Statistical Analysis Plan for Study M15-736

A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study Comparing the Efficacy, Safety and Tolerability of ABBV-951 to Oral Carbidopa/Levodopa in Advanced Parkinson's Disease Patients

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Version 3.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for ABBV-951 Study M15-736 "A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study Comparing the Efficacy, Safety and Tolerability of ABBV-951 to Oral Carbidopa/Levodopa in Advanced Parkinson's Disease Patients."

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless stated otherwise, all analyses will be performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

This SAP includes changes to analyses described in the protocol. Details are outlined in Section 12.0.

2.0 Study Design and Objectives

2.1 Objectives and Hypotheses

The primary objective of the study is to demonstrate the superiority of continuous subcutaneous infusion (CSCI) of ABBV-951 over oral carbidopa/levodopa (CD/LD) immediate release (IR) tablets for the treatment of motor fluctuations in subjects with advanced Parkinson's disease (aPD) after 12 weeks of therapy.

Clinical Hypothesis: The 24-hour/day CSCI of ABBV-951 will increase "On" time without troublesome dyskinesia ("On" time without dyskinesia plus "On" time with non-troublesome dyskinesia), reduce "Off" time, and improve the Motor Aspects of Experiences of Daily Living compared to CD/LD IR tablets in patients with aPD whose motor fluctuations are inadequately controlled by their current PD medications.

The secondary objective of the study is to assess the local and systemic safety and tolerability of ABBV-951 delivered as a CSCI for 24 hours daily for 12 weeks.

Subject must be judged to be inadequately controlled by current therapy in the investigator's opinion and

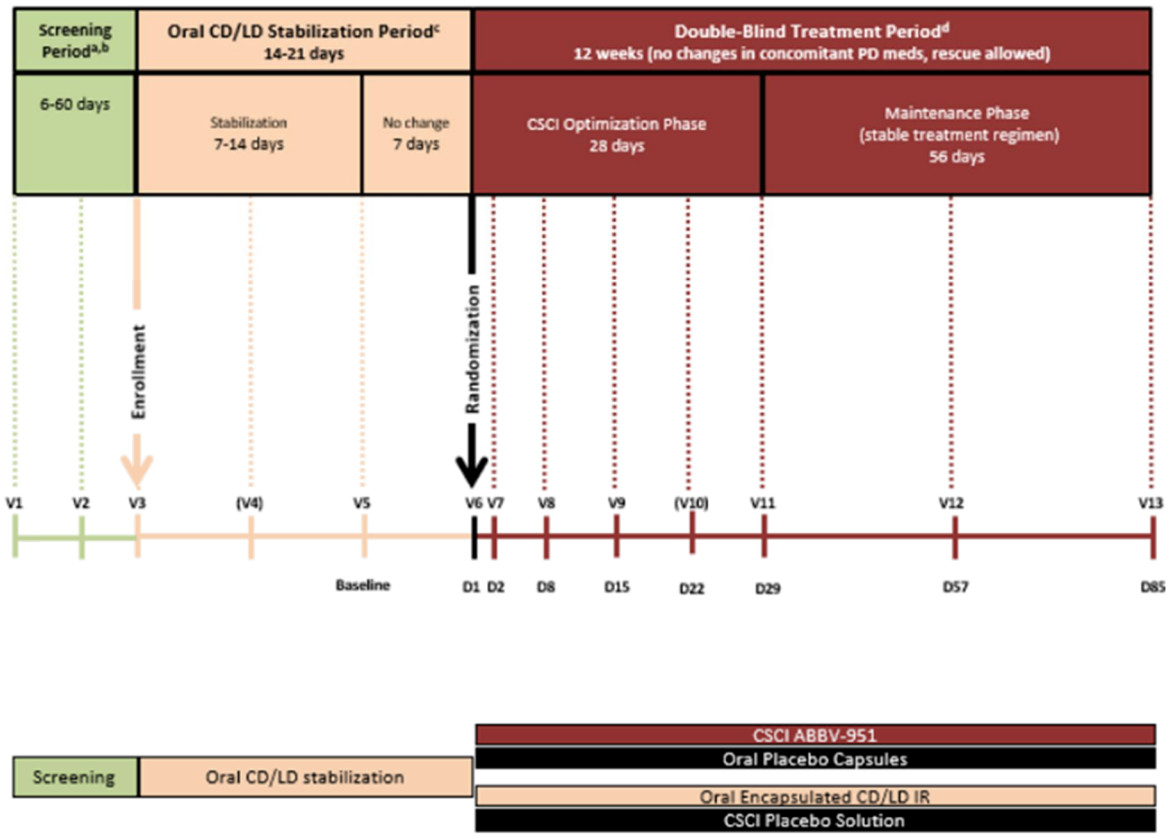
- experience a minimum daily average of 2.5 hours of "Off" time (with a minimum of 2 hours of "Off" time each day) as assessed by PD Diary for 3 consecutive days prior to V3 (Enrollment Visit)

  AND
- maintain at least 2 hours of "Off" time each day for 3 consecutive days before V6 (Randomization Visit).

2.2 Study Design Overview

The schematic of the study is shown in Figure 1.

Figure 1. Study Design Schematic



CD/LD = carbidopa/levodopa; CSCI = continuous subcutaneous infusion; D = Day; IR = immediate release; PD = Parkinson's disease; V = Visit

a. V3 can occur at least 6 days after V1 to allow for V1 results to be fully available for review and for adequate infusion delivery system training and familiarity.

b. Screening Period activities will last at least 6 days; PD Diaries will be collected for at least 3 consecutive days during the Screening Period prior to V3; collection of PD Diaries may be repeated only once for 3 additional consecutive days leading up to V3 prior to the start of the Oral CD/LD Stabilization Period.

c. The activities of the Oral CD/LD Stabilization Period are expected to take 14 to 21 days to accommodate scheduling, additional unscheduled visits, and, when allowed, repeated assessments. PD Diaries will be collected for at least 3 consecutive days before Day -1.

d. If a subject prematurely discontinues study participation or completes the study and does not enter the open-label extension Study M20-098, a follow-up visit or follow-up phone call will be completed 30 days after the last day of study drug, if the subject is willing, to ensure all treatment-emergent AEs/SAEs have resolved.

Screening Period

This 6- to 60-day period consists of 2 screening visits (V1 and V2).

Oral CD/LD Stabilization Period

This 14-to 21-day period consists of 3 visits (V3, V4, and V5). V4 is an optional visit. V5 is the Baseline Visit for the majority of assessments.

Double-Blind Treatment Period

This 12-week period starts with initiation of blinded study drug solution and blinded oral capsule and consists of 2 parts: a 4-week CSCI Optimization Phase and an 8-week Maintenance Phase.

Post-treatment Period Activities

There are no post-treatment activities except for subjects who prematurely discontinue study participation. See Protocol Section 5.7 for additional information.

2.3 Treatment Assignment and Blinding

At the end of the Oral CD/LD Stabilization Period, eligible subjects will be randomized in a 1:1 ratio to one of the two treatment arms for the 12-week Double-Blind Treatment Period:

- 24-hour/day CSCI of ABBV-951 plus oral placebo capsules for CD/LD IR (also referred to as investigational group or ABBV-951 group in this document) OR
- 24-hour/day CSCI of placebo solution for ABBV-951 plus oral encapsulated CD/LD IR tablets (also referred to as active control group or Oral CD/LD group in this document)

Randomization will be stratified by study site with a block size of 2.

The first day of the blinded study drug administration is defined as Day 1.

To help evaluate maintenance of the blind, an exit interview will be conducted when subjects prematurely discontinue from the study or when subjects complete the study. The data collected during the exit interview will be summarized.

2.4 Sample Size Determination

Assuming that the difference in change from Baseline to Week 12 in average daily normalized "On" time without troublesome dyskinesia is 1.86 hours between the investigational group and the active control group, and the common standard deviation is 2.9 hours, a sample size of 52 subjects per arm will have 90% power to detect a statistically significant difference between the 2 treatment arms with a 2-sided significance level of 0.05 (using nQuery Version 8.4.0.0). Approximately 130 subjects will be randomized assuming that approximately 20% of subjects will prematurely discontinue blinded study drug during the Double-Blind Treatment Period. This sample size also has approximately 90% power for key secondary endpoints of change from baseline in average daily normalized "Off" time, Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II score and presence of morning akinesia at Week 12 ("Off" status as the first morning symptom upon awakening).

An adequate number of subjects will be enrolled in the Oral CD/LD Stabilization Period to meet the randomization goal of the study.

3.0 Endpoints

3.1 Primary Endpoint

The primary efficacy endpoint is the change from Baseline to Week 12 of the Double-Blind Treatment Period in average daily normalized "On" time without troublesome dyskinesia (hours) as assessed by the PD Diary. Baseline value definition details are provided in Section 8.1 and Section 8.2.1.

3.2 Secondary Endpoints

The following key secondary and other secondary endpoints of the Double-Blind Treatment Period will be included in multiplicity adjustment of the Type I error to control the familywise error rate (FWER) at 2-side significance level of 0.05 for the entire study. These variables will be tested in the following fixed sequence as a gatekeeping procedure.

