1.0 Title Page

Statistical Analysis Plan

Study S187.3.005

Open-Label Continuation Treatment Study with Levodopa-Carbidopa Intestinal Gel in Subjects with Advanced Parkinson's Disease and Severe Motor Fluctuations Who Have Exhibited a Persistent and Positive Effect to Treatment in Previous Studies

08 November 2016

2.0 Table of Contents

List of Tables

List of Figures

3.0 Abbreviations and Definitions of Terms

General Abbreviations

AE	adverse event
ATC	Anatomical Therapeutic Chemical (class)
BMI	body mass index
bpm	beats per minute
CGI-I	Clinical Global Impression – Improvement
CLES	Carbidopa/levodopa enteral suspension
CRF	case report form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DDT	data definition table
DSMB	data safety monitoring board
ECG	electrocardiogram
HLGT	High Level Group Term
HLT	High Level Term
kg	kilogram
LCIG	Levodopa-Carbidopa Intestinal Gel
LLT	Lowest Level Term
m	meter
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MIDI	Minnesota Impulsive Disorders Interview
min	minimum
mL	milliliter
mmHg	millimeters of mercury
N,n	number of observations
NA	not applicable
P(-Value)	exceedance probability for testing the null hypothesis
PCS	Potentially clinically significant
PD	Parkinson's Disease

PDQ-39	Parkinson's Disease Questionnaire
PEG-J	Percutaneous endoscopic gastrostomy – with jejunal extension tube
PT	Preferred Term
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
S.I.	System International
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TLF/T,L,F	tables, listings and figures
UKPDS	United Kingdom Parkinson Disease Society
UPDRS	Unified Parkinson's Disease Rating Scale
WHO-DD	World Health Organization – Drug Dictionary

Defined Terms

Day 1	First day of 3005 LCIG infusion
LDA	Duration of 3005 LCIG infusion
RFENDTN	Date of the last 3005 LCIG infusion
RFENDT2N	Date of the last 3005 PEG-J exposure
RFSTDTN	Date of the first 3005 LCIG infusion

Clinical Domain Abbreviations

AE	Adverse events
CM	Concomitant medication
DA	Drug accountability
DC	Device complications
DI	Device information
DM	Demographics
DS	Disposition
DV	Protocol deviations
EG	ECG test results
EX	Study drug exposure
HU	Healthcare utilization
IE	Inclusion/exclusion
KV	Key variables
LB	Laboratory test results
MH	Medical history
PE	Physical examination
QS	Questionnaire
SC	Subject characteristics
VS	Vital signs

4.0 Introduction

This statistical analysis plan (SAP), describes the analysis to be completed for Levodopa-Carbidopa Intestinal Gel (LCIG, also known as Carbidopa/Levodopa Enteral Suspension [CLES] in the United States) Study S187.3.005 (Study 3005), dated 17 December 2013, which incorporates Global Amendments 1, 2, 3 and 4 and UK Amendments 2 and 3.01. It contains a technical elaboration of the principal features of the statistical analyses described in the protocol and is intended to guide the statistical programming work for the interim analysis to be conducted following the interim database lock completed in October 2015 as well as for the final analysis to be summarized in the Clinical Study Report (CSR).

A previous interim analysis was completed as described in SAP Version 2. For the previous interim analysis, all subject assessments completed on or before 04 May 2012 were included.

For the October 2015 interim analysis, all subject assessments completed on or before 30 September 2015 (the "Cutoff Date") will be included in the analysis.

All analysis data sets and statistical output will be produced by the Biostatistics department of Quintiles, Inc, Research Triangles Park, North Carolina, USA using the SAS® system Version 9.4 or higher.[1]

5.0 Summary of the Protocol and Amendments

5.1 Study Schedule of Assessments

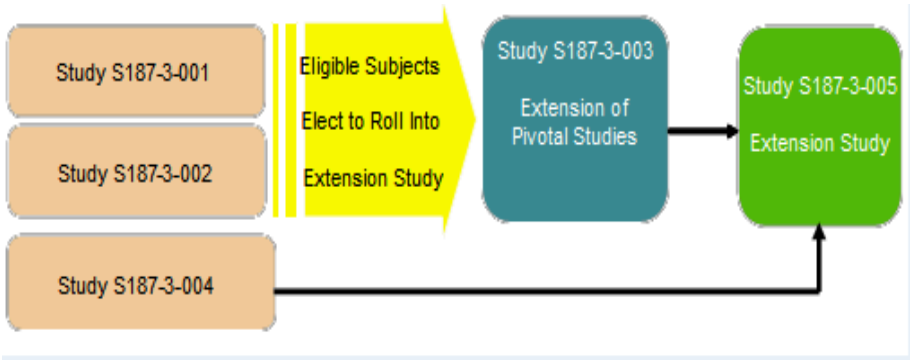
The assessments performed in Study 3005 under Amendments 1, 2, 3 and 4 are summarized in the Study Schedules of Assessments (Appendix 12.1.1, Appendix 12.1.2, Appendix 12.1.3, and Appendix 12.1.4). Subject visit days should ideally match the target clinic visit days; however, a 14-day visit window will be allowed as necessary.

