1.0 Title Page

Statistical Analysis Plan

Study M12-927

An Open-Label, Randomized 26-Week Study Comparing Levodopa-Carbidopa INteStInal Gel (LCIG) THerapy to Optimized Medical Treatment (OMT) on Non-Motor Symptoms (NMS) in Subjects with Advanced Parkinson's Disease

INSIGHTS Study

Date: 11 Apr 2018

Version 2.0

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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 M12-927 with a protocol dated 25 January 2018 (original protocol: 23 January 2015, Amendment 1: 07 May 2015, Administrative Change 1: 27 October 2015, Amendment 2: 28 March 2016, Amendment 3: 15 November 2016, Administrative Change 2: 16 March 2017, Amendment 4: 31 May 2017, Administrative Change 3: 27 July 2017, Administrative Change 4: 02 August 2017, South Korean only Amendment 4.01: 13 September 2017, United States only Amendment 4.02: 13 September 2017, United States only Administrative Change 5: 11 October 2017, South Korea only Administrative Change 6: 25 January 2018, United States only Administrative Change 7: 25 January 2018). 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 study is to examine the effect of LCIG relative to that of optimized medical treatment (OMT) on non-motor symptoms associated with advanced Parkinson's disease (PD) as assessed by the Non-Motor Symptoms Scale (NMSS) Total Score and the Modified Parkinson's Disease Sleep Scale (PDSS-2) Total Score.

4.2 Design Diagram

This is a Phase 3b, open-label, randomized multicenter 26-week study comparing LCIG to OMT for the treatment of non-motor symptoms 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 can 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 NMS. All anti-PD medications and medications to treat NMS 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 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, 6, 12, and 26. All subjects randomized to the LCIG group should have all anti-PD medications, with the exception of levodopa formulations, tapered off within 14 days after randomization. Optional nasojujunal 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, 6, 12, and 26.

Part 3: Extension Period. Subjects in the United States or South Korea from both treatment arms who complete the 26 week study may continue into the Extension Period of the study. South Korea subjects in the LCIG arm will have study drug dispensation every 4 weeks and will have study visits every 6 months. South Korea subjects from the OMT arm will undergo the NJ (optional) and PEG-J procedures, titration, plus have visits at 2 weeks, 6 weeks, 3 months and 6 months post NJ or PEG-J. Subjects will then continue to receive study drug every 4 weeks and will have study visits every 6 months until Duodopa is commercially available.

United States subjects in LCIG arm will continue to have study drug dispensation every 4 weeks and will have study visits at 3 and 6 months, or the day prior to transition to commercial if that happens before the scheduled study visits. United States subjects from the OMT arm will undergo the NJ (optional) and PEG-J procedures, titration, plus have visits at 2 weeks, 6 weeks, 3 months and 6 months post NJ or PEG-J, or the day prior to transition to commercial if that happens before the scheduled study visits. Subjects will receive study drug every 4 weeks. The Extension Period will last for a maximum of 6 months to allow for continuity of care while the transition to commercially available drug occurs.

Part 4: Follow-up period. For subjects who elect to discontinue LCIG treatment at any time during the study, the PEG-J tube will be removed following the End of Study activities. A follow-up clinic visit will occur approximately 1 week later. For study subjects 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 26 will be scheduled to monitor subject safety and allow for drug resupply until the subject transfers to commercial LCIG.

Figure 1. Study Design Schematic (All Countries Except for United States and South Korea)

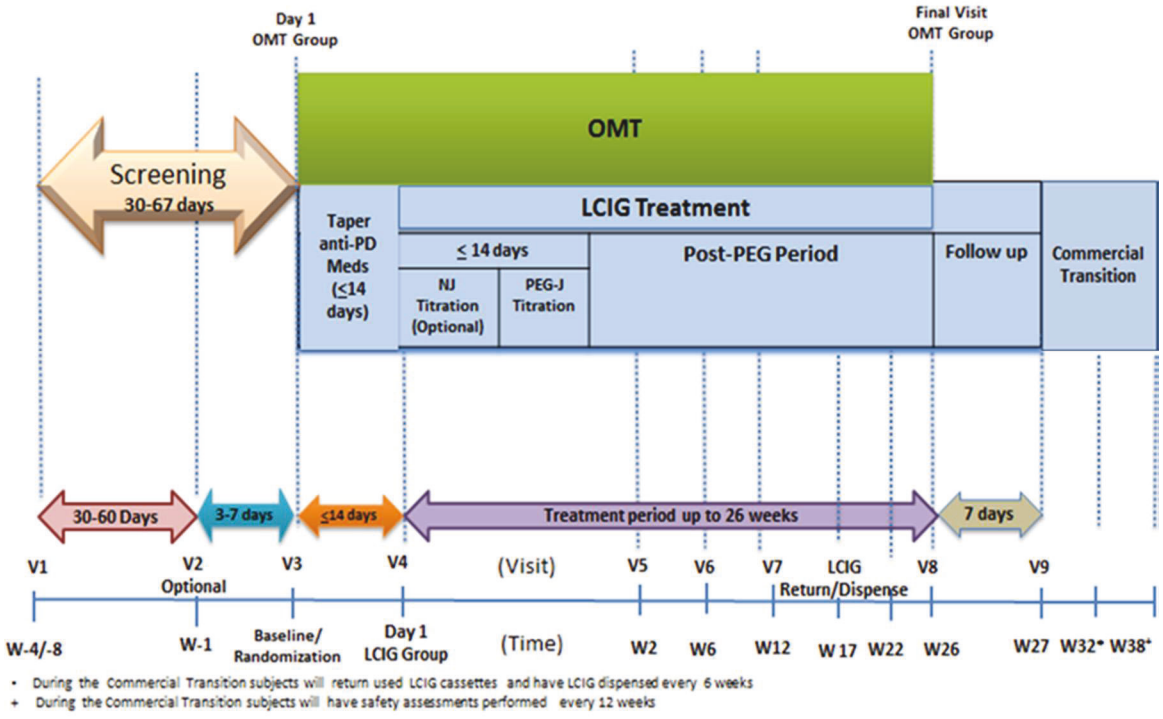
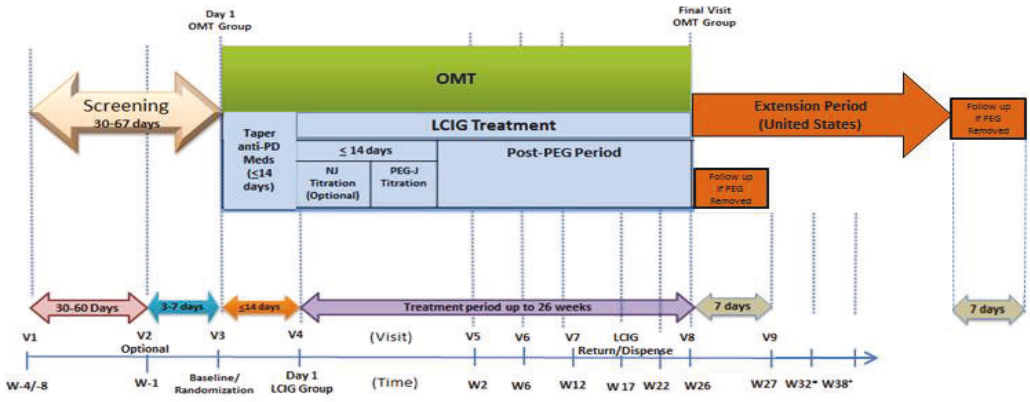
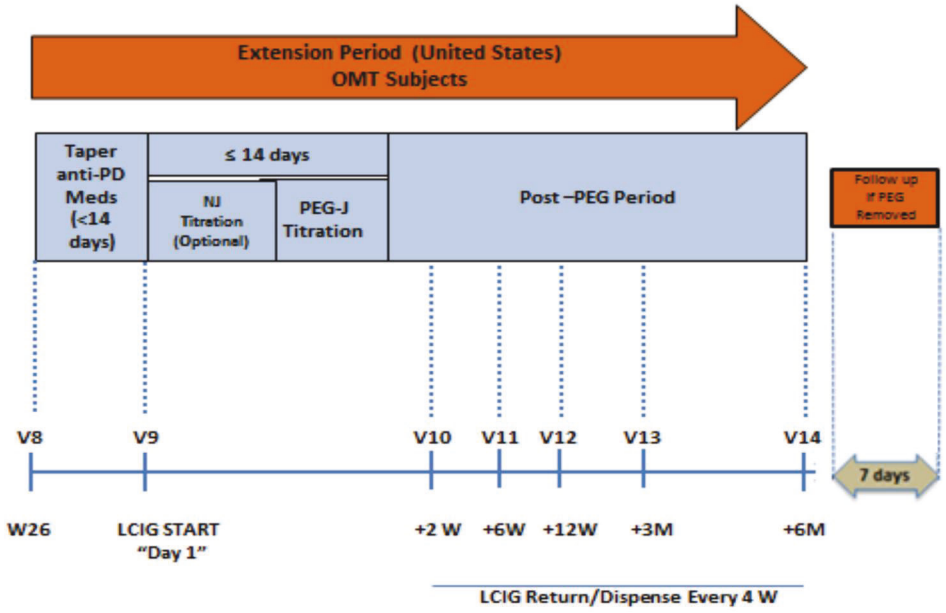


