1.0 Title Page

Clinical Study Protocol 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

Incorporating Administrative Changes 1, 2 and Amendments 1, 2, 3, and 4

AbbVie Investigational Product:	Levodopa-Carbidopa Intestinal Gel (LCIG)
Date:	31 May 2017
Development Phase:	3b
Study Design:	A Phase 3b, open-label, multicenter 26-week study comparing LCIG to optimized medical treatment on non-motor symptoms associated with advanced Parkinson's disease.
EudraCT Number:	2014-004865-26
Investigator:	Investigator information on file at AbbVie
Sponsor:	AbbVie
Sponsor/Emergency Contact:	[redacted] AbbVie 1 North Waukegan Road, [redacted] North Chicago, IL 60064 Phone: Mobile: Fax: [redacted]

This study will be conducted in compliance with the protocol, Good Clinical Practice ICH-GCP E6(R1) and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	23 January 2015
Amendment 1	21 May 2015
Administrative Change 1	27 October 2015
Amendment 2	28 March 2016
Amendment 3	15 November 2016
Administrative Change 2	16 March 2017

The purpose of this amendment is to:

- Change the study Reference Safety Information (RSI) from the Duodopa Summary of Product Characteristics (SmPC) to the Levodopa-Carbidopa Intestinal Gel (LCIG), (also known as Duopa or Duodopa) Investigator Brochure (IB).

  Rationale: *This change was made to align the study with AbbVie's Standard Operating Procedures (SOPs).*

Throughout the protocol changes were made to update language per the new protocol template, correct typographical errors, and provide clarity.

An itemized list of all changes made to this protocol under this amendment can be found in Appendix E.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M12-927
Name of Study Drug: Levodopa-Carbidopa intestinal gel (SLV-187)	**Phase of Development:** 3b
Name of Active Ingredient: Levodopa-Carbidopa	**Date of Protocol Synopsis:** 31 May 2017
Protocol Title: An Open-label, Randomized 26-Week Study Comparing Levodopa-Carbidopa **IN**te**S**t**I**nal **G**el (LCIG) T**H**erapy to Optimized Medical **T**reatment (OMT) on Non-Motor **S**ymptoms (NMS) in Subjects with Advanced Parkinson's Disease – INSIGHTS Study	
Objectives: **Primary** The primary objective of this study is to examine the effect of LCIG relative to that of 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. **Secondary** To assess the effect of LCIG relative to that of OMT on the motor symptoms/motor complications, safety, tolerability and health-related outcome measures. Motor symptoms/motor complications will be measured by: • Unified Parkinson's Disease Rating Scale (UPDRS) Parts III and IV Safety and tolerability will be assessed by: • Adverse event monitoring • Neurological exams • Clinical laboratory evaluations • Electrocardiogram • Vital signs and weight • Columbia Suicide Severity Rating Scale (C-SSRS) • Minnesota Impulsive Disorders Interview (MIDI) • Sleep Attacks Questionnaire (SAQ) Health Related Outcomes will be measured by: • Parkinson's Disease Questionaire-8 (PDQ-8) • Clinical Global Impression of Change (CGI-C) • UPDRS Parts I and II • Patient Global Impression of Change (PGIC) • Parkinson Anxiety Scale (PAS) • Geriatric Depression Scale (GDS-15) • King's Parkinson's Disease (PD) Pain Scale	
Investigators: Multi-center	

Study Sites: This study will be conducted at approximately 40 – 50 sites in approximately 10 countries worldwide

Study Population:

Levodopa-responsive Parkinson's disease patients with severe motor fluctuations and hyperkinesia/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results.

Number of Subjects to be Enrolled: Approximately 88 subjects (44 per each treatment group)

Methodology:

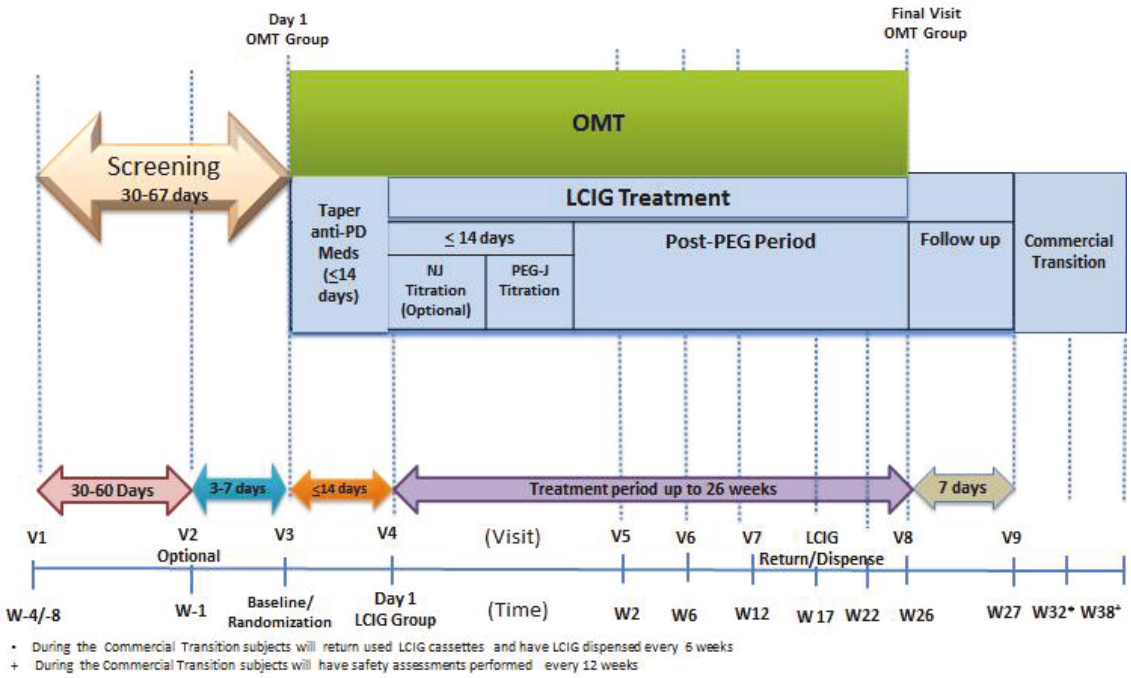


Figure 1: Study Design Schematic

This is a Phase 3b, open-label, randomized multicenter 26-week study comparing LCIG to optimized medical treatment (OMT). The study will consist of 3 sequential periods: Screening, Treatment and Follow-Up. The OMT group will have the same schedule of visits/procedures throughout the study as the LCIG group except for visits related to NJ/PEG procedures and titration of LCIG.

Methodology (Continued):

The Screening Period (V1 – V3)

The Screening Period will be the same for all subjects screened into the study. 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. A movement disorder specialist should perform an interview of the subject at screening. The duration of the Screening Period can be between 30 – 67 days to accommodate the required procedures, training and collection of diaries, and allow for stabilization of anti-PD medications and medications to treat NMS. All anti-PD medications and any other medications used to treat individual non-motor symptoms (e.g., Insomnia, depression, anxiety), must be stable with no adjustments to the frequency of administration, dose of administration or total daily dose. Both anti-PD medications and medications to treat NMS are required to be stable for a minimum of 30 days. During the Screening Period, no study drug (LCIG) will be administered. Visit 2 is optional and is based on the PIs discretion of individual subject need during stabilization of anti-PD medications and medications to treat NMS. Subjects who are deemed eligible by randomization criteria at Visit 3 will be randomized at the end of Visit 3 to receive LCIG or continue on OMT following baseline assessments.

Treatment Period (V4 – V8)

OMT Group:

Those subjects randomized to continue OMT will remain on their current optimized regimen and will have study visits at the end of Weeks 2, 6, 12, and 26 following randomization (V3). The OMT group will not have a V4 (NJ/PEG-J Placement). The day after randomization (V3) will be considered Day 1 of their treatment period.

During the treatment phase, changes to anti-PD and NMS medications should remain stable and can only be made if medically indicated. Changes to the OMT arm can be made "if medically justified," not only for serious safety reasons.

LCIG Group:

In accordance with the LCIG approved Product Label for countries participating in the study, those subjects randomized to LCIG must discontinue all other anti-PD medications (e.g., dopamine agonists, COMT-inhibitors, amantadine, MAO-B inhibitors, anti-cholinergics, and subcutaneous apomorphine etc.) prior to LCIG initiation on Day 1 (V4); these medications should be tapered off according to the prescribing information and the discretion of the Investigator. With the exception of continuous subcutaneous delivery of apomorphine or levodopa containing formulations, these medications may be restarted if indicated by the subject's individual condition, but not within the first 28 days after LCIG initiation.

For those subjects randomized to LCIG, an optional, temporary nasojejunal (NJ) tube may be used initially to titrate the dose of LCIG. Following the NJ phase, a percutaneous endoscopic gastrostomy with a jejunal tube (PEG-J) will be performed by a gastroenterologist proceduralist. Total time to titration via the NJ and PEG-J should not exceed 14 days. Alternatively, subjects may proceed directly to placement of the permanent PEG-J tube without the NJ phase at the discretion of the principal investigator. If the subject proceeds directly to PEG-J, titration should be completed within 7 days. However, at the PI's discretion additional days of optimization may be made if indicated. Subjects on LCIG will return for study visits at the end of Weeks 2, 6, 12, 26 and 27 following PEG-J placement.

Methodology (Continued):

LCIG Group (Continued):

Subjects and/or caregivers must come into the clinic or pharmacy between V7 (Week 12) and V8 (Week 26) for clinical LCIG return and supply visits so that there is no risk of medication expiring. The drug dispensing visits will occur at Weeks 17 and 22 (± 7 days). Other assessments may be completed during these visits if required.

During the treatment phase, medications used to treat specific non-motor symptoms must remain stable for the duration of the study unless medically warranted.

Study Follow-Up

The OMT subjects will not have a follow-up visit (V9).

For LCIG subjects who elect to discontinue LCIG and not continue with commercially available product, a V9 will be conducted one week after NJ/PEG-J removal and the follow-up period will be up until 30 days after NJ/PEG-J removal. For LCIG subjects who will transition to commercial product, the SAE/AE follow-up period will be 30 days after conversion to commercial.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject must have a diagnosis of idiopathic Parkinson's disease according to the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank Criteria. See Appendix C for UKPDS.
2. Subject demonstrates persistent motor fluctuations in spite of individually optimized treatment.
3. The subject's Parkinson's disease is levodopa-responsive.
4. Subject has had optimal treatment with available anti-PD medication and their motor symptoms are judged inadequately controlled on this optimized treatment. Optimized treatment is defined as the maximum therapeutic effect obtained with pharmacological antiparkinsonian therapies when no further improvement is expected regardless of any additional manipulations of levodopa and/or other antiparkinsonian medication. This will be based on the Investigator's clinical judgment.
5. Subject and/or if applicable, their care-partner must be able to complete the Subject Dosing Diary and must be able to demonstrate the ability to operate, manipulate and care for the infusion pump and tubing.
6. Subject is eligible to transfer to commercial treatment of Duodopa after completing the study based on local country requirements.
7. Subject must have a minimum PDSS-2 total score of 18 at Baseline assessment.*
8. Subject must be able to understand the nature of the study and has had the opportunity to have any questions answered. Prior to the conduct of any study procedures (including any changes occurring in the subject's current therapeutic regimen), the subject, if judged by the PI to have decision making capacity, must have voluntarily signed the Independent Ethics Committees/Institutional Review Board (IEC/IRB) approved Informed Consent. In the absence of subject's ability to provide the informed consent, the informed consent must have been signed by a person who has the legal right to act on behalf of the subject following national laws
9. Male or female subjects at least 30 years of age.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

10. If female, subject must be either postmenopausal, OR permanently surgically sterile OR for Women of Childbearing Potential practicing at least one protocol specified method of birth control, starting at Study Day 1 through at least 30 days after the last dose of study drug.

    If the male subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through 4 weeks after the last dose of study drug, to practice the protocol specified contraception.
11. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.
12. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing.

* If previously excluded because of this inclusion criterion, subject is eligible to re-screen.

Main Exclusion:

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject's PD diagnosis is unclear or there is a suspicion that the subject has a parkinsonian syndrome such as secondary parkinsonism (e.g., caused by drugs, toxins, infectious agents, vascular disease, trauma, brain neoplasm), parkinson-plus syndrome (e.g., Multiple System Atrophy, Progressive supranuclear Palsy, Diffuse Lewy Body disease) or other neurodegenerative disease that might mimic the symptoms of PD.
2. Subject has undergone neurosurgery for the treatment of Parkinson's disease.
3. Subject has discontinued apomorphine continuous infusion for the treatment of Parkinson's disease less than 3 months prior to screening visit.
4. Subject has any neurological deficit that might interfere with the study assessments (e.g., hemiparesis).
5. Known hypersensitivity to levodopa, carbidopa or radiopaque material.
6. Subject has contraindications to levodopa, (e.g., narrow angle glaucoma, malignant melanoma).
7. Subject experiencing clinically significant sleep attacks or clinically significant impulsive behavior (e.g., pathological gambling, hypersexuality) at any point during the three months prior to the Screening evaluation) as judged by the Investigator.
8. Current diagnosis or history of drug or alcohol abuse (DSM-V-TR criteria) within 12 months prior to screening visit.
9. Current primary psychiatric diagnosis of uncontrolled acute psychotic disorder or primary psychiatric diagnoses of bipolar disorder, schizophrenia, obsessive compulsive disorder or currently experiencing a major depressive episode with psychotic features per Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-V-TR).
10. Currently experiencing or any known history of psychosis (e.g., troublesome hallucinations with or without insight) or delusions within 3 months prior to Screening.
11. A Mini-Mental State Examination (MMSE) score of < 24 or significant cognitive impairment that, in the opinion of the Investigator, could impact the subject's ability to participate in the trial.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

12. Serum glutamic-oxaloacetic transaminase (AST) or serum glutamic-pyruvic transaminase (ALT) 3 × the upper limit of normal (ULN), or any abnormal laboratory value that is considered clinically significant by the Investigator or could interfere with safety assessments.
13. Current evidence of clinically significant hematological, autoimmune, endocrine, cardiovascular, renal or gastrointestinal disorder that would possibly interfere with the subject's participation in the study (e.g., treated and controlled stable hypertension would not be considered an Exclusion).
14. Subject has current or a history of gastrointestinal, liver, kidney or other condition which may interfere with the absorption, distribution, metabolism or excretion of the study drug (e.g., gastric or intestinal surgery).
15. Any malignant disease other than carcinoma in situ of the cervix or basal cell carcinoma of the skin within the past five years prior to Screening. Subjects with prostate cancer or completely excised squamous cell carcinoma of the skin without reoccurrence within two years prior to Screening may be permitted to enroll following Investigator and study designated physician discussion and documentation of approval. No history of antineoplastic and immunosuppressants administered for cancer treatment (within last 5 years). Note: Biopsy and diagnosis must be completed for any suspicious lesion at dermatology or physical exam.
16. A planned surgical procedure scheduled when the subject would be participating in this study. Subject may subsequently be considered for the study following full recuperation from the surgical procedure.
17. Exposure to any investigational drug within 30 days prior to Screening.
18. Previous enrollment in this study, any other LCIG study or any prior exposure to LCIG.
19. Current enrollment in another clinical study.
20. Subject for whom the placement of a PEG-J tube for LCIG treatment is contraindicated or is considered a high risk for the PEG-J procedure according to the gastroenterology evaluation.
21. Subject has significant current suicidal ideation within one year prior to Screening as evidenced by answering "yes" to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) completed at Screening or a history of suicidal attempts within the last 2 years.
22. A low B_{12} level or low-normal B_{12} level (less than 300 pg/mL) with elevated methylmalonic acid (MMA) at Screening Visit 1.*
23. Positive screen for drugs of abuse or medical marijuana at Screening Visit 1.
24. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive LCIG.
25. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
26. Male subject who is considering fathering a child or donating sperm during the study or for approximately 30 days after the last dose of study drug.

* If treated and repeat labs confirm levels rise above 300 pg/mL, subject is eligible to re-screen.

Investigational Products:	Levodopa (20 mg/mL) and Carbidopa monohydrate (5 mg/mL) in an aqueous intestinal gel (carboxymethylcellulose) dispensed in a medication cassette reservoir of 100 mL. Devices are listed below but are not limited to:

Devices in LCIG System

Description	Manufacturer
Pump CADD Legacy 1400	Smiths Medical
NJ Tube	AbbVie or Covidien
Safety Adapter	Vygon
Extension Tube FR	Vygon
PEG Tube	AbbVie
Intestinal Tube	AbbVie
Y-Adapter for PEG Tube	AbbVie
Click Adapter for PEG Tube	AbbVie

Doses:	LCIG: For those randomized to LCIG, each subject's dose will be individually optimized in accordance with the LCIG approved product label for countries participating in the study. The dose should be adjusted to an optimal clinical response for the individual patient, which means maximizing the functional ON-time during the day by minimizing the number and duration of OFF episodes (bradykinesia) and minimizing ON-time with disabling dyskinesia. Once optimized, dose adjustments to LCIG can be made up to Day 28. After Day 28 the dose should remain stable for the duration of the study unless adjustments are absolutely needed for safety reasons. If modifications are needed, this should first be discussed with the medical monitor. The total daily dose of LCIG will be composed of three components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses. The continuous infusion is expected to run over a period of 16 consecutive hours each day.
Mode of Administration:	LCIG is dispensed in a medication cassette reservoir of 100 mL, designed to be connected to a portable subject-operated pump for infusion via NJ or PEG-J.
Reference Therapy:	Optimized Medical Treatment
Doses:	PI discretion and/or in accordance with approved product label of the prescribed medications
Mode of Administration:	Oral, sub-lingual or transdermal
Duration of Treatment: 26 weeks	

Criteria for Evaluation:

Efficacy:

There will be two alternative primary efficacy variables.

- Change from baseline to Week 26 in NMSS total score
- Change from baseline to Week 26 in PDSS-2 total score

Key secondary endpoints will consist of the following validated scales:

- PDQ-8 summary index
- CGI-C
- UPDRS Part II score

Health Outcome will be assessed by the following measurements that are part of the secondary endpoints:

- PDQ-8
- CGI-C
- UPDRS Parts I and II
- PGIC
- PAS
- GDS-15
- King's PD Pain Scale

Safety:

Safety and tolerability over the course of the study will be assessed by the following measurements:

- Adverse event monitoring
- Neurological exams
- Clinical laboratory evaluations
- Electrocardiogram
- Vital signs and weight
- C-SSRS
- MIDI
- SAQ

Statistical Methods:

Efficacy:

Efficacy Dataset and Treatment Period

The efficacy analysis will be performed on the intent-to-treat dataset which 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. For assessments of efficacy the treatment period will begin the day after randomization (V3) for subjects randomized to OMT, and the day of first LCIG infusion following PEG-J placement for subjects randomized to LCIG treatment. The treatment period will end on the day of the final visit for subjects randomized to OMT, and on the last day of LCIG study drug infusion for subjects randomized to LCIG treatment. The last assessment prior to randomization will be considered baseline and the last assessment that is no more than 2 days after the end of the treatment period will be considered the final evaluation.

Statistical Methods (Continued):

Efficacy (Continued):

Primary Efficacy Analysis

There are 2 alternative primary efficacy variables, change from baseline to Week 26 for NMSS total score and change from baseline to Week 26 for PDSS-2 total score. Either variable considered statistically significant after multiplicity adjustment is sufficient to declare success of the study.

The primary efficacy analysis model is a likelihood-based mixed-effects model repeated measures (MMRM) analysis of the change from baseline for each post-baseline observation using all observed data. The model will include fixed, categorical effects for treatment, site, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline score and the baseline score-by-visit interaction. The primary comparison will be the contrast between LCIG and optimized oral treatment at the Week 26 Visit.

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* values 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.

Secondary Efficacy Analyses

There are 3 key secondary endpoints:

- PDQ-8 summary index
- CGI-C
- UPDRS Part II score

The key secondary efficacy endpoints will be analyzed with the same MMRM model as the primary efficacy variables. For CGI-C, the scores collected at the visits will be the dependent variable.

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.

