Statistical Analysis Plan

A Randomized, Double-Blind, Placebo-Controlled Phase IIb Study Evaluating the Efficacy of Mesdopetam on Daily ON-Time Without Troublesome Dyskinesia in Patients with Parkinson's Disease

Protocol Number: *IRL790C005*

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Previous SAP Versions

Not Applicable

SAP Amendments Before Database Lock

Version	Issue Date	Section	Revision / Addition	Rationale
	Not Applicable			

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Events
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
b.i.d.	Twice a Day
BDR	Blind Data Review
BLQ	Below the Limit of Quantification
CDISC	Clinical Data Interchange Standards Consortium
CGI-S	Clinician's Global Impression of Severity
CI	Confidence Intervals
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	Coefficient of Variation (%)
ECG	Electrocardiograms
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FWER	Family Wise Error Rate
IMP	Investigational Medicinal Product
IP	Independent Programming
IRS	Interactive Response System
LID	Levodopa-Induced Dyskinesia
LS	Least Squares
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary of Regulated Activities
M-EDL	Motor Aspects of Experiences of Daily Living
MMRM	Mixed Model For Repeated Measures
MMSE	Mini-Mental State Examination
MNAR	Missing Not at Random

Abbreviation	Description
NTEAE	Non-Treatment-Emergent Adverse Event
PD	Parkinson's Disease
PDev	Protocol Deviations
PK	Pharmacokinetic
PPS	Per Protocol Set
PT	Preferred Term
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SI	Système International
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO Drug	World Health Organization Drug Dictionary

1 INTRODUCTION

This document details the planned statistical analyses for Integrative Research Laboratories Sweden AB, protocol "IRL790C005" study titled "A Randomized, Double-Blind, Placebo-Controlled Phase IIb Study Evaluating the Efficacy of Mesdopetam on Daily ON-Time Without Troublesome Dyskinesia in Patients with Parkinson's Disease". The proposed analyses are based on the contents of protocol Version 5.0, dated 05 March 2021.

This is a multi-centre, randomized, double-blind, placebo-controlled study with the primary objective to evaluate the efficacy of 84 days' treatment with mesdopetam compared to placebo in patients with Parkinson's Disease (PD) exhibiting ON-phase dyskinesia.

The study comprises a screening period of up to 8 weeks, followed by a 12-week treatment period. A follow-up visit will be performed approximately 1 week after the last Investigational Medicinal Product (IMP) dose.

Patients will be randomized to receive one of three doses of mesdopetam (2.5 mg, 5 mg, or 7.5 mg) or placebo b.i.d. For patients to adjust to the new medication, a run-in phase with either 5 mg mesdopetam or placebo b.i.d. will take place during the first week (Day 1 evening dose to Day 9 morning dose).

A dose reduction is permitted if the patient manifests increased parkinsonism and/or a consistent increase in motor OFF-time. The dose can only be reduced once (and only by 2.5 mg b.i.d.). Dose reductions are permitted from Visit 2 until Visit 3 (i.e., Day 9 - Day 28), after which the reduced dose should be kept stable until end of treatment (EOT) period (Visit 5, Week 12).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

- To evaluate the effectiveness of adjunctive treatment with mesdopetam dosed at 2.5 mg, 5 mg, or 7.5 mg b.i.d. (permitting a single 2.5 mg dose reduction to a minimum dose of 2.5 mg, up to Day 28) compared to placebo in patients with PD exhibiting troublesome ON-phase dyskinesia.

2.2 Secondary Objectives

- To establish the dose response relationship with 3 dose levels of mesdopetam.
- To evaluate the effects of mesdopetam on severity of ON-phase dyskinesia and motor symptoms of PD.
- To evaluate the effects of mesdopetam on the daily hours spent in different motor states.
- To evaluate the safety and tolerability of mesdopetam given twice daily during 84 consecutive days.
- To evaluate trough and 2-hour post dose plasma concentrations of mesdopetam and its two main metabolites (IRL902 (N-dealkylated) and IRL872 (acetylated)).

2.3 Exploratory Objectives

- To assess overall PD symptoms.
- To assess cognitive function.

3 ENDPOINTS

3.1 Primary Efficacy Endpoint

- Change in average daily hours of ON-time without troublesome dyskinesia with mesdopetam compared to placebo as assessed with 24-hour patient home diaries from baseline to end of treatment (EOT) (Visit 5, Week 12).

3.2 Key Secondary Efficacy Endpoints

- Change from baseline with mesdopetam compared to placebo in ON-phase dyskinesia assessed by MDS-UPDRS part 4 question 4.2 (Functional impact of dyskinesias).
- Change from baseline with mesdopetam compared to placebo in disability associated with ON-phase dyskinesia assessed with the sum score of parts 1b and 4 of the UDysRS.

3.3 Other Key Secondary Efficacy Endpoints

- Change from baseline with mesdopetam compared to placebo in motor symptoms of PD assessed with MDS-UPDRS total score of part 2 (M-EDL).
- Change from baseline with mesdopetam compared to placebo in average daily OFF-time.

3.4 Other Secondary Efficacy Endpoints

- Change from baseline in average daily hours spent in each motor state (ON-time without troublesome dyskinesia, ON-time with troublesome dyskinesia, OFF, and asleep) for each individual dose level (2.5 mg, 5 mg, 7.5 mg b.i.d.).
- Change from baseline with mesdopetam compared to placebo in ON-phase dyskinesia assessed with the sum score of the modified UDysRS (parts 1, 3 and 4).
- Change from baseline with mesdopetam compared to placebo in ON-phase dyskinesia assessed by MDS-UPDRS part 4 question 4.1 (Time spent with dyskinesias).
- Change from baseline with mesdopetam compared to placebo in average daily total ON-time (defined as the sum of ON-time with and without troublesome dyskinesia).
- Change from baseline with mesdopetam compared to placebo in Clinician's Global Impression of Severity (CGI-S) of ON-phase dyskinesia.
- Change from baseline with mesdopetam compared to placebo in the total score for the MDS-UPDRS Part 3, Motor Examination.

3.5 Exploratory Efficacy Endpoints

- Change from baseline with mesdopetam compared to placebo in CGI-S of overall PD symptoms.
- Change from baseline with mesdopetam compared to placebo in Total MMSE score.
- Change from baseline with mesdopetam compared to placebo in the total scores for component parts of the MDS-UPDRS (Part 1, and Part 4).

- Change from baseline with mesdopetam compared to placebo in freezing and freezing of gait, assessed by MDS-UPDRS: Question 2.13 + Question 3.11.

3.6 Safety Endpoints

- Frequency and nature of adverse events (AEs), laboratory results, vital signs, physical examinations, Columbia-Suicide Severity Rating Scale (C-SSRS) and 12-lead electrocardiograms (ECG) at each visit from baseline to follow-up.
- Change from baseline with mesdopetam compared to placebo in features of dopamine dysregulation syndrome assessed by MDS-UPDRS Question 1.6.

3.7 Pharmacokinetic Endpoints

- Plasma concentrations of mesdopetam and its two main metabolites at pre-dose and 2 hours post-dose at 8 and 12 weeks of treatment.

4 SAMPLE SIZE

Analysis of the Phase IIa study Efficacy and Tolerability of IRL790 in 74 PD patients with levodopa-induced dyskinesia (LID) on stable antiparkinsonian medication (NCT03368170) suggested that daily ON-time with troublesome dyskinesia decreased to an observed difference of approximately 1.6 hours (p=0.0274) among treated patients (n=39) versus placebo (n=36). Dose-response analysis suggested a dose dependent effect with an observed difference vs. placebo around 4.6 h at the 7.5 mg dose. A pooled standard deviation of 3.2-3.3 hours was observed among the doses studied. This observed data provided the assumptions for the sample size calculation.

140 randomized patients (35 per group) are thought to be enough to demonstrate a treatment difference of 3 hours with pooled standard deviation 3.5, between a single dose level of active treatment and control (i.e., 2.5 mg, 5 mg, or 7.5 mg mesdopetam vs placebo b.i.d.) for the primary endpoint with 92% power using a hierarchical testing strategy, with key secondary endpoints tested using a truncated Hochberg procedure with truncation parameter γ equal to 0.7 for the 7.5 and then the 5 mg doses and a standard Hochberg procedure for the 2.5 mg dose to maintain control of the family wise error rate (FWER) at the nominal 0.05 level.