5.2 Overall Study Plan

This is a Phase 3B, open-label, multicenter study of the long-term safety and tolerability of LCIG in the treatment of approximately 275 advanced PD subjects with a good therapeutic response on LCIG with regard to the treatment of persistent severe motor fluctuations. The study will be conducted at approximately 70 centers.

Study 3005 is an extension study in the LCIG United States registration program. In this program, subjects who completed 12 weeks of treatment in double-blind double-dummy Study S187.3.001 (3001) or Study S187.3.002 (3002) were eligible to enroll in the 12-month open-label Study S187.3.003 (3003) and then in Study 3005. All subjects in Study 3001 and Study 3002 received a PEG-J and were randomized to receive either LCIG and placebo capsules or levodopa-carbidopa capsules and placebo gel. All subjects in Study 3003 received LCIG. Subjects who completed the 12-month open-label Study S187.3.004 (3004), were also qualified to enroll in Study 3005. Subjects in Canada were allowed to participate with a minimum of 6 months of exposure to LCIG in Study 3004.

Figure 1. LCIG United States Registration Program Overview



Following informed consent, subjects had their inclusion/exclusion criteria assessed prior to beginning treatment in Study 3005. Subjects are allowed to have a caregiver, if

appropriate, to assist them with study requirements, i.e., care of the pump and tubing, etc. and the caregiver will have been trained accordingly.

The initial LCIG dose in Study 3005 was identical to the dose that the subject was receiving at the end of the previous open-label LCIG study. Subsequent dose adjustments will be made as clinically indicated by the Investigator. In addition to the morning dose and the continuous infusion, subjects will be allowed to self-administer additional doses of LCIG to address immediate subjective needs, such as the deterioration of motor function. If a subject finds it necessary to self-administer an increasing number of extra doses (> 5/day) of LCIG, they will be instructed to contact the Investigator for appropriate follow-up care (adjustment of continuous infusion) as needed.

In this open-label study, a recommendation will be made to Investigators to withhold concomitant PD treatments if deemed medically safe and clinically appropriate. The initiation of additional PD medication may be medically indicated and is allowed at the discretion of the Investigator. Also, the dosages of these other PD medications can be adjusted upward or downward as needed based on the status of the subject's condition or the development of adverse effects; resumption of discontinued PD medications may also be necessary.

The final visit in the previous open-label LCIG study will provide baseline assessments for Study 3005. Subjects will be reassessed every 6 months for the appropriateness of the continuation of treatment with LCIG. If the subject is deemed inappropriate for continued treatment by the Investigator, the subject will be discontinued from treatment. Subjects who discontinue LCIG treatment will have the PEG-J removed, and a follow-up clinic visit will occur 1 week later.

Safety assessments include physical examination, neurological exam, orthostatic vital signs, weight, adverse event monitoring, assessment of impulsive behavior and sleep attacks, melanoma check, and special labs to monitor for vitamin deficiencies.

At each visit, adverse events or complications with the infusion device (i.e., the tubing system and the pump) will also be recorded and reported. Tube placement will be checked by radiography if there is a clinical indication that the tube has been displaced. The tube will be repositioned, if needed, to the original placement site just beyond the ligament of Treitz. At each visit the tube insertion site, including the stoma, will also be inspected. On a yearly basis, at a minimum, an assessment will be made of the need for a replacement of the PEG-J. The frequency of replacement should be in accordance with local practice.

Protocol Amendment 4 added the following efficacy assessments at US sites only: Parkinson's Disease Diary, the Unified Parkinson's Disease Rating Scale (UPDRS), and the Parkinson's Disease Questionnaire-39 (PDQ-39).

The protocol duration is planned until the finished product is available commercially in the respective countries where subjects are participating in the study.

5.3 Treatments

LCIG is a homogeneous suspension of levodopa (20 mg/mL) and carbidopa (5 mg/mL) in an aqueous intestinal gel (carboxymethycellulose). LCIG is delivered to the proximal small intestine through a jejeunal extension tube inserted via percutaneous endoscopic gastrostomy (PEG-J). The intestinal gel is dispensed in a medication cassette reservoir of 100 mL, designed to be connected to a portable subject-operated pump. LCIG is to be administered over approximately 16 waking hours. At night, after disconnecting the pump for sleeping, the tubing is to be flushed with potable water.

Each subject's LCIG dose will be individually optimized. The initial LCIG dose will be identical to the dose that the subject was receiving at the end of the previous open-label LCIG study. Dose adjustments, either upward or downward, can be made at any time throughout the study based on the clinician's judgment of effectiveness. No dosing restrictions are given with relation to meals.

The total daily dose of LCIG infusion will be composed of three components: the morning dose, the continuous maintenance infusion dose, and extra doses. The morning dose is administered as a bolus infusion by the pump to fill the dead space of the intestinal tube and rapidly achieve therapeutic dose level (within 10 to 30 minutes). The total morning dose is typically 5 – 10 mL (100 – 200 mg levodopa) and will usually not exceed 15 mL (300 mg levodopa). The continuous maintenance dose is administered over approximately 16 waking hours. The infusion rate for the continuous maintenance dose is typically 2 – 6 mL/hour (40 – 120 mg levodopa/hour) and will usually be within 0.5 – 10 mL/hour (10 – 200 mg levodopa/hour). During the continuous infusion, subjects may self-administer a pre-set extra infusion dose (at intervals of no less than 2 hours) to address immediate medical needs, such as the rapid deterioration of motor function. The extra infusion dose will normally be set at 0.5 – 2.0 mL (10 – 40 mg levodopa). In rare cases a higher dose may be needed.