- Key secondary endpoints:
  - Change from Baseline to Week 12 in hours of average daily normalized "Off" time as assessed by the PD diary.
  - Change from Baseline to Week 12 in Motor Aspects of Experiences of Daily Living as assessed by the MDS-UPDRS Part II score.
  - Presence of morning akinesia at Week 12 (defined as reporting "Off" status as the first morning symptom upon awakening) as assessed by the PD Diary.
- Other secondary endpoints included in FWER control:
  - Change from Baseline to Week 12 in hours of average daily normalized "On" time without dyskinesia as assessed by the PD Diary.
  - Change from Baseline to Final Visit in sleep symptoms as assessed by Parkinson's Disease Sleep Scale-2 (PDSS-2) total score
  - Change from Baseline to Final Visit in PD-related quality of life as assessed by the Parkinson's Disease Questionnarie-39 Item (PDQ-39) summary index
  - Change from Baseline to Final Visit in health-related quality of life as assessed by the EQ-5D-5L summary index
  - Change from Baseline to Week 12 in median bradykinesia score (BK50) as assessed by the Parkinson's KinetiGraph™/Personal KinetiGraph™ (PKG) wearable device
  - Change from Baseline to Week 12 in interquartile range of bradykinesia score (BK75-BK25) as assessed by the PKG wearable device
  - Change from Baseline to Week 12 in median dyskinesia score (DK50) as assessed by the PKG wearable device

- Change from Baseline to Week 12 in interquartile range of dyskinesia score (DK75-DK25) as assessed by the PKG wearable device

3.3 Other Efficacy Endpoints

The primary and secondary efficacy endpoints included in multiplicity adjustment of the FWER are listed in Section 3.1 and Section 3.2, respectively. The additional efficacy endpoints during the Double-Blind Treatment Period are:

- Percent change from Baseline to Week 12 in time of tremor and daytime somnolence as assessed by the PKG wearable device
- Change from Baseline to Week 12 in MDS-UPDRS Part I score, Part III score, Part IV score, and total score of Parts I - III
- Change from Baseline to Week 12 in average daily normalized "On" time with non-troublesome dyskinesia, and "On" time with troublesome dyskinesia as assessed by the PD Diary
- Percent change from Baseline to Week 12 in average daily normalized "Off" time, "On" time without troublesome dyskinesia, "On" time without dyskinesia, "On" time with non-troublesome dyskinesia, and "On" time with troublesome dyskinesia as assessed by the PD Diary
- Change from Baseline to Week 12 in average daily absolute "Off" time, "On" time without troublesome dyskinesia, "On" time without dyskinesia, "On" time with non-troublesome dyskinesia, "On" time with troublesome dyskinesia, and "Asleep" time as assessed by the PD Diary without normalizing
- Change from Baseline to Final Visit in PDSS-2 domain scores
- Change from Baseline to Final Visit in PDQ-39 domain scores
- Change from Baseline to Final Visit in EQ-5D-5L visual analogue scale (VAS) score

3.4 Safety Endpoints

Safety endpoints are:

- Adverse events (AEs), serious AEs (SAEs) and AEs of special interest (AESIs)
- Local tolerability as measured by the Infusion Site Evaluation scale
- Clinical laboratory values
- Vital signs
- Electrocardiograms (ECG)
- The Columbia-Suicide Severity Rating Scale (C-SSRS)
- The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS)

3.5 Endpoints During the Oral CD/LD Stabilization Period

The following variables for the Oral CD/LD Stabilization Period will be summarized:

- Change from Screening value to study Baseline (prior to randomization) in average daily normalized "Off" time, "On" time without troublesome dyskinesia, "On" time without dyskinesia, "On" time with non-troublesome dyskinesia, and "On" time with troublesome dyskinesia as assessed by the PD Diary
- Change from Screening value to study Baseline (prior to randomization) in PD symptoms (including tremor, bradykinesia, dyskinesia, and daytime somnolence) as assessed by the PKG wearable device

4.0 Analysis Populations

The following analysis sets will be used for analyses.

The **Oral CD/LD Analysis Set** includes all subjects who received at least 1 dose of open-label CD/LD IR tablets during the Oral CD/LD Stabilization Period. The Oral CD/LD Analysis Set will be used to summarize premature discontinuations, and adverse events during the Oral CD/LD Stabilization Period.

The **Full Analysis Set (FAS)** includes all randomized subjects who received any dose of study drug during the Double-Blind Treatment Period and who have baseline and at least

1 post-baseline observation for at least 1 efficacy assessment. The FAS will be used for all efficacy analyses unless stated otherwise. Subjects will be included in the analysis according to the treatment group to which they were randomized.

The **Safety Analysis Set** consists of all subjects who received any dose of study drug during the Double-Blind Treatment Period. The Safety Analysis Set will be used for all demographic, baseline, and safety analyses unless stated otherwise. Subjects will be included in the analysis according to the study drug that they actually received regardless of randomization. It is unlikely that a subject will receive a wrong study drug kit due to dispensing errors. If that happens, the various scenarios that could occur are following:

- Double placebo (placebo solution + placebo capsule): The subject will be included in the active treatment group that they received regardless of randomization or duration on placebo.
- Double active (ABBV-951 + CD/LD capsule): The subject will be included in the active treatment group that they received for >50% of the time regardless of randomization.
- Wrong kits resulting in the exact opposite of assigned treatment, i.e.,
    - Oral CD/LD group (placebo solution + CD/LD capsule) subject was dispensed ABBV-951 solution and placebo capsule

      OR
    - ABBV-951 group (ABBV-951 solution + placebo capsule) subject was dispensed placebo solution and CD/LD capsule
- The subject will be included in the active treatment group that they received for >50% of the time regardless of randomization.

5.0 Subject Disposition

The total number of subjects who were screened, entered Oral CD/LD Stabilization Period, randomized, and received blinded study drug will be summarized. Reasons for exclusion, including screen failure, will be summarized.

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized by dose subgroup (low dose or high dose) within each treatment group:

- Subjects enrolled in the Oral CD/LD Stabilization Period;
- Subjects who prematurely discontinued during the Oral CD/LD Stabilization Period (all reasons and primary reason);
- Subjects randomized;
- Subjects who took any dose of blinded study drug;
- Subjects who completed the Double-Blind Treatment Period;
- Subjects who prematurely discontinued blinded study drug during the Double-Blind Treatment Period (all reasons and primary reason);
- Subjects who prematurely discontinued study participation during the Double-Blind Treatment Period (all reasons and primary reason);
- Subjects in each analysis set.

Each subject will be categorized to a dose subgroup based on the modal total daily dose over the treatment period. The calculation of modal total daily dose is defined in Section 7.4.3.

A listing of all subjects affected by the COVID-19 related study disruption by subject number and by site ID, and a description of how the subject's participation was altered because of Covid-19:

- Subjects prematurely discontinued study drug
- Subjects prematurely discontinued from study
- Study drug interrupted
- Subjects missed a visit
- Subjects conducted virtual visit

6.0 Study Drug Duration and Compliance

For the Safety Analysis Set, duration of treatment will be summarized by dose subgroup (low dose or high dose) within each treatment group and for both treatment groups combined. Duration (days) of the double-blind treatment is defined for each subject as last dose date minus first dose date plus 1. Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, minimum, and maximum. In addition, the number and percentage of subjects in each treatment duration interval (1 to 7, 8 to 14, 15 to 28, 29 to 56, and > 56 days) will be summarized.

For each subject, percent treatment compliance for both study drug solution and study drug capsules will be calculated and is defined as

- Study drug solution (ABBV-951 CSCI or placebo solution CSCI): calculated as the number of hours the pump is infusing relative to the 24-hour/day goal and averaged over valid dosing diary days.
- Study drug capsules (placebo capsules or encapsulated CD/LD 25/100 mg IR tablets): calculated as the actual study drug capsules taken relative to the number prescribed and averaged over valid dosing diary days.

A valid dosing diary day is defined as one in which the pump infuses (ABBV-951 or placebo solution) ≥ 80% of the entire 24-hour period (i.e., ≥ 19.2 hours).

Percent treatment compliance will be summarized for the entire Double-Blind Treatment Period by treatment group and for both groups combined for the Safety Analysis Set using the number of subjects with non-missing observations, mean, standard deviation, median, minimum, and maximum.

Rescue medication is defined as the use of open-label CD/LD IR tablets while the subjects are on blinded study drug during the Double-Blind Treatment Period. The average daily levodopa dose from blinded study drug, from rescue medication, and the total of blinded study drug and rescue medication will be calculated for each visit that the dosing diary is collected. The average daily levodopa equivalent dose (LED) from all PD medications

(blinded study drug, loading dose, rescue medication, and concomitant PD medications) will also be calculated using conversion factors for each PD medication (Tomlinson et al 2010[1]) for each visit that the dosing diary is collected. The average daily levodopa dose and average daily LED will be summarized by treatment group and for both groups combined for the Safety Analysis Set using the number of subjects with non-missing dosing diaries, mean, standard deviation, median, minimum, and maximum.

7.0 Demographic and Baseline Clinical Characteristics, Medical History, Prior/Concomitant Medications and Dosing

Demographic and baseline clinical characteristics, medical history, and prior and concomitant medications will be summarized by dose subgroup (low dose or high dose) within each treatment group and the Safety Analysis Set overall. Each subject will be categorized to a dose subgroup based on the modal total daily dose over the treatment period. The calculation of modal total daily dose is defined in Section 7.4.3.

Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum, and maximum).

7.1 Demographic and Baseline Clinical Characteristics

Continuous demographic and clinical variables are age, weight, height, body mass index (BMI), Mini-Mental State Examination (MMSE) score, baseline levodopa dose, and baseline LED. Categorical demographic and clinical variables are sex, ethnicity, race, age category (< 50, 50 to < 65, 65 to < 75, or ≥ 75 years), BMI (< 18.5, 18.5 - < 25.0, 25.0 - < 30.0, ≥ 30.0), country, tobacco user (current, former, never, unknown), alcohol user (current, former, never, unknown), and all Brief Neurological Examination variables.

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA used will be specified in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class [SOC] and preferred term [PT]) will be summarized overall and by treatment group. The SOC will be presented in alphabetical order, and PTs will be presented in alphabetical order within each SOC. Subjects who report more than one condition/diagnosis will be counted only once in each row (SOC or PT).