Other secondary endpoints below will be analyzed with the same MMRM model as the primary efficacy variables:

- NMSS domain scores
- PDSS-2 domain scores
- UPDRS total score, Part I score, Part III score, Part IV score
- PGIC
- Parkinson Anxiety Scale (PAS) total and subscale scores
- Geriatric Depression Scale (GDS-15) score

For the analysis on PGIC, the scores collected at the visits will be the dependent variable.

Statistical Methods (Continued):

Safety:

Safety Dataset and Treatment Period

All safety analyses will be performed on the safety dataset which 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 treatment period for safety is the same as what is defined for efficacy.

Safety Analyses

Safety analyses will include summaries of adverse events, device-related product complaints, vital signs and special labs.

Determination of Sample Size

Approximately 88 subjects will be enrolled into the study and randomized in a 1:1 ratio to either OMT or LCIG. There are no results 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 arm 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.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AE	adverse event
AESI	adverse event of special interest
β-HCG	beta-human chorionic gonadotropin
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression – Change
CHMP	Committee for Medicinal Products for Human Use
CMQ	Company MedDRA Query
CNE or DSS	Clinical Nurse Educator – Duodopa Study Specialist
COMT	Catechol O methyltransferase
CR	controlled release
CS	Clinically Significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DBS	Deep Brain Stimulation
DDI	DOPA decarboxylase inhibitor
DO	Doctor of Osteopath
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSS	Duodopa Study Specialist
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EQ VAS	EuroQol Visual Analogue Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDS-15	Geriatric Depression Scale
GDSM	Global Drug Supply Management
GI	gastro-intestinal
GMP	Good Manufacturing Practice
HLGT	high level group term

HLT	high level term
HRQoL	health related quality of life
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IV	Intravenous
IR	Immediate Release
IRB	Institutional Review Board
IRT	Interactive Response Technology
LAR	Legally acceptable representative
LCIG	levodopa-carbidopa intestinal gel
LC-CR	Levodopa/Carbidopa-Continuous Release
LC-IR	Levodopa/Carbidopa-Immediate Release
LLT	lowest level term
MAO-A	monoamine oxidase A
MAO-B	monoamine oxidase B
MAO Inhibitors	monamine oxidase inhibitors
Max	Maximum
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MIDI	Minnesota Impulsive Disorders Interview
Min	Minimum
MMA	methylmalonic acid
MMSE	Mini-Mental State Examination
MMRM	Mixed-effect Repeated-Measures Model
MoCA	Montreal Cognitive Assessment
NCS	Not Clinically Significant
NDC	National Drug Code
N-J	Nasojejunal
NMS	Non-motor symptoms
NMSS	Non-Motor Symptom Scale
NP	Nurse Practitioner
NONMEM®	nonlinear mixed effects modeling

3-OMD	3-O-methyldopa
OMT	Optimized Medical Therapy
PA	Physician Assistant
PAS	Parkinson Anxiety Scale
PC	Product Complaints
PCS	Potentially Clinically Significant
PD	Parkinson's disease
PDQ-8	Parkinson's Disease Questionnaire-8
PDQ-39	Parkinson's Disease Questionnaire-39
PDSS-2	Parkinson's Disease Sleep Scale
PEG	percutaneous endoscopic gastrostomy
PEG-J	percutaneous endoscopic gastrostomy – with jejunal extension
PGIC	Patient Global Impression of Change
PhD	Doctor of Philosophy
PK	Pharmacokinetic
PLMS	periodic limb movements of sleep
PT	preferred term
QoL	Quality of Life
RBD	behavioral sleep disorder
REM	rapid eye movement
RLS	restless leg syndrome
RSI	Reference Standard Information
SAP	Statistical Analysis Plan
SAQ	Sleep Attacks Questionnaire
SBP	systolic blood pressure
SD	standard deviation
SGOT/AST	aspartate aminotransferase
SGPT/ALT	alanine aminotransferase
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SOC	system organ class
SOP	standard operating procedure
TA MD	Therapeutic Area Medical Director
UKPDS	United Kingdom Parkinson's Disease Society

UPDRS	Unified Parkinson's Disease Rating Scale
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

Definition of Terms

Dose Titration Diary	A paper record used to document the date, time and dose changes during subject titration.
Duodopa Study Specialist	An external nurse specialist who may be provided by the Sponsor to assist the Investigator with initiation and titration of LCIG.
LCIG Cassette Use Form	A paper record used to document dates of individual LCIG cassette use.
LCIG Optimization	Following the introduction of LCIG, maximizing the functional "On" time and minimizing the number of "Off" (bradykinesia) episodes during the day and the total time the subject is "Off;" in addition, minimizing the "On" time with troublesome dyskinesia.
LCIG Prescription Record	A paper record of the LCIG pump settings for a subject's morning dose, flow rate and extra doses that is recorded at every visit by the site.
Optimized Treatment	The maximum therapeutic effect obtained with pharmacological antiparkinsonian therapies when no further improvement is expected regardless of any additional manipulations of levodopa and/or other antiparkinsonian medication.
PRN	Per Diem or As Needed.
Subject Dosing Worksheet	A paper record used to document the date, time and dose of LCIG and levodopa-carbidopa tablets used by the subject during the initial titration period.
Subject Dosing Diary	A paper record used to document the date, time and dose of either (i) LCIG and levodopa-carbidopa tablets used by the subject during the study, after initial titration or (ii) all anti-PD medications taken during the study, depending on randomized treatment arm.

2.0 Table of Contents

List of Tables

List of Figures

List of Appendices

3.0 Introduction

The combination of levodopa-carbidopa continues to be a mainstay in the treatment of Parkinson's disease (PD).[1-3] As PD progresses, PD patients treated with oral levodopa may develop persistent motor fluctuations characterized by unpredictable swings from mobility to immobility ("On-Off" phenomenon) or levodopa-induced dyskinesia. Motor fluctuations occur in about 40% of patients after 4 to 6 years of treatment with levodopa and up to 90% of patients may experience motor fluctuations after 10 years of levodopa therapy.[4] The mechanisms by which response fluctuations occur are only partially understood but are thought to include presynaptic neuronal degeneration leading to a lack of buffering of released levodopa, postsynaptic changes in dopamine receptor sensitivity and number, and pharmacokinetic and pharmacodynamic influences of exogenously administered dopaminergic agents.[5,6] Fluctuations in plasma levels of levodopa occur due to the short half-life of levodopa and the unpredictable variability of gastric emptying. As a result, advanced PD patients suffer severe disability due to constant or unpredictable motor fluctuations, despite increases in the dose or frequency of their oral levodopa treatment.

Various approaches have been taken to cope with the increasingly unstable levodopa response. Levodopa dose and frequency of administration are usually adjusted, although many patients find it challenging to take frequent oral doses of medication. Oral formulations of levodopa are often prescribed in combination with long-acting dopamine agonists, monoamine oxidase inhibitors (MAO Inhibitors) and catechol O methyltransferase (COMT) inhibitors as well as apomorphine injection on an as needed basis. However, despite individually optimized treatment with these conventional medications, patients with advanced PD experience inadequate control of their motor performance. A number of more invasive approaches have been explored and utilized with varying degrees of success; they include the continuous intravenous (IV) administration of levodopa,[7-10] and deep brain stimulation (DBS).[11] DBS has been used in the treatment of advanced PD patients and has demonstrated improvement of motor fluctuations in this patient population, but serious and severe adverse events have been

reported in approximately 13% – 40% of patients including intracerebral hemorrhage, intracranial infection and death.[12,13] The procedure is also not available in all settings and not all PD patients are candidates for brain surgery.[14] Continuous administration of IV levodopa is not clinically feasible due to technical limitations. However, studies with constant-rate delivery (infusion) of levodopa to the blood have clearly resulted in marked stabilization of motor performance in advanced PD patients.[9,10,15]

In addition to motor symptoms and motor fluctuations, patients with advanced PD also suffer from a constellation of non-motor symptoms (NMS) that is often overlooked yet also causes significant disability and impairment to quality of life. The pathophysiology of NMS is poorly understood, but dysfunction of both dopaminergic and nondopaminergic systems are implicated in their development. Non-motor symptoms consist of autonomic dysfunction (orthostatic hypotension, constipation, sialorrhea, sexual dysfunction, urinary retention, temperature dysregulation, and sweating), cognitive and affective disturbances, sleep disorders, and sensory complaints.

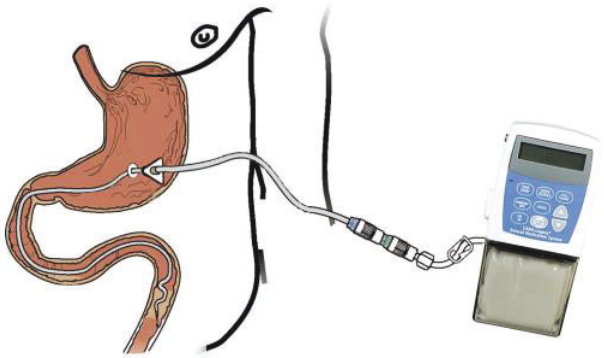
Martinez-Martin et al have recently demonstrated that non-motor symptoms have, as a whole, a greater impact on health related quality of life (HRQoL) than motor symptoms.[16] Moreover, they have demonstrated that NMS progression contributes importantly to HRQoL decline in patients with Parkinson's disease. Similarly, Hinnell et al demonstrated that depression, anxiety, and other non-mood, non-cognitive NMS had a greater impact on HRQoL (as measured by the Parkinson's Disease Questionnaire [PDQ]-8) than motor symptoms.[17] In the PRIAMO study,[18] which assessed NMS in over 1,000 PD subjects using a semi-structured interview questionnaire consisting of 12 NMS domains defined by the steering committee, 98.6% of subjects reported the presence of NMS. The prevalence of NMS was evaluated by dividing PD subjects into 3 groups: "naïve" subjects who had not been treated with dopaminergic agents, "stable" subjects who were under dopaminergic treatment and had no motor complications, and "complicated" subjects who had developed motor fluctuations and/or dyskinesia under dopaminergic treatment. The most common NMS and their prevalence in PD subjects were as follows: fatigue (58%), anxiety (56%), leg pain (38%), insomnia (37%), urgency

and nocturia (35%), drooling of saliva, and difficulties in maintaining concentration (31%). The NMS domains of gastrointestinal, pain, urinary, sleep, and skin disorders and "miscellaneous" were more frequent in the "stable" and "complicated" subjects than in the "naïve" subjects. However, the frequency of cardiovascular symptoms, fatigue, apathy, attention/memory, psychiatric, and respiratory symptoms did not differ across the 3 groups. The prevalence of sleep disorders increased with disease severity. Sleep disorders were reported by 47.9% and 81.6% of subjects with mild (Hoehn and Yahr stage = 1) and severe (Hoehn and Yahr stage = 4 – 5) disease respectively. The mean number of NMS per subject was 7.8 during the prior month and the frequency of NMS increased with disease duration and severity of disease. Using a structured questionnaire of 54 questions on various NMS, Witjas et al found that 64% of PD patients had experienced drenching sweats, 44% flushing, 44% oral dryness, and 40% constipation.[19] These symptoms were associated with a high disability rating and poorer quality of life. Other prevalent NMS include sleep disturbances (insomnia, daytime sleepiness, restless legs and intense vivid dreams), impaired memory and concentration, depression, and dribbling.[20] PD patients suffer from a variety of sleep disturbances including excessive daytime sleepiness, fragmented sleep, REM (rapid eye movement) behavioral sleep disorder (RBD), periodic limb movements of sleep (PLMS), restless leg syndrome (RLS), sleep apnea and insomnia. Ondo et al evaluated the prevalence of nocturnal sleep disorders in over 300 PD subjects with an average disease duration of 9 years and a mean Hoehn and Yahr score of 2.5 using a survey combining questions from various sleep scales.[21] The study demonstrated that 43% of subjects experienced RBD, 51% somniloquism (talking in their sleep), 39% snoring (indicative of sleep apnea), 20% RLS, and an average of almost 3 awakenings per night. Additionally, the PRIAMO study found that 64% of PD subjects suffered from sleep disorders overall with 75% in Hoehn and Yahr stage 2.5 – 3 and 82% in Hoehn and Yahr stage 4 – 5.[18] Non-motor symptoms also lead to increased hospitalizations, morbidity, and mortality in PD patients. Finding effective treatments for NMS in PD is equally important as treating motor symptoms to address significant patient impairment and reduced quality of life.

Levodopa-Carbidopa Intestinal Gel (LCIG) has been marketed for 10 years. The LCIG System is currently approved in 42 countries for the treatment of levodopa-responsive advanced PD. In the majority of countries, it is marketed under the trade name Duodopa. LCIG is a suspension of levodopa-carbidopa monohydrate (4:1) in an aqueous gel (carboxymethyl cellulose) with a viscosity that permits homogeneous distribution of micronized substance particles. Upon upper intestinal administration, the compounds are dissolved in situ and levodopa is rapidly absorbed by an active carrier mechanism localized in the proximal small intestine. LCIG provides continuous rather than intermittent stimulation of the dopaminergic receptors in the brain by permitting plasma concentrations of levodopa within the individual's therapeutic window. When delivered via continuous intestinal infusion therapy, LCIG reduces "Off" time and increases "On" time compared to oral levodopa-carbidopa.[22] Some studies suggest that the improvement of LCIG infusion may be correlated with the severity of Parkinsonian symptoms while on oral treatment.[23] The delivery of LCIG directly to the upper intestine is anticipated to result in the following:[2,15]

- Continuous delivery of levodopa-carbidopa
- Avoidance of the effects of pulsatile gastric emptying
- Reduced variability in plasma-levodopa concentrations
- Decreased motor fluctuations and dyskinesia

Figure 1. Levodopa-Carbidopa Intestinal Gel Infusion System



LCIG is delivered to the proximal small intestine through a percutaneous endoscopic gastrostomy with jejunal extension tube (PEG-J). The LCIG is dispensed in medication cassette reservoirs. The contents of the medication cassette reservoir are delivered via continuous administration by an infusion pump as illustrated in Figure 1. Efficacy of upper-intestinal administration of LCIG has been demonstrated in Phase 3 studies. In the pivotal Phase 3 study (Study S187.3.001/Study S187.3.002), compared to Levodopa-Carbidopa Immediate Release (LC-IR), LCIG significantly improved "Off" time (LS Mean difference = –1.91 hours, $P = 0.0015$) and "On" time without troublesome dyskinesia ("On" time without dyskinesia + "On" time with non-troublesome dyskinesia, LS Mean difference = 1.86 hours, $P = 0.0059$) at Week 12. At Week 12, compared with LC-IR, LCIG significantly decreased the percentage of the waking day in the "Off" state and significantly increased the percentage of waking day in the "On" state without troublesome dyskinesia. LCIG also produced a significantly greater change from baseline in "On" time without dyskinesia compared to LC-IR. Most adverse events were transient and were mild or moderate in intensity and were generally associated with the PEG-J procedure and its complications. The most common adverse events were complication of device insertion (56.8%), abdominal pain (51.4%), nausea (29.7%), procedural pain (29.7%), constipation (21.6%) and incision site erythema (18.9%).[16]

Improvements were also seen with LCIG in disease-specific and global Quality of Life (QoL) measures, as assessed by Clinical Global Impression-Improvement scale (CGI-I), Parkinson's Disease Questionnaire-39 Item (PDQ-39) total scores, and EuroQol Visual Analogue Scale (EQ VAS) scores.[24]

In a long-term open-label safety study (Study S187-3-004) conducted over 54 weeks with 324 subjects, a clinically meaningful reduction in "Off" time was apparent by Week 4 and persisted to the Week 54 endpoint. All of the reduction in "Off" time (4.44 hours, $P < 0.001$) was accompanied by an increase in "On" time without troublesome dyskinesia (4.80 hours, $P < 0.001$), as was observed in the pivotal study. This improvement was achieved with the majority of subjects (> 75%) requiring only levodopa-carbidopa therapy for treating their PD symptoms throughout the study. The most common adverse events

(≥ 10% of subjects) were complication of device insertion (34.9%), abdominal pain (31.2%), procedural pain (20.7%), nausea (16.7%), excessive granulation tissue (16.0%), postoperative wound infection (15.4%), fall (15.1%), constipation (14.5%), insomnia, (13.6%), incision site erythema (13.0%), and urinary tract infection (11.4%). For each of these preferred terms, the adverse events for the majority of subjects were mild to moderate as assessed by the investigator.

Just as LCIG is effective in treating motor fluctuation in advanced PD, it has the potential to treat many of the NMS associated with PD as well. Typically, treatment of any of these NMS require additive therapy and exposes the patient to drug-drug interactions as well as the potential side effect from these therapies. Non-motor symptoms can be present early in the course of the disease and even predate motor symptoms, but remain present in all stages of the disease and become more prominent as the disease progresses.[18] These symptoms can be more troublesome than the cardinal parkinsonian motor symptoms and contribute to significant disability, and to the worsening of quality of life of both patients and caregivers.[16,24]

Although NMS have been implicated in PD since the original description by James Parkinson in 1817, only recently have they been well recognized as important features of the disease.[26] There are 2 primary reasons why NMS has not been recognized as important features of disease: 1) Lack of disease specific instruments to assess NMS and 2) Treatments for PD typically focus on control of motor symptoms; consequently, NMS tend to be underreported and inadequately treated in the clinical setting.[27,28] One study in the US demonstrated that existing depression, anxiety and fatigue are not identified by neurologists in over 50% of consultations, and existing sleep disturbances in over 40%.[29] To date, there have been a few small investigator initiated studies assessing the effect of LCIG on NMS. In a pilot study by Honig et al switching from oral medications to continuous infusion of LCIG reduced motor complications in advanced PD, as well as the burden of NMS.[30] In this prospective open-label observational study, 22 advanced PD patients (mean age 58.6 years, duration of disease 15.3 years) were followed for 6 months and the effect of LCIG on NMS was assessed by the NMSS, Parkinson's disease sleep

scale (PDSS) and PDQ-8. A statistically significant beneficial effect was shown in the NMSS total score (56% improvement from baseline) and 6 of the 9 domains of the NMSS: cardiovascular, sleep/fatigue, attention/memory, gastrointestinal, urinary, and miscellaneous (including pain and dribbling). These results paralleled the improvement observed in motor symptoms. In addition, significant improvements were found on the PDSS (33% improvement from baseline) and in health-related quality of life (assessed by the PDQ-8). The improvement in PDQ-8 scores was significantly correlated with changes in NMSS scores.

Reddy et al compared the effect of LCIG on NMS in 17 advanced PD subjects treated with LCIG versus 9 matched PD controls not treated with LCIG over 6 months.[31] There were no significant changes in NMS as measured by the Non-Motor Symptoms Scale (NMSS) in the control group while the LCIG treated subjects demonstrated a significant improvement in NMSS total score ($P = 0.004$) and the subdomains of sleep, gastrointestinal, urinary, and sexual function. The differences in change from baseline to follow-up between the Duodopa treated group and the control group was statistically significant for NMSS total score ($P = < 0.027$) and for the subdomains of cardiovascular, sleep, gastrointestinal, urinary, sexual function, and miscellaneous.

Pusuiainen et al examined the effects of LCIG on NMS in 9 PD subjects over two months.[32] Statistically significant improvement was seen in the NMSS total score (52% decrease, $P = 0.008$) and the subdomains of sleep/fatigue, gastrointestinal, and miscellaneous.

A retrospective study that evaluated change from baseline in NMS using the NMSS instrument in 14 subjects with advanced PD treated with LCIG for an average of 25 months also demonstrated 14% improvement in the NMSS total score but the results did not reach statistical significance.[30] Although some of the individual domains showed improvement with LCIG, none reached statistical significance. Psychiatric symptoms were significantly improved as revealed by a significant reduction in Unified Parkinson's Disease Rating Scale (UPDRS) Part I, Neuropsychiatric Inventory, and Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease. Additionally, an improvement

in sleep quality and diurnal somnolence was demonstrated by the significant reduction of the PDSS.

