1.0 Title Page

Statistical Analysis Plan

Study M15-535

An Open-Label, Randomized 12 Week Study Comparing Efficacy of Levodopa-Carbidopa Intestinal Gel/Carbidopa-Levodopa Enteral Suspension and Optimized Medical Treatment on Dyskinesia in Subjects with Advanced Parkinson's Disease

DYSCOVER (DYSkinesia COmparative interventional trial on Duodopa VERsus oral medication)

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by AbbVie clinical statisticians for Levodopa-Carbidopa Intestinal Gel (LCIG) Study M15-535 with a protocol dated 26 May 2016 incorporating one amendment (original protocol: 03 May 2016, Amendment 1: 26 May 2016). It provides details to further elaborate statistical methods as outlined in the protocol and describes analysis conventions to guide the statistical programming work.

Unless noted otherwise, all analyses will be performed using SAS version 9.2 or higher (SAS Institute Inc., Cary, NC 27513) under the Unix operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objective of this interventional study is to examine the effect of LCIG treatment relative to that of Optimized Medical Treatment (OMT) on dyskinesia as measured by the Unified Dyskinesia Rating Scale (UDysRS) Total Score.

The Secondary objective is to assess the effect of LCIG treatment relative to that of OMT on dyskinesia as measured by PD Diaries, motor symptoms, motor complications, health-related outcome measures, safety and tolerability.

4.2 Design Diagram

This is a Phase 3b, open-label, randomized multicenter 12 week study assessing the efficacy of LCIG treatment compared to OMT on dyskinesia in subjects with Advanced Parkinson's Disease.

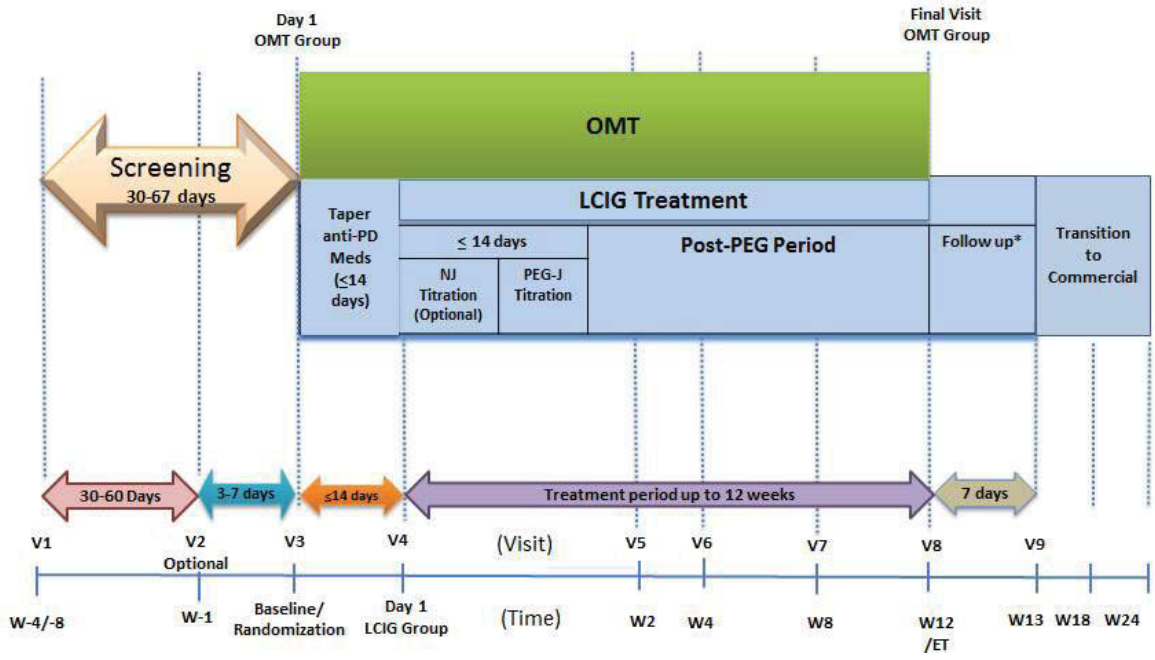
The study will consist of three sequential parts:

Part 1: Screening period. The screening period will consist of three visits, Visit 1 (V1), Visit 2 ([V2] [optional]) and the Randomization Visit (V3) in which the subject will be

assessed to determine eligibility. The duration of the Screening Period will be between 30 – 67 days to accommodate the required procedures, training and collection of diaries, and to allow for stabilization of anti-PD medications and medications to treat dyskinesia. All anti-PD medications and medications to treat dyskinesia are required to be stable for a minimum of 30 days prior to randomization.

Part 2: Treatment period. Those subjects randomized to OMT at the end of V3 will remain on their current optimized anti-PD regimen. The day after randomization will be considered Day 1 of their treatment period and subjects will have study visits at the end of Weeks 2, 4, 8, and 12. Subjects randomized to LCIG treatment must discontinue all other anti-PD medications other than amantadine (e.g., dopamine agonists, COMT-inhibitors, MAO-B inhibitors, anti-cholinergics, and subcutaneous apomorphine, etc.) prior to LCIG treatment initiation on Day 1 (V4); these medications should be tapered off within 14 days after randomization according to the discretion of the Investigator. With the exception of apomorphine, levodopa containing formulations or amantadine, these medications may be restarted if indicated by the subject's individual condition, but not within the first 28 days after LCIG treatment initiation. Optional nasojujunal (NJ) and/or percutaneous endoscopic gastrostomy with a jejunal tube (PEG-J) placement will then be placed. After that, the subject may begin initiation and titration of LCIG infusion to be adjusted to obtain the optimal clinical response in 14 days. The day of initial NJ or PEG-J placement will be considered Day 1 for subjects in the LCIG group. Study visits happen at the end of Weeks 2, 4, 8, and 12.

Figure 1. Study Design Schematic



Part 3: Follow-up period. The OMT subjects will not have a follow-up visit (V9). Study subjects in the OMT group who complete participation in the study are eligible to transition to commercial LCIG after end of study procedures if judged appropriate by their personal physician. For LCIG subjects who elect to discontinue LCIG and not continue with commercially available product, a V9 will be conducted 1 week after PEG-J removal and the SAE/AE follow-up period will be up until 30 days after PEG-J removal. For LCIG treatment subjects who will transition to commercial product, the SAE/AE follow-up period will be up until 30 days after the transition. For study subjects in the LCIG group who complete participation in the study and will continue to receive LCIG, subjects will return every 6 weeks to return used LCIG cassettes and be dispensed cassettes. Additional visits every 12 weeks from Week 12 will be scheduled to monitor subject safety and allow for drug resupply until the subject transfers to commercial LCIG.

4.3 Sample Size

Approximately 60 subjects will be enrolled into the study and randomized in a 1:1 ratio to either optimized medical treatment (OMT) or LCIG treatment. Subject randomization will be stratified by country. For sample size determination, it is assumed that the difference of improvement is 10 points on UDysRS total score between the LCIG treatment group and OMT group based on results reported by Pahwa et al (2015). The pooled standard deviation is assumed to be 12 based on results reported by Goetz et al (2013). Assuming that the treatment group difference is 10 points and the pooled standard deviation is 12, 27 subjects per group will have 85% power to declare statistical significance on the primary endpoint at a two-sided significance level of 0.050 based on calculations using nQuery + nTerim 4.0. It is further assumed that 10% of randomized subjects in either treatment group will not provide post-randomization efficacy assessment. Therefore the total planned enrollment is decided to be approximately 60 subjects.

4.4 Interim Analysis

After all randomized subjects have completed the 12-week Treatment Period, or have discontinued during the Treatment Period and those randomized to LCIG have completed Follow-up Period, the primary objective of the study will have been fulfilled. A database lock will occur. Primary analyses of efficacy and safety data comparing LCIG and OMT arms will be conducted at that time.

4.5 Efficacy and Health-Related Outcome Measures

4.5.1 Motor Symptoms/Motor Complications

Motor symptoms will be assessed by the following measures.

- Unified Dyskinesia Rating Scale (UDysRS)
- Parkinson's Disease Diary (PD Diary): normalized average daily hours of OFF time, ON time with troublesome dyskinesia, ON time without troublesome dyskinesia

- Unified Parkinson's Disease Rating Scale (UPDRS) Part III
- Modified Abnormal Involuntary Movement Scale (mAIMS)

4.5.2 Health-Related Outcomes

Health-related outcomes will be assessed by the following measures.

- UPDRS Part II
- Parkinson's Disease Questionaire-8 (PDQ-8)
- King's PD Pain Scale
- Clinical Global Impression of Severity (CGI-S)
- Clinical Global Impression of Change (CGI-C)

A description of each measure is included in Protocol Section 5.3.1.1 Study Procedures. Each measure will be assessed at the times indicated in the relevant study activities flow chart (Appendix A).

4.6 Safety Measures

Safety and tolerability over the course of the study will be assessed by the following measures.

- Adverse event monitoring
- Neurological exams
- Clinical laboratory evaluations
- Electrocardiogram
- Vital signs and weight
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Minnesota Impulsive Disorders Interview (MIDI)
- Sleep Attacks Questionnaire (SAQ)

A description of each measure is included in Protocol Section 5.3.1.1 Study Procedures. Each measure will be assessed at the times indicated in the study activities flow chart (Appendix A).

5.0 Analysis Populations

Analyses will be performed utilizing the following datasets.

