Randomised, double-blind, placebo-controlled, clinical study to evaluate the effect of opicapone 50 mg on Parkinson's disease patients with end-of-dose motor fluctuations and associated pain.

Sponsor Project Code: BIA-91067-404
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STATISTICAL ANALYSIS PLAN

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DOCUMENT REVISION HISTORY

Version Draft 0.1 (18-MAR-2022): Document was created.
Version Draft 0.2 (06-FEB-2023): Document was updated according to Sponsor's comments. Major changes:

- Primary efficacy analysis model from ANCOVA changed to MMRM, under the assumption that data are missing at random (MAR).
- Multiple imputation method under the assumption that data are missing not at random (MNAR) will be used instead of last observation carried forward (LOCF) approach within the sensitivity analysis.
- Secondary efficacy endpoints will be analysed using MMRM in those continuous endpoints where 3 post-baseline visits are planned to be collected.
- Added improvement analysis for CGIC and PGIC: number of responses (improved vs. not improved) will be compared among two treatment groups using Fisher's exact test.
- Rescue medication adherence will be calculated.

Version Draft 0.3 (05-MAY-2023): Document was updated according to Sponsor's comments. Major changes:

- Added specification in full analysis set definition that patients must have at least one post-baseline assessment.
- COVID-19 related protocol deviations will not be provided.
- Details for sensitivity analysis of rescue medication will be specified during blind data review meeting.
- New shift tables added for morning dystonia.

Version Draft 0.4 (30-NOV-2023): Document was updated according to Sponsor's comments. Major changes:

- EDV visit will be used for analysis only if no more than 3 days have passed since the IP was discontinued.
- In addition, IP compliance by periods will be calculated.
- Added new listing - Listing 16.2.3.6.2 Hauser's Parkinson's Disease Diary for Analysis

Version Draft 0.5 (16-MAY-2024): Document was updated. The following major changes were made:

- Randomised set added as analysis set.
- Hauser's Parkinson disease diary will be analysed using visit windows.
- Subgroups and subgroup analysis added.
- Last IP intake date imputation rules provided for partially or fully missing last IP intake date.
- Compliance by periods will not be calculated.
- Sensitivity analysis of rescue medication impact to the primary efficacy endpoint will be conducted if more than 10% of subjects were using tramadol during the last 30 days prior to the primary endpoint.
- Periods for rescue diary analysis agreed.

Version Final 1.0 (21-MAY-2024): Document was finalised. Minor changes were made.

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LIST OF ABBREVIATIONS AND KEY TERMS

Abbreviation	Description of abbreviation
AE	Adverse event
ALT/GPT	Alanine aminotransferase / glutamic-pyruvic transaminase
AST/GOT	Aspartate aminotransferase / glutamic-oxaloacetic transaminase
BDR	Blind data review
BMI	Body mass index
BUN	Blood urea nitrogen
CGIC	Clinical Global Impression of Change
CK	Creatine kinase
CS	Clinically significant
DDCI	Dopa decarboxylase inhibitor
eCRF	Electronic case report form
EDV	Early discontinuation visit
EOS	End of study
FAS	Full analysis set
FU	Follow-up
H	Higher
hCG	Human chorionic gonadotropin
HLGT	High level group term
HLT	High level term
IP	Investigational product
IWRS	Interactive web response system
KPPS	King's Parkinson's Disease Pain Scale
L	Lower
L-DOPA	Levodopa
LLT	Lowest level term
LOCF	Last observation carried forward
LS	Least squares
MAR	Missing at random
max	Maximum
MCH	Mean corpuscular/cellular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MDS-NMS	Movement Disorder Society-sponsored Non-motor Rating Scale
MDS-UPDRS	Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
min	Minimum
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
n	Number of observations/ frequency count
PD	Parkinson's disease
PDQ-8	Parkinson's Disease Questionnaire
PGIC	Patient's Global Impression of Change
PPS	Per-protocol set
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation

Abbreviation	Description of abbreviation
SOC	System organ class
SS	Safety set
TLF	Tables, listings, figures
WBC	White blood cell
WHO	World Health Organization

INTRODUCTION

This statistical analysis plan (SAP) contains a more technical and detailed elaboration of the principal features of the statistical analyses as described in the clinical study protocol and its modifications:

Final Protocol Version(s), Date(s):	Final 1.0, 04-JUN-2020
Protocol Amendment Date(s):	Final 1.0 Germany, 03-DEC-2020 Final 2.0 Germany, 19-FEB-2021 Final 2.0, Phase III, 04-JUL-2022 (for Poland) Final 2.0 Czech Republic, 17-OCT-2022

The SAP includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data, and it is structured according to different data types.

The SAP will supersede all the statistical considerations previously described into the Clinical Trial Protocol. The SAP will be finalised and signed-off prior to unblinding the study.

All analysis data sets and statistical output will be produced by the statistics department using SAS for Windows (SAS Institute Inc., Cary, NC, USA) [1] version 9.4 or higher. The actual version used will be documented in the Validation Plan for Statistical Programming.

1. VISIT SCHEDULE

Visit no./name	**V1**	**V2a[1]**	**V2b**	**V3[2]**	**V4**	**V5**	**V6/ EDV[3]**	**FU**
			Double-blind treatment period					
	Screening		**Baseline**				**End of Study**	**Follow-up**
Day	-7 (±2)	5-6 days after V1	1	8 (±2)	29 (±2)	85 (±4)	169 (±4)	183 (±4)
On-site visit ⊗ / telephone contact ☎	⊗		⊗	☎	⊗	⊗	⊗	⊗
Initiation procedures								
Informed consent	●							
Demographics	●							
Height and weight	●							
Medical/neurological history	●							
Previous medications/therapies	●							
In-/exclusion criteria	●		●					
Modified Hoehn & Yahr staging at ON	●							
Review of Hauser's PD diary		●	●[4]		●	●	●	
Instructions on use and delivery of Hauser's PD diary	●	●[4]	●		●	●		
Urine pregnancy test[6]	●		●			●	●	
Medication								
Concomitant medications/therapies	●		●	●	●	●	●	●
Record L-DOPA/DDCI dose	●		●	●	●	●	●	●
Adjust L-DOPA/DDCI dose, if necessary			●	●	●			
Randomisation (1:1)			●					
IP dispensing			●		●	●		
Dispensing rescue medication			●		●	●		
Instructions on use and dispensing of rescue medication diary.			●					
Review of rescue medication diary					●	●	●	
Drug accountability (IP and rescue medication)					●	●	●	
First IP administration[5]			●					
Efficacy								
KPPS	●		●		●	●	●	
MDS-NMS			●		●	●	●	
MDS-UPDRS Part I and II			●					
MDS-UPDRS Part III and IV			●		●	●	●	
PDQ-8			●		●	●	●	
Early morning dystonia			●		●	●	●	
CGIC					●	●	●	
PGIC					●	●	●	
Safety								
Record adverse events	●	●[4]	●	●	●	●	●	●
Vital signs (blood pressure, heart rate)	●		●		●	●	●	
Physical and neurological examinations	●					●	●	
Blood samples for routine laboratory	●						●	

CGIC: Clinical Global Impression of Change; DDCI: Dopa decarboxylase inhibitor; EDV: early discontinuation visit; FU: Follow-up; KPPS: King's Parkinson's Disease Pain Scale; L-DOPA: levodopa; IP: investigational product; MDS-NMS: Movement Disorder Society-sponsored Non-motor Rating Scale; MDS-UPDRS: Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; PD: Parkinson's disease; PDQ-8: Parkinson's Disease Questionnaire; PGIC: Patient's Global Impression of Change.

1) If self-rating diary (Hauser's PD diary) entries are non-compliant, the patient will be re-trained on correct use of the diary and V2b will be postponed for 3 to 4 days. If the patient completed the diary satisfactorily, V2b is to be performed immediately, at the same day.
2) If L-DOPA/DDCI adjustment is deemed necessary, an unscheduled on-site visit for dose adjustment may be performed at the investigator's discretion. After L-DOPA/DDCI adjustment, either the phone call should be repeated up to 7 days after dose adjustment or V4 should be performed, whatever applies first.
3) An EDV should be performed as soon as possible (not exceeding 7 days) after early discontinuation.
4) Only to be performed if V2a and V2b will not take place on the same day.
5) The first intake of opicapone will take place on the day of V2b, at least 1 hour before or after the last daily dose of L-DOPA/DDCI.
6) In females of childbearing potential.

2. OBJECTIVES AND DESIGN

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to investigate the efficacy of 50 mg opicapone when administered with the existing treatment of L-DOPA plus a DDCI, in Parkinson's disease (PD) patients with end-of dose motor fluctuations and associated pain.

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- to investigate the efficacy of opicapone 50 mg in reducing further symptoms
- to investigate the safety and tolerability of opicapone 50 mg once daily

2.2 Study Endpoints

2.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint of this study is change from baseline in Domain 3 (fluctuation-related pain) of King's Parkinson's Disease Pain Scale (KPPS).

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- change from baseline in Domain B (anxiety) of Movement Disorder Society-sponsored Non-motor Rating Scale (MDS-NMS)
- change from baseline in Domain A (depression) of MDS-NMS
- change from baseline in Domain K (sleep and wakefulness) of MDS-NMS
- change from baseline in total score of MDS-NMS
- change from baseline in Domain 4 (nocturnal pain) of KPPS
- change from baseline in total score of KPPS
- change from baseline in Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III and IV
- change from baseline in Parkinson's Disease Questionnaire (PDQ-8)
- Clinical Global Impression of Change (CGIC)
- Patient's Global Impression of Change (PGIC)
- change from baseline in functional status via Hauser's PD diary
- changes from baseline in morning dystonia
- frequency of use of rescue medication

2.2.3 Safety Endpoints

The safety endpoints of this study are:

- incidence of adverse events (AEs) including serious adverse events (SAEs); relatedness to opicapone and severity will also be evaluated
- changes from baseline in vital signs
- changes from baseline in physical and neurological examinations
- changes from baseline in routine laboratory parameters

2.3 Overall Study Design

This is a randomised, double-blind, placebo-controlled, multi-centre, parallel group, interventional clinical study in PD patients with end-of-dose motor fluctuations and associated pain. The study consists of a 1-week screening period, a 24-weeks double-blind treatment period and 2 weeks of follow-up period.

At Visit 1, the patient will complete initiation procedures. Moreover, the patient will be provided with a paper-based self-rating diary (Hauser's PD diary) and will be instructed how to complete it.

Completion of Hauser's PD diary entries will be reviewed at Visit 2a. In case the patient completed the diary satisfactorily the investigator will immediately continue with Visit 2b at the same day. If diary entries are non-compliant (i.e. more than 3 missing entries per day in the 3 days prior to Visit 2a), the patient will be re-trained on the correct use of the diary and Visit 2b will be postponed for 3 to 4 days.

At Visit 2b (Day 1) and if eligibility is confirmed, the patient will be randomised to 50 mg opicapone or placebo once daily (1:1) and start treatment in addition to current treatment with L-DOPA/DDCI.

Opicapone enhances the effects of L-DOPA. Hence, it may be necessary to reduce the patient's L-DOPA/DDCI dose within the first days or weeks of opicapone treatment. If dose decrease of L-DOPA/DDCI is deemed necessary, it may be adjusted by phone at Visit 3 or an unscheduled on-site visit may be performed at the investigator's discretion. The dosage of L-DOPA/DDCI should not be changed from Visit 4 through the end of the study.

No new anti-PD drugs should be started during the study and any that are ongoing at the start of the study must be kept at a stable dose throughout the study, unless for safety reasons. No new pain medication should be started during the study except the allowed rescue medication.

Patients who discontinue study participation prematurely will be asked to come to the site for an early discontinuation visit (EDV) as soon as possible (not exceeding 7 days after early discontinuation).

2.4 Randomisation

Randomisation will follow a 1:1 allocation rate for each of the treatment arms (50 mg opicapone or placebo). No stratification factors were considered for randomisation.

At Visit 1, each patient will be assigned in a chronological order via electronic case report form (eCRF) to a patient unique number within the study. The patient number will be transferred by the site staff to the interactive web response system (IWRS). At Visit 2b, after confirming that the patient is eligible for entry into the treatment phase, the site staff will contact the IWRS in order to get the appropriate medication number from the system.

Patient recruitment will be competitive. It is possible for clinical study sites with a high recruitment rate to enrol more patients. Other clinical study sites could be slow at enrolling.

2.5 Treatments

Each patient will continue with his/her current daily L-DOPA/DDCI dose (3 to 8 daily doses) and will additionally take one capsule of IP (opicapone 50 mg as test product of this study or matching placebo) once daily for the duration of 24 weeks, starting in the evening of Visit 2b.

Table 1: IP Description

Name of IP	**Opicapone**	**Placebo**
Dosage form	Hard capsule	Hard capsule
Active ingredient	Opicapone (BIA 9-1067), (2,5-dichloro-3-[5-{3,4-dihydroxy-5-nitrophenyl}-1,2,4-oxadiazol-3-yl]-4,6-dimethylpyridine 1-oxide)	Not applicable
Strength/concentration	50 mg	Not applicable

The last IP intake will take place in the evening prior to Visit 6. The IP should be taken once daily at bedtime, at least 1 hour before or after the last daily dose of L-DOPA/DDCI. The patients will be instructed to swallow the capsule whole with a glass of water.

In case one dose of IP is missed, the next dose should be taken as scheduled. The patient should not take a double dose to make up for the missed dose.