The sample size calculation was based on an expected dropout rate of 10%, i.e., assuming 31 patients per group will provide evaluable data on the primary endpoint at Week 12. The actual dropout rate was evaluated by the Sponsor after 70 randomized patients had completed Visit 3 (Week 4) and due to a higher-than-expected dropout rate, it was decided to increase the sample size to 154 (+10%) randomized patients as permitted by the protocol.

5 RANDOMIZATION

At the baseline visit (Visit 1, Day 1) patients will be randomized 1:1:1:1 to receive one of three doses of mesdopetam (2.5 mg, 5 mg, or 7.5 mg) or placebo b.i.d. based on the randomization schedule prepared by the unblinded statistician.

During the first week (Day 1 evening dose to Day 9 morning dose) a run-in phase with either 5 mg mesdopetam or placebo b.i.d. will take place, during which all patients allocated to mesdopetam will receive 5 mg mesdopetam b.i.d. and patients allocated to placebo will receive placebo b.i.d. The purpose of the run-in period with 5 mg b.i.d. is to allow for a one-week dose titration for patients randomized to 7.5 mg b.i.d. In a previous Phase 2a study most patients tolerated 5 mg b.i.d. At Visit 2 (Day 9), patients will receive mesdopetam 2.5 mg, 5 mg or 7.5 mg or placebo b.i.d., as randomized.

Randomization will be performed via a web-based Interactive Response System (IRS), using a dynamic balancing (minimization) algorithm. Randomization will be stratified by average (based on at least two valid home diaries) of <6 daily hours and ≥6 hours of daily ON-time with troublesome dyskinesia at baseline.

During the one-week run-in phase, the IRS will ensure all patients allocated to mesdopetam treatment will receive 5 mg mesdopetam b.i.d., followed by the randomized dose during the treatment period. Patients allocated to placebo will receive placebo during the first week run-in and then continue placebo during the whole treatment period. Any dose reduction will also be managed through the IRS to ensure that blinding is maintained.

6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be definitive and the final Clinical Study Report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Sets

6.1.1 Safety Analysis Set

The Safety Analysis Set (SAS) will include all randomized patients who received at least 1 dose of IMP. All safety and tolerability evaluations will be presented by the treatment received for the SAS.

6.1.2 Full Analysis Set

The Full Analysis Set (FAS) will include all randomized patients who received at least 1 dose of IMP and who provided at least one valid post baseline diary. All efficacy analyses will be presented by randomized treatment for patients in the FAS.

6.1.3 Per Protocol Set

The Per Protocol Set (PPS) will consist of patients from the FAS without protocol deviations that impact the efficacy assessment. Situations which impact the efficacy assessment may include (but are not limited to) those patients who:

- Did not satisfy all of the inclusion/exclusion criteria
- Any patients with treatment administration errors
- Any patients taking inadmissible concomitant medications

Patients who are to be included or excluded from the PPS will be identified and listed following a Blind Data Review (BDR) performed prior to the conclusion of the clinical investigation, database lock and unblinding. Any deviation considered to have a serious impact on the efficacy results will lead to the relevant patient being excluded from the PPS. Any patient exclusions from PPS will be documented in a patient evaluability document before database lock.

6.1.4 Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all randomized patients who received at least 1 dose of IMP and who have at least one evaluable PK concentration data.

6.1.4.1 CYP Genotype Subset

The CYP Genotype Subset will be a subset of the PK Analysis Set including patients who consented to genotyping with respect to CYP2D6 and who received a genotype classification result.

6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.2.1 Race

Where more than one race category has been selected for a patient, these race categories will be combined into a single category labelled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

6.2.2 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the patient receives the first dose of study drug.

6.2.3 Early Withdrawal Assessments

Early withdrawal assessments will be summarized as a separate visit and will be mapped to an expected visit window as follows:

- During the run-in period
- Post run-in and prior to visit 3
- At visit 3 or post visit 3

6.2.4 Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of study drug.

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose

6.2.5 Conventions for Missing and Partial Dates

All rules explained below for partial / missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual patient listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

Missing and partial start and stop dates will be imputed to identify treatment-emergent AEs and concomitant medications as follows.

Partial or missing stop date will be imputed as follows:

- If the stop date is completely missing and the event has resolved, or the patient has stopped taking the concomitant medication, the stop date will be imputed as the date of the patient's last clinic visit in the study.
- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the patient's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the patient's last clinic visit in which case the date of patient's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the patient's screening date or the stop date of the event / concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as the date of the first dose of study drug. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.
- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

If the start time is missing it will be imputed only in the case where the start date of the concomitant medication / event corresponds to the date of the first dose of study drug. The time will be imputed as the same time as the first dose of study drug. In all other cases the time will not be imputed.

6.2.6 Missing Last Dates of Study Drug Dosing

If the date of last dose of study drug is completely missing, then the date of last dose of study drug will be taken for analysis purposes as the date when the patient would have run out of study drug assuming full compliance from the date the study drug was last dispensed, or the date of patient's last clinic visit in the study or early termination or death whichever the earlier.

If only the month and year of the last dose was recorded, then the date of last dosing will be taken for analysis purposes as the date the patient would have run out of study drug assuming full compliance from the date the study drug was last dispensed, the last day of the month of the recorded last dose or the date of patient's last clinic visit in the study or early termination or death whichever the earlier.

6.2.7 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.2.8 Electrocardiogram Data

For electrocardiogram (ECG) data recorded on continuous scales, if more than one value is recorded at a time point, the mean value (taken from the non-missing values) rounded to the integer will be presented. For overall interpretation, if more than one value is recorded, the most severe (worst case) of the respective readings will be taken.

6.2.9 Vital Signs

For blood pressure and pulse rate, the orthostatic changes will be calculated as standing minus supine readings. Patients meeting the following criteria will be identified:

- Patients with > 20 mmHg reduction (standing minus supine) in systolic blood pressure at 1 minute or 3 minutes of standing.
- Patients with > 10 mmHg reduction (standing minus supine) in diastolic blood pressure at 1 minute or 3 minutes of standing.

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

The following outcomes are C-SSRS categories and have binary responses (yes / no). The categories have been re-ordered from the actual scale to facilitate the definition of composite endpoints:

Category 1	Wish to be Dead
Category 2	Non-specific Active Suicidal Thoughts
Category 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5	Active Suicidal Ideation with Specific Plan and Intent
Category 6	Preparatory Acts or Behaviour
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non-fatal)
Category 10	Completed Suicide

Suicidal Ideation since baseline – A “yes” answer at any time during double blind treatment to any one of the 5 suicidal ideation questions (categories 1-5) on the C-SSRS.

Suicidal Behaviour since baseline – A “yes” answer at any time during double blind treatment to any one of the 5 suicidal behaviour questions (categories 6-10) on the C-SSRS.

There will be no imputation of missing data for C-SSRS.

6.2.11 Unscheduled Visits

Only scheduled post-baseline assessments will be summarized and tabulated. Post-baseline repeat or unscheduled assessments will not be tabulated but will be included in listings of individual patient data.

6.2.12 24-Hour Patient Home Diary

Patients will complete the 24-hour home diary on 3 separate days during the week preceding a visit. Patients will record their motor function in 30-minute intervals over 24-hours, beginning at midnight. For each 30-minute interval, the patient will rate the motor state he or she has been in for the past 30 minutes. Diary data will then be transcribed to the CRF by the clinic staff (ON without troublesome dyskinesia, ON with troublesome dyskinesia, OFF, Asleep, Missing entry, Invalid entry).

6.2.12.1 Motor States

Variables will be obtained from the diary data as follows:

- ON-Time without troublesome dyskinesia
- ON-Time with troublesome dyskinesia
- Total ON-Time (ON-Time with and without troublesome dyskinesia)
- OFF-Time
- Asleep
- Missing (or invalid) entry (missing + invalid)

'ON' time is also referred to as 'good ON time' and is considered equivalent to 'ON time without troublesome dyskinesia'.

6.2.12.2 Identification of a Valid Diary

A valid diary will not have ≥ 2 hours of invalid data entries (i.e., ≥4 invalid entries) over a given 24-hour period. An invalid diary entry is defined as one having either more than one entry recorded in each half-hour interval, an unreadable entry, or the absence of an entry in a half-hour interval. The average diary information from 3 valid diaries (if available) for each visit will be used to calculate diary-based efficacy endpoints. If there are only 2 valid diaries for a visit, then the

average information from the 2 valid diaries will be used. If only one diary is valid, information from the single valid diary will be used. If no valid diaries are available for a patient visit, then the diary information is considered missing.