Intent-to-Treat Dataset

The intent-to-treat dataset will include all subjects who are randomized to the optimized medical treatment, and all subjects who are randomized to LCIG and received at least one dose of study drug following PEG-J placement. The intent-to-treat dataset will be used to summarize efficacy and health outcome measures.

Safety Dataset

The safety dataset will include all subjects who are randomized to the optimized medical treatment, and all subjects who are randomized to LCIG and have a study device (NJ and/or PEG-J) placement procedure. The safety dataset will be used to summarize safety data during the OMT and LCIG treatment period.

6.0 Analysis Conventions

6.1 Statistical Significance

This is a randomized open-label study. Unless otherwise specified, statistical tests will be two-sided and the null hypothesis will be rejected at the significance level of $\alpha = 0.050$. *P* values will be rounded to three decimal points before assessing statistical significance. If the primary efficacy variable UDysRS total score is statistically significant, each of the secondary efficacy variables will be tested using the fixed sequence below as a gatekeeping procedure and at α level of 0.050. Testing will cease at the point that a secondary variable fails to demonstrate statistical significance.

- "ON" time without troublesome dyskinesia as measured by the PD Diary

- Parkinson's Disease Questionaire-8 (PDQ-8) summary index
- Clinical Global Impression of Change (CGI-C) Score
- UPDRS Part II Score
- "OFF" time as measured by the PD Diary
- UPDRS Part III Score

6.2 Definition of Study Epochs and LCIG Treatment Period Reference Variables

The following study epochs have been defined to track each subject's progression from screening through study completion or premature discontinuation.

Epoch Name	Epoch Description
Pre	[redacted]
Device Before (LCIG group only)	
Open	
Transition (LCIG group only)	
Device After (LCIG group only)	
Off	

For subjects in the LCIG group, the date and time of the earliest LCIG tube placement (NJ or PEG-J) recorded on the Device Information eCRF will be considered the treatment start reference date (REFDT) and time (DMREFTM). The date of the last LCIG tube removal, or the date of the last LCIG infusion if there is no device removal will be considered the end of the LCIG treatment period and the following day will be the post-treatment start reference date (REFEDT). For subjects in the OMT group, the date after randomization will be considered the start of treatment period and will be the treatment start reference date (REFDT). The date of the final visit will be considered the end of the OMT treatment period and the following day will be the post-treatment start reference date (REFEDT).

Study Days will be calculated based on the treatment start reference date (REFDT). For time points before REFDT, the Study Day = time point – REFDT. For time points on or after REFDT, the Study Day = time point – REFDT + 1. Thus, the Study Day is a negative value when the time point of interest is prior to REFDT and the Study Day is a positive value when the time point of interest is on or after REFDT. There is no Study Day 0. The Study Day will be labeled as Rx Day on the data listings. RxEnd Day is calculated for each post-treatment time point as the number of days between REFEDT and the specific time point: RxEnd Day = date of time point – REFEDT + 1.

6.3 Definition of Baseline and Final Observation

Baseline for PD Diary variables will be the average of the last 3 valid diaries completed on or before the day of randomization. Baseline for all efficacy, health outcome and safety measures, other than the PD Diary, will be defined as the last non-missing observation that is on or before the day of randomization.

The final visit for PD Diary variables for the OMT group will be the average of the last 3 valid diaries that are after the day of randomization during the 12-week Treatment Period. The final visit for PD Diary variables for the LCIG group will be the average of the last 3 valid diaries that are after the date of the first LCIG infusion following PEG-J placement and on or before the date of the last LCIG infusion during the 12-week

Treatment Period. The final visit for efficacy and health outcome measure, other than PD Diary variables, for the OMT group will be defined as the last non-missing observation that is after the day of randomization during the 12-week Treatment Period. The final visit for efficacy and health outcome measures, other than PD Diary variables, for the LCIG group will be defined as the last non-missing observation that is after the date of the first LCIG infusion following PEG-J placement and no more than 1 day after the last LCIG infusion during the 12-week Treatment Period.

For subjects who discontinue LCIG treatment during the 12-week Treatment Period or complete the 12-week Treatment Period but not going to transit to commercial product, the final visit for safety assessments will be defined based on the final removal of all LCIG devices and will be the last non-missing observation that is after the date and time of the first LCIG tube (NJ or PEG-J) placement procedure and no more than 1 day after the final removal of all LCIG tubes. For subjects who transit to commercial product, the final visit will be the last non-missing observation during the 12-week Treatment Period in the database. Safety assessments on the date of the first PEG-J placement procedure that do not have a time of assessment or sample collection recorded will be assumed to be post-procedure. For subjects in the OMT group, the final visit for safety assessments will be defined as the last non-missing observation that is after the day of randomization during the 12-week Treatment Period.

6.4 Analysis by Planned Visit for PD Diary Variables

The PD Diary will be used by the subject and/or their caregiver to record parkinsonian symptoms on the 3 days prior to clinic visits as indicated in the Schedule of Study Activities. The total daily awake time will be calculated for each diary as described in Section 9.4. Only diaries with at least 12 hours of awake time will be considered valid and included in the analyses.

The PD Diary is planned to be completed on each of 3 days prior to selected scheduled visits. It is expected that all 3 diary days will fall in the same visit window as long as the subject is on schedule. However, there may be rare instances where the timing of a

subject's visit schedule shifts due to unforeseen circumstances. To ensure that each adjacent diary day will be assigned to the same visit window, each diary day will be linked to the nearest scheduled visit that occurred after the date on which the diary was completed. The PD diary data will be assigned to a visit window based on the date of this scheduled visit.

Assessment	Planned Visit	Nominal Study Day	Study Day Range[a]
PD Diary	Baseline		≤ date of randomization
	Week 2	14	2 – 21
	Week 4	28	22 – 42
	Week 8	56	43 – 70
	Week 12	84	≥ 71

a. For subjects in LCIG group, all post-baseline PD Diaries must also be after start of LCIG infusion through PEG-J and on or before the date of the last LCIG infusion in the 12-week Treatment Period.

The valid diary days (at least 12 awake hours) will be used to compute the average daily times. For post-baseline visits, the valid diary days must be within 7 days of the scheduled visit but not on or after the day of the scheduled visit. If more than 3 valid diary days are available, the last 3 days in each visit window will be used. If only 1 or 2 valid diary days are available prior to a scheduled visit, data from the available days will be used to calculate the average daily times. Subjects that do not have any valid diary days for a visit will have the average daily times set to missing for that visit.

6.5 Analysis by Planned Visit for Non-Diary Variables

A midpoint convention will be used to assign all observations to a planned visit based on the Study Day of the observation. If there are multiple observations on the same day, the average will be taken and considered the observation for the day. If more than one observation is assigned to a planned visit, the last observation will be selected and considered the observation for the planned visit.

The following Study Day windows will be used to assign efficacy and health outcome assessments to planned study visits during the 12-week Treatment Period. Assessments

on the day of first day of LCIG infusion via PEG-J are not planned and will not be included in the analysis.

Assessment	Planned Visit	Nominal Study Day	Study Day Range[a]
UDysRS, UPDRS, mAIMS, CGI-C	Baseline		≤ date of randomization
	Week 2	14	2 – 21
	Week 4	28	22 – 42
	Week 8	56	43 – 70
	Week 12	84	≥ 71
PDQ-8	Baseline		≤ date of randomization
	Week 8	56	2 – 70
	Week 12	84	≥ 71
King's PD Pain Scale	Baseline		≤ date of randomization
	Week 4	28	2 – 42
	Week 8	56	43 – 70
	Week 12	84	≥ 71

a. For subjects in LCIG group, all post-baseline assessments must also be after start of LCIG infusion through PEG-J and no more than 1 day after the date of the last LCIG infusion in the 12-week Treatment Period.

The following Study Day windows will be used to assign safety assessments during the 12-week Treatment Period to planned study visits.

Assessment	Planned Visit	Nominal Study Day	Study Day Range[a]
Vital signs and weight, MIDI, Sleep Attacks Questionnaire, C-SSRS	Baseline		≤ date of randomization
	Week 2	14	2 – 21
	Week 4	28	22 – 42
	Week 8	56	43 – 70
	Week 12	84	≥ 71
	Week 13 FU[b]	91	2 ≤ RxEnd Days
Clinical labs and Electrocardiograms, Special labs	Baseline		≤ date of randomization
	Week 8	56	1 – 70
	Week 12	84	≥ 71

a. For subjects in LCIG group, all post-baseline assessments must also be no more than 1 day after the final PEG-J removal for subjects who do not transit to commercial product or no more than 1 day after the final Study M15-535 LCIG infusion during 12-week Treatment Period for subjects who transit to commercial product.

b. Applicable only to LCIG subjects who will not continue on commercial product.

For LCIG subjects who enter the Transition Period, vital signs and weight, special labs, C-SSRS and MIDI will be assessed every 12 weeks.

6.6 Adverse Event Analysis by Study Week

Treatment-emergent adverse events during the 12-week Treatment Period will be assigned to study week intervals based on the Study Day of onset as follows.

Study Week(s)	Study Day Range
Week 1	1 – 7
Week 2	8 – 14
Week 3	15 – 21
Week 4	22 – 28
Weeks 5 – 8	29 – 56
Weeks 9 – 12	≥ 57

6.7 Derived Datasets

The study database will include the following derived datasets which will be used for the analyses described in this SAP.