5.4 Data Safety Monitoring Board

Prior to the completion of the pivotal, Phase 3 studies, Study 3001 and Study 3002, a Data Safety Monitoring Board (DSMB) reviewed the safety data in accordance with the DSMB Charter. Planned safety analyses for the DSMB were presented in a separate document and are not discussed in any detail in the body of this SAP.

6.0 General Definitions, Methods, Naming Conventions and Data Handling

In order to avoid ambiguity during the analysis, a number of definitions and conventions for data handling are described in this section.

The following information for each subject will be summarized in a Key Variable (KV) derived dataset:

- Treatment group as described in Section 6.2.
- Reference dates as described in Section 6.4.1.
- Inclusion in subject samples as described in Section 8.1.1.

6.1 General Methodology and Presentation

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max), for those subjects with data.

All summary statistics will be rounded (using the SAS® function ROUND) and presented to one more decimal place than the raw value, except for the minimum and maximum values that will be presented with the same decimal precision as the raw value.

For qualitative variables, the number (n) and percentage (%) of subjects with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category.

Percentage values are to be rounded and presented to one decimal place, for example, 52.3%. If the calculated percentage is > 0.0% but < 0.1% then < 0.1% is to be presented in the relevant table and/or listing.

The exceedance probabilities for testing the null hypothesis will be denoted by "*P* value." *P* values are to be rounded (using the SAS® function ROUND) and printed with three decimals. *P* values below 0.0005 will be denoted as < 0.001.

6.2 Treatment Group Names and Labels

Statistical output (SAS® tables) will be presented. The treatment name/label to be used in the tables, listings and figures (TLFs) is defined in the table below.

Treatment Code Number	Treatment Description	Treatment Label
1	Levodopa-carbidopa intestinal gel (LCIG) supplied as a water suspension of 20 mg/mL levodopa and 5 mg/mL carbidopa	Levodopa-Carbidopa Intestinal Gel

6.3 Visit Names and Labels

The visit names/labels to be used in the analysis data sets and in the TLFs are defined in Table 1 below.

Table 1. Visit Names and Labels

Visit Number	Visit Name	Visit Label
1	Baseline	Baseline
2	Month 6	Month 6
3	Month 12	Month 12
4	Month 18	Month 18
5	Month 24	Month 24
6	Month 30	Month 30
7	Month 36	Month 36
8	Month 42	Month 42
9	Month 48	Month 48
10	Month 54	Month 54
11	Month 60	Month 60
12	Month 66	Month 66
13	Month 72	Month 72
14	Month 78	Month 78
15	Month 84	Month 84
99	Follow-up	Follow-up

6.4 Day Numbers, Study Periods and Visit Windows: Related Definitions

6.4.1 General Definitions

Assessment days will be related to the date of the first infusion of 3005 study drug (First 3005 LCIG Infusion). Baseline is defined in Section 6.4.5 (Baseline Period). The Cutoff Date for the 2015 interim analysis will be 30 September 2015. Assessments and/or measurements performed after the Cutoff Date, adverse events or device complications with start dates after the Cutoff Date, and concomitant medications with start dates after

the Cutoff Date will not be included in the 2015 interim analysis. No cutoff date will be applied to the analysis for the final CSR.

The following reference dates will be defined for all subjects in the All Subjects Consented subject sample defined in Section 8.1.1.

- **Date of the First 3005 LCIG Infusion (Day 1, RFSTDTN):**

  The actual dates of study drug administration are not recorded in the 3005 database. The dates when 3005 study drug is dispensed are recorded in the DA raw data panel. For analysis, the date of the first 3005 LCIG infusion will be defined as the first date that 3005 study drug was dispensed to the subject. The visit date recorded in the DM raw data panel will be used if the date the first study drug was dispensed is not available.

  The date of the first 3005 LCIG infusion will be defined as Day 1 and is the key variable RFSTDTN and is used in the calculation of relative days.

- **Date of the Last 3005 LCIG Infusion (RFENDTN):**

  For subjects who have prematurely discontinued or completed the study, the date of the last 3005 LCIG infusion will be the earliest of 1) the date of last study drug administration collected on the DS raw data panel, 2) the date of discontinuation or study completion collected on the DS raw data panel and 3) the Cutoff Date (interim analysis only).

  For the 2015 interim analysis, the date of the last 3005 LCIG infusion for all ongoing subjects will be the Cutoff Date.

- **Duration of 3005 LCIG Infusion (LDA):**

  The Duration of 3005 LCIG Infusion or exposure to treatment is equal to the day number of the Last 3005 LCIG Infusion (LDA) and is derived as follows from the previous two dates:

  LDA (days) = (Date of the Last 3005 LCIG Infusion [RFENDTN] – Date of the First 3005 LCIG Infusion [RFSTDTN]) + 1

  LDA then indicates the relative day of the last 3005 LCIG infusion for each subject.

- **Date of Last 3005 PEG-J Exposure (RFENDT2N):**

  LCIG is administered as part of a therapeutic system that includes devices and implantation procedures. Subjects who discontinue LCIG therapy are to have their PEG-J removed.