Therefore, a Valid diary = diary where Missing + Invalid < 4 intervals. Diaries where Missing + Invalid $\geq$ 4 intervals will be excluded from the analysis.

6.2.12.3 Total Daily Hours in Each Motor State

Total daily hours for each motor state will be calculated as follows,

Total daily hours = Number of 30-minute intervals with corresponding motor state / 2

6.2.13 Modified Unified Dyskinesia Rating Scale (UDysRS)

The modified Unified Dyskinesia Rating Scale (UDysRS) consists of two primary sections, Historical and Objective. For this study, Part 1 (On-Dyskinesia) of the Historical section will be administered, and Part 2 (Off-Dystonia) will be omitted. The Objective section consists of Part 3 (Impairment) and Part 4 (Disability) including a total of 11 items, each rated 0-4, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe. The subtotals of the Objective parts are summed to give an overall score.

For efficacy analyses, the scores from the following parts will be analysed:

- Parts 1, 3, and 4 (sum score)
- Parts 1b and 4 (sum score)

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

The Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) consists of four parts:

- Part 1, non-motor aspects of experiences of daily living [nM-EDL] (13 items)
- Part 2, motor aspects of experiences of daily living [M-EDL] (13 items)
- Part 3, motor examination (18 items)
- Part 4, motor complications (6 items)

Each item is rated 0-4, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

For efficacy analyses, the scores from the following parts will be analysed:

- Part 1 nM-EDL (13 items) (total score)
- Part 2 M-EDL (13 items) (total score)
- Part 3 Motor Examination (18 items) (total score)
- Part 4 Motor Complications (6 items) (total score)
- Question 1.6 Features of Dopamine Dysregulation Syndrome (1 item) (score)
- Questions 2.13 Freezing + Question 3.11 Freezing of Gait (2 items) (sum score)
- Question 4.1 Time Spent with Dyskinesias (1 item) (score).
- Question 4.2 Functional Impact of Dyskinesias (1 item) (score)

6.2.15 Definition of a Responder

Patients who achieve any improvement (that is, at least 1 hour increase) in average daily ON-time without troublesome dyskinesia at Week 12 will be considered 'responders' and 'non-responders' (less than 1 hour increase) otherwise. Patients with missing data at Week 12, or who withdrew prior to Week 12 will be classified as non-responders.

6.2.16 Definition of Adjusted Dose Group

To account for patients who have a permitted dose reduction and remain stable thereafter, adjusted dose groups will be defined. Patients randomly allocated to mesdopetam and who had a permitted dose reduction of 2.5 mg recorded at Visit 3, will be counted in the treatment group one dose lower than their randomized treatment. Patients randomly allocated to placebo but who had a dose reduction will remain in the placebo group.

6.3 Conventions

6.3.1 Medical Coding

Adverse events and medical history will be coded using the Medical Dictionary of Regulated Activities (MedDRA) Version 24.1 (or higher). Conditions will be assigned to a System organ class (SOC) and preferred term (PT) based on the Investigator-reported verbatim term.

Any medications taken (other than study drug) will be coded using the World Health Organization Drug Dictionary (WHO Drug) September 2021 Version (or higher). Medications (both prior and

concomitant) will be assigned to an Anatomical Therapeutic Chemical (ATC) Level 4 drug classification and Preferred Name based on the medication name reported on the eCRF.

6.3.2 Data Handling

All clinical data programming will be performed using SAS® statistical software package (Statistical Analysis System, Version 9.4 or higher)[1] and based on Clinical Data Interchange Standards Consortium (CDISC) data standards.

6.3.3 Validation Methods

All programming of datasets and outputs will be validated by fully independent double programming of values and manual review of format compared to the SAP and agreed shell template. Figures will be validated by manual review of format and visual inspection of graphical display compared to tabulated data. Independent programming (IP) by a Statistician (Stat IP) will be performed for all statistical analyses.

6.3.4 Summary Statistics

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

Plasma concentration data will be summarized by number of non-missing observations (n), number of observations with concentrations below the limit of quantification (BLQ), arithmetic mean (mean), geometric mean, standard deviation (SD), median, minimum (min), maximum (max), and coefficient of variation (CV%). Concentrations that are BLQ will be set to zero for summary statistics. BLQ concentrations will be retained as BLQ in listings.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the patient population unless otherwise specified. For each variable, all categories will be shown, including a category for missing where appropriate. Zero frequencies (but not the percent) within a category will be presented.

Incidences of adverse events, medical history and concomitant medications will be reported at the patient level. Patients can only be counted once within each PT and SOC under the highest severity and most related. Percentages will be calculated using the number of patients in the treatment group for the SAS. AE and medical history event tabulations will be presented by SOC and PT in

descending overall frequency of incidence and then alphabetically for ties. Medications will be tabulated by ATC level 4 and preferred name in alphabetical order.

6.3.5 Decimal Places

Decimal places for derived data described in Section 6.2 will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement. Two decimal places will be displayed for the calculation of average daily hours in each motor state.

For summary statistics, n will be reported as a whole number. Means, medians, and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place. P-values will be quoted to 3 decimal places. P-values < 0.001 will be presented as p<0.001 unless otherwise specified. Plasma concentration data will be reported to 3 significant figures.

All data presented in the individual patient listings will be as recorded on the eCRF.

6.3.6 Data Displays

All observed data and change from baseline to scheduled post-baseline visits will be summarized unless otherwise specified. All collected data will be listed.

All clinical data tabulations, figures and listings will be generated as individual Rich Text Format (.rtf) files using SAS® (Version 9.4 or higher)[1]. Data summaries and graphical analyses will be reported within Section 14 of the CSR and individual patient data listings within Appendix 16.2 of the CSR.

Patient disposition, baseline characteristics, demographic, compliance, concomitant medication, and adverse event data will be presented by treatment group and overall. All other data will be presented by treatment group only.

Treatment group labels will be displayed as follows:

Mesdopetam 2.5 mg b.i.d. (N=XX)	Mesdopetam 5 mg b.i.d. (N=XX)	Mesdopetam 7.5 mg b.i.d. (N=XX)	All Mesdopetam (N=XX)	Placebo b.i.d. (N=XX)

Listings will be sorted in the following order: treatment group, patient, visit, and parameter, unless otherwise stated. All collected data will be listed.

6.4 Patient Disposition

Patient disposition will be summarized by randomized treatment group and overall, as follows:

- The number of patients entering the study.
- The number of patients completing the study
- The number of patients with early termination and the reasons for early termination.
- The number of patients who were screened, who were re-screened, and who failed screening, with the reason for screen failure (for re-screened patients, the most recent reason for screen failure will be taken).
- The number of patients in each analysis set.
- The number of patients excluded from the PPS and the reason for exclusion.
- The number of patients in each analysis set by country.
- The number of patients attending each visit.
- The number of patients with missed or remote visits due to COVID-19.

By-patient listings of all disposition data will be presented for all enrolled patients as follows:

- Study completion or early termination and reason for early termination.
- Randomization details including randomization stratum.
- Screening, re-screening and reason for screen failure.
- Inclusion in analysis sets.
- Missed or remote visits due to COVID-19.

6.5 Protocol Deviations

All reported protocol deviations (PDev) will be summarized by treatment group, PDev category and PDev classification (Major and Minor). PDevs related to COVID-19 will also be summarized

separately. All reported PDevs will be listed, and a separate listing of PDevs related to COVID-19 will be provided.

6.6 Baseline Comparability

Comparability of treatment groups with respect to patient demographics and baseline characteristics will be assessed in a descriptive manner.

Demographic and baseline characteristic summaries will be presented by treatment group and overall, based on the randomized treatment group for the FAS and the SAS. If these sets are equal, only the FAS will be presented. All collected data will be listed. Summaries will be presented for the following variables:

Demographic Data

- Age at Screening (years)
- Age by category (< 65 years and ≥ 65 years)
- Gender
- Fertility status (female only)
- Ethnicity
- Race (where more than one race is selected the patient will be presented under the 'Multiple races' category in the summary but each selected race will be identified in the listing).