Parkinson's Disease history will be summarized with the following variables:

- Continuous variables: age at PD onset (years), duration of PD since symptom onset (years), age at PD diagnosis (years), duration of PD since diagnosis (years), age at onset of motor fluctuation (years), duration since onset of motor fluctuation (years).
- Categorical variables: duration of PD since diagnosis (< 10 years, ≥ 10 years), history of levodopa induced dyskinesia (Yes, No), levodopa response for more than 5 years (Yes, No), and Hoehn and Yahr Stage.

7.3 Prior and Concomitant Medications

Prior and concomitant PD medications and non-PD medications will be summarized separately. A prior medication is defined as any medication taken prior to the start of the Oral CD/LD Stabilization Period. A concomitant medication during the Double-Blind Treatment Period is defined as any medication that started prior to the date of the first dose of blinded study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug. The number and percentage of subjects taking medications will be summarized by ATC level 3, ATC level 4, and by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant PD medications. The number and percentage of subjects taking medications

will be summarized by ATC level 3 and by generic drug name based on the WHO Drug Dictionary for non-PD medications.

PD medications used at Screening (on the day prior to the start of open-label study drug of the Oral CD/LD Stabilization Period) and at Baseline (on Day -2) will be summarized

- By the number of classes of PD medications taken for all subjects overall and by treatment group.
- In the following categories
  - LD alone
  - LD + only concomitant dopaminergic agonists
  - LD + only concomitant MAO-B inhibitor
  - LD + only istradefylline
  - LD + only any amantadine formulation
  - LD + 2 different classes of Parkinson's disease drugs
  - LD + 3 different classes of Parkinson's disease drugs

7.4 Analysis of Dosing

Based on molecular weight, 100 mg of levodopa phosphate (LDP) is equivalent to 71 mg of levodopa. Unless otherwise stated, all study drug doses will be presented as LD equivalents.

Unless otherwise stated, all analyses of dosing diary data will be performed on valid dosing diary days.

7.4.1 Analysis of Daily Prescribed Dose

Summary statistics (mean, SD, median, minimum, and maximum) will be provided for prescribed dose information, including loading dose and continuous infusion rates for the investigation group, and oral levodopa dose (from encapsulated CD/LD IR) for the active control group.

When available, the summary statistics will be provided at initial prescription, first maintenance prescription following the Optimization Phase, final prescription in the 8-week Maintenance Phase, and final prescription in study. Change from initial to first maintenance, initial to maintenance final, initial to final and maintenance first to final will also be summarized.

7.4.2 Analysis of Initial Optimization

Duration of initial optimization of pump infusion rate is defined as the number of days from Day 1 to the first day where there is no change to the infusion rate setting on the pump for at least 7 days.

Duration of initial optimization will be summarized by the following interval (days): 1, 2, 3, 4, 5, 6, 7, 8 - 14, 15 - 21, 22 - 28, and > 28. When applicable, the summary statistics will include mean, SD, median, minimum, and maximum.

7.4.3 Analysis of Daily Levodopa Dose

Daily levodopa dose will be summarized for blinded study drug and open-label oral CD/LD IR tablet at each protocol defined visit. Summary statistics are mean, SD, median, minimum, and maximum.

The modal total daily levodopa dose during the study will be determined for each subject by first assigning the subject's total daily levodopa doses to narrow dose ranges in 100-mg increments (e.g., 1000 to < 1100 mg, 1100 to < 1200 mg) and then selecting the most frequent narrow dose range for the subject. If 2 or more dose ranges are of the same highest frequency, the highest dose range will be selected.

The modal continuous pump infusion rate for the ABBV-951 treatment group will be similarly defined for each subject.

The modal total daily dose will be summarized for the Safety Analysis Set. The modal pump infusion rate will be summarized for the ABBV-951 treatment group in the Safety Analysis Set.

7.4.4 Other Dosing Analysis

The frequency of subjects taking rescue medication will be summarized by 0 time, 1 time, 2 times and ≥ 3 times categories and by the following study day intervals: 1 - 7, 8 - 14, 15 - 21, 22 - 28, 29 - 42, ≥ 43. In addition, the number of subjects with at least one occurrence and the total number of occurrences will be summarized by mean, SD, median, minimum, and maximum.

7.5 Other Descriptive Analyses

A summary of protocol deviations will be provided.

8.0 Efficacy Analyses

8.1 General Considerations

All efficacy analyses will be conducted on the FAS. All tests will be 2-sided at an alpha level of 0.05.

The Primary Analysis will be performed after all subjects have completed the Double-Blind Treatment Period and the database has been locked.

Unless otherwise specified, continuous variables will be analyzed using the Mixed-Effect Model Repeat Measurement (MMRM) method.

Baseline for PD Diary variables will be the average of the 3 valid diaries completed before Day -1. Baseline for all efficacy measures, other than the PD Diary, will be defined as the last non-missing observation that is before the day of initiation of double-blinded study drug.

Post-baseline efficacy and safety measures, other than AE and Infusion Site Evaluation, collected more than 1 day after the last dose of double-blind study drug will not be used for efficacy and safety analyses because data after discontinuation of study drug may be confounded by the various PD treatments that the subjects may be on after discontinuing study treatment.

Variables Derived from PD Diary

The primary, 2 of the key secondary and several other secondary efficacy variables will be obtained from the PD Diary. On PD Diary recording days, the subject will be instructed to make an entry upon awakening from time asleep and every 30 minutes during their normal waking time for a full 24-hour period of each day from 12:00am to 11:30pm (48 entries, with each entry representing 0.5 hours). Each entry could be in one of 5 categories: Asleep, "Off," "On" without dyskinesia, "On" with non-troublesome dyskinesia, and "On" with troublesome dyskinesia. For each diary day, the absolute time spent in each category will be summed. The daily awake time will be the sum of the absolute time spent in the 4 non-asleep categories. Daily "Off" and "On" times will be normalized to a typical waking day (16 hours) to account for different sleep patterns across subjects, e.g.,

Normalized "On" time without troublesome dyskinesia = (Absolute "On" time without troublesome dyskinesia/Awake time) × 16

Daily normalized "Off" and "On" times are averaged over valid PD Diary days for each visit to obtain the average daily normalized "Off" and "On" times. A valid PD Diary day is defined in Section 8.2.1.

First morning status upon awakening is determined by examining the PD Diary entries between 0:00 am and 12:00 pm on the last valid PD Diary day. First morning status upon awakening is defined as the first non-sleep and non-missing entry on the PD Diary after at least 4 consecutive entries of "Asleep" (i.e., at least 2 hours of continuous sleep).

8.2 Handling of Missing Data

8.2.1 Handling of Missing Items in Efficacy Instruments

PD Diary

A valid PD Diary day is defined as one within 7 days prior to a clinical visit but not on or after the day of the visit and with no more than 2 hours of missing data (4 or fewer missing 30-minute entries) for the entire 24-hour diary.

For Baseline, a valid PD Diary day also cannot be on the day prior to the Randomization Visit (V6) because the subjects are asked not to take any PD medications for at least 12 hours before V6.

An invalid PD Diary day will not be used in the calculation of the average daily normalized or absolute "Off" or "On" times for the visit it is associated with.

If more than 3 valid PD Diary days are available for Baseline or post-baseline visits, the 3 days closest to the clinical visit will be used. If only 2 valid PD Diary days are available prior to a clinic visit, data from the 2 days will be used to calculate the average daily normalized "Off" or "On" times. If only 1 valid PD Diary day is available, the value from the 1 valid PD Diary day will be the visit value. If no valid PD Diary day is available for a visit, the average daily normalized "Off" or "On" times will be missing for that visit.

MDS-UPDRS

The MDS-UPDRS total score and score of each part will be calculated as long as no more than 15% of the answers are missing for that assessment. The missing item will be imputed as the average of the non-missing items from the same MDS-UPDRS assessment. Imputation for Part I, Part II, Part III, or Part IV scores will use the non-missing items within the particular part, but the imputation for the total score of Parts I - III will use the non-missing items from all 59 items across the 3 parts.

PDSS-2

There is no imputation of missing responses for the PDSS-2. If any item score is missing, the total score and the corresponding domain score will not be calculated.

PDQ-39

The PDQ-39 summary index will be calculated as long as no more than 15% (i.e., 5) of the answers are missing for that assessment. It will be imputed as the average of the non-missing items from the same PDQ-39 assessment. The domain score will only be calculated if all the questions are answered.

EQ-5D-5L

The EQ-5D-5L summary index will only be calculated if answers are provided for all 5 individual questions. The EQ-5D-5L VAS is a single value collected and there is no imputation if the VAS value is missing.

8.2.2 Handling of Intercurrent Events and Missing Visit Values in Efficacy Endpoints

The probability of having missed visits and missing data due to COVID-19 infection or logistical restrictions can be reasonably assumed to be unrelated to unobserved values. For the purpose of the statistical analysis, it is reasonable to assume that these missing data are missing at random (MAR) and the statistical models that require MAR assumptions are appropriate.

Intercurrent events and missing data will be handled using the following methods for efficacy analyses:

- The primary approach for handling missing data for all efficacy endpoints will use Mixed-Effect Model Repeat Measurement (MMRM). All observations during the period from Day 1 to 1 day after the last dose of double-blind study drug (regardless of rescue medication use during this time period) will be included. Rescue medication is defined in Section 6.0. The repeated measures

analysis will be conducted using a mixed model including observed measurements at all visits. The mixed model includes the categorical fixed effects of treatment, country and visit, treatment-by-visit and treatment-by-baseline interactions, and the continuous fixed covariate of baseline measurement. An unstructured variance covariance matrix will be used. The compound symmetry variance covariance matrix will be used if the model does not converge with the unstructured matrix. The "hypothetical" strategy will be used to handle the intercurrent event of discontinuation of study drug in the sense that all data collected more than 1 day after the last dose of blinded study drug will not be used in analyses. In addition, the "treatment policy" strategy will be used to handle the intercurrent event of rescue medication use in the sense that collected data (from Day 1 to 1 day after the last dose of double-blind study drug) will be used regardless of rescue medication use. Parameter estimation is based on the assumption of data being MAR and using the method of restrictive maximum likelihood (REML). MMRM will be the primary approach in the analysis of continuous variables in the Double-Blind Treatment Period.

