Carbidopa Levodopa Enteral Suspension

M15-535 Protocol Amendment 1 EudraCT 2016-001403-23

1.0 **Title Page**

Clinical Study Protocol M15-535

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

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

Incorporating Amendment 1

AbbVie Investigational

Levodopa-Carbidopa Intestinal Gel (LCIG)/Carbidopa Levodopa Enteral

Product:

Suspension (CLES)

Date: 26 May 2016

Development Phase: 3b

Study Design: A Phase 3b, open-label, multicenter, 12 week study comparing LCIG/CLES

to Optimized Medical Treatment (OMT) on dyskinesia associated with

advanced Parkinson's disease.

EudraCT Number: 2016-001403-23

Investigators: Investigators information on file at AbbVie

Sponsor: AbbVie



Sponsor/Emergency Contact:

MD AbbVie 1 North Waukegan Road North Chicago, IL 60064-6145 Phone: Mobile: Fax:

The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.



1.1 **Protocol Amendment: Summary of Changes**

Previous Protocol Versions

Protocol	Date
Original	03 May 2016

The purpose of this amendment is to:

• Change the study duration from 26 weeks to 12 weeks.



• Remove the exclusion criterion for excluding patients previously treated with continuous subcutaneous apomorphine infusion.



• Add language for additional analysis to provide evidence on the construct validity of the UDysRS.



1.2 **Synopsis**

AbbVie Inc.	Protocol Number: M15-535	
Name of Study Drug: Levodopa-Carbidopa Intestinal Gel (Outside United States)/Carbidopa- Levodopa Enteral Suspension (United States)	Phase of Development: 3b	
Name of Active Ingredient:	Date of Protocol Synopsis: 26 May 2016	
Levodopa-Carbidopa Intestinal Gel (OUS)/ Carbidopa-Levodopa Enteral Suspension (US)		

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

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

Rationale and Background:

The rationale to conduct this open-label, interventional study is to investigate the comparative effectiveness of Levodopa-Carbidopa Intestinal Gel (LCIG)/Carbidopa-Levodopa Enteral Suspension (CLES) versus optimized medical treatment on the duration and severity of dyskinesia. LCIG is marketed as Duopa in the US and as Duodopa in most other countries. Optimized medical treatment (OMT) 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.

Dyskinesias are among the most troublesome symptoms of Advanced Parkinson's Disease (APD): Approximately 50% of patients present with Dyskinesia 4 – 5 years after initiation of treatment; approximately 90% of patients after 9 years.

Peak-dose dyskinesia are linked to peak plasma levels of levodopa, while the less frequent and phenomenologically different biphasic dyskinesia occur during switch from low to high plasma levels and vice versa. Moderate to severe dyskinesia can be painful and disabling, compromising quality of life. Therefore dyskinesia is one of the main reasons for recommending invasive treatments in APD patients.

Levodopa-Carbidopa Intestinal Gel (LCIG)/Carbidopa-Levodopa Enteral Suspension (CLES) is a stable 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. In contrast to oral therapy, LCIG/CLES provides continuous dopaminergic delivery which is believed to stimulate the dopaminergic receptors in the brain within the individual's therapeutic window resulting in decreased motor fluctuations and dyskinesia. Over the past years many clinical investigations have been performed and published demonstrating that functional ON time during the day is increased, OFF time and ON time with disabling dyskinesia are reduced with a marked effect on quality of life (Olanow et al 2014, Slevin et al 2015, Fernandez et al 2015).



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Rationale and Background (Continued):

Interventional studies (Studies S187-3-001/S187-3-002, S187-3-004, Antonini et al 2013) and observational studies (GLORIA, Poewe et al 2015) suggests that LCIG/CLES may decrease duration and severity of dyskinesia in studies of up to 2 years in duration. This will be the first large interventional controlled study of LCIG for Advanced Parkinson's Disease patients specifically investigating the effectiveness on dyskinesia.

* Duodopa/Duopa will be referred to as Levodopa-Carbidopa Intestinal Gel (LCIG) throughout this protocol. In the US, the product name is Duopa (Carbidopa Levodopa Enteral Suspension (CLES)).

Objectives:

Primary: The primary objective of this interventional study is to examine the effect of LCIG treatment relative to that of optimized medical treatment (OMT) on dyskinesia as measured by the change from baseline to Week 12 in the Unified Dyskinesia Rating Scale (UDysRS) Total Score.

Secondary: To assess the effect of LCIG treatment relative to that of OMT on dyskinesia as measured by PD Diaries, motor and non-motor symptoms, motor complications, safety, tolerability and healthrelated outcome measures.

Motor Symptoms/Motor Complications and Non-Motor Symptoms Will Be Measured by:

- Unified Dyskinesia Rating Scale (UDysRS)
- Parkinson's Disease Diary (PD Diary) normalized average daily hours of OFF time, ON time with troublesome dyskinesia, ON time without troublesome dyskinesia
- Unified Parkinson's Disease Rating Scale (UPDRS) Part III
- Modified Abnormal Involuntary Movement Scale (mAIMS)

Health Related Outcomes Will Be Measured by:

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

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)

Investigators: Multi-center

Study Sites: This study will be conducted at approximately 22 – 28 sites that specialize in movement disorders in approximately 6 – 8 countries (WEC, EEMEA, USA) where LCIG is commercially available.

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Study Population: Levodopa-responsive advanced 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: A total of approximately 60 subjects with advanced PD will be enrolled (approximately 30 per treatment group).

Methodology:

This is an open-label, randomized multicenter 12 week study comparing LCIG treatment to 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 treatment group, except for visits related to NJ/PEG procedures, titration of LCIG and follow-up period.

Patients, who in collaboration with their physicians at participating centers, have been found eligible for inclusion into this study in a screening visit will be enrolled into this study.

The treatment goal is to achieve 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.

Final Visit Day 1 **OMT Group** OMT Screening **LCIG Treatment** Transition anti-PD ≤ 14 days Follow up* Post-PEG Period Meds NJ PEG-J Commercial (≤14 Titration Titration (Optional) 30-60 Days Treatment period up to 12 weeks V4 V1 V2 (Visit) V7 Day 1 Baseline/ W-1 (Time) W13 W18 W24 W-4/-8 W4 W8 W12 Randomization LCIG Group

Figure 1: Study Design Schematic

Follow up period only applicable to LCIG treatment arm subjects that have discontinued the study for any reason. 7 days after the PEG-J removal, a follow-up visit (V9) will be conducted.



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. Results from lab samples collected at V3 will only be used as baseline level and are not intended to determine eligibility for randomization. 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 dyskinesia. All anti-PD medications, including those used to treat dyskinesia, must be stable with no adjustments to the frequency of administration, dose of administration or total daily dose for a minimum of 30 consecutive days before the randomization visit. During the Screening Period, no study drug (LCIG) will be administered. Visit 2 is optional and is based on the Investigator's discretion of individual subject need during stabilization of anti-PD medications. Subjects who are deemed eligible by randomization criteria at Visit 3 will be randomized after all planned assessments have been completed to receive LCIG treatment or to continue on OMT.

Treatment Period (V4 – V8)

Those subjects randomized to continue OMT will remain on their current optimized regimen and will have study visits at the end of Weeks 2, 4, 8, and 12 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, anti-PD medications should remain stable and changes can only be made if medically indicated.

A stable regimen is defined as no changes to the frequency of administration, dose of administration or total daily dose. Those subjects randomized to LCIG treatment must discontinue all other anti-PD medications except amantadine (e.g., dopamine agonists, COMT-inhibitors, MAO-B inhibitors, anticholinergies, and subcutaneous apomorphine, etc.) prior to LCIG treatment initiation on Day 1 (V4); these medications should be tapered off according to their individual package insert, and at the discretion of the Investigator, over a period of up to 14 days. With the exception of apomorphine, levodopa containing formulations or amantadine (see next paragraph), these medications may be restarted if indicated by the subject's individual condition, but not within the first 28 days after PEG placement procedure.

As an exception, subjects in both groups who take amantadine at the randomization visit (V3) must not discontinue this treatment and are required to continue this treatment for the entire study duration with the regimen kept stable unless the Investigator decides that it is medically indicated to discontinue this treatment. If subjects do not take amantadine at the Visit 1 (Screening Visit 1), this treatment must not be initiated during the entire study duration.

For those subjects randomized to LCIG treatment, 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, surgeon or interventional radiologist. Total time on 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 Investigator. If the subject proceeds directly to PEG-J, titration should be completed within 7 days. However, at the Investigator's discretion additional days of optimization may be used if clinically indicated. Subjects on LCIG treatment will return for study visits at the end of Weeks 2, 4, 8, and 12 and following PEG-J placement.



Methodology (Continued):

Treatment Period (V4 – V8) (Continued)

If a subject is prematurely discontinued for any reason, the Week 12 procedures and assessments will be completed.

Study Follow-Up

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

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

For all study visits apart from V1 to V3 a \pm 3 days visit window will be allowed.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

- 1. Subject must be able to understand the nature of the study and has had the opportunity to have any questions answered by the Investigator.
- 2. 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 Investigator to have decision making capacity, must have voluntarily signed the Independent Ethics Committees/Institutional Review Board (IEC/IRB) approved Informed Consent.
- 3. 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
- 4. Male or female subjects of at least 30 years old at the time of Visit 3.
- 5. 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 Brain Bank Criteria.
- 6. Patients with advanced levodopa-responsive Parkinson's disease and persistent motor fluctuations who have not been controlled with optimized medical treatment. "Optimized medical treatment" is defined as the maximum therapeutic effect obtained with pharmacological antiparkinsonian therapies when no further improvement is expected with regard to any additional manipulations of levodopa and/or other antiparkinsonian medication. This will be based on the Investigator's clinical judgment.
- 7. UDysRS Total score \geq 30 at Visit 3 based on Central Blinded Rater's score.
- 8. Subject must demonstrate at least 75% concordance with the Investigator's or qualified designee's assessment of symptoms on the Parkinson's Disease Diary following training at Screening Visit 1 with concordance on at least 1 time interval of "Off," concordance on at least 1 time interval of "ON regardless of dyskinesia" and at least 1 time interval of "ON with dyskinesia" irrespective of whether the dyskinesia are troublesome or not troublesome.



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

Main Inclusion (Continued):

- 9. Subject (or subject's proxy/caregiver) must be able to complete both the Subject Dosing Diary and the PD Diary and must be able to demonstrate the ability to operate, manipulate, and care for the pump and tubing.
- 10. Subject is eligible to transfer to commercial treatment of Duodopa after completing the study based on local country requirements.

Main Exclusion:

- Predominantly di-phasic dyskinesia, as per Investigator discretion.
- Patients who were treated with LCIG before.
- Patients who have had previous surgery for PD including, but not limited to deep brain stimulation (DBS) or cell transplantation.
- Participation in a concurrent interventional or observational study. 4.
- Lack of motivation or insufficient language skills to complete the study questionnaires
- Subject experiencing clinically significant sleep attacks or clinically significant impulsive behavior (e.g., pathological gambling, hypersexuality) at any point during the 3 months prior to the Screening evaluation as judged by the Investigator.
- Current diagnosis or history of drug or alcohol abuse (DSM-V-TR criteria) within 12 months prior to screening visit.
- 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).
- 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), atypical Parkinson Syndrome (e.g., Multiple System Atrophy, Progressive supranuclear Palsy, Diffuse Lewy Body disease) or other neurodegenerative disease that might mimic the symptoms of PD.
- 10. A Mini-Mental State Examination (MMSE) score < 24 at Visit 1 or significant cognitive impairment that, in the opinion of the Investigator, could impact the subject's ability to participate in the trial.



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Investigational Products:	Levodopa (20 mg/mL	and Carbidopa monoh	ydrate (5 mg/mL) in an
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aqueous intestinal gel (carboxymethylcellulose) dispensed in a

medication cassette reservoir of 100 mL.

LCIG: For those randomized to LCIG treatment, each subject's dose **Doses:**

will be individually optimized in accordance with the LCIG approved

product label for countries participating in the study.

Treatment goal is to achieve a balanced improvement of both OFF time and dyskinesia according to physicians' judgment, optimal clinical response for the individual subject, 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 medically indicated. 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 approximately

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: Investigator discretion and/or in accordance with approved product

label of the prescribed medications

Mode of Administration: Oral, sub-lingual or transdermal

Duration of Treatment: 12 weeks

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:

The primary efficacy variable will be the mean change from baseline to Week 12 in UDysRS Total

The UDysRS was chosen for the assessment of the primary endpoint because it was developed specifically for the assessment of dyskinesia in PD and is endorsed by the International Parkinson and Movement Disorder Society [Goetz 2013]. Containing both self-evaluation questions by the subject alone and physician-assessed items to objectively rate dyskinesia and off-dystonia, its clinimetric properties are excellent [Goetz 2008] and it has been demonstrated to be superior for detecting treatment effects compared to other available dyskinesia scales [Goetz 2013].

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Criteria for Evaluation (Continued):

Efficacy (Continued):

Secondary Endpoints (with hierarchical analysis)

- ON time without troublesome dyskinesia as measured by the PD Diary
- PDQ-8 Summary Index
- CGI-C
- UPDRS Part II Score
- OFF time as measured by PD Diary
- UPDRS Part III Score

Additional Efficacy Endpoints are:

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

Additional Health Outcome Endpoints are:

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
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Minnesota Impulsive Disorders Interview (MIDI)
- Sleep Attacks Questionnaire(SAQ)

Statistical Methods:

Efficacy:

Efficacy Dataset and Treatment Period

The efficacy analysis will be performed on the intent-to-treat (ITT) dataset which will include all subjects who are randomized to the OMT, and all subjects who are randomized to LCIG treatment and received at least one dose of study drug following PEG-J placement. 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

The primary efficacy variable is the change from baseline to Week 12 for UDysRS total score. 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 treatment and OMT at the Week 12 Visit.

Secondary Efficacy Analyses

The secondary efficacy variables are the mean change from baseline to Week 12 in the following measures:

- ON time without troublesome dyskinesia as measured by the PD Diary
- PDQ-8 summary index
- CGI-C
- UPDRS Part II Score
- OFF time as measured by PD Diary.
- UPDRS Part III Score

Each secondary efficacy variable will be analyzed with the same MMRM model as the primary analysis. PD Diary variables will be the average time recorded by the subject on the 3 diaries prior to each visit after normalization to a 16 hour day.

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

Additional Efficacy and Health Outcome Analyses

Efficacy will also be assessed using the following additional measures:

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

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

King's PD Pain Scale

Continuous endpoints will be analyzed with the same MMRM model as the primary analysis.



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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 OMT, and all subjects who are randomized to LCIG treatment and had a study device placement procedure. For assessments of safety, the treatment period will begin the day after randomization for subjects randomized to OMT, and the day of initial study tube placement (NJ or PEG-J) for subjects randomized to LCIG. The treatment period will end on the day of the final visit for subjects randomized to OMT. For subjects randomized to LCIG, the treatment period will end on the day of the final study tube removal if all study tubes are removed on or after the last day of LCIG study drug infusion. For all other subjects randomized to LCIG treatment, the treatment period will end on the day of the final visit. 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 Analyses

Safety analyses will include summaries of adverse events, clinical laboratory evaluations, vital signs and weight, special labs and the C-SSRS, and MIDI.

Determination of Sample Size

Approximately 60 subjects will be enrolled into the study and randomized in a 1:1 ratio to either OMT or LCIG. Subject randomization will be stratified by country. A treatment group difference of 10 points is assumed for the mean change from baseline to Week 12 in the UDysRS total score based on results reported by Pahwa et al and a pooled standard deviation of 12 is assumed based on results reported by Goetz et al. Assuming that the treatment group difference between LCIG and OMT groups is 10 points and the pooled standard deviation is 12, 27 subjects per group will have 85% power to detect a treatment group difference at a two-sided significance level of 0.050. It is further assumed that 10% of randomized subjects in either treatment group will not provide post-randomization efficacy assessment. Therefore the total planned enrollment is decided to be approximately 60 subjects.