  For subjects who have prematurely discontinued or completed the study, and have reported a final PEG-J removal on the DI raw data panel that is after their last day of study drug administration and before the Cutoff Date (interim analysis only), their date of last 3005 PEG-J exposure will be the date of PEG-J removal. For all other subjects who have prematurely discontinued or completed the study, their date of last 3005 PEG-J exposure will be the earlier of 1) the date of discontinuation or study completion collected on the DS raw data panel, and 2) the Cutoff Date (interim analysis only).

  For the 2015 interim analysis, the date of the last 3005 PEG-J exposure for all ongoing subjects will be the Cutoff Date.

  The date of the last 3005 PEG-J exposure is the key variable RFENDT2N.

6.4.2 Initial Screening Period

Height and background information related to medical and neurological history and PD diagnosis was only collected during the Screening Period of the first LCIG study that a subject participated in. For example, subjects who entered the 3005 study after completing the 3003 open-label study would have completed one of the two Phase 3, double-blind studies, Study 3001 or 3002, before their enrollment in Study 3003. For these subjects, certain background information, e.g., medical history, neurological history and PD diagnosis information, was only collected prior to Study 3001 or 3002. This information will be retrieved from the relevant study databases and summarized for the subjects enrolled in Study 3005.

6.4.3 Initial PEG-J Placement

Subjects enrolled in Study 3005 had their initial PEG-J placement in Study 3001, 3002 or 3004. To allow the overall duration of PEG-J exposure to be summarized for each subject

in Study 3005, the date of initial PEG-J placement will be retrieved from the relevant study database.

6.4.4 Initial LCIG Infusion

Subjects enrolled in Study 3005 had their first LCIG infusion in the same study as their initial PEG-J placement (Studies 3001, 3002 or 3004) except for subjects who received levodopa-carbidopa capsules and placebo gel in Study 3001 or Study 3002. These subjects had their first LCIG infusion in Study 3003. To allow the overall duration of LCIG exposure to be summarized for each subject in Study 3005, the date of initial LCIG infusion will be retrieved from the relevant study database.

For US subjects who completed Daily Dosing Diaries in Study 3005 following Amendment 4, the total daily levodopa dose at the end of the subject's initial LCIG titration period will be retrieved from the relevant database to allow the change in dose from initial titration to final Study 3005 visit to be determined.

To provide context for changes in efficacy measures observed during Study 3005, the respective change observed between initial LCIG infusion and Study 3005 final visit will be determined and summarized. For subjects who completed efficacy assessments in Study 3005, their baseline value from the study in which they had their first LCIG infusion will be retrieved from the relevant database and considered their value at initial LCIG infusion.

6.4.5 Baseline Period for Study 3005

The Baseline Period for Study 3005 is defined as the time before the first 3005 LCIG infusion. For efficacy measures, the final value in the previous study (Study 3003 or Study 3004) will be retrieved from the relevant database and will be considered the 3005 baseline value. For safety evaluations, the final assessment in the previous open-label LCIG study or in 3005 that is on or before the date of the first 3005 LCIG infusion will be used as the 3005 Baseline value. For systolic blood pressure, diastolic blood pressure and

pulse, the final assessment where results are present for both the supine and standing position will be considered baseline.

6.4.6 Treatment Period

Data collected on the Date of the First 3005 LCIG Infusion (Day 1) will be assigned to the Baseline Period. However, adverse events and concomitant medications starting on Day 1 will be assigned to the Treatment Period (worst case scenario).

A Gap Period (number of days) is defined to include data collected after the end of the relevant Treatment Period in the analysis. For this study, the Gap Period will be 30 days for adverse events and 1 day for all other assessments.

For efficacy assessments the Treatment Period is defined as the Period from the Date of the First 3005 LCIG Infusion up to and including the Date of the Last 3005 LCIG Infusion + Gap Period (1 day). For safety assessments the Treatment Period is defined as the Period from the Date of the First 3005 LCIG Infusion up to and including the Date of the Last 3005 PEG-J Exposure + Gap Period (30 days for adverse events and 1 day for all other assessments).

The Endpoint value for a variable is defined as the last non-missing value assigned to the Treatment Period for the subject.

6.4.7 Post-Treatment Period

For efficacy assessments, the Post-Treatment Period is defined as the period after the Date of the Last 3005 LCIG Infusion + Gap Period (1 day). For safety assessments, the Post-Treatment Period is defined as the period after the Date of the Last 3005 PEG-J Exposure + Gap Period (30 days for adverse events and 1 day for all other assessments).

6.4.8 Visit Windowing Conventions

Assessments will be assigned to the Baseline Period if the date is on or before the Date of the First 3005 LCIG Infusion as defined in Section 6.4.1 and to the Post-Treatment Period if the date is after the end of the relevant Treatment Period as defined in Section 6.4.6.

Assignment of assessments to visits during the Treatment Period will use visit windows based on the day of the assessment relative to the Date of the First 3005 LCIG Infusion as described in Table 2 below.