- The "Jump-to-reference" (J2R) missing not at random (MNAR) analytic approach (Liu and Pang 2016[2]) will be used as Sensitivity Analysis #1 for the primary efficacy endpoint and other "On" times as well as "Off" time derived from the PD Diary. All observations during the period from Day 1 to 1 day after the last dose of double-blind study drug (regardless of rescue medication use during this time period) will be included.
    - In this approach missing data in the active control arm will be assumed to be MAR.
    - Non-monotonic missing data in the investigational group will also be assumed to be MAR.
    - For subjects in the investigational group with monotonic missing values due to reasons other than COVID-19 infection or COVID-19 logistical restrictions, the missing values will be assumed to be MNAR and have a profile for visits after discontinuation of blinded study drug that equals the profile of the active control group.

- The J2R analytic approach will be implemented to estimate the mean treatment group difference and standard error using MMRM estimates from the primary analysis model, observed proportions of missing data pattern in the investigational group due to reasons other than COVID-19, and the variance covariance matrix of the estimates from the MMRM (Liu and Pang 2016[2]).

- The last available value approach will be used as Sensitivity Analysis #2 for the primary efficacy endpoint and other "On" times as well as "Off" time derived from the PD Diary. Missing Week 12 data will be imputed based on the subject's last available value (regardless of rescue medication use while the subject is on blinded study drug) in estimating the change from Baseline to Week 12. An analysis of covariance (ANCOVA) model with the categorical fixed effects of treatment and country, and baseline score as a covariate will be used for treatment group comparison.

8.3 Primary Efficacy Endpoint and Analyses

8.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline to Week 12 of the Double-Blind Treatment Period in average daily normalized "On" time without troublesome dyskinesia (hours) ("On" time without dyskinesia plus "On" time with non-troublesome dyskinesia).

The estimand corresponding to the primary objective for the study is: the treatment group difference in "On" time without troublesome dyskinesia change from Baseline to Week 12 between investigational and active control groups without premature discontinuation of double-blind study drug but regardless of rescue medication use in the FAS population.

8.3.2 Primary Efficacy Analysis

The primary analysis will use MMRM and include data on change from Baseline to each post-baseline visit of the Double-Blind Treatment Period in average daily normalized "On" time without troublesome dyskinesia obtained from the PD Diary. The mixed

model includes the categorical fixed effects of treatment, country and visit, treatment-by-visit and treatment-by-baseline interactions, and the continuous fixed covariate of baseline measurement. Although randomization is stratified by study site, the MMRM model will not include the "site" effect due to the large number of sites planned compared to the number of subjects that will be randomized in the study. If the final number of sites that randomized at least 1 subject is less than or equal to 30, the "site" effect may be added to the model. The primary approach for handling intercurrent events and missing data will be based on the MMRM method as specified in Section 8.2.2.

An unstructured variance covariance matrix will be used. Due to the short half-life (~1.5 hours) of ABBV-951, the compound symmetry variance covariance matrix will be used if the model does not converge with unstructured matrix. Parameter estimation is based on the REML method. The primary comparison will be the contrast on change from Baseline between the investigational and active control groups at Week 12.

Change from Baseline in average daily normalized "On" time without troublesome dyskinesia conducted on MMRM will be displayed by investigational group and active control group in a figure.

The proportion of subjects who met average daily normalized 'On' time without troublesome dyskinesia responder criteria at Week 12 will be summarized by investigational group and active control group at the thresholds from 0% to 100% with 10% as an increment. The P-value for test difference in the distribution between the 2 groups will be provided by conducting the Monte Carlo exact Kolmogorov-Smirnov test. The percentage of subjects who achieved at least one certain percent reduction in average daily normalized "On" time without troublesome dyskinesia at endpoint will be displayed by investigational group and active control group in a figure. The same analysis will also be conducted for average daily normalized 'Off' time.

8.3.3 Additional Analyses of the Primary Efficacy Endpoints

Two sensitivity analyses will be conducted on the efficacy endpoints to account for missing data.

- Sensitivity analysis #1: A "jump-to-reference" analytic approach to account for missing data due to subjects who prematurely discontinue blinded study drug during the Double-Blind Treatment Period will be implemented as described in Section 8.2.2.
- Sensitivity analysis #2: The change from Baseline to the last available value in average daily normalized "On" time without troublesome dyskinesia and other "On" times as well as "Off" time derived from the PD Diary will be analyzed using an ANCOVA model with the categorical fixed effects of treatment and country, and baseline score as a covariate. If the final number of sites that randomized at least 1 subject is less than or equal to 30, the "site" effect may be added to the model. Missing Week 12 data will be handled using the last available value approach as specified in Section 8.2.2.

A summary of the primary and 2 sensitivity analyses of the primary efficacy endpoint is presented in Table 1.

Table 1. Summary of Primary and Sensitivity Analysis for the Primary Efficacy Endpoint of Change from Baseline to Week 12 in Average Daily Normalized "On" Time Without Troublesome Dyskinesia and other "On" times as well as "Off" time derived from the PD Diary

Analysis	Dependent Variable	Data Included	Analysis Method
Primary Analysis	Change from baseline to post-baseline visits through Week 12	During the period from Day 1 to 1 day after the last dose of double-blind study drug, regardless of rescue medication use during this time period.	MMRM with categorical fixed effects of treatment, country and visit, treatment-by-visit and treatment-by-baseline interactions, and the continuous fixed covariate of baseline measurement. Missing data will be handled using MMRM as specified in Section 8.2.2.
Sensitivity Analysis #1			Jump-to-Reference will be used to handle missing data in the investigational arm. The details for this approach are described in Section 8.2.2.
Sensitivity Analysis #2	Change from baseline to the Week 12 visit		ANCOVA model with the categorical fixed effects of treatment and country, and baseline score as a covariate. Missing Week 12 data will be imputed using last available value.

8.4 Secondary Efficacy Analyses

8.4.1 Key Secondary and Other Secondary Efficacy Analyses

Key secondary efficacy endpoints and other secondary endpoints included in FWER control are described in Section 3.2.

Change from Baseline to Week 12 in average daily normalized "Off" time, MDS-UPDRS Part II score, average daily normalized "On" time without dyskinesia, and PKG variables will be analyzed using the same MMRM model as the primary efficacy analysis.

Change from Baseline to Final Visit in the PDSS-2 total score, PDQ-39 summary index, and EQ-5D-5L summary index will be analyzed using an ANCOVA model with categorical fixed effects of treatment and country, and baseline score as a covariate. If the

final number of sites that randomized at least 1 subject is less than or equal to 30, the "site" effect may be added to the model.

The percent of subjects in each category of first morning status upon awakening ("Off," "On" without dyskinesia, "On" with non-troublesome dyskinesia, and "On" with troublesome dyskinesia) will be presented by visit and treatment group. The number of hours from the last dose of blinded oral study drug to the first morning non-sleep status will be summarized.

The first morning status upon awakening ("Off" or not "Off") on the last valid PD Diary day at each post-baseline visit will be analyzed using a generalized linear mixed model (GLMM) with a logit link function to compare the probability of having morning akinesia between the treatment groups. The model will include fixed, categorical effects of treatment, country, visit, treatment-by-visit interaction, and baseline first morning status upon awakening. An unstructured variance covariance matrix will be used. The compound symmetry variance covariance matrix will be used if the model does not converge with unstructured matrix. The odds ratio for treatment comparison at Week 12 and their associated 95% CIs will be estimated from the GLMM.

Change from Baseline in average daily normalized "Off" time conducted on MMRM will be displayed by investigational group and active control group in a figure.

8.4.2 Other Efficacy Analyses

Other supportive efficacy variables are described in Section 3.3. Variables derived from the PD diary, MDS-UPDRS, and PKG wearable device will be analyzed using the same MMRM model as the primary efficacy analysis. Variables derived from the PDSS-2, PDQ-39, and EQ-5D-5L will be analyzed with the same ANCOVA model described in Section 8.4.1.

Distribution of time spent in different motor symptoms based on PD Diary data will be displayed in pie charts for the Baseline Visit and the Week 12 Visit.

8.5 Efficacy Analyses During the Oral CD/LD Stabilization Period

Additional efficacy variables for the Oral CD/LD Stabilization Period are described in Section 3.5. These variables will be summarized by investigational and active control groups and for all subjects in the FAS. No statistical testing will be performed.

8.6 Efficacy Subgroup Analyses

Subgroup analyses of change from Baseline to Final Visit of the Double-Blind Treatment Period in average daily normalized "On" and "Off" times will be conducted for the following subgroups:

- Age category (< 65 years or ≥ 65 years)
- Sex (male or female)
- Race (white or other)
- Country (US or Australia)
- Duration of PD (time since diagnosis to randomization) (< 10 years or ≥ 10 years)
- Concomitant dopamine agonist use (yes or no)
- Dose category (low or high levodopa dose). Each subject will be categorized to a dose subgroup based on the modal total daily dose over the treatment period. The calculation of modal total daily dose is defined in Section 7.4.3.

A subgroup analysis will be conducted on dose subgroup for the key secondary and other secondary endpoints described in Section 3.2 except for the variables that were derived from the PD diaries, which were analyzed by all subgroups described in the above paragraph.

A subgroup analysis may not be conducted if one stratum of the subgroup variable comprises of < 20% of the FAS Analysis Set.