Baseline Characteristics

- Weight at Screening (kg)
- Height at Screening (cm)
- BMI at Screening (kg/m^2)

Clinical Characteristics

- Hoehn and Yahr Scale
- Years from PD diagnosis at baseline and will be calculated as follows: Years from PD Diagnosis at Baseline = (Day 1 – Start Date of PD from the medical history) / 365.25. If the start date of PD is partial, then only year portion will be used for calculation and will follow Section 6.3.5 for rounding of decimals
- Average levodopa dose based on evaluable reported usage (in mg) taken on or after first dose of study drug

- ON-time (hours) with troublesome dyskinesia
- Randomisation strata (<6 hours or ≥6 hours of ON-time with troublesome dyskinesia)
- MDS-UPDRS question 4.2 score (functional impact of dyskinesias)
- MMSE at Baseline
- Physical examination by body system at baseline

6.7 CYP Genotyping

The number and percent of patients consenting to CYP2D6 genetic testing as well as the number and percent of patients within each genotype category (poor, intermediate, normal, and ultrarapid metabolizer) will be summarized by treatment group and overall, for the PK set. Consent date, blood sample collection data and all reported genotyping data will be listed separately for patients consenting to CYP2D6 genetic testing.

6.8 Medical History

Separate tabulations of prior and ongoing conditions at screening will be presented by treatment group and overall, for the SAS. Prior conditions are those with a stop date prior to screening and conditions are ongoing otherwise. Tabulations will be presented by SOC and PT in descending frequency of incidence in the pooled mesdopetam arm and then alphabetically for ties. All reported medical history will be listed.

6.9 Prior and Concomitant Medications

Prior medications are defined as any medications starting and stopping prior to date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug.

Prior and concomitant medications will be presented alphabetically by ATC Level 2 classification followed by ATC level 4 classification and Preferred Name for each treatment group in the SAS.

A separate tabulation will also be provided for all medications reported under ATC Level 1 = Nervous System, Level 2 = Anti-Parkinson Drugs. Medications will be presented by ATC Level 3 and Preferred Name by treatment group and overall.

Average levodopa dose will also be obtained from the medication log. The first reported levodopa dose taken on or after first dose of study drug will be summarized per treatment group alongside clinical characteristics.

All reported medications will be listed. Medication logs will also be reviewed by the Sponsor and any non-permitted medications will be identified and listed separately.

6.10 Exposure to Study Drug

Exposure to study drug will be calculated as follows from the date of last dosing minus the first day of dosing + 1. The exposure calculation will not take into account breaks in therapy.

Exposure to each dose level will be calculated as follows:

Exposure	Calculation
Exposure to 5 mg during run-in period (all patients)	Dispensing Date (Visit 2, Day 9) – Date of First Dose + 1
Exposure to randomized dose if the patient did not have a dose reduction	Date of Last Dose – Dispensing Date (Visit 2, Day 9) + 1
Exposure to randomized dose if the patient had a dose reduction	First dispensing date where dose is different to randomized dose – Dispensing Date (Visit 2, Day 9) + 1
Exposure to adjusted dose if the patient had a dose reduction	Date of Last Dose – First dispensing date where dose is different to randomized dose + 1 (programming checks should be made to ensure the adjusted dose was also dispensed at Visit 3, Day 28)

In the rare case that a kit was dispensed containing the wrong dose then those records will be excluded from calculations.

Extent of exposure (number of days of exposure to study drug) will be presented by each treatment group and combined based on the randomized treatment. A separate tabulation will also be provided to present the exposure during the run-in period and the period after receiving the randomized dose.

All reported data will also be listed.

6.11 Treatment Compliance

Treatment compliance will be calculated as follows:

- Compliance (%) = (Actual number of doses taken / Expected number of doses) *100

The actual number of doses = Sum of quantity dosed across all records.

The expected number of doses is obtained as follows:

- If the last dose is a morning dose: [(End of treatment (Visit 5) date – Date of first dose – 1) * 2] + 2
- If the last dose is an evening dose: [(End of treatment (Visit 5) date – Date of first dose – 1) * 2] + 3

The expected number of doses is obtained by first calculating the number of full days on study treatment and multiplying by 2 doses per full day per protocol. Then one dose is added for the Day 1 evening dose and either one dose is added if the last dose was a morning dose, or two doses are added if the last dose was an evening dose.

Compliance (%) will be summarized by treatment group, combined treatment groups, and overall based on the actual treatment received for the SAS and will be presented following the decimal convention in Section 6.3.5. The number and percent of patients with compliance <80% will also be provided by treatment group, combined treatment groups, and overall.

All drug accountability data will be listed as recorded on the eCRF.

6.12 Primary Efficacy Analyses

All applicable statistical tests will be performed at a local significance level consistent with an overall FWER of 5% and the multiple testing strategy described in Section 0. All comparisons between treatments will be reported with 95% confidence intervals (CI) for the difference. All efficacy analyses will be performed by randomized treatment group and adjusted dose group for patients in the FAS, as well as all active doses grouped compared to placebo.

6.12.1 Estimand

The main study estimand will follow the ‘treatment policy’ strategy to estimate the treatment effect of mesdopetam (2.5 mg, 5 mg, or 7.5 mg b.i.d.) compared to placebo b.i.d. (treatment) on the

change from baseline to Week 12 (population-level summary) in average daily ON-time (hours) (variable) in patients with Parkinson's Disease exhibiting ON-phase dyskinesia, as defined by the inclusion/exclusion criteria (population) regardless of missing motor diary data, any permitted dose reduction, use of amantadine (if any), or discontinuation for any reason.

6.12.2 Primary Endpoint

The primary endpoint is the change from baseline to Week 12 in average daily hours of ON-time without troublesome dyskinesia with mesdopetam compared to placebo as assessed with 24-hour patient home diaries.

The hypothesis that will be tested is as follows:

$$H_0 = \mu_{mesdopetam} - \mu_{placebo} = 0 \qquad \text{versus} \qquad H_1 = \mu_{mesdopetam} - \mu_{placebo} \neq 0$$

Where $\mu_{mesdopetam}$ denotes the mean change from baseline to Week 12 in the mesdopetam treatment group (2.5 mg b.i.d., 5 mg b.i.d., or 7.5 mg b.i.d.), and $\mu_{placebo}$ denotes the mean change from baseline to Week 12 in the placebo group.

The null hypothesis is that there is no difference between mesdopetam and placebo for the primary efficacy endpoint and the alternative hypothesis is that there is a difference between mesdopetam and placebo for the primary efficacy endpoint.

6.12.3 Primary Analysis

The number and percent of patients with valid diaries will be tabulated by treatment group and visit and a listing of diary completion will be provided. Descriptive statistics for the actual values by visit (including baseline) and change from baseline to each post-baseline visit (Visits 3, 4 and 5/EOT) in average daily ON-time without troublesome dyskinesia (hours) will be presented.

Change from baseline in average daily ON-time without troublesome dyskinesia (hours) will be analysed using a mixed model for repeated measures (MMRM) for all patients in the FAS. Change from baseline to Week 12 is the timepoint of interest for this analysis. Any missing data is assumed to be missing at random (MAR) for this analysis.

The model will include randomized treatment (2.5 mg, 5.0 mg, 7.5 mg, or placebo b.i.d.), visit, country, and treatment by visit interaction as explanatory, fixed effect variables. Country will be

weighted by the number of patients participating from each county. Baseline value for average daily hours of ON time without troublesome dyskinesia will be included as a continuous covariate along with the randomisation stratification factor of daily hours spent in ON-time with troublesome dyskinesia (<6 hours, ≥6 hours).

An unstructured covariance matrix will be assumed for within-patient correlation over time. If the model fails to converge, the first approach for which the model converges among the following will be used: banded Toeplitz (TOEP), compound symmetry (CS) and variance component (VC).

The LS mean estimate, corresponding SE, and 95% CI for the change from baseline at each post-baseline visit will be obtained from the model and presented for each treatment group. The estimated treatment difference for each dose level compared to placebo and the combined dose levels compared to placebo, the corresponding SE, and p-value will also be presented by visit.

A line plot showing the LS mean (±95% CI) change from baseline at each visit for each treatment group will also be provided.