Patients are allowed to use rescue medication provided by sponsor:

- paracetamol (500 mg tablets; 4 g (3 g for German sites) per day at maximum) (unless patient already receives tramadol)
- tramadol (50 mg capsules; 400 mg per day at maximum).

Concomitant use of both types of rescue medication during the same day is not allowed. In case the patient needs to switch to tramadol, an unscheduled visit for dispensation of tramadol may be performed as required.

2.6 Sample Size

For the primary endpoint (change from baseline in Domain 3 of KPPS), a difference to placebo of 3.0 is regarded as clinically meaningful and from a former study (Rascol O et al 2016; DOI: 10.1002/jcph.678) a standard deviation of 5.8 can be assumed in both arm groups. With a two-sided significance level α of 0.05, a power of 80%, a 1:1 treatment allocation ratio and with the abovementioned assumptions, 2 x 60 = 120 evaluable patients are required. An approximate drop-out rate of 15% is assumed, therefore 140 patients need to be randomised.

Post-BDRM note: 144 patients were screened and 127 were randomised. Sample size differs from planned because study was early terminated. As the drop-out rate was less than 15%, the early termination will not have an impact. A total of 120 evaluable patients were required and 122 subjects belong to the full analysis set.

2.7 Blinding

Opicapone and placebo capsules will be identical in size, colour, taste and appearance. The packaging and labelling will not allow for any distinction between test and reference drug.

No person involved in conducting the study may have access to the randomisation code before the blind is officially broken.

Unblinding will not be done unless an actual emergency occurs, and knowledge of the patient's allocated treatment arm affects his/her medical treatment. If possible, before breaking the blind the principal investigator or an authorised delegate consults with the SCOPE 24/7 medical contact to ascertain the necessity of breaking the code. The result of unblinding should be kept confidential and will not be recorded in the eCRF.

3. ANALYSIS SETS AND SUBGROUPS

3.1 Analysis Sets

The **Enrolled Set** will be defined as all patients who signed informed consent.

The **Randomised Set** will be defined as all randomised patients.

The **Safety Set (SS)** will be defined as all patients randomised who took at least one dose of IP. Subjects will be analysed according to actual treatment taken.

The **Full Analysis Set (FAS)** will be defined as all patients who were randomised and who had at least one post-baseline assessment of primary efficacy measurement. Subjects will be analysed according to randomised treatment.

The **Per-Protocol Set (PPS)** will be defined as all patients who were included into the FAS and had no major protocol deviations that could have an influence on the primary efficacy endpoint. Subjects will be analysed according to randomised treatment. Patients that will belong to or will be excluded from the PPS will be discussed case-by-case by reviewing protocol deviations during Blind Data Review (BDR) meeting.

3.2 Subgroups

The following subgroups are defined for primary efficacy analysis:

- Age group (years): ≤ 65, > 65
- Modified Hoehn and Yahr Staging: 1 – 2 and 2.5 - 3
- PD duration (years): ≤ 5, > 5
- Motor-fluctuations (wearing-off) duration (years): < 2, ≥ 2
- L-DOPA total dose at baseline (mg): < 600, ≥ 600.

The primary statistical model will be used for each subgroup analysis. Details are provided in Section 5.5.1.

4. GENERAL DEFINITIONS AND NAMING CONVENTIONS

In order to avoid ambiguity during the analysis, a number of definitions and conventions for data handling are described here.

4.1 General Methodology and Presentation of the Results

The default summary statistics for quantitative (continuous) variables will be

- the number of patients (n),
- the number of patients with missing data (nmiss),
- mean,
- standard deviation (SD),
- median,
- first quartile (Q1) and third quartile (Q3),
- minimum (min) and maximum (max).

Mean, median, and the quartiles will be presented to one more decimal place than the raw value. The minimum and maximum values will be presented with the same decimal precision as the raw value. SD will be reported to two decimal places greater than the original value.

For qualitative (categorical) variables, the frequency count (n) and percentage (%) of patients with non-missing data per category will be the default frequency tabulations. Where appropriate and present, the number of missing values will be displayed as "Missing" category.

Percentage values such as proportions are to be presented to one decimal place, for example, 52.3%.

The denominator used for calculation of the percentages will be specified in a footnote to the tables for clarification.

4.2 Statistical Output Layout

All titles and column headers (consisting of one or several words) will be capitalised; articles, prepositions, and conjunctions, and "To" in infinitives will not be capitalised, except they are at the beginning of titles or headers.

All pages will be numbered according to the table/listing/figure to which the page belongs to. Every table/listing/figure will be numbered from page 1, "Page X of Y" at the bottom of each page.

The definition of baseline and endpoint value will be described in a footnote in every table, listing, figure (TLF) where applicable. Other important definitions will also be presented if necessary.

Dates will be listed in the format: yyyy-mm-dd (e.g. 2003-11-20). Times will be listed in the format: hh:mm (e.g. 13:15) or in the format hh:mm:ss if seconds are collected. When date and time are collected, these are listed in the format: yyyy-mm-ddThh:mm (e.g. 2003-11-20T09:15), yyyy-mm-ddThh, or yyyy-mm-ddThh:mm:ss.

Partial missing dates will be listed in the format yyyy-mm (e.g. 2013-11) if only day is missing or in the format yyyy (e.g. 2013) if month and day are missing.

Missing data including missing dates or times will be displayed in listings as blank fields, unless otherwise specified.

Listings will be sorted by patient number and visit number where applicable, unless specified otherwise.

4.3 Treatment Group Names and Labels

Statistical output will be presented by treatment group and the treatment labels to be used in the tables, listings and figures are defined in Table 2 below.

Table 2: Treatment Group Labels

Description	Label in TLFs
Placebo	Placebo
Opicapone 50 mg	Opicapone 50 mg

4.4 Visit Names and Labels

The names to be used in the analysis datasets and the labels to be used in the tables, listings and figures for the different study visits are defined in Table 3 below.

Table 3: Visit Labels

Name	Description	Label in TLFs
Visit 1	Screening visit	Visit 1
Visit 2a		Visit 2a
Visit 2b	Baseline visit	Visit 2b
Visit 3		Visit 3
Visit 4		Visit 4
Visit 5		Visit 5
Visit 6/EDV	End of study visit	Visit 6/EDV*
Follow-up Visit	Follow-up	Follow-up

Unscheduled visits will be labelled as "Unscheduled Visit X.Y", where X is the previous attended scheduled visit, and Y is the number of consecutive unscheduled visits. For example, two unscheduled visits after Visit 2b would be labelled as Unscheduled Visit 2b.1 and Unscheduled Visit 2b.2.

* This label is applicable for safety analysis. For efficacy analysis and for data split by periods EDV will be assigned as defined in Section 4.8.

4.5 Study Day Numbering

All assessment dates will be related to the date of first IP intake. The date of first IP intake is referred to as Day 1. Day –1 is the day preceding Day 1 and Day 0 will not be defined. The numbering is such that Day –2 is the day before Day -1, Day 2 is the day after the first IP intake, etc.

4.6 Study Periods

Baseline period

The baseline period will be defined as the period from informed consent signature date to the first IP intake.

Treatment period

The period from the date of first IP intake to the date of last IP intake is defined as the treatment period.

Follow-up period

The follow-up period is a period lasting from the end of the treatment period until study termination date.

4.7 Baseline and Endpoint Value

Baseline value

The baseline value for a variable is defined as the last non-missing value collected before the first IP intake on the day of Visit 2b.

If a different baseline value will be used, it will be defined in the respective subsection.

Endpoint value

The endpoint value for a variable is defined as value recorded at Visit 6/EDV.

EDV usage rule is defined in Section 4.8.

If a different endpoint value will be used, it will be defined in that subsection.

Absolute change from baseline will be calculated as

$$Absolute\ Change\ from\ Baseline\ at\ Visit\ X = Value\ at\ Visit\ X - Baseline\ Value$$

4.8 Visit Windows

No visit windowing will be applied, and all data will be analysed using the nominal visit number for safety analysis.

Use of EDVs Data

Data collected at EDV will be used for efficacy analysis, only if EDV assessments were performed no later than 3 days after last IP intake. The EDV which follows the rule will be assigned to the closest scheduled post-baseline analysis visit by target day (same visit windows as in Table 4). If the EDV is assigned to already performed scheduled visit, then non-missing assessment which is closest to the target day will be selected for the analysis. Other visits will be used according to analysis time windows as in Table 4..

This rule will be used for the total scores and subscores of KPPS, MDS-NMS, MDS-UPDRS and PDQ-8 analysis, as well as for the Clinical Global Impression of Change (CGIC), Patient's Global Impression of Change (PGIC) and morning dystonia.

EDV data will be assigned to the closest scheduled post-baseline analysis visit by target day if period analysis is needed for change of L-DOPA, rescue diary.

Post-BDRM note:

- All EDVs allocation to scheduled visit were reviewed case-by-case during the BDR and no modifications were needed.
- The Hauser's PD diary data will be analysed using analysis windows. Within each analysis time window three diary entries closest to the target day will be used for the analysis. See the table below for slotting:

Table 4: Visit Slotting

Visit	Visit Schedule (Protocol)	Target Day	Analysis Time Window
Visit 3	8 days ± 2	8	2 to 18
Visit 4	29 days ± 2	29	19 to 56
Visit 5	85 days ± 4	85	57 to 127
Visit 6	169 days ± 4	169	128 to 200

It will be checked that diary filling days for EDV do not exceed 3 days after the last IP intake. If it does exceed, those days will not be used in the analysis.

Data from Visit 3 will not be used for efficacy analysis.

4.9 Coding Systems and Conventions

4.9.1 Coding of Adverse Events and Medical History

Adverse event (AE) and medical history investigator terms are assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term (HLGT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.1 [2].

4.9.2 Coding of Medications

Medications are classified according to active drug substance using the World Health Organization (WHO) drug dictionary WHODrug Global, March 2020 version [3]. The WHO drug code has 11 digits. The generic name is defined by the first 6 of the 11 digits. In addition, the Anatomical Therapeutic Chemical (ATC) classes are assigned to the drug code. In this study, ATC codes are defined to the 4th level.

4.10 Handling of Missing Data

For the primary analysis, missing change from baseline to Visit 6 in Domain 3 of KPPS will be handled with mixed model for repeated measures (MMRM) assuming the data is missing at random (MAR). This missingness mechanism assumes the unobserved data are similar to the observed data. For sensitivity purpose, multiple imputation (MI) approach under the assumption that data are missing not at random (MNAR) will be used for primary efficacy endpoint. More details about the MI approach will be presented in Section 5.5.1.

MI approach will not be performed for secondary efficacy endpoints.

Missing data regarding safety endpoints will not be imputed and only observed data will be reported and analysed.

5. STATISTICAL ANALYSIS: DEFINITIONS, DERIVATIONS, CALCULATIONS AND METHODOLOGY

5.1 Patient Disposition

5.1.1 Disposition and Withdrawals

The following disposition data will be collected:

- date of informed consent
- did the patient complete the study as scheduled (yes, no)
- reason for premature study termination

Screening failures will be all patients who have been enrolled in the study (informed consent signed) but discontinue the study prior to randomisation due to whatever reason.

Withdrawals will be all patients who have been enrolled and, for whatever reason, discontinue the study prematurely after randomisation.

Completers will be all patients who completed the treatment phase (from Visit 2b to Visit 6) as scheduled, even if no follow-up visit was performed.

Subgroups as defined in Section 3.2 will be summarised.

The following statistical output will be provided:

Table 15.1.1.1 Analysis Sets – Enrolled Set
The number and percentage of patients included in the enrolled, randomised, safety, full analysis and per-protocol sets will be provided. Percentages will be based on the number of patients in the randomised set.

Table 15.1.1.2 Reasons for Exclusions from Analysis Sets – Randomised Set
The number and percentage of patients excluded from the safety, full analysis and per-protocol sets will be provided. Percentages will be based on the number of patients in the randomised set. The reasons of exclusion from the analysis sets will be incorporated into the table.

Table 15.1.2 Screening Failures – Enrolled Set
Counts and percentages of patients who discontinued the study during the screening phase prior to randomisation will be summarised by reasons associated with the discontinuation. Percentages will be based on the number of patients in the enrolled set.

Table 15.1.4 Patient Disposition – Safety Set
Counts and percentages of patients who completed the treatment phase as scheduled or as withdrawals during the treatment phase will be summarised. Reasons for discontinuation will be included. Percentages will be based on the number of patients in the safety set.

Table 15.1.5 Number of Patients by Country and Site – Randomised Set
Counts and percentages of patients in each country and site. Percentages will be based on the number of patients in the respective analysis set.

Table 15.1.6 Number of Patients by Visit – Safety Set
Counts and percentages of patients attending each scheduled visit will be presented. Percentages will be based on the number of patients in the safety set.

Table 15.1.7.1 Summary of Subgroups – Full Analysis Set
Table 15.1.7.2 Summary of Subgroups – Per-Protocol Set
Counts and percentages of patients in each subgroup will be presented. Percentages will be based on the number of patients in the respective analysis set.

Figure 15.1.1 Flow Chart of Patient Disposition – Enrolled Set
The number of enrolled, randomised patients and completers will be displayed. The number of screening failures and withdrawals as well as their reasons will also be summarised.

Figure 15.1.2 Flow Chart of Analysis Sets – Enrolled Set
The number of patients in each analysis set will be displayed.

Listing 16.2.1.1 Patient Disposition – Safety Set
Patients who enter the treatment period and complete the study as scheduled or as withdrawal will be listed. Reasons for premature study termination will be displayed for withdrawals.