Subgroup analyses will be performed on the FAS using an ANCOVA model with the terms of treatment, subgroup variable, the treatment-by-subgroup variable interaction, and Baseline as a covariate. The hypothesis that consistent response to treatment across strata of a subgroup variable will be tested at the significance level of 0.100 by examining the P value of the treatment-by-subgroup interaction term in the ANCOVA model specified above. The statistical comparison of the investigational and active control groups within each subgroup stratum will be performed when the statistical significance of the treatment-by-subgroup interaction term is achieved at 0.100 level.

9.0 Safety Analyses

9.1 General Considerations

Safety data will be summarized for the Double-Blind Treatment Period using the Safety Analysis Set unless otherwise specified. Safety summaries during the Double-Blind Treatment Period will be presented by dose subgroup (low dose or high dose) within each treatment group unless otherwise specified. For safety analyses of the Double-Blind Treatment Period, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

Baseline for all safety measures will be defined as the last non-missing observation that is before the day of randomization, with the exception of vital sign variables, which will be the average of observations if multiple measurements are obtained on the same day.

For continuous safety outcomes, the change from Baseline will be analyzed in a descriptive manner by visit for each dose category subgroup and overall subjects. For categorical safety outcomes, the number and percentage of each category will be summarized by visit for each dose category subgroup and overall subjects. Hypothesis testing will not be performed.

To evaluate the time dependency of effects, select analyses will be prepared for treatment intervals: Optimization Phase, Maintenance Phase, and persistent from Optimization

Phase to Maintenance Phase for at least 7 days into the Maintenance Phase, which begin in the Optimization Phase and continue in the Maintenance Phase.

9.2 Adverse Events

AEs will be summarized and presented using primary MedDRA SOCs and PTs according to the version of the MedDRA used for the study at the time of database lock. The actual version of the MedDRA used will be specified in the AE tables and in the clinical study report. Specific AEs will be counted only once for each subject for calculating percentages, unless stated otherwise. In addition, if the same AE occurs multiple times within a subject, the highest severity and level of relationship to study drug will be reported. Subjects for whom more than one AE for a given PT was reported will be counted only once for that term. Subjects for whom more than one AE within an SOC was reported will be counted only once for the SOC total. Subjects for whom more than one AE was reported will be counted only once in the overall AE total. For summaries by SOC and PT, the SOCs will be presented in alphabetical order and the PTs will be presented in alphabetical order within each SOC.

9.2.1 Treatment-Emergent Adverse Events

Treatment emergent AEs (TEAEs) for the Oral CD/LD Stabilization Period will be defined as all events that begin or worsen on or after first dose of open-label CD/LD IR tables during the Oral CD/LD Stabilization Period and prior to first dose of blinded study drug during the Double-Blind Treatment Period. TEAEs for the Double-Blind Treatment Period will be defined as all events that begin or worsen on or after first dose of study drug during the Double-Blind Treatment Period and within 30 days after the last dose of double-blinded study drug. AEs with onset on the first day of blinded study drug will be considered treatment-emergent for the Double-Blind Treatment Period. All TEAEs will be summarized by treatment intervals and entire Double-Blind Treatment Period, by primary MedDRA SOC and PT. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC. The number of subjects who experienced the same TEAE recurrently during the Optimization Phase, the

Maintenance Phase, and the entire Double-Blind Treatment Period will be presented by frequency counts: 1 time, 2-4 times, 5-10 times, and >10 times.

9.2.2 Adverse Event Overview

An overview of AEs during the Oral CD/LD Stabilization Period will be presented for the Oral CD/LD Analysis Set, consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any TEAE
- Any TEAE are considered associated with study drug
- Any severe TEAE
- Any serious TEAE
- Any TEAE considered associated with COVID-19
- Any TEAE leading to discontinuation of study drug
- Any TEAE leading to death
- AESI: Polyneuropathy
- AESI: Weight loss
- AESI: Hallucinations/psychosis
- AESI: Somnolence
- AESI: Falls and associated injuries
- All deaths
- Death related to COVID-19

An overview of AEs during the Double-Blind Treatment Period will be presented for the Safety Analysis Set, consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any TEAE
- Any TEAE are considered associated with study drug
- Any severe TEAE
- Any serious TEAE

- Any TEAE associated with any product complaint
- Any TEAE considered associated with product complaint: ABBV-951 or Placebo solution
- Any TEAE considered associated with product complaint: CD/LD IR or Placebo capsules
- Any TEAE considered associated with product complaint: Open label CD/LD IR tablets
- Any TEAE considered associated with product complaint: Infusion Pump (Phillips-Medisize - Parkinson's Disease subcutaneous pump [PM-PDSC pump])
- Any TEAE considered associated with product complaint: Vial Adapter
- Any TEAE considered associated with product complaint: Syringes
- Any TEAE considered associated with product complaint: Neria Guard Infusion Set 6 mm Cannula
- Any TEAE considered associated with product complaint: Neria Guard Infusion Set 9 mm Cannula
- Any TEAE considered associated with product complaint: PKG Wearable Device
- Any TEAE considered associated with COVID-19
- Any serious TEAE considered associated with the PM-PDSC infusion pump
- Any TEAE leading to discontinuation of study drug
- Any TEAE leading to death
- AESI: Infusion Site Related Non-Infection Reactions
- AESI: Infusion Site Related Infections
- AESI: Polyneuropathy
- AESI: Weight loss
- AESI: Hallucinations/psychosis
- AESI: Somnolence
- AESI: Falls and associated injuries
- All deaths

- Death related to COVID-19

9.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

TEAEs during the Double-Blind Treatment Period will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator (i.e., reasonable possibility or no reasonable possibility) and SOC and PT; and by maximum severity and SOC and PT for the Safety Analysis Set. Specific AEs will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same AE occurs multiple times within a subject, the highest severity and level of relationship to the study drug will be reported.

TEAE reported in ≥ 2% of subjects in the ABBV-951 group and greater than the Oral CD/LD group will be summarized.

In addition, TEAEs will be summarized by PT and sorted by decreasing frequency for the ABBV-951 group. The number and percentage of subjects with TEAEs during the Double-Blind Treatment Period associated with product complaint, loading dose, and rescue medication will be presented by SOC and PT for both the ABBV-951 group and oral CD/LD group.

TEAEs during the Oral CD/LD Stabilization Period will be summarized by SOC and PT for the Oral CD/LD Analysis Set.

9.2.4 Adverse Event by Maximum Severity

The number and percentage of subjects who experienced one or more TEAEs will also be summarized by maximum severity category (mild, moderate, severe, or unknown) and primary SOC and PT for the entire study. Subjects for whom more than one TEAE for a given PT was reported will be counted only once for that term in the most severe category reported. If a subject has an AE with unknown severity, then the subject will be counted in the severity category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another

occurrence of the same AE with the most extreme severity – "severe." In this case, the subject will be counted under the "severe" category.

9.2.5 Adverse Event by Relationship to Study Drug

The number and percentage of subjects who experienced one or more TEAEs will also be summarized by maximum relationship category (reasonable possibility, no reasonable possibility, or unknown), as assessed by the investigator, and primary SOC and PT for the entire study. Subjects for whom more than one TEAE for a given PT was reported will be counted only once for that term in the most related category reported. If a subject has an AE with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same AE with a relationship assessment of "reasonable possibility." In this case, the subject will be counted under the "reasonable possibility" category.

9.2.6 Treatment-Emergent Adverse Events per Patient-Years of Exposure

Exposure-adjusted AEs per 100 patient-years will be provided, where AEs per 100 patient-years of exposure are defined as the number of AEs divided by the total exposure in 100 patient-years.

9.2.7 Adverse Events of Special Interest

Adverse events of special interest during the Double-Blind Treatment Period in each of the following categories will be defined based on the search strategy defined in Appendix B:

- Infusion site related non-infection reactions
- Infusion site related infections
- Polyneuropathy
- Weight loss
- Hallucinations/psychosis

- Somnolence
- Falls and associated injuries

An overview of AESIs will be summarized. The number and percentage, difference of percentage between the active control group and investigational group and its 95% CI of each AESI category will be summarized by treatment intervals and entire Double-Blind Treatment Period by descending PT. AESI that develop into an SAE or that led to study drug discontinuation will be summarized by treatment intervals and entire Double-Blind Treatment Period by descending PT.

In addition, for each AESI, the time of first onset, number of events and duration of events will be summarized given sufficient data.

9.2.8 Adverse Event by Relationship to Product Quality Complaints

The number and percentage of subjects experiencing one or more TEAEs that are associated with Product Quality Complaints will also be summarized by SOC and PT for the products listed below:

- ABBV-951 or placebo solution
- CD/LD IR or placebo capsules
- Open label CD/LD IR tablets
- PM-PDSC infusion pump
- Vial adapter
- Syringes
- Neria Guard Infusion Set 6 mm Cannula
- Neria Guard Infusion Set 9 mm Cannula
- PKG wearable device

9.2.9 Adverse Event Leading to Study Drug Discontinuation, Interruption, and Dose Reduction

The number and percentage of subjects who experienced one or more TEAEs that led to study drug discontinuation, interruption, and dose reduction will also be summarized by primary SOC and PT, respectively.

AEs during the Double-Blind Treatment Period that led to study drug discontinuation will be summarized by treatment intervals and entire Double-Blind Treatment Period by SOC and PT. All death subjects will be listed for both the Oral CD/LD Analysis Set and Safety Analysis Set.

9.2.10 Adverse Event Associated with Rescue Medication

The number and percentage of subjects who experienced one or more TEAEs associated with rescue medication will also be summarized by primary SOC and PT, respectively.

9.2.11 Serious Adverse Events

The number and percentage of subjects who experienced one or more SAEs related to the PM-PDSC infusion pump and Neria Guard infusion set will be summarized by primary SOC and PT for the entire study and in listing format. All SAEs will be summarized by treatment intervals and entire Double-Blind Treatment Period by SOC and PT.