Figure 2. Study Design Schematic (United States)



Extension Period:

OMT Subjects



LCIG Subjects

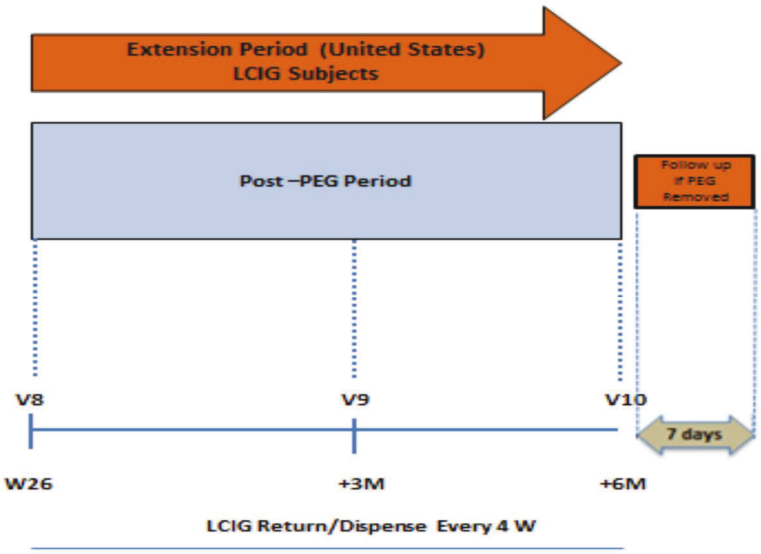
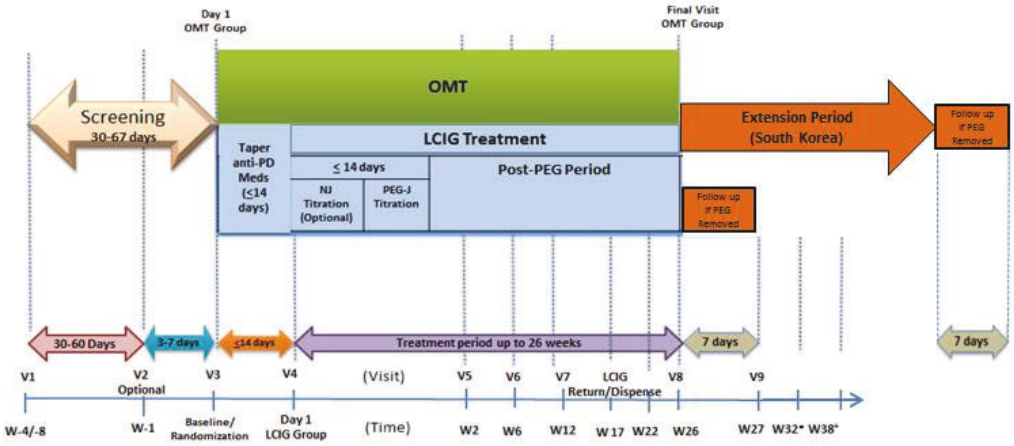
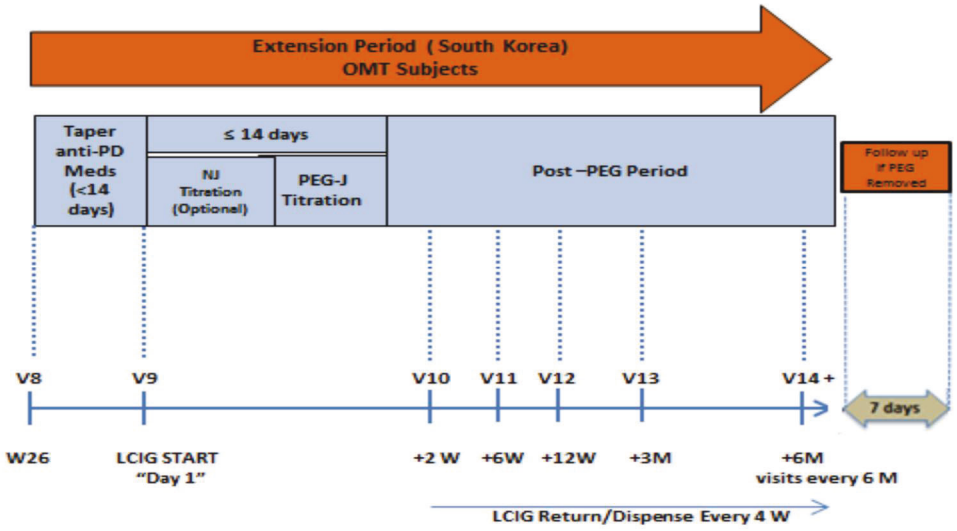


Figure 3. Study Design Schematic (South Korea)

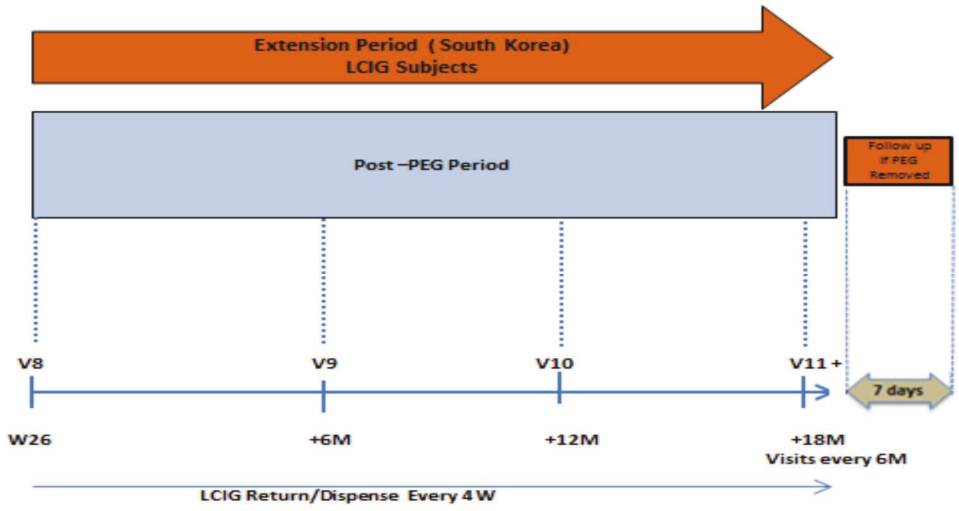


Extension Period:

OMT Subjects



LCIG Subjects



4.3 Sample Size

Approximately 88 subjects will be enrolled into the study and randomized in a 1:1 ratio to either optimized medical treatment or LCIG. There are no data on NMSS or PDSS-2 available from randomized trials comparing LCIG and OMT. Interim data from ongoing Phase 3b Study M12-920 showed that the improvement in NMSS total score from baseline to Week 12 is 24.8 in the LCIG group with standard deviation of 24. Results from Zibetti et al (2013) showed that the improvement in PDSS 2 total score after an average of 3.5 months of LCIG treatment was 13.1. The standard deviation was not provided and is estimated to be 12.2 assuming the correlation between baseline and follow-up visits is 0.5.