Table 2. Visit Windowing Conventions

Visit Label	Target Visit Day	Study Day Range
Baseline	≤ 1	
Month 6	180	2 to 270
Month 12	360	271 to 450
Month 18	540	451 to 630
Month 24	720	631 to 810
Month 30	900	811 to 990
Month 36	1080	991 to 1170
Month 42	1260	1171 to 1350
Month 48	1440	1351 to 1530
Month 54	1620	1531 to 1710
Month 60	1800	1711 to 1890
Month 66	1980	1891 to 2070
Month 72	2160	2071 to 2250
Month 78	2340	2251 to 2430
Month 84	2520	> 2430

If a subject has two or more assessments in the same visit window, the assessment closest to the target visit day will be used. If two assessments are equidistant from the target visit day, the later assessment will be used.

Each reported post-baseline lab and vital sign measurement shall be evaluated to determine if it meets potentially clinically significant criteria. For all other analyses of

labs and vital signs, if two measurements are on the same date, the average will be calculated and treated as the value for that date.

6.4.9 3005 Treatment Year

The following events will be summarized by 3005 Treatment Year using the study day intervals described in Table 3 below: premature study discontinuations, prevalence of concomitant anti-parkinsonian medication use, the incidence and prevalence of adverse events, the incidence of device complications, and the number of PEG tube and J-tube replacements.

Table 3. 3005 Treatment Year

3005 Treatment Year	Study Day Range
Year 1	2 to 365
Year 2	366 to 730
Year 3	731 to 1095
Year 4	1096 to 1460
Year 5	1461 to 1825
> Year 5	> 1825

6.5 Handling of Missing Data

The handling of missing data, if applicable, is discussed in Section 8.0 (Analysis Variables: Definitions, Derivations, Calculations and Conventions). Presentation of missing data is discussed in the relevant subsections of Section 9.0 (Statistical Analysis).

7.0 Objectives

7.1 Primary Objective

The primary objective of this study is to provide, under well controlled conditions, continued access to LCIG treatment to subjects who have already participated in an open label efficacy and safety trial with the same treatment (Study S187.3.003 or

Study S187.3.004), and in whom the need for such continuation is indicated, as confirmed by periodic evaluation, until the product is commercially available.

7.2 Secondary Objectives

To assess the long-term safety and tolerability of the LCIG therapeutic system by the following:

- Physical examination, including weight
- Neurological examination
- Vital signs
- Resting ECGs
- Clinical laboratory assessments including biochemistry, hematology, urinalysis, and special labs to monitor for vitamin deficiencies
- Concomitant medication usage
- Adverse event monitoring, including for the development of sleep attacks, melanoma, or excessive impulsive behavior
- Monitoring complications of the infusion device
- Tolerability assessed by number of subjects who complete the study

To assess the maintenance of efficacy using the following data collected from US subjects:

- Off time, On time with troublesome dyskinesia, and On time without troublesome dyskinesia as measured by the Parkinson's Disease Diary
- UPDRS total score, Parts I, II, III and IV scores, and dyskinesia item score
- PDQ-39 summary index and domain scores

8.0 Analysis Variables: Definitions, Derivations, Calculations and Conventions

8.1 Subject Disposition

8.1.1 Subject Samples

There will be three hierarchical subject samples of interest.

The "All Subjects Consented" subject sample will be used to summarize subject disposition and will consist of all subjects who:

- Gave their informed consent.

The Safety subject sample will consist of all subjects who:

- Were in the "All Subjects Consented" subject sample and
- Received at least 1 infusion of 3005 study drug

The Safety subject sample will be used for all analyses of safety unless noted otherwise.

The Efficacy subject sample will consist of all subjects who:

- Were in the Safety subject sample and
- Have at least 1 efficacy assessment in 3005

The Efficacy subject sample will be used for all analyses of efficacy unless noted otherwise.

For subjects enrolled in the United States, efficacy assessments were added with Protocol Amendment 4. To evaluate efficacy and safety in these subjects, analyses will be completed including only the subjects in the relevant subject sample who were enrolled in the United States (the "US Subset").

To evaluate the association between polyneuropathy events and vitamin deficiencies, additional analyses will be completed for the subset of subjects who experienced a TEAE coded to either the Standardized MedDRA Query (SMQ) of Peripheral Neuropathy – narrow search or Guillain-Barre Syndrome – narrow search (the "Narrow Polyneuropathy Subset").

8.1.2 Subgroups

Subgroups to evaluate the robustness of efficacy observations will be based on the following:

- the study in which the subject received their first LCIG infusion (3001/2, 3003, 3004)
- troublesome dyskinesia at initial LCIG infusion (< 1 hour, > 1 hour as recorded on the PD Diary)
- total daily levodopa dose at initial LCIG infusion (< 1250 mg/day, > 1250 mg/day), and
- levodopa monotherapy in Study S187.3.005 (yes, no)

To evaluate the robustness of observations, the change in total daily levodopa dose will be evaluated after grouping subjects by the study in which they received their first LCIG infusion.

Subgroups defined for exploratory analyses of safety will include gender, age category (< 65, ≥ 65 years), duration of Parkinson's disease (< 10 years, ≥ 10 years) and country.

Due to the similarity in study design, Studies 3001 and 3002 will be combined and considered a single study (Study 3001/3002) for the subgroup analysis based on the study in which the subject received their first LCIG infusion.