The following is the sample SAS code that will be used for this analysis:

```
PROC MIXED DATA= analysis (where = (avisitn ne 0));
    ODS OUTPUT LSMeans=LSMeans Diffs=Diffs LSMEstimates=Estimates;
    CLASS USUBJID STRATF TRT01PN AVISITN COUNTRY;
    MODEL CHG = BASE STRATF TRT01PN AVISITN COUNTRY TRT01PN*AVISITN / DDFM=KR
s;
    REPEATED AVISITN / SUBJECT=USUBJID TYPE=UN;
    LSMEANS TRT01PN*AVISITN / CL DIFF OM;

    LSMESTIMATE TRT01PN*AVISITN 'Difference at Week 4' 1 0 0 1 0 0 1 0 0 -3 0
0 divisor = 3 / CL e OM;
    LSMESTIMATE TRT01PN*AVISITN 'Combined at Week 4' 1 0 0 1 0 0 1 0 0 0 0 0
divisor = 3 / CL e OM;
    LSMESTIMATE TRT01PN*AVISITN 'Placebo at Week 4' 0 0 0 0 0 0 0 0 0 3 0 0
divisor = 3 / CL e OM;

    LSMESTIMATE TRT01PN*AVISITN 'Difference at Week 8' 0 1 0 0 1 0 0 1 0 0 -3
0 divisor = 3 / CL e OM;
    LSMESTIMATE TRT01PN*AVISITN 'Combined at Week 8' 0 1 0 0 1 0 0 1 0 0 0 0
divisor = 3 / CL e OM;
    LSMESTIMATE TRT01PN*AVISITN 'Placebo at Week 8' 0 0 0 0 0 0 0 0 0 0 3 0
divisor = 3 / CL e OM;

    LSMESTIMATE TRT01PN*AVISITN 'Difference at Week 12' 0 0 1 0 0 1 0 0 1 0 0
-3 divisor = 3 / CL e OM;
```

```
    LSMESTIMATE TRT01PN*AVISITN 'Combined at Week 12' 0 0 1 0 0 1 0 0 1 0 0 0
divisor = 3 / CL e OM;
    LSMESTIMATE TRT01PN*AVISITN 'Placebo at Week 12' 0 0 0 0 0 0 0 0 0 0 0 3
divisor = 3 / CL e OM;

RUN;
```

Where USUBJID = Subject Number; TRT01PN = Planned Treatment Group Number; AVISITN = Visit Number; BASE = Baseline Value; CHG = Change from Baseline Value; COUNTRY = Country; STRATF = Stratification Factor.

6.12.4 Sensitivity Analyses

6.12.4.1 Pattern-Mixture Model

To assess the robustness of the results to deviations from the MAR assumption in the primary analysis, a sensitivity analysis will be conducted such that non-monotone missing data is imputed under the MAR assumption while the monotone missing data is imputed under the missing not at random (MNAR) assumption (i.e., that missingness is also dependent on the unobserved variable values).

This analysis will therefore provide a stress test of the MAR assumption in the primary analysis and will provide a conservative estimate of the treatment effect.

The pattern-mixture modeling will be implemented by first turning the non-monotone missing data pattern into a monotone missing pattern under the MAR assumption using the Markov Chain Monte Carlo (MCMC) method in SAS' PROC MI with the IMPUTE = MONOTONE and the PRIOR = JEFFREYS options to specify a non-informative prior for the imputation process. Then the MONOTONE statement along with the MNAR statement with option MODEL in SAS' PROC MI will be utilized to implement the MNAR assumptions and control-based pattern imputation[2,3]. The inference of this sensitivity analysis will be based on the combined estimates using the standard multiple imputation technique via Rubin's[4] rules.

Missing data will be imputed using a pattern-mixture model approach that uses a control-based pattern imputation. With this approach, patients who discontinued from active treatment groups will be assumed to follow a similar outcome trajectory as patients from the placebo (control) group, and patients who discontinued from placebo (control) group are modeled as completers within their own group (MAR within control group). That is, the imputation model for the missing observations in the active treatment groups is constructed not from the observed data in the active treatment groups, but rather from the observed data in the placebo group. This model is also the

imputation model that will be used to impute missing observations in the placebo group. The missing values for each variable will be imputed based on a model simulated from the posterior predictive distribution of the conditional regression model fitted on the imputed variable using only the observations from the placebo group.

This will be implemented by utilizing the MONOTONE REG statement and MNAR statement with option MODEL of SAS' PROC MI with options nimpute = 20 and seed = 32641726.

The following is the sample SAS code that will be used to implement the control-based pattern mixture imputation:

```
PROC MI DATA=DATAIN OUT=DATAIN_MONO SEED=32641726 NIMPUTE=1;
BY TRT01PN;
VAR BASE ONHOURS3-ONHOURS5;
MCMC CHAIN=MULTIPLE IMPUTE=MONOTONE PRIOR = JEFFREYS;
RUN;

PROC MI DATA= DATAIN_MONO SEED=32641726 NIMPUTE=20
OUT=DATA_IMPUTED;
CLASS TRT01PN STRATF;
MONOTONE REG(BASE ONHOURS3-ONHOURS5);
MNAR MODEL(ONHOURS3-ONHOURS5 / MODELOBS=(TRT01P='Placebo'));
VAR STRATF BASE ONHOURS3-ONHOURS5;
RUN;
```

Once the missing diary data has been imputed for all visits, the change from baseline at each visit will be calculated and consequently will be analysed using the same MMRM model employed in the primary analysis for each iteration of the imputed dataset.

Then the results are to be summarized using PROC MIANALYZE, where the treatment group LS means and their differences between treatments will be combined across all 20 imputed datasets:

```
PROC SORT DATA= LSMEANS; BY TRT01PN AVISITN _IMPUTATION_; RUN;

PROC MIANALYZE DATA= LSMEANS;
MODELEFFECTS ESTIMATE;
STDERR STDERR;
ODS OUTPUT PARAMETERESTIMATES= LSMEANS_COMB;
BY TRT01PN AVISITN;
RUN;
```

```
PROC SORT DATA= DIFFS; BY TRT01PN; RUN;

PROC MIANALYZE DATA= DIFFS(WHERE=(AVISITN=_AVISITN));
MODELEFFECTS ESTIMATE;
STDERR STDERR;
ODS OUTPUT PARAMETERESTIMATES= DIFFS_COMB;
BY TRT01PN AVISITN;
RUN;
```

LS means, SEs, and 95% CIs for each treatment group based on the imputed data will be presented at each week as well as the estimate of treatment difference, SE, and p-value at each week with Week 12 as the primary timepoint of interest.

6.12.4.2 Tipping Point Analysis

If the primary efficacy analysis significantly favours mesdopetam, a tipping-point sensitivity analysis for the primary efficacy endpoint will be conducted on the significant dose groups to investigate how severe the departure from the MAR assumption must be to overturn the conclusion from the primary analysis. In this analysis, the assumption will be that missing data in the active treatment groups follows a MNAR pattern.

A tipping-point approach will be used such that the trajectories of the patients in the active treatment groups after early termination from study are assumed to be worse than placebo by a fixed amount (δ). Missing values will first be imputed using a MAR approach and then the value of δ will be deducted from all imputed values occurring after early termination for patients in the active treatment groups only. The value of δ will be applied in increments of 0.5 hours (i.e., 0.5h, 1h, 1.5h, 2h) up to the point at which the treatment difference at Visit 5 (Week 12) is no longer statistically significant at the local level (see Section 0). This analysis provides a measure of the degree by which the patients in the active treatment groups who discontinued early would need to be worse, compared to patients with similar trajectories up to the point of discontinuation in the same treatment arm, at each post-discontinuation visit for the null hypothesis of no treatment difference to no longer be rejected.

6.12.4.3 Modified stratification factor

The analysis of the primary endpoint will be repeated using the modified stratification factor in the mixed model for repeated measures (MMRM) on the randomised dose group.

6.12.5 Supportive Analyses

6.12.5.1 Per Protocol Analysis

The per protocol analysis will follow the same analysis method as the primary analysis, with the exception that the analysis will be based on the PPS.

6.12.5.2 ANCOVA Analysis

An analysis of covariance (ANCOVA) will also be performed using the FAS. The ANCOVA model will be adjusted for the following covariates: randomized treatment, baseline value for average daily hours of ON time without troublesome dyskinesia (continuous covariate), as well as randomisation stratification factor for daily hours spent in ON-time with troublesome dyskinesia (<6 hours, ≥6 hours). The dependent variable is the change from baseline in average daily ON-time (hours) at Week 12. Missing observations will not be imputed.

The LS means, SEs, and 95% CIs will be provided for each treatment group, as well as treatment difference estimates, SEs, and p-values for each dose level and combined dose groups compared to placebo.

The following is the sample SAS code that will be used to implement this analysis:

```
PROC MIXED DATA= DATAIN;
CLASS TRT01PN STRATF;
MODEL CHG_WEEK12 = TRT01PN BASE STRATF / SOLUTION;
LSMEANS TRT01PN / CL DIFF OM;

LSESTIMATE TRT01PN "Difference at Week 12" 1 1 1 -3 / CL e OM;

LSESTIMATE TRT01PN "Combined at Week 12" 1 1 1 0 / CL e OM;
RUN;
```

Where TRT01PN = Planned Treatment Group Number; BASE = Baseline Value; CHG_WEEK12 = Change from Baseline at Week 12; STRATF = Stratification Factor.