When specifically evaluating the effect of LCIG on sleep in Parkinson's disease patients, no previous studies have compared LCIG to optimized medical therapy using the PDSS-2 as an endpoint. Results from a prospective baseline control study conducted by Zibetti et al showed that the improvement in PDSS-2 total score was 13.1 (34% improvement) after an average of 3.5 months of LCIG treatment.[33]

Until recently, NMS were thought to be resistant to dopaminergic therapy. However, dopaminergic agents have now been shown to improve depression, REM behavioral sleep disorder, nocturia, and erectile dysfunction.[34] Dopaminergic agents can also improve "Off"-related NMS, such as pain, anxiety, flushing, and depression. Although it is becoming more recognized that dopaminergic agents can treat certain NMS, their supposed effectiveness was limited by the lack of scales to assess NMS, and quantify their impact on a patient's overall wellbeing. Motor and non-motor symptoms closely correlate with fluctuating plasma concentrations of levodopa and the corresponding pulsatile concentration of dopamine in the striatum.[35-37] Plasma levels of orally administered levodopa fluctuate significantly due to its short half-life and the variability in gastric emptying.[38,39] Treatments that offer continuous levodopa administration result in less variability in levodopa plasma concentration and are believed to provide more continuous dopaminergic stimulation, and, therefore, reduce the frequency and severity of motor fluctuations, dyskinesia, and non-motor symptoms.[40,41] Therefore, reducing the amount of "Off" time should improve those fluctuating NMS. Additionally, since LCIG is initiated and often maintained as monotherapy, tapering off of other anti-PD medications may also lead to improvement in certain non-motor symptoms. Continuous delivery of levodopa, which has the potential to offer continuous dopaminergic stimulation has potential to lead to neuroplastic changes that may also improve those non-fluctuating NMS.

An understanding of LCIG effects on NMS can provide important information for physicians, patients and caregivers when assessing the benefits of advanced treatment.

3.1 Differences Statement

In previous Phase 3 LCIG studies as part of the US registration package which studied adult subjects with advanced levodopa-responsive PD with persistent motor-fluctuations despite optimized treatment with available PD medications, the primary efficacy endpoint was change in motor fluctuations (specifically "Off" time). Study M12-920, an ongoing Phase 3b open-label single arm, baseline-controlled study, with an out-patient PEG-J procedure, evaluated the effect of LCIG on non-motor symptoms in advanced PD in 36 subjects using the NMSS; however effect of LCIG on sleep using the PDSS-2 is not being evaluated. This study will be the largest, randomized, parallel group study evaluating the effect of LCIG on NMS compared to optimized medical therapy as assessed by both the NMSS and PDSS-2.

3.2 Benefits and Risks

Benefits

LCIG provides continuous rather than intermittent stimulation of the dopaminergic receptors in the brain by maintaining constant plasma concentrations of levodopa. The gel formulation, typically applied in a monotherapy regimen, allows a greater flexibility in individualized dosing, thereby allowing the plasma concentration to be within the narrow therapeutic window of these advanced PD patients.

Efficacy of LCIG on motor symptoms in subjects with advanced PD has been demonstrated in Phase 3 studies. In the pivotal Phase 3 study (3.001/3.002), compared to LC-IR, LCIG significantly improved "Off" time (LS Mean difference = –1.91 hours) and "On" time without troublesome dyskinesia (LS Mean difference = 1.86 hours) at Week 12. LCIG also demonstrated a statistically and clinically significant impact on subject's quality of life as assessed with the PDQ-39 summary index and the UPDRS Part II score. Subjects with advanced Parkinson's disease who qualify for the study are expected to benefit through better control of the motor fluctuations that are not adequately controlled with PD medications.[17] Additionally, as described above, small studies have

demonstrated improvement in NMSS total score, NMSS subdomains and PDSS-2 with LCIG either versus optimized medical therapy or in open-label, single-group studies.

Risks

Due to the long experience with the oral drug combination of levodopa and carbidopa for the treatment of PD, the risks that are associated with both active pharmaceutical ingredients are well known. These and additional information on risks are available in the Investigator's Brochure.[42]

Adverse events of special interest (AESI) related to LCIG, a therapeutic system consisting of the drug, the devices, and the placement procedure for the NJ or PEG-J tubing, have been identified and form the basis of the European Union Risk Management Plan.[43] AESIs for this study are defined in Section 6.1.1.3 and comprise the following:

Known Risks

- Gastrointestinal and Gastrointestinal Procedure Related Events

Potential Risks

- Polyneuropathy
- Weight Loss

In the previous Phase 3 clinical program, as observed in an integrated summary of safety, AEs were common and occurred in 93.9% of the 412 subjects in the Open-Label LCIG Analysis Set (Phase 3 Studies S187.3.003, S187.3.004, and S187.3.005). The most common treatment emergent adverse events (TEAEs) were complication of device insertion (33.3%), abdominal pain (28.2%), postoperative wound infection (23.5%), insomnia (23.3%), fall (23.1%), procedural pain (20.9%), excessive granulation tissue (20.6%), nausea (20.4%), constipation (20.4%), and incision site erythema (20.1%) (Table 1). These AEs are commonly associated with underlying PD or are frequently observed following PEG-J placement. Treatment emergent adverse events reported in ≥ 10% of subjects by descending frequency in a pooled open-label analysis set

representing a mean treatment duration of 854 days (open-label LCIG analysis set) are in Table 1.

Table 1. TEAEs Reported in ≥ 10% of Subjects by Descending Frequency (Open-Label LCIG Analysis Set)

Preferred Term	N = 412 Number (%) of Subjects
Any adverse event	387 (93.9)
Complication of device insertion	137 (33.3)
Abdominal pain	116 (28.2)
Postoperative wound infection	97 (23.5)
Insomnia	96 (23.3)
Fall	95 (23.1)
Procedural pain	86 (20.9)
Excessive granulation tissue	85 (20.6)
Nausea	84 (20.4)
Constipation	84 (20.4)
Incision site erythema	83 (20.1)
Urinary tract infection	71 (17.2)
Vitamin B_6 decreased	65 (15.8)
Anxiety	61 (14.8)
Procedural site reaction	61 (14.8)
Dyskinesia	60 (14.6)
Parkinson's disease	59 (14.3)
Weight decreased	59 (14.3)
Depression	55 (13.3)
Blood homocysteine increased	56 (13.6)
Back pain	46 (11.2)
Post procedural discharge	45 (10.9)
Orthostatic hypotension	44 (10.7)
Vomiting	43 (10.4)
Diarrhoea	43 (10.4)
Headache	41 (10.0)

SAEs occurred in 47.1% of the 412 subjects in a pooled Open-Label LCIG Analysis Set (Phase 3 Studies S187.3.003, S187.3.004, and S187.3.005). SAEs that occurred in ≥ 2% of subjects were as follows: Complications of device insertion (7.8%), pneumonia (4.9%), abdominal pain (4.1%), hip fracture (2.4%), Parkinson's disease (2.4%), peritonitis (2.4%), weight decreased (2.4%), fall (2.4%), polyneuropathy (2.2%) and device dislocation (2.2%). These data are on file at AbbVie.

4.0 Study Objective

Primary Objective:

The primary objective of this study is to examine the effect of LCIG relative to that of OMT on NMS associated with advanced PD as assessed by the NMSS Total Score and the Modified PDSS-2 Total Score.

Secondary Objectives:

To assess the effect of LCIG relative to that of OMT on the motor symptoms/motor complications, safety, tolerability and health-related outcome measures.

Motor symptoms/motor complications will be measured by:

- UPDRS Parts III and IV

Safety and tolerability will be assessed by:

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

Health Related Outcomes will be measured by:

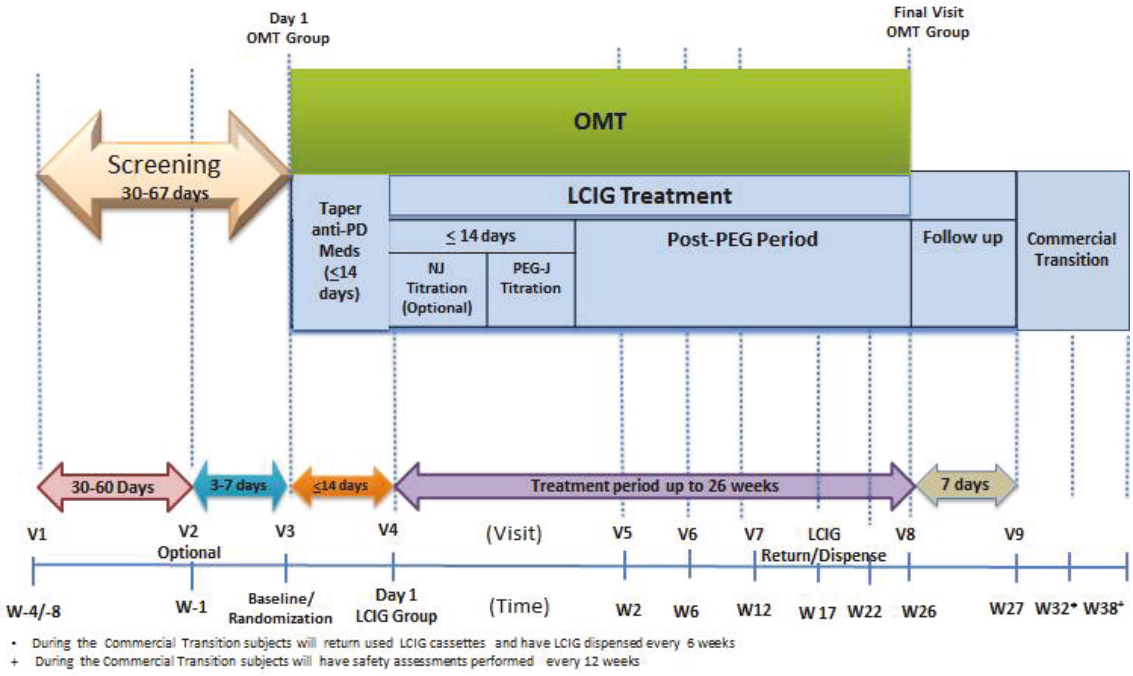
- Parkinson's Disease Questionaire-8 (PDQ-8)
- Clinical Global Impression of Change (CGI-C)
- UPDRS Parts I and II
- Patient Global Impression of Change (PGIC)
- Parkinson Anxiety Scale (PAS)
- Geriatric Depression Scale (GDS-15)
- King's PD Pain Scale

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3b, open-label, multicenter 26-week study comparing LCIG to OMT on NMS associated with advanced PD. This study will be conducted at approximately 40 – 50 sites that specialize in movement disorders in approximately 10 countries.

Figure 2. Study Design Schematic



The study is designed to enroll an adequate number of subjects such that approximately 88 subjects will be randomized in a 1:1 ratio to either treatment group of OMT or LCIG in order to meet scientific and regulatory objectives without over-enrolling an undue number of subjects in alignment with ethical considerations.

The study will consist of 3 sequential periods: Screening, Treatment and Follow-Up.

5.1.1 Screening Period

The Screening Period visits will be the same for all subjects screened into the study. 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. A movement disorder specialist should perform a screening interview of the subject. The duration of the Screening Period can be between 30 – 67 days to accommodate the required procedures, training and collection of diaries, and allow for stabilization of

anti-PD medications and medications to treat NMS. A stable regimen is defined as no changes to the frequency of administration, dose of administration or total daily dose. During the Screening Period, no study drug will be administered.

Visit 1 (V1)

Following informed consent, at V1, study eligibility will be assessed through a series of tests and scales. V1 assessments may be performed over a period of multiple days. Refer to Table 3 of Section 5.3.1.1 for a detailed list of assessments and procedures.

- Laboratory results should be available before V3 (or optional V2) to review for continued subject eligibility.
- The UPDRS, Part III, will be completed during the subject's "Off" and best "On" times. 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 will usually be done 1 to 2 hours post any morning dose of study drug or anti-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; all other UPDRS assessments will be done during "On" time.
- The PI should discuss with the subject the placement of an NJ and/or PEG-J and a decision made at this time if they will do the optional NJ period or go directly to PEG-J should they be randomized to the LCIG treatment group. This is to allow for scheduling of the NJ and/or PEG-J at this time.
- The time period between V1 and optional V2 should not exceed 60 days.
- Additionally, a GI exam to determine suitability for PEG-J placement and a dermatologic evaluation for the presence of melanoma must be performed prior to V3 (or optional V2).
- All anti-PD medications and medications to treat NMS must be stable for at least 30 days prior to V3.

Optional Visit 2 (V2)

Visit 2 will occur between 30 to 60 days after V1. 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. Subjects must be on stable anti-PD medications and medications to treat NMS for at least 30 days before V2. However, the time period between V1 and V2 must not exceed 60 days. If, in the PIs opinion, it is medically necessary for the time frame between V1 and V2 to exceed 60 days, the PI should discuss this with the medical monitor.

All anti-PD medications and medications to treat NMS must remain stable between V2 and V3.

Visit 3 (V3)

Visit 3 will be the randomization visit. The timeframe from V2 to the V3 will be 3 – 7 days.

Only those subjects who meet the following randomization criterion will be randomized at the end of V3 to one of the treatment groups:

- **Subject must have a minimum PDSS-2 total score of 18 at Baseline assessment**.

In addition at V3 the following should occur:

- Concomitant Medication (including anti-PD medications); Subjects' anti-PD medications must be stable during the 3 – 7 days between V2 and V3.
- Anti-PD Medication History: NMS Medication History: medications used to treat individual non-motor symptoms (e.g., Insomnia, depression, anxiety). Subjects' medications to treat NMS must be stable during the 3 – 7 days between V2 and V3.
- Training on the LCIG System and Pump will be initiated only for subjects randomized for LCIG and their caregivers, as applicable.

- UPDRS, Parts I – V will be completed during the subject's "On" time.

5.1.2 The Treatment Period

5.1.2.1 OMT Group

Those subjects randomized to OMT at the end of V3 will continue on their current anti-PD medication regimen for the duration of the study. The PI will provide the prescription for continued OMT. PIs should make any effort to keep all anti-PD medications and medications to treat NMS stable for the duration of the study. Changes to the OMT arm can be made "if medically justified" or if absolutely indicated for safety reasons. The day after V3 will be considered Day 1 of the treatment period for the OMT group. Subjects in the OMT Group will not have a Visit 4, while visits 5 through 8 will take place at the end of Weeks 2 through 26 respectively. Data from all visits will be recorded on the appropriate eCRF and the assessments completed as in Table 3.

5.1.2.2 LCIG Treatment Group

Tapering of Anti-PD Medications Other Than Levodopa

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 according to the prescribing information and the discretion of the Investigator. All other antiparkinsonian medication, including dopamine-agonists, apomorphine, COMT-inhibitors, selective MAO-B inhibitors, amantadine, etc., must be discontinued prior to LCIG initiation. All anti-PD medications, other than subcutaneous continuous delivery of apomorphine and levodopa formulations as outlined in the allowable medications section can be restarted 28 days after LCIG initiation if medically necessary for the treatment of Parkinsonian symptoms.

NJ and/or PEG-J Placement

LCIG is intended for continuous intestinal administration. A temporary NJ tube may be used initially with the infusion pump to determine if the subject responds favorably to this

method of treatment and to optimize the dose of LCIG before treatment with a permanent percutaneous endoscopic gastrostomy with a jejunal (PEG-J) tube is started. Alternatively, subjects may proceed directly to placement of the permanent PEG-J tube and perform titration without the NJ phase if deemed appropriate by the Investigator.

Visit 4 (V4), Day 1 Optional Nasojejunal (NJ) Phase and/or PEG-J Placement

Subjects will have the NJ and/or PEG-J tube placement procedure performed on Study Day 1 by a gastroenterologist proceduralist or qualified radiologist (or delegated experienced nurse for NJ). V4 assessments must be performed on the same day that the NJ and/or PEG-J tube is placed with the following exception: if NJ is used and placed via the passive method, the radiological check will be completed when the tube is expected to be located in the correct position (which may take around 48 hours and local practice procedures should be followed). The NJ and/or PEG-J tube will be placed such that the end of the tubing is just beyond the ligament of Treitz. Once there is confirmation of tube placement all necessary procedures will be followed to attach the pump, with the LCIG cassette, to the NJ and/or PEG-J tube to initiate treatment with LCIG. The gastroenterologist proceduralist or surgeon will check the subject's stoma site within 24 hours of the PEG-J placement.

The optional NJ Period will end with the decision to either continue with treatment and the placement of a permanent jejunal extension tube by PEG-J placement procedure or to discontinue further treatment.

Certain procedures will be repeated prior to PEG-J placement for those who underwent the NJ period as outlined in the table of activities (Table 3). The NJ tube will be removed at the time of the PEG-J procedure, or upon discontinuation of treatment with LCIG. If the subject does not enter the PEG-J placement procedure phase of the study, all End-of-Study Treatment assessments, defined for Visit 9, Week 27, should be completed.

LCIG Initiation and Titration

Following optional NJ and/or PEG-J placement on Study Day 1 and, at the discretion of the Investigator, the subject may begin initiation and titration of LCIG infusion on Study Day 1 once tube placement is confirmed. All other oral anti-PD medications must be stopped prior to LCIG initiation. The dose of LCIG should be adjusted to obtain the optimal clinical response for the individual subject. Optimal clinical response, or optimization, is defined as maximizing the functional "On" time during the day and minimizing the number of "Off" episodes (bradykinesia) and the time the subject is "Off." In addition, optimization minimizes "On" time with troublesome dyskinesia. This determination is made by the Investigator. The dosage procedures for LCIG are described in Section 5.5.1 Treatments Administered.

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.

Oral levodopa medication may only be used as a supplement during the night following discontinuation of the LCIG infusion. During the day it should be used ONLY as rescue medication in case of acute deterioration, presumably caused by failure of the tubes and/or the pump or the onset of an acute illness.

It may take several days to optimize LCIG treatment. In some subjects, optimization may take longer and subjects may remain hospitalized at the discretion of the Investigator. For those subjects with an NJ placement they may or may not continue the NJ Period at home until the PEG-J is inserted.

During the initial titration phase, extra doses may be administered by the Investigator or subject every hour. Pump programming should only be done by trained site personnel and all dose changes must be approved by the Investigator. After the nightly discontinuation of LCIG drug administration, levodopa-DDI (DOPA decarboxylase

inhibitor) tablets may be taken up to 2 hours (for oral LC-IR) or 4 hours (for oral LC-CR) prior to the administration of the next morning dose of LCIG and should not be counted as rescue. 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. It is up to the discretion of the Investigator to determine how many titration days are necessary to obtain optimal clinical response. Once optimized, dose adjustments to LCIG can be made up to Day 28. After Day 28 the dose should remain stable for the duration of the study unless adjustments are absolutely needed for safety reasons.

During the titration, the subject (and if applicable, their care-partner) will receive refresher training on stoma care, tube care and the use of the pump, as well as all the necessary procedures for device maintenance and documentation of LCIG cassette use.

Titration can be done as an inpatient or outpatient. In the event the subject is no longer hospitalized but still being titrated to LCIG the subject will visit the site or clinic as needed for treatment optimization. These visits will be recorded on the appropriate eCRF and the assessments completed as in Table 3.

The gastroenterologist proceduralist or surgeon will check the subject's stoma site anytime from Day 2 to 7 after the PEG-J procedure.

Treatment: Visit 5 (Week 2) Initial Post-PEG-J Evaluation Through Visit 8 (Week 26)

Visit 5 will be conducted at Week 2, 14 days post NJ and/or PEG-J insertion. If subjects are hospitalized for the full 14 days of the NJ and/or PEG-J Placement Procedure Period this visit will take place when the subject is still in the hospital. If subjects have been discharged prior to V5, it will be conducted as a site visit. Study activities at V5 (Week 2) must be completed even if the subject titration is still occurring. Visits 6, 7 and 8 at the

end of Weeks 6, 12 and 26 respectively will be recorded on the appropriate eCRF and the assessments completed as in Table 3.

Allowed anti-PD medications (as indicated in Section 5.2.3.2) may be restarted or initiated if indicated by the condition of the subject, but not within 28 days after PEG placement procedure.

Drug Dispensing Visits

Subjects and/or caregivers must come into the clinic or pharmacy between V7 (Week 12) and V8 (Week 26) for clinical LCIG return and supply visits so that there is no risk of medication expiring. The drug dispensing visits will occur at Weeks 17 and 22 (± 7 days). Other assessments may be completed during these visits if required.