1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADR Adverse drug reaction

ΑE Adverse event

AESI Adverse event of special interest

ANCOVA Analysis of covariance ANOVA Analysis of variance

β-HCG beta-human chorionic gonadotropin **BOCF** Baseline observation carried forward

BUN Blood urea nitrogen

CFR Code of Federal Regulations

CGI-C Clinical Global Impression - Change CGI-S Clinical Global Impression - Severity

CHMP Committee for Medicinal Products for Human Use

CLES Carbidopa Levodopa Enteral Suspension

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

DNS Duodopa Nurse Specialist

EC **Ethics Committee ECG** Electrocardiogram

eCRF electronic case report form **EDC** Electronic Data Capture

EQ VAS EuroQol Visual Analogue Scale **FDA** Food and Drug Administration



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GCP Good Clinical Practice

GDSM Global Drug Supply Management

GI Gastroenterologist

GMP Good Manufacturing Practice **HCP** Health Care Professional IΒ Investigator's Brochure

ICC Intra-class correlation coefficient

ICH International Council 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

Levodopa/Carbidopa-Continuous Release LC-CR LC-IR Levodopa/Carbidopa-Immediate Release

LLT lowest level term

mAIMS Modified Abnormal involuntary movement scale

MAO-A monoamine oxidase A MAO-B monoamine oxidase B

MAO Inhibitors monamine oxidase inhibitors

Maximum Max

MD Doctor of Medicine

MDS Movement Disorder Society

MedDRA Medical Dictionary for Regulatory Activities **MIDI** Minnesota Impulsive Disorders Interview

Min Minimum

MMA methylmalonic acid

MMSE Mini-Mental State Examination

MMRM Mixed-effect Model Repeated-Measures

NCS Not Clinically Significant

NDC National Drug Code



SD

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NJ Nasojejunal

NMS Neuroleptic Malignant Syndrome

NP Nurse Practitioner

NONMEM[®] nonlinear mixed effects modeling

3-OMD 3-O-methyldopa

OMT Optimized Medical Treatment

OUS Outside United States PA Physician Assistant PC **Product Complaints**

PCS Potentially Clinically Significant

PD Parkinson's disease

PDQ-8 Parkinson's Disease Questionnaire-8 **PEG** percutaneous endoscopic gastrostomy

PEG-J percutaneous endoscopic gastrostomy - with jejunal extension

PhD Doctor of Philosophy PK Pharmacokinetic PT preferred term QoL Quality of Life **REM** rapid eye movement SAP Statistical Analysis Plan SAQ Sleep Attacks Questionnaire SBP systolic blood pressure

SGOT/AST aspartate aminotransferase SGPT/ALT alanine aminotransferase

SmPC Summary of Product Characteristics

SOC system organ class

TA MD Therapeutic Area Medical Director **UDysRS** Unified Dyskinesia Rating Scale

UKPDS United Kingdom Parkinson's Disease Society **UPDRS** Unified Parkinson's Disease Rating Scale

standard deviation

WHO World Health Organization

WOCBP Women Of Child Bearing Potential



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Definition of Terms

Dose Titration Diary 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.

Duodopa Nurse Specialist*

An external nurse specialist which 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.

A paper record of the LCIG pump settings for a subject's morning dose, LCIG Prescription Record

flow rate and extra doses that is recorded at every visit by the site.

Optimized Medical 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 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.

Therapeutic Area Medical

Director (TA MD)

Physician from AbbVie who is assigned in the protocol as the sponsor and emergency contact (also known as Study Designated Physician or Medical

Monitor).

Alternative titles for this function are as below:

AbbVie Duodopa Specialist (ADS)

Nurse Educator (NE)

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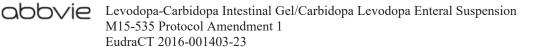
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3.0 Introduction

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 50% of patients after 4 to 5 years of treatment with levodopa and up to 90% of patients may experience motor fluctuations after 9 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 may still 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 apomorphine continuous infusion, 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

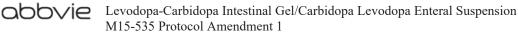


been reported in approximately 13% – 40% of patients including intracerebral hemorrhage, intracranial infection and death. ^{12,13} The procedure is also not available in all settings and not all PD patients are candidates for brain surgery. ¹⁴ Continuous administration of IV levodopa is not clinically 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}

Dyskinesia are among the most troublesome symptoms of Advanced Parkinson's Disease (APD): approximately 50% of patients present with Dyskinesia 4 - 5 years after initiation of treatment; approximately 90% of patients after 9 years.

Peak-dose dyskinesia are linked to peak plasma levels of levodopa, while the less frequent and phenomenologically different biphasic dyskinesia occur during switch from low to high plasma levels and vice versa. Moderate to severe dyskinesia can be painful and disabling, compromising quality of life. Therefore dyskinesia is one of the main reasons for recommending invasive treatments in APD patients.

Levodopa-Carbidopa Intestinal Gel (LCIG) is a stable 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. In contrast to oral therapy, LCIG treatment provides continuous dopaminergic delivery which is believed to stimulate the dopaminergic receptors in the brain within the individual's therapeutic window resulting in decreased motor fluctuations and dyskinesia. Over the past years many clinical investigations have been performed and published demonstrating that functional ON time during the day is increased, OFF time is reduced and ON time without troublesome dyskinesia is increased with a marked effect on quality of life. ¹⁶⁻¹⁸



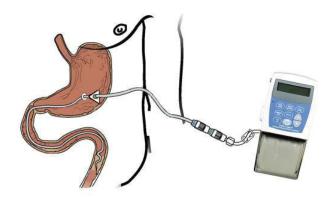
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Levodopa-Carbidopa Intestinal Gel (LCIG) treatment has been marketed for more than 10 years in many countries. The LCIG System is currently approved in 48 countries for the treatment of levodopa-responsive advanced PD. In the majority of countries, it is marketed under the trade name Duodopa while in the US it is marketed as Duopa. 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 treatment 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 treatment reduces "Off" time and increases "On" time compared to oral levodopa-carbidopa. ¹⁹ Some studies suggest that the improvement of LCIG infusion may be correlated with the severity of Parkinsonian symptoms while on oral treatment.²⁰ The delivery of LCIG treatment directly to the upper intestine is anticipated to result in the following:^{2,15}

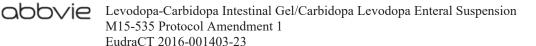
- Continuous delivery of levodopa-carbidopa
- Avoidance of the effects of pulsatile gastric emptying
- Reduced variability in plasma-levodopa concentrations
- Decreased motor fluctuations and dyskinesia

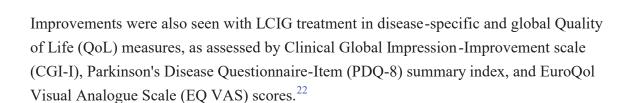


Figure 1. Levodopa-Carbidopa Intestinal Gel Infusion System



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 treatment 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 treatment 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 $(18.9\%)^{21}$





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 ($\geq 10\%$ 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.

LCIG treatment also has been shown to be effective in controlling troublesome Dyskinesia in patients with advanced Parkinson's disease. Post hoc analyses of patient data from a 12-week, randomized, double-blind study and a 54-week open-label study were performed. Efficacy was assessed in the subgroup of patients defined by at least 1 hour of "on" time with troublesome dyskinesia at baseline as recorded in Parkinson's disease symptom diaries (double blind: n = 11 levodopa-carbidopa intestinal gel, n = 12 oral levodopa-carbidopa; open label: n = 144 levodopa-carbidopa intestinal gel). The changes in "off" time, "on" time with and without troublesome dyskinesia, and the overall safety and tolerability of LCIG were analyzed. Although not significantly different from oral levodopa treatment (P > 0.05) in the double-blind study, levodopa-carbidopa intestinal gel treatment resulted in a reduction from baseline in "On" time with troublesome dyskinesia (mean [standard deviation] hours: baseline = 3.1 [1.7], change



from baseline to final = -1.8 [1.8], P = 0.014), increase in "On" time without troublesome dyskinesia (baseline = 7.4 [2.2], change = 4.4 [3.6], P = 0.004), and decrease in "Off" time (baseline = 5.5 [1.3], change = -2.7 [2.8], P = 0.015). Similar trends were found in the open-label study. An increase in levodopa-carbidopa intestinal gel dose was not significantly correlated with increased "On" time with troublesome dyskinesia in either study (double blind: r = -0.073, P = 0.842; open label: r = -0.001, P = 0.992). Adverse events were usually mild to moderate in severity and related to the gastrointestinal procedure.

When specifically evaluating the effect of LCIG treatment on dyskinesia in Parkinson's disease patients, no previous interventional studies have compared LCIG treatment to optimized medical treatment using the UDysRS as an endpoint.

UDysRS

The Unified Dyskinesia Rating Scale (UDysRS) is a rating tool specifically designed to assess dyskinesia in PD. It is composed of modified versions of previously existing rating scales and in a comprehensive way assesses both the subjective and the objective aspects of the presence of dyskinesia. Although relatively new, multiple clinical trials of new putative anti-dyskinesia agents are currently underway using UDysRS as the primary endpoint. The UDysRS contains both self-evaluation questions (completed by the patient alone or with their caregivers) and items that are assessed directly by the physician to objectively rate the abnormal movements associated with PD. The UDysRS contains four sections. Two sections examine the historical disability of ON-dyskinesia (Part 1) and OFF-dystonia (Part 2) as perceived by the patient. Two sections assess the objective impairment (Part 3) and disability (Part 4) caused by the dyskinesia during the time of assessment. All parts consist of several items and each item is scored on a scale from 0 – 4 in a Likert model (0 = normal to 4 = severe) and the total score can range from 0 - 104. Table 1 lists the sections and corresponding parts of the UDysRS.



Table 1. **UDysRS Sections**

Section	Part	Completed by	Measure	Number of Items	Score Range
Historical disability	Part 1	Patient/Caregiver	Patient perception of on-dyskinesia impact	11 items	0 – 44
	Part 2	Patient/Caregiver	Patient perception of off-dystonia impact	4 items	0 – 16
Objective	Part 3	НСР	Rating of dyskinesia (severity, anatomical distribution and type of dyskinesia (chorea, dystonia) based on HCP's observation of patients performing 4 motor tasks (communication, drinking, dressing ambulation)	7 items	0 – 28
	Part 4	НСР	Disability scale rating based on HCP's observation of activities performed by patient in Part 3	4 items	0 – 16

UDysRS Validation and Psychometric Properties

The original development and validation study was conducted by Goetz et al (2008). ²³ Twenty international movement disorder experts participated in the study. Internal consistency, factor structure and reproducibility of the scale were determined in 70 PD patients. The UDysRS showed high internal consistency for both the subjective (Cronbach's alpha = 0.92) and objective rating sections (Cronbach's alpha = 0.97). The scale demonstrated a very good level of inter-rater agreement for both, the summary score of impairment (ICC = 0.87) and the summary score of disability (ICC = 0.91). The intraclass correlation coefficient of the overall total objective score (sum of Parts 3 and 4 scores) was 0.89. Similarly, the scale demonstrated very good levels of intra-rater reliability. The intra-class correlation coefficients for the intra-rater reliability were 0.91, 0.84 and 0.90 for the total impairment, total disability and total objective score, respectively. Repeated measures ANOVA was used to assess ability to detect change in UDysRS Parts 3 and 4; the UDysRS demonstrated an effect size = 0.138, with sensitivity to detect a treatment difference as small as 80% of a standard deviation (Goetz 2013). ²⁴ Evidence is supportive of the ability of Parts 3 and 4 to detect change, however Parts 1



and 2 were not assessed. Convergent and discriminant validity have also not been assessed.

In conclusion, the UDysRS, which has been endorsed by the Movement Disorder Society (MDS), is a comprehensive rating tool to measure dyskinesia and has been shown to be both a consistent and a reliable measure.

3.1 **Differences Statement**

So far no prospective controlled data have been generated on the efficacy of LCIG on dyskinesia. Preliminary evidence from post-hoc analyses from both interventional²⁵ and observational studies suggests that LCIG may decrease duration and severity of dyskinesia for up to 2 years. ^{25,26} This will be the first large interventional controlled study of LCIG for advanced Parkinson's disease patients specifically investigating the effectiveness on dyskinesia.

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 infusion of the gel formulation, 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 treatment on motor symptoms in subjects with advanced PD has been demonstrated in Phase 3 studies. In the pivotal Phase 3 study (Studies S187-3-001/S187-3-002), compared to LC-IR, LCIG treatment 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 treatment 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 other PD medications.

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.²⁷

Important Identified Risks

- Gastrointestinal, Gastrointestinal Device, and Gastrointestinal Procedure Related Events
- Dyskinesia
- Psychosis Associated Events
- Impulsive Control Disorders (ICDs)
- Orthostatic Hypotension
- Sudden Onset of Sleep/Somnolence
- Neuroleptic Malignant Syndrome (NMS)

Adverse events of special interest (AESI) related to LCIG treatment, 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. AESIs for this study are defined in Section 6.2.3 and comprise the following:

Known Risks

• Gastrointestinal and Gastrointestinal Procedure Related Events

Potential Risks

- Polyneuropathy
- Weight Loss



Christian Cel/Carbidopa Levodopa Enteral Suspension M15-535 Protocol Amendment 1 EudraCT 2016-001403-23

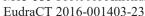
In the previous Phase 3 clinical program, as observed in an integrated summary of safety, AEs were common and occurred in 93.9% of the 412 subjects in the Open-Label LCIG Analysis Set (Phase 3 Studies S187.3.003, S187.3.004, and S187.3.005). The most common treatment emergent adverse events (TEAEs) were 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 2). 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 mean treatment duration of 854 days (open-label LCIG analysis set) are in Table 2.



TEAEs Reported in ≥ 10% of Subjects by Descending Frequency Table 2. (Open-Label LCIG Analysis Set)

	N = 412	
Preferred Term	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 $\geq 2\%$ 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

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

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

Motor Symptoms/Motor Complications Will Be Measured by:

- Unified Dyskinesia Rating Scale (UDysRS)
- Parkinson's Disease Diary (PD Diary): normalized average daily hours of OFF time, ON time with troublesome dyskinesia, ON time without troublesome dyskinesia
- Unified Parkinson's Disease Rating Scale (UPDRS) Part III
- Modified Abnormal Involuntary Movement Scale (mAIMS)

Health Related Outcomes Will Be Measured by:

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

Safety and Tolerability Will Be Assessed by:

Adverse event monitoring

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- 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)

Investigational Plan 5.0

5.1 Overall Study Design and Plan: Description

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

This study will be conducted at approximately 22 - 28 sites that specialize in movement disorders in approximately 6 - 8 countries where LCIG is commercially available.

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 treatment group, except for visits related to NJ/PEG procedures, titration of LCIG and follow-up period.

Patients, who in collaboration with their physicians at participating centers have been found eligible for inclusion into this study during the screening period, will be enrolled into this study.



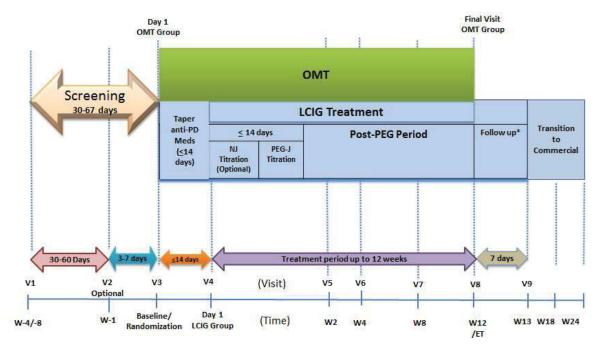


Figure 2. Study Design Schematic

* Follow up period only applicable to LCIG treatment arm subjects that have discontinued the study for any reason. 7 days after the PEG-J removal, a follow-up visit (V9) will be conducted.

The study is designed to enroll an adequate number of subjects such that approximately 60 subjects will be randomized in a 1:1 ratio to either treatment group of OMT or LCIG treatment in order to meet scientific and regulatory objectives without over-enrolling an undue number of subjects in alignment with ethical considerations.

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 will 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 dyskinesia. 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. OMT 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.

<u>Visit 1 (V1)</u>

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 4 of Section 5.3.1 for a detailed list of assessments and procedures and to Section 5.3.1.1 for detailed information on each procedure.