8.1.3 Protocol Deviations

The number and percentage of subjects with one or more of the following major protocol deviations will be summarized overall as well as by category:

- Those who entered the study even though they did not satisfy the entry criteria. adherence to the inclusion and exclusion criteria will be the determining factor for this category of protocol deviations.
- Those who developed withdrawal criteria during the study but were not withdrawn. The only criterion defined in the protocol that required withdrawal from the study was the development of melanoma.

8.1.4 Inclusion/Exclusion Criteria

The study specific inclusion/exclusion criteria are presented in Section 8.1 and Section 8.2 of the protocol.

8.1.5 Subject Enrollment and Disposition

As previously described, Study 3005 is an extension study. Subjects will be assigned to an enrollment cohort based on the study in which they received their first LCIG infusion. Due to the similarity in study design, Study 3001 and Study 3002 will be considered a single enrollment cohort. The number and percentage of subjects in each of the following enrollment cohorts will be summarized:

- Subjects who received their first LCIG infusion in Study S187.3.001 or Study S187.3.002
- Subjects who received their first LCIG infusion in Study S187.3.003
- Subjects who received their first LCIG infusion in Study S187.3.004

Subjects are expected to continue in the study until commercial LCIG becomes available to them. If commercial LCIG becomes available to a subject, a final visit shall be scheduled and the subject will be regarded as having completed the study if they complete this final visit. If at any time after providing informed consent, a subject prematurely discontinues their participation in the study, the primary reason for premature discontinuation shall be recorded on the "Study Termination" CRF. The primary reason can include one of the following:

- Adverse Event
- Lack of Efficacy
- Lost to Follow-up
- Withdrew Consent
- Administrative
- Protocol Violation

Premature discontinuations will be summarized by 3005 treatment year after allocating each premature discontinuation to a 3005 treatment year based on the study day of the subject's last dose date and the study day intervals described in Section 6.4.9.

8.2 Subject Characteristics

8.2.1 Demographic Data

Standard demographic data collected includes:

- Date of Birth
- Gender
- Race (American Indian or Alaska native, Asian, black of African heritage or African American, native Hawaiian or other Pacific Islander, or white)
- Ethnicity (Hispanic or Latino)
- Country

Age (years) will be derived in SAS® using Date of Birth, and calculated relative to Day 1, as follows:

Age (years) = Day1_Y – Birth_Y – (0 < Day1_M < Birth_M OR [Day1_M = Birth_M AND 0 < Day1_D < Birth_D])

Where:

Day1_D: Day of Day 1 date.

Day1_M: Month of Day 1 date.

Day1_Y: Year of Day 1 date.

Birth_D: Day of Birth.

Birth_M: Month of Birth.

Birth_Y: Year of Birth.

Where the Date of Birth is incomplete the following convention will be used:

- Where the day is missing and month and year are available the day will be completed as the 15th. For example, Date of Birth specified as – JAN1980 will be completed as **15**JAN1980.
- If the day and month are missing and the year is available the day and month will be completed as 02JUL (the 183rd day of the year). For example, Date of Birth specified as – 1980 will be completed as **02JUL**1980.

8.2.2 Other Baseline Characteristics

Other Baseline characteristics include:

Vital Signs:

- Height (m) as measured during the Initial Screening Period
- Weight (kg)
- BMI (kg/m^2)
- Body Temperature (degrees Celsius) including route of measurement
- Systolic Blood Pressure (SBP [mmHg]) supine, standing and orthostatic
- Diastolic Blood Pressure (DBP [mmHg]) supine, standing and orthostatic
- Pulse Rate (beats per minute [bpm]) supine, standing and orthostatic

Study specific calculations and/or conversions include:

Height (m): If applicable, height will be converted from inches to meters for the calculation of Body Mass Index (BMI), using the following formula:

Height (m) = (XX inches * 2.54)/100 and presented to two decimal precision.

Weight (kg): If applicable, weight will be converted from pounds to kilograms for the calculation of BMI, using the following formula:

Weight (kg) = (XX pounds * 0.4536) and presented to one decimal precision.

Body Mass Index calculated as:

BMI (kg/m^2) = Weight (kg)/Height $(m)^2$ and presented to one decimal precision.

Temperature (degrees Celsius): If applicable, temperature will be converted from degrees Fahrenheit to Celsius, using the following formula:

Temperature (degrees C) = (XX degrees F – 32)/1.8 and presented to one decimal precision.

8.2.3 Medical History and Other Disease History

8.2.3.1 Medical History

Medical history (MH) is defined as any condition, with the exception of the study indication, that the subject reported during the Initial Screening Period. Medical history will include findings reported on either the medical history or neurological history CRF.

Medical history findings will be coded using the Medical Dictionary for Regulatory Activities (MedDRA),[2] Version 14.0 or later and will be presented by primary System Organ Class (SOC) and by Preferred Term (PT) within SOC. The SOCs and PTs will be sorted alphabetically at each coded level. Medical history will be reported on a by-subject basis. This implies that if the subject reported the same condition (conditions mapped to the same PT) repeatedly, the condition will only be counted once. The earliest date will be regarded as the start date of the condition and the last available date, as the stop date of the condition.

Missing or partial dates for medical history will not be completed, for example, if only a month and year are available as – FEB2005, the day will not be imputed in order to

complete the date. If "End Date" information is not available it will be assumed that the finding is "Ongoing" at the time of enrollment in the study.