9.2.12 TEAE identified by Abuse Liability Company MedDRA Query

The number and percentage of subjects with TEAEs, with TESAEs, and with TEAEs leading to study drug discontinuation during the Double-Blind Treatment Period identified by the Abuse Liability Company MedDRA Query (CMQ) will be summarized in descending frequency for ABBV-951 group by PT and will be presented in listing format as well.

9.2.13 COVID-19 related Adverse Events

Subjects with TEAEs related to COVID-19 will be summarized by treatment intervals and entire Double-Blind Treatment Period by PT. Subjects' COVID-19 status, signs, and symptoms for all screened subjects will be summarized and listed as well.

9.2.14 Listings of Adverse Events

The following additional summaries of AEs will be prepared.

- Listing of all deaths for all subjects screened
- Listing of all serious TEAEs
- Listing of all TEAEs that led to discontinuation of study treatment
- Listing of all AESIs (as defined in Section 9.2.7)
- Listing of all TEAEs by the Abuse Liability CMQ
- Listing of all TEAEs related to COVID-19
- Listing of subjects' COVID-19 status, signs, and symptoms

9.3 Safety Subgroup Analyses

Any TEAE, any SAE, any AE that led to study drug discontinuation, any AESI, any AESI that developed to an SAE, and any AESI that led to study drug discontinuation will be summarized for dose category (low or high levodopa dose) within each treatment group and within each of the following subgroup variables, and treatment intervals and entire Double-Blind Treatment Period by SOC and PT.

- Age category (< 65 years or ≥ 65 years)
- Sex (male or female)
- Race (white or other)
- Country (US or Australia)
- Duration of PD (time since diagnosis to screening) (< 10 years or ≥ 10 years)
- BMI (< 25 or ≥ 25)
- Concomitant dopamine agonist use (yes or no)

- Dose category (low or high levodopa dose) defined by the modal total daily dose over the treatment period. The calculation of modal total daily dose is defined in Section 7.4.3. All safety variables will be summarized by dose subgroup within each treatment group unless otherwise specified.

Change from Baseline analyses and safety parameter abnormalities that meet Potentially Clinically Significant (PCS) criteria analyses of laboratory parameters, vital sign, and ECG parameters will also be analyzed by subgroups and by dose category. Details are described in following sections.

9.4 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline where SAE-related laboratory assessments on or before the first dose of study drug will be excluded. The clinical laboratory tests defined in the protocol operations manual will be summarized.

Mean change from Baseline to the final value of the Double-Blind Treatment Period will be summarized for chemistry, hematology, urinalysis, and special laboratory variables, with the number of observations, baseline mean, and visit mean by subgroup variables listed in Section 9.3. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from Baseline within each treatment group and difference between treatment groups (investigational group vs. active control group).

Changes in laboratory parameters from Baseline to the final value will be tabulated using shift tables by Common Terminology Criteria for Adverse Events (CTCAE) grades if available, and categorized as low, normal, or high based on the normal ranges of the laboratory that performed the assay.

Laboratory abnormalities will be evaluated based on sponsor PCS criteria (Appendix C). For each laboratory sponsor PCS criterion (includes the Hy's Law lab criteria), the number and percentage of subjects who have a laboratory value that meets the criteria and is more extreme than their baseline value will be summarized by the subgroup variables listed in

Section 9.3. Listings will be provided to summarize subject-level laboratory data for subjects who meet sponsor PCS criteria by subgroups.

Laboratory abnormalities will be evaluated based on FDA PCS criteria (Appendix C). For each laboratory FDA PCS criterion, the number and percentage of subjects who have a laboratory value meeting the criteria and is more extreme than their baseline value will be summarized by subgroup variables listed in Section 9.3. Listings will be provided to summarize subject-level laboratory data for subjects meeting FDA PCS criteria by subgroups.

Subjects who meet the criteria for liver-related laboratory elevations will be summarized and a listing will be provided for subjects with ALT or AST ≥ 3 × ULN.

- ALT > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- AST > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- TBL > 1.5 × ULN, > 2 × ULN
- ALT and/or AST > 3 × ULN and TBL > 1.5 × ULN
- ALT and/or AST > 3 × ULN and TBL > 2 × ULN
- ALT > 3 × ULN and TBL > 1.5 × ULN
- ALT > 3 × ULN and TBL > 2 × ULN
- Alkaline phosphatase > 1.5 × ULN

9.5 Analysis of Vital Signs

Vital sign measurements including blood pressure both supine, standing, orthostatic systolic blood pressure (SBP) changes and orthostatic diastolic blood pressure (DBP) change, pulse rate both supine, standing and orthostatic pulse rate changes, and body temperature will be summarized. Orthostatic changes are defined as change in values from supine to standing (standing value minus supine value) position in SBP, DBP, and pulse rate.

Weight variables are weight and BMI.

Each vital sign variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum, and maximum. Mean change from Baseline to each applicable post-baseline visit of the Double-Blind Treatment Period will be summarized by subgroup variables listed in Section 9.3 for each vital sign variable and weight, with the number of observations, baseline mean, and visit mean.

An MMRM analysis will be conducted for blood pressure and pulse variables by position (supine and standing) and will include data on change from Baseline to each post-baseline visit of the Double-Blind Treatment Period. The mixed model includes the categorical fixed effects of treatment and visit, treatment-by-visit and treatment-by-baseline interactions, and the continuous fixed covariate of baseline measurement. The change from Baseline mean, standard error, and 95% confidence interval will be presented for the mean change from Baseline within each treatment group and difference between treatment groups (investigational group vs. active control group).

Vital sign values and change from Baseline by visit will be summarized with dose category and with the number of non-missing observations, mean and standard deviation, median, minimum and maximum per FDA request for blood pressure and pulse variables.

Vital sign variables will be evaluated based on sponsor PCS criteria (Appendix C). For each vital sign PCS criterion, the number and percentage of subjects who have a vital sign value that meets the criteria and is more extreme than their baseline value will be summarized for the Optimization Phase, the Maintenance Period, any time in the Double-Blind Treatment Period and at each planned visit and the final visit. The summary will also be generated by the subgroup variables listed in Section 9.3. Listings will be provided to summarize subject-level vital sign data for subjects who meet PCS criteria by subgroups.

Vital sign variables will be evaluated based on PCS criteria recommended by FDA. For each vital sign FDA PCS criterion, the number and percentage of subjects who have a vital sign value that meets the criteria and is more extreme than their baseline value will

be summarized by subgroup variables listed in Section 9.3. Listings will be provided to summarize subject-level vital sign data for subjects who meet FDA PCS criteria by subgroups. For all vital sign analyses described above, Baseline will be the average of the 3 sets of values collected at V5.

In addition, each vital sign variable will be summarized for Day 1 pre-dose, post-dose, and change from pre-dose to post-dose with the number of non-missing observations, mean and standard deviation, median, minimum, and maximum.

9.6 Other Safety Analyses

9.6.1 Analysis of ECG Parameters

Electrocardiogram (ECG) variables are: heart rate (HR), PR interval, QRS interval, uncorrected QT interval, and QT interval corrected for heart rate using the Fridericia's formula (QTcF).

Change from Baseline to each planned visit and to the minimum, maximum, and final value will be summarized in a descriptive manner for each ECG variable.

For each change from baseline analysis, the following summary statistics will be presented: sample size, baseline mean, visit mean, and the mean, standard deviation, and median of the change from Baseline by subgroup variables listed in Section 9.3 and by dose category. The baseline and visit means will be calculated for each visit for subjects who have both a baseline and visit value.

Criteria for PCS values have been predefined for selected ECG variables as outlined in Appendix C. For each variable, a summary of the number and percentage of subjects who have at least one post-baseline observation that meets the PCS criteria and is more extreme than their baseline value will be provided for the Optimization Phase, the Maintenance Period, any time in the Double-Blind Treatment Period and at each planned visit and the final visit. The summary will also be generated by the subgroup variables listed in Section 9.3. A listing will also be prepared that will include, for each variable, all

observations for each subject that met the PCS criteria for that variable at any time during the study by subgroups.

9.6.2 Infusion Site Evaluation Scale

The number and percentage of subjects with each category for numeric and letter grade will be presented by treatment group and for both treatment groups combined at each planned visit during the Double-Blind Treatment Period. The number and percentage of subjects with numeric grade equal to or higher than 5 or letter grade equal to or higher than D at any time during the Double-Blind Treatment Period will be presented by treatment group and for both treatment groups combined.

A listing will also be prepared that includes all subjects with numeric grade equal to or higher than 5 and letter grade equal to or higher than D at any time during the Double-Blind Treatment Period.

9.6.3 Analysis of Questionnaire for Impulsive-Compulsive Disorders in PD-Rating Scale (QUIP-RS)

Change from Baseline to each applicable post-baseline visit of the Double-Blind Treatment Period will be summarized in a descriptive manner for the QUIP-RS total score and domain scores.

For each change from baseline analysis, the following summary statistics will be presented: sample size, baseline mean, visit mean, and the summary statistics (i.e., mean, SD, and median) of the change from Baseline. Summary statistics for the change from Baseline will only be calculated for subjects who have both baseline and visit values.

In addition, a summary of the number and percentage of subjects with a score of at least 6 on each of the subscales and any one or more of the subscales will be prepared. A listing of QUIP-RS scores will also be prepared for any subjects having a score of at least 6 on any of the subscales.

9.6.4 Analysis of Columbia-Suicide Severity Rating Scale (C-SSRS)

Affirmative responses on the C-SSRS will be summarized for the initial screening and each subsequent visit by treatment group.

Each summary will include the number and percentage of subjects within each treatment group with one or more affirmative responses to each of the 5 suicidal ideation questions, each of the 6 suicidal behavior questions, any of the 5 suicidal ideation questions, any of the 6 suicidal behavior questions, any suicidal ideation or behavior question, and the non-suicidal self-injurious behavior question.