- 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. For the OFF time rating the subject should be at a minimum of 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 Visit 1; all other UPDRS assessments will be done during "On" time.
- The Investigator 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.
- Parkinson's Disease Diary training and concordance testing: The subject and caregiver, if applicable, will be required to have a PD Diary training. Following this training, the subject will be given a PD Diary to be filled in

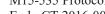


over a minimum period of 3 hours for a concordance evaluation on site. During this period, the subject must experience at least one transition from "Off" to "On" or from "On" to "Off," which must be observed by the Investigator. The Investigator will also complete a separate PD Diary for this period. There must be at least 75% concordance overall between the subject's Parkinson's Disease Diary and the Parkinson's Disease Diary completed by the Investigator or Investigator's qualified designee including concordance on at least 1 time interval of "Off," concordance on at least 1 time interval of "On" regardless of dyskinesia and at least 1 time interval of "On with dyskinesia" irrespective of whether the dyskinesia are troublesome or not troublesome. The testing time can be extended in order to capture all required states. If the concordance criteria are not met, the subject will undergo re-training of Parkinson's Disease Diary completion and repeat the concordance evaluation. If the concordance criteria are not met again the subject should be considered not-eligible for the study.

- 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, including those used to treat dyskinesia, must be stable with no adjustments to the frequency of administration, dose of administration or total daily dose for a minimum of 30 consecutive days before the randomization visit.

Optional Visit 2 (V2)

Visit 2 will occur between from 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, including those used to treat dyskinesia. Subjects must be on stable anti-PD medications, including those used to treat dyskinesia, for at least 30 consecutive days before V3. However, the time period between V1 and V2 must not exceed 60 days. If, in the Investigator's opinion, it is medically necessary for the time frame between V1 and V2



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to exceed 60 days, the Investigator should discuss this with the AbbVie TA MD (also known as Study Designated Physician or Medical Monitor).

<u>Visit 3 (V3)</u>

Visit 3 will be the randomization visit. V3 assessments will be split over 2 days and both visits should occur within a maximum period of 1 week (7 days). The UDysRS shall be administered and the videotape forwarded to the Central Blinded Rater on the first day of assessments.

The IRT randomization transaction should be made on the second day of V3 randomization visit after the subject's eligibility has been confirmed.

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 UDysRS total score of 30 at Visit 3 as assessed by the Central Blinded Rater to qualify for randomization.

Results from lab samples collected at V3 will only be used as baseline level and are not intended to determine eligibility for randomization.

In addition at V3 the following should occur:

Training on the LCIG System and Pump will be initiated only for subjects randomized for LCIG treatment and their caregivers, as applicable.

5.1.2 The Treatment Period

For all study visits apart from V1 to V3 a \pm 3 days visit window will be allowed.

5.1.2.1 **OMT Group**

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 Investigator will provide the



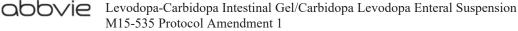
prescription for continued OMT. All anti-PD medications, including those to treat dyskinesia, must remain stable for the duration of the study unless medically indicated. A stable regimen is defined as no changes to the frequency of administration, dose of administration or total daily dose. If changes to anti-PD medications or medications to treat dyskinesia are needed, this should first be discussed with the AbbVie TA MD unless there is immediate safety concern. The day after randomization will be considered Day 1 of the treatment period for the OMT group. Subjects in the OMT Group will not have a Visit 4. Visits 5 through 8 will take place at the end of Weeks 2 through 12 respectively. If at any time a subject early terminates the study, all procedures related to Week 12 visit should be completed. For all visits, the assessments will be completed as indicated in Table 4.

5.1.2.2 **LCIG Treatment Group**

Tapering of Anti-PD Medications Other Than Levodopa

Subjects randomized to LCIG treatment must discontinue all other anti-PD medications other than amantadine (e.g., dopamine agonists, COMT-inhibitors, MAO-B inhibitors, anti-cholinergics, and subcutaneous apomorphine, etc.) prior to LCIG treatment initiation on Day 1 (V4); these medications should be tapered off within 14 days after randomization according to the discretion of the Investigator. With the exception of apomorphine, levodopa containing formulations or amantadine (see next paragraph), these medications may be restarted if indicated by the subject's individual condition, but not within the first 28 days after LCIG treatment initiation.

As an exception, subjects in both OMT and LCIG groups who take amantadine at the randomization visit (V3) must not discontinue this treatment and are required to continue this treatment for the entire study duration with the regimen kept stable unless the Investigator decides that it is medically indicated to discontinue this treatment. If subjects do not take amantadine at the Visit 1 (Screening Visit 1), this treatment must not be initiated during the entire study duration.



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NJ and/or PEG-J Placement

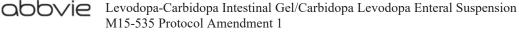
LCIG treatment is intended for continuous intestinal administration. A temporary NJ tube may be used initially with the infusion pump to determine if the subject responds favorably to this method of treatment and to optimize the dose of LCIG before treatment with a permanent percutaneous endoscopic gastrostomy 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.

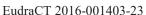
Visit 4 (V4), Day 1 Optional Nasojejunal (NJ) Phase and/or PEG-J Placement

Subjects will have the NJ and/or PEG-J tube placement procedure performed on Study Day 1 (V4) by a gastroenterologist proceduralist, surgeon or interventional 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, surgeon or interventional radiologist as applicable 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 4). 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/V8 (Week 12) procedures and assessments will 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 other than amantadine 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.

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 if required, at the discretion of the investigator or local practitioner, subjects may be admitted and remain hospitalized for the duration of the titration period. 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.

During the titration, the subject (and if applicable, their caregiver) will receive 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 4.

The gastroenterologist proceduralist, surgeon or interventional radiologist as applicable will check the subject's stoma site within 24 hours and anytime from Day 2 to 7 after the PEG-J procedure. The stoma check will be recorded on the appropriate eCRF.

Treatment: Visit 5 (Week 2) Initial Post-PEG-J Evaluation Through Visit 8 (Week 12)

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 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 4, 8 and 12 respectively will be recorded on the appropriate eCRF and the



assessments completed as in Table 4. If at any time a subject early terminates the study, all procedures related to Week 12 visit should be completed.

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.

5.1.3 Study Follow-Up

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

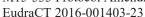
For LCIG subjects who elect to discontinue LCIG and not continue with commercially available product, a V9 will be conducted 1 week after PEG-J removal and the SAE/AE follow-up period will be up until 30 days after PEG-J removal.

Commercial Transition Visits (LCIG Treatment Subjects Continuing on Commercial Product)

For LCIG treatment subjects who will transition to commercial product, the SAE/AE follow-up period will be up until 30 days after the transition.

Study subjects in the LCIG treatment 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 treatment until transition to commercial product is coordinated with the Sponsor's commercial affiliate.

Upon transfer of subjects to commercial LCIG treatment 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, following the 30 day SAE/AE follow-up period, no formal collection of data will be conducted except for regular Adverse Drug Reaction (ADR) reporting in accordance with local instructions.



OMT Subjects

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

Study subjects in the OMT group who complete participation in the study are eligible to transition to commercial LCIG treatment 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 be able to understand the nature of the study and has had the opportunity to have any questions answered by the Investigator.
- 2. 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 Investigator to have decision making capacity, must have voluntarily signed the Independent Ethics Committees/Institutional Review Board (IEC/IRB) approved Informed Consent.
- 3. 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.
- 4. Male or female subjects of at least 30 years old at the time of Visit 3.



- 5. 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.
- 6. The subject's Parkinson's disease is levodopa-responsive.
- 7. Patients with advanced levodopa-responsive Parkinson's disease and persistent motor fluctuations who have not been controlled with optimized medical treatment. "Optimized medical 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.
- 8. UDysRS Total score \geq 30 at Visit 3 based on Central Blinded Rater's score.
- 9. Subject must demonstrate at least 75% concordance with the Investigator's or qualified designee's assessment of symptoms on the Parkinson's Disease Diary following training at Screening Visit 1 with concordance on at least 1 time interval of "Off," concordance on at least 1 time interval of "ON regardless of dyskinesia" and at least 1 time interval of "ON with dyskinesia" irrespective of whether the dyskinesia are troublesome or not troublesome.
- 10. Subject (or subject's proxy/caregiver) must be able to complete both the Subject Dosing Diary and the PD Diary and must be able to demonstrate the ability to operate, manipulate, and care for the pump and tubing.
- 11. Subject must have a 75% or greater compliance rate on the PD Diary completion at Visit 3.
- 12. Subject is eligible to transfer to commercial treatment of Duodopa after completing the study based on local country requirements.
- 13. For Female Subjects:
 - 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 (Section 5.2.4), starting at Study Day 1 through at least 30 days after the last dose of study drug.

For Male Subjects:

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 (Section 5.2.4).

No male contraception is required.

14. Females of childbearing potential must have a negative serum pregnancy test result at Visit 1, and a negative urine pregnancy test at Visit 3.

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

Rationale for Inclusion Criteria

- 1 3In accordance with harmonized GCP
- 5 12To select the adequate subject population with appropriate disease severity
- 4 For the safety of the study subjects
- 13 14The impact of LCIG treatment 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. Predominantly di-phasic dyskinesia, as per Investigator discretion.
- 2. Patients who were treated with LCIG before.
- 3. Patients who have had previous surgery for PD including, but not limited to deep brain stimulation (DBS) or cell transplantation.
- 4. Participation in a concurrent interventional or observational study.



- 5. Lack of motivation or insufficient language skills to complete the study questionnaires.
- 6. 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), atypical Parkinson Syndrome (e.g., Multiple System Atrophy, Progressive supranuclear Palsy, Diffuse Lewy Body disease) or other neurodegenerative disease that might mimic the symptoms of PD.
- 7. Subject has any neurological deficit that might interfere with the study assessments (e.g., hemiparesis).
- 8. Known hypersensitivity to levodopa, carbidopa or radiopaque material.
- 9. Subject has contraindications to levodopa, (e.g., narrow angle glaucoma, malignant melanoma).
- 10. 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.
- 11. Current diagnosis or history of drug or alcohol abuse (DSM-V-TR criteria) within 12 months prior to screening visit.
- 12. 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).
- 13. Currently experiencing or any known history of psychosis (e.g., troublesome hallucinations with or without insight) or delusions within 3 months prior to Screening.



- A Mini-Mental State Examination (MMSE) score of < 24 at Visit 1 or significant 14. cognitive impairment that, in the opinion of the Investigator, could impact the subject's ability to participate in the trial.
- 15. 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.
- 16. 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).
- 17. 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).
- 18. Any malignant disease other than carcinoma in situ of the cervix or basal cell carcinoma of the skin within the past 5 years prior to Screening. Subjects with prostate cancer or completely excised squamous cell carcinoma of the skin without reoccurrence within 2 years prior to Screening may be permitted to enroll following Investigator and AbbVie TA MD 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.
- 19. 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.
- 20. Exposure to any investigational drug within 30 days prior to Screening.
- 21. Previous enrollment in this study, any other LCIG study or any prior exposure to LCIG treatment.



22. 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.

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- 23. Subject has significant current suicidal ideation within 1 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.
- 24. A low B₁₂ level or low-normal B₁₂ level (less than 300 pg/mL or 221.4 pmol/L) with elevated methylmalonic acid (MMA), at Screening Visit 1.*
- 25. Positive screen for drugs of abuse or medical marijuana, at Screening Visit 1.
- 26. 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.
- 27. 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.
- 28. Consideration by the Investigator, for any reason, that the subject is an unsuitable candidate to receive LCIG treatment.
 - If treated and repeat labs confirm B₁₂ levels rise above 300 pg/mL or 221.4 pmol/L, subject is eligible to re-screen.

Rationale for Exclusion Criteria

1, 6, 7, 9, 15 – 18, 24, 25	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 treatment for safety events
5, 8, 10 – 14, 19, 22 – 23	To ensure safety of the subjects throughout the study
2-4, 20-21, 28	To exclude, or to minimize, the number of medications or other factors that could interfere with the LCIG treatment, or could add unnecessary variance or bias to safety evaluations

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The impact of LCIG treatment on pregnancies and lactation is unknown

5.2.3 **Prior and Concomitant Therapy**

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving from 30 days prior to signing the Informed Consent Form, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 **Prior Therapy (Prior to Randomization)**

All medications taken by the subject during the study and 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.

Allowable Medications

Anti-Parkinsonian Medications

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

Levodopa formulations

- For the OMT group, all levodopa formulations are allowed
- For the LCIG treatment group:



- o 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

Dopamine agonists (not including apomorphine continuous infusion or PRN injection)

MAO-B inhibitors

Anti-cholinergics

Amantadine –

As an exception, subjects in both groups who take amantadine at the randomization visit (V3) must not discontinue this treatment and are required to continue this treatment for the entire study duration with the regimen kept stable unless the Investigator decides that it is medically indicated to discontinue this treatment. If subjects do not take amantadine at the Visit 1 (Screening Visit 1), this treatment must not be initiated during the entire study duration.

General Requirements

Screening to Visit 3: All anti-Parkinson's disease medications must be stable* for at least 30 consecutive days prior to V3 baseline assessments.

*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 12 visit and study assessments unless medically indicated.
- LCIG treatment Group: Those subjects randomized to LCIG treatment must discontinue all other anti-PD medications other than amantadine (e.g., dopamine agonists, COMT-inhibitors, MAO-B inhibitors, anticholinergies, 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, over a period of up to 14 days. With the exception of apomorphine, levodopa containing formulations or amantadine (see next paragraph), these medications may be restarted if indicated by the subject's individual condition, but not within the first 28 days after the PEG placement procedure.

As an exception, subjects in both groups who take amantadine at the randomization visit (V3) must not discontinue this treatment and are required to continue this treatment for the entire study duration with the regimen kept stable unless the Investigator decides that it is medically indicated to discontinue this treatment. If subjects do not take amantadine at the Visit 1 (Screening Visit 1), this treatment must not be initiated during the entire study duration.

Anti-PD medications should only be adjusted if medically indicated

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 appropriate eCRF, except for study drug for subjects randomized to LCIG treatment. All changes to concomitant medications, this includes all medications taken by subjects randomized to OMT, must be carefully documented on the Concomitant Medication eCRF.

Medications for Management of Dyskinesia (OMT Treatment Group)

All medications used for the management of dyskinesia must be stable for at least 30 consecutive days before the Randomization visit (V3). These medications should then also remain stable for the duration of the study.

The Investigator can make modifications to these medications or additional medications if medically indicated after discussion with the AbbVie TA MD.

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 Treatment Groups)

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

Table 3. **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

treatment 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,

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



5.2.3.3 Rescue Therapy (LCIG Treatment 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.

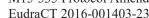
5.2.3.4 Post Infusion Night Time Therapy (LCIG Treatment Group Only)

Those subjects randomized to the LCIG Treatment group will be permitted to selfadminister 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 treatment drug administration, levodopa-DOPA decarboxylase inhibitor (DDI) tablets or similar such as Levodopa + carbidopa = Sinemet, LD + CD + entacapone = Stalevo, Levodopa + Benserazide = Madopar 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. 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.

5.2.4 **Contraception Recommendations and Pregnancy Testing**

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 surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
- 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.
 - o Bilateral tubal occlusion/ligation.
 - Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the women of child bearing potential (WOCBP) trial participant.
 - o Intrauterine device (IUD).
 - Intrauterine hormone-releasing system (IUS).
 - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 1 month prior to Study Day 1.
 - O 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).



If male subject must be surgically sterile (vasectomy with medical assessment confirming surgical success) or have a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), OR if sexually active with female partner(s) of childbearing potential must agree from Study Day 1 through 4 weeks after the last dose of study drug to practice contraception with:

- Condom use.
- True abstinence: Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).
- Additionally, male subject agrees not to donate sperm from Study Day 1 through 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 4 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. For all study visits apart from V1 to V3 a \pm 3 days visit window will be allowed. All attempts should be made to return the subject to the planned visit schedule (e.g., if the subject is 2 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 Treatment and the day after randomization for subjects randomized to OMT).