Listing 16.2.1.2 Screening Failures – Enrolled Set
Patients who discontinued the study prior to the randomisation will be listed. Reasons associated with the discontinuation will be displayed.

Listing 16.2.1.3 Patient Visits – Enrolled Set
All visit dates will be listed by patient.

Listing 16.2.1.4 Exclusions from Analysis Sets – Enrolled Set
Patients excluded from any analysis set and corresponding reasons for exclusion will be listed.

Listing 16.2.1.5 Patient Allocation to Treatments – Randomised Set
Randomisation codes and treatment allocations will be listed for all randomised patients.

5.1.2 Protocol Deviations

Protocol deviations are deviations from the procedures outlined in the clinical study protocol or from subsequent protocol-related instructions like missed evaluations, incorrect timing of evaluations, non-compliance with IP and intake of prohibited medications or any non-adherence to the clinical study protocol that impacts patient's rights, safety or welfare.

Major protocol deviations will be summarised. Protocol deviations will be evaluated as major or minor during Blind Data Review (BDR) (See Section 6).

The following statistical output will be provided:

Table 15.1.3 Major Protocol Deviations – Full Analysis Set
The number and percentage of patients with major protocol deviations will be summarised by treatment and overall. The categories of major protocol deviations will be included. Percentages will be based on the number of patients in the respective analysis set.

Listing 16.2.1.6 Major Protocol Deviations – Safety Set
Patients with major protocol deviations will be listed.

5.1.3 Inclusion/Exclusion

The study specific inclusion/exclusion criteria are presented in Section 9.2 and 9.3 of the clinical study protocol. For each criterion, as appropriate, a response of "Yes/No/NA (only for exclusion criterion no. 17)" is to be obtained at screening and checked again prior to randomisation at Visit 2b.

The following statistical output will be provided:

Listing 16.2.1.7 Inclusion Criteria Not Met and Exclusion Criteria Met – Enrolled Set
Inclusion criteria which were not met and exclusion criteria which were met will be listed.

5.2 Demographic and Other Baseline Characteristics

5.2.1 Demographics

The following demographic characteristics will be presented:

- Age
- Gender (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Unknown)
- Childbearing potential
- Height (cm)
- Weight (kg).

Body mass index (BMI) will be calculated as:

$$BMI\ (\mathrm{kg}/m^2) = \frac{Weight\ (kg)}{Height\ (m)^2}$$ and presented to 1 decimal precision.

The following statistical output will be presented:

Table 15.1.8.1 Demographics and Baseline Characteristics – Safety Set
Table 15.1.8.2 Demographics and Baseline Characteristics – Full Analysis Set
Table 15.1.8.3 Demographics and Baseline Characteristics – Per-Protocol Set
Demographic data, weight, height and BMI will be summarised for each treatment group in the specified set. Overall summary will also be included. Percentages for categorical variables will be based on the number of patients in the respective analysis set.

Listing 16.2.1.8 Demographics and Baseline Characteristics – Enrolled Set
Demographic and baseline characteristic data will be listed for patients in the enrolled set.

5.2.2 Neurological History

The following information about the PD history and status at baseline will be collected:

- Date of PD diagnosis
- Start date of wearing-off motor fluctuations
- Start date of PD associated pain
- Modified Hoehn & Yahr staging at ON (stages: 0, 1, 1.5, 2, 2.5, 3, 4, 5)

Time since diagnosis, time since wearing-off motor fluctuations and **time since associated pain** will be calculated as follows:

Time since parameter (years) = (Visit 1 date - Date of parameter)/365.25

In case of incomplete date, one of the following will be imputed:

- The 15th day of the month will be used if the month and year are available, but the day is missing.
- If year is available, but month and day are missing, 2nd of July will be imputed. If the year of the incomplete date coincides with the year of Visit 1, then the 1st of January will be imputed.
- If the year is missing, time since will not be calculated.

The following statistical output will be presented:

Table 15.1.9.1 Summary of Neurological History – Safety Set
Table 15.1.9.2 Summary of Neurological History – Full Analysis Set
Table 15.1.9.3 Summary of Neurological History – Per-Protocol Set
Time since diagnosis, time since wearing-off motor fluctuations, time since PD associated pain and modified Hoehn & Yahr staging will be summarised in the respective analysis set.

Listing 16.2.1.9 Neurological History – Enrolled Set
Parkinson's disease characteristic data will be listed for patients in the enrolled set.

5.2.3 Medical History

Medical history encompasses relevant prior or ongoing relevant diseases, conditions, hospitalisation and surgical procedures. Medical history records are collected at Visit 1.

Medical history of the patients includes:

- Medical condition/procedure
- Start date
- Stop date
- Ongoing
- Treatment used (yes, no)

Medical history is classified as:

- **Prior conditions** are the conditions which started and ended prior to Visit 1.
- **Ongoing conditions** are the conditions which are marked as ongoing at Visit 1 or with a stop date at or after Visit 1

If the stop date of a medical history condition is incomplete or missing, it will be assumed to be ongoing except if the incomplete stop date indicates that the condition stopped prior to Visit 1.

The following statistical output will be provided:

Table 15.1.10.1.1 Prior Medical Conditions – Safety Set
Table 15.1.10.1.2 Prior Medical Conditions – Full Analysis Set
Table 15.1.10.2.1 Ongoing Medical Conditions – Safety Set
Table 15.1.10.2.2 Ongoing Medical Conditions – Full Analysis Set
Medical history will be summarised displaying counts and percentages of patients having at least one medical condition and will be presented by primary System Organ Class (SOC) and by Preferred Term (PT) within SOC. SOCs and PT within SOC are to be sorted by descending order of overall incidence. Patients with two or more occurrences of the same condition (as qualified by its PTs) will be counted only once for the respective PT. Percentages will be based on the number of patients in the respective analysis set.

Listing 16.2.1.10 Medical History – Enrolled Set
Medical history conditions will be listed for patients in the enrolled set.

5.3 Prior and Concomitant Medications

Prior and concomitant medications and therapies are documented in the eCRF.

The following information is collected:

- Medication/ therapy
- Indication
- Route
- Total daily dose
- Units
- Frequency
- Start date of medication
- Stop date of medication
- Ongoing (yes, no)

Medications will be classified as ‘prior’, ‘concomitant’ or ‘post-treatment’ based on start/stop dates:

- **Prior medications** are defined as those medications starting and ending prior to the first IP intake.
- **Concomitant medications** are defined as medications started at or after first IP intake but before the last IP intake and include medications started prior to the first IP intake but continued after the first IP intake.
- **Post-treatment medications** are defined as medications/therapies which started after the last IP intake.

If the start or stop date of a medication is incomplete or missing, it will be assumed to be concomitant except if the incomplete start or stop date indicates that the medication stopped prior to the first IP intake or started after the last IP intake.

Moreover, tramadol taken within 30 days before the endpoint will be summarised separately.

Additionally, L-DOPA/DDCI medication usage will be documented at Visit 1 and afterwards any change will be documented, if applicable. The following data are collected:

- Start date of L-DOPA/DDCI treatment
- Medication/ therapy
- Indication

- Route
- Total daily dose
- Units
- Frequency
- Start date of medication
- Stop date of medication
- Ongoing (yes, no)
- L-DOPA/DDCI dose adjusted since previous visit
- Slow release formulation:
  - Time of intake (morning, during day-time, evening)
  - Total daily dose
  - Units

L-DOPA/DDCI dose could be adjusted until Visit 4.

The following statistical output will be provided:

Table 15.1.11.1.1 Prior Medications – Safety Set
Table 15.1.11.1.2 Prior Medications – Full Analysis Set
Table 15.1.11.2.1 Concomitant Medications – Safety Set
Table 15.1.11.2.2 Concomitant Medications – Full Analysis Set
Table 15.1.11.3.1 L-DOPA/DDCI Medication – Safety Set
Table 15.1.11.3.2 L-DOPA/DDCI Medication – Full Analysis Set
The number and percentage of patients with at least one medication within each ATC 2nd level subgroup and substance name (or combination of substances) will be presented by treatment and overall for the respective set. The ATC 2nd level subgroups and substance names within ATC 2nd level subgroup will be ordered by descending overall incidence.

Table 15.1.11.4 Tramadol Taken Within 30 Days Before the Endpoint – Safety Set
Number of subjects using tramadol within 30 days before the endpoint will be counted in safety set, full analysis set and per-protocol. Percentage will be based on each analysis set.

Table 15.1.11.5.1 Change of L-DOPA/DDCI Medication – Safety Set
Table 15.1.11.5.2 Change of L-DOPA/DDCI Medication – Full Analysis Set
Table 15.1.11.5.3 Change of L-DOPA/DDCI Medication – Per-Protocol Set
Change of L-DOPA/DDCI dose by adjustment type from Visit 2b to Visit 4, and from Visit 4 to Visit 6 will be presented for patients in the specified analysis set. Moreover, L-DOPA/DDCI dose per day and number of intakes will be summarised at all visits.

Listing 16.2.1.11 Medications – Enrolled Set
All medications, prior, concomitant and subsequent, will be listed for patients in the enrolled set.

Listing 16.2.1.12.1 L-DOPA/DDCI Medications – Enrolled Set
L-DOPA/DDCI medications will be listed for patients in the enrolled set.

Listing 16.2.1.12.2 Change of L-DOPA/DDCI Medications – Safety Set
L-DOPA/DDCI adjustment will be listed for patients in the safety set.

5.4 Exposure to IP and Rescue Medication and Compliance

5.4.1 Exposure to IP

Exposure data from eCRF include:

- Date/ Time of the first IP intake
- Date of last IP intake
- Start/ Stop interruption date
- IP interruption cause (AE number)

Following information will be delivered by IWRS provider:

- Kit no.

- Number of dispensed/ returned IP capsules

Post-BDRM note:

It was decided that in case of a partial or missing last IP intake date the following imputation rules will be applied:

- In case of a partially missing last IP intake date the last visit date (excluding follow-up visit) minus 1 day or the last day of month whichever is earlier will be used.
- In case of a completely missing last IP intake date the last visit date (excluding follow-up visit) minus 1 day will be used.

The list of imputed last IP dates is provided below:

- Subject: 44402 – Date: 2021-10-28
- Subject: 48401 – Date: 2021-08-15
- Subject: 48502 – Date: 2022-09-30

The **overall treatment duration** and **actual treatment duration** in days will be calculated as follows:

Overall treatment duration (days) = Date of last IP intake – Date of first IP intake + 1

Actual treatment duration (days) = Overall treatment duration – Total interruption duration

Each not overlapping treatment interruption duration will be calculated as:

$$Stop\ date\ of\ interruption_i - Start\ date\ of\ interruption_i + 1$$

If treatment duration overlaps, then not already calculated days will be added to interruption duration.

The following statistical output will be provided:

Table 15.1.12.1.1 Treatment Duration – Safety Set
Table 15.1.12.1.2 Treatment Duration – Full Analysis Set
Table 15.1.12.1.3 Treatment Duration – Per-Protocol Set
The default summary statistics of treatment duration will be presented.

Listing for exposure and IP interruption data will be present with compliance data in Section **Error! Reference source not found.**.

5.4.2 IP Compliance

Treatment compliance will be calculated as:

$$Overall\ compliance\ (\%) = \frac{(N\ of\ capsules\ dispensed - N\ of\ capsules\ returned)}{Overall\ treatment\ duration} \times 100$$

Post-BDRM note: The listing of all subjects who lost at least one IP kit including explanation and decision can be found in Appendix 3. This appendix will be used to correct drug accountability data.

If from the explanation presented in the PD log/ query it is not possible to identify the lost number of capsules, compliance will not be calculated. In case a subject discontinued the study due to lost to follow-up reason, lost kits will be counted as not used.

Compliance will be categorised as:

- < 80%
- ≥ 80% and ≤ 120%
- > 120%
- Missing

The following statistical output will be provided:

Table 15.1.12.2.1 Treatment Compliance – Safety Set
Table 15.1.12.2.2 Treatment Compliance – Full Analysis Set
Table 15.1.12.2.3 Treatment Compliance – Per-Protocol Set
The default summary statistics of compliance will be presented by treatment group and overall. The number and percentage of patients within each compliance category (< 80%, ≥ 80%, ≤ 120%, > 120% and Missing) will also be summarised. Percentages will be based on the number of patients in the corresponding analysis set.

Listing 16.2.2.1 Exposure to IP and Treatment Compliance – Safety Set
Drug accountability data as well as their overall compliance will be displayed for each patient in the safety set.

5.4.3 Exposure to Rescue Medication

The rescue medication (paracetamol or tramadol) will be dispensed at Visit 2b, Visit 4 and Visit 5.

Following information will be delivered by IWRS provider:

- Type of rescue medication
- Number of dispensed/ returned rescue medication tablets/ capsules

Detailed description of usage of rescue medication is provided in Section 5.5.2.8.

The following statistical output will be provided:

Listing 16.2.2.2 Exposure to Rescue Medication – Safety Set
Drug accountability of rescue medication data will be displayed for each patient in the safety set.

5.5 Efficacy Analysis

Efficacy analysis of the primary endpoint will be based on the FAS and PPS (under MAR assumption for primary evaluation and MNAR for sensitivity purposes). The efficacy of the secondary endpoints will be based on the FAS and PPS.

