete date then the end date will be set to the study end date.
- If the end date of a therapy is null and the start date is a complete date
  - and the start date is prior to the study end date then the end date will be set to the study end date.
  - otherwise, the end date will be set to the start date of the therapy.