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Table 4. Study Activities

		OMT/LCIG	D	LCIG Treatment	ıtment	0	MT/LC	OMT/LCIG Treatment	atment	TCIG I	LCIG Treatment
	V1	V2	V3	V4 NJ/PEG-J	Titration	V5 Wk	V6 Wk	V7 Wk	8A	64	Transition to Commercial
Activity	Screening	Screening	Randomization	Placement D1	Visits	2	4	8	Wk 12/ET	$ m Wk13FU^a$	Visits ^D
Visit Number for OMT/LCIG	V1	V2 ^c (Optional)	V3	V4 ^d		V5	9/	77	8Λ	6Λ	Every 6 and 12 Weeks
Informed Consent ^e	×										
Medical/Neurological/PD History	×		X ^f								
Concomitant Medication (including anti-PD and Dyskinesia medications)	×	×	X	X	X	×	×	×	X	X	X
Anti-PD Medication History	×										
Physical Examination ^g	×	×	X	X		×	×	×	X	X	
Neurological Exam	X	X	X			X	X	X	X	X	
Dermatological Exam ^g	X								X		
GI Exam ^g	X								X		
NJ or PEG-J decision	X										
Nasojejunal Tube Placement/Titration (Optional)				X							
PEG-J Placement Procedure				X							

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Table 4. Study Activities (Continued)

		OMT/LCIG	S)	LCIG Treatment	ıtment	0	MT/LC	OMT/LCIG Treatment	ıtment	LCIG 1	LCIG Treatment
						VS	9/	V7			Transition to
Activity	V1 Screening	V2 Screening	V3 Randomization	V4 NJ/PEG-J Placement D1	Titration Visits	2 Wk	≱ 4	× ××	V8 Wk 12/ET	V9 Wk 13 FU ^a	Commercial Visits ^b
Radiological Check of Tube Placement				X							
PEG-J Site (Stoma) Check				X^{j}	×					×	
Vital Signs/Weight	X		X	X	×	×	×	×	X	×	X
Height	X										
ECG	X							×	X		
Clinical Labs	X^k		X^k					×	X		
Urine Drug/Alcohol Screen	X										
Special Laboratory Tests	X		X					×	X		X
Pregnancy Test ^m	X			X					X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Product Complaints				X	X	X	×	×	X	X	X
Dose Titration Diary				X	×						
Subject Dosing Diary Completion					X	X	X	X	X		
PD Diary training and concordance evaluation	X										
PD Diary ^o			X			X	×	X	X		

Table 4. Study Activities (Continued)

Activity V1 V2 V3 V4M/PEG-J Tirration Tirration Wish Assignment Wish Subject and Carcegives) V2 V3 V4 V6 V7 V8 V8 V8 V8 Common Activity LCIG System and Pump Carcegives) Training (Subject and Carcegives) X <th></th> <th></th> <th>OMT/LCI</th> <th>10</th> <th>LCIG Treatment</th> <th>tment</th> <th>0</th> <th>MT/LC</th> <th>OMT/LCIG Treatment</th> <th>ıtment</th> <th>TCIG T</th> <th>LCIG Treatment</th>			OMT/LCI	10	LCIG Treatment	tment	0	MT/LC	OMT/LCIG Treatment	ıtment	TCIG T	LCIG Treatment
yearm and Pump (system and Pump (system) an	:	ĪA	. V2	V3	V4 NJ/PEG-J	Titration	V5 Wk	V6 Wk	V7 Wk	8/	60	Transition to
ystem and Pump (c) g (Subject and Pump (c) triation** Tritation** Dug Prescription Tritation** Dug Prescription And	Activity	Screening	Screening	Randomization	Placement D1	Visits	2	4	œ	Wk 12/ET	Wk 13 FU"	Visits
TirrationPrough Turning Programment Angle Prescription (LCIG treatment Angle) X	LCIG System and Pump Training (Subject and Caregiver)			×	×							
Dug Prescription (LCIG treatment mily) X	LCIG Titration ^p				X	X						
al of PEG.1** Assettes Dispensed X Attacks X XI A X X X X X X X X X X X X	Study Drug Prescription Record (LCIG treatment group only)				X	X	X	×	X	X	X	
Cassettes Dispensed X	Removal of PEG-J ^a									X		
Cassettes Returned X	LCIG Cassettes Dispensed				X		X	×	X	X	X	X
Attacks X </td <td>LCIG Cassettes Returned</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td> <td>X</td>	LCIG Cassettes Returned						X	X	X	X	X	X
Attacks X </td <td>MMSE</td> <td>X</td> <td></td>	MMSE	X										
Si	Sleep Attacks Questionnaire ^q	X	X	X			Х	Х	Х	X	X	
Ss	C-SSRS ^r	X	X	X	X		X	X	X	X	X	X
SSs X	MIDI	X	X	X			X	X	X	X	X	X
S II and III [†] Su X X X X X X X X X X X X X	$\mathrm{UDysRS}^{\mathrm{s}}$			X			X	X	X	X		
x x x x x x x x x x x x x x x x x x x	UPDRS II and III ^t	X		X			X	X	X	X		
	mAIMS ^u			X			X	X	X	X		
	PDQ-8			X					X	X		
	CGI-C						X	X	X	X		

Table 4. Study Activities (Continued)

		OMT/LCIG	B	LCIG Treatment	ıtment	[0	MT/LC	OMT/LCIG Treatment	atment	TCIG T	LCIG Treatment
	VI	V2	V3	V4 NJ/PEG-J Titration	Titration	V5 Wk	V6 Wk	V7 Wk	8/	6/	Transition to Commercial
Activity	Screening	Screening Screening	Randomization	Placement D1	Visits		4	∞	Wk 12/ET Wk 13 FU ^a	Wk 13 FU ^a	Visits ^b
S-I9O			X								
King's PD Pain Scale			X				X	X	X		

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

Applicable only to LCIG subjects who prematurely discontinue LCIG treatment, or complete LCIG study treatment but will not transition to commercial LCIG. a. 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. Visit 2 is optional and is based on the Investigator's discretion of individual subject need during stabilization of anti-PD medications and medications to treat dyskinesia.

Visit 4 for LCIG Treatment (LCIG) group only.

d.

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

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

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

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 should not last longer than 7 days. Following the NJ test phase, a PEG-J will be performed by a gastroenterologist proceduralist, surgeon or interventional radiologist. Total For subjects randomized to LCIG treatment, a temporary NJ tube may be used to optimize the dose of LCIG before treatment with a PEG-J is started. The NJ test phase number of days to titrate will vary for each subject. þ.

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

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

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

Table 4. Study Activities (Continued)

- Special labs to detect vitamin deficiencies, listed in Table 5, will be performed at the times indicated in Table 4. 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.
- All females of childbearing potential must have a serum pregnancy test performed at Screening Visit 1 and Premature Discontinuation/End of Study. Additional testing may be required per local regulations. A negative urine pregnancy test result is required prior to the NJ and/or PEG-J placement procedure and any radiological procedures. ij.
- 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. 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 ij.
- The Subject Dosing Diary and the Parkinson's Disease Diary will be completed by the subjects or their caregivers for the 3 consecutive days prior to each visit. ö
- It is up to the discretion of the Investigator to determine how many titration days are necessary to obtain optimal clinical response.

р.

- The Sleep Attacks Questionnaire will be used to screen for sleep attacks. Results should be recorded in source but will not be entered in the clinical database. 4
- 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.
- The subject's expected time of peak dose dyskinesia should be determined during screening and the UDysRS should be administered at this time throughout the study ò
- morning prior to the subject taking their first daily dose of anti-PD medication. At a minimum a subject should be 8 hours without anti-PD medication before the UPDRS is completed. The best "On" time rating should be done approximately 1 to 2 hours post any morning dose of study drug or PD medications but prior to lunch. If possible, the UPDRS should be done at the same time of day throughout the trial. The "Off" time UPDRS Part III will only be done during Screening; all other UPDRS assessments will 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
- The mAIMS should be completed following the UDysRS at the subject's expected time of peak dose dyskinesia. 'n.

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



5.3.1.1 **Study Procedures**

The study procedures outlined in Table 4 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 multiple days.

Informed Consent

Voluntary written informed consent must be obtained from each subject (and if appropriate, their caregiver) by the Investigator 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 4. 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.

Mini-Mental State Examination (MMSE)

The MMSE²⁸ 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 subject 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

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eligible for study participation. Lower scores indicate greater impairment. The MMSE will be administered at Visit 1 as indicated in Table 4.

Sleep Attacks Questionnaire

To prospectively monitor for possible development of sleep attacks, the subject will be evaluated for sleep attacks at the times indicated in Table 4. 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 3 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.



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Physical Examination

At Screening V1, V2 (optional visit) 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 including light touch and pinprick sensation, vibratory sensation, deep tendon reflexes, and strength assessments will be performed at the times indicated in Table 4. 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 that change in severity or frequency following randomization for the OMT group and the first dose of IP for the LCIG treatment group will be recorded as adverse events.

The Neurological Examination will assess:

- Cranial nerves assessment of cranial nerves II XII, including fundoscopic examination
- 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
- 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 V3 and at Week 12/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 Treatment 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, surgeon or interventional radiologist. Total time to titration via NJ and PEG-J should not exceed 14 days. Alternatively, subjects may proceed directly to placement of the PEG-J if deemed appropriate by the 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 Treatment Group Only)

Radiological check of NJ and PEG-J to determine correct location should occur prior to LCIG infusion initiation and prior to restart of LCIG treatment 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 Treatment 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-giver 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 or interventional radiologist (preferably the physician who placed the PEG-J), or their designated qualified personnel within 24 hours and 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 4. 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.

Vital signs will include body weight will be measured at the times indicated in Table 4. 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 4. 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 5. The laboratory test results obtained at Visit 3 will serve as baseline for clinical assessment and are not intended to determine eligibility for randomization. All clinical laboratory



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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 only Screening Visit 1.

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 5. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis	Special Tests ^d
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 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	Thyroid Function Tests ^e Vitamin B ₁₂ f Vitamin B ₆ f Folic Acid Methylmalonic Acid (MMA) f Homocysteine f

- a. Only done at Visit 1.
- 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 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 labs at Visit 1 are exclusionary.
- e. Includes TSH and free T4 (Visit 1 only).
- f. Special labs to detect vitamin deficiencies, including: Vitamin B₁₂, Vitamin B₆, folic acid, MMA, and homocysteine levels will be performed at the times indicated in Table 4. Abnormal Vitamin B₁₂ of questionable clinical significance (indeterminate or low normal results at screening) require MMA and homocysteine laboratory assessments be reviewed for determination of B₁₂ 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 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 in Table 5. The urine drug screen analysis at Visit 1 will be performed by the certified central laboratory chosen for the study.

Special Laboratory Tests

Special labs to detect vitamin deficiencies, including: Vitamin B₁₂, Vitamin B₆, folic acid, MMA, and homocysteine levels will be performed at the times indicated in Table 4. Abnormal Vitamin B₁₂ of questionable clinical significance (indeterminate or low normal results at screening) require MMA and homocysteine laboratory assessments be reviewed for determination of B₁₂ deficiency prior to entry into the study. Only lab results 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

For all females of childbearing potential a serum pregnancy test will be performed at V1 and Premature Discontinuation/End of Study. A negative urine pregnancy test result is required to be done by the site prior to the NJ and/or PEG-J placement procedure and/or any radiological procedures. Additional testing may be required per local regulations.

Minnesota Impulsive Disorders Interview (MIDI)

To monitor for development of intense impulsive behavior, the Minnesota Impulsive Disorders Interview (MIDI)²⁹ will be administered at the times indicated in Table 4 or whenever relevant symptoms emerge. 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 AbbVie TA MD should also be notified. The MIDI will be administered as indicated in Table 4.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS)³⁰ 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 AbbVie TA MD 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 AbbVie TA MD.

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 "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.

The C-SSRS will be administered at the times outlined in Table 4.



Unified Parkinson's Disease Rating Scale (UPDRS)

The Unified Parkinson's Disease Rating Scale (UPDRS)³¹ 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

Only Part II and Part III will be administered in this study.

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; all other UPDRS assessments will be done during "On" time.

The UPDRS will be obtained at the times indicated in Table 4.

Unified Dyskinesia Rating Scale UDysRS

The Unified Dyskinesia Rating Scale (UDysRS) is a tool used to evaluate involuntary movements often associated with treated Parkinson's disease.



The UDysRS is made up of the following sections:

- Part 1 Historical Disability (patient perceptions) of On-Dyskinesia impact
- Part 2 Historical Disability (patient perceptions) of Off-Dystonia impact
- Part 3 Objective Impairment (dyskinesia severity, anatomical distribution over seven body regions and type (choreic or dystonic) based on four observed activities
- Part 4 Objective Disability based on Part 3 activities

The Historical Score is the sum of Parts 1 and 2 and the Objective Score is the sum of Parts 3 and 4. The dimensions are evaluated through both an investigation and interview carried out by the physician/rater and self-administered questionnaire. The UDysRS assessment will be performed by an experienced rater. Rater training will be provided by the Sponsor as appropriate. The subject's expected time of peak dose dyskinesia should be determined during screening and the UDysRS should be administered at this time throughout the study.

A Site Administrator will administer the UDysRS. Subjects will be videotaped during the completion of the Part 3 activities. The videotape will be transmitted to the Central Blinded Rater for scoring of Parts 3 and 4. All subjects will be required to wear a pump during each videotape session to blind the assessor. All subjects will wear a dummy pump at V3 and subjects randomized to OMT will wear a dummy pump at each treatment period assessment. A detailed description of the process will be provided in the rater manual.

A mock UDysRS administration to allow subjects to familiarize themselves with the pump should be conducted before the actual study UDysRS assessment.

For the communication assessment the UDysRS administrator will comment on camera on the understandability of the speech using a standardized text.

The UDysRS will be obtained at the times indicated in Table 4.



Modified Abnormal Involuntary Movement Scale (mAIMS)

The AIMS is a reliable and frequently used scale to assess tardive dyskinesia and thus has an emphasis on orofacial dyskinesia.³² For the purposes of dyskinesia assessment in PD, modifications of the original scale have been developed. The mAIMS uses a uniform Likert type scoring system where each item is rated from 0 = none to 4 = severe. 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 mAIMS 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 assessments for mAIMS should be completed following the UDysRS at the subject's expected time of peak dose dyskinesia as per the times indicated in Table 4.

Parkinson's Disease Diary/PD Diaries

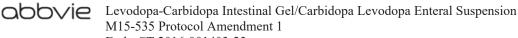
The core of the Parkinson's Disease Diary (PD Diary) is the tool that the subject will use to record Parkinsonian symptoms. The subject and/or caregiver will be prompted to answer the PD Diary whether the subject has been "ON," "OFF," or "ASLEEP" and what has been the severity of the dyskinesia (troublesome or not troublesome). On PD Diary recording days, subjects will be instructed to make an entry upon waking and every 30 minutes during their normal waking time.

Study site staff should make a call to the subjects in advance of their clinic visit to review with them the need to complete the PD Diary for the visit.

The PD Diary is to be recorded at the times indicated in Table 4.

Parkinson's Disease Diary Subject Training and Screening Requirements

During the Screening period, the subject and caregiver, if applicable, will be required to have Parkinson's Disease Diary training which will include how to understand their PD



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symptomatology and how to complete the Parkinson's Disease Diary. The "Parkinson's Disease Motor Diary Video Instruction" DVD may be used for this training.

Site personnel should emphasize the importance of completing the Parkinson's Disease Diary accurately. It is to be completed for the full 24 hours of each day at half-hour time points in real-time during waking hours to ensure true evaluation of the subject's condition, reflecting both time awake and time asleep. On the recording days (the 3 days prior to the visits indicated in Table 4), subjects will be instructed to make an entry every 30 minutes during their waking time and upon awakening from time asleep. The time the subject slept will also be indicated. The subject should bring the completed Parkinson's Disease Diaries with them to the visits indicated in Table 4.