- Subject Characteristics for all subjects who participated in the study: one record per subject with demographic, baseline characteristic, analysis population and subgroup variables.
- Study Drug Exposure for the Safety Dataset: For LCIG subjects, one record per subject for each exposure variable (morning dose, extra dose, etc.) and each planned assessment time with the prescribed dose and actual dose. For OMT subjects, one record per subject per medication.
- Efficacy Endpoints for the All Randomized Dataset: one record per subject for each variable and each planned assessment time with the baseline value, time point value, and change from baseline value for the UDysRS, PDQ-8, CGI-C, UPDRS Part II, UPDRS Part III, mAIMS, King's PD Pain Scale, and "ON" time without troublesome dyskinesia, "OFF" time, "ON" time with

troublesome dyskinesia and "ON" time without dyskinesia as measured by PD Diary.

A Derived Dataset Specification that includes a detailed description of the dataset's structure and variables will be developed for each derived dataset.

7.0 Subject Disposition, Baseline Characteristics and Concomitant Medications

7.1 Subject Disposition

An overall summary of the disposition of all screened subjects will be prepared. The total number of subjects in each of the following categories as well as the number at each site will be presented: screened, screen failed; randomized to OMT group, prematurely discontinued treatment from OMT group, completed the planned 12 weeks of treatment in OMT group; randomized to LCIG group, prematurely discontinued treatment from LCIG group, completed the planned 12 weeks of treatment in LCIG group. The total number of subjects in LCIG group in each of the following categories as well as the number at each site will be presented: Randomized, No NJ/PEG-J placed, NJ placed, prematurely discontinued treatment during NJ, PEG-J placed, prematurely discontinued treatment during 12-week Treatment Period, prematurely discontinued treatment during commercial transition, transit to commercial.

An additional summary of screen failures will be prepared with the number and percentage of screened subjects who screen failed overall and for each specific screen failure reason.

Additional summaries of premature study drug discontinuations during the first 12 weeks of treatment for both treatment groups, during the transition period (LCIG group only) and during the entire study (including first 12 weeks and transition period for LCIG group only) will be prepared for the Safety Dataset with the number and percentage of subjects who prematurely discontinued for any reason, for each specific primary reason, and for each specific reason.

A listing will be prepared of all randomized subjects who are not included in the primary efficacy analysis. The listing will include each subject number and reason for exclusion.

7.2 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by treatment group and for overall subjects in the safety dataset unless otherwise specified.

- Gender (male/female)
- Race (white, black, American Indian/Alaska native, native Hawaiian or other Pacific Islander, Asian, Other, Multi-Race)
- Ethnicity (Hispanic or Latino, ne)
- Age (years)
- Age category (< 65, ≥ 65)
- Age category (< 75, ≥ 75)
- Weight for all subjects (kg)
- Weight for all male subjects (kg)
- Weight for all female subjects (kg)
- Height (cm)
- Body mass index (BMI, kg/m^2)
- Body mass index category (< 25 kg/m^2, ≥ 25 kg/m^2)
- Mini-Mental State Examination (MMSE) total score
- Parkinson's disease duration (years)
- Motor fluctuation duration (years)
- Parkinson's disease duration category (< 10 years, ≥ 10 years)
- Time from Parkinson's disease diagnosis to start of first levodopa medication (years)
- Proportion of subjects meeting each of the following United Kingdom Parkinson's Disease society (UKPDS) Brain Bank diagnostic criteria for PD
  - Diagnosis of bradykinesia
  - Diagnosis of muscular rigidity

- Diagnosis of 4 – 6 Hz resting tremor
- Diagnosis of postural instability

Alcohol and nicotine use will also be summarized. For alcohol use the number and percentage of subjects who are drinkers, ex-drinkers and non-drinkers (defined as those who have never been a drinker) will be presented. For nicotine use the number and percentage of users, ex-users and non-users (defined as those who have never been a user) will be presented. A subject reporting multiple use categories for the different types of nicotine (cigarettes, pipes, cigars and chewing tobacco) will be counted in the nicotine use category closest to user.

Categorical variables will be summarized with the number and percentage of subjects in each category. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum).

7.3 Medical History

The conditions/diagnoses recorded in medical/surgery history eCRF will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). Medical/surgical history data will be summarized by primary MedDRA system organ class (SOC) and preferred term (PT) for each treatment group and overall subjects in the Safety Dataset. Subjects reporting more than one condition/diagnosis for a given PT will be counted only once for that term. Subjects reporting more than one condition/diagnosis within an SOC will be counted only once for the SOC total. Subjects reporting more than one condition/diagnosis will be counted only once in the overall medical history total. The SOCs will be presented in alphabetical order and the PTs will be presented in alphabetical order within each SOC.

7.4 Prior and Concomitant Medications

Medications prescribed for the treatment of Parkinson's disease (anti-PD medications) will be identified by the investigator and will be entered into the database and summarized

separately from other medications. All medications will be coded using the World Health Organization (WHO) dictionary and will be summarized by generic name.

Summaries of 3 categories of anti-PD medications (anti-PD motor symptom medications, anti-PD non-motor symptom medications, and anti-PD sleep medications) will be prepared for the Safety Dataset for the following periods:

- from V1 prior to Day 1
- during the 12-week Treatment Period (start date before or on the last date of the 12-week Treatment Period and end date on or after Day 1)

Each summary will include the number and percentage of subjects who took each specific medication, each incremental number of medications (1, 2, 3, 4, 5, and 6 or more) and each cumulative number of medications (1 or more, 2 or more, 3 or more, 4 or more, and 5 or more). For the summary of anti-PD motor symptom medications, the count will be for medications other than levodopa-carbidopa.

The following summaries of other medications will be prepared for the Safety Dataset.

- Other medications prior to treatment (start date before Day 1)
- Other medications during the 12-week Treatment Period (start date before or on the last date of the 12-week Treatment Period and end date on or after Day 1)

Each summary will include the number and percentage of subjects who took each specific medication and the number who took 1 or more medications.

8.0 Treatment Exposure and Compliance

Summaries of treatment exposure and compliance will be prepared for the Safety Dataset.

8.1 Duration of Treatment and PEG-J Exposure

During the 12-Week Treatment Period

The duration of study drug exposure for LCIG subjects and the duration of study participation for OMT subjects during the 12-week Treatment Period will be summarized with descriptive statistics (number of subjects with non-missing data, mean, standard deviation, median, minimum and maximum). The duration of LCIG study drug exposure will be calculated for each subject as the date of the last infusion of LCIG study drug during the 12-week Treatment Period minus the date of the first infusion of LCIG study drug plus 1. The duration of study participation for OMT subjects will be calculated for each subject as the date of the last visit minus the date of randomization.

The duration of PEG-J exposure for LCIG subjects during the 12-week Treatment Period will be summarized with descriptive statistics (number of subjects with non-missing data, mean, standard deviation, median, minimum and maximum). For subjects who don't have Transition Period, the duration of PEG-J exposure for each subject will be calculated as the date of their final PEG-J removal or the date of their last infusion of LCIG study drug during the 12-week Treatment Period if there is no PEG-J removal minus the date of their initial PEG-J placement + 1. For subjects who have Transition Period, the duration of PEG-J exposure for each subject will be calculated as the date of their last infusion of LCIG study drug during the 12-week Treatment Period minus the date of their initial PEG-J placement + 1.

The number and percentage of subjects in each of the following exclusive duration categories during the 12-week Treatment Period will be summarized for LCIG infusion exposure and PEG-J exposure in the LCIG group and study participation for the OMT group:

- 1 to 28 days (1 – 4 weeks)
- 29 to 56 days (5 – 8 weeks)
- ≥ 57 days (≥ 9 weeks)

In addition, duration of exposure during the 12-week Treatment Period will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum duration and total subject-years) and by total subject-years. Total subject-years of OMT, LCIG and PEG-J exposure will be calculated by summing the duration of exposure across the respective set of subjects and dividing this sum by 365.25 (1 year will be considered to be 365.25 days).

During the Transition Period

The duration of study drug exposure for LCIG subjects during the Transition Period will be summarized with descriptive statistics (number of subjects with non-missing data, mean, standard deviation, median, minimum and maximum). The duration of LCIG study drug exposure will be calculated for each subject as the date of the last infusion of LCIG study drug during the Transition Period minus the date of the last infusion of LCIG study drug during the 12-week Treatment Period.

The duration of PEG-J exposure for LCIG subjects during the Transition Period will be summarized with descriptive statistics (number of subjects with non-missing data, mean, standard deviation, median, minimum and maximum). For subjects with a PEG-J tube removal after their last infusion of LCIG study drug during the Transition Period, the duration of PEG-J exposure for each subject will be calculated as the date of their final PEG-J removal minus the date of their last infusion of LCIG study drug during the 12-week Treatment Period. For subjects without a PEG-J tube removal after their last infusion of LCIG study drug during the Transition Period, the duration of PEG-J exposure for each subject will be calculated as the date of their final participation in Study M15-535 (last contact or visit date) minus the date of their last infusion of LCIG study drug during the 12-week Treatment Period.

Overall

The overall duration of study drug exposure for LCIG subjects and the overall duration of study participation for OMT subjects will be summarized with descriptive statistics (number of subjects with non-missing data, mean, standard deviation, median, minimum

and maximum). The overall duration of LCIG study drug exposure will be calculated for each subject as the date of the last infusion of LCIG study drug minus the date of the first infusion of LCIG study drug plus 1. The overall duration of study participation for OMT subjects will be calculated for each subject as the date of the last visit minus the date of randomization.