5.1.3 Study Follow-Up

Follow-Up Visit (V9) (LCIG Subjects not Continuing on Commercial Product)

For subjects who are not continuing on LCIG (through commercial sources in countries where LCIG is approved and marketed), the PEG-J tube will be removed following the End of Study activities. A follow-up clinic visit will occur approximately one week later.

Commercial Transition Visits (LCIG Subjects Continuing on Commercial Product)

Study subjects in the LCIG group who complete participation in the study and for whom continuation of treatment with LCIG is judged appropriate by the Investigator will continue to receive LCIG until transition to commercial product is coordinated with the Sponsor's commercial affiliate.

Additional visits every 12 weeks from Week 26 will be schedule to monitor subject safety and allow for drug resupply until the subject transfer to commercial LCIG. Refer to Table 3 of Section 5.3.1.1 for list of assessments. Drug resupply visits will also occur at 6 week intervals between the every 12 week safety assessments.

Upon transfer of subjects to commercial LCIG the monitoring of such therapy will be the responsibility of the subject's personal physician. All necessary support will be provided by the Sponsor's local representative. Follow-up care in these circumstances will be based on the judgment of the subject's personal physician and no formal collection of data will be conducted except for regular ADR-reporting in accordance with local instructions.

OMT Subjects

Study subjects in the OMT group who complete participation in the study are eligible to transition to commercial LCIG after end of study procedures if judged appropriate by their personal physician. This transition is not study related.

5.2 Selection of Study Population

A careful evaluation of any significant change(s) in the subject's PD symptomatology during the Screening Period should be performed by the Investigator prior to randomization to ensure that the subject still meets Inclusion/Exclusion criteria. Subjects who successfully complete all screening and baseline visits procedures and who satisfy all of the Inclusion Criteria and do not meet any of the Exclusion Criteria are eligible for randomization.

5.2.1 Inclusion Criteria

Subjects must meet the following criteria in order to participate in this study.

1. Subject must have a diagnosis of idiopathic Parkinson's disease according to the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank Criteria. See Appendix C for UKPDS.
2. Subject demonstrates persistent motor fluctuations in spite of individually optimized treatment.
3. The subject's Parkinson's disease is levodopa-responsive.
4. Subject has had optimized treatment with available anti-PD medication and their motor symptoms are judged inadequately controlled on this optimized treatment.

Optimized treatment is defined as the maximum therapeutic effect obtained with pharmacological antiparkinsonian therapies when no further improvement is expected regardless of any additional manipulations of levodopa and/or other antiparkinsonian medication. This will be based on the Investigator's clinical judgment.

5. Subject and/or if applicable, their care-partner must be able to complete the Subject Dosing Diary and must be able to demonstrate the ability to operate, manipulate and care for the infusion pump and tubing.
6. Subject is eligible to transfer to commercial treatment of Duodopa after completing the study based on local country requirements.
7. Subject must have a minimum PDSS-2 total score of 18 at Baseline assessment.*
8. Subject must be able to understand the nature of the study and has had the opportunity to have any questions answered. Prior to the conduct of any study procedures (including any changes occurring in the subject's current therapeutic regimen), the subject, if judged by the PI to have decision-making capacity, must have voluntarily signed the Independent Ethics Committees/Institutional Review Board (IEC/IRB) approved Informed Consent. In the absence of subject's ability to provide the informed consent, the informed consent must have been signed by a person who has the legal right to act on behalf of the subject following national laws.
9. Male or female subjects at least 30 years of age.

   If female, subject must be either postmenopausal defined as:

   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

     OR

- Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

  OR

- a Woman of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control (Section 5.2.3.5), starting at Study Day 1 through at least 30 days after the last dose of study drug.

If the male subject is sexually active, he must agree, from Study Day 1 through at least 4 weeks after the last dose of study drug, to practice the protocol specified contraception (Section 5.2.3.5).

10. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.

11. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing.

* If initially excluded based on this inclusion criterion (from Amendment 2), subject is eligible to re-screen.

Rationale for Inclusion Criteria

1 – 7	To select the adequate subject population with appropriate disease severity
8	In accordance with harmonized GCP
9	For the safety of the study subjects
10 – 12	The impact of LCIG on pregnancies is unknown

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject's PD diagnosis is unclear or there is a suspicion that the subject has a parkinsonian syndrome such as secondary parkinsonism (e.g., caused by drugs,

toxins, infectious agents, vascular disease, trauma, brain neoplasm), parkinson-plus syndrome (e.g., Multiple System Atrophy, Progressive supranuclear Palsy, Diffuse Lewy Body disease) or other neurodegenerative disease that might mimic the symptoms of PD.

2. Subject has undergone neurosurgery for the treatment of Parkinson's disease.
3. Subject has discontinued apomorphine continuous infusion for the treatment of Parkinson's disease less than 3 months prior to screening visit.
4. Subject has any neurological deficit that might interfere with the study assessments (e.g., hemiparesis).
5. Known hypersensitivity to levodopa, carbidopa or radiopaque material.
6. Subject has contraindications to levodopa, (e.g., narrow angle glaucoma, malignant melanoma).
7. Subject experiencing clinically significant sleep attacks or clinically significant impulsive behavior (e.g., pathological gambling, hypersexuality) at any point during the three months prior to the Screening evaluation as judged by the Investigator.
8. Current diagnosis or history of drug or alcohol abuse (DSM-V-TR criteria) within 12 months prior to screening visit.
9. Current primary psychiatric diagnosis of uncontrolled acute psychotic disorder or primary psychiatric diagnoses of bipolar disorder, schizophrenia, obsessive compulsive disorder or currently experiencing a major depressive episode with psychotic features per Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, Text Revision (DSM-V-TR).
10. Currently experiencing or any known history of psychosis (e.g., troublesome hallucinations with or without insight) or delusions within 3 months prior to Screening.

11. A Mini-Mental State Examination (MMSE) score of < 24 or significant cognitive impairment that, in the opinion of the Investigator, could impact the subject's ability to participate in the trial.

12. Serum glutamic-oxaloacetic transaminase (AST) or serum glutamic-pyruvic transaminase (ALT) 3 × the upper limit of normal (ULN), or any abnormal laboratory value that is considered clinically significant by the Investigator or could interfere with safety assessments.

13. Current evidence of clinically significant hematological, autoimmune, endocrine, cardiovascular, renal or gastrointestinal disorder that would possibly interfere with the subject's participation in the study (e.g., treated and controlled stable hypertension would not be considered an Exclusion).

14. Subject has current or a history of gastrointestinal, liver, kidney or other condition which may interfere with the absorption, distribution, metabolism or excretion of the study drug (e.g., gastric or intestinal surgery).

15. Any malignant disease other than carcinoma in situ of the cervix or basal cell carcinoma of the skin within the past five years prior to Screening. Subjects with prostate cancer or completely excised squamous cell carcinoma of the skin without reoccurrence within two years prior to Screening may be permitted to enroll following Investigator and study designated physician discussion and documentation of approval. No history of antineoplastic and immunosuppressants administered for cancer treatment (within last 5 years). Note: Biopsy and diagnosis must be completed for any suspicious lesion at dermatology or physical exam.

16. A planned surgical procedure scheduled when the subject would be participating in this study. Subject may subsequently be considered for the study following full recuperation from the surgical procedure.

17. Exposure to any investigational drug within 30 days prior to Screening.

18. Previous enrollment in this study, any other LCIG study or any prior exposure to LCIG.
19. Current enrollment in another clinical study.
20. Subject for whom the placement of a PEG-J tube for LCIG treatment is contraindicated or is considered a high risk for the PEG-J procedure according to the gastroenterology evaluation.
21. Subject has significant current suicidal ideation within one year prior to Screening as evidenced by answering "yes" to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) completed at Screening or a history of suicidal attempts within the last 2 years.
22. A low B_{12} level or low-normal B_{12} level (less than 300 pg/mL) with elevated methylmalonic acid (MMA), at Screening Visit 1.*
23. Positive screen for drugs of abuse or medical marijuana, at Screening Visit 1.
24. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive LCIG.
25. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
26. Male subject who is considering fathering a child or donating sperm during the study or for approximately 30 days after the last dose of study drug.

* If treated and repeat labs confirm levels rise above 300 pg/mL, subject is eligible to re-screen.

Rationale for Exclusion Criteria

1, 6, 12 – 15, 22, 23	To reduce the risk to subjects or others and/or to exclude underlying conditions that would compromise the ability to make causality assessments relative to LCIG for safety events

2, 4 – 5, 7 – 11, 16, 20, 21	To ensure safety of the subjects throughout the study
3, 17 – 19, 24	To exclude, or to minimize, the number of medications or other factors that could interfere with the LCIG, or could add unnecessary variance or bias to safety evaluations
25 – 26	The impact of LCIG on pregnancies and lactation is unknown

5.2.3 Prior and Concomitant Therapy

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prior Therapy (Prior to Randomization)

All medications taken by the subject during the study from 30 days prior to signing the Informed Consent Form are to be recorded in the eCRF.

5.2.3.2 Concomitant Therapy

All changes to concomitant medications must be carefully documented on the Concomitant Medication eCRF form.

Allowable Medications

Anti-Parkinsonian Medications

The following classes of anti-Parkinsonian medications will be allowed during the study:

1. Levodopa formulations
    - For the OMT group, all levodopa formulations are allowed
    - For the LCIG group:
        - levodopa formulations can only be used at nighttime (the 8 hours when the pump is not in use) or as rescue medication

- long-acting levodopa formulations can only be used at nighttime (at least 4 hours prior the next day's morning dose)
- short-acting levodopa formulations with the exception of formulations containing entacapone can only be used at nighttime (at least 2 hours prior to the next day's morning dose) or as rescue medication

2. Dopamine agonists (not including apomorphine continuous infusion or PRN injection)
3. MAO-B inhibitors
4. Anti-cholinergics
5. Amantadine

General Requirements

Screening to Visit 3: All anti-Parkinson's disease medications must be stable* for at least 30 days prior to V3 baseline assessments (NMSS and PDSS-2).

* A stable regimen is defined as no changes to the frequency of administration, dose of administration or total daily dose.

Randomization to End of Treatment Period:

- **OMT Group:** all anti-PD medications should remain stable from randomization to the Week 26 visit and study assessments. Changes to the OMT arm can be made "if medically justified."
- **LCIG Group:** all anti-PD medications except levodopa formulations must be tapered off after randomization and prior to LCIG initiation via NJ or PEG-J (in those going directly to PEG-J). Time of inverse titration should be done following the prescribing information and the Investigator's discretion, but should not exceed 14 days after randomization. For those randomized to LCIG, all allowable anti-PD medications listed above can be restarted 28 days after LCIG initiation if medically necessary for the treatment of Parkinsonian symptoms.

All medication taken by the subject during the study (from signing the Informed Consent form through post-study follow-up) is to be recorded on the Concomitant Medication eCRF, except for study drug for subjects randomized to LCIG. All changes to concomitant medications, this includes all medications taken by subjects randomized to OMT, must be carefully documented on the Concomitant Medication eCRF form.

Medications to Treat Non-Motor Symptoms (OMT and LCIG Groups)

Medications used for the treatment of non-motor symptoms (e.g., orthostatic hypotension, sleep disorders, fatigue, depression, anxiety, hallucinations, attention, sialorrhea, dysphagia, constipation, sexual dysfunction, pain, appetite, sweating) are allowed during the study except those for cognition or that have pharmacokinetic or pharmacodynamics interactions with levodopa as listed in Table 2. Medications have to be taken on a regular basis and will not be allowed if they are taken on an as needed basis with the exception of medication to treat pain post PEG-J procedure. All medications for the treatment of non-motor symptoms must be stable for at least 30 days between V1 and V2 and through the Randomization assessments (NMSS and PDSS-2) at the Randomization visit (V3). These medications must then also remain stable for the duration of the study. However, if absolutely necessary for a significant medical need related to patient safety, the Investigator can make modifications to these medications or add additional medications after discussion with the medical monitor. This will be considered a protocol deviation but the subject will not be discontinued from the study. Caffeine is allowed during the screening period and the duration of the study, but the same pattern of consumption should be maintained to avoid potential confounds of caffeine.

Required Concomitant Medication, Antibiotics

The use of prophylactic antibiotics is required prior to PEG-J procedure. At minimum, a single dose of a 1st or 3rd generation cephalosporin (or an antibiotic with similar coverage) must be administered approximately 30 minutes prior to the PEG-J procedure.

Prohibited Medications (OMT and LCIG Groups)

The following medications (not comprehensive) are prohibited during the study.

Table 2. Prohibited Medications and Treatments

Antipsychotics Both typical and atypical antipsychotics (except quetiapine and clozapine), including but not limited to: Aripiprazole Fluphenazine Haloperidol Perphenazine Pimozide Thiothixene Trifluoperazine Loxapine Molindone Chlorpromazine Mesoridazine Thioridazine Olanzapine Risperidone Ziprasidone Depot neuroleptics **Antiparkinsonian** Apomorphine (PRN injection or continuous infusion) Levodopa-carbidopa-entacapone (**LCIG group only**) **Antihypertensives** Centrally acting (including but not limited to reserpine, α-methyldopa, clonidine) Cinnarizine Flunarizine **Procedures** Neurosurgical procedure for the treatment of Parkinson's disease **Benzodiazepines** Long acting benzodiazepines	**Psychostimulants or Sympathomimetics** Psychostimulants (amphetamine, dextroamphetamine, methylphenidate, pemoline, etc.) Weight loss agents (phentermine, sibutramine) **Anticonvulsants** Barbiturates (such as phenobarbital, primidone) Hydantoins (phenytoin, fosphenytoin) Succinimides (ethosuximide) Others (felbamate, lamotrigine, tiagabine, topiramate, carbamazepine and valproic acid) **Cognition**: Any medication for the treatment of cognition (including but not limited to cholinesterase inhibitors or memantine) **Other** Metoclopramide Oral corticosteroids Catechol-structured drugs (such as adrenaline, dopamine, dobutamine, and isoprenaline) Rifampicin Bupropion Nefazodone Isoniazide Tricyclics MAO-A inhibitors (such as, isocarboxazid, phenelzine, tranylcypromine) or nonselective MAO inhibitors Prochlorperazine Promethazine Tetrabenazine Lithium **As needed use of medications to treat Sleep Disorders (not a comprehensive list)**: Short-acting benzodiazepines Sedating Anti-histamines (also prohibited for PRN use for allergic reaction) Anti-depressants

5.2.3.3 Rescue Therapy (LCIG Group Only)

After NJ and/or PEG-J placement, subjects randomized to LCIG should fill a prescription provided by the Investigator for oral LC-IR tablets in case oral rescue therapy is needed. Once LCIG treatment has been initiated, the prescribed oral LC-IR rescue tablets should only be used during scheduled LCIG use (16-hour infusion) in case of serious medical needs such as the rapid deterioration of motor symptoms that does not respond to an extra dose of LCIG. The subject should be instructed to record all oral levodopa tablets on the Subject Dosing Diary on the assigned days.

5.2.3.4 Post Infusion Night Time Therapy (LCIG Group Only)

Those subjects randomized to the LCIG group will be permitted to self-administer their typical night-time regimen of oral LC-IR or levodopa-carbidopa continuous-release (LC-CR) following the daily discontinuation of the 16-hour infusion, only if they were taking this during the 30 day stable medication period during screening and the dose must remain unchanged. (The Investigator will provide a prescription for the doses of oral LC-IR or LC-CR that the subject takes on a regular nightly basis.) After the nightly discontinuation of LCIG drug administration, levodopa-DDI tablets may be taken up to two hours (for oral LC-IR) or 4 hours (for oral LC-CR) prior to the administration of the next morning dose of LCIG and should not be counted as rescue. The subject should record all oral levodopa-carbidopa tablets on the Subject Dosing Diary on the assigned days.

Those subjects randomized to the OMT group will remain on their normal, stable nighttime regimen if applicable.

5.2.3.5 Contraception Recommendations

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a Woman of Childbearing Potential, practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

Male subjects who are sexually active with a WOCBP, even if the male subject has undergone a successful vasectomy, must agree from Study Day 1 through at least 4 weeks after the last dose of study drug to use condoms and his female partner(s) must use at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).

Male subject agrees not to donate sperm from Study Day 1 through at least 4 weeks after the last dose of study drug.

5.3 Efficacy and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

After a subject has signed the Informed Consent, the study activities described in Table 3 will be completed. Subject visit days should ideally match the target clinic visit days. Every attempt should be made to bring the subject back on the target visit day. A ± 3 day visit window will be allowed as necessary beginning with the Week 2 visit and a ± 7 day visit window will be allowed as necessary beginning with the Week 6 visit. All attempts should be made to return the subject to the planned visit schedule (e.g., if the subject is two days late for a Study Visit, the scheduling of the next visit date should be based on the original planned visit date). All scheduled visits are calculated based on Study Day 1 (NJ and/ or PEG-J Placement Day for subjects randomized to LCIG and day after randomization for subjects randomized to OMT).

Table 3. Study Activities

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]
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									

Table 3. Study Activities (Continued)

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												
Special Laboratory Tests[o]	X		X					X			X		X
Pregnancy Test[p]	X			X			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		

Table 3. Study Activities (Continued)

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]
CGI-C (Clinical Global Impression of Change)											X		
PGIC											X		
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

Table 3. Study Activities (Continued)

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.

Table 3. Study Activities (Continued)

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 Table 4, will be performed at the times indicated in 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. Pregnancy Testing WOCBP must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1. Monthly pregnancy testing should be performed during treatment, including at the last dose and until 5 × the half-life of the AbbVie product.

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.

5.3.1.1 Study Procedures

The study procedures outlined in Table 3 are discussed in this section, with the exception of the collection of adverse event information and product complaints (Section 6.0).

Due to the length of assessments on Visit 1, assessments may be performed over 2 days.

Informed Consent

Voluntary written informed consent must be obtained from each subject (and if appropriate, their caregiver) prior to performing any study-related procedures. Consenting will be performed according to local regulations.

Subject Medical and Neurological History

A complete medical history, including alcohol, drug, tobacco and nicotine-containing product use histories will be taken at the time indicated in Table 3. Additionally, chronic disorders (e.g., diabetes and hay fever) that began prior to Screening and are still present at Screening should be recorded on the Medical History Form. The Medical History obtained at V1 will serve as the baseline for clinical assessment. All psychiatric, neurological, behavioral and/or cognitive diagnosis should be reported. Updates should be made to the Medical/Neurological/PD History with any findings from Labs, Dermatologists, etc.

Subject Parkinson's Disease and NMS Treatment History

In order to qualify for enrollment in the study, the subject should provide the Investigator with a comprehensive history of their past anti-PD and NMS drug treatments. This should be done according to the patient and/or caregiver recollection as well as available history in a subject's chart.

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).

A careful review of the subject's PD history, previous and current PD treatments should be performed by the Investigator (e.g., dosages, frequency of administration, duration of treatment, assessment and evaluation of the subject's response to those previous PD treatments) to determine if the subject is eligible for study participation.

Mini-Mental State Examination (MMSE)

The MMSE[44] is a brief, 30-point questionnaire, administered by a trained rater, which provides a quantitative measure of cognitive mental status in adults and is widely used to screen for cognitive impairment and to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in a patient over time, and to document response to treatment. In this study, MMSE will be used to screen for cognitive impairment. The subject must have a score ≥ 24 at Screening Visit 1 to be eligible for study participation. Lower scores indicate greater impairment. The MMSE will be administered at Visit 1 as indicated in Table 3.

Sleep Attack Assessment

To prospectively monitor for possible development of sleep attacks, the subject will be evaluated for sleep attacks at the times indicated in Table 3. The subject will be asked the following Sleep Attack Assessment questions:

Since your last visit or last time this question was asked, have you experienced any events in which you fell asleep suddenly or unexpectedly, including while engaged in some activity (e.g., eating/drinking, speaking, or driving) or at rest, without any previous warning of sleepiness (e.g., feeling tired)?

- If yes, what specifically happened?
- How many times did you experience such events?
- What were you doing at the time of each event?