Following the initial Parkinson's Disease Diary training during Screening Visit 1, the subject will be given a Parkinson's Disease Diary to be filled in over a minimum period of 3 hours for a concordance evaluation while they are in the clinic. During this period, the subject must experience at least one transition from "Off" to "On" or from "On" to "Off," which must be observed by the Investigator. The Investigator or an experienced and medically qualified study site designee (e.g., NP, PA, DO, MD, or PhD) assigned by the Investigator will also complete a separate Parkinson's Disease Diary for this period indicating their assessment of the subject's motor state. There must be at least 75% concordance overall between the subject's Parkinson's Disease Diary and the Parkinson's Disease Diary completed by the Investigator or Investigator's qualified designee including concordance on at least 1 time interval of "Off," concordance on at least 1 time interval of "On" regardless of dyskinesia and at least 1 time interval of "On with dyskinesia" irrespective of whether the dyskinesia are troublesome or not troublesome. The testing time can be extended in order to capture all required states. If the concordance criteria are not met, the subject will undergo re-training of Parkinson's Disease Diary completion and repeat the concordance evaluation. If the concordance criteria are not met again the subject should be considered not-eligible for the study.

After successful concordance evaluation, the subject will be instructed to complete 3 consecutive days of Parkinson's Disease Diaries and return the completed diaries at



Randomization Visit 3. The Parkinson's Disease Diary dispensed at Screening Visit 1 will be collected at the start of Randomization Visit 3, and will be reviewed prior to the conduct of any Visit 3 procedures. The subject's compliance in entering Parkinson's Disease Diary data over the consecutive 3-day period should be evaluated. Subjects must demonstrate a 75% or greater compliance rate of diary completion. If the completion compliance rate is not met, the subject may be re-trained and the evaluation of compliance may be repeated. An additional visit will be required.

The PD diary should be completed during the 72-hour period (3 days) prior to each clinic visit, as indicated in Table 4. Subjects should be reminded with a phone call prior to each visit to complete the PD Diaries and to reinforce the importance of PD Diary completion.

Clinical Global Impression of Change (CGI-C)

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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. Average score and 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 4.

Clinical Global Impression of Severity (CGI-S)

The Clinical Global Impression-Severity is a global assessment of current symptomatology and impact of illness on functioning. The ratings are as follows:

- 1 = normal
- 2 = borderline ill
- 3 = mildly ill
- 4 = moderately ill
- 5 = markedly ill



6 =severely ill 7 =among the most extremely ill

A qualified rater will administer the CGI-S to the subject at the times indicated in Table 4.

King's PD Pain Scale

The King's PD Pain Scale is an easy to administer 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.³³ A qualified rater will administer the King's PD Pain Scale to the subject to assess for PD specific pain at the times indicated in Table 4.

Parkinson's Disease Questionnaire (PDQ-8)

The PDQ-8³⁴ 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 4.



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Dose Titration Diary

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.

Study Drug Prescription Record (LCIG Treatment Group Only)

The subject's pump settings (morning dose volume in mL, continuous infusion rate in mL/hr, extra dose volume in mL and lock level) will be recorded on the Study Drug Prescription eCRF at the time of the first infusion of LCIG via NJ (if applicable), at the time of the first infusion of LCIG via PEG-J, and at the conclusion of each clinic visit in the study drug prescription record.

Subject Dosing Diary (LCIG Treatment 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 4. 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 treatment 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.

Site Rater Training Requirements

The study scales/questionnaires will be administered only by individuals qualified by the Sponsor and the rater training vendor. The UDysRS Parts 1 and 2 will be assessed and scored by site raters who are qualified based on MDS training. Prior to administration, designated raters (Investigator or an experienced and qualified study site assigned by the Investigator) will be trained and where applicable certified in the use of the study scales/questionnaires. 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 rating scale and/or 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 where appropriate 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 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 Central Rater Training Requirements

The objective portion of the UDysRS (Parts 3 and 4) will be assessed and scored by experienced blinded central raters who are qualified based on MDS training.

The blinded central raters will be blinded to the study protocol and the tested hypotheses and 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 a video recording of the interview with the subject.

The blinded central rater will score the UDysRS assessment at the times indicated in Table 4 with the baseline assessment occurring at Visit 3.

5.3.1.3 **Ancillary Support**

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

Duodopa Nurse Specialist (DNS)/AbbVie Duodopa Specialist (ADS)/Nurse Educator (NE)

The Sponsor may provide ancillary support to the study sites by utilizing a Duodopa Nurse Specialist (DNS) to provide additional training to the Investigator and site personnel. DNS services and training are methods of support in the implementation of the LCIG administration system at clinical sites.



The functions of the DNS may include:

- Provide ongoing education and support to the site personnel (Investigator, gastroenterologist or interventional radiologist, 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**

5.3.3.1 **Primary Efficacy Variable**

The primary efficacy variable will be the change from baseline to Week 12 in UDysRS Total Score.

The UDysRS was chosen for the assessment of the primary endpoint because it was developed specifically for the assessment of dyskinesia in PD and is endorsed by the International Parkinson and Movement Disorder Society.²⁴ Containing both selfevaluation questions by the patient alone and physician-assessed items to objectively rate dyskinesia and off-dystonia, its clinimetric properties are excellent²³ and it has been

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demonstrated to be superior for detecting treatment effects compared to other available dyskinesia scales.²⁴

5.3.3.2 Additional Efficacy and Health Outcome Variables

Secondary Endpoints (with hierarchical analysis)

- ON time without troublesome dyskinesia as measured by the PD Diary
- PDQ-8 Summary Index
- CGI-C
- UPDRS Part II Score
- OFF time as measured by PD Diary
- UPDRS Part III Score

Additional Efficacy Endpoints are:

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

Additional Health Outcome Endpoints:

• 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
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Minnesota Impulsive Disorders Interview (MIDI)
- Sleep Attacks Questionnaire

Removal of Subjects from Therapy or Assessment 5.4

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 an End of Treatment/Week 12 (V8) should be performed as soon as possible.

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 Treatment Group Only)

For subjects randomized to LCIG treatment, 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, surgeon or interventional radiologist. 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 treatment.

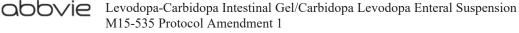
5.5.1.1 OMT

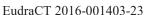
Those subjects randomized to OMT, will continue on their current anti-PD medication regimen for the duration of the study. All anti-PD medications and medications to treat dyskinesia must remain stable for the duration of the study unless adjustments are medically indicated. The Investigator will provide the prescription for continued OMT.

If modifications are needed, this should first be discussed with the AbbVie TA MD.

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.

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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. 35

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).

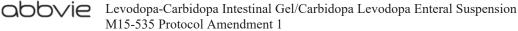
Morning Dose

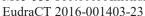
A morning dose will be administered as a bolus infusion by the pump to rapidly achieve a therapeutic dose level (over approximately 10 to 30 minutes). This morning dose is generally 5 to 10 mL and corresponds to 100 to 200 mg of levodopa.

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, interventional radiologist or experienced nurse if done via 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.

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.

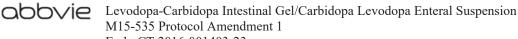
Percutaneous Endoscopic Gastrostomy with Jejunal Extension (PEG-J)

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, surgeon or interventional radiologist 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 interventional 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 interventional radiologist experienced with the placement of PEG-J tubes. Each study site should have one study designated gastroenterologist proceduralist, surgeon, or interventional radiologist and one backup who has experience with and a



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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 AbbVie TA MD. 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 caregiver 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, interventional radiologist, or their designated qualified personnel will examine the subject's stoma site between 2 to 7 days after PEG-J placement, and 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-αmethylhydrocinnamic acid monohydrate. Levodopa-carbidopa intestinal gel for upperintestinal infusion is a suspension of levodopa-carbidopa monohydrate (4:1) in an aqueous gel (carboxymethylcellulose).

5.5.2.1 **Investigational Product and Supplies**

Table 6. **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 those alone.



Table 7. 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 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 Drugs

LCIG Storage

At the LCIG distribution depot, the cassettes with the LCIG suspension can be stored in the freezer (between -15°C/5°F and -25°C/-13°F) for up to 2 years. After thawing, the LCIG suspension can be stored in a refrigerator (between 2°C/35.6°F and 8°C/46.4°F) for up to 12 weeks for US sites and up to a maximum of 15 weeks for OUS. 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 to the study site (devices and 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 4-digit number by the IRT system. At the end of 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 treatment, the site will obtain the study drug kit numbers from IRT 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 treatment in the study through the IRT.

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

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 receives extra or, if required, rescue doses.

5.5.5 Blinding

This is an open-label study with randomized treatment assignment. All eligible subjects will be randomized in a 1:1 ratio through the IRT system to receive OMT or LCIG treatment in an open-label manner. Site personnel will be blinded to the randomization schedule.

Central blinded raters will be used to rate Parts 3 and 4 of the UDysRS, the primary efficacy endpoint for this study. Assessment obtained at V3 will serve as the baseline for clinical assessment. The scales will also be performed at Weeks 2, 4, 8, and 12. The scoring for Parts 3 and 4 are to be performed by a trained central blinded 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 on the video recording of the subject.



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 to be received intact and in the correct amounts. This will be documented by the Investigator or designee 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 destructed by the depot.

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.

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 treatment 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 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
- 6. The majority of subjects 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



5.6.2 **Appropriateness of Measurements**

The Unified Dyskinesia Rating Scale (UDysRS) is a tool used to evaluate involuntary movements often associated with treated Parkinson's disease.

The Unified Dyskinesia Rating Scale (UDysRS) is a comprehensive rating tool that captures patient perceptions, time factor of dyskinesia, anatomical distribution, phenomenology (dystonia versus other dyskinesias), objective impairment, severity and disability of dyskinesia and dystonia in PD. The UDysRS was developed specifically to assess dyskinesia in PD and has been applied to PD populations. Although relatively new, multiple clinical trials of new putative anti-dyskinesia agents are currently using UDysRS as the primary endpoint. The UDysRS contains both self-evaluation questions (by the patient alone or with their caregivers) and items that are assessed directly by the physician to objectively rate the abnormal movements associate with PD. The UDysRS contains two primary sections (historical and objective) and each section is divided into two parts. All parts consist of several items and each item is scored on a scale from 0-4in a Likert model (0 = normal to 4 = severe) and the total score can range from 0 - 104. Table 8 lists the sections and corresponding parts of the UDysRS.

Table 8. **UDysRS Sections**

Section	Part	Completed by	Measure	Number of Items	Score Range
Historical disability	Part 1	Patient/Caregiver	Patient perception of on-dyskinesia impact	11 items	0 – 44
	Part 2	Patient/Caregiver	Patient perception of off-dystonia impact	4 items	0 – 16
Objective	Part 3	НСР	Rating of dyskinesia based on HCP observation of patients performing 4 motor tasks (communication, drinking, dressing ambulation)	7 items	0 – 28
	Part 4	НСР	Disability scale rating based on HCP's observation of activities performed by patient in Part 3	4 items	0 – 16



UDysRS Validation and Psychometric Properties

The original development and validation study was conducted by Goetz et al (2008). Twenty international movement disorder experts participated in the study. Internal consistency, factor structure and reproducibility of the scale were determined in 70 PD patients. The UDysRS showed high internal consistency for both the subjective (Cronbach's alpha = 0.92) and objective rating sections (Cronbach's alpha = 0.97). Interrater reliability for impairment and disability ranged from fair (kappa 0.4 - 0.59) to very good (kappa ≥ 0.8). The inter-rater reliability for the total score was very good (kappa 0.89). Intra-rater reliability also ranged from fair (kappa 0.4 - 0.59) to very good (kappa > 0.8) for both impairment and disability. The intra-rater reliability for the total score was also very good (kappa 0.90). Repeated measures ANOVA used to assess ability to detect change in UDysRS Parts 3 and 4; the UDysRS demonstrated an effect size = 0.138, with sensitivity to detect a treatment difference as small as 80% of a standard deviation (Goetz 2013).²⁴ Evidence is supportive of the ability of Parts 3 and 4 to detect change, however Parts 1 and 2 were not assessed. Convergent and discriminant validity have also not been assessed.

The UDysRS is a comprehensive rating tool to measure dyskinesia and has been studied clinimetrically as both a consistent and reliable measure. The scale however has not been assessed for construct and content validity.

Additional analysis will be performed to provide evidence on the construct validity of the UDysRS. Convergent validity will be evaluated by Spearman rank correlations between UDysRS total score (and sub-scores) and the AIMS score and Parkinson's Disease Diary assessment of severity of dyskinesia. In addition, the association with indirectly related constructs to dyskinesia, the PDQ-8 total score (measuring the PD-specific health status and quality of life) as well as the UPDRS scores for Parts II – III will be determined. Correlations ≥ 0.30 are hypothesized to support convergent validity. Discriminative validity will be explored by sub-group analyses. The UDysRS total score will be stratified by the Hoehn and Yahr stages and tested using the Kruskal-Wallis test.



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.³⁶

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 treatment, 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 12 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 6.8.2). For adverse events, please refer to Sections 6.1 through 6.6. For product complaints, please refer to Section 6.8.

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.

6.2 **Definitions**

6.2.1 **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.

6.2.2 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, 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 Life-Threatening

An event that results in the death of a subject.

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.



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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, lifethreatening, 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.

6.2.3 **Adverse Events of Special Interest**

Adverse events of special interest (AESI) are:

- Gastrointestinal and gastrointestinal procedure related events
- Polyneuropathy



Severe

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 will be issued within the Electronic Data Capture (EDC) system once applicable. The Investigator will 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 6.6.

6.3 **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. The adverse event causes the subject discomfort and interrupts the Moderate subject's usual activities.

> The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.



6.4 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	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

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.

6.5 **Adverse Event Collection Period**

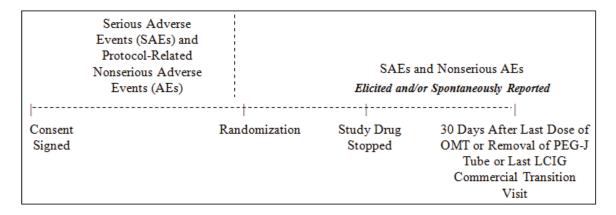
Protocol-related non-serious adverse events that occur after signing the informed consent, prior to the start of study drug administration, will be collected. All adverse events reported from the time of randomization until 30 days following last OMT dose, last study visit, discontinuation of study drug administration and 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 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**



6.6 **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) 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 the site being made aware of the serious adverse event.

Email:	
FAX to:	



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For safety concerns, contact the Neuroscience Safety Team at:

Neuroscience Clinical Safety Management Team

AbbVie	150	_	
1 North Waukegan Re	oad		
North Chicago, IL 60)064-6075		
Telephone Contact In	formation:		
Office:			
Fax:			
Fmail:			

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

Primary Medical Director:



In emergency situations involving study subjects when the primary Medical Director 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 Medical Director:

1		
Phone:		
A MOME.		



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.

6.7 **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. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.8 **Product Complaint**

6.8.1 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 components.

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.

6.8.2 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 the 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.

Protocol Deviations 7.0

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal Investigator is responsible for notifying



Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitors:

Primary Contact: Alternate Contact: Avenida de Burgos, 91 1 North Waukegan Road **28050 MADRID** North Chicago, IL 60064 **SPAIN USA** Email: Email: Office: Office: Mobile: Mobile Fax: 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**

Efficacy Dataset

Unless specified otherwise, the efficacy analyses will be performed on the intent-to-treat (ITT) dataset which will include all subjects who are randomized to the optimized medical treatment (OMT), and all subjects who are randomized to LCIG treatment and received at least one dose of study drug following PEG-J placement. For assessments of efficacy, the



treatment period will begin the day after randomization 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.

Safety Dataset

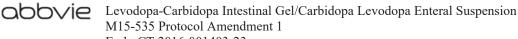
The safety analyses will be performed on the safety dataset which will include all subjects who are randomized to OMT and all subjects who are randomized to LCIG treatment and have a study tube (NJ or PEG-J) placement procedure. For assessments of safety, the treatment period will begin the day after randomization for subjects randomized to OMT, and the day of initial study tube placement (NJ or PEG-J) for subjects randomized to LCIG treatment. The treatment period will end on the day of the final visit for subjects randomized to OMT. For subjects randomized to LCIG treatment, the treatment period will end on the day of final study tube removal if all study tubes are removed on or after the last day of LCIG study drug infusion. For all other subjects randomized to LCIG treatment, the treatment period will end on the day of the final visit. 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



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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.