5.5.1 Primary Efficacy Analysis

The King's Parkinson's Disease Pain Scale (KPPS) evaluates the burden (global and bedside) and characterises various phenotypes of pain in PD. Its seven domains include 14 items, each item scored by severity (0-3) multiplied by frequency (0-4), resulting in subscores of 0 to 12. The total possible KPPS score (0 to 168) represents the symptomatic burden by pain. The questionnaire will be fill out on Visit 1, Visit 2b, Visit 4, Visit 5 and Visit 6/EDV.

The primary efficacy endpoint of this study is the change from baseline to Visit 6/EDV in the Domain 3 of KPPS. The Domain 3 is about fluctuation-related pain and consists of 3 questions and the total possible Domain 3 score ranges from 0 to 36. The primary efficacy endpoint will be analysed using a two-sided alpha 0.05 using a mixed model for repeated measures (MMRM) assuming the unobserved data is missing at random (MAR) to demonstrate differences in the fluctuation-related pain score between opicapone 50 mg and placebo in addition to current treatment with L-DOPA/DDCI for PD patients with end-of dose motor fluctuations and associated pain.

The following statistical hypotheses will be tested:

$$H_0: \mu_T = \mu_C$$

$$H_1: \mu_T \neq \mu_C$$

where μ_T is mean change in Domain 3 of KPPS from baseline in the opicapone treatment arm and μ_C is mean change in Domain 3 of KPPS from baseline in the placebo arm. For the rational used under the sample size and hypotheses see section 2.6.

Only subjects without missing baseline score will be used for analysis using MMRM. The MMRM is longitudinal approach which analyse data as collected (including missing values). Analyses will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the

continuous, fixed covariates of baseline score. The two-sided test estimated results with alpha level of 0.05 will be provided.

An unstructured variance structure will be used to model the within-patient errors. If this analysis fails to converge, the following structures will be tested in order defined below until model convergence is reached:

- Heterogeneous Toeplitz
- Heterogeneous autoregressive
- Toeplitz
- Autoregressive
- Compound symmetry
- Variance components

The Kenward-Roger approximation will be used to estimate degrees of freedom.

Following SAS code will be used to fit MMRM model:

```
PROC MIXED DATA = <DATASET>;
      CLASS <TREATMENT> <VISIT> <SUBJECT ID>;
      MODEL <CHANGE FROM BASELINE> = <TREATMENT> <VISIT> <BASELINE>
<TREATMENT>*<VISIT> / S DDFM=KENROG;
      REPEATED <VISIT> / TYPE=<UN> SUBJECT=<SUBJECT ID>;
      LSMEANS <TREATMENT>*<VISIT> / CL PDIFF;
RUN;
```

Moreover, exploratory analysis of each subgroup as defined in Section 3.2 will be performed. The primary model as described above will be used by each subgroup. In addition, forest plots will be generated representing the difference of LS Means and corresponding 95% CI.

For sensitivity purposes, missing data for the primary efficacy endpoint will be imputed using MI under the missing not at random (MNAR) assumption by creating control-based pattern imputation, assuming that those subjects who have missing data will behave as if they were taking placebo (worst-case scenario). The missing efficacy endpoint data at Visit 4, Visit 5, Visit 6 will be imputed using pattern mixture models. The regression method will be used which fits a regression model. Based on the fitted regression model, a new regression model is simulated and used to impute the missing values for each variable. The number of imputations will be at least 100.

The variables to be used in the MI are treatment, baseline score, and observed values at appropriate visits. Observations from the placebo group will be used to impute the missing data.

The following SAS code will be used for imputations:

```
PROC MI DATA=<DATASET> SEED=14442 NIMPUTE=100 OUT=<OUTPUT DATASET>
      ROUND =. . 1 1 1
      MINIMUM =. . 0 0 0
      MAXIMUM =. . 36 36 36;
      CLASS <TREATMENT>;
      FCS REG(/ DETAILS);
      MNAR MODEL (<VISIT 4> <VISIT 5> <VISIT 6> /
MODELOBS=(<TREATMENT>=”PLACEBO”));
      VAR <BASELINE VALUE> <VISIT 4> <VISIT 5> <VISIT 6>;
RUN;
```

The MMRM model described earlier will be applied to each of the imputed datasets, and the resulting least squares (LS) means/LS means differences and including their respective standard errors will be aggregated and further evaluated using the following SAS statements:

```
PROC MIANALYZE DATA = <DATASET>;
      MODELEFFECTS <LS MEAN ESTIMATES/LS MEAN DIFFERENCE ESTIMATES>;
      STDERR <LS MEAN STANDARD ERRORS/LS MEAN DIFFERENCE STANDARD ERRORS>;
RUN;
```

Additional sensitivity analysis of rescue medication impact to the primary efficacy endpoint will be performed. MMRM model will be used for analysis. Details will be specified during BDR meeting.

Post-BDRM note: It was decided that sensitivity analysis of rescue medication impact to the primary efficacy endpoint will be conducted if more than 10% of subjects were using tramadol during the last 30 days prior to the primary endpoint. As in total only 12 subjects used tramadol 30 days before V6/EDV the sensitivity analysis will not be performed as 12 out of 122 subjects correspond to 9.8%.

The following statistical output will be provided:

Table 15.2.1.1.1.1 Summary of KPPS – Full Analysis Set
Table 15.2.1.1.1.2 Summary of KPPS – Per-Protocol Set
The KPPS domains and total scores will be summarised by visit, including changes from baseline, using default summary statistics.

Table 15.2.1.1.2.1 Summary of the Domain 3 of KPPS by Subgroup – Full Analysis Set
Table 15.2.1.1.2.2 Summary of the Domain 3 of KPPS by Subgroup – Per-Protocol Set
The KPPS domain 3 score will be summarised using default summary statistics by each subgroup and visit, including changes from baseline.

Table 15.2.1.2.1.1 Analysis of the Domain 3 of KPPS – Full Analysis Set
Table 15.2.1.2.1.2 Analysis of the Domain 3 of KPPS – Per-Protocol Set
Table 15.2.1.2.2.1 Analysis of the Domain 3 of KPPS (MI) – Full Analysis Set
Table 15.2.1.2.2.2 Analysis of the Domain 3 of KPPS (MI) – Per-Protocol Set
Table 15.2.1.2.3.1 Analysis of the Domain 3 of KPPS by Subgroup – Full Analysis Set
Table 15.2.1.2.3.2 Analysis of the Domain 3 of KPPS by Subgroup – Per-Protocol Set
The LS means associated with treatments and treatment differences will be presented with 95% confidence intervals and corresponding p-value for each visit for the Domain 3 of KPPS.

Figure 15.2.1.1 Domain 3 of KPPS Change from Baseline LS-Means by Visit – Full Analysis Set
Figure 15.2.1.2 Domain 3 of KPPS Change from Baseline LS-Means by Visit – Per-Protocol Set
A line chart with error bars will be used to display the LS-means and 95% confidence intervals.

Figure 15.2.2.1 Forest Plot of Domain 3 of KPPS by Subgroup – Full Analysis Set
Figure 15.2.2.2 Forest Plot of Domain 3 of KPPS by Subgroup – Per-Protocol Set
Forest plots will be used to display difference of LS Means and 95% CI for Visit 6 by each subgroup. Primary model difference of LS Means, and 95% CI will be included as well.

Listing 16.2.3.1 KPPS – Enrolled Set
KPPS data and total score will be displayed for each patient in the enrolled set.

5.5.2 Analysis of Secondary Variables

The secondary variables will be tested in an exploratory manner and p-values will not be considered confirmatory. No multiplicity adjustments will be conducted. Same MMRM models with MAR assumption defined for the primary analysis will be fitted for the next secondary efficacy endpoints: total score and Domain 4 of KPSS, Domain A, Domain B, Domain K and total score of MDS-NMS, MDS-UPDRS part III and part IV separately, and PDQ-8. The LS means associated with treatments and treatment differences will be presented with 95% confidence intervals and corresponding p-values for each visit.

5.5.2.1 Total Score and Domain 4 of KPPS

The KPPS questionnaire description, summary and listing are already presented in Section 5.5.1.

Domain 4 consists of 2 questions about nocturnal pain.

Change from baseline in total score and Domain 4 score will be analysed using MMRM as described in Section 5.5.1.

The following statistical output will be provided:

Table 15.2.2.1.1 Analysis of the Domain 4 of KPPS – Full Analysis Set
Table 15.2.2.1.2 Analysis of the Domain 4 of KPPS – Per-Protocol Set
Table 15.2.2.2.1 Analysis of KPPS Total Score – Full Analysis Set
Table 15.2.2.2.2 Analysis of KPPS Total Score – Per-Protocol Set
The LS means associated with treatments and treatment differences will be presented with 95% confidence intervals and corresponding p-values.

5.5.2.2 Movement Disorder Society-sponsored Non-motor Rating Scale

The Movement Disorder Society-sponsored Non-motor Rating Scale (MDS-NMS) consists of 13 domains: depression (A), anxiety (B), apathy (C), psychosis (D), impulse control and related disorders (E), cognition (F), orthostatic hypertension (G), urinary (H), sexual (I), gastrointestinal (J), sleep and wakefulness (K), pain (L), other (M). In addition, a subscale for non-motor fluctuations to assess changes in non-motor symptoms in relation to the timing of anti-PD medications across 8 domains.

The MDS-NMS will be filled out at Visit 2b, Visit 4, Visit 5 and Visit 6/EDV.

Each questionnaire item is scored for frequency and severity:

- Frequency:
  0 Never
  1 Rarely
  2 Sometimes
  3 Frequently
  4 Majority of time
- Severity
  0 Not present
  1 Minimal
  2 Mild
  3 Moderate
  4 Severe

Then item score is calculated as frequency multiplied by severity. A domain total score will be calculated as sum of all items. If any item score is missing, then corresponding domain score will not be calculated.

The total score will be calculated by summing the domains from A to M. In case, where any domain score is missing, then total score will not be calculated.

The lower total scores represent better quality of life.

Change from baseline in total score, domain A (depression), domain B (anxiety) and domain K (sleep and wakefulness) score will be analysed using MMRM as described in Section 5.5.1.

The following statistical output will be provided:

Table 15.2.3.1.1 Summary of MDS-NMS – Full Analysis Set
Table 15.2.3.1.2 Summary of MDS-NMS – Per-Protocol Set
The MDS-NMS domains and total scores will be summarised by visit, including changes from baseline, using default summary statistics.
Table 15.2.3.2.1 Analysis of MDS-NMS – Full Analysis Set
Table 15.2.3.2.2 Analysis of MDS-NMS – Per-Protocol Set
The LS means associated with treatments and treatment differences will be presented with 95% confidence intervals and corresponding p-values for each visit using MDS-NMS total score, Domain A, Domain B and Domain K score.

Listing 16.2.3.2 MDS-NMS – Enrolled Set
MDS-NMS each question of domain, domain and total scores will be displayed for each patient in the enrolled set.

5.5.2.3 Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale

The Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) consists of 4 parts:

- Part IA and IB: Non-Motor Aspects of Experiences of Daily Living (nM-EDL) (13 questions)
- Part II: Motor Aspects of Experiences of Daily Living (M-EDL) (13 questions)
- Part III: Motor Examination (33 items based on 18 questions)
- Part IV: Motor Complications (6 questions).

Part I and Part II will be filled out only once at Visit 2b. Part III and Part IV will be filled out at Visit 2b, Visit 4, Visit 5 and Visit 6/EDV. Every item can be scored on a 5-point scale: 0 ("normal"), 1 ("slight"), 2 ("mild"), 3 ("moderate"), 4 ("severe"), with higher scores indicating more severe impairment. The maximum total MDS-UPDRS score is 260, indicating the worst possible disability from PD.

The total score for each part will be calculated as the sum of each item. According to Goetz et al. [4], valid score for the MDS-UPDRS parts can be calculated if the respective part contains a number of missing values less than or equal to the following:

- Part I – 1
- Part II – 1
- Part III – 3
- Part IV – 0

For patients with partially missing data, a prorated score will be calculated by taking the mean of the observed scores and multiplying it by the total number of items in each part. The prorated score will be rounded to the nearest whole number. Otherwise, total score for that part will be set to missing.

Change from baseline in Part III and Part IV will be analysed using MMRM as described in Section 5.5.1

The following statistical output will be provided:

Table 15.2.4.1.1 Summary of MDS-UPDRS – Full Analysis Set
Table 15.2.4.1.2 Summary of MDS-UPDRS – Per-Protocol Set
The MDS-UPDRS parts and total scores will be summarised by visit, including changes from baseline, using default summary statistics.

Table 15.2.4.2.1 Analysis of MDS-UPDRS Part III/IV Total Score – Full Analysis Set
Table 15.2.4.2.2 Analysis of MDS-UPDRS Part III/IV Total Score – Per-Protocol Set
The LS means associated with treatments and treatment differences will be presented with 95% confidence intervals and corresponding p-values.

Listing 16.2.3.3.1 MDS-UPDRS – Enrolled Set
MDS-UPDRS items and total scores will be displayed for each patient in the enrolled set.

Listing 16.2.3.3.2 MDS-UPDRS Part III Additional Information – Enrolled Set
MDS-UPDRS part III additional information about medication, clinical state, dyskinesias impact, Hoehn and Yahr stage will be displayed for each patient in the enrolled set.