- Prior to each event did you experience any sleepiness or drowsiness? If yes, please explain/clarify.
- How long did each event last?
- Did you suffer any "bad" outcome/problem from each falling asleep event?

During the Screening Period, subjects should be asked to answer these questions based on their experiences during the three months prior to Screening Visit 1. During the Screening Period, if the subject is currently or has been recently experiencing sleep attacks, they will be excluded from participation in the study and referred for appropriate follow-up care if the Investigator feels these are clinically significant. The assessment of Sleep Attacks completed at the Screening Visit 1 will serve as baseline for clinical assessment.

Physical Examination

At Screening V1, V2 and Randomization V3 a full physical examination will be performed. Symptom-driven physical examinations will be performed at subsequent visits.

Neurological Examination

A Neurological Examination focusing on symptoms and signs of polyneuropathy (light touch and pinprick sensation, vibratory sensation), deep tendon reflexes, and strength assessments will be performed at the times indicated in Table 3. The Neurological Examination should be bilateral and be done during the subject's "On" time.

Any abnormalities or symptoms identified at Visits 1, 2 and 3 will not be recorded as adverse events but will be recorded in Medical History eCRF. Any new abnormalities or symptoms or symptoms that change in severity or frequency following randomization for the OMT group and the first dose of IP for the LCIG group will be recorded as adverse events.

The Neurological Examination will assess:

- Cranial nerves – assessment of cranial nerves II – XII
- Motor system – assessment of tone, strength and abnormal movements
- Sensory system – including light touch, pinprick, joint position and vibratory sense
- Reflexes – assessment of deep tendon reflexes and plantar responses (Babinski sign)
- Coordination – assessment of upper and lower extremities
- Gait – assessment of base and tandem gait

The Neurological Examination performed at Visit 1, will serve as baseline for clinical assessment.

Dermatological Assessment

A comprehensive assessment by an experienced dermatologist for the presence of any suspicious skin lesions and subsequent evaluation for melanoma will be performed prior to V2 and at Week 26/Premature Discontinuation. If a suspicious lesion is present, a biopsy should be obtained for proper diagnosis and confirmation that lesion does not meet exclusion criteria.

Positive screens will be exclusionary.

GI Examination

On or prior to V2, the Investigator and GI/surgeon will thoroughly evaluate the subject's risk of undergoing PEG-J procedure.

NJ and/or PEG-J Placement (LCIG Group Only)

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. Total time to titration via the NJ and PEG-J should not exceed 14 days. The number of days to titrate will vary for each subject.

Radiological Check of Tube Placement (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. It can also be done at any time during treatment if indicated for worsening of Parkinsonian symptoms or non-responsiveness to extra doses.

PEG-Site (Stoma) Check (LCIG Group Only)

Following the PEG-J placement, site personnel will review proper after-care instructions and checking of the stoma instructions with the subject and/or care-partner as provided in the patient care materials/booklets.

After the initial PEG-J procedure, the PEG-J and stoma must be inspected by a gastroenterologist proceduralist/surgeon/qualified radiologist (preferably the physician who placed the PEG-J), or their designated qualified personnel 2 – 7 days post PEG-J procedure.

Vital Signs/Weight

Body temperature, orthostatic vital signs and weight will be performed at the times indicated in Table 3. All systolic and diastolic blood pressure and pulse rate measurements are to be measured orthostatically. Orthostatic systolic and diastolic blood pressure and pulse rate are to be measured while the subject is supine (after 3 to 5 minutes) and standing (after 2 minutes). Study staff should make efforts to measure with the same arm and method including recording of arm and method in the subject's source documentation.

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.

Vital signs will include body weight will be measured at the times indicated in Table 3. The subject will wear lightweight clothing and no shoes during weighing.

Height

Height will be measured only at V1; the subject will not wear shoes.

12-Lead Electrocardiogram (ECG)

A single 12-lead resting ECG will be obtained at study visits indicated in Table 3. An attempt should be made to obtain all other ECGs at a consistent time of day.

ECGs will be recorded after the subject has been supine for at least 5 minutes. The subject should be instructed to remain completely stationary during the recording, without talking, laughing, deep breathing or swallowing during the time of recording (10 seconds).

ECG Data Review

Site personnel will transmit ECG data to an ECG central laboratory for central processing and reading by a qualified cardiologist (central reader) who will independently review each ECG. The central reader will evaluate a single ECG lead (Lead II, with V5 or V2 [in that order] evaluated if Lead II cannot be evaluated). Heart rate, RR interval, PR interval, QRS duration and QT interval will be measured for each ECG with 3 to 5 beats. QT interval corrected for heart rate (QTc) will be determined using Fridericia's correction method (QTcF).

The central reader will also provide the interpretation of the ECG (i.e., "Normal" or "Abnormal"). The central ECG laboratory will send the ECG report to the site within 3 business days. The Investigator (or physician designee) will review the central reader's report/assessment and document his/her review by signing and dating the central ECG laboratory report. Only the central ECG laboratory's data will be collected into the database. The Investigator should review and reconcile if necessary his/her interpretation of the ECG (normal/abnormal) with the central ECG laboratory in case of relevant divergent assessments and reconcile as he/she determines is appropriate.

The original ECG tracing and the central reader's interpretation, each with the Investigator's signature and date, will be retained in the subject's records at the study site as source documents.

Clinical Laboratory Tests

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. All clinical laboratory samples will be collected as indicated in Table 3 (see Table 4 for list of laboratory evaluations). The laboratory test results obtained at Visit 1 will serve as baseline for clinical assessment. All clinical laboratory samples should be collected after the completion of all other assessments. The Investigator must review the laboratory assessments (initialed and dated) after the receipt of results.

All laboratory abnormalities that occur during the study must be evaluated by the investigator to determine if they indicate a new disease process, an exacerbation or worsening of an existing condition, or require further action to be taken and therefore may need to be reported as adverse events. Accordingly, for any values outside of the reference range, the Investigator will indicate on the report if the result is Clinically Significant (CS) or Not Clinically Significant (NCS). If a laboratory abnormality meets criteria for a Potentially Clinically Significant (PCS) laboratory value, as defined in Appendix D, the investigator must either report an associated adverse event or document in source the reason(s) the finding was not considered an adverse event.

The 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.

Any laboratory value that remains abnormal at Premature Discontinuation/End of Study and was judged to be clinically significant will be followed according to accepted medical standards until resolution of the abnormality.

Table 4. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count Platelet count (estimate not acceptable) White Blood Cell (WBC) count Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCHC) Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils PT/INR (Prothrombine Time/International Normalized Ratio)[a] PTT (Partial Thromboplastin Time)[a]	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (ALT) Serum glutamic-oxaloacetic transaminase (AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin Chloride Creatine kinase Gamma-glutamyl transpeptidase (GGT) Bicarbonate Lactate dehydrogenase LDH Pregnancy test[b] Beta human chorionic gonadotropin (hCG)	Specific gravity Ketones pH Protein Blood Glucose Microscopic Examination Urine pregnancy Test[c] Drug/Alcohol screening:[d] Ethanol U-etylglucuronide (U-Etg) U-etylsulphate (U-Ets) Cannabinoids Barbiturates Benzodiazepines Opiates Methadone Cocaine Amphetamines **Special Tests[d]** Thyroid Function Tests[e] Vitamin B_{12}[f] Vitamin B_6[f] Folic Acid Methylmalonic Acid (MMA)[f] Homocysteine[f]

a. 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.

b. For all females of childbearing potential; a serum pregnancy test will be performed at Visit 1 and Premature Discontinuation/End of Study. Additional testing may be required per local regulations. A negative serum pregnancy result is required before oral study drug is dispensed.

c. For all females of childbearing potential; a negative urine pregnancy test result is required prior to the PEG-J placement procedure and any radiological procedures.

d. Only performed at Visit 1. Positive Alcohol test is not exclusionary criteria.

e. Includes TSH and free T4 (Visit 1 only).

Table 4. Clinical Laboratory Tests (Continued)

f. Special labs to detect vitamin deficiencies, including: Vitamin B_{12}, Vitamin B_6, folic acid, MMA, and homocysteine levels will be performed at the times indicated in Table 3. Abnormal Vitamin B_{12} of questionable clinical significance (indeterminate or low normal results at screening) require MMA and homocysteine laboratory assessments be reviewed for determination of B_{12} deficiency prior to entry into the study. 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.

Urine Screens for Drugs of Abuse and Alcohol

A urine screen for drugs of abuse and medical marijuana and alcohol will be performed at V1 (Table 4).

The panel for drugs to be tested will minimally include the tests listed Table 4. The urine drug screen analysis at Visit 1 will be performed by the certified central laboratory chosen for the study, and will be used for screening purposes.

The alcohol lab values will be recorded, as required by VHP and will be use as quantitative value for assessment of risk factors (e.g., polyneuropathy, etc.).

Special Laboratory Tests

Special labs to detect vitamin deficiencies, including: Vitamin B_{12}, Vitamin B_6, folic acid, MMA, and homocysteine levels will be performed at the times indicated in Table 3. Abnormal Vitamin B_{12} of questionable clinical significance (indeterminate or low normal results at screening) require MMA and homocysteine laboratory assessments be reviewed for determination of B_{12} deficiency prior to entry into the study. Only labs at Visit 1 are exclusionary. 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 Visit 1 only.

Pregnancy Testing

- WOCBP must have a negative serum/urine pregnancy test result at Screening, and a negative serum/urine pregnancy test at Study Day 1. Monthly pregnancy

testing should be performed during treatment, including at the last dose and until 5 × the half-life of the AbbVie product.

- Subjects with borderline pregnancy tests at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
- Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing at any time.

Montreal Cognitive Assessment (MoCA)

The MoCA has been widely utilized in clinical settings to study cognition in PD. It was originally developed as a screening tool to assess mild cognitive impairment in the general population. The MoCA will be administered to assess for cognitive impairment and will be administered at Visits 3, 6, 7 and 8. The scale assesses seven cognitive domains, including visuospatial/executive, naming, memory/delayed recall, attention, language, abstraction and orientation. The maximum total score that can be obtained is 30 and a cut off score of 25/26 on MoCA has demonstrated a diagnostic sensitivity of 90% for individuals diagnosed with mild cognitive impairment. Additionally the movement disorder society has recommended the use of this scale due to its acceptable clinimetric properties[45] and diagnostic utility.

Minnesota Impulsive Disorders Interview (MIDI)

To monitor for development of intense impulsive behavior, the Minnesota Impulsive Disorders Interview (MIDI)[46] will be administered at the times indicated in Table 3 or whenever relevant symptoms emerge. The entire interview is to be completed at V1. If the subject's impulsivity during the Screening Period is judged to be clinically significant in the judgment of the Investigator, they will be excluded from participation in the study and referred for appropriate follow-up care. Any subject noted to have intense impulsive behavior during the study as assessed by the MIDI, or via clinical interview, will be evaluated immediately by the Investigator. The study designated physician should also be notified. The MIDI will be administered as indicated in Table 3.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS)[47] is a systematically administered instrument designed to assess suicidal behavior and ideation, track and assess all suicidal events, as well as the lethality of attempts. Additional features assessed include frequency, duration, controllability, reason for ideation, and deterrents. The C-SSRS is considered a low-burden instrument as it takes less than 5 minutes to administer.

Any subject noted to have suicidal ideation with plan within the last year, either via answering "yes" to question 4 and/or question 5 to the suicidal ideation portion of the C-SSRS, or via clinical interview, will be evaluated immediately by the Investigator. The study designated physician will also be notified. In addition, if the subject expresses suicidal ideation at any time during the study, the Investigator should be immediately notified as well as the study designated physician.

Under no circumstances should a subject who has positively endorsed or expressed suicidal ideation be left alone, be allowed to exit the site, or go home before a qualified medical professional has evaluated the subject's risk.

The "Already Enrolled Subjects" 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.

The C-SSRS will be administered at the times outlined in Table 3.

Non-Motor Symptom Scale (NMSS)

Non-motor symptoms associated with Parkinson's disease can result in substantial patient burden. The NMSS is a comprehensive validated tool measuring a broad range of non-motor symptoms in PD patients. The scale is aimed to be practical and quantitative, encompassing the whole range of non-motor symptoms experienced by people with PD. The NMSS measures the frequency and severity of these symptoms and is comprised of 30 questions that cover 9 domains of patient symptom experience (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]).[48,49] The NMSS measures the burden of non-motor symptoms by weighting each symptom by its frequency and severity; thereby, providing a quantitative measure that captures infrequent but severe symptoms (e.g., hallucinations) and less serious but frequent symptoms (e.g., fatigue, constipation) and provides the overall global burden for patients. Scores are calculated for each domain as well as a total score. Severity and frequency are rated using a 4-point scale ranging from 0 (none) to 3 (severe; major source of distress or disturbance to subject) for severity and from 1 (rarely) to 4 (very frequent [daily or all the time]) for frequency. The total NMSS score ranges from 0 to 360. A negative change from Baseline to end of Maintenance indicates an improvement in NMSS. It is required that only trained and certified health professionals will administer the scale. For this study the NMSS will be performed by an approved, trained, blinded, central rater, who should be a specialist on movement disorders with previous experience using the NMSS scale in advanced PD patients. To be qualified by the Sponsor and the rater vendor, all raters must have participated in the Rater Training and have a current valid Rater Certificate. The qualified rater will complete the NMSS at the times indicated in Table 3.

PDSS-2

Although a number of scales exist in evaluating sleep disturbances, only 3 are endorsed and recommended by the Movement Disorders Society.[50] One such scale specific for Parkinson's disease is the Parkinson's Disease Sleep Scale (PDSS), which has been modified to the PDSS-2. The purpose of the PDSS-2 scale is to characterize the various aspects of nocturnal sleep problems in PD patients. The PDSS-2 instrument has been shown to be reliable, valid, precise, and a potentially treatment responsive tool for measuring nocturnal disabilities and sleep disorders in PD.[51] PDSS-2 consists of 15 questions evaluating motor and NMS at night and upon wakening, as well as disturbed sleep grouped into 3 domains: motor symptoms at night (5 items), PD symptoms at night (5 items), and disturbed sleep (5 items). Specifically, questions assess overall sleep

quality, insomnia, sleep fragmentation, RLS and PLMS, RBD, hallucinations, nocturia, nocturnal immobility, pain and cramps, morning akinesia, cramps and tremor, and sleep apnea. 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 RLS, akinesia, pain, and sleep apnea. Daytime sleepiness was removed from the PDSS-2, as it is a more complex PD symptom. To increase ease of use, the visual analogue scale of the PDSS was transformed into a frequency measure in the PDSS-2. 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 domain as well as a total score. The recall period is for the past week. For this study the PDSS-2 will be performed by an approved, trained, blinded central rater, who should be specialist on movement disorders with previous experience using the NMSS scale in advanced PD patients. To be qualified by the Sponsor and the rater vendor, all raters must have participated in the Rater Training and have a current valid Rater Certificate. The qualified rater will complete the PDSS-2 at the times indicated in Table 3.

The PDSS-2 will be completed at the times indicated in Table 3.

Unified Parkinson's Disease Rating Scale (UPDRS)

The Unified Parkinson's Disease Rating Scale (UPDRS)[52] is an Investigator-used rating tool to follow the longitudinal course of Parkinson's disease. Every effort should be made by the Investigative sites to ensure that each subject is rated by the same rater throughout the subject's participation in the study. The UPDRS assessment will be performed by an approved, trained rater. To be qualified by the Sponsor and the rater vendor, all raters must have participated in the Rater Training and have a current valid Rater Certificate.

The UPDRS is made up of the following sections:

- Part I – Mentation, Behavior, and Mood
- Part II – Activities of Daily Living

- Part III – Motor Examination
- Part IV – Complications of Therapy (including dyskinesias)
- Part V – Modified Hoehn and Yahr Staging

Some sections require multiple grades assigned to each extremity. UPDRS total score ranges from 0 to 176, with 176 representing the worst (total) disability, and 0 no disability. Additionally, Questions 32, 33, and 34 of the UPDRS will be totaled to evaluate dyskinesias.

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. 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 1 through 5) will be done during "On" time.

The UPDRS will be obtained at the times indicated in Table 3.

Health Outcome Measurements

Clinical Global Impression of Change (CGI-C)

The CGI-C is a clinician's rating scale for assessing Global Improvement or Change. The CGI-C rates improvement by 7 categories: very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse. Proportion of responders who had at least "minimally improved" in CGI-C ratings will be assessed.

A qualified rater will administer the CGI-C to the subject at the times indicated in Table 3.

Patients' Global Impression of Change (PGIC)

The PGIC[53] is a 7-point response scale. The subject will be asked by the Investigator or qualified designee to rate their change in status using the following 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.

The responses of "Very much improved," "Much improved" and "Minimally improved" on the PGIC will be used to define responders. A qualified rater will administer the PGIC to the subject at the times indicated in Table 3.

Parkinson's Disease Questionnaire (PDQ-8)

The PDQ-8[54] is a disease-specific instrument designed to measure aspects of health that are relevant to subjects with PD, and which may not be included in general health status questionnaires. The PDQ-8 is a self-administered questionnaire. Each item is scored on the following 5-point scale: 0 = Never, 1 = Occasionally, 2 = Sometimes, 3 = Often, 4 = Always (or cannot do at all, if applicable).

Higher scores are consistently associated with the more severe symptoms of the disease such as tremors and stiffness. The results are presented as eight discrete domain scores and as a summary index. The PDQ-8 domain scores and summary index range from 0 to 100, where lower scores indicate a better perceived health status.

A qualified rater will administer the PDQ-8 to the subject at the times indicated in Table 3.

Parkinson Anxiety Scale (PAS)

The Parkinson Anxiety Scale (PAS) is a new scale developed specifically to measure severity in anxiety in Parkinson's disease. Lack of adequate validation data in the existing anxiety scales led to the development of the PAS. The PAS is a brief scale designed to measure anxiety in PD, rated by patients or clinicians. It contains three dimensions: persistent anxiety, episodic anxiety, and avoidance behavior. It is an easy and brief to

administer, and has better clinimetric properties than existing anxiety rating scales.[55] Additionally a recent study has found that the PAS modified dimensions A and B provide valid and reliable measures of anxiety in PD that are comparable across raters.[56] A qualified rater will administer the PAS to the subject at Visits 3, 6, 7 and 8.

Geriatric Depression Scale (GDS-15)

The Geriatric Depression Scale (GDS) is a short, self-report reliable and valid screening instrument for depression in the elderly. The response items are in a "Yes/No" format. The GDS was originally developed as a 30-item instrument but it was time-consuming and difficult for some patients to complete hence a 15-item version of the GDS was developed. The shortened form consists of 15 items chosen from the Geriatric Depression Scale-Long Form (GDS-L). These 15 items were chosen because of their high correlation with depressive symptoms in previous validation studies.[57] The GDS-15 has adequate discriminant validity for the diagnosis of major and minor depressive disorder.[58] Of the 15 items, 10 indicate the presence of depression when answered positively while the other 5 are indicative of depression when answered negatively. The GDS items focus on the psychological aspects of depression, thus avoiding symptom overlap with other disorders or aging in general. The GDS-15 can be completed in approximately 5 to 7 minutes, making it ideal for patients who are easily fatigued or are limited in their ability to concentrate for longer periods of time. A qualified rater will administer the GDS-15 to the subject to assess depression at Visits 3, 6, 7 and 8.

King's PD Pain Scale

The King's PD Pain Scale is an easy to administer novel clinical PD specific pain scale developed with a focus on sub classification of nociceptive and neuropathic pain. It was specifically developed to assess pain among Parkinson's disease patients since no validated PD specific scales existed to characterize the various types of pain in PD. The scale consists of seven domains of pain including musculoskeletal, chronic, fluctuation related, nocturnal, oro-facial, local limb pain/edema/swelling and radicular pain. The scale measures the frequency and severity of these symptoms. The clinimetric properties

of this instrument have been recently evaluated.[59] A qualified rater will administer the King's PD Pain Scale to the subject to assess for PD specific pain at Visits 3, 6, 7 and 8.[59]

Titration Visits (LCIG Group Only)

Dose Titration Diary and LCIG Prescription Record (LCIG Group Only)

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.