The significance level for this study is 0.05. For sample size determination, it is assumed that the improvement in the OMT group is 33% of the LCIG group, i.e., the improvement is 8.2 on NMSS total score and 4.3 on PDSS-2 total score, and that the correlation between these 2 measures is 0.5. Simulation showed that a study with 37 subjects per

group will have 90% power to declare statistical significance on at least one of these 2 alternative primary endpoints after multiplicity adjustment using Hochberg procedure. It is further assumed that 10% of randomized subjects in either treatment group will not provide post-randomization efficacy assessment. Additional simulations showed that 44 subjects per group will provide 90% power in the sensitivity analysis using baseline observation carried forward for subjects without post-randomization assessment. Therefore the total planned enrollment is decided to be 88 subjects.

4.4 Interim Analysis

After all randomized subjects have completed the 26-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 Non-Motor Symptoms

The burden of non-motor symptoms of Parkinson's disease will be evaluated using the Non-Motor Symptom Scale (NMSS) and Modified Parkinson's Disease Sleep Scale (PDSS-2).

4.5.2 Motor Symptoms

Motor symptoms will be assessed by Unified Parkinson's Disease Rating Scale (UPDRS) Parts III and IV.

4.5.3 Health-Related Outcomes

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

- Parkinson's Disease Questionnaire-8 (PDQ-8)
- Clinical Global Impression – Change (CGI-C)

- Unified Parkinson's Disease Rating Scale (UPDRS Parts I and II)
- Patient Global Impression of Change (PGIC)
- Parkinson Anxiety Scale (PAS)
- Geriatric Depression Scale (GDS-15)
- King's PD Pain Scale

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 (including special labs to detect vitamin deficiencies)
- 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. 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 study device (NJ and/or PEG-J) placement. The safety dataset will be used to summarize safety data during the OMT and LCIG treatment period.

All Randomized Dataset

The all randomized dataset will include all subjects who are randomized to the optimized medical treatment, and all subjects who are randomized to LCIG treatment. The all randomized dataset will be used to perform sensitivity analysis.

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. Adjustments for multiple comparisons for the two primary endpoints will be made using the Hochberg procedure. If the primary endpoints are statistically significant, a Hochberg procedure will be used to test the 3 key secondary efficacy variables.

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	OMT group: prior to and including the day of randomization. LCIG group: prior to the day of initial device (NJ or PEG-J) placement.
Device Before in Randomized Treatment Period (LCIG group only)	From the date of the first device (NJ or PEG-J) placement procedure up to, but not including, the date of the first LCIG infusion for subjects in the LCIG group during the 26-week randomized treatment period. This Epoch is missing for subjects whose infusion started the same day as initial device placement.
Open in Randomized Treatment Period	OMT group: from the day after randomization through the end of study (date of last visit) during the 26-week randomized treatment period. LCIG group: from the date of the first LCIG infusion through the date of the last LCIG infusion during the 26-week randomized treatment period.
Pre in Extension Period (OMT group entering Extension Period only)	From the day after the last visit during 26-week randomized treatment period up to, but not including date of the first device (NJ or PEG-J) placement.
Device Before in Extension Period (OMT group entering Extension Period only)	From the date of the first device (NJ or PEG-J) placement procedure up to, but not including, the date of the first LCIG infusion.
Open in Extension Period	For subjects in OMT group entering extension period: from the date of the first LCIG infusion through the date of the last LCIG infusion. For subjects in LCIG group entering extension period: from the date after the last LCIG infusion during the 26-week randomized treatment period through the date of the last LCIG infusion during the extension period.
Device After	From the first day after the last LCIG infusion through the date of the final device removal (Note: Subjects who have their last infusion on the same date as their final device removal will progress directly from the Open in Randomized Treatment Period/Open in Extension Period to the Off epoch).
Off	Time period after final device removal for subjects who are discontinuing LCIG treatment. Time period after end of study (date of last visit) for all other subjects.

For subjects randomized to 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 (REFDT1) 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 in the 26-week randomized period will be considered as end of the LCIG 26-week randomized treatment period and the following day will be the post-treatment start reference date (REFEDT1). For LCIG subjects who enter the Extension Period, treatment start reference date in extension period (REFDT2) equals REFEDT1. The date of the last LCIG tube removal or the date the last LCIG infusion if there is no device removal, will be the post-treatment reference date (REFEDT2) of Extension Period.

For subjects in the OMT group, the date after randomization will be considered the treatment start reference date (REFDT1). The date of the final visit during 26-week randomized period will be considered the end of the OMT treatment period and the following day will be the post-treatment start reference date (REFEDT1). For OMT subjects who enter the Extension Period, the date of earliest LCIG tube placement (NJ or PEG-J) recorded on the Device Information eCRF will be considered the treatment start reference date (REFDT2) in Extension period. The date of the last LCIG tube removal, or the date the last LCIG infusion if there is no device removal, will be considered the end of the Extension Period and the following day will be the post-treatment start reference date (REFEDT2).

Study Days during 26-week randomized treatment period will be calculated based on the treatment start reference date (REFDT1). For time points before REFDT1, the Study Day = time point – REFDT1. For time points on or after REFDT1, the Study Day = time point – REFDT1 + 1. Thus, the Study Day is a negative value when the time point of interest is prior to REFDT1 and the Study Day is a positive value when the time point of interest is on or after REFDT1. There is no Study Day 0. The Study Day will be labeled as Rx Day on the data listings. Study Days during Extension Period will be calculated based on the Extension Period start reference date (REFDT2) with the same rule as in 26-week randomized treatment period. For OMT subjects who enter the Extension Period, the study day of Pre in Extension Period will be calculated based on REFDT2.

6.3 Definition of Baseline and Final Observation

Baseline for efficacy, health outcome and safety measures during the 26-week randomized treatment period will be defined as the last non-missing observation that is on or before the day of randomization.

Baseline for safety assessment during the Extension Period is defined as the last non-missing observation that is on or before the day of NJ/PEG-J placement for OMT subjects who enter the Extension Period. For LCIG subjects who enter the Extension Period, baseline of 26-week randomized treatment period will be used as the baseline of Extension Period.

The final visit for efficacy and health outcome measure will be defined as the last non-missing observation that is after the day of randomization for the OMT group during the 26-week randomized treatment period. The final visit for efficacy and health outcome measures 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 26-week randomized treatment period.

The final observation for safety assessment during the 26-week randomized Treatment Period is defined as:

- For subjects in the OMT group and LCIG subjects who enter the Extension/Transition Period: the last non-missing observation that is after the day of randomization (for the OMT group) or after the initial device placement (for the LCIG group) and during the 26-week randomized treatment period.
- For LCIG subjects who do not enter the Extension/Transition Period: 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 during the 26-week randomized treatment period.

The final observation for safety assessment during the Extension/Transition Period is defined as last non-missing observation for OMT/LCIG subjects who enter the Extension/Transition period.

Safety assessments on the date of the initial device placement procedure that do not have a time of assessment or sample collection recorded will be assumed to be post-procedure.

6.4 Analysis by Planned Visit

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 26-week randomized treatment period.

Table 1. Analysis Windows for Efficacy Variables

Assessment	Planned Visit	Nominal Study Day	Study Day Range[a]
NMSS, PDSS-2, PDQ-8, PAS, GDS-15, UPDRS and King's PD Pain Scale	Baseline		≤ date of randomization
	Week 6	42	2 – 63
	Week 12	84	64 – 133
	Week 26	182	134 – 222
CGI-C and PGIC	Week 26	182	≥ 2

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 26-week Treatment Period.

The following Study Day windows will be used to assign safety assessments to planned study visits.

Table 2. Analysis Windows for Safety Variables During the 26-Week Treatment Period

Assessment	Planned Visit	Nominal Study Day	Study Day Range[a]
Vital signs and weight	Baseline		≤ date of randomization
	Week 2	14	2 – 28
	Week 6	42	29 – 63
	Week 12	84	64 – 133
	Week 26	182	134 – 186
	Week 27 FU[b]	189	187 – 301
Clinical labs and Electrocardiograms	Baseline		≤ date of randomization
	Week 12	84	2 – 133
	Week 26	182	> 133
Special labs	Baseline		≤ date of randomization
	Week 12	84	2 – 133
	Week 26	182	134 – 231

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 have their study device removed after their last infusion of Study M12-927 LCIG.

b. Applicable only to LCIG subjects who will not transition to commercial LCIG and have study device removed.

The following Study Day windows for Extension Period will be used to assign safety assessments to planned study visits for LCIG subject entering Extension Period.