Baseline UDysRS total score will be summarized for the ITT dataset. One-way analysis of variance (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 be summarized for the ITT dataset.

Subject Disposition

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

The number and percentage of subjects who prematurely discontinue study drug will be summarized by treatment group and overall for the safety data set 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 drug, 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**

Unless otherwise specified, all efficacy analyses will be performed on the ITT dataset and comparisons between the OMT and LCIG treatment groups will be performed with twosided tests at the significance level of 0.050.

8.1.3.1 **Primary Efficacy Analysis**

The primary efficacy variable is the mean change from baseline to Week 12 for the UDysRS total score.

UDysRS Total Score

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

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

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

Part 1 contains 11 questions about the on time dyskinesia and the impact of on-dyskinesia on experiences of daily living. Part 2 contains 4 questions of off-dystonia rating. Part 3 contains 7 questions about objective evaluation of dyskinesia impairment and Part 4 contains 4 questions regarding dyskinesia disability. Each question is scored with respect to severity, which is rated on a scale where 0 = normal, 1 = slight, 2 = mild, 3 = moderateand 4 = severe. The UDysRS total score is obtained by summing the item scores, ranging from 0 to 104.



Primary Analysis Model

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 OMT treatment at the Week 12 Visit.

Additional Analysis of the Primary Efficacy Variable

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Analysis of covariance (ANCOVA) analyses will be carried out on change from baseline to final UDysRS total score. The ANCOVA model will contain treatment and country as the main effects and baseline score as the covariate.

The ITT dataset will not include subjects randomized to LCIG who prematurely discontinue before receiving their first LCIG infusion. To evaluate the impact of not including these subjects in the primary efficacy analysis, a sensitivity analyses will be carried out 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 a post-randomization assessment of UDysRS.

8.1.3.2 **Secondary Efficacy Analysis**

The secondary efficacy variables are the mean change from baseline to Week 12 in the following measures:

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



Each secondary efficacy variable will be analyzed with the same MMRM model as the primary analysis. PD Diary variables will be normalized to a 16 hour awake time and the time recorded by the subject on the 3 diaries completed prior to each visit will be averaged.

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

8.1.3.3 **Additional Efficacy and Health Outcomes Analyses**

Efficacy will also be assessed using the following additional measures:

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

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

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

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

Missing data are expected to occur at random and to be largely due to co-morbidities in this advanced Parkinson's disease population. To evaluate this assumption, the MMRM analysis of the primary and secondary variables will be repeated using only subjects who completed the planned treatment period and additional sensitivity analyses to evaluate the



impact of missing data on the primary efficacy results will be performed. These sensitivity analyses will be described in the Statistical Analysis Plan (SAP).

8.1.4 **Safety Analysis**

All safety analysis will be performed on the safety dataset unless otherwise specified. Comparisons between LCIG treatment and OMT groups will be performed with twosided 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 Fisher's exact test.

8.1.4.1 **OMT and LCIG Treatment 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 LCIG device exposure will be calculated for each subject as the date of the last study tube exposure minus the date of the first study tube placement procedure plus 1. For subjects with all study tubes removed on or after the last day of LCIG study drug infusion, the date of last study tube exposure will be the last tube removal date. For all other subjects randomized to LCIG treatment, the date of last study tube exposure will be the day of the final visit. The duration of OMT and LCIG study drug exposure and LCIG device exposure will be summarized with descriptive statistics (number of subjects with non-missing data, mean, and 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 an SAP prior to database lock.

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

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

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 treatment group, as well as adverse events during the transition period for LCIG treatment 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 and for both treatment groups combined. For this analysis, the average of multiple observations on the same day will be calculated and treated as the observation for the day.

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 for each treatment group.

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 for each treatment group and for both treatment groups combined.

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 and for both treatment groups combined. For this analysis, the average of multiple observations on the same day will be calculated and treated as the observation for the day.



Criteria for potentially clinically significant (PCS) values for selected vital sign and weight variables will be pre-specified 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.

8.1.4.5 **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 and for both treatment groups combined. For this analysis, the average of multiple observations on the same day will be calculated and treated as the observation for the day.

Criteria for potentially clinically significant (PCS) values for selected ECG variables will be pre-specified 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 for each treatment group and for both treatment groups combined.

8.1.4.6 **Additional Safety Variables**

The following additional summaries of safety measures will be prepared.

- The number of subjects with 1 or more positive screens on a Minnesota Impulsive Disorders Interview (MIDI) module at baseline as well as during the treatment period, and
- The number of subjects with 1 or more affirmative responses to the Columbia Suicide Severity Rating Scale (C-SSRS) at baseline as well as during the treatment period.

8.1.5 **Interim Analysis**

No interim analysis is planned for this study.



8.2 **Determination of Sample Size**

Approximately 60 subjects will be enrolled into the study and randomized in a 1:1 ratio to either optimized medical treatment (OMT) or LCIG treatment. Subject randomization will be stratified by country. For sample size determination, it is assumed that the difference of improvement is 10 points on UDysRS total score between the LCIG treatment group and OMT group based on results reported by Pahwa et al. 37 The pooled standard deviation is assumed to be 12 based on results reported by Goetz et al. 24 Assuming that the treatment group difference is 10 points and the pooled standard deviation is 12, 27 subjects per group will have 85% power to declare statistical significance on the primary endpoint at a two-sided significance level of 0.050. It is further assumed that 10% of randomized subjects in either treatment group will not provide post-randomization efficacy assessment. Therefore the total planned enrollment is decided to be approximately 60 subjects.

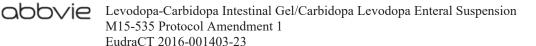
8.3 **Randomization Methods**

Approximately 60 subjects will be enrolled into the study and randomized in a 1:1 ratio to either LCIG or OMT 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.

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. The subject must be able to understand the nature of the study and have the opportunity to have any questions answered by the Investigator. 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 Investigator will prepare the 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 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 Investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB 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(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.

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.

Completion of the Study 13.0

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 retain any records related to the study according to local 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.



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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 12 Week Study Comparing Efficacy of Levodopa-Carbidopa Intestinal Gel/Carbidopa-Levodopa Enteral Suspension and Optimized Medical Treatment on Dyskinesia in Subjects with Advanced Parkinson's Disease DYSCOVER (DYSkinesia COmparative interventional trial on Duodopa VERsus oral medication) Protocol Date: 26 May 2016

Signature of Principal Investigator	Date	
Name of Principal Investigator (printed or typed)		



15.0 Reference List

- 1. Nyholm D, Aquilonius SM. Levodopa infusion therapy in Parkinson disease: state of the art in 2004. Clin Neuropharmacol. 2004;27(5):245-56.
- Nyholm D, Nilsson Remahl AI, Dizdar N, et al. Duodenal levodopa infusion 2. monotherapy vs oral polypharmacy in advanced Parkinson disease. Neurology. 2005;64(2):216-23.
- 3. Agid Y, Ahlskog E, Albanese A, et al. Levodopa in the treatment of Parkinson's disease: a consensus meeting. Mov Disord. 1999;14(6):911-3.
- 4. van Laar T. Levodopa-induced response fluctuations in patients with Parkinson's disease: strategies for management. CNS Drugs. 2003;17(7):475-89.
- Mouradian MM, Heuser IJ, Baronti F, et al. Pathogenesis of dyskinesias in 5. Parkinson's disease. Ann Neurol. 1989;25(5):523-6.
- 6. Stocchi F, Vacca L, Ruggieri S, et al. Intermittent vs continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. Arch Neurol. 2005;62(6):905-10.
- 7. Movement Disorder Society. Management of Parkinson's disease: an evidence based review. Mov Disord. 2002;17 (Suppl 4):S1-166.
- 8. Shoulson I, Glaubiger GA, Chase TN. On-off response. Clinical and chemical correlations during oral and intravenous levodopa administration in parkinsonian patients. Neurology. 1975;25(12):1144-8.
- 9. Quinn N, Marsden CD, Parkes JD. Complicated response fluctuations in Parkinson's disease: response to intravenous infusion of levodopa. Lancet. 1982;2(8295):412-5.
- 10. Quinn N, Parkes JD, Mardsen CD. Control of on/off phenomenon by continuous intravenous infusion of levodopa. Neurology. 1984;34(9):1131-6.
- 11. Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med. 2001;345(13):956-63.



- 12. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med. 2006;355(9):896-908.
- 13. Weaver F, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009;301(1):63-73.
- 14. Hariz MI. Complications of deep brain stimulation surgery. Mov Disord. 2002;17 (Suppl 3):S162-6.
- 15. Nyholm D, Askmark H, Gomes-Trolin C, et al. Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. Clin Neuropharmacol. 2003;26(3):156-63.
- 16. Olanow CW, Kieburtz K, Odin P, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol. 2014;13(2):141-9.
- 17. Slevin JT, Fernandez HH, Zadikoff C, et al. Long-term safety and maintenance of efficacy of levodopa-carbidopa intestinal gel: an open-label extension of the double-blind pivotal study in advanced Parkinson's disease patients. J Parkinsons Dis. 2015;5(1):165-74.
- 18. Fernandez HH, Standaert DG, Hauser RA, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord. 2015;30(4):500-9.
- 19. Olanow CW, Antonini A, Kieburtz K, et al. Randomized, double-blind, doubledummy study of continuous infusion of levodopa-carbidopa intestinal gel in patients with advanced parkinson's disease: efficacy and safety. In: Movement Disorder Society International Congress; June 17-21, 2012; Dublin, Ireland. Abstract 411.
- 20. Westin J, Nyholm D, Groth T, et al. Outcome prediction of enteral levodopa/carbidopa infusion in advanced Parkinson's disease. Parkinsonism Relat Disord. 2006;12(8):509-13.



- Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, et al; NMSS Validation 21. Group. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord. 2011;26(3):399-406.
- 22. Kieburtz K, Antonini A, Olanow CL, et al. Randomized, double-blind, doubledummy study of continuous infusion of levodopa-carbidopa intestinal gel in patients with advanced parkinson's disease: functional and quality-of-life outcomes. In: Movement Disorder Society International Congress; June 17-21, 2012; Dublin, Ireland. Abstract 385.
- 23. Goetz CG, Nutt JG, Stebbins GT, et al. T The Unified Dyskinesia Rating Scale: presentation and clinimetric profile. Mov Disord. 2008;23(16):2398-403.
- 24. Goetz CG, Stebbins GT, Chung KA, et al. Which dyskinesia scale best detects treatment response? Mov Disord. 2013;28(3):341-6.
- 25. Antonini A, Fung VS, Boyd JT, et al. Effect of levodopa-carbidopa intestinal gel on dyskinesia in advanced Parkinson's disease patients. Mov Disord. 2016;31(4):530-7.
- 26. Poewe et al. Global Long-term Registry on Efficacy and Safety of Levodopa-Carbidopa Intestinal Gel in Patients with Advanced Parkinson's Disease in Routine Care (GLORIA) – Interim Results in a Subgroup of Patients with Dyskinesia at Baseline. 2015.
- 27. AbbVie. Levodopa-Carbidopa Investigator's Brochure Edition 11. 06 April 2016.
- 28. Folstein SE, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res. 1975;12(3):189-98.
- 29. Christenson GA, Faber JR, de Zwann M. Compulsive buying: descriptive characteristics and psychiatric comorbidity. J Clin Psychiatry. 1994;55(1):5-11.
- 30. Columbia-Suicide Severity Rating Scale (C-SSRS) [homepage on the Internet]. Columbia University Medical Center. Available from: http//www.cssrs.columbia.edu/.



- Martinez-Martin P, Gil-Nagel A, Gracia LM, et al. Unified Parkinson's Disease 31. Rating Scale characteristics and structure. The Cooperative Multicentric Group. Mov Disord. 1994;9(1):76-83.
- 32. Guy W. ECDEU Assessment Manual for Psychopharmacology: US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, Rockville, Md, USA.; 1976;534-7.
- 33. Rizos AM, Martinez-Martin P, Pal S, et al. Validation of a novel Parkinson's disease pain scale (King's PD pain scale): a multicentre pilot study. Poster presented at: The 18th International Congress of Parkinson's Disease and Movement Disorders; June 8-12, 2014; Stockholm, Sweden. Poster 510.
- 34. Jenkinson C, Fitzpatrick R, Peto V. The Parkinson's Disease Questionnaire: User Manual for the PDQ-39, PDQ-8 and the PDQ Summary Index. Oxford: Health Services Research Unit. 1998.
- Weintrub D, Oehlberg KA, Katz IR, et al. Test characteristics of the 15-item 35. geriatric depression scale and Hamilton depression rating scale in Parkinson disease. Am J of Geriatr Psychiatry. 2006;14(2):169-75.
- 36. Duodopa Intestinal Gel [Summary of Product Characteristics]. North Chicago, IL; AbbVie Inc., 2014.
- 37. Pahwa R, Tanner CM, Hauser RA, et al. Amantadine extended release for levodopa-induced dyskinesia in Parkinson's disease (EASED Study). Mov Disord. 2015;30(6):788-95.



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.



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



Levodopa-Carbidopa Intestinal Gel/Carbidopa Levodopa Enteral Suspension M15-535 Protocol Amendment 1 EudraCT 2016-001403-23

Appendix B. **List of Protocol Signatories**

Name	Title	Functional Area
		Global Medical Affairs
		Global Medical Affairs
		Clinical
		Statistics
		Statistics

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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
 - 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.

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Potentially Clinically Significant Laboratory Values for Study M15-535 Appendix D.

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	ŀ
Hemaglobin decreased	2	$< 10.0 \mathrm{~g/dL}$	<LLN -10.0 g/dL	< 10.0 - 8.0 g/dL	<8.0 g/dL	Life-threatening
		< 6.2 mmol/L	< LLN – 6.2 mmol/L	< 6.2 – 4.9 mmol/L	< 4.9 mmol/L	consequences; urgent intervention indicated
		$< 100 \mathrm{~g/L}$	<LLN -100 g/L	$< 100 - 80 \mathrm{g/L}$	< 80 g/L; transfusion indicated	
Hemaglobin increased	3	> 4 gm/dL above	Increase in	Increase in	Increase in > 4 gm/dL above	:
		OLN	> 0 - 2 gm/dL above	> 2 - 4 gm/dL above	ULN or above baseline if	
			ULN or above	ULN or above	baseline is above ULN	
			baseline if baseline is above ULN	baseline if baseline is above ULN		
INR increased	1	> ULN	>1-1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN	1
			> 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	۳	> 100.000/mm ³	:	1	> 100.000/mm ³	Clinical
(WBC increased))					manifestations of
						leucostasis; urgent
						IIItel velition marcated
Lymphocyte count	3	$< 500 / \text{mm}^3$	< LLN $-$ 800/mm ³	$< 800 - 500/\text{nm}^3$	$< 500 - 200/\text{mm}^3$	$< 200 / \text{mm}^3$
decreased		$<0.5\times10^9/{\rm L}$	$< LLN - 0.8 \times 10^9/L$	$< 0.8 - 0.5 \times 10^9 / L$	$< 0.5 - 0.2 \times 10^9 / L$	$< 0.2 \times 10^9/\mathrm{L}$
Lymphocyte count increased	3	$> 20,000/{ m mm}^3$	1	> 4000 – 20,000/mm ³	$>20,\!000/\mathrm{mm}^3$:

CTCAE v4.0 Term	PCS Value/Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hematology (continued)	(p					
Neutrophil count	3	< 1000/mm ³	$<$ LLN -1500 /mm 3	$< 1500 - 1000/\text{mm}^3$	$< 1000 - 500 / \text{mm}^3$	< 500/mm ³
decreased		$< 1.0 \times 10^9/L$	$<$ LLN -1.5×10^9 /L	$< 1.5 - 1.0 \times 10^9 / L$	$< 1.0 - 0.5 \times 10^9 / L$	$< 0.5 \times 10^9/L$
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
		$< 75.0 \times 10^{9}/L$	$< LLN - 75.0 \times 10^9/L$	$< 75.0 - 50.0 \times 10^9 / L$	$< 50.0 - 25.0 \times 10^9 / L$	$< 25.0 \times 10^{9}/L$
White blood cell	3	< 2000/mm ³	< LLN – 3000/mm ³	$< 3000 - 2000/\text{mm}^3$	$< 2000 - 1000 / \text{mm}^3$	< 1000/mm ³
decreased		$< 2.0 \times 10^9/L$	$<$ LLN -3.0×10^9 /L	$< 3.0 - 2.0 \times 10^9 / L$	$< 2.0 - 1.0 \times 10^9 / L$	$< 1.0 \times 10^{9}/L$
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	$> 1.5 \times ULN$	$> 1 - 1.5 \times baseline$	$> 1.5 - 3.0 \times baseline$	> 3.0 baseline	NTO × 0.0 <
			> ULN – 1.5 × ULN	$> 1.5 - 3.0 \times ULN$	$> 3.0 - 6.0 \times \text{ULN}$	
GGT increased	2	$> 2.5 \times ULN$	$>$ ULN $-2.5 \times$ ULN	$> 2.5 - 5.0 \times ULN$	$> 5.0 - 20.0 \times ULN$	$> 20.0 \times ULN$
				Corrected Serum Calcium of:	um 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	cose 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
Hypermagnesemia	3	> 3.0 mg/dL	> ULN - 3.0 mg/dL	1	> 3.0 - 8.0 mg/dL	> 8.0 mg/dL
		> 1.23 mmol/L	> ULN - 1.23 mmol/L		> 1.23 – 3.30 mmol/L	> 3.30 mmol/L; life-threatening consequences
Hypernatremia	С	> 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	4	> 10 mg/dL	> ULN - 10 mg/dL	1	> ULN -10 mg/dL (0.59	> 10 mg/dL
Acid Increased)		> 0.59 mmol/L	(0.59 mmol/L) without physiologic consequences		mmol/L) with physiologic consequences	> 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
		$< 20 \mathrm{~g/L}$	< LLN – 30 g/L	<30 – 20 g/L	< 20 g/L	consequences; urgent intervention indicated
				Corrected Serum Calcium	cium	
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;	< 0.9 – 0.8 mmol/L;	< 0.8 mmol/L;
				symptomatic	hospitalization indicated	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	8	< 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
Hypomagnesemia	3	< 0.9 mg/dL	< LLN - 1.2 mg/dL	< 1.2 – 0.9 mg/dL	$< 0.9 - 0.7 \mathrm{mg/dL}$	< 0.7 mg/dL
		< 0.4 mmol/L	< LLN – 0.5 mmol/L	< 0.5 – 0.4 mmol/L	< 0.4 – 0.3 mmol/L	< 0.3 mmol/L; life-threatening consequences
Hyponatremia	3	< 130 mmol/L	< LLN – 130 mmol/L	ŀ	< 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	2	> 3 × ULN	> ULN - 3.0 × ULN	$> 3.0 - 5.0 \times ULN$	> 5.0 – 20.0 × ULN	> 20.0 × ULN
aminotransferase (ALT) increased						
Alkaline phosphatase increased	2	> 2.5 × ULN	> ULN – 2.5 × ULN	$> 2.5 - 5.0 \times \text{ULN}$	$> 5.0 - 20.0 \times \text{ULN}$	> 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	$> 25 \times \text{ULN} - 5 \times \text{ULN}$	$> 5 \times \text{ULN} - 10 \times \text{ULN}$	> 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.

Global Protocol Change

Change the study duration from 26 weeks to 12 weeks.

Specific Protocol Changes

Section 1.1 Synopsis "Name of Study Drug:" previously read:

Levodopa-Carbidopa Intestinal Gel (OUS)/Carbidopa-Levodopa Enteral Suspension (US)

Has been changed to read:

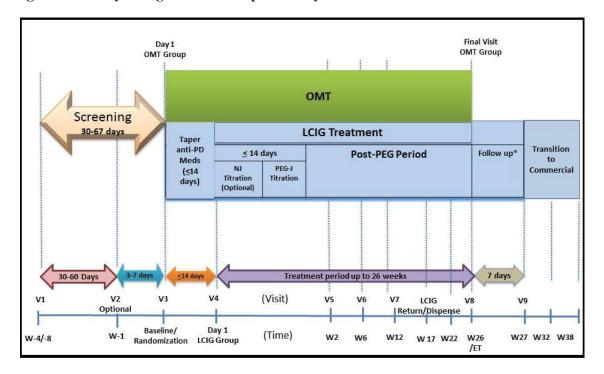
Levodopa-Carbidopa Intestinal Gel (Outside United States)/Carbidopa-Levodopa Enteral Suspension (United States)

Section 1.1 Synopsis Subsection Objectives: Heading "Health Related Outcomes Will Be Measured by:" Add: new fourth bullet

Clinical Global Impression of Severity (CGI-S)

Section 1.1 Synopsis Subsection Methodology:

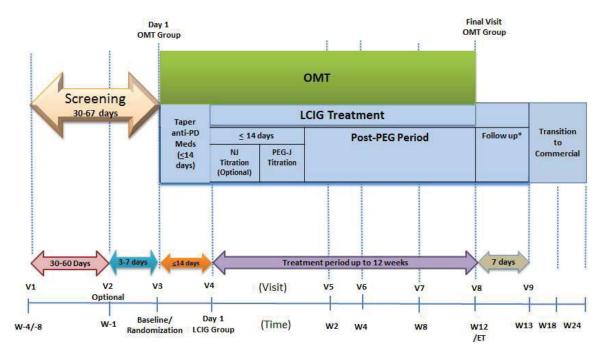
Figure 1: Study Design Schematic previously read:



* Follow up period only applicable to LCIG treatment arm subjects that have discontinued the study for any reason. 7 days after the PEG-J removal, a follow-up visit (V9) will be conducted.



Has been changed to read:



Follow up period only applicable to LCIG treatment arm subjects that have discontinued the study for any reason. 7 days after the PEG-J removal, a follow-up visit (V9) will be conducted.

Section 1.1 Synopsis Subsection Methodology: Heading "Treatment Period V4 - V8" First paragraph, first sentence previously read:

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).

Has been changed to read:

Those subjects randomized to continue OMT will remain on their current optimized regimen and will have study visits at the end of Weeks 2, 4, 8, and 12 following randomization (V3).



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Section 1.1 Synopsis Subsection Methodology: Heading "Treatment Period V4 - V8" Second paragraph, second sentence previously read:

Those subjects randomized to LCIG treatment must discontinue all other anti-PD medications (e.g., dopamine agonists, COMT-inhibitors, MAO-B inhibitors, anticholinergies, and subcutaneous apomorphine, etc.) prior to LCIG treatment initiation on Day 1 (V4); these medications should be tapered off according to their individual package insert, and at the discretion of the Investigator, over a period of up to 14 days.

Has been changed to read:

Those subjects randomized to LCIG treatment must discontinue all other anti-PD medications except amantadine (e.g., dopamine agonists, COMT-inhibitors, MAO-B inhibitors, anti-cholinergics, and subcutaneous apomorphine, etc.) prior to LCIG treatment initiation on Day 1 (V4); these medications should be tapered off according to their individual package insert, and at the discretion of the Investigator, over a period of up to 14 days.

Section 1.1 Synopsis Subsection Methodology: Heading "Treatment Period V4 - V8" Fourth paragraph, last sentence previously read:

Subjects on LCIG treatment will return for study visits at the end of Weeks 2, 6, 12 and 26 and following PEG-J placement.

Has been changed to read:

Subjects on LCIG treatment will return for study visits at the end of Weeks 2, 4, 8, and 12 and following PEG-J placement.

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Section 1.1 Synopsis Subsection Methodology:

Heading "Treatment Period V4 - V8"

Delete: fifth paragraph

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 (\pm 7 days). Other assessments may be completed during these visits if required.

Section 1.1 Synopsis Subsection Methodology: Heading "Study Follow-Up" Last paragraph previously read:

For all study treatment visits (V4 to V9) $a \pm 3$ days visit window will be allowed. The drug dispensing visits will occur at Weeks 17 and 22 with an allowed visit window of \pm 7 days if deemed necessary

Has been changed to read:

For all study visits apart from V1 to V3 a \pm 3 days visit window will be allowed.

Section 1.1 Synopsis

Subsection Diagnosis and Main Criteria for Inclusion/Exclusion:

Heading "Main Exclusion:"

Delete: Criterion 4

Patients with previous treatment with continuous subcutaneous apomorphine infusion.

Section 1.1 Synopsis

Subsection Criteria for Evaluation:

Heading "Efficacy:"

Subheading "Additional Efficacy Endpoints are:"

Add: new first bullet

UDysRS Historical Score, Objective Score and Parts 1 through 4 Scores

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Section 1.1 Synopsis

Subsection Criteria for Evaluation:

Heading "Efficacy:"

Subheading "Additional Health Outcome Endpoints are:"

Delete: last bullet

Percentage (%) of CGI-C responders ("minimally improved," "much improved" or "very much improved")

Section 1.1 Synopsis

Subsection Statistical Methods:

Heading "Efficacy:"

Subheading "Additional Efficacy and Health Outcome Analyses"

First paragraph

Add: new first bullet

UDysRS Historical Score, Objective Score and Parts 1 through 4 Scores

Section 1.1 Synopsis

Subsection Statistical Methods:

Heading "Efficacy:"

Subheading "Additional Efficacy and Health Outcome Analyses"

Second paragraph **Delete: last bullet**

Percentage (%) of CGI-C responders ("minimally improved," "much improved" or "very much improved")

Section 1.1 Synopsis

Subsection Statistical Methods:

Heading "Efficacy:"

Subheading "Additional Efficacy and Health Outcome Analyses"

Last paragraph

Delete: last sentence

Categorical endpoints will be analyzed with a Fisher's exact test.

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Section 1.2 List of Abbreviations and Definition of Terms Subsection Abbreviations

Add: "OUS"

OUS Outside United States

Section 3.0 Introduction Subsection <u>UDysRS Validation and Psychometric Properties</u> First paragraph, last sentence previously read:

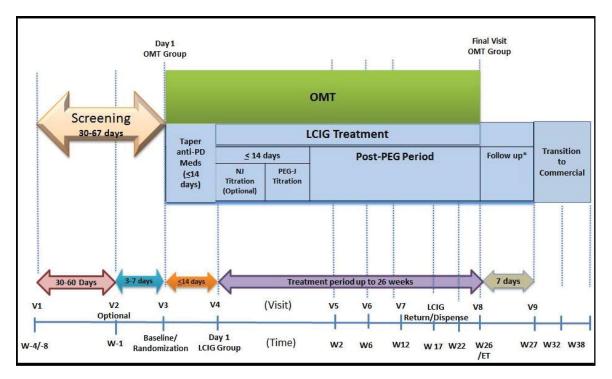
Convergent, content and discriminant validity have also not been assessed.

Has been changed to read:

Convergent and discriminant validity have also not been assessed.



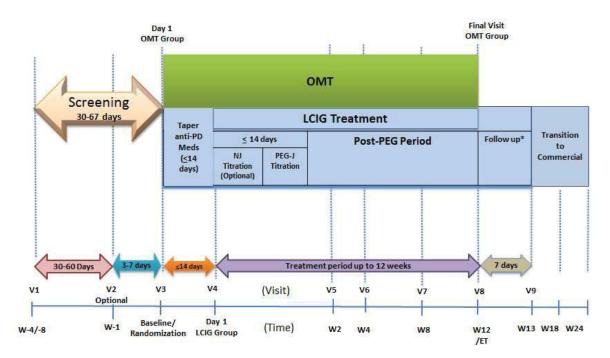
Figure 2. Study Design Schematic Previously read:



Follow up period only applicable to LCIG treatment arm subjects that have discontinued the study for any reason. 7 days after the PEG-J removal, a follow-up visit (V9) will be conducted.

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Has been changed to read:



* Follow up period only applicable to LCIG treatment arm subjects that have discontinued the study for any reason. 7 days after the PEG-J removal, a follow-up visit (V9) will be conducted.

Section 4.0 Study Objective Subsection <u>Health Related Outcomes Will Be Measured by:</u> Add: new fourth bullet

Clinical Global Impression of Severity (CGI-S)

Section 5.1.1 Screening Period Subsection <u>Visit 1 (V1)</u> Fourth bullet Add: new last sentence

If the concordance criteria are not met again the subject should be considered not-eligible for the study.

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Section 5.1.1 Screening Period Subsection Visit 3 (V3) First paragraph Add: new last sentence

The UDysRS shall be administered and the videotape forwarded to the Central Blinded Rater on the first day of assessments.

Section 5.1.2 The Treatment Period Previously read:

For all study treatment visits (V4 to V9) $a \pm 3$ days visit window will be allowed. The drug dispensing visits will occur at Weeks 17 and 22 with an allowed visit window of \pm 7 days if deemed necessary.

Has been changed to read:

For all study visits apart from V1 to V3 a \pm 3 days visit window will be allowed.

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

Subjects randomized to LCIG treatment must discontinue all other anti-PD medications (e.g., dopamine agonists, COMT-inhibitors, MAO-B inhibitors, anti-cholinergies, and subcutaneous apomorphine, etc.) prior to LCIG treatment initiation on Day 1 (V4); these medications should be tapered off within 14 days after randomization according to the discretion of the Investigator.

Has been changed to read:

Subjects randomized to LCIG treatment must discontinue all other anti-PD medications other than amantadine (e.g., dopamine agonists, COMT-inhibitors, MAO-B inhibitors, anti-cholinergics, and subcutaneous apomorphine, etc.) prior to LCIG treatment initiation on Day 1 (V4); these medications should be tapered off within 14 days after randomization according to the discretion of the Investigator.

Section 5.1.2.2 LCIG Treatment Group Subsection LCIG Initiation and Titration

First paragraph, second sentence previously read:

All other oral anti-PD medications must be stopped prior to LCIG initiation.

Has been changed to read:

All other oral anti-PD medications other than amantadine must be stopped prior to LCIG initiation.

Section 5.1.2.2 LCIG Treatment Group Subsection LCIG Initiation and Titration Fourth paragraph

Delete: eighth and ninth sentence

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.

Section 5.1.2.2 LCIG Treatment Group

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

First paragraph, first sentence previously read:

Visit 5 will be conducted at Week 2, 14 days post PEG-J insertion.

Has been changed to read:

Visit 5 will be conducted at Week 2, 14 days post NJ and/or PEG-J insertion.

Section 5.1.2.2 LCIG Treatment Group

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

First paragraph, fifth sentence previously read:

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 4.

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Has been changed to read:

Visits 6, 7 and 8 at the end of Weeks 4, 8 and 12 respectively will be recorded on the appropriate eCRF and the assessments completed as in Table 4.

Section 5.1.2.2 LCIG Treatment Group

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

Heading "Drug Dispensing Visits" Delete: heading title and text

Drug Dispensing Visits

The drug dispensing will occur during each of the study visit from V4 (Day1) until V8 (Week 26). In addition, LCIG 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.

Section 5.1.3 Study Follow-Up

Subsection Commercial Transition Visits (LCIG Treatment Subjects Continuing on **Commercial Product)**

Last paragraph, last sentence previously read:

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 Adverse Drug Reaction (ADR) reporting in accordance with local instructions.

Has been changed to read:

Follow-up care in these circumstances will be based on the judgment of the subject's personal physician and, following the 30 day SAE/AE follow-up period, no formal collection of data will be conducted except for regular Adverse Drug Reaction (ADR) reporting in accordance with local instructions.

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Section 5.2.2 Exclusion Criteria

Delete: Criterion 4

Patients with previous treatment with continuous subcutaneous apomorphine infusion.

Section 5.2.2 Exclusion Criteria **Subsection Rationale for Exclusion Criteria Previously read:**

1, 7, 8, 10, 16 – 19, 25, 26	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 treatment for safety events
6, 9, 11 - 15, 20, 23 - 24	To ensure safety of the subjects throughout the study
2 – 5, 21 – 22, 29	To exclude, or to minimize, the number of medications or other factors that could interfere with the LCIG treatment, or could add unnecessary variance or bias to safety evaluations
27 – 28	The impact of LCIG treatment on pregnancies and lactation is unknown

Has been changed to read:

1, 6, 7, 9, 15 – 18, 24, 25	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 treatment for safety events
5, 8, 10 – 14, 19, 22 – 23	To ensure safety of the subjects throughout the study
2-4, 20-21, 28	To exclude, or to minimize, the number of medications or other factors that could interfere with the LCIG treatment, or could add unnecessary variance or bias to safety evaluations
26 – 27	The impact of LCIG treatment on pregnancies and lactation is unknown

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

LCIG treatment Group: Those subjects randomized to LCIG treatment must discontinue all other anti-PD medications (e.g., dopamine agonists, COMT-inhibitors, 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, over a period of up to 14 days.