The overall duration of PEG-J exposure for LCIG subjects will be summarized with descriptive statistics (number of subjects with non-missing data, mean, standard deviation, median, minimum and maximum). The overall duration of PEG-J exposure for each subject will be calculated as the date of their final PEG-J removal or the date of their final participation in Study M15-535 (last contact or visit date) if there is no PEG-J removal minus the date of their initial PEG-J placement + 1.

8.2 Duration of NJ Period

Duration of NJ Period for each subject who undergoes the optional NJ period will be calculated as the date of NJ removal minus the first NJ infusion date + 1. The first NJ infusion date will be recorded on the Study Drug Administration eCRF. The number and percentage of subjects with each specific number of days will be summarized. In addition, the duration of NJ Period in days will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum duration).

8.3 LCIG Daily Prescribed Dose

Each subject's LCIG dose will be individually titrated by adjustment of the LCIG pump settings for the morning dose (mL), continuous flow rate (mL/hr) and extra dose amount (mL). The initial LCIG pump settings and the LCIG pump settings at the conclusion of each clinic visit will be recorded on the Study Drug Prescription eCRF. Subjects are to administer LCIG over a full 16-hour period each day beginning with a morning dose. Extra doses are to be administered only if needed. The daily prescribed dose will be calculated as the morning dose plus 16 times the continuous flow rate. The daily

prescribed dose will be summarized in milligrams (mg) of levodopa using the conversion factor of 1 mL LCIG = 20 mg levodopa.

The daily prescribed dose will be summarized with descriptive statistics (number of subjects with non-missing observations, mean, standard deviation, median, minimum and maximum values) for the following.

- Initial LCIG prescription
- First optimized prescription following PEG-J placement
- Final prescription

Descriptive statistics will also be presented for the change in the daily prescribed dose from initial LCIG prescription to first optimized prescription following PEG-J placement and to final prescription and from first optimized prescription to final prescription.

8.4 Total Daily Levodopa Dose

For all randomized subjects, the total daily levodopa dose on the day prior to Visit 1 and on the day of randomization will be considered the subject's screening and baseline levodopa dose, respectively. Following Screening Visit 3, subjects randomized to the LCIG group will have NJ/PEG-J placement and discontinue all anti-PD medications other than levodopa-carbidopa that will be continued during LCIG treatment as post-infusion nighttime therapy. Subjects in the LCIG group are to record all LCIG infusions during the 3 days before each scheduled study visit on a Subject Dosing Diary. Subjects in the OMT group are to record all anti-parkinsonian medications taken on the Subject Dosing Diary.

For each Subject Dosing Diary, the overall total daily dose of levodopa will be determined for each subject in the Safety Dataset, as well as the total for each dosing source for each subject in the LCIG group: LCIG morning dose, LCIG continuous infusion, LCIG extra dose, and LCIG overall. Each subject's average daily dose at each visit, overall and by dosing source, will be calculated by summing the total dose on each Subject Dosing Diary assigned to the visit and dividing by the number of diaries recorded. For LCIG subjects,

only diaries reporting at least 12.8 hours of pump operation and only diaries after the initial LCIG titration will be included in this calculation.

For each scheduled visit the mean daily levodopa dose will be summarized, overall and by dosing source, with descriptive statistics (number of subjects with observations, mean, standard deviation, median, minimum and maximum values). The summaries for LCIG extra dose should only include the subjects who dosed in this manner at the visit.

8.5 Daily Treatment Duration

The LCIG pump start time and end time at each clinic visit will be recorded on the Dosing Diary eCRF. Daily treatment duration (hours of pump operation) will be summarized with descriptive statistics (mean, standard deviation, median, minimum and maximum duration) at each visit.

8.6 Tube Replacements

The number and percentage of LCIG subjects with each specific count of PEG-J tube replacements will be summarized as well as the number and percentage of LCIG subjects with one or more replacements. The number of PEG-J tube replacements will also be summarized by descriptive statistics. The time to the first PEG-J tube replacement will also be estimated using Kaplan-Meier methodology. For the Kaplan-Meier analysis, subjects who did not have a PEG-J tube replacement during the study will be censored at the end of their Study M15-535 PEG-J tube exposure. Subjects with a PEG-J tube removal after their last infusion of Study M15-535 study drug will be censored at this final tube removal date. Subjects without a PEG-J tube removal after their last infusion of Study M15-535 study drug will be censored on the date of their final participation in Study M15-535 (last contact or visit date).

8.7 Duration of Initial LCIG Titration

Duration of initial LCIG titration for each subject will be calculated as the date of the first optimized prescription minus the first LCIG infusion date + 1. The first LCIG infusion date will be recorded on the Study Drug Administration eCRF. The current

LCIG pump settings at the conclusion of each clinic visit will be recorded on the Study Drug Prescription eCRF. The first set of pump settings that remains unchanged for at least 7 days will be considered the first optimized prescription. The number and percentage of subjects with each specific number of titration days will be summarized. In addition, the duration of initial titration in days will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum duration).

9.0 Efficacy and Health Outcome Analysis

9.1 General Considerations

This is a randomized open-label study. Unless otherwise specified, statistical tests will be two-sided and the null hypothesis will be rejected at the significance level of $\alpha = 0.050$. *P* values will be rounded to 3 decimal places before assessing statistical significance. Unless noted otherwise, all analyses will be performed with the Intent-to-Treat Dataset. Missing data will not be imputed unless otherwise specified.

9.2 Primary Efficacy Analysis

UDysRS Total Score

The UDysRS was developed to evaluate dyskinesia in Parkinson's disease. It contains two primary sections with 26 questions:

Historical [Part 1 (On-Dyskinesia) and Part 2 (Off-Dystonia)]

Objective [Part 3 (Impairment) and Part 4 (Disability)]

Part 1 contains 11 questions about the on time dyskinesia and the impact of on-dyskinesia on experiences of daily living. Part 2 contains 4 questions of off-dystonia rating. Part 3 contains 7 questions about objective evaluation of dyskinesia impairment and Part 4 contains 4 questions regarding dyskinesia disability. Each question is scored with respect to severity, which is rated on a scale where 0 = normal, 1 = slight, 2 = mild, 3 = moderate

and 4 = severe. The UDysRS total score is obtained by summing the item scores, ranging from 0 to 104.

The primary efficacy variables will be the change from baseline to Week 12 in the UDysRS total scores. It will be estimated using PROC MIXED and a mixed-effect model repeated measures (MMRM) for the change from baseline to each scheduled post-baseline visit. The model will include fixed, categorical effects for treatment, country, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline score and the baseline score-by-visit interaction. The unstructured covariance structure will be used to estimate the within subject variance-covariance structure and Satterthwaite's approximation will be used to estimate the denominator degrees of freedom. If the model fails to converge, the first order autoregressive (AR[1]) covariance structure will be substituted. If the model still fails to converge, the compound symmetry (CS) covariance structure will be substituted. Type III sum-of-squares and least-square (LS) means will be used for statistical evaluations. The LS mean and 95% confidence interval obtained from the model will be presented. The primary comparison will be the contrast between LCIG and optimized medical treatment at the Week 12 Visit. The primary null and alternative hypotheses may be expressed as:

$$H_0: \mu_{LCIG} = \mu_{OMT}$$

$$H_A: \mu_{LCIG} \neq \mu_{OMT}$$

Where μ_{LCIG} is the mean change from baseline to Week 12 for LCIG group in the UDysRS total score and μ_{OMT} is the mean change from baseline to Week 12 for OMT group in the UDysRS total score. The statistical tests at other visits will be considered secondary.

The change in the UDysRS total score to each planned visit and to the final visit will also be summarized by the following descriptive statistics: number of non-missing observations, mean baseline score and standard deviation, mean visit score and standard deviation, median visit score and range, mean change from baseline and its standard

deviation and standard error, median change from baseline and range. The hypothesis of change from baseline will be evaluated at each visit with a one-sample t-test.

9.3 Additional Efficacy Analyses

Secondary Analysis of the Primary Efficacy Variables

Analysis of covariance (ANCOVA) analyses will be carried out on change from baseline to final UDysRS total score. The ANCOVA model will contain treatment and country as the main effects and baseline score as the covariate. Sensitivity analyses will be carried out on the above variables with the same ANCOVA model using all randomized subjects. In this analysis, Baseline Observation Carried Forward (BOCF) will be applied to subjects who do not have post-randomization assessment of UDysRS.

Analysis of Secondary Efficacy Variables

The MMRM model and the descriptive statistic summary described for the UDysRS total score will also be used to evaluate the change from baseline to Week 12 in each of the following efficacy endpoints (with the exception of the CGI-C, which the score itself shows the changes):

- "ON" time without troublesome dyskinesia as measured by the PD Diary
- Parkinson's Disease Questionaire-8 (PDQ-8) summary index
- Clinical Global Impression of Change (CGI-C) Score
- UPDRS Part II Score
- "OFF" time as measured by the PD Diary
- UPDRS Part III Score

PD Diary variables will be normalized to a 16 hour awake time and the time recorded by the subject on the 3 diaries completed prior to each visit will be averaged.

For CGI-C, an ANCOVA model containing treatment and country as the main effects and baseline CGI-S as covariate will be carried out.