The subject's pump settings for the first infusion of LCIG, the pump settings at the conclusion of each calendar day are to be recorded on the appropriate eCRF.

Following the initial titration period, the site should record the subject's pump settings (morning dose in mL, continuous infusion rate in mL/hr, and lock level) at the conclusion of each clinic visit on the study drug prescription record.

Subject Dosing Diary (LCIG and OMT Groups)

The subject dosing diary should be completed during the 72-hour period (3 days) prior to each clinic visit, as indicated in Table 3. Subjects should be reminded with a phone call prior to each visit to complete the Subject Dosing Diaries and to reinforce the importance of Subject Dosing Diary completion.

Subjects in the LCIG group will record the date and actual clock time of the LCIG pump start and pump stop as well as LCIG extra doses in the diary. In addition, the subject will be instructed to record all oral levodopa-carbidopa taken on the Subject Dosing Diary days.

Subjects in the OMT group will record all anti-parkinsonian medications taken on the Subject Dosing Diary days in the diary.

5.3.1.2 Rater Requirements

All applicable clinical, safety, health outcome and cognition assessments will be administered only by individuals qualified by the Sponsor. Every effort must be made by the Investigative sites to ensure that each subject is rated by the same rater throughout the subject's participation in the study.

Prior to administration of respective scale(s), designated raters will be trained on and certified (if appropriate) in the use of all the scales used in this study. The objective of this certification/training is to ensure uniformity across sites in the administration and scoring of these assessments.

The Sponsor, in conjunction with the approved rater training vendor, if applicable, will determine the minimum rater qualifications for each of the rating scales. All raters must meet these qualifications prior to participation in the training process. The names and qualifications of all site personnel to be involved in rating scale administration will be submitted for approval upon site selection. The qualifications of the raters will be verified through the training vendor. Qualified raters will be trained and tested for competency and, if they meet established requirements, certified at the Investigator meeting. Individual exceptions to these requirements must be approved by the Sponsor via the training vendor if applicable.

Only those persons who have been trained as raters for this study may rate the subjects. Raters who cannot participate in the initial pre-study training or who become involved in the study at a later time will not be permitted to perform study ratings until they have satisfactorily completed an individualized training program designed by the rater training vendor if applicable, approved by AbbVie, and supervised by the Investigator or his/her designee. Raters may be reassessed periodically throughout the study.

Specific Rater Training Requirements

The UPDRS will be administered only by individuals qualified by the Sponsor and the rater training vendor. Prior to administration, designated raters (Investigator or an experienced and medically qualified study site designee [e.g., NP, PA, DO, MD, or PhD] assigned by the Investigator) will be certified in the use of the UPDRS. The objective of this certification/training is to ensure uniformity across sites in the administration and scoring of the scale.

The Sponsor, in conjunction with the rater training vendor, will determine the minimum rater qualifications for the rating scale. All raters must meet these qualifications prior to participation in the training process. The names and qualifications of all site personnel to be involved in the UPDRS, rating scale administration will be submitted for approval upon site selection. The qualifications of the raters will be verified through the rater training vendor. Qualified raters will be trained and tested for competency and, if they meet established requirements, will be certified. Individual exceptions to these requirements must be approved by the Sponsor via the rater training vendor.

Only those persons who have been trained and certified as raters for this study may rate the subjects. Raters who cannot participate in the initial pre-study certification/training or who become involved in the study at a later time will not be permitted to perform study ratings until they have satisfactorily completed an individualized certification/training program designed by the rater training vendor, approved by the Sponsor, and supervised by the Investigator or his/her designee. It is the responsibility of the Investigator to ensure the raters at his/her site are appropriately trained and certified to administer the selected rating scales. Raters will be reassessed periodically throughout the study.

Blinded Rater Training Requirements

The NMSS and PDSS-2 will be administered by blinded central raters on the respective scales at Randomization, V3. This will serve as the baseline for clinical assessment. They will also administer both scales at Weeks 6, 12, and 26.

It is required that only trained and certified specialists on movement disorders with previous experience using the NMSS scale in advanced PD patients will serve as blinded central raters and administer NMSS and PDSS-2. The blinded raters will not have access to the results of other study assessments or medical records for the subject and will not participate in the care or management of the subject. Each rating is based exclusively on an interview with the subject (and the subject's caregiver when available).

The blinded central rater will complete the NMSS and PDSS-2 at the times indicated in Table 3 with the baseline assessment occurring at Screening Visit 3.

Rater Training Requirements for All Other Secondary Scales

Appropriate study site personnel will be trained on the use of all other secondary scales used in this study. Raters who become involved in the study after the Investigator's meeting will not be permitted to perform any study-specified ratings until they have satisfactorily completed the appropriate training program as designated by the Sponsor. It is the responsibility of the Investigator to ensure the raters at his/her site are appropriately trained to administer all rating scales.

5.3.1.3 Ancillary Support

Sites will be appropriately trained and provided support on the initiation and titration of LCIG prior to subject enrollment of the first subject at each site.

Duodopa Study Specialist (DSS)

The Sponsor may provide ancillary support to the study sites by utilizing a Duodopa Study Specialist (DSS) to provide additional training to the Investigator and site personnel. These DSS' training and consultation services will be similar to those provided in the previous Phase 3 program. DSS services and training are methods of support in the implementation of the LCIG administration system at clinical sites.

The functions of the DSS may include:

- Provide ongoing education and support to the site personnel (Investigator, gastroenterologist, study coordinators, research nurses, titration nurses and additional staff) throughout the enrollment period, initiation, titration and rest of the clinical trial
- Facilitate the implementation of the "Train the Trainer Model" by providing initial training to site staff. The Investigator or the appointed delegate may provide ongoing training to new staff.
- Educate the research site staff on medication, cassettes, basic/intermediate/advanced pump function, programming, troubleshooting, tubing, and stoma care
- Educate site personnel (e.g., nurses and physicians) in the proper handling, "Best Practices" for placement, and management of PEG-J tube
- Educate site personnel about Product Complaints and Adverse Events
- Meet local state and hospital/institution rules, laws, and regulations in regards to their role and responsibilities

5.3.2 Drug Concentration Measurements

No drug concentration measurements will be completed during the study.

5.3.3 Efficacy Variables

There will be two alternative primary efficacy variables.

- Change from baseline to Week 26 in NMSS total score
- Change from baseline to Week 26 in PDSS-2 total score

Secondary endpoints will consist of the following validated scales:

- UPDRS total score and section scores during "On" time
- PDQ-8 summary index and domain scores
- CGI-C

- PGIC
- PAS
- GDS-15
- King's PD Pain Scale

5.3.4 Safety Variables

Safety and tolerability over the course of the study will be assessed by the following measurements:

- Adverse event monitoring
- Neurological exams
- Clinical laboratory evaluations
- Electrocardiogram
- Vital signs and weight
- C-SSRS
- MIDI
- SAQ

5.3.5 Health Outcome Variables

The following measurements (already described in Section 5.3.3) are considered health outcomes:

- PDQ-8
- CGI-C
- UPDRS Parts I and II
- PGIC
- PAS
- GDS-15
- King's PD Pain Scale

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a subject from the study at any time if the Investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol. Subjects who withdraw from the study will not be replaced.

Subjects may develop adverse events or abnormalities in vital signs, ECGs, physical examinations, neurological examinations or laboratory determinations during their participation in the study. If these occur, the Investigator may discontinue a subject from the study if, in their clinical judgment, continued participation would result in undue risk or further worsening of the condition.

The following adverse events require Premature Discontinuation:

- Subjects who develop a melanoma during the course of the study should be discontinued from participation and referred for appropriate follow-up care
- Subjects who develop impulsive behavior that is clinically significant, in the judgment of the Investigator, should be discontinued from participation in the study and referred for appropriate follow-up care
- As indicated by answering yes to question 4 or 5 on the C-SSRS, subjects should be discontinued from participation in the study and referred for appropriate follow-up care
- Subjects who become pregnant should be discontinued from participation in the study and referred for appropriate follow-up care

In the event that a subject withdraws or is discontinued from the study after they have begun the PEG-J placement procedure, the assessments for a Premature Discontinuation Visit should be performed as soon as possible after discontinuation from the study.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the Investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

The Study Termination eCRF must be completed for all subjects who have entered the study (i.e., have signed the Informed Consent). Subjects dropping out prior to randomization will be considered Screen Failures and the reason for Screen Failure will be entered in the eCRF. In case of Premature Discontinuation of the subject after randomization, the primary reason for Premature Discontinuation will be entered in the eCRF.

5.4.2 Removal of the PEG-J (LCIG Group Only)

For subjects randomized to LCIG, in case of premature discontinuation of the subject or subject not continuing on commercial treatment, after the PEG-J has been placed, the PEG-J should be removed via endoscopy. The PEG-J should not be removed for 10 to 14 days after placement or until the stoma-tract is formed. Institutional standards for follow-up care after removal of the PEG-J should be followed. The tube must be removed endoscopically by a qualified gastroenterologist proceduralist or surgeon. Follow-up visit with examination should occur 1 week following the PEG-J removal.

5.4.3 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Subjects may be randomized to one of two treatment groups, OMT or LCIG.

5.5.1.1 OMT

Those subjects randomized to OMT at the end of V3 will continue on their current anti-PD medication regimen for the duration of the study. The PI will provide the prescription for continued OMT. PIs should make any effort to keep all anti-PD medications and medications to treat NMS stable for the duration of the study. Changes to the OMT arm can be made "if medically justified" or if absolutely indicated for safety reasons. The day after V3 will be considered Day 1 of the treatment period for the OMT group. Subjects in the OMT Group will not have a Visit 4, while visits 5 through 8 will take place at the end of Weeks 2 through 26 respectively. All data will be recorded on the appropriate eCRF and the assessments completed as in Table 3.

5.5.1.2 LCIG

LCIG is supplied as a homogenous suspension of levodopa (20 mg/mL) and carbidopa monohydrate (5 mg/mL) in an aqueous intestinal gel (carboxymethyl cellulose). The intestinal gel is dispensed in a medication cassette reservoir of 100 mL, designed to be connected to a portable subject-operated pump. LCIG infusion is administered over a full 16-hour period each day. At night, after disconnecting the pump, the tubing is flushed with potable water.

The total daily dose of infusion LCIG will be composed of three components: (i) the morning dose, (ii) continuous maintenance infusion dose and (iii) extra doses.

Subject dosing is determined individually. The starting total daily dose of LCIG infusion after placement of the PEG-J tube will be based solely on the daily dose of the oral levodopa component from the tablets of levodopa-immediate (IR) taken immediately prior to NJ (or PEG-J) placement during the 16 hour waking day it was anticipated the subject

would be on LCIG therapy. The rate of LCIG infusion is typically within the range of 1 to 10 mL/hour (20 to 200 mg of levodopa/hour) in most instances and runs over a period of 16 consecutive hours. The PEG-J tube should be disconnected from the infusion pump before bedtime and the tube should be flushed with 20 mL potable water (both the gastric and jejunal port).

The timing (time of day, interval) of dosing and specific instructions to subjects about when or how to take the dose will be supplied to the subject. No restrictions are given with relation to the time of LCIG dosing relative to meals.

Initial Dose Titration

The initial infusion will be based on calculations described in this section. Extra doses of LCIG may be administered to address immediate medical need throughout the day during initial titration and should be carefully recorded on the Dose Titration Diary.

The daily LCIG infusion dose may be adjusted based on the subject's response to the previous day's treatment and the amount of, if any of extra LCIG doses required. If both the Investigator and subject are satisfied with the effectiveness of treatment, then no change in the LCIG infusion dose is required. If clinically indicated, changes in the dose either upward or downward can be made to further optimize the subject's treatment response.

If at any time during titration the subject develops severe dyskinesia or other levodopa-related complications, the LCIG infusion can be paused, if judged absolutely necessary by the Investigator, until symptoms improve to a clinically acceptable level.

Additionally, if at any time during titration, the subject develops a prolonged "Off" state that is unsafe or causes the subject unacceptable discomfort, rescue oral LC-IR dose can be administered, if judged necessary by the Investigator, until symptoms improve.[58]

The continuous dose of LCIG should be adjusted to obtain the optimal clinical response for the individual subject. Optimal clinical response is defined by maximizing the

functional "On" time and minimizing the number of "Off" episodes during the day. This optimization also minimizes "On" time with troublesome dyskinesia. This determination is made by the Investigator.

LCIG Infusion

LCIG concentration = 1 mL LCIG contains 20 mg of levodopa and 5 mg carbidopa (20 mg/mL).

Morning Dose

A morning dose will be administered as a bolus infusion by the pump to rapidly achieve a therapeutic dose level (over approximately 10 to 30 minutes). This morning dose is generally 5 to 10 mL and corresponds to 100 to 200 mg of levodopa.

The total morning dose typically does not exceed 15 mL (300 mg levodopa). Subjects are not administered a full equivalent of their usual oral morning dose of levodopa-carbidopa.

Continuous Maintenance Dose

The Maintenance Dose is adjustable in steps of 2 mg/hour (0.1 mL/hour). The dose should be calculated according to the subject's previous daily intake of levodopa. The continuous maintenance dose is adjusted individually. It is usually kept at 2 to 6 mL/hour (40 to 120 mg levodopa/hour). However, higher doses may be clinically indicated. During the titration period, the continuous dose can be titrated in a step wise fashion that meets the clinical and medical needs of the subject. The continuous maintenance dose is first calculated based on the subject's usual total daily dose minus the morning dose.

During treatment, pump alarms may indicate kinking or knotting of the tube. Additionally there may be a sudden deterioration in treatment response with recurring motor fluctuations due to the distal part of the tube becoming displaced from the upper intestine into the stomach. The location of the tube should be determined radiographically. If necessary, the end of the tube can be repositioned to the proximal small intestine and the new placement confirmed radiographically.

If a problem develops with the LCIG system and the LCIG infusion needs to be temporarily discontinued, the Investigator should then place the subject on a regimen of oral levodopa-IR tablets until the problem is resolved and the LCIG infusion can be resumed the following morning. If the subject is placed on an oral regimen of levodopa IR tablets; the dose prescribed should be based on the dose the subject was receiving just prior to the LCIG infusion interruption and adjust the dose as clinically indicated to stabilize the subject.

Extra LCIG Doses

During initial titration, extra doses may be administered on an hourly basis at the Investigator's discretion based on the subject's response. Subsequently, subjects will be allowed to self-administer additional extra doses of LCIG (at intervals of no less than 2 hours) to address immediate medical needs, such as the rapid deterioration of motor function. Extra doses may be given as required if the subject becomes hypokinetic during the day. If the need for extra doses exceeds 5 times per day, the subject should be instructed to contact the Investigator. The Investigator should then consider the need to increase the subject's continuous daily maintenance infusion dose. After the initial dose setting, fine adjustments of the morning dose, the maintenance dose and extra doses can be made as needed.

Nasojejunal Tube

LCIG is intended for continuous intestinal administration. A temporary nasojejunal tube may be used initially with the infusion pump to determine if the subject responds favorably to this method of treatment and to optimize the dose of LCIG before treatment with a permanent PEG-J tube is started. Only the NJ sets available through this clinical study should be used with LCIG. The NJ should be inserted by a gastroenterologist proceduralist, surgeon or interventional radiologist. NJ may also be inserted by the passive method.

Following the placement of the NJ it will be necessary to perform a radiological check for proper tube placement before initiating LCIG. If NJ is placed via the passive method, the

radiological check will be completed when the tube is expected to be located in the correct position (which may take around 48 hours and local practice procedures should be followed).

Alternatively, subjects may proceed directly to placement of the permanent PEG-J tube and start titration without the NJ test phase if deemed appropriate by the Investigator.

Percutaneous Endoscopic Gastrostomy with Jejunal Extension (PEG-J)

LCIG will be administered via the components of the percutaneous endoscopic gastrostomy – with jejunal extension (PEG-J) set. Only the PEG-J sets available through this clinical study should be used with LCIG.

A thorough evaluation of the subject's risk of undergoing the PEG-J procedure will be performed by the Investigator and study gastroenterologist proceduralist or surgeon as part of the verification of Inclusion/Exclusion criteria prior to Screen V2. Subjects deemed unsuitable for the PEG-J procedure will not be enrolled in the study.

The study gastroenterologist proceduralist, surgeon or qualified radiologist must take appropriate steps to evaluate and minimize the risk to subjects undergoing the PEG-J procedure including aftercare. Additional evaluations for safety, other than those required by the protocol, are permitted at the Investigator's or Study GIs discretion (i.e., additional lab tests).

Placement of the PEG-J will be performed by a qualified gastroenterologist proceduralist, surgeon or qualified radiologist experienced with the placement of PEG-J tubes. Each study site should have one study designated gastroenterologist proceduralist, surgeon, or qualified radiologist and one backup who has experience with and a thorough knowledge of endoscopy and PEG placement, aspects of PD and neurological patients, placement and maintenance of PEG-J tubes, the LCIG System and any related procedures. They must also participate in study staff guided training or equivalent.

The placement target for the end of the jejunal extension tubing is in the proximal small intestine past the ligament of Treitz. Study site personnel will be trained with regard to the proper care and maintenance of the LCIG Infusion System to ensure that high quality care is provided to each subject.

The use of prophylactic antibiotics is required prior to PEG-J procedure. At minimum, a single dose of a 1st or 3rd generation cephalosporin (or an antibiotic with similar coverage) must be administered approximately 30 minutes prior to the PEG-J procedure.

Following PEG-J placement and, at the discretion of the Investigator, the subject may begin initiation and titration of LCIG infusion. LCIG initiation and titration will be performed in the hospital but may be continued as an outpatient (e.g., at a study site, titration center) with appropriate medical supervision. The Sponsor will ensure the Investigator and site personnel are trained on LCIG initiation and titration.

The gastric port of the PEG-J should not be used for the delivery of nutrition and/or other medications unless judged medically necessary following consultation with the study designated physician. If determined medically necessary, it is imperative that nutrition and/or other medications are delivered only through the gastric port and not the jejunal port. The gastric port must be properly flushed and maintained as outlined in the provided aftercare procedure instructions for the PEG-J set.

Following the PEG-J placement procedure, aftercare of the PEG-J system will initially be performed by trained study staff. Instruction and confirmation that the subject and/or care-partner have a good understanding of proper stoma aftercare and check of the stoma is required before discharge. To ensure adequate adaptation of the stomach and abdominal walls and to reduce PEG-J infections, the aftercare procedure instructions provided by the Sponsor must be utilized. During aftercare procedures, it is very important not to turn, rotate or twist the jejunal extension tube.

The gastroenterologist proceduralist, surgeon, or qualified radiologist, or their designated qualified personnel will examine the subject's stoma site between Study Day 2 and Study

Day 7 after PEG-J placement, and will continue to follow the subject's progress as an outpatient. The gastroenterologist proceduralist/surgeon will continue to follow the subject's progress as an outpatient.

5.5.2 Identity of Investigational Product

The chemical nomenclature for levodopa is (-)-3-(3, 4-dihydroxyphenyl)-L-alanine. The chemical name for carbidopa is (-)-L-α-h-ydrazino-3, 4-dihydroxy-α-methylhydrocinnamic acid monohydrate. Levodopa-carbidopa intestinal gel for upper-intestinal infusion is a suspension of levodopa-carbidopa monohydrate (4:1) in an aqueous gel (carboxymethylcellulose).

5.5.2.1 Investigational Product and Supplies

Table 5. Study Drug

Study Drug	Route of Administration	Manufacturer
100 mL Levodopa (20 mg/mL)-carbidopa monohydrate (5 mg/mL) intestinal gel medication cassette reservoirs	upper-intestinal infusion	Fresenius Kabi for AbbVie

Devices are listed below but are not limited to them alone.

Table 6. Investigational Devices Provided for Delivery of Drug

Devices in LCIG System	
Description	**Manufacturer**
Pump CADD Legacy 1400	Smiths Medical
NJ Tube	AbbVie or Covidien
Safety Adapter	Vygon
Extension Tube FR	Vygon
PEG Tube	AbbVie
Intestinal Tube	AbbVie
Y-Adapter for PEG Tube	AbbVie
Click Adapter for PEG Tube	AbbVie

The Pump comes in a kit form that includes a holster, 2 batteries and an instruction booklet. Should the holster get damaged due to wear and tear, an additional pump bag and/or holster can be provided to the subject.