6.12.5.3 Impact of Permitted Dose Reduction

The impact of permitted dose reductions on the primary analysis will be explored.

The change from baseline in average daily ON-time without troublesome dyskinesia (hours) by visit will be analysed and reported (including line plots) using the same MMRM approach as for

the primary analysis, except the adjusted dose groups will be used as the treatment factor and pooled dose will be excluded from tabulations.

LS means, SE, and 95% CI for the change from baseline by treatment group as well as the estimated treatment difference, SE, and p-value for each dose level compared to placebo, will be reported, and compared to the primary analysis at Week 12.

6.12.5.4 Impact of Amantadine Usage

The number and percent of patients taking amantadine treatment during the study (if any) will be presented alongside concomitant medications. If amantadine usage is reported among >5% of patients, the impact of amantadine usage on the primary analysis will be explored. Any diary data collected after commencing amantadine treatment will be discarded and the primary analysis will be repeated for all patients in the FAS, excluding any values obtained after initiation of amantadine.

6.13 Secondary Efficacy Analyses

All secondary efficacy analyses will be performed on the FAS for all dose levels of mesdopetam (2.5 mg b.i.d., 5.0 mg b.i.d., 7.5 mg b.i.d., and pooled) and placebo.

6.13.1 Key Secondary Analyses

6.13.1.1 Functional Impact of Dyskinesia, MDS-UPDRS Question 4.2

Change from baseline with mesdopetam compared to placebo in ON-phase dyskinesia will be assessed by MDS-UPDRS part 4 question 4.2 (Functional impact of dyskinesias).

MDS-UPDRS Question 4.2 will be completed at all in-person visits up to end of treatment. A shift table for the change from baseline in number and percent of patients rated in each score category (0 to 4) will be presented by treatment group and visit. Percentages will be based on the number of patients with non-missing score at baseline and post-baseline for the relevant visit. Descriptive statistics for the score as a continuous measure for observed values and change from baseline to each post-baseline visit will also be provided.

Change from baseline with mesdopetam compared to placebo in MDS-UPDRS Question 4.2 score will be analysed as a continuous variable using a MMRM, conducted in the same manner as for the primary analysis, and reported (including model estimates and line plot) as described in

Section 6.12.3. The analysis will be repeated using the modified stratification factor in the MMRM on the randomised dose group.

6.13.1.2 Disability Associated with ON-Phase Dyskinesia, UDysRS Parts 1b and 4 Sum Score

Change from baseline with mesdopetam compared to placebo in disability associated with ON-phase dyskinesia will be assessed with the sum score of parts 1b and 4 of the UDysRS.

Descriptive statistics for the sum score of parts 1b and 4 and change from baseline by visit will be provided by treatment group. Change from baseline in the sum score of parts 1b and 4 will be analysed and reported (including line plots) in the same manner as for the primary analysis, as described in Section 6.12.3. The analysis will be repeated using the modified stratification factor in the MMRM on the randomised dose group.

6.13.2 Other Key Secondary Analyses

6.13.2.1 Average Daily OFF-Time (Hours)

Any observed changes in the average daily time spent in the OFF-state with mesdopetam compared to placebo will be evaluated. The change from baseline in average daily OFF-time (hours) by visit will be analysed and reported using the same MMRM approach as for the primary analysis, with Week 12 as the timepoint of interest.

The endpoint of interest will be the upper and lower bounds of the 95% CI for estimated difference in LS mean of OFF-time (hours) for mesdopetam dose levels compared to placebo. As the study is not powered to detect equivalence of mesdopetam treatment compared to placebo, the 95% CI will be provided for discussion only and no inference will be made.

6.13.2.2 Motor Symptoms of PD, MDS-UPDRS Part 2 (M-EDL) Total Score

Change from baseline with mesdopetam compared to placebo in motor symptoms of PD will be assessed with the total score obtained from Part 2 of the MDS-UPDRS (M-EDL).

Descriptive statistics for the M-EDL total score (0 to 52) and change from baseline by visit will be provided by treatment group. Change from baseline in M-EDL total score will be analysed and reported (including line plots) in the same manner as for the primary analysis, as described in Section 6.12.3.

6.13.3 Other Secondary Analyses

6.13.3.1 ON-Phase Dyskinesia, Modified UDysRS Parts 1, 3 and 4 Sum Score

Change from baseline with mesdopetam compared to placebo in ON-phase dyskinesia will be assessed with the sum score of the modified UDysRS (parts 1, 3 and 4).

Descriptive statistics for the sum score of parts 1, 3 and 4 and change from baseline by visit will be provided by treatment group. Change from baseline in parts 1, 3 and 4 sum score will be analysed and reported (including line plots) in the same manner as for the primary analysis, as described in Section 6.12.3.

6.13.3.2 Time Spent with Dyskinesias, MDS-UPDRS Question 4.1

Change from baseline with mesdopetam compared to placebo in ON-phase dyskinesia will be assessed by MDS-UPDRS Question 4.1 (Time spent with dyskinesias).

MDS-UPDRS Question 4.1 will be completed at all in-person visits up to end of treatment. A shift table for the change from baseline in number and percent of patients rated in each score category (0 to 4) will be presented by treatment group and visit. Percentages will be based on the number of patients with non-missing score at baseline and post-baseline for the relevant visit. Descriptive statistics for the score as a continuous measure for observed values and change from baseline to each post-baseline visit will also be provided.

Change from baseline with mesdopetam compared to placebo in MDS-UPDRS Question 4.1 score will be analysed as a continuous variable using a MMRM, conducted in the same manner as for the primary analysis, and reported (including model estimates and line plot) as described in Section 6.12.3.

6.13.3.3 Analysis of All Active Doses Pooled Compared to Placebo

All active doses will be pooled into one mesdopetam dose group and will be analysed compared to placebo alongside the individual doses for each of the primary, secondary, and exploratory analyses.

6.13.3.4 Dose Response Relationship with 3 Dose Levels of Mesdopetam

The dose response relationship will be explored by first considering the significance of the treatment effect in the primary model and then by visually assessing the relationship using line plots of LS mean (±95% CI) over time. If a significant effect is observed, a Jonckheere-Terpstra (JT) trend test may be performed using the contrast statement in PROC GLM to construct a T trend statistic to test a one-side hypothesis for increasing trend. If a normal distribution of values is not observed, a non-parametric approach may be pursued. However, if a significant treatment effect is not observed, or there is a significant departure from a linear trend between doses, a test for trend will not be performed.

6.13.3.5 Average Daily Hours Spent in Different Motor States

Descriptive statistics for the average daily hours and change from baseline by visit will be provided for each motor state (ON-time without troublesome dyskinesia, ON-time with troublesome dyskinesia, OFF-time, and asleep). Additionally, average daily total ON-time (defined as the sum of ON-time with and without troublesome dyskinesia) will be summarized. Change from baseline in average daily hours for each motor state will be analysed and reported in the same manner as for the primary analysis, as described in Section 6.12.3.

Boxplots showing the distribution of values (minimum value, first quartile, median, third quartile and maximum value) for each motor state will be presented by treatment group and visit. If the presence of outliers affects the interpretation of the distribution, boxplots showing 1.5* interquartile range (IQR) may be shown.

A line chart showing the change from baseline in mean (±SD) hours spent in each motor state (ON-time without troublesome dyskinesia, ON-time with troublesome dyskinesia, OFF-time) will be presented by treatment group and visit (one panel per visit). A separate line chart will also be presented as above, showing the change in daily total ON-time (defined as the sum of ON-time with and without troublesome dyskinesia) versus the change in daily OFF-time.

A stacked bar chart will be produced showing the mean percentage of time spent in each motor state during the day (ON-time without troublesome dyskinesia, ON-time with troublesome dyskinesia, OFF-time, or asleep) by treatment group and visit (one panel per visit).

6.13.3.6 ON-Phase Dyskinesia, Clinician's Global Impression of Severity

Severity of the patient's ON-phase dyskinesia will be rated by the investigator, considering his or her total clinical experience with the PD population, using the CGI-S scale. Severity will be rated based on a 1–7-point weighted scale ranging from "normal", not at all ill" (1) to "among the most extremely ill patients" (7).