"ON" time without troublesome dyskinesia as measured by the PD Diary, PDQ-8 summary index, CGI-C score, UPDRS Part II and Part III score, and "OFF" time as measured by the PD Diary are key secondary endpoints. If the primary efficacy variable is statistically significant, each of the secondary variables will be tested using the fixed sequence above as a gatekeeping procedure and at α level of 0.050. Testing will cease at the point that a secondary variable fails to demonstrate statistical significance.

All secondary efficacy variables will be summarized by the number of subjects with non-missing data, mean, standard deviation, median, minimum and maximum.

Analysis of Additional Efficacy and Health Variables

Efficacy will also be assessed using the following additional measures:

- UDysRS Historical Score, Objective Score and Parts 1 through 4 Scores
- "ON" time with troublesome dyskinesia and "ON" time without dyskinesia as measured by the PD Diary
- mAIMS

Health outcomes will also be assessed using the following additional measures:

- King's PD Pain Scale
- Percentage (%) of CGI-C responders (response of "minimally improved," "much improved" or "very much improved")

Continuous endpoints will be analyzed with the same MMRM model as the primary analysis. Categorical endpoints will be analyzed with a Fisher's exact test.

9.4 Calculation of Efficacy and Health Outcome Variable

The primary and secondary efficacy variables derived from the above measures are presented in Table 1.

Table 1. Primary and Secondary Efficacy Variables, and Derivations

Instrument	Efficacy Variable	Derivation	Range/Direction
UDysRS: 26 questions, Part 1 (Questions 1 – 11), Part 2 (Questions 12 – 15), Part 3 (Questions 16 – 22), and Part 4 (Questions 23 – 26). All questions are 5-point (0 – 4). There is no imputation of missing responses. If one or more item scores are missing, the total score and respective domain score will not be calculated.	Part 1 score	Sum of Questions 1 – 11	0 – 44/lower value desirable
	Part 2 score	Sum of Questions 12 – 15	0 – 16/lower value desirable
	Part 3 score	Sum of Questions 16 – 22	0 – 28/lower value desirable
	Part 4 score	Sum of Questions 23 – 26	0 – 16/lower value desirable
	Historical score	Sum of Part 1 score and Part 2 score	0 – 60/lower value desirable
	Objective score	Sum of Part 3 score and Part 4 score	0 – 44/lower value desirable
	Total score	Sum of Part 1, Part 2, Part 3, and Part 4 scores	0 – 104/lower value desirable
PD Diary: 48 entries each diary day starting at 6:00 am and goes thru 6:00 am on the following chronological day, each represents 0.5 hour. Subjects were instructed to record whether "Asleep," "Off," "On without dyskinesia," "On with non-troublesome dyskinesia" or "On with troublesome dyskinesia" for each 0.5 hour. Daily awake time (hr) = time spent in "Off," "On without dyskinesia," "On with non-troublesome dyskinesia" or "On with troublesome dyskinesia." The "Off" and various "On" times are normalized to 16-hour awake period based a typical person's day. Only diaries with at least 12 hours of daily awake time will be considered valid and used in the analysis.	Normalized "ON" time without troublesome dyskinesia	(Absolute "On" time without dyskinesia + Absolute "On" time with non-troublesome dyskinesia)/Daily awake time * 16	0 – 16 hours/higher value desirable
	Normalized "OFF" time	Absolute "Off" time/Daily awake time * 16	0 – 16 hours/lower value desirable
	Normalized "ON" time with troublesome dyskinesia	Absolute "On" time with troublesome dyskinesia/Daily awake time * 16	0 – 16 hours/lower value desirable
	Normalized "ON" time without dyskinesia	Absolute "On" time without dyskinesia/Daily awake time * 16	0 – 16 hours/higher value desirable

Table 1. Primary and Secondary Efficacy Variables, and Derivations (Continued)

Instrument	Efficacy Variable	Derivation	Range/Direction
PDQ-8: 8 question including the mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, bodily discomfort. 5-point scale: 0 = Never, 1 = Occasionally, 2 = Sometimes, 3 = Often, 4 = Always (or cannot do at all, if applicable).	PDQ-8 Summary Index (PDQ-SI)	Sum of each question divided by 32 and multiplied by 100. The PDQ-8 total score will be calculated as long as at least 7 questions have been answered. Missing values in a question will be replaced by the patient population's mean of the question, and rounded to an integer.	0 – 100/lower value desirable
CGI-C: 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)	CGI-C score	7-point score as collected	1 – 7/lower score desirable
UPDRS: 42 questions, Part I (Questions 1 – 4), Part II (Questions 5 – 17), Part III (Questions 18 – 31), and Part IV (Questions 32 – 42). Questions 35 – 38 and 40 – 42 are 2-point (0 and 1), all other questions are 5-point (0 – 4).	Part II score	Sum of Questions 5 – 17. Part II score will be calculated as long as at least 12 questions have been answered. If 1 answer is missing the Part II score will be calculated by multiplying the sum of questions answered by the ratio of the total number of Part II questions to the number of questions answered.	0 – 52/lower value desirable
	Part III score	Sum of Questions 18 – 31 with Questions 20 – 26 apply to multiple body parts, resulting in 27 answers total. Part III score will be calculated as long as at least 23 answers have been recorded. If 4 or fewer answers are missing the Part III score will be calculated by multiplying the sum of the answers provided by the ratio of the total number of Part III answers possible (27) to the number of answers provided.	0 – 108/lower value desirable

Table 1. Primary and Secondary Efficacy Variables, and Derivations (Continued)

Instrument	Efficacy Variable	Derivation	Range/Direction
mAIMS: 6 questions, all questions are 5 points (0 – 4). There is no imputation of missing responses.	mAIMS score	Sum of Questions 1 – 6	0 – 24/lower value desirable
King's PD Pain Scale (KPPS): 14 items addressing the following 7 domains (musculoskeletal pain, chronic pain, fluctuation-related pain, nocturnal pain, oro-facial pain, discoloration, oedema/swelling, radicular pain). Each item is scored by severity (0 = None to 3 = Very severe) multiplied by frequency (0 = Never to 4 = All the time) resulting in a subscore of 0 to12.	King's PD Pain Scale score	Sum of severity x frequency for all 14 items. The KPPS score will be calculated as long as at least 13 questions have been answered. Missing values in a question will be replaced by the patient population's mean of the question, and rounded to an integer.	0 – 168/lower value desirable
	Musculoskeletal Pain	Severity × frequency for item 1	0 – 12/lower value desirable
	Chronic Pain	Sum of severity × frequency for item 2 and 3	0 – 24/lower value desirable
	Fluctuation-related Pain	Sum of severity × frequency for item 4 – 6	0 – 36/lower value desirable
	Nocturnal Pain	Sum of severity × frequency for item 7 and 8	0 – 24/lower value desirable
	Oro-facial Pain	Sum of severity× frequency for item 9 – 11	0 – 36/lower value desirable
	Discoloration, Oedema/Swelling	Sum of severity × frequency for item 12 and 13	0 – 24/lower value desirable
	Radicular Pain	Severity x frequency for item 14	0 – 12/lower value desirable

9.5 Handling of Multiplicity

If the primary efficacy variable is statistically significant, each of the key secondary variables will be tested using the fixed sequence in Section 9.3 as a gatekeeping procedure and at α level of 0.050. Testing will cease at the point that a secondary variable fails to demonstrate statistical significance.

9.6 Efficacy Subgroup Analysis

To determine if the following factors have an impact on the response to treatment, subgroup analyses will be conducted on the change from baseline to final visit on the UDysRS total score:

- Gender
- Age category (< 65, ≥ 65)
- Duration of Parkinson's disease (< 10 years, ≥ 10 years)
- Total daily dose of levodopa (< 1250 mg, ≥ 1250 mg) at the end of initial LCIG titration for the LCIG group and in the first set of dosing diary for the OMT group
- Number of anti-PD medications other than levodopa taken at any time during the week prior to randomization (0 or 1, 2 or more)

The subgroup analyses will be performed using an ANCOVA model contain treatment, country, and subgroup as main effects, treatment by subgroup interaction, and baseline score as the covariate. The LS mean change for each stratum of the subgroup with associated 95% confidence interval will be presented.

The descriptive statistic summary described for the UDysRS total scores will also be prepared for each subgroup stratum.

10.0 Safety Analysis

10.1 General Considerations

Unless noted otherwise, all safety analyses will be performed on the Safety Dataset. Treatment group differences in safety parameters are evaluated using two-sided test at the significance of 0.050.

Unless otherwise specified, treatment group differences in continuous safety variables (e.g., changes from baseline to final observation on laboratory test variables) will be assessed using an ANOVA model with the term of treatment, and the treatment group differences in binary safety variables will be evaluated using a Fisher's exact test.

10.2 Analysis of Adverse Events

All adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be summarized by primary MedDRA system organ class (SOC) and preferred term (PT). Subjects reporting more than one adverse event for a given PT will be counted only once for that term. Subjects reporting more than one adverse event within an SOC will be counted only once for the SOC total. Subjects reporting more than one adverse event will be counted only once in the overall adverse event 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.

A treatment-emergent adverse event (TEAE) is defined as any adverse event with onset during the treatment period or within 30 days of the end of the treatment period:

- For the OMT group this includes all adverse events with onset after the day of randomization and within 30 days following the last visit.
- For LCIG treatment subjects who have all study tubes removed after their last study drug infusion, this includes all adverse events with onset on or after the date of the initial tube placement procedure and no more than 30 days

following the last study tube removal, or no more than 30 days following the last LCIG infusion if there is no final device removal in the study.