5.5.2.4 Parkinson's Disease Questionnaire

The Parkinson's Disease Questionnaire (PDQ-8) will be filled out at Visit 2b, Visit 4, Visit 5 and Visit 6/EDV. The questionnaire contains eight aspects: mobility, activities of daily live, emotional well-being, stigma, social support, cognitions, communication and bodily discomfort. Every question is rated on a 5-point scale: 0 ("never"), 1 ("occasionally"), 2 ("sometimes"), 3 ("often"), 4 ("always or cannot do at all"). The PDQ-8 index will be calculated as follows:

$$\text{PDQ-8 index} = \frac{Sum\ of\ items}{Maximum\ possible\ score} \times 100,$$

where the maximum possible score is 32. If one item answer is missing, then PDQ-8 index will not be calculated. The higher index scores indicate more difficulty due to having PD.

Change from baseline in PDQ-8 index will be analysed as described in Section 5.5.1.

The following statistical output will be provided:

Table 15.2.5.1.1 Summary of PDQ-8 Index – Full Analysis Set
Table 15.2.5.1.2 Summary of PDQ-8 Index – Per-Protocol Set
The PDQ-8 index will be summarised by visit, including changes from baseline, using default summary statistics.

Table 15.2.5.2.1 Analysis of PDQ-8 Index – Full Analysis Set
Table 15.2.5.2.2 Analysis of PDQ-8 Index – Per-Protocol Set
The LS means associated with treatments and treatment differences will be presented with 95% confidence intervals and corresponding p-values.

Listing 16.2.3.4 PDQ-8 – Enrolled Set
PDQ-8 items and index will be displayed for each patient in the enrolled set.

5.5.2.5 Clinical Global Impression of Change and Patient's Global Impression of Change

The Clinical Global Impression of Change (CGIC) scale requires the investigator to assess how much the patient's overall status has improved or worsened since the start of the study. The Patient's Global Impression of Change (PGIC) consists of a general evaluation of patient own overall status in comparison to the start of the study. Both questionnaires will be evaluated at Visit 4, Visit 5 and Visit 6/EDV.

The CGIC and PGIC will be rated on a 7-point scale: 1 ("very much improved"), 2 ("much improved"), 3 ("minimally improved"), 4 ("no change"), 5 ("minimally worse"), 6 ("much worse"), 7 ("very much worse").

Improvement analysis will be performed. Parameters will be categorised into 2 groups based on response given: improved (which include answers from 1 to 3) and not improved (answers from 4 to 7). The number of responses (improved vs. not improved) will be compared among two treatment groups using Fisher's exact test. The following SAS code will be used:

```
PROC FREQ DATA = <DATASET>;
      TABLES <TREATMENT>*<CATEGORY> / FISHER OR;
RUN;
```

The following statistical output will be provided:

Table 15.2.6.1.1 Summary of CGIC and PGIC – Full Analysis Set
Table 15.2.6.1.2 Summary of CGIC and PGIC – Per-Protocol Set
CGIC and PGIC will be summarised for each visit where assessments were made.

Table 15.2.6.2.1 Improvement Analysis of CGIC and PGIC – Full Analysis Set
Table 15.2.6.2.2 Improvement Analysis of CGIC and PGIC – Per-Protocol Set
Improvement groups of CGIC and PGIC will be summarised for each visit where assessments were made. Odds ratio, 95% CI and P-values of Fisher's exact test by visit will be provided.

Listing 16.2.3.5 CGIC and PGIC – Safety Set
The CGIC and PGIC data will be displayed for each patient in the safety set.

5.5.2.6 Hauser's Parkinson Disease Diary

Functional status will be assessed via the Hauser's PD diary. Patient's will categorise their status every half-hour interval of the 24-hour day as: asleep, OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, ON with trouble dyskinesia. The diary must be completed on the 3 days before Visit 2a,

Visit 2b (only if diary is not completed as instructed [more than 3 missing entries per day] at Visit 2a), Visit 4, Visit 5 and Visit 6/EDV.

The average ON/OFF-times of the last 3 diary days within 7 days before Visit 2a/ Visit 2b will be considered as the baseline value.

The average ON/OFF-time at each post-baseline visit will be calculated based on 3 diary entries closest to the target day within the analysis time window as defined in Section 4.8

The diary day begins at 6 AM and ends at 5:30 AM of the next day.

Percentage ON/OFF-time at baseline and each visit will be calculated as the ON/OFF-time as defined above, divided by the total time awake (calculated as the addition of all 30-minute periods in each day where the patient has recorded any state other than asleep).

If only diary data from less than 3 days are available for visit, the mean of the data from the available days will be used.

Handling of missing data:

If a day has less than 8 hours assessable waking time that day will be set to missing. In all other cases and in case of inconsistencies in the data, the following rules will be applied:

- If multiple states are recorded for one 30-minute period, the 30 minutes of the period will be equally divided among the multiple states, i.e. time with state X = 30 minutes / number of states recorded for this period.
- If a single entry of 30 minutes is missing within a day, adjacent available diary values carried forward and backward will be used for imputation of the missing record, i.e. 15 minutes will be allocated to the state of the adjacent periods, each. If any of the adjacent periods had multiple states recorded, these 15 minutes will be equally divided among the multiple states.
- If the first or last 30 minutes period of a day is missing, the state recorded immediately after or prior to this period, respectively, will be used for imputation of the missing record, using the same algorithm as described above.
- If two or more consecutive 30 minutes periods are missing within a day, these will not be imputed but set to missing.

Additionally, ON without troublesome dyskinesia will be summarised as ON with non-troublesome dyskinesia + ON without dyskinesia and ON-time will be summarised as ON without dyskinesia + ON with non-troublesome dyskinesia + ON with troublesome dyskinesia.

Responder analysis will be performed as:

- OFF-time responders: 1 hour or more reduction in OFF-time from baseline to each post-baseline visits.
- ON-time responders: 1 hour or more increase in ON-time from baseline to each post-baseline visit.

In addition, 1.5, 2, 2.5 hours reduction in OFF-time and increase in ON-time from baseline to all post-baseline visits will be calculated.

The following statistical output will be provided:

Table 15.2.7.1.1 Summary of Functional Status (Time in Minutes) – Full Analysis Set
Table 15.2.7.1.2 Summary of Functional Status (Time in Minutes) – Per-Protocol Set
OFF, ON, ON with troublesome dyskinesia, ON without troublesome dyskinesia, ON with non-troublesome dyskinesia, ON without dyskinesia, asleep and change from baseline will be summarised for baseline and endpoint.

Table 15.2.7.2.1 Summary of Functional Status (Percentage) – Full Analysis Set
Table 15.2.7.2.2 Summary of Functional Status (Percentage) – Per-Protocol Set

OFF, ON, ON with troublesome dyskinesia, ON without troublesome dyskinesia, ON with non-troublesome dyskinesia, ON without dyskinesia and change from baseline will be summarised for baseline and endpoint.

Table 15.2.7.3.1 Responder Analysis of OFF-time and ON-time – Full Analysis Set
Table 15.2.7.3.2 Responder Analysis of OFF-time and ON-time – Per-Protocol Set
OFF-time reduction and ON-time increase from baseline to each post-baseline visit will be summarised by defined responder categories.

Listing 16.2.3.6.1 Hauser's Parkinson's Disease Diary – Enrolled Set
Hauser's Parkinson's Disease Diary data will be listed for each patient in enrolled set.

Listing 16.2.3.6.2 Hauser's Parkinson's Disease Diary Analysis Parameters – Enrolled Set
Hauser's Parkinson's Disease Diary analysis parameters will be listed for each patient in enrolled set by analysis visit.

5.5.2.7 Morning Dystonia

Patients will be asked if they experienced any morning dystonia within the last week before Visit 2b, Visit 4, Visit 5 and Visit 6/EDV.

The following statistical output will be provided:

Table 15.2.8.1.1 Summary of Morning Dystonia – Full Analysis Set
Table 15.2.8.1.2 Summary of Morning Dystonia – Per-Protocol Set
Morning dystonia evaluation will be summarised for each visit at which the assessment was performed.

Table 15.2.8.2.1 Shift Table of Morning Dystonia – Full Analysis Set
Table 15.2.8.2.2 Shift Table of Morning Dystonia – Per-Protocol Set
Shift tables will be provided showing changes between Visit 2b (baseline) and all post-baseline visits in the number and frequency of patients with morning dystonia (yes) and without morning dystonia (no). Patients with missing data will be presented as part of a "missing" category.

Listing 16.2.3.7 Morning Dystonia – Enrolled Set
Morning dystonia data will be displayed for each patient at all applicable visits in the enrolled set.

5.5.2.8 Use of Rescue Medication

The intake of rescue medication will be recorded in a patient diary. Starting with Visit 2b, the patients will receive a rescue medication diary and will be trained to daily record if any rescue medication was taken or not. In case of intake, the name of the rescue medication (paracetamol or tramadol) and the number of tablets/capsules taken have to be recorded.

The frequency of rescue medication intakes will be summarised by type of rescue medication, by overall and periods as described below:

- overall – from first IP intake day to the day before Visit 6/EDV
- from first IP to Visit 4 - from first IP intake day to the day before Visit 4
- from Visit 4 to Visit 5 - from Visit 4 day to the day before Visit 5
- from Visit 5 to Visit 6 - from Visit 5 day to the day before Visit 6
- within 30 days before Visit 4 (this period could contain less than 30 days)
- within 30 days before Visit 5
- within 30 days before Visit 6.

If both medications are used on the same day, then both will be used for calculation. If duplicated entries are present the worst case will be applied for the analysis, i.e. in case a record with and without rescue medication intake is documented in the diary, the record with rescue medication intake will be used.

Additionally, diary adherence by overall and periods will be calculated as:

$$Diary\ adherence\ in\ period\ (\%) = \frac{100 * filled\ days\ in\ period}{end\ date\ of\ period - start\ date\ of\ period + 1}$$

The frequency of rescue medication intakes and diary adherence will be summarised using data from first IP intake day to the day before Visit 6/EDV. Other collected data outside this period will be listed.

The following statistical output will be provided:

Table 15.2.9.1.1 Summary of Usage Frequency of Rescue Medication – Full Analysis Set
Table 15.2.9.1.2 Summary of Usage Frequency of Rescue Medication – Per-Protocol Set
Usage frequency of rescue medication will be summarised by type of rescue medication, by overall and periods.

Table 15.2.9.2.1 Summary of Rescue Medication Diary Adherence – Full Analysis Set
Table 15.2.9.2.2 Summary of Rescue Medication Diary Adherence – Per-Protocol Set
Rescue medication adherence will be summarised by overall and periods.

Listing 16.2.3.8 Use of Rescue Medication – Safety Set
Use of rescue medication data will be displayed for each patient in the safety set.

5.6 Safety Analysis

The SS will be used for the analysis of safety data.

5.6.1 Adverse Events

AEs will be coded according to latest MedDRA® Version 23.1.

Adverse event data includes:

- adverse event name
- onset date/time and stop date
- action taken with study medication (dose not changed, dose increased, dose reduced, drug interrupted, drug withdrawn, not applicable, unknown)
- other actions (none, medication required, tests required, hospitalisation required or prolonged, withdrawn from study, other – specified)
- outcome of event (recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, unknown)
- seriousness (yes or no)
- severity (mild, moderate, severe)
- relationship (unrelated, unlikely possible, probable, definite)

All AEs will be presented in listings.

Summaries of AE will include AEs defined as **treatment-emergent adverse events (TEAEs)**, defined as AEs with the first onset or worsening after the first IP intake until 14 days after the last IP intake.

If the start date of an AE is incomplete or missing, it will be assumed to be treatment-emergent except if the incomplete start date or the stop date indicates that the event started prior to the first IP intake or later than 14 days after last IP intake.

Adverse events will be further assigned to the following categories:

- **Serious Adverse Events (SAEs):** defined as AEs considered by the investigator as serious, including AEs with an unknown or missing seriousness assessment.
- **Related TEAEs**: AEs assessed as “Possible”, “Definite” or “Probable” to IP, including events with missing IP relationship assessment.
- **Unrelated TEAEs**: AEs assessed as “Unrelated” or “Unlikely” to IP.
- **Severe TEAEs**: AEs assessed as “Severe” in intensity, including events with missing severity assessments.
- **TEAEs leading to discontinuation:** AEs for which “Action taken with IP” is indicated as “drug withdrawn” or “other actions taken” is “withdrawn from study”.
- **TEAEs leading to death:** AEs documented as having a “fatal” outcome.

The following statistical output will be provided:

Table 15.3.1.1 Overall Summary of TEAEs – Safety Set
An overview of TEAEs:

- TEAEs
- Ongoing TEAEs at EOS
- Non-serious TEAEs
- Serious TEAEs
- Related TEAEs
- Related Serious TEAEs
- Severe TEAEs
- TEAEs leading to discontinuation
- Related TEAEs leading to discontinuation
- Serious TEAEs leading to discontinuation
- TEAEs leading to death

will be displayed by treatment and overall for the patients in the safety set.

Table 15.3.1.2 Incidence of TEAEs – Safety Set
Table 15.3.1.3 Incidence of Non-Serious TEAEs – Safety Set
Table 15.3.1.4 Incidence of Serious TEAEs – Safety Set
Table 15.3.1.5 Incidence of Related TEAEs – Safety Set
Table 15.3.1.6 Incidence of Related Serious TEAEs – Safety Set
Table 15.3.1.7 Incidence of TEAEs Leading to Discontinuation – Safety Set
Table 15.3.1.8 Incidence of TEAEs Leading to Death – Safety Set
TEAEs will be summarised by treatment and overall by displaying the numbers of AEs, as well as counts and percentages of patients having experienced AEs. Percentages will be based on the number of patients in the safety set. SOCs and PTs within each SOC will be ordered by descending number of AEs in the total column.