Table 3. Analysis Windows for Safety Variables During the Extension/Transition Period for the LCIG Group

Assessment	Planned Visit	Nominal Study Day	Study Day Range[a]
Vital signs and weight, Clinical labs[a], Electrocardiograms[a], and special labs	Baseline[b]		≤ date of last visit in 26-week randomized treatment period for subjects randomized to LCIG group.
	Month 3[c]	84	1 – 126
	Month 6	168	127 – 200
	Every 3 months following until subjects' transition to commercial LCIG	Previous + 84	Previous lower bound + 84 through previous upper bound + 84

a. Clinical labs and Electrocardiograms will not be collected during the Transition Period.

b. Baseline refers the baseline of Extension Period. All days refer to study day in Extension Period. All post-baseline assessments must also be no more than 1 day after the final PEG-J removal for subjects who have their study device removed after their last infusion of Study M12-927 LCIG.

c. Applicable only to US subjects.

The following Study Day windows for Extension Period will be used to assign safety assessments to planned study visits for OMT subject entering Extension Period.

Table 4. Analysis Windows for Safety Variables During the Extension/Transition Period for the OMT Group

Assessment	Planned Visit	Nominal Study Day	Study Day Range[a]
Vital signs and weight,	Baseline[a]		< date of NJ/PEG-J placement for subjects randomized to OMT group and entering Extension Period
	Week 2	14	2 – 28
	Week 6	42	29 – 63
	Month 3	84	64 – 126
	Month 6	168	127 – 200
	Every 3 months following until subjects' transition to commercial LCIG[c]	Previous + 64	Previous lower bound + 84 through previous upper bound + 84
Clinical labs[b], Electrocardiograms[b], and special labs	Baseline[a]		< date of NJ/PEG-J placement for subjects randomized to OMT group and entering Extension Period
	Month 3	84	2 – 126
	Month 6	168	127– 252
	Every 3 months following until subjects' transition to commercial	Previous + 168	Previous lower bound + 168 through previous upper bound + 168

a. Baseline refers the baseline of Extension Period. All days refer to study day in Extension Period. All post-baseline assessments must also be no more than 1 day after the final PEG-J removal for subjects who have their study device removed after their last infusion of Study M12-927 LCIG.

b. Clinical labs and Electrocardiograms will not be collected during the Transition Period.

6.5 Analysis of Vital Signs by Planned Time

Vital sign measurements were to be performed at hourly intervals on the first day of LCIG infusion via NJ and via PEG-J. Observations on the first day of LCIG infusion will be assigned to a planned time based on the time of assessment relative to the reported start time of the first LCIG infusion as follows.

Table 5. Analysis Windows for Vital Signs on the Day of LCIG Infusion for the LCIG Group

Planned Time	Nominal Relative Time (Minutes)	Relative Time Range (Minutes)
Hour 0	0	≤ 0
Hour 1	60	> 0 – 90
Hour 2	120	91 – 150
Hour 3	180	> 150

6.6 Adverse Event Analysis by Study Week

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

Table 6. Analysis Windows for Treatment Emergent Adverse Events During the 26-Week Treatment Period

Study Week(s)	Study Day Range
Week 1	1 – 7
Week 2	8 – 14
Week 3	15 – 21
Week 4	22 – 28
Week 5	29 – 35
Weeks 6 – 26	36 – 182

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 during the 26-week randomized Treatment Period 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 NMSS, PDSS-2, UPDRS, PDQ-8, CGI-C, PGIC, PAS, GDS-15 and King's PD Pain Scale total and domain scores.

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 26 weeks of treatment in OMT group, continued to Extension Period, prematurely discontinued during the Extension Period, completed the Extension Period; Randomized to LCIG group, no NJ/PEG-J placed, NJ placed, prematurely discontinued during NJ, PEG-J placed, prematurely discontinued treatment during PEG-J, completed the planned 26 weeks of treatment in LCIG group, continued to Extension Period, prematurely discontinued during the Extension Period, completed the Extension Period.

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 26-week Treatment Period for both treatment groups, and during the Extension/Transition Period, 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 26-week randomized treatment period (start date before or on the last date of the 26-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 26-week randomized treatment period (start date before or on the last date of the 26-week randomized 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 26-Week Randomized Treatment Period

The duration of study drug exposure for LCIG subjects and the duration of study participation for OMT subjects during the 26-week randomized Treatment Period will be summarized with descriptive statistics (number of subjects with non-missing data, mean, standard deviation, median, minimum and maximum). In the 26-week randomized treatment period, the duration of LCIG study drug exposure will be calculated for each subject as the date of the last dose of LCIG study drug during the randomized treatment period minus the date of the first dose 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 during the 26-week randomized treatment period minus the date of randomization.

For subjects with a PEG-J tube removal after their last infusion of Study M12-927 study drug during the 26-Week Randomized Treatment 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 initial PEG-J placement + 1. For subjects without a PEG-J tube removal after their last infusion of study drug during the 26-Week Randomized Treatment Period, the duration of PEG-J exposure during the 26-Week Randomized Treatment Period for each subject will be calculated as the date of their final participation in Study M12-927 (last contact or visit date) during the 26-Week Randomized 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 will be summarized for LCIG infusion 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 to 84 days (9 – 12 weeks)
- ≥ 85 days (≥ 13 weeks)

In addition, duration of exposure 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 exposure 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 Extension Period

For LCIG subjects who continue LCIG exposure after the 26-week randomized treatment period, the continuing LCIG exposure will be calculated as the last day of LCIG study drug in Extension Period minus the date of the last dose of LCIG study drug during the 26-week randomized treatment period. The first and last treatment dates will be recorded on the Study Drug Administration eCRF.

For OMT subjects who continue into Extension Period, the duration of LCIG study drug exposure during Extension Period will be calculated for each subject as the date of the last dose of LCIG study drug minus the date of the first LCIG infusion plus 1.

For LCIG subjects who continue with a PEG-J tube after the 26-week randomized treatment period, and with a PEG-J tube removal after their last infusion of Study M12-927 study drug, 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 final

participation in Study M12-927 (last contact or visit date) during the 26-Week Randomized Treatment Period + 1. For subjects without a PEG-J tube removal after their last infusion of study drug, the duration of PEG-J exposure for each subject will be calculated as the date of their final participation in Study M12-927 (last contact or visit date) minus the date of their final participation in Study M12-927 (last contact or visit date) during the 26-Week Randomized Treatment Period + 1.

For OMT subjects who continue into Extension Period and with a PEG-J tube removal after their last infusion of Study M12-927 study drug, 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 initial PEG-J placement + 1. For OMT subjects who continue into Extension Period and without a PEG-J tube removal after their last infusion of study drug, the duration of PEG-J exposure for each subject will be calculated as the date of their final participation in Study M12-927 (last contact or visit date) minus the date of their initial PEG-J placement + 1.

8.2 OMT Daily Prescribed Dose

Those subjects randomized to OMT, will continue on their current anti-PD medication regimen for the duration of the 26-week randomized treatment period. All anti-PD medications should remain stable for the duration of the study unless adjustments are needed if medically justified. The PI will provide the prescription for continued OMT. Use of medications to treat sleep disorders on an, as needed basis, are prohibited.

8.3 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).

8.4 Duration of Initial LCIG Titration Following PEG-J Placement

Duration of initial LCIG titration for each subject will be calculated as the date of the first optimized prescription following PEG-J placement minus the first LCIG infusion date via PEG-J + 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).

8.5 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.

8.6 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 during the 26-treatment period 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.

For each scheduled visit during the Extension Period, 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) will also be provided for OMT/LCIG subjects who enter the Extension Period.

8.7 Daily Treatment Duration

The LCIG pump start time and end time at each clinic visit will be recorded on the Study Drug Prescription 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.

8.8 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 M12-927 PEG-J tube exposure. Subjects with a PEG-J tube removal after their last infusion of Study M12-927 study drug will be censored at this final tube removal date. Subjects without a PEG-J tube removal after their last infusion of Study M12-927 study drug will be censored on the date of their final participation in Study M12-927 (last contact or visit date).

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

NMSS Total Score

The NMSS was developed to assess non-motor symptoms in PD. It is obtained by interview and rated by health professionals. It contains 30 questions grouped into 9 domains as follows.