10.2.1 Adverse Event Overview

The number and percentage of subjects experiencing one or more adverse events in the following adverse event categories during the 12-week Treatment Period will be summarized.

- Any TEAE
- Any TEAE that was rated by the investigator as having a reasonable possibility of relationship to levodopa-carbidopa intestinal gel
- Any severe TEAE
- Any serious TEAE
- Any TEAE that led to discontinuation of study drug
- Any treatment emergent GI event (as defined in Section 10.2.3)
- Any TEAE other than a GI event (as defined in Section 10.2.3)
- A fatal TEAE
- All deaths

The number and percentage of subjects experiencing one or more adverse events in the following adverse event categories during the Transition Period will be summarized.

- Any TEAE
- Any TEAE that was rated by the investigator as having a reasonable possibility of relationship to levodopa-carbidopa intestinal gel
- Any severe TEAE
- Any serious TEAE
- Any TEAE that led to discontinuation of study drug
- Any treatment emergent GI event (as defined in Section 10.2.3)
- Any TEAE other than a GI event (as defined in Section 10.2.3)

- A fatal TEAE
- All deaths

Serious adverse events with onset during the Screening Period for all subjects screened, adverse events and serious adverse events with onset after day of randomization and before day of initial device placement for the LCIG group, as well as adverse events during the transition period for LCIG subjects continuing LCIG commercial treatment will also be summarized.

10.2.2 Adverse Event Incidence

The number and percentage of subjects experiencing one or more adverse events in the following adverse event categories during the 12-week Treatment Period will be summarized for each treatment group and for overall subjects by primary SOC and PT for overall treatment interval.

- Any TEAE
- Any serious TEAE
- Any TEAE that led to discontinuation of study drug

The percentage of subjects in the LCIG group and in the OMT group will be compared using Fisher's exact test. Only P values ≤ 0.100 when rounded to three digits will be presented.

The number and percentage of subjects experiencing one or more adverse events in the following adverse event categories during the Transition Period will be summarized for LCIG subjects who enter the Transition Period by primary SOC and PT.

- Any TEAE
- Any serious TEAE
- Any TEAE that led to discontinuation of study drug

The number and percentage of subjects experiencing one or more TEAEs during the 12-week Treatment Period will also be summarized for each treatment group and for overall subjects by maximum severity category (mild, moderate, severe, or unknown) and primary SOC and PT for overall treatment interval. Subjects reporting more than one TEAE for a given PT will be counted only once for that term in the most severe category reported. If a subject has an adverse event 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 adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Severe" category.

The number and percentage of subjects experiencing one or more TEAEs during the 12-week Treatment Period will also be summarized for each treatment group and for overall subjects by maximum relationship category (reasonable possibility, no reasonable possibility, or unknown), as assessed by the investigator, and primary SOC and PT for overall treatment interval. Subjects reporting more than one TEAE for a given PT will be counted only once for that term in the most related category reported. If a subject has an adverse event 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 adverse event with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.

The number and percentage of subjects experiencing one or more adverse events in the following adverse event categories during the 12-week Treatment Period will be summarized by PT for overall treatment period interval and overall. The PTs will be presented by decreasing frequency overall.

- Any TEAE
- Any TEAE that was moderate or severe

A list of subject numbers associated with each PT will also be presented for all TEAEs.

10.2.3 Adverse Events of Special Interest

Adverse events of special interest (AESIs) will be composite events made up of TEAEs meeting the following MedDRA search strategies.

- GI events will include the MedDRA preferred terms (PTs) in the GI and GI procedure related events Company MedDRA Query (CMQ 80000145). This summary will be done for the LCIG group only.
- POLY events will include the PTs in either the Peripheral Neuropathy Standard MedDRA Query (SMQ 20000034) broad search or Guillain-Barre Syndrome SMQ (SMQ 20000131) broad search.
- WEIGHT events will include the PTs in the Weight loss CMQ (CMQ 80000109).

For each AESI, the number and percentage of subjects experiencing one or more adverse events during the 12-week Treatment Period will be summarized for each treatment group and for overall subjects by primary SOC and PT for overall treatment period interval. Similar summaries will be prepared for all TEAEs that are not GI events as well as for all TEAEs that are in either the Peripheral Neuropathy Standard MedDRA Query (SMQ 20000034) narrow search or Guillain-Barre Syndrome SMQ (SMQ 20000131) narrow search.

10.2.4 Adverse Events by Subgroup

The number and percentage of subjects in each of the following subgroups experiencing one or more TEAEs during the 12-week Treatment Period will be summarized for each treatment group and for overall subjects by primary SOC and PT.

- Gender (male, female)
- Age category (< 65 years, ≥ 65 years)
- Baseline BMI category (< 25 kg/m^2, ≥ 25 kg/m^2)
- Duration of Parkinson's disease (< 10 years, ≥ 10 years)

10.2.5 Listings of Adverse Events

The following additional summaries of adverse events 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 drug
- Listing of all GI AESIs (as defined in Section 10.2.3)
- Listing of all POLY AESIs (as defined in Section 10.2.3)
- Listing of all WEIGHT AESIs (as defined in Section 10.2.3)

10.3 Analysis of Laboratory Tests

Hematology variables include: partial thromboplastin time (PTT), hematocrit, hemoglobin, international normalized ratio (INR), mean corpuscular hemoglobin (MCHC), mean corpuscular volume (MCV), platelet count, prothrombin time (PT), red blood cell (RBC) count, white blood cell (WBC) count and WBC differentials.

Chemistry variables include: albumin, alkaline phosphatase, bicarbonate, total bilirubin, blood urea nitrogen (BUN), calcium, chloride, cholesterol, creatine phosphokinase (CPK), creatinine, gamma-glutamyl transpeptidase (GGT), glucose, lactate dehydrogenase (LDH), inorganic phosphorus, potassium, serum glutamic-oxaloacetic transaminase (SGOT/AST), serum glutamic pyruvic transaminase (SGPT/ALT), total protein, sodium, TSH, free T4, triglycerides and uric acid.

Urinalysis variables include: blood, glucose, ketones, pH, protein, specific gravity, and the results of microscopic analysis.

Special laboratory variables include: Vitamin B_{12}, Vitamin B_6, methylmalonic acid (MMA), folic acid and homocysteine levels.

10.3.1 Analysis of Mean Changes for Laboratory Tests

Analyses of mean change from baseline to each planned visit and to the minimum, maximum and final value during the 12-week Treatment Period will be presented by treatment group for each continuous hematology, chemistry, urinalysis, and special laboratory variable.

For each change from baseline analysis, the following summary statistics for each treatment group will be presented: sample size, baseline mean, visit mean, and the mean, standard deviation, and median of the change from baseline. The baseline and visit means will be calculated for each visit for subjects who have both a baseline and visit value. The mean changes for the LCIG group and for the OMT group will be compared using an ANOVA with treatment as the factor. LS mean, standard error, 95% confidence interval and *P* value will be presented.

Analyses of mean change from baseline to each planned visit and to the minimum, maximum and final value during the Transition Period will be presented for each continuous special laboratory variable for LCIG subjects who enter the Transition Period.

10.3.2 Shifts Between Normal and Abnormal for Laboratory Tests

Laboratory observations will be categorized as normal, low, or high relative to the reference (normal) range associated with the laboratory that performed the assay. For each hematology, chemistry, urinalysis and special laboratory variable with a reference range, shift tables will be prepared for shifts from baseline to lowest, highest and final value during the 12-week Treatment Period for each treatment group and overall subjects.

The tables will present:

- The numbers and percentages of subjects with low or normal observations at baseline who have a high observation at any post-baseline visit
- The numbers and percentages of subjects with normal or high observations at baseline who have a low observations at any post-baseline visit

- The numbers and percentages of subjects with low or normal observations at baseline who have a high observation at the final visit
- The numbers and percentages of subjects with normal or high observations at baseline who have a low observations at the final visit

10.3.3 Potentially Clinically Significant (PCS) Laboratory Values

Criteria for potentially clinically significant (PCS) values have been predefined for selected laboratory variables as outlined in Appendix C. For each variable, a summary of the number and percentage of subjects in each treatment group who have at least one post-baseline observation during the 12-week Treatment Period that meets the PCS criteria and is more extreme than their baseline value will be provided.

A summary of the number and percentage of subjects who have at least one observation during the Transition Period that meets the PCS criteria and is more extreme than their baseline value will be provided for LCIG subjects who enter the Transition Period.

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. No comparisons of treatment groups will be performed.

10.4 Analysis of Vital Signs and Weight

Vital sign variables include: body temperature, pulse (sitting, standing and orthostatic), diastolic blood pressure (sitting, standing and orthostatic), and systolic blood pressure (sitting, standing and orthostatic).

Weight variables include: weight and BMI.

Orthostatic variables will be calculated as the change from sitting to standing (standing measurement minus sitting measurement).

BMI will be calculated using height as measured during screening.

10.4.1 Vital Sign and Weight Mean Changes

Analyses of mean change from baseline to each planned visit and to the minimum, maximum and final value during the 12-week Treatment Period will be presented by treatment group for each vital sign and weight variable.