Table 15.3.1.9 Incidence of TEAEs by Severity – Safety Set
Table 15.3.1.10 Incidence of TEAEs by Relationship – Safety Set
TEAEs will be summarised as above within each severity/relationship category.

Listing 16.2.4.1.1 Adverse Events: MedDRA Coding
MedDRA SOC and PTs assigned to each reported AE name will be displayed.

Listing 16.2.4.1.2 Adverse Events: General – Enrolled Set
Listing 16.2.4.1.3 Non-Serious Adverse Events – Safety Set
Listing 16.2.4.1.4 Serious Adverse Events – Safety Set
Listing 16.2.4.1.5 AEs Leading to Discontinuation – Safety Set
Listing 16.2.4.1.6 AEs Leading to Death – Safety Set
All AEs will be displayed by patient including the PT of an AE, onset datetime and stop date, duration and other characteristics of AEs.

5.6.2 Vital Signs

Following vital signs will be collected at Visit 1, Visit 2b, Visit 4, Visit 5 and Visit 6/EDV in siting/standing/supine position:

- systolic blood pressure
- diastolic blood pressure
- heart rate

The following statistical output will be provided:

Table 15.3.2 Summary of Vital Signs – Safety Set
Vital sign parameters will be summarised including change from baseline at each visit where assessments were made by treatment and overall.

Listing 16.2.4.2 Vital Signs – Enrolled Set
Vital signs data will be listed.

5.6.3 Physical Examination

Physical examinations are performed at Visit 1, Visit 5 and Visit 6/EDV on relevant body systems (appearance, skin, eyes, ears-nose-throat, lungs-chest, heart, abdomen, extremities, other). Clinical significance (CS) (yes/no) of any abnormal physical examination finding is assessed by the investigator.

The following statistical output will be presented:

Table 15.3.3.1 Summary of Physical Examination Findings – Safety Set
The number and percentage of patients with normal, abnormal, or CS abnormal physical examinations findings will be displayed by treatment and overall. Percentages will be based on the number of patients with data available at the specified visit.

Table 15.3.3.2 Shift Table of Physical Examination Findings – Safety Set
Shift tables will be provided showing changes between Visit 1 and each post-baseline visit where assessments were made in the number and frequency of patients with normal, abnormal, and clinically relevant abnormal physical examinations findings. Patients with missing data will be presented as part of a "Missing" category.

Listing 16.2.4.3 Physical Examinations – Enrolled Set
Physical examination findings will be listed.

5.6.4 Neurological Examination

Neurological examinations are performed at Visit 1, Visit 5 and Visit 6/EDV on:

- mental status
- cranial nerves
- motor system
- sensory system
- reflexes
- co-ordination

Clinical significance (yes/no) of any abnormal neurological examination finding is assessed by the investigator.

The following statistical output will be presented:

Table 15.3.4.1 Summary of Neurological Examination Findings – Safety Set
The number and percentage of patients with normal, abnormal, or CS abnormal neurological examinations findings will be displayed. Percentages will be based on the number of patients with data available at the specified visit.

Table 15.3.4.2 Shift Table of Neurological Examination Findings – Safety Set
Shift tables will be provided showing changes between Visit 1 and each post-baseline visit where assessments were made in the number and frequency of patients with normal, abnormal, and clinically relevant abnormal neurological examinations findings. Patients with missing data will be presented as part of a "Missing" category.

Listing 16.2.4.4 Neurological Examinations – Enrolled Set
Neurological examination findings will be listed.

5.6.5 Clinical Laboratory Evaluation

Clinical laboratory values (haematology, biochemistry) are collected at Visit 1 and Visit 6/EDV for each laboratory parameter.

If re-test results are available, then the last test result on that visit will be used for the analysis.

Urine samples (in females of childbearing potential only) for pregnancy tests will be collected and analysed on-site via dip-stick analysis at Visit 1, Visit 2b, Visit 5 and Visit 6/EDV.

The following parameters are collected:

Haematology: haemoglobin, haematocrit, red blood cell (RBC) count, mean corpuscular volume (MCV), mean corpuscular/cellular haemoglobin, (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) count, differential WBC count (neutrophiles, lymphocytes, monocytes, eosinophiles, basophiles), platelet count.

Biochemistry: albumin, alanine aminotransferase / glutamic-pyruvic transaminase (ALT/GPT), aspartate aminotransferase / glutamic-oxaloacetic transaminase (AST/GOT), blood urea nitrogen (BUN), chloride, creatine kinase (CK), creatinine, glucose, potassium, sodium, bicarbonate.

Pregnancy test: urine human chorionic gonadotropin (hCG) dipstick analysis.

Haematology and biochemistry test results are assigned an LH classification according to whether the value is lower (L) than or higher (H) than the reference range for that parameter as provided by the corresponding laboratory.

The following statistical output will be provided:

Table 15.3.5.1.1 Summary of Clinical Laboratory Tests: Haematology – Safety Set
Table 15.3.5.1.2 Summary of Clinical Laboratory Tests: Biochemistry – Safety Set
The default summary statistics of clinical laboratory test results will be presented by treatment and overall at Visit 1 and Visit 6/EDV. The absolute change from baseline will be presented as well.

Table 15.3.5.2.1 Clinical Laboratory Tests: Incidence of Haematology Abnormalities – Safety Set
Table 15.3.5.2.2 Clinical Laboratory Tests: Incidence of Biochemistry Abnormalities – Safety Set
The number and percentage of patients with Low, Normal or High categories of each laboratory parameter will be displayed by treatment and overall. Percentages will be based on the number of patients at the specified visit.

Table 15.3.5.3.1 Clinical Laboratory Tests: Shift Table of Haematology Results – Safety Set
Table 15.3.5.3.2 Clinical Laboratory Tests: Shift Table of Biochemistry Results – Safety Set
Shift tables showing changes in the number and frequency of patients with respect to the normal range between Visit 1 and Visit 6/EDV will be provided. Patients with missing data will be presented as part of a "Missing" category.

Listing 16.2.4.5.1 Laboratory Data: Haematology – Enrolled Set
Listing 16.2.4.5.2 Laboratory Data: Biochemistry – Enrolled Set
Safety laboratory test results will be listed.

Listing 16.2.4.5.3 Laboratory Data: Pregnancy Test – Enrolled Set
Urine pregnancy (dipstick) data will be listed.

6. BLIND DATA REVIEW

A BDR will be performed after data entry and following a database lock. The following goals are defined for the BDR:

- to identify major/minor protocol deviations
- to identify patients that are not eligible for the per-protocol population
- to identify protocol deviations that may affect the primary endpoint
- review of rescue medication data
- to discuss any open data issues

All decisions made during the BDR will be documented in the BDR report before the closure of the database and the randomisation code release.

An appropriate clinical study team, including a physician, will review potential protocol deviations and relevant information regarding those deviations to determine a possible impact on efficacy endpoints. An assessment will be made as to the effect of each of the possible deviations to determine if it is considered major or minor. The status, major or minor, of each protocol deviation will be documented in the BDR report. A patient may have one or more major protocol deviations resulting in the exclusion of that patient from the per-protocol analysis set.

Protocol deviations of the following categories will be reviewed during the BDR.

Inclusion Criteria at Visit 1

No.	Inclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#01.	1. Able to comprehend and willing to sign an informed consent form and to comply with all aspects of the study.	Case by case
PD#02.	2. Male or female patients aged 30 years or older. *Protocol Germany* 2. Male or female patients aged 50 to 85 years.	Case by case
PD#03.	3. Experiencing PD associated pain for at least 4 weeks prior to V1.	Case by case
PD#04.	4. Diagnosed with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (2006) or according to MDS Clinical Diagnostic Criteria (2015).	Case by case
PD#05.	5. Disease severity Stages I-III (modified Hoehn & Yahr staging) at ON.	Case by case
PD#06.	6. Treated with 3 to 8 intakes per day of L-DOPA/DDCI (which may include a slow-release formulation), on a stable regimen for at least 4 weeks before V1.	Case by case
PD#07.	7. In case of any other anti-PD-treatment, it should be on a stable regimen for at least 4 weeks before V1, and not likely to need any adjustment until V6.	Case by case
PD#08.	8. No changes in chronic treatment regimen for pain within the last 4 weeks before V1. This includes medication (including but not limited to paracetamol, opioids, nonsteroidal anti-inflammatory drugs [NSAIDS], antidepressants, anticonvulsants and corticosteroids) and non-medication therapies (including but not limited to transcutaneous electrical nerve stimulation and bioelectrical therapy).	Case by case
PD#09.	9. Signs of "wearing-off" phenomenon (end-of-dose motor fluctuations) with average total daily OFF time while awake of at least 1.5 hours, excluding the early morning pre-first dose OFF, despite optimal anti-PD therapy (based on investigator's assessment).	Case by case

No.	Inclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#10.	10. Domain 3 of KPPS ≥ 12.	Case by case
PD#11.	11. For females: Postmenopausal for at least 2 years before V1, surgically sterile for at least 6 months before V1, or practicing effective contraception until V6. Female patients who request to continue with oral contraceptives must be willing to use non-hormonal methods of contraception in addition during the course of this study. For males: Male patients who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of highly effective contraception during the treatment period until V6. *Protocol Germany* 11. For females: Postmenopausal for at least 2 years before V1 or surgically sterile for at least 6 months before V1. For males: Male patients who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of highly effective contraception during the treatment period until V6. *Protocol Czech Republic* 11. For females: Postmenopausal for at least 2 years before V1, surgically sterile for at least 6 months before V1, or practicing highly effective contraception until V6. Female patients who request to continue with oral contraceptives must be willing to use non-hormonal methods of contraception in addition during the course of this study. For males: Male patients who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of highly effective contraception during the treatment period until V6.	Case by case

Inclusion Criteria at Visit 2b

No.	Exclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#12.	12. Have filled-in self-rating diary in accordance with the diary instructions and with ≥ 3 missing entries per day, in the 3 days preceding V2a/V2b.	Case by case
PD#13.	13. With at least 1.5 OFF hours per day, excluding the early morning pre-first dose OFF period (i.e. the time between wake-up and response to the first L-DOPA/DDCI dosage), as recorded in at least 2 of the 3 days in the self-rating diary for the 3 days preceding V2a/V2b.	Case by case
PD#14.	14. Results of the screening laboratory tests are considered acceptable by the investigator (i.e. not clinically relevant for the well-being of the patient or for the purpose of the study).	Case by case
PD#15.	15. Domain 3 of KPPS ≥ 12.	Case by case
PD#16.	16. Adequate compliance to relevant (PD and pain related) concomitant medication during the screening period (based on the investigator's judgment).	Case by case

Exclusion Criteria

No.	Exclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#17.	1. Non-idiopathic PD (atypical parkinsonism, secondary [acquired or symptomatic] parkinsonism, Parkinson-plus syndrome).	Case by case
PD#18.	2. Severe and/or unpredictable OFF periods, according to investigator judgement.	Case by case
PD#19.	3. Major/prominent non-PD-related pain (e.g. due to malignant disease).	Case by case
PD#20.	4. Treatment with prohibited medication: entacapone, tolcapone, monoamine oxidase (MAO) inhibitors (except selegiline up to 10 mg/day in oral formulation or 1.25 mg/day in buccal absorption formulation, rasagiline up to 1 mg/day or safinamide up to 100 mg/day), or antiemetics with antidopaminergic action (except domperidone) within the last 4 weeks before V1.	Case by case
PD#21.	5. Previous or planned (during the entire study duration) L-DOPA/carbidopa intestinal gel infusion, deep brain stimulation or stereotactic surgery (e.g. pallidotomy, thalamotomy).	Case by case
PD#22.	6. Treatment with apomorphine within the last 4 weeks before V1 or likely to be needed at any time until V6.	Case by case
PD#23.	7. Previous or current use of opicapone.	Case by case
PD#24.	8. Use of any other IP, currently or within the 3 months (or within 5 half-lives of the IP, whichever is longer) before V1.	Case by case
PD#25.	9. Past (within the past year) or present history of suicidal ideation or suicide attempts.	Case by case
PD#26.	10. Current or previous (within the past year) alcohol or substance abuse excluding caffeine or nicotine.	Case by case
PD#27.	11. Phaeochromocytoma, paraganglioma, or other catecholamine secreting neoplasms.	Case by case
PD#28.	12. Known hypersensitivity to the excipients of IP (including lactose intolerance, galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption) or of rescue medication.	Case by case
PD#29.	13. History of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis.	Case by case
PD#30.	14. History of severe hepatic impairment (Child-Pugh Class C).	Case by case
PD#31.	15. Previous history of psychosis or psychiatric disorders, including severe major depression.	Case by case
PD#32.	16. Any medical condition that might place the patient at increased risk or interfere with assessments.	Case by case
PD#33.	17. For females: Pregnant or breastfeeding.	Case by case
	Protocol Germany Not Applicable.	
PD#34.	18. Employees of the investigator, study centre, sponsor, clinical research organisation and study consultants, when employees are directly involved in this study or other studies under the direction of this investigator or study centre, and their family members.	Minor
PD#35.	19. Persons committed to an institution by virtue of an order issued either by the judicial or other authorities.	Minor

Additional study conduct deviations

No.	Deviation	Major/ Minor/ Case by case review
PD#36.	IP treatment compliance <80% or >120%	Case by case
PD#37.	Intake of prohibited medications	Case by case
PD#38.	Visits performed not according to the study protocol schedule	Case by case
PD#39.	Missing efficacy assessments	Case by case
PD#40.	The dosage of L-DOPA/DDCI changed from Visit 4 to the Visit 6/EDV or dosage of L-DOPA/DDCI increased more than baseline dose level from Visit 2b to Visit 6/EDV.	Case by case
PD#41.	PDs from the global Protocol deviations log that may significantly affect the primary study objective and are not covered by other listings	Case by case
PD#42.	Paracetamol and tramadol taken on the same day according to rescue medication diary.	Case by case

Reference listings will be made available to facilitate the review of the protocol deviations. The specific content and format of listings to be reviewed during the BDR meeting (including any additional requirements that may be necessary to aid in review) will be determined outside the scope of this SAP.