CGI-S of ON-phase dyskinesia will be completed at all in-person visits up to end of treatment, including baseline. A shift table for the change from baseline in number and percent of patients rated in each score category (1 to 7) will be presented by treatment group and visit. Percentages will be based on the number of patients with non-missing score at baseline and post-baseline for the relevant visit. Descriptive statistics for the score as a continuous measure for observed values and change from baseline to each post-baseline visit will also be provided.

Change from baseline with mesdopetam compared to placebo in CGI-S of ON-phase dyskinesia will be analysed as a continuous variable using a MMRM, conducted in the same manner as for the primary analysis, and reported (including model estimates and line plot) as described in Section 6.12.3.

6.13.4 Motor Examination, MDS-UPDRS - Part 3 Total Score

MDS-UPDRS Part 3 total score, will be summarized by treatment group and visit. Change from baseline will be summarised, analysed, and reported (including model estimates and line plot) in the same manner as for the primary analysis, as described in Section 6.12.3.

6.14 Exploratory Efficacy Analyses

All exploratory efficacy analyses will be performed on the FAS for all dose levels of mesdopetam (2.5 mg b.i.d., 5.0 mg b.i.d., 7.5 mg b.i.d., and pooled) and placebo.

6.14.1 Overall PD Symptoms, Clinician's Global Impression of Severity

Severity of the patient's PD will be rated by the investigator, considering his or her total clinical experience with the PD population, using the CGI-S scale. CGI-S of the patient's overall PD symptoms will be completed at all in-person visits up to end of treatment, including baseline. Actual scores and changes in scores will be summarized, analysed, and reported by visit and treatment group as described in Section 6.13.3.6.

6.14.2 Cognitive Function, Mini-Mental State Examination

Descriptive statistics for the MMSE total score at each visit (Baseline, Visit 5 (Week 12)) and the change from baseline will be provided per treatment group.

Change from baseline to Week 12 with mesdopetam compared to placebo in the MMSE total score will be analysed using an ANCOVA. The model will include randomized treatment as a factor, and the baseline value for average daily ON time without troublesome dyskinesia (hours) as a continuous covariate. The LS mean estimate, SE, and 95% CI, for each treatment group as well as the estimated treatment difference for each dose level compared to placebo, corresponding SE and p-value will be obtained from the model.

6.14.3 Improvement in Daily ON-time, Responder Analysis

The number and percent of responders (at least 1h improvement in average daily ON-time) versus non-responders at Week 12 will be tabulated by treatment group.

Each dose level will be compared to placebo using a Cochran-Mantel-Haenszel (CMH) test. The risk difference for each dose level compared to placebo, corresponding 95% CI and p-value for the CMH statistic will be provided.

The following is the sample SAS code that will be used for this analysis:

```
PROC FREQ DATA=DATAIN;
TABLES TRT01PN*RESP / RISKDIFF CMH;
ODS OUTPUT RISKDIFFCOL2 = RISK CMH = CMH_PVAL;
RUN;
```

Where TRT01PN = Planned Treatment Group Number; RESP = Responder (0/1).

6.14.4 MDS-UPDRS: Part 1, and Part 4 Total Scores

MDS-UPDRS Part 1 total score, and Part 4 total score will be summarized separately by treatment group and visit. Change from baseline for each part total score will be summarised, analysed, and reported (including model estimates and line plot) in the same manner as for the primary analysis, as described in Section 6.12.3.

6.14.5 Freezing and Freezing of Gait, MDS-UPDRS: Question 2.13 + Question 3.11

MDS-UPDRS Question 2.13 + Question 3.11 sum score and change from baseline by visit will be provided by treatment group. Change from baseline in question 2.13 + question 3.11 sum score will be analysed and reported (including model estimates and line plot) in the same manner as for the primary analysis, as described in Section 6.12.3.

6.15 Multiplicity

Multiple dose levels have been included in the study design to evaluate the dose-response relationship of mesdopetam with the hypothesis that the 7.5 mg b.i.d. dose will be the most efficacious of the dose levels studied.

Two key secondary endpoints (change from baseline in ON-phase dyskinesia assessed by MDS-UPDRS Question 4.2 and change from baseline in disability associated with ON-phase dyskinesia assessed with the sum score of UDysRS parts 1b and 4) will also be evaluated and thus a strategy for controlling the overall error rate whilst maintaining the planned study power is required.

To such aim, a hierarchical testing strategy will be used whereby first the 7.5 mg b.i.d. will be tested at a 5% level on the primary endpoint, and should the test be significant, the 2 key secondary endpoints will be tested for the 7.5 mg b.i.d. dose using a truncated Hochberg procedure with a truncation parameter $\gamma = 0.7$. This procedure works as follows for $n = 2$ tests:

1) p-values are sorted in ascending order as p_1 and p_2;
2) The largest p-value, p_2, is compared against the modified critical value c_2 below:

$$c_2 = \left[\frac{\gamma}{n-i+1} + \frac{1-\gamma}{n}\right]\alpha = \left[\gamma + \frac{1-\gamma}{2}\right]\alpha = \left[0.7 + \frac{0.3}{2}\right]0.05 = 0.0425$$

(where $n = 2$ and $i = 2$)

3) If $p_2 \leq c_2$ then all key secondary hypotheses are rejected, otherwise the hypothesis associated with p_2 is retained and the other p-value, p_1, is compared against the critical value c_1, which can be obtained from the formula in 2) by replacing i with 1, leading to a critical value of 0.025;
4) If $p_1 \leq c_1$ then the associated hypothesis is rejected, otherwise all hypotheses are retained and no more testing of primary or key secondary hypotheses for the lower doses is performed.

If at least one hypothesis is rejected in the above steps, then the primary endpoint is tested for the 5 mg b.i.d. dose at an alpha level that depends on how many hypotheses were rejected in the truncated Hochberg procedure and the truncation parameter γ.

To derive the amount of alpha level to carry over to the next level of testing, we account for how many hypotheses were rejected:

a) If all or none were rejected, then we carry over, respectively, 0.05 (full α) or 0 (no α);

b) If only one hypothesis were rejected, the amount of alpha to carry forward is given by:

$$((1-\gamma)|I|\alpha)/n \;=\; ((1-0.7)|1|0.05)/2 \;=0.0075$$

Testing of the primary endpoint for the 5 mg b.i.d. dose is then conducted at the specified alpha-level and then, depending on the significance of this test, another truncated Hochberg procedure with the same truncation parameter is conducted for the key secondary endpoints, using the same alpha level carried over to test for the primary endpoint at 5 mg b.i.d. to derive the critical values for the testing using the same formulas shown above.

Once the truncated procedure has been conducted, the same approach to derive the amount of alpha that can be carried forward to the testing of the primary endpoint for the lower dose is then followed. Once this testing is complete, if the primary endpoint is significant at the pre-specified alpha level, the key secondary endpoints are tested using a standard Hochberg procedure, which is conducted similarly to its truncated version but with c_1 and c_2 being equal to $\alpha/2$ and α, respectively (where α is the significance level at which the primary endpoint was tested for the 2.5 mg b.i.d. dose).

An ordered tabulation of the endpoints tested, p-values observed, alpha-level tested against and acceptance or otherwise of the null hypothesis at each stage will be presented.

6.16 Pharmacokinetic Analyses

Plasma concentrations of mesdopetam and its two main metabolites (IRL902 [N-dealkylated] and IRL872 [acetylated]) will be obtained pre-dose and 2 hours post-dose (as an estimate of C_{max}) at Visit 4 (Week 8) and Visit 5 (Week 12).

Concentration data will be summarized by analyte, adjusted dose level, and visit at each scheduled sample time (nominal time) for the PK analysis set, using descriptive statistics. Line plots will also be provided showing mean (SD) by dose level and visit for each analyte.

In addition, concentration data will be summarized by genotype (poor, intermediate, normal, and ultrarapid metabolizer), adjusted dose level, and visit at each scheduled sample time (nominal time) using descriptive statistics and line plots for the CYP Genotype Subset.

All concentration data will be listed.

6.17 Safety Analyses

Safety analyses will be presented by actual treatment group as well as adjusted dose group for all patients in the SAS.

6.17.1 Adverse Events

Adverse events will be collected from the time of informed consent and continues through the last follow-up assessment in the study.

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug through the last follow-up assessment in the study.
- Any pre-existing AE that has worsened in severity on or after the first dose of study drug through the last follow-up assessment in the study.