NMSS Domain	Number of Questions	Score Range
Cardiovascular including falls	2	0 – 24
Sleep/fatigue	4	0 – 48
Mood/cognition	6	0 – 72
Perceptual problems/hallucinations	3	0 – 36
Attention/memory	3	0 – 36
Gastrointestinal tract	3	0 – 36
Urinary	3	0 – 36
Sexual function	2	0 – 24
Miscellaneous	4	0 – 48

Each question is scored with respect to severity and frequency. Severity is rated on a scale where 0 = none, 1 = mild, 2 = moderate and 3 = severe. Frequency is rated on a scale where 1 = rarely, 2 = often, 3 = frequent, and 4 = very frequent. Item scores are calculated as the product of severity and frequency. Domain scores and a total score are obtained by summing the item scores. The NMSS total score ranges from 0 to 360. 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.

PDSS-2 Total Score

The PDSS-2 was developed from the PDSS based upon the need for a treatment-measuring tool containing PD-specific sleep disorders. The instrument was extended to address specific sleep disturbances such as restless leg syndrome (RLS), morning akinesia, pain, and sleep apnea. The frequency is assessed for the 15 sleep problems based on a 5-point Likert-type scale (ranging from 0 [never] to 4 [very often]). Scores are

calculated for each of the 3 domains (motor symptoms at night, PD symptoms at night, and disturbed sleep) as well as a total score. The PDSS-2 domain scores range from 0 to 20 and the total score ranges from 0 to 60. 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.

The primary efficacy variables will be the change from baseline to Week 26 in the NMSS and PDSS-2 total scores. They will each be estimated using PROC MIXED and a mixed-effect repeated measures model (MMRM) for the change from baseline to each scheduled visit. The model will include the fixed effects of treatment, country and visit, with baseline score as a covariate, 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 26 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 26 for LCIG group in the NMSS (or PDSS-2) total score and μ_{OMT} is the mean change from baseline to Week 26 for OMT group in the NMSS (or PDSS-2) total score. The statistical tests at other visits will be considered secondary.

The change in the NMSS (or PDSS-2) 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.

The two-sided *P* values obtained from the MMRM model for NMSS total score change from baseline to Week 26 and PDSS-2 total score change from baseline to Week 26 will be adjusted for multiplicity using the Hochberg procedure. This method controls the family-wise error rate (FWER) at a pre-specified significance level (alpha = 0.05). Specifically, the following steps will be followed:

- If the larger of the 2 *P* values is ≤ 0.05 (i.e., both *P* values are ≤ 0.05), both primary endpoints are considered statistically significant.
- If the larger of the 2 *P* value is > 0.05, then compare the smaller *P* value with 0.025. The second primary endpoint is statistically significant if the *P* value is ≤ 0.025; otherwise, neither primary endpoint is considered statistically significant.

The mean NMSS and PDSS-2 total scores at baseline, Week 6, Week 12 and Week 26 and the mean changes in NMSS and PDSS-2 total scores from baseline to Week 6, Week 12 and Week 26 will be summarized by domain. Each mean domain score as well as the percentage it represents of the NMSS and PDSS-2 total score will be presented.

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 NMSS total score and change from baseline to final PDSS-2 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 (BLOCF) will be applied to subjects who do not have post-randomization assessment of NMSS or PDSS-2.

Analysis of Secondary Efficacy Variables

The MMRM model, and the descriptive statistic summary described for the NMSS and PDSS-2 total score will also be used to evaluate the change from baseline in each of the following efficacy endpoints:

- UPDRS Part II score
- Parkinson's Disease Questionnaire-8 (PDQ-8) summary index
- NMSS domain scores
- PDSS-2 domain scores
- UPDRS total score, Part I score, Part III score, Part IV score
- Parkinson Anxiety Scale (PAS) total and subscale scores
- Geriatric Depression Scale (GDS-15)
- King's PD Pain Scale total and domain scores

For CGI-C and PGIC, an analysis of variance (ANOVA) model containing treatment and country as the main effects will be carried out.

UPDRS Part II score, CGI-C score and PDQ-8 summary index are key secondary endpoints. If both primary efficacy variables are statistically significant after adjusting for multiplicity, the Stepwise Gatekeeping Procedure will be utilized and the 3 key secondary endpoints will be tested using the Hochberg procedure with significance level of 0.05. Specifically, the following steps will be followed:

- If the largest of the 3 P values is ≤ 0.05 (i.e., all 3 P values are ≤ 0.05), all 3 key secondary endpoints are considered statistically significant.
- If the largest of the 3 P value is > 0.05, then compare the middle P value with 0.025. The second and third key secondary endpoints are both statistically significant if the middle P value is ≤ 0.025.

- If the largest of the 3 *P* value is > 0.05 and the middle *P* value is > 0.025, then compare the smallest *P* value with 0.0167. If the smallest *P* value is ≤ 0.0167, then the third key secondary endpoint is statistically significant. Otherwise, none of the 3 key secondary endpoints can be considered statistically significant.

All secondary efficacy variables will be summarized by the number of subjects with non-missing data, mean, standard deviation, median, minimum and maximum. CGI-C and PGIC variables will also be summarized by the number of subjects with non-missing data and the number and percentage of subjects in each response category. In addition, the summary of the PGIC will also include the number and percentage of subjects reporting improvement (response of either "very much improved," "much improved," or "minimally improved").

9.4 Calculation of Efficacy and Health Outcome Variable

The primary and secondary efficacy variables derived from the above measures are presented in Table 7.

Table 7. Primary and Secondary Efficacy Variables, and Derivations

Instrument	Efficacy Variable	Derivation	Range/Direction
NMSS: 30 questions, 9 domains (cardiovascular/falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, GI tract, urinary, sexual function, miscellaneous). Score of each question is calculated by multiplying severity•frequency. Severity and frequency are rated using a scale ranging from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. 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.	Cardiovascular/falls	Sum of Questions 1 – 2	0 – 24/lower value desirable
	Sleep/fatigue	Sum of Questions 3 – 6	0 – 48/lower value desirable
	Mood/cognition	Sum of Questions 7 – 12	0 – 72/lower value desirable
	Perceptual problems/hallucinations	Sum of Questions 13 – 15	0 – 36/lower value desirable
	Attention/memory	Sum of Questions 16 – 18	0 – 36/lower value desirable
	GI tract	Sum of Questions 19 – 21	0 – 36/lower value desirable
	Urinary	Sum of Questions 22 – 24	0 – 36/lower value desirable
	Sexual function	Sum of Questions 25 – 26	0 – 24/lower value desirable
	Miscellaneous	Sum of Questions 27 – 30	0 – 48/lower value desirable
	Total score	Addition of 9 domains	0 – 360/lower value desirable
PDSS-2: 15 questions, 3 domains. Score of each question is based on a 5-point Likert-type scale (ranging from 0 [never] to 4 [very often]). 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.	motor symptoms at night	Sum of Questions 1 – 5	0 – 20/lower value desirable
	PD symptoms at night	Sum of Questions 6 – 10	0 – 20/lower value desirable
	disturbed sleep	Sum of Questions 11 – 15	0 – 20/lower value desirable
	Total score	Addition of 3 domains	0 – 60/lower value desirable

Table 7. Primary and Secondary Efficacy Variables, and Derivations (Continued)

Instrument	Efficacy Variable	Derivation	Range/Direction
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 I score	Sum of Questions 1 – 4. No missing answers will be imputed so Part I score will be missing if any of the answers are missing.	0 – 16/lower value desirable
	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
	Total score (Part I, II, III)	Sum of Part I, Part II, Part III scores. Will be missing if any one of Part I, Part II, Part III scores is missing.	0 – 176/lower value desirable

Table 7. Primary and Secondary Efficacy Variables, and Derivations (Continued)

Instrument	Efficacy Variable	Derivation	Range/Direction
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). (continued)	Part IV score	Sum of Questions 32 – 42. Part IV score will be calculated as long as at least 10 answers have been recorded. If 1 answer is missing the Part II score will be calculated by multiplying the sum of the answers provided by the ratio of the total number of Part III answers possible to the number of answers provided.	0 – 23/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
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
PGIC: patient's opinion of degree of change since beginning care at the clinic, 7-point scale (1 = no change, 2 = almost the same, 3 = a little better, 4 = somewhat better, 5 = moderately better, 6 = better, 7 = a great deal better)	PGIC score	7-point score as collected	1 – 7/higher score desirable