7. INTERIM ANALYSIS

No interim analysis is planned for this study.

8. CHANGES TO THE ANALYSIS AS LAID DOWN IN THE PROTOCOL AND MODIFICATIONS

The following changes were made to the analysis as laid down in the clinical study protocol and protocol modification(s):

- The primary hypothesis was changed from H_0: $\mu_T - \mu_C \leq 3$ scores, H_1: $\mu_T - \mu_C > 3$ scores to H_0: $\mu_T = \mu_C$, H_1: $\mu_T \neq \mu_C$.
- The primary efficacy analysis model was changed from ANCOVA to MMRM.
- Imputation using LOCF approach will not be used. For sensitivity purpose, multiple imputation (MI) approach under the assumption that data are missing not at random (MNAR) will be used.
- Endpoint of change from baseline in Domain B (anxiety) of Movement Disorder Society-sponsored Non-motor Rating Scale (MDS-NMS) will be referred to as secondary endpoint instead of key secondary endpoint.
- Hauser's Parkinson disease diary baseline definition changed. Instead of using the last 3 days before the visit, it was agreed to use the last 3 diary days within 7 days before Visit 2a/ Visit 2b.

9. REFERENCES

1. SAS® Institute Inc., Cary, North Carolina, United States of America, Version 9.4.
2. MedDRA – Medical Dictionary for Regulated Activities. International Federation of Pharmaceutical Manufacturers Associations (IFPMA), c/o TRW, VAR1/8A/MSSO, 12011 Sunset Hills Road, Reston, VA 20190-3285, USA, 23.1.
3. WHO – Drug Dictionary. World Health Organization Collaborating Center for International Drug Monitoring, P.O. Box 26, S-751 03 Uppsala, Sweden, March 2020.
4. Goetz CG, Luo S, Wang L, Tilley BC, LaPelle NR, Stebbins GT. Handling missing values in the MDS-UPDRS. Movement Disorders. 2015;30(12):1632-1638.

10. APPENDICES

Shells for tables, listings, and figures are available in the following attachments:

1. BIA-91067-404_Table_Shells_Final_1.0_20240521.docx

2. BIA-91067-404_Listing_Shells_Final_1.0_20240521.docx

3. BIA-91067-404_Figure_Shells_Final_1.0_20240521.docx

10.1 Tables

Appendix tables defined below will be provided in separate .rtf files for each output.

No	Table Identifier, Title	Output File
Baseline Characteristics		
1	Table 15.1.1.1 Analysis Sets – Enrolled Set	BIA-91067-404-T-150101010000-sets-es.rtf
2	Table 15.1.1.2 Reasons for Exclusion from Analysis Sets – Randomised Set	BIA-91067-404-T-150101020000-sets-excl-rs.rtf
3	Table 15.1.2 Screening Failures – Enrolled Set	BIA-91067-404-T-150102000000-sf-es.rtf
4	Table 15.1.3 Major Protocol Deviations – Full Analysis Set	BIA-91067-404-T-150103000000-pd-fas.rtf
5	Table 15.1.4 Patient Disposition – Safety Set	BIA-91067-404-T-150104000000-ds-ss.rtf
6	Table 15.1.5 Number of Patients by Country and Site – Randomised Set	BIA-91067-404-T-150105000000-cntr-site-rn.rtf
7	Table 15.1.6 Number of Patients by Visit – Safety Set	BIA-91067-404-T-150106000000-visit-ss.rtf
8	Table 15.1.7.1 Summary of Subgroups – Full Analysis Set	BIA-91067-404-T-150107010000-subgr-fas.rtf
9	Table 15.1.7.2 Summary of Subgroups – Per-Protocol Set	BIA-91067-404-T-150107020000-subgr-pps.rtf
10	Table 15.1.8.1 Demographics and Baseline Characteristics – Safety Set	BIA-91067-404-T-150108010000-dm-basechar-ss.rtf
11	Table 15.1.8.2 Demographics and Baseline Characteristics – Full Analysis Set	BIA-91067-404-T-150108020000-dm-basechar-fas.rtf
12	Table 15.1.8.3 Demographics and Baseline Characteristics – Per-Protocol Set	BIA-91067-404-T-150108030000-dm-basechar-pps.rtf
13	Table 15.1.9.1 Summary of Neurological History – Safety Set	BIA-91067-404-T-150109010000-neuro-h-ss.rtf
14	Table 15.1.9.2 Summary of Neurological History – Full Analysis Set	BIA-91067-404-T-150109020000-neuro-h-fas.rtf
15	Table 15.1.9.3 Summary of Neurological History – Per-Protocol Set	BIA-91067-404-T-150109030000-neuro-h-pps.rtf
16	Table 15.1.10.1.1 Prior Medical Conditions – Safety Set	BIA-91067-404-T-150110010100-mh-pr-ss.rtf
17	Table 15.1.10.1.2 Prior Medical Conditions – Full Analysis Set	BIA-91067-404-T-150110010200-mh-pr-fas.rtf
18	Table 15.1.10.2.1 Ongoing Medical Conditions – Safety Set	BIA-91067-404-T-150110020100-mh-ong-ss.rtf
19	Table 15.1.10.2.2 Ongoing Medical Conditions – Full Analysis Set	BIA-91067-404-T-150110020200-mh-ong-fas.rtf
20	Table 15.1.11.1.1 Prior Medications – Safety Set	BIA-91067-404-T-150111010100-prmed-ss.rtf
21	Table 15.1.11.1.2 Prior Medications – Full Analysis Set	BIA-91067-404-T-150111010200-prmed-fas.rtf
22	Table 15.1.11.2.1 Concomitant Medications – Safety Set	BIA-91067-404-T-150111020100-cm-ss.rtf
23	Table 15.1.11.2.2 Concomitant Medications – Full Analysis Set	BIA-91067-404-T-150111020200-cm-fas.rtf
24	Table 15.1.11.3.1 L-DOPA/DDCI Medication – Safety Set	BIA-91067-404-T-150111030100-ldopa-ddci-ss.rtf
25	Table 15.1.11.3.2 L-DOPA/DDCI Medication – Full Analysis Set	BIA-91067-404-T-150111030200-ldopa-ddci-fas.rtf
26	Table 15.1.11.4 Tramadol Taken Within 30 Days Before the Endpoint – Safety Set	BIA-91067-404-T-150111040000-tramadol30-ss.rtf

No	Table Identifier, Title	Output File
27	Table 15.1.11.5.1 Change of L-DOPA/DDCI Medication – Safety Set	BIA-91067-404-T-150111050100-ldopa-ddci-chg-ss.rtf
28	Table 15.1.11.5.2 Change of L-DOPA/DDCI Medication – Full Analysis Set	BIA-91067-404-T-150111050200-ldopa-ddci-chg-fas.rtf
29	Table 15.1.11.5.3 Change of L-DOPA/DDCI Medication – Per-Protocol Set	BIA-91067-404-T-150111050300-ldopa-ddci-chg-pps.rtf
30	Table 15.1.12.1.1 Treatment Duration – Safety Set	BIA-91067-404-T-150112010100-trtdur-ss.rtf
31	Table 15.1.12.1.2 Treatment Duration – Full Analysis Set	BIA-91067-404-T-150112010200-trtdur-fas.rtf
32	Table 15.1.12.1.3 Treatment Duration – Per-Protocol Set	BIA-91067-404-T-150112010300-trtdur-pps.rtf
33	Table 15.1.12.2.1 Treatment Compliance – Safety Set	BIA-91067-404-T-150112020100-trtcompl-ss.rtf
34	Table 15.1.12.2.2 Treatment Compliance – Full Analysis Set	BIA-91067-404-T-150112020200-trtcompl-fas.rtf
35	Table 15.1.12.2.3 Treatment Compliance – Per-Protocol Set	BIA-91067-404-T-150112020300-trtcompl-pps.rtf
Efficacy Data		
36	Table 15.2.1.1.1.1 Summary of KPPS – Full Analysis Set	BIA-91067-404-T-150201010101-kpps-fas.rtf
37	Table 15.2.1.1.1.2 Summary of KPPS – Per-Protocol Set	BIA-91067-404-T-150201010102-kpps-pps.rtf
38	Table 15.2.1.1.2.1 Summary of the Domain 3 of KPPS by Subgroup – Full Analysis Set	BIA-91067-404-T-150201010201-sub-kpps-fas.rtf
39	Table 15.2.1.1.2.2 Summary of the Domain 3 of KPPS by Subgroup – Per-Protocol Set	BIA-91067-404-T-150201010202-sub-kpps-pps.rtf
40	Table 15.2.1.2.1.1 Analysis of the Domain 3 of KPPS – Full Analysis Set	BIA-91067-404-T-150201020101-kpps-d3-mmrm-fas.rtf
41	Table 15.2.1.2.1.2 Analysis of the Domain 3 of KPPS – Per-Protocol Set	BIA-91067-404-T-150201020102-kpps-d3-mmrm-pps.rtf
42	Table 15.2.1.2.2.1 Analysis of the Domain 3 of KPPS (MI) – Full Analysis Set	BIA-91067-404-T-150201020201-kpps-d3-mmrm-mi-fas.rtf
43	Table 15.2.1.2.2.2 Analysis of the Domain 3 of KPPS (MI) – Per-Protocol Set	BIA-91067-404-T-150201020202-kpps-d3-mmrm-mi-pps.rtf
44	Table 15.2.1.2.3.1 Analysis of the Domain 3 of KPPS by Subgroup – Full Analysis Set	BIA-91067-404-T-150201020301-sub-kpps-d3-mmrm-fas
45	Table 15.2.1.2.3.2 Analysis of the Domain 3 of KPPS by Subgroup – Per-Protocol Set	BIA-91067-404-T-150201020302-sub-kpps-d3-mmrm-pps
46	Table 15.2.2.1.1 Analysis of the Domain 4 of KPPS – Full Analysis Set	BIA-91067-404-T-150202010100-kpps-d4-mmrm-fas.rtf
47	Table 15.2.2.1.2 Analysis of the Domain 4 of KPPS – Per-Protocol Set	BIA-91067-404-T-150202010200-kpps-d4-mmrm-pps.rtf
48	Table 15.2.2.2.1 Analysis of KPPS Total Score – Full Analysis Set	BIA-91067-404-T-150202020100-kpps-tot-mmrm-fas.rtf
49	Table 15.2.2.2.2 Analysis of KPPS Total Score – Per-Protocol Set	BIA-91067-404-T-150202020200-kpps-tot-mmrm-pps.rtf
50	Table 15.2.3.1.1 Summary of MDS-NMS – Full Analysis Set	BIA-91067-404-T-150203010100-mds-nms-fas.rtf
51	Table 15.2.3.1.2 Summary of MDS-NMS – Per-Protocol Set	BIA-91067-404-T-150203010200-mds-nms-pps.rtf
52	Table 15.2.3.2.1 Analysis of MDS-NMS – Full Analysis Set	BIA-91067-404-T-150203020100-mds-nms-a-fas.rtf
53	Table 15.2.3.2.2 Analysis of MDS-NMS – Per-Protocol Set	BIA-91067-404-T-150203020200-mds-nms-a-pps.rtf
54	Table 15.2.4.1.1 Summary of MDS-UPDRS – Full Analysis Set	BIA-91067-404-T-150204010100-mds-updrs-fas.rtf
55	Table 15.2.4.1.2 Summary of MDS-UPDRS – Per-Protocol Set	BIA-91067-404-T-150204010200-mds-updrs-pps.rtf
56	Table 15.2.4.2.1 Analysis of MDS-UPDRS Part III/IV Total Score – Full Analysis Set	BIA-91067-404-T-150204020100-mds-updrs-a-fas.rtf
57	Table 15.2.4.2.2 Analysis of MDS-UPDRS Part III/IV Total Score – Per-Protocol Set	BIA-91067-404-T-150204020200-mds-updrs-a-pps.rtf