A listing will also be prepared that includes all subjects with 1 or more affirmative responses.

10.0 Interim Analyses

No interim analysis on efficacy or safety data is planned for this study.

11.0 Overall Type I Error Control

A multiple testing procedure will be used to provide strong control of the Type I error rate at alpha = 0.05 (2-sided) across analyses comparing the investigational group to the active control group with respect to the primary efficacy endpoint and ranked secondary endpoints. Specifically, testing will use a sequence of hypothesis testing for the primary endpoint followed by the ranked secondary endpoints. If the primary endpoint achieves statistical significance with a P-value ≤ 0.05, continued testing will proceed in the following order:

- Key secondary endpoints:
  - Change from Baseline to Week 12 in hours of average daily normalized "Off" time
  - Change from Baseline to Week 12 in MDS-UPDRS Part II score
  - Presence of morning akinesia at Week 12

- Other secondary endpoints included in FWER control:
  - Change from Baseline to Week 12 in hours of average daily normalized "On" time without dyskinesia
  - Change from Baseline to Final Visit in PDSS-2 total score
  - Change from Baseline to Final Visit in PDQ-39 summary index
  - Change from Baseline to Final Visit in EQ-5D-5L summary index
  - Change from Baseline to Week 12 in median bradykinesia score (BK50) as assessed by the Parkinson's KinetiGraph™/Personal KinetiGraph™ (PKG) wearable device
  - Change from Baseline to Week 12 in interquartile range of bradykinesia score (BK75-BK25) as assessed by the PKG wearable device
  - Change from Baseline to Week 12 in median dyskinesia score (DK50) as assessed by the PKG wearable device
  - Change from Baseline to Week 12 in interquartile range of dyskinesia score (DK75-DK25) as assessed by the PKG wearable device

12.0 Version History

Table 2. SAP Version History Summary

Version	Date	Summary
1.0	12 August 2020	Original version
2.0	13 September 2021	1. Made changes to the list and ranking of secondary endpoints included in Type I error control prior to database lock and unblinding of Study M15-736. The changes to secondary endpoints are based on results from an interim analysis of open-label Phase 3 Study M15-741 as follows (Section 3.2 and Section 11.0): • Moved presence of morning akinesia at Week 12 from other secondary endpoints to a key secondary endpoint. • Added change from Baseline to Week 12 in hours of average daily normalized "On" time without dyskinesia to the list of other secondary endpoints included in Type I error control. • Moved PDSS-2 total score up in the list of other secondary endpoints included in Type I error control so that it is ranked before the PDQ-39 summary index and EQ-5D-5L summary index. 2. Change from Screening to Baseline of data derived from PD Diary and PKG wearable device will be analyzed on Full analysis set instead of Oral CD/LD analysis set to assign subjects to high dose or low dose in analysis table which is evaluated by double-blind study drug (Section 4.0). 3. Updated criteria regarding how to assign subjects who receive both placebo or both active treatments to a treatment group in analyses (Section 4.0). 4. Compliance will be assessed based on valid dosing diary days rather than all dosing diary days. This is because unlike all dosing information being required on 3 days prior to certain visits, all rescue medication use during the Double-Blind Treatment Period is required to be recorded. Therefore, blinded study drug information is not required on some dosing diary days. Compliance definition is revised such that only valid dosing diary days will be used (Section 6.0). 5. Baseline MDS-UPDRS Part I-IV scores is removed from PD history summary because it will be included in Baseline efficacy analysis (Section 7.2). 6. Deleted APD tool as the data is not collected in this study (Section 7.2)

Table 2. SAP Version History Summary (Continued)

Version	Date	Summary
		7. Changed 'Titration' to 'Optimization' to be consistent with protocol term (Section 7.4.2). 8. Changed definition of Baseline of PD Diary variables from "… before the day of randomization" to "… before the day of initiation of double-blinded study drug" to be consistent with analysis criteria (Section 8.1). 9. Clarified that responder analysis of both average daily normalized "On" time without troublesome dyskinesia and "Off" time will be conducted (Section 8.3.2). 10. Updated that all "On" times and "Off" time from PD Diary will be conducted for subgroup analyses (Section 8.6). 11. Clarified that how AEs will be summarized (Section 9.2) 12. Added analysis of AEs overview during Oral CD/LD Stabilization Period (Section 9.2.2). 13. Added "PM-PDSC" to infusion pump name (Section 9.2.2). 14. Changed "investigational group" to "ABBV-951 group" and changed "active-control group" to "Oral CD/LD group" (Section 9.2.3). 15. Added "Neria Guard infusion set" in SAE related summary analyses (Section 9.2.11). 16. Added "TEAE identified by Abuse Liability Company MedDRA Query" analysis (Section 9.2.12). 17. Added detailed description lab variables that will be analyzed (Section 9.4). 18. Added "more extreme than their baseline value" condition to lab and vital sign PCS criteria definition (Section 9.4 and Section 9.5). 19. Added analysis of subjects meeting criteria for liver-related laboratory elevations (Section 9.4). 20. Added analysis of infusion site evaluation scale (Section 9.6.2). 21. Added other analysis and listing of QUIP-RS (Section 9.6.3). 22. Updated the AESI definition and search criteria in Appendix B. 23. Updated the PCS criteria for Lab, VS, and ECG in Appendix C.

Table 2. SAP Version History Summary (Continued)

Version	Date	Summary
3.0	19 October 2021	1. Added inclusion criterion regarding hours of "Off" time at Screening and Randomization (Section 2.1). 2. Clarified how treatment group assignment will be done for Safety Analysis Set in the event a subject is dispensed wrong study drug kit from randomized (Section 4.0). 3. Added additional summary of PD medications at Screening and Baseline (Section 7.3). 4. Added sensitivity analysis for "On" times and "Off" time in addition to the primary endpoint (Section 8.2.2). 5. Added summary of number of hours from the last dose of blinded oral study drug to the first morning non-sleep status (Section 8.4.1) 6. Added that lab shift tables will be produced by lab normal range in additional to CTCAE criteria (Section 9.4). 7. Revise the calculation of orthostatic vital sign as standing value minus supine value (Section 9.5 and Appendix C-4). 8. Clarified that vital sign PCS summaries will be done for the Optimization Phase, the Maintenance Period, any time in the Double-Blind Treatment Period and at the final visit (Section 9.5). 9. Clarified that ECG PCS summaries will be done for the Optimization Phase, the Maintenance Period, any time in the Double-Blind Treatment Period and at the final visit (Section 9.6.1).

13.0 References

1. Tomlinson CL, Stowe R, Patel S, et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010;25(15):2649-53.
2. Liu GF, Pang L. On analysis of longitudinal clinical trials with missing data using reference-based imputation. J Biopharm Stat. 2016;26(5):924-36.

Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject randomized into the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study drug.
- Subject took prohibited concomitant medication.

Appendix B. Definition of Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) will be identified using the following search

Adverse Event of Special Interest	Search Criteria
Infusion site related infections	Infusion Site Related Infections (AbbVie ABBV-951 product-specific) CMQ (code 10000089)
Infusion site related non-infection reactions	Infusion Site Related Non Infection Reactions (AbbVie ABBV-951 product-specific) CMQ (code 10000178)
Hallucinations/Psychosis	Combined search: • Hallucinations CMQ (code 10000072) • Psychosis and Psychotic Disorders SMQ – narrow search (code 20000117).
Polyneuropathy	Peripheral Neuropathy SMQ – broad and narrow search (code 20000034)
Somnolence	Any of the following PTs: • Hypersomnia • Microsleep • Sleep attacks • Sleep disorder due to general medical condition, hypersomnia type • Somnolence • Sudden onset of sleep
Weight loss	Weight Loss CMQ (code 10000125)
Falls and associated injuries	Separate and combined searches: • Falls and Associated Injuries (AbbVie ABBV-951 product-specific) CMQ (code 10000056) • Orthostatic Hypotension PT search including any of the following PTs: "blood pressure ambulatory decreased," "blood pressure orthostatic," "blood pressure orthostatic decreased," "dizziness," "dizziness postural," "orthostatic hypotension," "syncope"

CMQ = Company MedDRA Query; PT = MedDRA preferred term; SMQ = Standardized MedDRA Query

Appendix C. Potentially Clinically Significant Criteria for Safety Endpoints

Appendix C-1. Potentially Clinically Significant (PCS) Hematology Criteria

	Sponsor Criteria		FDA Criteria[a]	
Variable	**Very Low**	**Very High**	**Very Low**	**Very High**
Activated partial thromboplastin time (aPTT) prolonged	-----	> ULN	-----	-----
Bands				≥ 14.0%
Bands, abs				≥ 1.4×10^9/L
Basophils				≥ 4.0%
Basophils, abs	-----	-----	-----	≥ 0.25×10^9/L
Eosinophils				≥ 8.0%
Eosinophils, abs	-----	-----	-----	≥ 0.7×10^9/L
Erythocytes (red blood cells)	-----	-----	≤ 3.0×10^{12}/L	-----
Hematocrit	-----	-----	Female ≤ 65: ≤ 30% Female ≥ 66: ≤ 28% Male ≤ 65: ≤ 34% Male ≥ 66: ≤ 32%	Female ≤ 65: ≥ 54% Female ≥ 66: ≥ 52% Male ≤ 65: ≥ 60% Male ≥ 66: ≥ 58%
Hemoglobin	< 100 g/L	> 40 g/L above ULN	Female ≤ 65: ≤ 99 g/L Female ≥ 66: ≤ 94 g/L Male ≤ 65: ≤ 110 g/L Male ≥ 66: ≤ 107 g/L	Female ≤ 65: ≥ 186 g/L Female ≥ 66: ≥ 186 g/L Male ≤ 65: ≥ 200 g/L Male ≥ 66: ≥ 204 g/L
INR	-----	> ULN	-----	-----
Leukocytes (white blood cells)	< 2×10^9/L	>100×10^9/L	≤ 3.0×10^9/L	≥ 16.0×10^9/L
Lymphocytes	-----	-----	≤ 13.0%	≥ 54.0%
Lymphocytes, abs	< 0.5×10^9/L	> 20×10^9/L	≤ 0.8×10^9/L	≥ 4.0×10^9/L