Has been changed to read:

LCIG treatment Group: Those subjects randomized to LCIG treatment must discontinue all other anti-PD medications other than amantadine (e.g., dopamine agonists, COMT-inhibitors, MAO-B inhibitors, anti-cholinergics, and subcutaneous apomorphine, etc.) prior to LCIG initiation on Day 1 (V4); these medications should be tapered off according to their individual package insert, and at the discretion of the Investigator, over a period of up to 14 days.

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

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 treatment.

Has been changed to read:

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 appropriate eCRF, except for study drug for subjects randomized to LCIG treatment.



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Section 5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart Third and fourth sentence previously read:

For all study treatment visits (V4 to V9) $a \pm 3$ days visit window will be allowed. The drug dispensing visits will occur at Weeks 17 and 22 with an allowed visit window of \pm 7 days if deemed necessary.

Has been changed to read:

For all study visits apart from V1 to V3 a \pm 3 days visit window will be allowed.

Table 4. Study Activities Header row previously read:

		OMT/LCIG	9	LCIG Treatment	eatment	ON Tr	OMT/LCIG Treatment	ر ن	LCIG Treatment (Drug Dispensing Visits Only)		OMT/ LCIG Treatment	TCIC	LCIG Treatment
Activity	V1 Screening	V1 V2 Screening Screening	V3 Randomization	V4 NJ/PEG-J Placement D1	Titration Visits	V5 Wk	V6 Wk 6	V7 Wk	17 Wk	Wk 22	V8 Wk 26/ET	V9 Wk 27 FU ^a	Transition to Commercial Visits

Has been changed to read:

		OMT/LCI	ŭ	LCIG Treatmen	eatment)	OMT/LCIG Treatme	IG Tre	atment	TCI	LCIG Treatment
				V4						6A	
				NJ/PEG-J		V 5	9/	V7		Wk	Transition to
	V1	V2	V3	Placement	Titration	Wk	Wk	Wk	8/	13	Commercial
Activity	Screening	Screening	Randomization	D1	Visits	7	4	∞	Wk 12/ET	${ m FU}^{ m a}$	Visits ^b

Activity "Concomitant Medication (including anti-PD and Dyskinesia medications)" previously read: Table 4. Study Activities

		OMT/LCIG	9	LCIG Treatment	eatment	ON	OMT/LCIG Treatment	Ţ Ġ	LCIG Treatment (Drug Dispensing Visits Only)	,	OMT/ LCIG Treatment	TCIG	LCIG Treatment
Activity	V1 Screening	V1 V2 Screening Screening	V3 Randomization	V4 NJ/PEG-J Placement D1	Titration Visits	VS Wk	V6 Wk	V7 Wk	Wk v	Wk	V8 Wk 26.F.T	V9 Wk 27 FII ^a	Transition to Commercial Visite
Concomitant Medication (including anti-PD and Dyskinesia medications)	×	×	×	X	×	×		! ×			×	<u> </u>	

Has been changed to read:

		OMT/LCIG	G	TCIG Tr	LCIG Treatment	0	OMT/LCIG Treatment	IG Tre	atment	TCI	LCIG Treatment
	V1	V2	V3	V4 NJ/PEG-J Placement	Titration	V5 Wk	V6 Wk	V7 Wk	8/	V9 Wk 13	Transition to Commercial
Activity	Screening	Screening	Randomization	D1	Visits	2	4	8	Wk 12/ET	${ m FU}^{ m a}$	Visits ^b
Concomitant Medication (including anti-PD and Dyskinesia medications)	X	X	X	X	X	×	X	×	X	X	X



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Table 4. Study Activities Activity "PEG-J Placement Procedure" previously read:

PEG-J Placement Procedureⁱ

Has been changed to read:

PEG-J Placement Procedure^h

Table 4. Study Activities Activity "Dose Titration Diary" previously read:

		OMT/LCIG	<u></u>	LCIG Treatment	eatment	ON	OMT/LCIG Treatment	ن ن	LCIG Treatment (Drug Dispensing Visits Only)	ent gg ing ing	OMT/ LCIG Treatment	TCIC	LCIG Treatment
Activity	V1 Screening	V1 V2	V3 Randomization	V4 NJ/PEG-J Placement T D1	Titration Visits	V5 Wk	V6 Wk 6	V7 Wk	Wk 17	Wk 22	V8 Wk 26/ET	V9 Wk 27 FU ^a	Transition to Commercial Visits
Dose Titration Diary					X					\prod			

Has been changed to read:

		OMT/LCIG	G	LCIG Treatment	eatment)	OMT/LCIG Treatment	IG Tre	atment	TCI	LCIG Treatment
				V4						6A	
				NJ/PEG-J		V 5	9/	77		Wk	Transition to
	V1	V2	V3	Placement	Titration	Wk	Wk	Wk	8/	13	Commercial
Activity	Screening	Screening	Randomization	D1	Visits	7	4	∞	Wk 12/ET	FU^{a}	Visits
Dose Titration Diary				X	X						

Table 4. Study Activities Activity "UPDRS II and IIIs" previously read:

LCIG Treatment	Transition to Commercial Visits
LCIGT	V9 T Wk 27 Cc FU ^a
OMT/ LCIG Treatment	V8 Wk 26/ET X
LCIG Treatment (Drug Dispensing Visits Only)	Wk 22
LC Trea (D Dispo	Wk 17
IG nt	V7 Wk 12
OMT/LCIG Treatment	V5 V6 Wk Wk 2 6
O! T	V5 Wk
eatment	Titration Visits
LCIG Treatment	V4 NJ/PEG-J Placement D1
9	V3 Randomization X
OMT/LCIG	V2 Screening
	V1 Screening
	Activity UPDRS II and III ^s

Has been changed to read:

		OMT/LCIG	7 18	LCIG Treatmen	eatment)	OMT/LCIG Treatment	IG Tre	atment	ICI	LCIG Treatment
				V4						6Λ	
				NJ/PEG-J		V 5	9/	77		Wk	Transition to
		V2	V3	Placement	Titration	Wk	Wk	Wk	8/	13	Commercial
Activity	V1 Screening Screening	Screening	Randomization	D1	Visits	7	4	∞	Wk 12/ET	${ m FU}^{ m a}$	Visits ^b
UPDRS II and III ^t	X		X			X	X	X	X		



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Table 4. Study Activities Activity "UDysRS" previously read:

UDysRS

Has been changed to read:

UDysRS^s

Table 4. Study Activities Activity "mAIMS" previously read:

mAIMS

Has been changed to read:

 $mAIMS^{u}$

Table 4. Study Activities Table note "g.," first and second sentence previously read:

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 3, the Investigator and GI/surgeon or interventional radiologist, or their designated qualified personnel will thoroughly evaluate the subject's risk of undergoing PEG-J procedure.

Has been changed to read:

At Screening Visit 1 and Randomization Visit 3 a full physical examination will be performed. Symptom-driven physical examinations will be performed at subsequent visits. Prior to Visit 3, the Investigator and GI/surgeon or interventional radiologist, or their designated qualified personnel will thoroughly evaluate the subject's risk of undergoing PEG-J procedure.

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Table 4. Study Activities

Table note "i.," last sentence previously read:

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

Has been changed to read:

Additional checks can be done at any time during treatment if indicated for worsening of

Parkinsonian symptoms not responsive to extra doses.

Table 4. Study Activities

Table note "p."

Delete: second and third sentence

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.

Table 4. Study Activities

Add: table note "s." and "u."

The subject's expected time of peak dose dyskinesia should be determined during screening and the UDysRS

should be administered at this time throughout the study.

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

Section 5.3.1.1 Study Procedures

Subsection Unified Dyskinesia Rating Scale UDysRS

Third paragraph previously read:

The dimensions are evaluated through both an investigation and interview carried out by the physician/rater and self-administered questionnaire. The UDysRS assessment will be performed by an experienced rater. Rater training will be provided by the Sponsor as appropriate.

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Has been changed to read:

The Historical Score is the sum of Parts 1 and 2 and the Objective Score is the sum of Parts 3 and 4. The dimensions are evaluated through both an investigation and interview carried out by the physician/rater and self-administered questionnaire. The UDysRS assessment will be performed by an experienced rater. Rater training will be provided by the Sponsor as appropriate. The subject's expected time of peak dose dyskinesia should be determined during screening and the UDysRS should be administered at this time throughout the study.

Section 5.3.1.1 Study Procedures
Subsection <u>Unified Dyskinesia Rating Scale UDysRS</u>
Fourth paragraph, second sentence previously read:

The videotape will be transmitted to the central rater for scoring of Parts 3 and 4.

Has been changed to read:

The videotape will be transmitted to the Central Blinded Rater for scoring of Parts 3 and 4.

Section 5.3.1.1 Study Procedures
Subsection <u>Unified Dyskinesia Rating Scale UDysRS</u>
Delete: seventh paragraph

A Blinded Central Rater will receive the videotape of the UDysRS and will score the videotaped assessment of Parts 3 and 4. A scoring summary will be electronically submitted back to site.

Section 5.3.1.1 Study Procedures
Subsection Modified Abnormal Involuntary Movement Scale (mAIMS)
Last paragraph previously read:

The assessments for mAIMS will be obtained as per the times indicated in Table 4.

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Has been changed to read:

The assessments for mAIMS should be completed following the UDysRS at the subject's expected time of peak dose dyskinesia as per the times indicated in Table 4.

Section 5.3.1.2 Rater Requirements Subsection Site Rater Training Requirements First paragraph Add: new second sentence

The UDysRS Parts 1 and 2 will be assessed and scored by site raters who are qualified based on MDS training.

Section 5.3.1.2 Rater Requirements Subsection Blinded Rater Training Requirements Subsection title previously read:

Blinded Rater Training Requirements

Has been changed to read:

Blinded Central Rater Training Requirements

Section 5.3.1.2 Rater Requirements Subsection Blinded Rater Training Requirements First paragraph previously read:

The UDysRS will be assessed and scored by experienced blinded central raters who are qualified based on MDS training.

Has been changed to read:

The objective portion of the UDysRS (Parts 3 and 4) will be assessed and scored by experienced blinded central raters who are qualified based on MDS training.

Section 5.3.3.2 Additional Efficacy and Health Outcome Variables Subsection Additional Efficacy Endpoints are:

Add: new first bullet

UDysRS Historical Score, Objective Score and Parts 1 through 4 Scores

Section 5.3.3.2 Additional Efficacy and Health Outcome Variables **Subsection Additional Health Outcome Endpoints:**

Delete: last bullet

Percentage (%) of CGI-C responders ("minimally improved," "much improved" or "very much improved")

Section 5.5.1.2 LCIG

Subsection Nasojejunal Tube

First paragraph, last sentence previously read:

The NJ should be inserted by a gastroenterologist proceduralist, surgeon or interventional radiologist.

Has been changed to read:

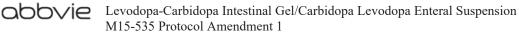
The NJ should be inserted by a gastroenterologist proceduralist, surgeon, interventional radiologist or experienced nurse if done via the passive method.

Section 5.5.3 Method of Assigning Subjects to Treatment Groups Second paragraph, first sentence previously read:

At Screening during Visit 1, each subject will be assigned a unique 5-digit number by the IRT system.

Has been changed to read:

At Screening during Visit 1, each subject will be assigned a unique 4-digit number by the IRT system.



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Section 5.5.5 Blinding Last paragraph, first, second, third, and fourth sentence previously read:

Blinded central raters will be used to administer the UDysRS, the primary efficacy endpoint for this study. Assessment obtained at V3 will serve as the baseline for clinical assessment. The scales will also be performed at Visits Week 2, 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.

Has been changed to read:

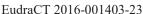
Central blinded raters will be used to rate Parts 3 and 4 of the UDysRS, the primary efficacy endpoint for this study. Assessment obtained at V3 will serve as the baseline for clinical assessment. The scales will also be performed at Weeks 2, 4, 8, and 12. The scoring for Parts 3 and 4 are to be performed by a trained central blinded 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.

Section 5.5.7 Drug Accountability Third paragraph, second sentence previously read:

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.

Has been changed to read:

This will be documented by the Investigator or designee 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.



Section 5.6.2 Appropriateness of Measurements Subsection <u>UDysRS Validation and Psychometric Properties</u> First paragraph, last sentence previously read:

Convergent, content and discriminant validity have also not been assessed.

Has been changed to read:

Convergent and discriminant validity have also not been assessed.

Section 5.6.2 Appropriateness of Measurements
Subsection <u>UDysRS Validation and Psychometric Properties</u>
Last paragraph previously read:

In conclusion, the UDysRS is a comprehensive rating tool to measure dyskinesia and has been studied clinimetrically as both a consistent and reliable measure. The scale however has not been assessed for construct and content validity.

Has been changed to read:

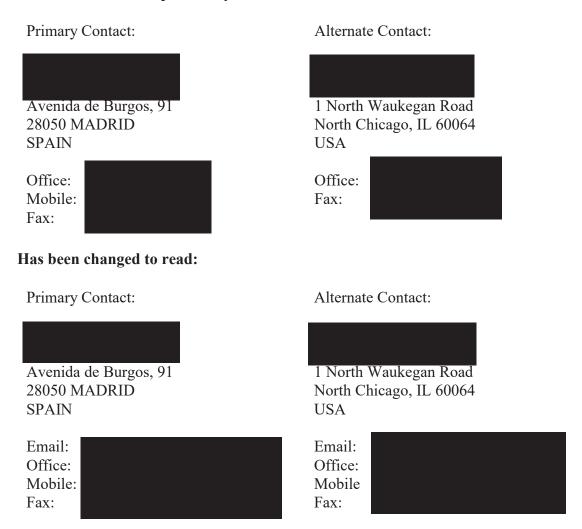
The UDysRS is a comprehensive rating tool to measure dyskinesia and has been studied clinimetrically as both a consistent and reliable measure. The scale however has not been assessed for construct and content validity.

Additional analysis will be performed to provide evidence on the construct validity of the UDysRS. Convergent validity will be evaluated by Spearman rank correlations between UDysRS total score (and sub-scores) and the AIMS score and Parkinson's Disease Diary assessment of severity of dyskinesia. In addition, the association with indirectly related constructs to dyskinesia, the PDQ-8 total score (measuring the PD-specific health status and quality of life) as well as the UPDRS scores for Parts II – III will be determined. Correlations ≥ 0.30 are hypothesized to support convergent validity. Discriminative validity will be explored by sub-group analyses. The UDysRS total score will be stratified by the Hoehn and Yahr stages and tested using the Kruskal-Wallis test.



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Section 7.0 Protocol Deviations Contact information previously read:



Section 8.1.3.3 Additional Efficacy and Health Outcomes Analyses First paragraph, first bullet previously read:

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

Has been changed to read:

• UDysRS Historical Score, Objective Score and Parts 1 through 4 Scores



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

Section 8.1.3.3 Additional Efficacy and Health Outcomes Analyses Last paragraph, last sentence previously read:

To evaluate this assumption, the MMRM analysis of the primary and secondary variables will be repeated using only subjects who completed the planned treatment period.

Has been changed to read:

To evaluate this assumption, the MMRM analysis of the primary and secondary variables will be repeated using only subjects who completed the planned treatment period and additional sensitivity analyses to evaluate the impact of missing data on the primary efficacy results will be performed. These sensitivity analyses will be described in the Statistical Analysis Plan (SAP).

Section 9.3 Subject Information and Consent First paragraph, first sentence previously read:

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study.

Has been changed to read:

The Investigator or his/her representative will explain the nature of the study to the subject. The subject must be able to understand the nature of the study and have the opportunity to have any questions answered by the Investigator.