No	Table Identifier, Title	Output File
58	Table 15.2.5.1.1 Summary of PDQ-8 Index – Full Analysis Set	BIA-91067-404-T-150205010100-pdq8-fas.rtf
59	Table 15.2.5.1.2 Summary of PDQ-8 Index – Per-Protocol Set	BIA-91067-404-T-150205010200-pdq8-pps.rtf
60	Table 15.2.5.2.1 Analysis of PDQ-8 Index – Full Analysis Set	BIA-91067-404-T-150205020100-pdq8-a-fas.rtf
61	Table 15.2.5.2.2 Analysis of PDQ-8 Index – Per-Protocol Set	BIA-91067-404-T-150205020200-pdq8-a-pps.rtf
62	Table 15.2.6.1.1 Summary of CGIC and PGIC – Full Analysis Set	BIA-91067-404-T-150206010100-cgic-pgic-fas.rtf
63	Table 15.2.6.1.2 Summary of CGIC and PGIC – Per-Protocol Set	BIA-91067-404-T-150206010200-cgic-pgic-pps.rtf
64	Table 15.2.6.2.1 Improvement Analysis of CGIC and PGIC – Full Analysis Set	BIA-91067-404-T-150206020100-cgic-pgic-a-fas.rtf
65	Table 15.2.6.2.2 Improvement Analysis of CGIC and PGIC – Per-Protocol Set	BIA-91067-404-T-150206020200-cgic-pgic-a-pps.rtf
66	Table 15.2.7.1.1 Summary of Functional Status (Time in Minutes) – Full Analysis Set	BIA-91067-404-T-150207010100-func-min-fas.rtf
67	Table 15.2.7.1.2 Summary of Functional Status (Time in Minutes) – Per-Protocol Set	BIA-91067-404-T-150207010200-func-min-pps.rtf
68	Table 15.2.7.2.1 Summary of Functional Status (Percentage) – Full Analysis Set	BIA-91067-404-T-150207020100-func-perc-fas.rtf
69	Table 15.2.7.2.2 Summary of Functional Status (Percentage) – Per-Protocol Set	BIA-91067-404-T-150207020200-func-perc-pps.rtf
70	Table 15.2.7.3.1 Responder Analysis of OFF-time and ON-time – Full Analysis Set	BIA-91067-404-T-150207030100-func-resp-fas.rtf
71	Table 15.2.7.3.2 Responder Analysis of OFF-time and ON-time – Per-Protocol Set	BIA-91067-404-T-150207030200-func-resp-pps.rtf
72	Table 15.2.8.1.1 Summary of Morning Dystonia – Full Analysis Set	BIA-91067-404-T-150208010100-morn-dyst-fas.rtf
73	Table 15.2.8.1.2 Summary of Morning Dystonia – Per-Protocol Set	BIA-91067-404-T-150208010200-morn-dyst-pps.rtf
74	Table 15.2.8.2.1 Shift Table of Morning Dystonia – Full Analysis Set	BIA-91067-404-T-150208020100-morn-dyst-shift-fas.rtf
75	Table 15.2.8.2.2 Shift Table of Morning Dystonia – Per-Protocol Set	BIA-91067-404-T-150208020200-morn-dyst-shift-pps.rtf
76	Table 15.2.9.1.1 Summary of Usage Frequency of Rescue Medication – Full Analysis Set	BIA-91067-404-T-150209010100-rescdiary-use-fas.rtf
77	Table 15.2.9.1.2 Summary of Usage Frequency of Rescue Medication – Per-Protocol Set	BIA-91067-404-T-150209010200-rescdiary-use-pps.rtf
78	Table 15.2.9.2.1 Summary of Rescue Medication Diary Adherence – Full Analysis Set	BIA-91067-404-T-150209020100-rescdiary-adh-fas.rtf
79	Table 15.2.9.2.2 Summary of Rescue Medication Diary Adherence – Per-Protocol Set	BIA-91067-404-T-150209020200-rescdiary-adh-pps.rtf

No	Table Identifier, Title	Output File
Safety Data		
80	Table 15.3.1.1 Overall Summary of TEAEs – Safety Set	BIA-91067-404-T-150301010000-teaesum-ss.rtf
81	Table 15.3.1.2 Incidence of TEAEs – Safety Set	BIA-91067-404-T-150301020000-teae-ss.rtf
82	Table 15.3.1.3 Incidence of Non-Serious TEAEs – Safety Set	BIA-91067-404-T-150301030000-teae-nonser-ss.rtf
83	Table 15.3.1.4 Incidence of Serious TEAEs – Safety Set	BIA-91067-404-T-150301040000-tesae-ss.rtf
84	Table 15.3.1.5 Incidence of Related TEAEs – Safety Set	BIA-91067-404-T-150301050000-teae-rel-ss.rtf
85	Table 15.3.1.6 Incidence of Related Serious TEAEs – Safety Set	BIA-91067-404-T-150301060000-tesae-rel-ss.rtf
86	Table 15.3.1.7 Incidence of TEAEs Leading to Discontinuation – Safety Set	BIA-91067-404-T-150301070000-teae-disc-ss.rtf
87	Table 15.3.1.8 Incidence of TEAEs Leading to Death – Safety Set	BIA-91067-404-T-150301080000-teae-death-ss.rtf
88	Table 15.3.1.9 Incidence of TEAEs by Severity – Safety Set	BIA-91067-404-T-150301090000-teae-bysev-ss.rtf
89	Table 15.3.1.10 Incidence of TEAE by Relationship – Safety Set	BIA-91067-404-T-150301100000-teae-byrel-ss.rtf
90	Table 15.3.2 Summary of Vital Signs – Safety Set	BIA-91067-404-T-150302000000-vs-ss.rtf
91	Table 15.3.3.1 Summary of Physical Examination Findings – Safety Set	BIA-91067-404-T-150303010000-pe-ss.rtf
92	Table 15.3.3.2 Shift Table of Physical Examination Findings – Safety Set	BIA-91067-404-T-150303020000-pe-shift-ss.rtf
93	Table 15.3.4.1 Summary of Neurological Examination Findings – Safety Set	BIA-91067-404-T-150304010000-neuro-ss.rtf
94	Table 15.3.4.2 Shift Table of Neurological Examination Findings – Safety Set	BIA-91067-404-T-150304020000-neuro-shift-ss.rtf
95	Table 15.3.5.1.1 Summary of Clinical Laboratory Tests: Haematology – Safety Set	BIA-91067-404-T-150305010100-lbh-ss.rtf
96	Table 15.3.5.1.2 Summary of Clinical Laboratory Tests: Biochemistry – Safety Set	BIA-91067-404-T-150305010200-lbb-ss.rtf
97	Table 15.3.5.2.1 Clinical Laboratory Tests: Incidence of Haematology Abnormalities – Safety Set	BIA-91067-404-T-150305020100-lbh-abnorm-ss.rtf
98	Table 15.3.5.2.2 Clinical Laboratory Tests: Incidence of Biochemistry Abnormalities – Safety Set	BIA-91067-404-T-150305020200-lbb-abnorm-ss.rtf
99	Table 15.3.5.3.1 Clinical Laboratory Tests: Shift Table of Haematology Results – Safety Set	BIA-91067-404-T-150305030100-lbh-shift-ss.rtf
100	Table 15.3.5.3.2 Clinical Laboratory Tests: Shift Table of Biochemistry Results – Safety Set	BIA-91067-404-T-150305030200-lbb-shift-ss.rtf

10.2 Listings

Appendix listings defined below will be provided in separate .rtf files for each output.

No	Listing Identifier, Title	Output File
Demographic and Study Population Data		
1	Listing 16.2.1.1 Patient Disposition – Safety Set	BIA-91067-404-L-1602010100-ds-ss
2	Listing 16.2.1.2 Screening Failures – Enrolled Set	BIA-91067-404-L-1602010200-sf-es
3	Listing 16.2.1.3 Patient Visits – Enrolled Set	BIA-91067-404-L-1602010300-visit-es
4	Listing 16.2.1.4 Exclusions from Analysis Sets – Enrolled Set	BIA-91067-404-L-1602010400-sets-excl-es
5	Listing 16.2.1.5 Patient Allocation to Treatments – Randomised Set	BIA-91067-404-L-1602010500-aloc-trt-rn
6	Listing 16.2.1.6 Major Protocol Deviations – Safety Set	BIA-91067-404-L-1602010600-pd-ss
7	Listing 16.2.1.7 Inclusion Criteria Not Met and Exclusion Criteria Met – Enrolled Set	BIA-91067-404-L-1602010700-ie-es
8	Listing 16.2.1.8 Demographics and Baseline Characteristics – Enrolled Set	BIA-91067-404-L-1602010800-dm-basechar-es
9	Listing 16.2.1.9 Neurological History – Enrolled Set	BIA-91067-404-L-1602010900-neuro-h-es
10	Listing 16.2.1.10 Medical History – Enrolled Set	BIA-91067-404-L-1602011000-mh-es
11	Listing 16.2.1.11 Medications – Enrolled Set	BIA-91067-404-L-1602011100-cm-es
12	Listing 16.2.1.12.1 L-dopa/DDCI Medications – Enrolled Set	BIA-91067-404-L-1602011201-ldopa-ddci-es
13	Listing 16.2.1.12.2 Change of L-dopa/DDCI Medications – Safety Set	BIA-91067-404-L-1602011202-ldopa-ddci-chg-ss
14	Listing 16.2.2.1 Exposure to IP and Treatment Compliance – Safety Set	BIA-91067-404-L-1602020100-ex-trtcompl-ss
15	Listing 16.2.2.2 Exposure to Rescue Medication – Safety Set	BIA-91067-404-L-1602020200-ex-rescmed-ss
Efficacy Data		
16	Listing 16.2.3.1 KPPS – Enrolled Set	BIA-91067-404-L-1602030100-kpps-es
17	Listing 16.2.3.2 MDS-NMS – Enrolled Set	BIA-91067-404-L-1602030200-mds-nms-es
18	Listing 16.2.3.3.1 MDS-UPDRS – Enrolled Set	BIA-91067-404-L-1602030301-mds-updrs-es
19	Listing 16.2.3.3.2 MDS-UPDRS Part III Additional Information – Enrolled Set	BIA-91067-404-L-1602030302-mds-updrs-add-es
20	Listing 16.2.3.4 PDQ-8 – Enrolled Set	BIA-91067-404-L-1602030400-pdq8-es
21	Listing 16.2.3.5 CGIC and PGIC – Safety Set	BIA-91067-404-L-1602030500-cgic-pgic-ss
22	Listing 16.2.3.6.1 Hauser's Parkinson's Disease Diary – Enrolled Set	BIA-91067-404-L-1602030601-pd-diary-es
23	Listing 16.2.3.6.2 Hauser's Parkinson's Disease Diary Analysis Parameters – Enrolled Set	BIA-91067-404-L-1602030602-pd-diary-a-es
24	Listing 16.2.3.7 Morning Dystonia – Enrolled Set	BIA-91067-404-L-1602030700-morn-dyst-es
25	Listing 16.2.3.8 Use of Rescue Medication – Safety Set	BIA-91067-404-L-1602030800-rescmed-ss

No	Listing Identifier, Title	Output File
Safety Data		
26	Listing 16.2.4.1.1 Adverse Events: MedDRA Coding	BIA-91067-404-L-1602040101-aecod
27	Listing 16.2.4.1.2 Adverse Events: General – Enrolled Set	BIA-91067-404-L-1602040102-ae-es
28	Listing 16.2.4.1.3 Non-Serious Adverse Events – Safety Set	BIA-91067-404-L-1602040103-ae-nonser-ss
29	Listing 16.2.4.1.4 Serious Adverse Events – Safety Set	BIA-91067-404-L-1602040104-sae-ss
30	Listing 16.2.4.1.5 AEs Leading to Discontinuation – Safety Set	BIA-91067-404-L-1602040105-ae-disc-ss
31	Listing 16.2.4.1.6 AEs Leading to Death – Safety Set	BIA-91067-404-L-1602040106-ae-death-ss
32	Listing 16.2.4.2 Vital Signs – Enrolled Set	BIA-91067-404-L-1602040200-vs-es
33	Listing 16.2.4.3 Physical Examinations – Enrolled Set	BIA-91067-404-L-1602040300-pe-es
34	Listing 16.2.4.4 Neurological Examinations – Enrolled Set	BIA-91067-404-L-1602040400-neuro-es
35	Listing 16.2.4.5.1 Laboratory Data: Haematology – Enrolled Set	BIA-91067-404-L-1602040501-lbh-es
36	Listing 16.2.4.5.2 Laboratory Data: Biochemistry – Enrolled Set	BIA-91067-404-L-1602040502-lbb-es
37	Listing 16.2.4.5.3 Laboratory Data: Pregnancy Test – Enrolled Set	BIA-91067-404-L-1602040503-preg-test-es

10.3 Figures

Appendix figures defined below will be provided in separate .rtf files for each output.

No	Figure Identifier, Title	Output File
Demographic and Study Population Data		
1	Figure 15.1.1 Flow Chart of Subject Disposition – Enrolled Set	BIA-91067-405-F-150101-ds-es.rtf
2	Figure 15.1.2 Flow Chart of Analysis Sets – Enrolled Set	BIA-91067-405-F-150102-sets-es.rtf
Efficacy Data		
4	Figure 15.2.1.1 Domain 3 of KPPS Change from Baseline LS-Means by Visit – Full Analysis Set	BIA-91067-405-F-150201-kpps-d3-mmrm-fas.rtf
5	Figure 15.2.1.2 Domain 3 of KPPS Change from Baseline LS-Means by Visit – Per-Protocol Set	BIA-91067-405-F-150201-kpps-d3-mmrm-pps.rtf
6	Figure 15.2.2.1 Forest Plot of Domain 3 of KPPS by Subgroup – Full Analysis Set	BIA-91067-405-F-150202-kpps-d3-forest-sub-fas.rtf
7	Figure 15.2.2.1 Forest Plot of Domain 3 of KPPS by Subgroup – Per-Protocol Set	BIA-91067-405-F-150202-kpps-d3-forest-sub-fas.rtf

11. SIGNATURES

_____ _____
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Author:
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Statistician, Scope International AG

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Reviewer:
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Principal Statistician, Scope International AG

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Signature *Date*
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Angelika Seedorf
Medical Writer, Scope International AG

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Signature *Date*
Reviewer:
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Note: Sarah Kern is signing on behalf of Miriam Reinhard

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Senior Clinical Operations Manager, Bial – Portela & Cª, S.A.

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