AbbVie will provide LCIG, devices and ancillaries to the site to initiate LCIG after NJ and/or PEG-J placement.

Any replacement LCIG pumps will be shipped to the Investigator allowing the Investigator to program and dispense the pump directly to the subject.

5.5.2.2 Packaging and Labeling

The medication will be packaged in accordance with the applicable local and federal regulations and Good Manufacturing Practices (GMP).

LCIG

Seven (7) medication cassette reservoirs of LCIG will be contained in an outer carton and this will comprise one kit. The medication cassette reservoirs of LCIG and the carton will be labeled with all information as required by local regulations. All labels must remain affixed to the primary and secondary packaging material.

5.5.2.3 Storage and Disposition of Study Drug

LCIG Storage

At the LCIG distribution depot, the cassettes with the LCIG suspension can be stored in the freezer (between –15°C and –25°C) for up to 2 years. After thawing, the LCIG suspension can be stored in a refrigerator (between 2°C and 8°C) for up to 15 weeks. Thawed LCIG suspension **should not** be re-frozen. The cassettes should be kept in the outer carton in order to protect from light. An LCIG cassette medication should be used **within 16 hours** after removal from the refrigerator. Once an LCIG cassette has been disconnected from the pump, it may not be reused at a later time.

All study site clinical drug supplies are to be stored in a secure, limited-access area in accordance with labeled storage conditions. The Investigator (or an authorized representative) will maintain accurate records of the disposition of clinical drug supplies received at the site. These records shall include the amounts of drug supplies and the dates on which drug supplies were received from the drug depot, dispensed to the subject (by the site), returned by the subject and returned to the study site (devices) (LCIG cassettes). If errors or damages in the clinical drug supply shipments occur, the Investigator and subsequently, the subject, will be instructed to contact the study site immediately.

5.5.3 Method of Assigning Subjects to Treatment Groups

Before the site is initiated, contact information and user guidelines for the IRT system will be provided to each site. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

At Screening during Visit 1, each subject will be assigned a unique 5-digit number by the IRT system. Following Visit 3, the site will contact the IRT to randomize the subject to OMT or LCIG. Subjects randomized to OMT will continue on their current anti-PD medication regimen for the duration of the study. For subjects randomized to LCIG, the site will obtain the study drug kit numbers to dispense at the designated Visits. Study drug must not be dispensed without contacting the IRT. Study drug may only be dispensed to subjects randomized to LCIG in the study through the IRT.

This is an open-label study and all eligible subjects will receive OMT or LCIG.

5.5.4 Selection and Timing of Dose for Each Subject

LCIG subject dosing will be individually optimized. Subject dosing will be titrated following either NJ placement or the PEG-J procedure. Dose adjustments can be made throughout the course of the study as clinically indicated. The LCIG infusion is expected to infuse over approximately 16 hours with a rate of infusion within the range of 1 to 10 mL/hour (20 to 200 mg of levodopa/hour) in most instances.

While the subject is titrated, the study staff should complete Dose Titration Diary hourly until the dose is optimized and then recording whenever the dosage is adjusted or the subject received extra or if required rescue doses.

5.5.5 Blinding

This is an open-label study. All eligible subjects will be randomized in a 1:1 ratio to receive OMT:LCIG.

Blinded centralized raters will be used to administer the NMSS and PDSS-2, the primary efficacy endpoints for this study, during Randomization at Visit 3 and Treatment Period visits. Randomization, V3 will serve as the baseline for clinical assessment. The scales will also be performed at Visits 6, 12, and 26. The scales are to be performed by a trained blinded central rater who will not have access to the results of other study assessments or medical records for the subject and who will not participate in the care or management of the subject. Each rating is based exclusively on an interview with the subject (and the subject's caregiver when available).

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense LCIG study drug only to subjects enrolled in the study and randomized to LCIG treatment in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol. The site will review LCIG cassette usage at drug resupply visits and assess compliance at each visit.

5.5.7 Drug Accountability

Initial study supplies and 6 weeks of LCIG cassettes will be supplied to the Investigator by the drug depot. It is at the discretion of AbbVie and/or the Investigator to discontinue subjects from the study who fail to take and/or return the appropriate amount of study drug.

Treatment regimen compliance will be also be assessed by the Subject Dosing Diary.

LCIG therapeutic systems are received intact and in the correct amounts. This will be documented by the Investigator signing and dating the Proof of Receipt (POR) after he/she receives LCIG from the depot for the initial supplies, and by signing the POR upon receipt of LCIG from the depot. A current (running) and accurate inventory will be kept by the Investigator or the designated representatives in the IRT system, and will include shipping invoices and the date on which study drug was dispensed to the subject. The IRT must be contacted when any subject discontinues the study. The IRT will maintain a current and accurate inventory of all LCIG supplies, accountability, reconciliation, and returns for each site. The investigational site and depot will also maintain current and accurate documentation of study drug details (i.e., kit number, number of used and unused cassettes) in the source document for each subject. Returned study drug cassettes will be retained by the depot until returned for destruction.

An overall accountability of LCIG will be performed and verified by the Sponsor and the depot throughout the study. All original LCIG cassettes (empty or containing unused LCIG) will be returned to the depot, according to instructions from AbbVie and according to local regulations. Labels must remain attached to the containers.

Non-investigational medicinal product (standard of care) (e.g., generic name or brand name) must be obtained commercially.

5.5.8 Device Accountability

All pumps dispensed and returned and all tubes placed and removed will be tracked in the IRT and EDC system on the appropriate eCRF. All devices must be accounted for throughout the study by the site. All pumps, tubes, and accessories dispensed and returned and all tubes placed and removed will be tracked in the IRT and EDC system on the appropriate eCRF. All devices must be accounted for throughout the study by the site.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This is an open label study and all subjects will receive OMT or LCIG in an open-label fashion.

An open-label study design is appropriate for the following reasons:

1. LCIG is an approved product with demonstrated efficacy
2. Advanced PD is an orphan populations with a limited patient population available for recruitment
3. An open-label design ensures that subjects randomized to optimized medical therapy do not have to undergo the invasive NJ and PEG-J procedure unnecessarily
4. NJ testing period is not possible in a blinded study
5. Per the Package Leaflet, Duodopa is initiated as monotherapy – tapering off of all other anti-PD medications besides levodopa at initiation would not be plausible in a blinded study
6. The majority of patients are on other anti-PD medications in addition to levodopa and those randomized to OMT, would not be able to be maintained on levodopa monotherapy for 28 days safely

As there are no approved medications which treat NMS as a whole, this optimized medical therapy population is considered appropriate as a comparison group.

5.6.2 Appropriateness of Measurements

The NMSS was developed to evaluate the severity of individual non-motor symptoms in a patient with Parkinson's disease and to monitor the effect of an intervention on non-motor symptoms.

The PDSS-2 was developed to assess the profile of nocturnal disturbances in PD patients.

The UPDRS and PDQ-8 are currently accepted and validated methods of evaluating subjects with PD. All safety assessments are standard measures used in pharmaceutical research.[48,61,62]

5.6.3 Suitability of Subject Population

Levodopa-responsive Parkinson's disease patients with severe motor fluctuations and hyperkinesia/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results are eligible to participate.[63]

5.6.4 Selection of Doses in the Study

Subject dosing is determined individually. Prior to subject enrollment, all anti-PD medications have been optimized and stabilized during the Screening Period. For subjects randomized to LCIG, the starting dose of the infusion after placement of the NJ and/or PEG-J tube will be based on the daily dose of the oral levodopa prior to or at the time of study entry. Subject dosing will be individually optimized.

The total dose/day of LCIG is composed of three individually adjusted doses: (i) the morning dose, (ii) the continuous maintenance dose and (iii) extra doses. The needs of individual subjects may vary depending on their particular condition and calculation of necessary dosing will be individualized based. The LCIG infusion is expected to infuse over approximately 16 hours each day with a rate of infusion within the range of 1 to 10 mL/hour (20 to 200 mg of levodopa/hour) in most instances. The maximum LCIG dose administered in this study should not exceed 200 mg of levodopa/hour for 26 weeks.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

- An active pharmacological agent
- Device component(s) (cassette, tubing, pump, connectors, etc.).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.6. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug or the study device components, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event. Also, fluctuating PD symptoms during titration should not be considered an adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

A hospitalization prior to the first screening visit (SV1), allowing the subject to arrive at the clinic in the "Off" state, will not be regarded as an SAE. If not associated with worsening of Parkinson's disease symptoms, a hospitalization for dose adjustments of LCIG will not be regarded as a SAE. A hospitalization because of a Product Complaint, such as a device dislocation without AE (i.e., without health impairment) will not be regarded as an SAE.

Hospitalization for scheduled tube placement/replacement should not be considered an SAE.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.1.3 Adverse Events of Special Interest

Adverse events of special interest (AESI) are:

- Gastrointestinal and gastrointestinal procedure related events
- Polyneuropathy
- Weight loss

For AESIs, serious and nonserious, meeting pre-defined criteria, specific questionnaires will be used to standardize the collection of follow-up information. The AESI questionnaires are either sent to the site after Sponsor review or issued within the Electronic Data Capture (EDC) system once applicable. The Investigator will email the completed questionnaires to the AbbVie Neuroscience Safety Management Team or enter the information into the EDC system once applicable. If a subject develops signs and symptoms of polyneuropathy a standard panel of examinations will be suggested to the Investigator and certain laboratory tests (specified in questionnaire) will be required by the Sponsor. The Investigator may perform additional other assessments that are deemed appropriate for further evaluation of polyneuropathy symptoms based on the presentation of the individual subject. If weight loss is considered to be clinically significant, preventative measures will be taken to counteract weight loss.

For all AESIs, if the event meets seriousness criteria, the Investigator will report the event to the Sponsor within 24 hours of the site being made aware of the event according to Section 6.1.5.

Neuroscience Clinical Safety Management Team
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064-6075

Telephone Contact Information:
Office: [redacted]
Fax:
Email:

6.1.2 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.1.3 Relationship to Study Drug

For the assessment of drug event relationship, LCIG should be considered a therapeutic system consisting of drug, devices and placement procedure. Causality assessments are always made over the system as a whole.

For the assessment of drug event relationship, those randomized to OMT should evaluate relatedness to any of the subject's anti-PD medication.

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, if the Investigator has not reported causality or deemed it not assessable, AbbVie will consider the event associated.

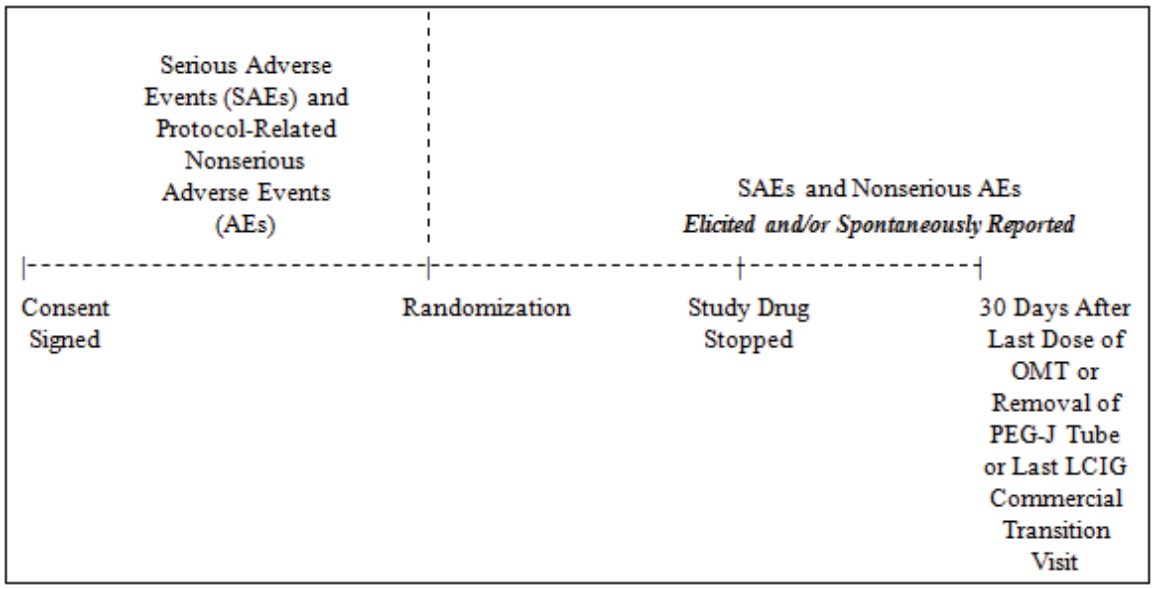
If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the Investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

Protocol-related nonserious adverse events that occur after signing the informed consent, prior to the start of study drug administration, will be collected. All adverse events reported from the time of randomization until 30 days following last OMT dose, last study visit, discontinuation of study drug administration, removal of the PEG-J tube or Last LCIG Commercial Transition Visit have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol related non serious adverse events will be collected from the time the subject signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) RAVE® system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

FAX to:	[redacted]
Email:	

For safety concerns, contact the Neuroscience Safety Team at:

Neuroscience Clinical Safety Management Team
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064-6075

Telephone Contact Information:
Office:
Fax:
Email: [redacted]

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:

[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Phone:
Mobile:
Fax:
Email: [redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: [redacted]

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an adverse event. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse

event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the eCRF or Product Complaint form if eCRF is unavailable. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (cassette, pump, tubing, etc.). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the

protocol is deemed necessary for an individual subject, the Investigator must contact the following AbbVie Clinical Monitors:

Primary Contact:	Alternate Contact:
[redacted]	[redacted]
1 North Waukegan Road North Chicago, IL 60064	1 North Waukegan Road North Chicago, IL 60064
Office: [redacted] Fax:	Office: [redacted] Fax:

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation. Protocol deviations affecting subject safety or data robustness should be reported in EU Member States where applicable.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 Analysis Datasets

Intent-to-Treat Dataset

Unless specified otherwise, the efficacy analyses will be performed on the intent-to-treat dataset which 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. For assessments of efficacy, the treatment period will begin the day after randomization for subjects randomized to optimized medical treatment, and the day of first LCIG infusion following PEG-J placement for subjects randomized to LCIG

treatment. The treatment period will end on the day of the final visit for subjects randomized to OMT, and on the last day of LCIG study drug infusion for subjects randomized to LCIG treatment.

The last assessment prior to randomization will be considered baseline and the last assessment that is no more than 2 days after the end of the treatment period will be considered the final evaluation.

Safety Dataset

The safety analyses will be performed on the safety dataset which 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. For assessments of safety, the treatment period will begin the day after randomization for subjects randomized to optimized medical treatment, and the day of NJ placement (or PEG-J placement if no NJ) for subjects randomized to LCIG. The treatment period will end on the day of the final visit for subjects randomized to optimized treatment, and on the last day of LCIG infusion or device removal (whichever is later) in the study for subjects randomized to LCIG. The last assessment prior to randomization will be considered baseline and the last assessment that is no more than 2 days after the end of the treatment period will be considered the final evaluation.

8.1.2 Demographic, Other Baseline Characteristics, Subject Disposition, and Concomitant Medication

Demographic and Other Baseline Characteristics

All demographic variables will be summarized for the safety dataset unless otherwise specified.

For continuous demographic variables, including age, weight, height and body mass index (BMI), descriptive statistics (number of subjects with non-missing data, mean, standard deviation, median, minimum, and maximum) will be provided for each treatment group,

and for both treatment groups combined. Overall treatment group differences will be tested using one-way ANOVA.

For categorical demographic variables, including gender and race, the number and percentage of subjects in each category will be provided for each treatment group, and for all treatment groups combined. Overall treatment group comparability will be tested using Fisher's exact test.

For the ITT data set, baseline NMSS total score and PDSS-2 total score will be summarized. One-way ANOVA will be used to assess the comparability of treatment groups.

Medical History

Medical history data will be summarized for the safety dataset using body systems and conditions/diagnoses as captured on the eCRF. Parkinson's disease history will also be summarized.

Subject Disposition

The number and percentage of subjects contributed by each country and site will be summarized for each treatment group and for all treatment groups combined for the safety dataset.

The number and percentage of subjects who prematurely discontinue study will be summarized by treatment group and overall for the safety dataset for the primary reason as well as for all reasons collected. In the summary, the number and percentage of subjects who discontinue due to any reason as well as due to each specific primary reason will be presented. Subjects may report multiple reasons for prematurely discontinuing study, but the primary reason for discontinuation will be indicated in the eCRF and used to infer treatment group difference in subject's disposition. The treatment group differences in the percentage of subjects who discontinued for any reason as well as for each specific reason will be assessed using Fisher's exact test.

Previous and Concomitant Medications

Previous and concomitant medications will be coded by the most recent World Health Organization (WHO) Drug dictionary. Previous and concomitant medications will be summarized by treatment group for the safety dataset. No statistical testing will be performed.

8.1.3 Efficacy Analysis

All efficacy analyses will be performed on the ITT dataset unless otherwise specified. Comparisons between OMT and LCIG groups will be performed with two-sided tests at the significance level of 0.050.

Unless otherwise specified, the "baseline" for efficacy variables is defined as the last assessment taken on or before the day of randomization, and the "final observation" refers to the last non-missing observation in the Treatment Period (including evaluations conducted within 2 days after the last dose of study drug for subjects randomized to LCIG).

8.1.3.1 Primary Efficacy Analysis

There are 2 alternative primary efficacy variables, change from baseline to Week 26 for NMSS total score and change from baseline to Week 26 for PDSS-2 total score. Either variable considered statistically significant after multiplicity adjustment is sufficient to declare success of the study.

NMSS Total Score

The NMSS was developed to assess non-motor symptoms in PD. It is obtained through interview and rated by health professionals. It contains 30 questions grouped into 9 domains: cardiovascular (2 items), sleep/fatigue (4 items), mood/cognition (6 items), perceptual problems/hallucinations (3 items), attention/memory (3 items), gastrointestinal tract (3 items), urinary (3 items), sexual function (2 items), and miscellaneous (4 items). 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.

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 RLS, 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 domain as well as a total score.

Primary Analysis Model and Multiplicity Adjustment

The primary efficacy analysis model is a likelihood-based mixed-effects model repeated measures (MMRM) analysis of the change from baseline for each post-baseline observation using all observed data. The model will include fixed, categorical effects for treatment, country, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline score and the baseline score-by-visit interaction. The primary comparison will be the contrast between LCIG and optimized oral treatment at the Week 26 Visit.

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.

8.1.3.2 Secondary Efficacy Analysis

Secondary Analysis of the Primary Efficacy Variables

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 (BOCF) will be applied to subjects who do not have post-randomization assessment of NMSS or PDSS-2.

Key Secondary Efficacy Variables

Key secondary endpoints will consist of the following validated scales:

- UPDRS Part II score
- CGI-C
- PDQ-8 summary index

The 3 key secondary variables will be analyzed with the same MMRM model as the primary analysis. For the analysis on CGI-C, the scores collected at the visits will be the dependent variable.

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.

Other Secondary Efficacy Variables

Other secondary endpoints include:

- 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
- King's PD Pain Scale total and domain scores

These variables will be analyzed with the same MMRM model as the primary analysis. For the analysis on PGIC, the scores collected at the visits will be the dependent variable.

8.1.4 Safety Analysis

All safety analysis will be performed on the safety dataset unless otherwise specified. Comparisons between LCIG and OMT groups will be performed with two-sided test at the significance level of 0.05.

Unless otherwise specified, the treatment group differences in continuous safety variables (e.g., change from baseline to final observation on laboratory tests) 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.

8.1.4.1 OMT and LCIG Study Drug Exposure

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

8.1.4.2 Adverse Events

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 MedDRA 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.

Each adverse event will be categorized by severity (mild, moderate, severe) and by relationship to study treatment (reasonable possibility, or no reasonable possibility). Detailed search criteria for adverse events of special interest (AESIs) will be defined in a SAP prior to database lock.