	Sponsor Criteria		FDA Criteria[a]	
Variable	**Very Low**	**Very High**	**Very Low**	**Very High**
Mean corpuscular volume (MCV)	-----	-----	≤ 65fL	≥ 115 fL
Mean corpuscular hemoglobin (MCH)	-----	-----	≤ 22 pg/cell	≥ 40 pg/cell
MCHC	-----	-----	≤ 264 gHb/L	≥ 426 gHb/L
Monocytes	-----	-----	≤ 2.6%	≥14.4%
Monocytes, abs	-----	-----	$\leq 0.12 \times 10^9$/L	$\geq 1.1 \times 10^9$/L
Neutrophils	-----	-----	≤ 30 %	≥90%
Neutrophils, abs	$< 1 \times 10^9$/L	-----	$\leq 1.7 \times 10^9$/L	$\geq 10 \times 10^9$/L
Thrombocytes (platelets)	$< 75 \times 10^9$/L	-----	$\leq 100 \times 10^9$/L	$\geq 550 \times 10^9$/L

a. Criteria requested by FDA DNP for Levodopa Carbidopa Intestinal Gel (LCIG) NDA 203952.

Appendix C-2. Potentially Clinically Significant (PCS) Chemistry Criteria

	Sponsor Criteria		FDA Criteria[a]	
Variable	**Very Low**	**Very High**	**Very Low**	**Very High**
Alanine aminotransferase (ALT, SGPT)		> 3 × ULN	-----	≥ 3 × ULN
Albumin	< 20 g/L	-----	≤ 65: ≤ 30 g/L	≤ 65: ≥ 60 g/L
	-----	-----	≥ 66: ≤ 27 g/L	≥ 66: ≥ 53 g/L
Alkaline phosphatase	-----	> 2.5 × ULN	-----	≥ 3 × ULN
Aspartate aminotransferase (AST, SGOT)	-----	> 3 × ULN	-----	≥ 3 × ULN
Bicarbonate	-----	-----	≤ 18 mmol/L	≥ 34 mmol/L
Bilirubin (total)	-----	> 1.5 × ULN	-----	≥ 2 × ULN
Blood urea nitrogen (BUN)	-----	-----	-----	≤ 65: ≥ 10.0 mmol/L ≥ 66: ≥ 9.5 mmol/L
Calcium (total)	Corrected: < 1.75 mmol/L	Corrected: ≥ 3.1 mmol/L	Corrected: ≤ 1.8 mmol/L	Corrected: ≥ 3.0 mmol/L
Chloride	-----	-----	≤ 87 mmol/L	≥ 116 mmol/L
Cholesterol (total)	-----	> 12.92 mmol/L	-----	≥ 6.5 mmol/L
Creatine phosphokinase (CPK)	-----	> 5 × ULN	-----	≥ 2 × ULN
Creatinine	-----	> 1.5 × ULN	-----	Female: ≥ 122 mcmol/L Male: ≥ 132 mcmol/L
Gamma glutamyl-transferase (GGT)	-----	> 2.5 × ULN	-----	≥ 3 × ULN
Glucose	< 2.2 mmol/L	> 13.9 mmol/L	≤ 3.0 mmol/L	≥ 9.0 mmol/L
Lactate dehydrogenase (LDH)	-----	-----	-----	≥ 3 × ULN

	Sponsor Criteria		FDA Criteria[a]	
Variable	**Very Low**	**Very High**	**Very Low**	**Very High**
Magnesium	< 0.4 mmol/L	> 1.23 mmol/L	-----	-----
Phosphate	< 0.6 mmol/L	-----	-----	-----
Potassium	< 3 mmol/L	> 6 mmol/L	≤ 3.0 mmol/L	≥ 6.0 mmol/L
Protein (total)	-----	-----	≤ 50 g/L	≥ 100 g/L
Sodium	< 130 mmol/L	> 155 mmol/L	≤ 126 mmol/L	≥ 156 mmol/L
Triglycerides	-----	> 5.7 mmol/L	-----	≥ 3.3 mmol/L
Uric acid	-----	> 0.59 mmol/L	-----	Female: ≥ 500 mcmol/L Male: ≥ 600 mcmol/L
Hy's Law lab criteria		ALT or AST ≥ 3 × ULN AND Total Bilirubin ≥ 2 × ULN		

a. Criteria requested by FDA DNP for Levodopa Carbidopa Intestinal Gel (LCIG) NDA 203952.

Appendix C-3. Potentially Clinically Significant (PCS) Special Lab Criteria

	FDA Criteria[a]	
Variable	**Very Low**	**Very High**
Vitamin B12, serum	≤ 125 pmol/L	-----
Vitamin B6	≤ 16 nmol/L	≥ 145 nmol/L
Folate, serum	≤ 1.7 nmol/L	-----
Homocysteine	≤ 4.2 mcmol/L	≥ 14.0 mcmol/L
Methylmalonic acid (MMA)	-----	≥ 0.5 mcmol/L

a. Criteria requested by FDA DNP for Levodopa Carbidopa Intestinal Gel (LCIG) NDA 203952.

Appendix C-4. Potentially Clinically Significant (PCS) Vital Sign and Weight Criteria

	Sponsor Criteria		FDA Criteria[a]	
Variable	**Very Low**	**Very High**	**Very Low**	**Very High**
SBP (mmHg, supine and standing)	≤ 80 and decrease ≥ 45 from Baseline	≥ 160 and increase ≥ 45 from Baseline	≥ 20 decrease from Baseline	≥ 20 increase from Baseline
			≥ 40 decrease from Baseline	≥ 40 increase from Baseline
			<90	> 140
				> 160
DBP (mmHg, supine and standing)	≤ 50 and decrease ≥40 from Baseline	≥ 95 and ≥ increase 40 from Baseline	≥ 10 mmHg decrease from Baseline	≥ 10 mmHg increase from Baseline
			≥ 20 mmHg decrease from Baseline	≥ 20 mmHg increase from Baseline
			<50	>90
				>100
Orthostatic SBP change (mmHg) (standing-supine)	≤ 30 decrease from supine to standing		≤ -20	------
			≤ -40	------
			≥ 20 decrease from Baseline	≥ 20 increase from Baseline
			≥ 40 mmHg decrease from Baseline	≥ 40 mmHg increase from Baseline
Orthostatic DBP change (mmHg) (standing-supine)	≤ 20 decrease from supine to standing		≤ -10	-----
			≤ -20	------
			≥ 10 decrease from Baseline	≥ 10 increase from Baseline
			≥ 20 decrease from Baseline	≥ 20 increase from Baseline

	Sponsor Criteria		FDA Criteria[a]	
Variable	**Very Low**	**Very High**	**Very Low**	**Very High**
Orthostatic SBP and DBP (mmHg)			Orthostatic SBP ≤ -20 and orthostatic DBP ≤ -10	-----
			Orthostatic SBP ≤ -40 and orthostatic DBP ≤ -20	------
			Orthostatic SBP ≥ 20 decrease from Baseline and orthostatic DBP ≥ 10 decrease from Baseline	------
			Orthostatic SBP ≥ 40 decrease from Baseline and orthostatic DBP ≥ 20 decrease from Baseline	-----
Pulse rate (bpm, supine and standing)	≤ 45 and decrease ≥ 35 from Baseline	≥ 120 and increase ≥ 35 from Baseline	≥ 15 decrease from Baseline	≥ 15 increase from Baseline
			≥ 30 decrease from Baseline	≥ 30 increase from Baseline
			≤ 60	≥ 100
Orthostatic pulse (bpm) (standing-supine)	NA	Increase ≥ 30 from supine to standing	≥ 15 decrease from Baseline	≥ 15 increase from Baseline
			≥ 30 decrease from Baseline	≥ 30 increase from Baseline
Weight (kg)	≥ 7% decrease from Baseline	≥ 7% increase from Baseline		
Temperature (°C)		≥ 38.3 and increase ≥ 1.1 from baseline	< 36.0	>38.0

a. Criteria requested by FDA DNP for Levodopa Carbidopa Intestinal Gel (LCIG) NDA 203952.

Appendix C-5. Criteria for Potentially Clinically Significant Electrocardiogram Values

	Definition of Potentially Clinically Significant	
ECG Variables	**Very Low (VL)**	**Very High (VH)**
Heart rate (bpm)	≤ 45 and decreased ≥ 35 from baseline	≥ 120 and increased ≥ 35 from baseline
PR (ms)	≤ 120	≥ 220
QTcF Interval (ms)		> 450
	NA	> 500
		> 480
		>480 or Increased ≥ 60 from Baseline
		Increased ≥ 30 from Baseline
		Increased ≥ 60 from Baseline

Appendix D. Additional Adverse Event Search Criteria

Additional Adverse Event Searches	Search Criteria
COVID-19	COVID-19 SMQ – narrow search (code 20000237)
Abuse potential	Abuse Liability CMQ (code 10000001)

CMQ = Company MedDRA Query; SMQ = Standardized MedDRA Query

Document Approval

Study M15736 - Statistical Analysis Plan Version 3 - 19Oct2021 (E3 16.1.9)

Version: 1.0 **Date:** 19-Oct-2021 10:25:52 PM **Company ID:** 10192021-00F9F684DB4E1A-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	19-Oct-2021 10:09:12 PM	Approver
	19-Oct-2021 10:09:28 PM	Approver
	19-Oct-2021 10:12:55 PM	Author
	19-Oct-2021 10:25:51 PM	Approver