Table 7. Primary and Secondary Efficacy Variables, and Derivations (Continued)

Instrument	Efficacy Variable	Derivation	Range/Direction
King's PD Pain Scale: 14 items addressing the following 7 domains (musculoskeletal pain, Chronic pain, fluctuation-related pain, nocturnal pain, orofacial pain, neuropathic pain, 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 to 12, the sum of which gives the total score with a range from 0 to 168.	King's PD Pain score	Sum of 14 item scores. The King's PD Pain Scale 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
PAS: 12-item including 1) Feeling anxious or nervous 2) Feeling tense or stressed 3) Being unable to relax 4) Excessive worrying about everyday matters 5) Fear of something bad, or even the worst, happening 6) Panic or intense fear 7) Shortness of breath 8) Heart palpitations or heart beating fast 9) Fear of losing control 10) Social situations 11) Public settings 12) Specific objects or situations Rated as: 0, Never; 1 Rarely; 2, Sometimes; 3, Often; 4, Nearly always	PAS score	Sum of 12 item scores. The PAS score will be calculated as long as at least 11 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 – 48/lower value desirable

Table 7. Primary and Secondary Efficacy Variables, and Derivations (Continued)

Instrument	Efficacy Variable	Derivation	Range/Direction
GDS-15: 15 yes/no as following 1) satisfied with life 2) Dropped many activities and interests 3) life is empty 4) Often get bored 5) In good spirits most of the time 6) Afraid that something bad is going to happen 7) Feel happy most of the time 8) Often feel helpless 9) Prefer to stay at home, rather than going out and doing things 10) Feel that have more problems with memory than most 11) Think it is wonderful to be alive now 12) Feel worthless 13) Feel full of energy 14) Situation is hopeless 15) Most subjects are better off. Answer YES to question 2.3.4.6.8.9.10.12.14.15 will be scored 1 point. Answer NO to questions 1.5.7.11.13 will be scored 1 point.	GDS-15 score	Sum of 15 item scores. The GDS-15 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 – 15/lower value desirable

9.5 Handling of Multiplicity

The two-sided *P* values obtained from the MMRM model for NMSS total score change from baseline to Week 26 and PDSS-2 total score change from baseline to Week 26 will be adjusted for multiplicity using the Hochberg procedure. This method controls the family-wise error rate (FWER) at a pre-specified significance level (alpha = 0.05). Specifically, the following steps will be followed:

- If the larger of the 2 *P* values is ≤ 0.05 (i.e., both *P* values are ≤ 0.05), both endpoints are considered statistically significant.
- If the larger of the 2 *P* value is > 0.05, then compare the smaller *P* value with 0.025. The second endpoint is statistically significant if the *P* value is ≤ 0.025; otherwise, neither endpoint is considered statistically significant.

If both primary efficacy variables are statistically significant after adjusting for multiplicity, the Stepwise Gatekeeping Procedure will be utilized and the 3 key secondary endpoints (UPDRS Part II score, CGI-C score and PDQ-8 summary index) will be tested using the Hochberg procedure with significance level of 0.05. Specifically, the following steps will be followed:

- If the largest of the 3 *P* values is ≤ 0.05 (i.e., all 3 *P* values are ≤ 0.05), all 3 key secondary endpoints are considered statistically significant.
- If the largest of the 3 *P* value is > 0.05, then compare the middle *P* value with 0.025. The second and third key secondary endpoints are both statistically significant if the middle *P* value is ≤ 0.025.
- If the largest of the 3 *P* value is > 0.05 and the middle *P* value is > 0.025, then compare the smallest *P* value with 0.0167. If the smallest *P* value is ≤ 0.0167, then the third key secondary endpoint is statistically significant. Otherwise, none of the 3 key secondary endpoints can be considered statistically significant.

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 NMSS total score and PDSS-2 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 NMSS and PDSS-2 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) during the 26-week randomized treatment period is defined as:

- For subjects in OMT group who don't continue into Extension Period: any adverse event that begins or worsens in severity the day after randomization and within 30 days following the last visit.
- For subjects in OMT group and continue into Extension Period: any adverse event that begins or worsens in severity the day after randomization and within 30 days following the last visit during 26-week randomized treatment period or before the insertion of NJ/PEG-J (whichever is earlier).
- 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 during the 26-week randomized treatment period.

A TEAE during Extension Period for OMT subjects will be defined as any adverse event that begins or worsens in severity after the NJ or PEG-J placement through 30 days after last LCIG infusion or final device removal (whichever is later).

A TEAE during the continuing LCIG treatment period will be defined as any adverse event in LCIG group that begins or worsens in severity after Week 26 visit through 30 days after last LCIG infusion or final device removal (whichever is later).

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 26-week Treatment Period and during the Extension/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 26-week Treatment Period will be summarized for each treatment group and for overall subjects by primary SOC and PT.

- 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 Extension/Transition Period will be summarized for OMT/LCIG subjects who enter the Extension/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 26-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. 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 26-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. 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 26-week randomized treatment period will be summarized by PT. 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).

- 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 26-week randomized Treatment Period will be summarized for each treatment group and for overall subjects by primary SOC and PT. 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 26-week randomized 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 26-week randomized 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 during the 26-week randomized treatment period 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 the Extension/Transition Period baseline to each planned visit and to the minimum, maximum and final value during the Extension/Transition Period will be presented for each continuous hematology, chemistry, urinalysis, and special laboratory variable for OMT/LCIG subjects who enter the Extension/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 by treatment group for reference range category shifts from baseline to lowest, highest and final value during the 26-week randomized treatment period. 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

No comparisons of treatment groups will be performed.

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 F. 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 26-week randomized 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 Extension/Transition Period that meets the PCS criteria and is more extreme than their Extension/Transition Period baseline value will be provided for OMT/LCIG subjects who enter the Extension/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 beginning with Day 7 and to the minimum, maximum and final value during the 26-week randomized treatment period will be presented by treatment group for each vital sign and weight variable. On the day

of the first LCIG infusion, orthostatic vital signs are to be collected at 0, 1, 2 and 3 hours post initial LCIG infusion start. Analyses of the mean change from pre-infusion baseline (planned time 0) to each post-infusion hourly time point will be presented for each vital sign variable other than body temperature for the LCIG group and subjects in OMT group entering Extension Period.

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 during the 26-week randomized treatment period 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 the Extension/Transition Period baseline to each planned visit and to the minimum, maximum and final value during the Extension/Transition Period will be presented for each vital sign and weight variable for OMT/LCIG subjects who enter the Extension/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 26-week randomized 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 F. 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 26-week randomized 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 Extension/Transition Period that meets the PCS criteria and is more extreme than their Extension/Transition Period baseline value will be provided for OMT/LCIG subjects who enter the Extension/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 26-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.

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

10.5.2 Potentially Clinically Significant (PCS) ECG Values

Criteria for PCS values have been predefined for selected ECG variables as outlined in Appendix H. 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 26-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 Extension/Transition Period that meets the PCS criteria and is more extreme than their Extension/Transition Period baseline value will be provided for OMT/LCIG subjects who enter the Extension/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.

10.6 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 26-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.

A summary of the number and percentage of subjects with one or more sleep attacks during the Extension/Transition Period will also be provided for LCIG subjects who enter the Transition Period.

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 26-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 Extension/Transition Period will also be provided for OMT/LCIG subjects who enter the Extension/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 26-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 Extension/Transition Period will also be provided for OMT/LCIG subjects who enter the Extension/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 4).

The changes in this SAP from SAP V1.0 is: Per protocol amendments, subjects from South Korean/United States who complete the 26-week clinical study will have the option to enter an extension of the study. This SAP added the description for Extension Period analyses.