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

- For OMT group: any adverse event that begins or worsens in severity the day after randomization and within 30 days following the last visit.
- For the LCIG group: any adverse event that begins or worsens in severity from the day of the initial device placement (NJ or PEG-J) through Week 26 Visit for those subjects continuing to LCIG commercial treatment, or through 30 days after final device removal for those subjects not continuing LCIG commercial treatment.

A summary of the number and percentage of subjects will be prepared for the following:

- TEAEs
- TE Serious AEs (including deaths)
- TEAEs leading to premature discontinuation of treatment
- TEAEs by maximum relationship to study drug
- TEAEs by maximum severity
- Treatment-emergent AESIs

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.

8.1.4.3 Clinical Laboratory Variables

For each continuous clinical laboratory variable, analyses of the mean change from baseline to each scheduled visit and to the minimum, maximum and final value will be presented by treatment group.

Clinical 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 clinical laboratory variable with a reference range, shift tables will be prepared for reference range category shifts from baseline to minimum, maximum and final value.

Criteria for potentially clinically significant (PCS) values will be pre-specified for selected laboratory variables in an SAP prior to database lock. For each variable, a summary of the number and percentage of subjects who have at least one post-baseline observation that meets the PCS criteria and is more extreme than their baseline value will be provided.

8.1.4.4 Vital Sign Variables and Weight

For each vital sign and weight variable, analyses of the mean change from baseline to each scheduled visit and to the final value will be presented by treatment group. For this analysis, the average of multiple observations on the same day will be calculated and treated as the observation for the day. For LCIG subjects' visits with multiple observations scheduled on the same day, the post-infusion change from the day's pre-infusion baseline will be summarized for each scheduled time point.

Criteria for potentially clinically significant (PCS) values will be pre-specified for selected vital sign and weight variables prior to database lock. For each variable, a summary of the number and percentage of subjects who have at least one post-baseline observation that meets the PCS criteria and is more extreme than their baseline value will be provided.

8.1.4.5 ECG Variables

For each ECG variable, analyses of the mean change from baseline to each scheduled visit and to the final value will be presented by treatment group. For this analysis, the average of multiple observations on the same day will be calculated and treated as the observation for the day. For LCIG subjects' visits with multiple observations scheduled on the same day, the post-infusion change from the day's pre-infusion baseline will be summarized for each scheduled time point.

Criteria for potentially clinically significant (PCS) values will be pre-specified for selected ECG variables prior to database lock. For each variable, a summary of the number and percentage of subjects who have at least one post-baseline observation that meets the PCS criteria and is more extreme than their baseline value will be provided.

8.1.4.6 Additional Safety Variables

The following additional summaries of safety measures will be prepared.

- The responses to the MIDI
- The responses to the C-SSRS
- The responses to the Sleep Attacks Questionnaire
- Percent of subjects who are cognitive impaired (MoCA score ≤ 26)

8.1.5 Interim Analysis

No interim analysis is planned for this study.

8.2 Determination of 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 results 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.

8.3 Randomization Methods

Approximately 88 subjects will be enrolled into the study and randomized in a 1:1 ratio to either optimized medical treatment or LCIG at the end of Visit 3. Subject randomization will be stratified by country.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP and all other applicable regulatory requirements.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

9.3.1 Informed Consent Form and Explanatory Material

The Principal Investigator will prepare the site-specific consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the Sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the Sponsor. Approval of the IRB/IEC will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

When important new information related to the subject's consent becomes available, the Principal Investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB/IEC prior to use in the study. The Investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The Investigator shall also provide a further explanation using

the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

If a subject has a Legally Authorized Representative (LAR), a revised informed consent shall be obtained from the LAR for subject's continued participation in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

Data from the NMSS and the PDSS-2 will be entered directly into the Rater Station by the Blinded Central Rater, and this will be the source for these data. The Rater Station Client and Rater Station are provided by the vendor Bracket, Wayne, PA. Bracket's databases and web portal are 21 CFR Part 11 compliant. Rater Station client is software that is loaded onto a laptop device and Rater Station web is the secure central database to which all data from the client is uploaded. Rater Station uses AES (Advanced Encryption Standard) encryption implementing a 256-bit encryption key.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

12.1 Subject Privacy

All information concerning LCIG and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of LCIG. This information may be disclosed as deemed necessary by AbbVie to other Clinical Investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for trial-related monitoring, audits, IEC/IRB review and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for Levodopa-Carbidopa Intestinal Gel and for subjects randomized to OMT will review the product label for the subjects' respective OMT.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	An Open-label, Randomized 26-Week Study Comparing Levodopa-Carbidopa **IN**te**S**t**I**nal **G**el (LCIG) T**H**erapy to Optimized Medical **T**reatment (OMT) on Non-Motor **S**ymptoms (NMS) in Subjects with Advanced Parkinson's Disease – INSIGHTS Study
Protocol Date:	31 May 2017

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Clinical
		Clinical
		Clinical
		CDSM
		Statistics

Appendix C. UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria

Step 1. Diagnosis of Parkinsonian Syndrome

1. Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions).
2. And at least one of the following:
   a. muscular rigidity
   b. 4 – 6 Hz rest tremor
   c. postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Step 2. Exclusion Criteria for Parkinson's Disease

1. history of repeated strokes with stepwise progression of Parkinsonian features
2. history of repeated head injury
3. history of definite encephalitis
4. oculogyric crises+
5. neuroleptic treatment at onset of symptoms
6. sustained remission
7. more than 1 affected relative*
8. strictly unilateral features after three years
9. supranuclear gaze palsy
10. cerebellar signs
11. early severe autonomic involvement
12. early severe dementia with disturbances of memory, language and praxis
13. Babinski's sign

14. presence of a cerebral tumor or communicating hydrocephalus on CT scan
15. negative response to large doses of levodopa (if malabsorption excluded)
16. MPTP exposure

Step 3. Supportive Prospective Positive Criteria for Parkinson's Disease
(Three or more required for diagnosis of definite Parkinson's disease)

1. unilateral onset
2. rest tremor present
3. progressive disorder
4. persistent asymmetry affecting the side of onset most
5. excellent response (70 – 100%) to levodopa
6. severe levodopa-induced chorea
7. levodopa response for ≥ 5 years
8. clinical course of ≥ 10 years

* Refers only to 1st and 2nd degree relatives.
\+ If present at the time of PD diagnosis.

Appendix D. Potentially Clinically Significant Laboratory Values for Study M12-927*

CTCAE v4.0 Term	PCS Value/Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hematology						
Activated partial thromboplastin time prolonged (aPTT)	1	**> ULN**	> ULN – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN; hemorrhage	--
Hemoglobin decreased	2	**< 10.0 g/dL**	< LLN – 10.0 g/dL	< 10.0 – 8.0 g/dL	< 8.0 g/dL	Life-threatening consequences; urgent intervention indicated
		< 6.2 mmol/L	< LLN – 6.2 mmol/L	< 6.2 – 4.9 mmol/L	< 4.9 mmol/L	
		< 100 g/L	< LLN – 100 g/L	< 100 – 80g/L	< 80 g/L; transfusion indicated	
Hemoglobin increased	3	**> 4 gm/dL above ULN**	Increase in > 0 – 2 gm/dL above ULN **or** above baseline if baseline is above ULN	Increase in > 2 – 4 gm/dL above ULN **or** above baseline if baseline is above ULN	Increase in > 4 gm/dL above ULN **or** above baseline if baseline is above ULN	--
INR increased	1	**> ULN**	> 1 – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN	--
			> 1 – 1.5 times above baseline if on anticoagulation	> 1.5 – 2.5 times above baseline if on anticoagulation	> 2.5 times above baseline if on anticoagulation	
Leukocytosis (WBC increased)	3	**> 100,000/mm^3**	--	--	> 100,000/mm^3	Clinical manifestations of leucostasis; urgent intervention indicated
Lymphocyte count decreased	3	**< 500/mm^3**	< LLN – 800/mm^3	< 800 – 500/mm^3	< 500 – 200/mm^3	< 200/mm^3
		< 0.5 × 10^9/L	< LLN – 0.8 × 10^9/L	< 0.8 – 0.5 × 10^9/L	< 0.5 – 0.2 × 10^9/L	< 0.2 × 10^9/L
Lymphocyte count increased	3	**> 20,000/mm^3**	--	> 4000 – 20,000/mm^3	> 20,000/mm^3	--

CTCAE v4.0 Term	PCS Value/Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hematology (continued)						
Neutrophil count decreased	3	**< 1000/mm^3**	< LLN – 1500/mm^3	< 1500 – 1000/mm^3	< 1000 – 500/mm^3	< 500/mm^3
		< 1.0 × 10^9/L	< LLN – 1.5 × 10^9/L	< 1.5 – 1.0 × 10^9/L	< 1.0 – 0.5 × 10^9/L	< 0.5 × 10^9/L
Platelet count decreased	2	**< 75,000/mm^3**	< LLN – 75,000/mm^3	< 75,000 – 50,000/mm^3	< 50,000 – 25,000/mm^3	< 25,000/mm^3
		< 75.0 × 10^9/L	< LLN – 75.0 × 10^9/L	< 75.0 – 50.0 × 10^9/L	< 50.0 – 25.0 × 10^9/L	< 25.0 × 10^9/L
White blood cell decreased	3	**< 2000/mm^3**	< LLN – 3000/mm^3	< 3000 – 2000/mm^3	< 2000 – 1000/mm^3	< 1000/mm^3
		< 2.0 × 10^9/L	< LLN – 3.0 × 10^9/L	< 3.0 – 2.0 × 10^9/L	< 2.0 – 1.0 × 10^9/L	< 1.0 × 10^9/L
Chemistry						
Blood bilirubin increased	2	**> 1.5 × ULN**	> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 10.0 × ULN	> 10.0 × ULN
Cholesterol high	4	**> 500 mg/dL**	> ULN – 300 mg/dL	> 300 – 400 mg/dL	> 400 – 500 mg/dL	> 500 mg/dL
		> 12.92 mmol/L	> ULN – 7.75 mmol/L	> 7.75 – 10.34 mmol/L	> 10.34 – 12.92 mmol/L	> 12.92 mmol/L
Creatinine increased	2	**> 1.5 × ULN**	> 1 – 1.5 × baseline	> 1.5 – 3.0 × baseline	> 3.0 baseline	> 6.0 × ULN
			> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 6.0 × ULN	
GGT increased	2	**> 2.5 × ULN**	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
		Corrected Serum Calcium of:				
Hypercalcemia	3	**> 12.5 mg/dL**	> ULN – 11.5 mg/dL	> 11.5 – 12.5 mg/dL	> 12.5 – 13.5 mg/dL	> 13.5 mg/dL
		> 3.1 mmol/L	> ULN – 2.9 mmol/L	> 2.9 – 3.1 mmol/L	> 3.1 – 3.4 mmol/L	> 3.4 mmol/L
		Ionized Calcium				
		> 1.6 mmol/L	> ULN – 1.5 mmol/L	> 1.5 – 1.6 mmol/L; symptomatic	> 1.6 – 1.8 mmol/L; hospitalization indicated	> 1.8 mmol/L; life-threatening consequences

CTCAE v4.0 Term	PCS Value/Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry (continued)						
			Fasting Glucose Value			
Hyperglycemia	3	**> 250 mg/dL**	> ULN – 160 mg/dL	> 160 – 250 mg/dL	> 250 – 500 mg/dL	> 500 mg/dL
		> 13.9 mmol/L	> ULN – 8.9 mmol/L	> 8.9 – 13.9 mmol/L	> 13.9 – 27.8 mmol/L; hospitalization indicated	> 27.8 mmol/L; life-threatening consequences
Hyperkalemia	3	**> 6.0 mmol/L**	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L; hospitalization indicated	> 7.0 mmol/L; life-threatening consequences
Hypernatremia	3	**> 155 mmol/L**	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L; hospitalization indicated	> 160 mmol/L; life-threatening consequences
Hypertriglyceridemia	3	**> 500 mg/dL mg/dL**	150 – 300 mg/dL	> 300 – 500 mg/dL	> 500 – 1000 mg/dL	> 1000 mg/dL
		> 5.7 mmol/L	1.71 – 3.42 mmol/L	> 3.42 – 5.7 mmol/L	> 5.7 – 11.4 mmol/L	> 11.4 mmol/L; life-threatening consequences
Hyperuricemia (Uric Acid Increased)	4	**> 10 mg/dL**	> ULN – 10 mg/dL (0.59 mmol/L) without physiologic consequences	--	> ULN – 10 mg/dL (0.59 mmol/L) with physiologic consequences	> 10 mg/dL
		> 0.59 mmol/L				> 0.59 mmol/L; life-threatening consequences

CTCAE v4.0 Term	PCS Value/Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry (continued)						
Hypoalbuminemia	3	**< 2 g/dL**	< LLN – 3 g/dL	< 3 – 2 g/dL	< 2 g/dL	Life-threatening consequences; urgent intervention indicated
		< 20 g/L	< LLN – 30 g/L	< 30 – 20 g/L	< 20 g/L	
		Corrected Serum Calcium				
Hypocalcemia	3	**< 7.0 mg/dL**	< LLN – 8.0 mg/dL	< 8.0 – 7.0 mg/dL	< 7.0 – 6.0 mg/dL	< 6.0 mg/dL
		< 1.75 mmol/L	< LLN – 2.0 mmol/L	< 2.0 – 1.75 mmol/L	< 1.75 – 1.5 mmol/L	< 1.5 mmol/L
		Ionized Calcium				
		< 0.9 mmol/L	< LLN – 1.0 mmol/L	< 1.0 – 0.9 mmol/L; symptomatic	< 0.9 – 0.8 mmol/L; hospitalization indicated	< 0.8 mmol/L; life-threatening consequences
Hypoglycemia	3	**< 40 mg/dL**	< LLN – 55 mg/dL	< 55 – 40 mg/dL	< 40 – 30 mg/dL	< 30 mg/dL
		< 2.2 mmol/L	< LLN – 3.0 mmol/L	< 3.0 – 2.2 mmol/L	< 2.2 – 1.7 mmol/L	< 1.7 mmol/L; life-threatening consequences; seizures
Hypokalemia	3	**< 3.0 mmol/L**	< LLN – 3.0 mmol/L	< LLN – 3.0 mmol/L; symptomatic; intervention indicated	< 3.0 – 2.5 mmol/L; hospitalization indicated	< 2.5 mmol/L; life-threatening consequences
Hyponatremia	3	**< 130 mmol/L**	< LLN – 130 mmol/L	--	< 130 – 120 mmol/L	< 120 mmol/L; life-threatening consequences

CTCAE v4.0 Term	PCS Value/Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry (continued)						
Hypophosphatemia	3	**< 2.0 mg/dL**	< LLN – 2.5 mg/dL	< 2.5 – 2.0 mg/dL	< 2.0 – 1.0 mg/dL	< 1.0 mg/dL
		< 0.6 mmol/L	< LLN – 0.8 mmol/L	< 0.8 – 0.6 mmol/L	< 0.6 – 0.3 mmol/L	< 0.3 mmol/L; life-threatening consequences
Enzymes						
Alanine aminotransferase (ALT) increased	2	**> 3 × ULN**	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
Alkaline phosphatase increased	2	**> 2.5 × ULN**	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
Aspartate aminotransferase (AST) increased	2	**> 3 × ULN**	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
CPK increased	3	**> 5 × ULN**	> ULN – 2.5 × ULN	> 2.5 × ULN – 5 × ULN	> 5 × ULN – 10 × ULN	> 10 × ULN

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

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

Appendix E. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.0 Title Page
"Sponsor/Emergency Contact:," building number previously read:

[redacted]

Has been changed to read:

[redacted]

Section 1.2 Synopsis
Subsection Methodology:
Heading "LCIG Group:"
First paragraph, first sentence previously read:

In accordance with the LCIG approved Product Label for countries participating in the study, those subjects randomized to LCIG must discontinue all other anti-PD medications (e.g., dopamine agonists, COMT-inhibitors, amantadine, MAO-B inhibitors, anti-cholinergics, and subcutaneous apomorphine etc.) prior to LCIG initiation on Day 1 (V4); these medications should be tapered off according to their individual package insert and at the discretion of the Investigator.

Has been changed to read:

In accordance with the LCIG approved Product Label for countries participating in the study, those subjects randomized to LCIG must discontinue all other anti-PD medications (e.g., dopamine agonists, COMT-inhibitors, amantadine, MAO-B inhibitors, anti-cholinergics, and subcutaneous apomorphine etc.) prior to LCIG initiation on Day 1 (V4); these medications should be tapered off according to the prescribing information and the discretion of the Investigator.

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Add: "RSI" and "SOP"

RSI	Reference Standard Information
SOP	standard operating procedure

Section 3.2 Benefits and Risks
Subsection Risks
First paragraph, last sentence previously read:

These and additional information on risks are available in the SmPC or Product Monograph.[42]

Has been changed to read:

These and additional information on risks are available in the Investigator's Brochure.[42]

Section 5.1 Overall Study Design and Plan: Description
First paragraph, last sentence previously read:

This study will be conducted at approximately 40 – 50 sites that specialize in movement disorders in approximately 10 countries where LCIG is available commercially.

Has been changed to read:

This study will be conducted at approximately 40 – 50 sites that specialize in movement disorders in approximately 10 countries.

Section 5.1.2.2 LCIG Treatment Group
Subsection Tapering of Anti-PD Medications Other Than Levodopa
First sentence previously read:

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 in accordance with individual SmPCs at the discretion of the Investigator.

Has been changed to read:

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 according to the prescribing information and the discretion of the Investigator.

Section 5.2.3.2 Concomitant Therapy
Subsection General Requirements
Heading "Randomization to End of Treatment Period:"
Last bullet, second sentence previously read:

Time of inverse titration should be done following the individual medications' SmPC and at the Investigator's discretion, but should not exceed 14 days after randomization.

Has been changed to read:

Time of inverse titration should be done following the prescribing information and the Investigator's discretion, but should not exceed 14 days after randomization.

Section 5.6.1 Discussion of Study Design and Choice of Control Groups
Item 5 previously read:

Per the SmPC, Duodopa is initiated as monotherapy – tapering off of all other anti-PD medications besides levodopa at initiation would not be plausible in a blinded study

Has been changed to read:

Per the Package Leaflet, Duodopa is initiated as monotherapy – tapering off of all other anti-PD medications besides levodopa at initiation would not be plausible in a blinded study

Section 6.1.1.3 Adverse Events of Special Interest
"Neuroscience Clinical Safety Management Team"
"Bldg." previously read:

[redacted]

Has been changed to read:

[redacted]

Section 6.1.3 Relationship to Study Drug
Delete: second paragraph

For a randomized study with an OMT arm:

Section 6.1.5 Adverse Event Reporting
"Neuroscience Clinical Safety Management Team"
"Bldg." previously read:

[redacted]

Has been changed to read:

[redacted]

Section 6.1.5 Adverse Event Reporting
"Primary Therapeutic Area Medical Director"
"Bldg." previously read:

[redacted]

Has been changed to read:

[redacted]

Section 6.1.5 Adverse Event Reporting
Last paragraph
Delete: second sentence

The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

Section 6.1.5 Adverse Event Reporting
Last paragraph, last sentence previously read:

The reference document used for SUSAR reporting in the EU countries will be the most current version of the Summary of Product Characteristics (SmPC).

Has been changed to read:

The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

Section 14.0 Investigator's Agreement
Item 1 previously read:

I have received and reviewed the country specific approved product label for Levodopa-Carbidopa Intestinal Gel and for subjects randomized to OMT will review the product label for the subjects' respective OMT.

Has been changed to read:

I have received and reviewed the Investigator's Brochure for Levodopa-Carbidopa Intestinal Gel and for subjects randomized to OMT will review the product label for the subjects' respective OMT.

Section 15.0 Reference List
Reference 42 previously read:

AbbVie. Levodopa-Carbidopa Investigator's Brochure Edition 7. 14 July 2011.

Has been changed to read:

AbbVie. Levodopa-Carbidopa Investigator's Brochure Edition 12. 07 April 2017.

Appendix B. List of Protocol Signatories

Previously read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Clinical
		Clinical
		GDSM
		Statistics

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Clinical
		Clinical
		Clinical
		CDSM
		Statistics