For each change from baseline analysis, the following summary statistics for each treatment group will be presented: sample size, baseline mean, visit (time point) mean, and the mean, standard deviation, and median of the change from baseline. The baseline and visit (time point) means will be calculated for each visit (time point) for subjects who have both a baseline and visit (time point) value. The mean changes for the LCIG group and for the OMT group will be compared using an ANOVA with treatment as the factor. LS mean, standard error, 95% confidence interval and *P* value will be presented.

Analyses of mean change from baseline to each planned visit and to the minimum, maximum and final value during the Transition Period will be presented for each vital sign and weight variable for LCIG subjects who enter the Transition Period.

10.4.2 Shifts in BMI Category

BMI values will be categorized as low (< 18.5 kg/m^2), normal (18.5 kg/m^2 to < 25 kg/m^2), overweight (25 kg/m^2 to < 30 kg/m^2) or obese (≥ 30 kg/m^2). Shift tables will be prepared summarizing BMI category shifts from baseline to lowest, highest and final value during the 12-week Treatment Period for each treatment group. No comparisons of treatment groups will be performed.

10.4.3 Potentially Clinically Significant (PCS) Vital Sign and Weight Values

Criteria for PCS values have been predefined for selected vital sign and weight variables as outlined in Appendix B. For each variable, a summary of the number and percentage of subjects in each treatment group who have at least one post-baseline observation during the 12-week Treatment Period that meets the PCS criteria and is more extreme than their baseline value will be provided.

A summary of the number and percentage of subjects who have at least one observation during the Transition Period that meets the PCS criteria and is more extreme than their baseline value will be provided for LCIG subjects who enter the Transition Period.

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. No comparisons of treatment groups will be performed.

10.5 Analysis of Electrocardiogram (ECG) Variables

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

QTcB and QTcF will be calculated for each uncorrected QT interval based on the following formulas:

- Bazett's correction (QTcB): $QT_CB = QT/\sqrt{(60/HR)}$
- Fridericia's correction (QTcF): $QT_CF = QT/\sqrt[3]{(60/HR)}$

10.5.1 ECG Mean Changes

Analyses of mean change from baseline to each planned visit and to the minimum, maximum and final value during the 12-week Treatment Period will be presented by treatment group for each ECG variable.

For each change from baseline analysis, the following summary statistics for each treatment group will be presented: sample size, baseline mean, visit mean, and the mean, standard deviation, and median of the change from baseline. The baseline and visit means will be calculated for each visit for subjects who have both a baseline and visit value. The mean changes for the LCIG group and for the OMT group will be compared using an ANOVA with treatment as the factor. LS mean, standard error, 95% confidence interval and *P* value will be presented.

10.5.2 Potentially Clinically Significant (PCS) ECG Values

Criteria for PCS values have been predefined for selected ECG variables as outlined in Appendix D. For each variable, a summary of the number and percentage of subjects in each treatment group who have at least one post-baseline observation during the 12-week Treatment Period that meets the PCS criteria and is more extreme than their baseline value will be provided. 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. No comparisons of treatment groups will be performed.

10.6 Analysis of Sleep Attack Questions

At Screening Visit 1, the sleep attack questions will collect history during the previous 3 months. At all other visits, the sleep attack questions will collect experience since the last visit. Affirmative responses to the sleep attack questions will be summarized by treatment for the study period on or before the date of randomization and for the study period on or after Day 1.

Each summary will include the number and percentage of subjects in each treatment group reporting a) 1 or more sleep attacks at any visit, b) 1 or more sleep attacks at any visit without sleepiness or drowsiness prior to sleep attack, and c) 1 or more sleep attacks at any visit with bad outcome during the 12-week Treatment Period. The highest number of sleep attacks reported at any visit (1, 2, 3, more than 3) will also be summarized by the number and percentage of subjects in each treatment group with each count.

A listing will also be prepared that includes all subjects who reported 1 or more sleep attacks at any visit.

10.7 Analysis of Minnesota Impulsive Disorders Interview (MIDI)

The Minnesota Impulsive Disorders Interview (MIDI) will be administered to monitor for the development of intense impulsive behavior. It includes the following modules: buying disorder, kleptomania, trichotillomania, intermittent explosive disorder,

pyromania, pathological gambling and compulsive sexual behavior. A subject's MIDI screen is positive for a module if:

- Buying Disorder: Positive screen if the subject answers "yes" to 1a, 2a, 3a, and 4a
- Kleptomania: Positive screen if the subject answers "yes" to 1a, 2a, 3a, and 4a
- Trichotillomania: Positive screen if the subject answers "yes" to 1, 3, 4a, 5, and 6
- Intermittent Explosive Disorder: Positive screen if the subject answers "yes" to 1a, 1b, 1c, and 1d; in addition, the subject must answer "no" to 1f
- Pyromania: Positive screen if the subject answers "yes" to 1a, 2, 3, 4, and 5; in addition, the subject must answer "no" to 1b, 1c, 1d, and 1e
- Pathological Gambling: Positive screen if the subject answers "yes" to 1, and to at least 5 of the rest of the questions
- Compulsive Sexual Behavior: Positive screen if the subject answers "yes" to 1, 2a, 3a, or 4a

Positive screens on the MIDI will be summarized for the study period on or before the date of randomization and during the 12-week Treatment Period. Each summary will include the number and percentage of subjects in each treatment group with a positive screen for each MIDI module as well as for any of the MIDI modules.

A summary of the number and percentage of subjects with a positive screen for each MIDI module as well as for any of the MIDI modules during the Transition Period will also be provided for LCIG subjects who enter the Transition Period.

A listing will also be prepared that includes all subjects with 1 or more positive screens for any of the MIDI modules.

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

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a systematically administered instrument developed to track suicidal adverse events across a treatment study. At Screening Visit 1 the C-SSRS will be administered to collect lifetime history as well as experience during the past year. At all other visits, the C-SSRS will collect experience since the last visit. Affirmative responses on the C-SSRS will be summarized for the following study periods and reporting timeframes: Screening: Lifetime and Past year; before randomization: Since last visit; and on or after Day 1: Since last visit.

Each summary will include the number and percentage of subjects in 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 during the 12-week Treatment Period. No comparisons of treatment groups will be performed.

A summary of the number and percentage of subjects with one or more affirmative responses to the questions listed above during the Transition Period will also be provided for LCIG subjects who enter the Transition Period.

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

11.0 Special Statistical Topics

There are no special statistical issues to be described or addressed.

12.0 Summary of Changes

This SAP contains no change in analysis from the latest version of the protocol (Protocol Amendment 1).

13.0 Appendices

Appendix A. Study Activities

	OMT/LCIG			LCIG Treatment		OMT/LCIG Treatment				LCIG Treatment	
Activity	**V1 Screening**	**V2 Screening**	**V3 Randomization**	**V4 NJ/PEG-J Placement D1**	**Titration Visits**	**V5 Wk 2**	**V6 Wk 4**	**V7 Wk 8**	**V8 Wk 12/ET**	**V9 Wk 13 FU[a]**	**Transition to Commercial Visits[b]**
Visit Number for OMT/LCIG	V1	V2[c] (Optional)	V3	V4[d]		V5	V6	V7	V8	V9	Every 6 and 12 Weeks
Informed Consent[e]	X										
Medical/Neurological/PD History[f]	X		X[f]								
Concomitant Medication (including anti-PD and Dyskinesia medications)	X	X	X	X	X	X	X	X	X	X	X
Anti-PD Medication History	X										
Physical Examination[g]	X	X	X	X		X	X	X	X	X	
Neurological Exam	X	X	X			X	X	X	X	X	
Dermatological Exam[g]	X								X		
GI Exam[g]	X								X		
NJ or PEG-J decision	X										
Nasojejunal Tube Placement/Titration[h] (Optional)				X							
PEG-J Placement Procedure[h]				X							

Activity	OMT/LCIG			LCIG Treatment		OMT/LCIG Treatment				LCIG Treatment	
	V1 Screening	V2 Screening	V3 Randomization	V4 NJ/PEG-J Placement D1	Titration Visits	V5 Wk 2	V6 Wk 4	V7 Wk 8	V8 Wk 12/ET	V9 Wk 13 FU[a]	Transition to Commercial Visits[b]
Radiological Check of Tube Placement[i]				X							
PEG-J Site (Stoma) Check				X[j]	X					X	
Vital Signs/Weight	X		X	X	X	X	X	X	X	X	X
Height	X										
ECG	X							X	X		
Clinical Labs	X[k]		X[k]					X	X		
Urine Drug/Alcohol Screen	X										
Special Laboratory Tests[l]	X		X					X	X		X
Pregnancy Test[m]	X			X					X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Product Complaints				X	X	X	X	X	X	X	X
Dose Titration Diary[n]				X	X						
Subject Dosing Diary Completion[o]					X	X	X	X	X		
PD Diary training and concordance evaluation	X										
PD Diary[o]			X			X	X	X	X		