13.0 Appendices

Appendix A. Study Activities

	OMT/LCIG			LCIG		OMT/LCIG			LCIG		OMT/LCIG	LCIG	
Study Day (End of Week)	**V1 Screening Wk –8/–4**	**V2 Screening Wk –1**	**V3 Randomization**	**V4 NJ/PEG-J Placement D1**	**Titration Visits**	**Wk 2**	**Wk 6**	**Wk 12**	**Wk 17**	**Wk 22**	**Wk 26 or Premature Discontinuation**	**Wk 27 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												
Concomitant Medication (including anti-PD and NMS medications)	X	X	X	X	X	X	X	X			X	X	
Anti-PD Medication History	X												
NMS Medication History[g]	X												
MMSE (Mini-Mental State Examination)	X												
Sleep Attacks Questionnaire	X	X	X			X	X	X			X	X	
Physical Examination[h]	X	X	X	X		X	X	X			X	X	
Neurological Exam	X	X	X			X	X	X			X	X	
Dermatological Exam[h]	X										X		
GI Exam[h]	X												
NJ or PEG-J decision	X												
Nasojejunal Tube Placement/Titration[i] (Optional)				X									
PEG-J Placement Procedure[j]				X									

Study Day (End of Week)	OMT/LCIG			LCIG		OMT/LCIG			LCIG		OMT/LCIG	LCIG	
	V1 Screening Wk –8/–4	V2 Screening Wk –1	V3 Randomization	V4 NJ/PEG-J Placement D1	Titration Visits	Wk 2	Wk 6	Wk 12	Wk 17	Wk 22	Wk 26 or Premature Discontinuation	Wk 27 FU[a]	Transition to Commercial Visits[b]
Radiological Check of Tube Placement[j]				X									
PEG-J Site (Stoma) Check				X[k]	X	X	X	X			X	X	
Vital Signs[l]/Weight	X		X	X	X	X	X	X			X	X	X
Height[m]	X												
ECG	X							X			X		
Clinical Labs[n] (+ urinalysis)[n]	X	X	X[n]					X			X		
Urine Drug/Alcohol Screen	X		X										
Special Laboratory Tests[o]	X		X					X			X		X
Pregnancy Test[p]	X			X							X		
MIDI (Minnesota Impulsive Disorders Interview)	X	X	X			X	X	X			X	X	X
C-SSRS[q]	X	X	X	X		X	X	X			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
NMSS (Non-Motor Symptom Scale)			X				X	X			X		
PDSS-2 (Modified Parkinson's Disease Sleep Scale)			X				X	X			X		
UPDRS Parts I – V[r]	X		X				X	X			X		
CGI-C (Clinical Global Impression of Change)											X		
PGIC											X		

Study Day (End of Week)	OMT/LCIG			LCIG		OMT/LCIG			LCIG		OMT/LCIG	LCIG	
	V1 Screening Wk –8/–4	V2 Screening Wk –1	V3 Randomization	V4 NJ/PEG-J Placement D1	Titration Visits	Wk 2	Wk 6	Wk 12	Wk 17	Wk 22	Wk 26 or Premature Discontinuation	Wk 27 FU[a]	Transition to Commercial Visits[b]
PDQ-8 (Parkinson's Disease Questionnaire-8)			X				X	X			X		
MoCA (Montreal Cognitive Assessment)			X				X	X			X		
PAS (Parkinson Anxiety Scale)			X				X	X			X		
GDS-15 (Geriatric Depression Scale)			X				X	X			X		
King's PD Pain Scale			X				X	X			X		
Dose Titration Diary[s]					X								
Subject Dosing/Diary Completion					X	X	X	X			X		
LCIG System and Pump Training (Subject and Caregiver)			X	X									
OMT and LCIG Administration				X	X	X	X	X			X		
LCIG Titration				X	X	X	X	X	X	X	X		
Study Drug Prescription Record (LCIG group only)				X	X	X	X	X			X	X	
Removal of PEG-J												X[t]	
LCIG Cassettes Dispensed and/or Returned				X		X	X	X	X	X	X	X[u]	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 NMS.

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

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

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

g. NMS Medication History is to be collected at V1. These include but are not limited to medications used for the treatment of the 9 NMS domains of experience of cardiovascular/falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, GI tract, urinary, sexual function, and miscellaneous (pain, taste/smell, weight change, excessive sweating) should be collected.

h. At Screening Visit 1 and 2 and Randomization Visit 3 a full physical examination will be performed. Symptom-driven physical examinations will be performed at subsequent visits. On or prior to Visit 2, 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 2. If a suspicious lesion is present, a biopsy should be obtained for proper diagnosis and confirmation that lesion does not meet exclusion criteria.

i. For subjects randomized to LCIG, 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 or surgeon. 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.

j. LCIG 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. Placement can be done at any time during treatment if indicated for worsening of Parkinsonian symptoms not responsive to extra doses.

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

l. On the day of the first LCIG infusion, orthostatic vital signs should be obtained at 0, 1, 2 and 3 hours post initial LCIG start. An attempt should be made to obtain all other vital signs at a consistent time of day. Vital signs should be repeated when PEG-J inserted.

m. Height will be measured at Visit 1 only.

n. PT/PTT will be performed at Screening Visits 1 and 3. In the event the PT/PTT result at V3 is abnormal the subject should not proceed with the NJ and/or PEG-J placement and should contact the medical monitor.

o. Special labs to detect vitamin deficiencies, listed in protocol amendment table 4, will be performed at the times indicated in Protocol Amendment Table 3. 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.

p. 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.

q. 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.

r. At V1, the UPDRS Part III is conducted in the on/off state, all other times in the on state. 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 will only be done during Screening; at all other times a complete UPDRS (Parts I through V) will be done during "On" time.

s. 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.

t. PEG-J removal will be complete 1 week before follow up visit.

u. At Week 27 follow up visit LCIG cassettes return only.

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

Appendix B. Study Activities For South Korea Subjects Entering the Extension Period from the OMT Arm

Study Day (End of Week)	V8 W26	V9 NJ/PEG-J Placement "D1"	Titration Visits	+ W2	+ W6	+ M3	+ M6	Every 6 Months or Premature Discontinuation	FU[a]
Visit Number	V8	V9[d]		V10	V11	V12	V13	V14 +	
Concomitant Medication (including anti-PD and NMS medications)	X	X	X	X	X	X	X	X	X
Physical Examination	X	X		X	X	X	X	X	X
Neurological Exam	X			X	X	X	X	X	X
Dermatological Exam[b]	X							X[d]	
GI Exam[b]	X								
NJ or PEG-J decision	X								
Nasojejunal Tube Placement/Titration[c] (Optional)		X							
PEG-J Placement Procedure[e]		X							
Radiological Check of Tube Placement[e]		X							
PEG-J Site (Stoma) Check		X[g]	X	X	X	X	X	X	X
Vital Signs[f]/Weight	X	X	X	X	X	X	X	X	X
ECG	X					X	X	X	
Clinical Labs (+ urinalysis)	X					X	X	X	
Special Laboratory Tests[h]	X					X	X	X	
Pregnancy Test[i]	X	X			X	X	X	X	
Visit Number	V8	V9[d]		V10	V11	V12	V13	V14 +	
C-SSRS	X	X		X	X	X	X	X	X

Study Day (End of Week)	V8 W26	V9 NJ/PEG-J Placement "D1"	Titration Visits	+ W2	+ W6	+ M3	+ M6	Every 6 Months or Premature Discontinuation	FU[a]
MIDI	X	X		X	X	X	X	X	X
SAQ	X	X		X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Product Complaints		X	X	X	X	X	X	X	X
Dose Titration Diary[j]			X						
Subject Dosing/Diary Completion			X	X	X	X	X	X	
LCIG System and Pump Training (Subject and Caregiver)		X							
LCIG Administration		X	X	X	X	X	X	X	
LCIG Titration		X	X	X	X	X	X	X	
Study Drug Prescription Record		X	X	X	X	X	X	X	
Removal of PEG-J									X[k]
LCIG Cassettes Dispensed and/or Returned		X		X	X	X	X	X	X[l]

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

b. On or prior to Visit 9, 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 9. If a suspicious lesion is present, a biopsy should be obtained for proper diagnosis and confirmation that lesion does not meet exclusion criteria.

c. 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 or surgeon. 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.

d. End of study or premature discontinuation only.

e. 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. Placement can be done at any time during treatment if indicated for worsening of Parkinsonian symptoms not responsive to extra doses.

f. On the day of the first LCIG infusion, orthostatic vital signs should be obtained at 0, 1, 2 and 3 hours post initial LCIG start. An attempt should be made to obtain all other vital signs at a consistent time of day. Vital signs should be repeated when PEG-J inserted.

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

h. Special labs to detect vitamin deficiencies, listed in protocol-amendment4-02-us Table 6, will be performed at the times indicated in above table. 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.

i. Pregnancy Testing WOCBP must have a negative urine pregnancy test at NJ/PEG-J Placement "D1." Monthly pregnancy testing should be performed during treatment, including at the last dose and until 5 × the half-life of the AbbVie product.

j. 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.

k. PEG-J removal will be complete 1 week before follow up visit.

l. At follow up visit LCIG cassettes return only.