8.2.3.2 Study Specific Disease History

Study specific disease history collected during the Initial Screening Period included the month and year of initial PD diagnosis and assessment of the following modified United Kingdom Parkinson Disease Society (UKPDS) brain bank criteria for Parkinsonian Syndrome:

- Diagnosis of bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- Diagnosis of muscular rigidity
- Diagnosis of 4 – 6 Hz resting tremor
- Diagnosis of postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

The duration of PD will be calculated as the time (in years) from the initial diagnosis of PD until the subject entered the Initial Screening Period. Missing months for initial PD diagnosis will be set to January resulting in the earliest possible onset and the longest possible duration.

8.2.4 Previous and Concomitant Medication

Medications are classified according to active drug substance using the World Health Organization-Drug Dictionary (WHO-DD), 01 March 2011.[3] The WHO drug code has 11 digits. The generic name (required for presentation in the tables and listings) is defined by the first 6 of the 11 digits. In addition, Anatomical Therapeutic Chemical (ATC) classes are assigned to the drug code. In this study, ATC codes are defined to the third level. Although there can be multiple ATC classes for a drug, each drug will be linked with one ATC class which will be assigned manually during the coding process, based on information about the indication and route in relation to the study therapeutic area. This one ATC class will be indicated as the "primary" ATC class.

Previous or prior medications are defined as medications that were being used at the end of the previous study and were continuing to be used when the subject entered the 3005 study. Summaries of previous medications will focus on anti-parkinsonian medications.

Concomitant medications (CM) are defined as medications taken at any time during the Treatment Period defined for safety assessments in Section 6.4.6 and include medications started prior to the first 3005 LCIG infusion but continued during the study as well as medications started at or after the first 3005 LCIG infusion and before the last 3005 PEG-J exposure.

Missing and/or incomplete dates for medications are imputed in a manner resulting in the earliest onset or the longest duration. However, the Stop Date will not be imputed if the medication is reported as "Ongoing."

Technically, this will be done as follows:

- If the day is missing and the month and year are available, the start (stop) date will be completed as the first (last) day of the month.
- If the day and month are missing and the year is available, the start (stop) date will be completed as the first (last) day of the year.
- If the date is completely missing, the start (stop) date will be completed as a very early (late) date, for example, 01JAN1000 (01JAN3000).

The prevalence of concomitant anti-parkinsonian medication (CM) use during each 3005 Treatment Year will be summarized using the study day intervals described in Section 6.4.9. CM start and stop days will be calculated relative to the start of 3005 LCIG infusion (RFSTDTN) as follows:

CM Start Day = (CM Start Date – Start of 3005 LCIG Infusion + 1)

CM Stop Day = (CM Stop Date – Start of 3005 LCIG Infusion + 1)

A subject will be considered to have taken a specific CM during an interval if:

- the CM Start Day is within the study day range for the interval and was not greater than the day of the last 3005 LCIG infusion, or
- the CM Start Day is less than the lower limit of the study day range and the CM Stop Day is later than the lower limit of the study day range or missing.

Note that this definition assumes that a missing CM Stop Day is an indication that the use of the CM is ongoing. The denominator for percentage calculations for each interval will be the number of subjects whose last day of 3005 LCIG infusion was within or after the interval day range.

8.3 Study Drug Accountability and Treatment Exposure

8.3.1 Study Drug Accountability

LCIG is dispensed in 100 mL medication cassette reservoirs that are designed to be connected to a portable subject-operated pump. Subjects are to return all used as well as all unused cassettes to the site at each clinic visit.

8.3.2 Duration of Study Drug and PEG-J Exposure

The duration of LCIG exposure as well as the duration of PEG-J exposure will be summarized for 3005 as well as overall. The duration of 3005 LCIG infusion (LDA) is described in detail in Section 6.4.1 (General Definitions). The duration of 3005 PEG-J exposure will be calculated as the Date of the Last 3005 PEG-J Exposure (as defined in Section 6.4.1) – the Date of the First 3005 LCIG Infusion (as defined in Section 6.4.1) +1. The total subject-years of exposure will be calculated as the sum of all subject exposures in days divided by 365.25.

As previously described, Study 3005 is an extension of the previous Studies 3001, 3002, 3003, and 3004. To determine the overall duration of each subject's LCIG and PEG-J exposure, the date of initial PEG-J placement and the date of initial LCIG infusion will be retrieved from the relevant study database. The overall duration of LCIG infusion will be

calculated as the Date of the Last 3005 LCIG Infusion – the Date of the Initial LCIG Infusion +1. The overall duration of PEG-J exposure will be calculated as the Date of Last 3005 PEG-J Exposure – the Date of the Initial PEG-J placement +1.

8.3.3 Prescribed Dose

The prescribed dose of LCIG is comprised of a morning dose, a continuous maintenance dose, and an extra dose to be administered as needed. Each subject's pump settings for the morning dose, extra dose and continuous infusion rate are individually optimized and programmed by the Investigator at a clinic visit. Subjects self-administer LCIG by starting and stopping the pump each day and by infusing extra doses as needed during the continuous infusion.