A treatment-related AE is defined as an AE relationship to study drug classified by the Investigator as ‘possible’, or ‘probable’. If an AE has missing relationship, ‘probable’ will be assumed for analysis purposes.

Severity of the AE will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) grading system (Version 5.0): Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-Threatening), Grade 5 (Fatal). Grade 3 (Severe) will be assumed for an AE with missing grade.

An overall summary table of AE incidence (number and percent of patients) and number of events, will be presented by treatment group and overall, for the following categories:

- Any Reported TEAE

- Treatment-Related TEAEs
- Serious TEAEs
- Serious Treatment-Related TEAEs
- TEAEs Leading to Reduction in Dose of Study Drug
- TEAEs Leading to Interruption of Study Drug
- TEAEs Leading to Withdrawal of Study Drug
- TEAEs Leading to Early Withdrawal from Study
- TEAEs Leading to Death

Summaries of TEAE incidence and number of events by SOC and PT will be presented by treatment group and overall, for the following:

- TEAEs
- Treatment-related TEAEs
- Serious TEAEs
- Serious Treatment-Related TEAEs
- TEAEs by Maximum Grade, (incidence only)
- Treatment-Related TEAEs by Maximum Grade, (incidence only)
- TEAEs by Strongest Relationship, (incidence only)
- Treatment-Related TEAEs by Strongest Relationship, (incidence only)

The following listings of AEs will be presented in Section 14.3.2 of the CSR:

- Serious AEs
- TEAEs Leading to Interruption of Study Drug
- TEAEs Leading to Withdrawal of Study Drug
- TEAEs Leading to Early Termination from Study
- Deaths

TEAE tabulations will be presented by SOC and PT in descending frequency of AE incidence in the pooled mesdopetam arm and then alphabetically for ties.

All reported AEs will be listed in Appendix 16.2.7 of the CSR with separate listings for TEAE and non-treatment-emergent AEs (NTEAE).

Overall ongoing TEAEs will be summarized by month 1, 2, and 3. Additionally, TEAEs that occur in >5% of all participants will be summarized by month 1, 2, and 3.

6.17.2 Laboratory Data

Blood samples for analysis of serum chemistry, haematology and coagulation parameters will be collected at screening, Visit 1 (if 29 days or more between Screening and Visit 1), Visit 4, 5 and 6 and sent to the certified central laboratory for analysis. Urine analysis will be performed at the clinic using dip sticks. Descriptive statistics for observed values and change from baseline will be presented by treatment group and visit for each continuous haematology, serum chemistry (including thyroid panel), and coagulation parameter. A shift table for the change from baseline in dipstick urinalysis (Normal, Abnormal NCS, Abnormal CS) will also be provided.

Each continuous measurement will be classified as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

Summaries and listings will be presented using the Système International (SI) unit for each parameter as received from the analytical laboratory.

A listing of any clinically significant laboratory measurements recorded throughout the study will be presented. All collected laboratory data will be listed. Any unscheduled samples analysed at local hospital laboratories will be listed separately with references ranges as provided by the analytical laboratory.

6.17.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group and visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Body weight (kg)

Both standing and supine values, as well as orthostatic changes (standing – supine) will be presented for blood pressure and pulse rate. Measurements taken either seated or prone will be considered taken supine. The number and percentage of patients with either >20 mmHg reduction in systolic blood pressure after standing, or >10 mmHg reduction in diastolic blood pressure after standing, or both will be summarized. All vital sign data will be listed.

6.17.4 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables will be presented by treatment group and visit:

- Heart rate (bpm)
- PR interval (ms)
- QRS duration (ms)
- QT interval (ms)
- QTc interval (ms)
- QTcB interval (ms) [Bazett's formula]
- QTcF interval (ms) [Fridericia's formula]
- RR interval (ms)

Shift tables in relation to the overall interpretation i.e., Normal, Abnormal NCS (Not Clinically Significant), and Abnormal CS (Clinically Significant) from baseline to each follow-up visit will be presented.

Any QTcF or QTcB Interval (ms) result meeting the following criteria will be identified as an electrocardiogram abnormality and a separate tabulation by treatment group will be provided:

- Interval at Baseline of >450 msec and ≤ 480 msec
- Interval at Baseline of >480 msec and ≤ 500 msec
- Interval at Baseline of >500 msec
- Post-Baseline value of >450 msec and ≤ 480 msec
- Post-Baseline value of >480 msec and ≤ 500 msec
- Post-Baseline value of >500 msec
- Post-Baseline increase of >30 msec and ≤ 60 msec
- Post-Baseline increase of >60 msec

All ECG data, including details of any abnormalities, will be listed.

6.17.5 Physical Examination

Shift tables for the observed change in status of each of the body systems, (Normal, Abnormal NCS, and Abnormal CS) from baseline to each follow-up visit will be tabulated by treatment group. All data, including details of clinically significant findings will be listed.

6.17.6 C-SSRS

C-SSRS outcomes (Suicidal Ideation and Suicidal Behaviour) since baseline will be tabulated by treatment group and overall, by visit. A shift table for the change in number and percent of patients in each category (No Suicidal Ideation or Behaviour, Suicidal Ideation, Suicidal Behaviour) from baseline to each visit will be presented. Patients with both Suicidal Ideation and Suicidal Behaviour will be included in the Suicidal Behaviour category.

All reported data will be listed.

6.17.7 Features of Dopamine Dysregulation Syndrome, MDS-UPDRS Question 1.6

MDS-UPDRS Question 1.6 will be completed at all in-person visits, (excluding Day 9 and Day 28) up to end of treatment. A shift table for the change from baseline in number and percent of patients rated in each score category (0 to 4) will be presented by treatment group and visit. Percentages will be based on the number of patients with non-missing score at baseline and post-baseline for the relevant visit. Descriptive statistics for the score as a continuous measure for observed values and change from baseline to each post-baseline visit will be provided and the number and percent of patients with a worsening post-baseline score of 2 or more points will also be presented.

6.17.8 Pregnancy

Pregnancy testing will be performed at Screening, Visit 1, Visit 3, Visit 4, and Visit 5 for women of childbearing potential. Patient counts within each category (positive/negative test result) will be summarized by visit. All pregnancy testing data will be listed. Any reported pregnancies and details of the condition of neonate(s) will be provided as separate listings.

7 INTERIM ANALYSIS

No interim analyses are planned for this study.

8 DATA SAFETY MONITORING BOARD ANALYSIS

No data safety monitoring board (DSMB) analyses are planned for this study.

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

1. The primary efficacy analysis will be adjusted for country and weighted by the number of subjects participating from each country to account for any observed imbalances in recruitment across countries.
2. Analyses will be conducted for individual active dose and pooled doses.
3. Secondary and exploratory endpoints have been itemized separately compared to the protocol for clarity.
4. Key Secondary Efficacy Endpoints were defined:
   - Change from baseline with mesdopetam compared to placebo in ON-phase dyskinesia assessed by MDS-UPDRS part 4 question 4.2 (Functional impact of dyskinesias).
   - Change from baseline with mesdopetam compared to placebo in disability associated with ON-phase dyskinesia assessed with the sum score of parts 1b and 4 of the UDysRS.
5. Other Key Secondary Efficacy Endpoints were defined:
   - Change from baseline with mesdopetam compared to placebo in motor symptoms of PD assessed with MDS-UPDRS total score of part 2 (M-EDL).
   - Change from baseline with mesdopetam compared to placebo in average daily OFF-time.
6. Exploratory endpoint added to reflect protocol section 14.7. Efficacy endpoints, Table 6 Other endpoints:
   - Change from baseline with mesdopetam compared to placebo in the total scores for each component part of the MDS-UPDRS (Part 1, Part 3, and Part 4).
   - Change from baseline with mesdopetam compared to placebo in freezing and freezing of gait, assessed by MDS-UPDRS: Question 2.13 + Question 3.11.
7. Safety endpoint added to reflect protocol section 14.7. Efficacy endpoints, Table 6 Other endpoints:
   - Change from baseline with mesdopetam compared to placebo in features of dopamine dysregulation syndrome assessed by MDS-UPDRS Question 1.6.
8. Improvement in Daily ON-time, Responder Analysis
9. PK Analysis Set was defined.
10. CYP Genotype Subset was defined.
11. Multiplicity strategy was refined to address Key Secondary Endpoints.

12. Exposure calculation was redefined.
13. Compliance calculated was redefined
14. Analysis of the primary and key secondary endpoints will be repeated using the modified stratification factor.

10 REFERENCES

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