Appendix C. Study Activities For South Korea Subjects Entering the Extension Period from the LCIG Arm

Study Day (End of Week)	**V8 W26**	**Every 6 Months Premature Discontinuation**	**FU[a]**
Visit Number for OMT/LCIG	V8	V9+	
Concomitant Medication (including anti-PD and NMS medications)	X	X	X
Physical Examination	X	X	X
Neurological Exam	X	X	X
Dermatological Exam	X	X[b]	
PEG-J Site (Stoma) Check	X	X	X
Vital Signs/Weight	X	X	X
ECG	X	X	
Clinical Labs (+ urinalysis)	X	X	
Special Laboratory Tests[c]	X	X	
Pregnancy Test[d]	X	X	
C-SSRS	X	X	X
MIDI	X	X	X
SAQ	X	X	X
Adverse Events	X	X	X
Product Complaints	X	X	X
Subject Dosing/Diary Completion	X	X	
LCIG Administration	X	X	
LCIG Titration	X	X	

Study Day (End of Week)	**V8 W26**	**Every 6 Months Premature Discontinuation**	**FU[a]**
Study Drug Prescription Record	X	X	
Visit Number for OMT/LCIG	V8	V9+	
Removal of PEG-J			X[e]
LCIG Cassettes Dispensed and/or Returned	X	X	X[f]

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

b. End of study or premature discontinuation only.

c. Special labs to detect vitamin deficiencies, listed in in protocol-amendment4-02-sk Table 6, will be performed at the times indicated in above table. 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.

d. Pregnancy Testing WOCBP must have a negative urine pregnancy test at NJ/PEG-J Placement "D1." Monthly pregnancy testing should be performed during treatment, including at the last dose and until 5 × the half-life of the AbbVie product.

e. PEG-J removal will be complete 1 week before follow up visit.

f. At follow up visit LCIG cassettes return only.

Appendix D. Study Activities For United States Subjects Entering Part 2 from the OMT Arm

Study Day (End of Week)	V8 W26	V9 NJ/PEG-J Placement "D1"	Titration Visits	+ W2	+ W6	+ M3	+ 6M/Premature Discontinuation	FU[a]
Visit Number	V8	V9		V10	V11	V12	V13	
Concomitant Medication (including anti-PD and NMS medications)	X	X	X	X	X	X	X	X
Physical Examination	X	X		X	X	X	X	X
Neurological Exam	X			X	X	X	X	X
Dermatological Exam[b]	X						X[d]	
GI Exam[b]	X							
NJ or PEG-J decision	X							
Nasojejunal Tube Placement/Titration[c] (Optional)		X						
PEG-J Placement Procedure[e]		X						
Radiological Check of Tube Placement[e]		X						
PEG-J Site (Stoma) Check		X[g]	X	X	X	X	X	X
Vital Signs[f]/Weight	X	X	X	X	X	X	X	X
ECG	X					X	X	
Clinical Labs (+ urinalysis)	X					X	X	
Special Laboratory Tests[h]	X					X	X	
Pregnancy Test[i]	X	X			X	X	X	
Visit Number	V8	V9		V10	V11	V12	V14	
C-SSRS	X	X		X	X	X	X	X

Study Day (End of Week)	**V8 W26**	**V9 NJ/PEG-J Placement "D1"**	**Titration Visits**	**+ W2**	**+ W6**	**+ M3**	**+ 6M/Premature Discontinuation**	**FU[a]**
Visit Number	V8	V9		V10	V11	V12	V13	
MIDI	X	X		X	X	X	X	X
SAQ	X	X		X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Product Complaints		X	X	X	X	X	X	X
Dose Titration Diary[j]			X					
Subject Dosing/Diary Completion			X	X	X	X	X	
LCIG System and Pump Training (Subject and Caregiver)		X						
LCIG Administration		X	X	X	X	X	X	
LCIG Titration		X	X	X	X	X	X	
Study Drug Prescription Record		X	X	X	X	X	X	
Removal of PEG-J								X[k]
LCIG Cassettes Dispensed and/or Returned		X		X	X	X	X	X[l]

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

b. On or prior to Visit 9, 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 9. If a suspicious lesion is present, a biopsy should be obtained for proper diagnosis and confirmation that lesion does not meet exclusion criteria.

c. 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 or surgeon. 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.

d. End of study or premature discontinuation only.

e. 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. Placement can be done at any time during treatment if indicated for worsening of Parkinsonian symptoms not responsive to extra doses.

f. On the day of the first LCIG infusion, orthostatic vital signs should be obtained at 0, 1, 2 and 3 hours post initial LCIG start. An attempt should be made to obtain all other vital signs at a consistent time of day. Vital signs should be repeated when PEG-J inserted.

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

h. Special labs to detect vitamin deficiencies, listed in protocol-amendment4-02-us Table 6, will be performed at the times indicated in above table. 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.

i. Pregnancy Testing WOCBP must have a negative urine pregnancy test at NJ/PEG-J Placement "D1." Monthly pregnancy testing should be performed during treatment, including at the last dose and until 5 × the half-life of the AbbVie product.

j. 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.

k. PEG-J removal will be complete 1 week before follow up visit.

l. At follow up visit LCIG cassettes return only.

Appendix E. Study Activities For United States Subjects Entering the Extension Period from the LCIG Arm

Study Day (End of Week)	**W26**	**+ 3M**	**+ 6M/Premature Discontinuation**	**FU[a]**
Visit Number for OMT/LCIG	V8	V9	V10	
Concomitant Medication (including anti-PD and NMS medications)	X	X	X	X
Physical Examination	X	X	X	X
Neurological Exam	X	X	X	X
Dermatological Exam	X		X[b]	
PEG-J Site (Stoma) Check	X	X	X	X
Vital Signs/Weight	X	X	X	X
ECG	X	X	X	
Clinical Labs (+ urinalysis)	X	X	X	
Special Laboratory Tests[c]	X	X	X	
Pregnancy Test[d]	X	X	X	
C-SSRS	X	X	X	X
MIDI	X	X	X	X
SAQ	X	X	X	X
Adverse Events	X	X	X	X
Product Complaints	X	X	X	X
Subject Dosing/Diary Completion	X	X	X	
LCIG Administration	X	X	X	
LCIG Titration	X	X	X	

Study Day (End of Week)	**W26**	**+ 3M**	**+ 6M/Premature Discontinuation**	**FU[a]**
Study Drug Prescription Record	X	X	X	
Visit Number for OMT/LCIG	V8	V9	V10	
Removal of PEG-J				X[e]
LCIG Cassettes Dispensed and/or Returned	X	X	X	X[f]

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

b. End of study or premature discontinuation only.

c. Special labs to detect vitamin deficiencies, listed in protocol-amendment4-02-us Table 6, will be performed at the times indicated in above table. 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.

d. Pregnancy Testing WOCBP must have a negative urine pregnancy test at NJ/PEG-J Placement "D1." Monthly pregnancy testing should be performed during treatment, including at the last dose and until 5 × the half-life of the AbbVie product.

e. PEG-J removal will be complete 1 week before follow up visit.

f. At follow up visit LCIG cassettes return only.

Appendix F. Potentially Clinically Significant Laboratory Values

Clinical Laboratory Tests	Very Low (VL)	Very High (VH)
Hematology		
Activated partial thromboplastin time (aPPT)	NA	> ULN
Hemoglobin	< 100 g/L (6.2 mmol/L)	> 40 g/L above ULN
Prothrombin Intl. Normalized Ratio (INR)	NA	> ULN
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
White blood cell	$< 2 \times 10^9$/L	$> 100 \times 10^9$/L
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)
Gamma-glutamyl transpeptidase (GGT)	NA	> 2.5 × ULN
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)
Uric Acid	NA	> 0.59 mmol/L (10 mg/dL)
Albumin	< 20 g/L	NA
Sodium	< 130 mmol/L	> 155 mmol/L
Magnesium	< 0.4 mmol/L (0.9 mg/dL)	> 1.23 mmol/L (3.0 mg/dL)
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
Creatine Phosphokinase (CPK)	NA	> 5 × ULN

Appendix G. 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 H. 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