Activity	OMT/LCIG			LCIG Treatment		OMT/LCIG Treatment				LCIG Treatment	
	V1 Screening	V2 Screening	V3 Randomization	V4 NJ/PEG-J Placement D1	Titration Visits	V5 Wk 2	V6 Wk 4	V7 Wk 8	V8 Wk 12/ET	V9 Wk 13 FU[a]	Transition to Commercial Visits[b]
LCIG System and Pump Training (Subject and Caregiver)			X	X							
LCIG Titration[p]				X	X						
Study Drug Prescription Record (LCIG treatment group only)				X	X	X	X	X	X	X	
Removal of PEG-J[a]									X		
LCIG Cassettes Dispensed				X		X	X	X	X	X	X
LCIG Cassettes Returned						X	X	X	X	X	X
MMSE	X										
Sleep Attacks Questionnaire[q]	X	X	X			X	X	X	X	X	
C-SSRS[r]	X	X	X	X		X	X	X	X	X	X
MIDI	X	X	X			X	X	X	X	X	X
UDysRS[s]			X			X	X	X	X		
UPDRS II and III[t]	X		X			X	X	X	X		
mAIMS[u]			X			X	X	X	X		
PDQ-8			X					X	X		
CGI-C						X	X	X	X		

Activity	OMT/LCIG			LCIG Treatment		OMT/LCIG Treatment				LCIG Treatment	
	V1 Screening	V2 Screening	V3 Randomization	V4 NJ/PEG-J Placement D1	Titration Visits	V5 Wk 2	V6 Wk 4	V7 Wk 8	V8 Wk 12/ET	V9 Wk 13 FU[a]	Transition to Commercial Visits[b]
CGI-S			X								
King's PD Pain Scale			X				X	X	X		

V = Visit; D = Day; FU = Follow-Up; Wk = Week

a. Applicable only to LCIG subjects who prematurely discontinue LCIG treatment, or complete LCIG study treatment but will not transition to commercial LCIG.

b. Applicable only to LCIG subjects who complete LCIG study treatment and will transition to commercial LCIG. Subjects will return every 6 weeks to return used LCIG cassettes and be dispensed cassettes. Safety assessments will be completed every 12 weeks until subjects' transition to commercial LCIG.

c. Visit 2 is optional and is based on the Investigator's discretion of individual subject need during stabilization of anti-PD medications and medications to treat dyskinesia.

d. Visit 4 for LCIG Treatment (LCIG) group only.

e. Study-related assessments, procedures or activities cannot occur prior to subject completing signed informed consent process.

f. Update Medical/Neurological/PD History with any findings from Labs, Dermatologists, etc.

g. At Screening Visit 1 and Randomization Visit 3 a full physical examination will be performed. Symptom-driven physical examinations will be performed at subsequent visits. Prior to Visit 3, the Investigator and GI/surgeon or interventional radiologist, or their designated qualified personnel will thoroughly evaluate the subject's risk of undergoing PEG-J procedure. The dermatological exam will be performed prior to Visit 3 and Week 12/ET visit. If a suspicious lesion is present, a biopsy should be obtained for proper diagnosis and confirmation that lesion does not meet exclusion criteria before the subject is randomized.

h. For subjects randomized to LCIG treatment, a temporary NJ tube may be used to optimize the dose of LCIG before treatment with a PEG-J is started. The NJ test phase should not last longer than 7 days. Following the NJ test phase, a PEG-J will be performed by a gastroenterologist proceduralist, surgeon or interventional radiologist. Total time to titration via NJ and PEG-J should not exceed 14 days. Alternatively, subjects may proceed directly to placement of PEG-J if deemed appropriate by Investigator. The number of days to titrate will vary for each subject.

i. LCIG treatment group only. Radiological check of NJ and PEG-J to determine correct location should occur prior to LCIG infusion initiation and prior to restart of LCIG post PEG-J placement. Additional checks can be done at any time during treatment if indicated for worsening of Parkinsonian symptoms not responsive to extra doses.

j. PEG-J site, stoma check will be done within 24 hours of PEG-J placement and anytime from Day 2 to 7 post PEG-J.

k. PT/PTT will be performed only at Screening Visit 1.

l. Special labs to detect vitamin deficiencies, listed in Table 5 in the protocol, will be performed at the times indicated in the Appendix A, Study Activities. If at any time during the study a subject displays symptoms of polyneuropathy, the Investigator must perform this lab panel and any other assessment that the Investigator feels is appropriate for further evaluation of polyneuropathy symptoms. Thyroid function tests will be done at Screening Visit 1 only.

m. All females of childbearing potential must have a serum pregnancy test performed at Screening Visit 1 and Premature Discontinuation/End of Study. Additional testing may be required per local regulations. A negative urine pregnancy test result is required prior to the NJ and/or PEG-J placement procedure and any radiological procedures.

n. While the subject is in the hospital, the study staff may use the Dose Titration Diary as a tool to achieve dose optimization. In the event it is used it should be completed hourly until the dose is optimized and then once AM and once PM it will be completed until the subject is discharged. All adjustments can be recorded on the Dose Titration Diary allowing the Investigator to appropriately adjust, if needed, the following day's morning dose, continuous infusion rate and extra dose until the subject is optimized.

o. The Subject Dosing Diary and the Parkinson's Disease Diary will be completed by the subjects or their caregivers for the 3 consecutive days prior to each visit.

p. It is up to the discretion of the Investigator to determine how many titration days are necessary to obtain optimal clinical response.

q. The Sleep Attacks Questionnaire will be used to screen for sleep attacks. Results should be recorded in source but will not be entered in the clinical database.

r. The "Baseline/Screening" C-SSRS will be the first assessment scale administered to the subject. At each subsequent visit, the "Since Last Visit" C-SSRS scale should be administered.

s. The subject's expected time of peak dose dyskinesia should be determined during screening and the UDysRS should be administered at this time throughout the study.

t. During Visit 1 the UPDRS Part III will be done during practically defined "Off" time and best "On" time. The practically defined "Off" time UPDRS will be done in the morning prior to the subject taking their first daily dose of anti-PD medication. At a minimum a subject should be 8 hours without anti-PD medication before the UPDRS is completed. The best "On" time rating should be done approximately 1 to 2 hours post any morning dose of study drug or PD medications but prior to lunch. If possible, the UPDRS should be done at the same time of day throughout the trial. The "Off" time UPDRS Part III will only be done during Screening; all other UPDRS assessments will be done during "On" time.

u. The mAIMS should be completed following the UDysRS at the subject's expected time of peak dose dyskinesia.

Note: All applicable clinical, safety, health outcome and cognition assessments will be administered only by individuals qualified by the Sponsor.

Appendix B. Potentially Clinically Significant Laboratory Values

Clinical Laboratory Tests	Very Low (VL)	Very High (VH)
Hematology		
Activated partial thromboplastin time	NA	> ULN
Hemoglobin	< 100 g/L (6.2 mmol/L)	> 40 g/L above ULN
Prothrombin Intl. Normalized Ratio	NA	> ULN
Leukocytes	$< 2 \times 10^9$/L	$> 100 \times 10^9$/L
Lymphocyte	$< 0.5 \times 10^9$/L	$> 20 \times 10^9$/L
Neutrophil	$< 1 \times 10^9$/L	NA
Platelets	$< 75 \times 10^9$/L	NA
Chemistry		
Bilirubin	NA	> 1.5 × ULN
Cholesterol	NA	> 12.92 mmol/L (500 mg/dL)
Creatinine	NA	> 1.5 × ULN
Calcium (corrected serum)	< 1.75 mmol/L (7.0 mg/dL)	> 3.1 mmol/L (12.5 mg/dL)
Glucose (fasting)	< 2.2 mmol/L (40 mg/dL)	> 13.9 mmol/L (250 mg/dL)
Potassium	< 3.0 mmol/L	> 6.0 mmol/L
Triglycerides	NA	> 5.7 mmol/L (500 mg/dL)
Urate	NA	> 590 umol/L (10 mg/dL)
Albumin	< 20 g/L	NA
Sodium	< 130 mmol/L	> 155 mmol/L
Phosphate	< 0.6 mmol/L (2.0 mg/dL)	NA
Enzymes		
Alanine aminotransferase (ALT)	NA	> 3 × ULN
Alkaline phosphatase	NA	> 2.5 × ULN
Aspartate aminotransferase (AST)	NA	> 3 × ULN

NA = not applicable; ULN = upper limit of normal

Adapted from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix C. Criteria for Potentially Clinically Significant Vital Sign and Weight Values

Vital Signs	Unit	Very Low (VL)	Very High (VH)
Systolic blood pressure (supine and standing)	mmHg	≤ 90 and decreased > 30 from baseline	≥ 180 and increased > 40 from baseline
Orthostatic systolic blood pressure	mmHg	Decrease ≥ 30 from supine to standing	NA
Diastolic blood pressure (supine and standing)	mmHg	≤ 50 and decreased > 30 from baseline	≥ 105 and increased > 30 from baseline
Orthostatic diastolic blood pressure	mmHg	Decrease ≥ 20 from supine to standing	NA
Pulse rate	bpm	≤ 50 and decreased > 30 from baseline	≥ 120 and increased > 30 from baseline
Temperature (C)	degrees C	NA	≥ 38.3 and increase ≥ 1.1 from baseline
Weight (kg)	kg	Decreased ≥ 7% from baseline	Increased ≥ 7% from baseline

Appendix D. Criteria for Potentially Clinically Significant ECG Values

ECG Parameters	Unit	Very Low (VL)	Very High (VH)
Heart rate	bpm	≤ 50 and decreased > 30 from baseline	≥ 120 and increased > 30 from baseline
PQ/PR	ms	≤ 120	≥ 220
QTcB interval	ms	NA	≥ 480 Increased ≥ 60 from baseline
QTcF Interval	ms	NA	≥ 480 Increased ≥ 60 from baseline