8.3.4 Dose Administered

Beginning with Protocol Amendment 4, subjects enrolled at US sites were to record all LCIG infusions (including pump start time, pump stop time and the time of any extra dose administration) and all oral levodopa/carbidopa doses on a Daily Dosing Diary for the 3 days before each clinic visit. The average total daily LCIG dose at the final 3005 visit will be calculated by summing the total mL of LCIG infused on each Daily Dosing Diary completed within 14 days of the final Daily Dosing Diary and dividing by the number of diaries recorded. The average total daily dose of LCIG will then be converted to the average total daily dose of levodopa using the conversion factor of 1 mL LCIG = 20 mg levodopa. Only diaries reporting at least 12.8 hours of pump operation will be included in this calculation.

The average total daily levodopa dose at the final 3005 visit will be summarized with descriptive statistics for each component (morning dose, continuous maintenance dose, and extra dose) as well as for the total levodopa dose. Each subject's total daily levodopa dose at the end of their initial LCIG titration in Studies 3001, 3002, 3003 or 3004 will be retrieved from the relevant database. The total daily levodopa dose at the end of initial LCIG titration and the change in total daily levodopa dose from the end of initial LCIG titration to final 3005 visit will be summarized with descriptive statistics. To evaluate the

robustness of observations, the same summary will be prepared after grouping subjects based on the study in which they received their first LCIG infusion.

8.4 Efficacy Analysis Variables

The original Protocol included the following efficacy measures:

- Parkinson's Disease Diary[4]
- Parkinson's Disease Questionnaire (PDQ-39)
- Clinical Global Impression – Improvement (CGI-I)

These measures were removed from the schedule of assessments with Protocol Amendment 1. With Protocol Amendment 4, the following measures were added to the schedule of assessments for subjects enrolled at US sites:

- Parkinson's Disease Diary
- Unified Parkinson's Disease Rating Scale (UPDRS)
- Parkinson's Disease Questionnaire (PDQ-39)

The change in each efficacy measure from 3005 baseline to 3005 final visit will be determined and summarized. To provide context, the change in each efficacy measure from initial LCIG infusion to 3005 final visit will also be determined and summarized.

8.4.1 Parkinson's Disease Diary (PD Diary)

The core of the Parkinson's Disease Diary (PD Diary)[4] is the questionnaire that the subject will use to record parkinsonian symptoms. The subject and/or caregiver will be prompted to answer the PD questionnaire on whether the subject has been "on" without dyskinesia, "on" with non-troublesome dyskinesia, "on" with troublesome dyskinesia, "off," or "asleep." The diary is completed for the full 24 hours of each day reflecting both time awake and time asleep. On the recording days, subjects will be instructed to make an entry every 30 minutes during their normal waking time and upon awakening from time

asleep. Beginning with Protocol Amendment 4, US subjects were to complete a PD Diary during the 3 consecutive days prior to each clinic visit.

Average normalized "off" time will be calculated as follows:

Valid Diary Days

1. For subjects with more than one observation for the same 30 minute time period, the 30-minute time will be evenly split among the number of observations checked.
2. Subjects who do not complete at least 12 awake hours of symptom diary data (not including "ASLEEP" time) will have that daily data set to missing (i.e., will not be considered as a valid symptom diary day). There will be no imputation of data for these diary days.

Absolute and Normalized Daily "OFF" Time

3. Absolute "off" time, "on" time without dyskinesia, "on" time with non-troublesome dyskinesia, "on" time with troublesome dyskinesia and "asleep" time will be determined from each 24-hour PD symptom diary.
4. Daily awake time is the sum of absolute "off" time, "on" time without dyskinesia, "on" time with non-troublesome dyskinesia, and "on" time with troublesome dyskinesia.
5. "Off" time, "on" time without dyskinesia, "on" time with non-troublesome dyskinesia, and "on" time with troublesome dyskinesia will be normalized to a 16 hour waking time due to the variance in sleep patterns. For example, normalized "off" time is calculated as:

   Normalized "off" time = (Absolute "off" time/Awake time) * 16.

   All times are expressed in decimal hours.

Daily Average

6. Valid symptom diary days (at least 12 awake hours) will be used to compute the average daily normalized "off" time. For post-baseline visits, the valid symptom diary day must be within 7 days of the clinic visit but not on or after the day of the clinic visit. If more than 3 valid symptom diary days are available, the 3 days closest to the clinic visit will be used.
7. If only 2 valid symptom diary days are available prior to a clinic visit, data from the 2 days will be used to calculate the average daily normalized "off" time.
8. If only one valid symptom diary day is available the average daily from the previous visit will be averaged with the daily normalized "off" time from the one valid diary day.
9. Subjects that do not have any valid symptom diary days for a visit or who are completely missing a visit will have the average daily normalized "off" time set to missing for that visit.

The change from baseline in average daily normalized "on" time with troublesome dyskinesia, normalized "on" time with non-troublesome dyskinesia, and normalized "on" time without dyskinesia will be calculated for each subject using the 3 diary days prior to the visit and the same strategy employed for the calculation of normalized "off" time. Normalized "on" time without troublesome dyskinesia will be calculated for each PD Diary as the sum of normalized "on" time without dyskinesia and normalized "on" time with non-troublesome dyskinesia.

8.4.2 Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS is an Investigator-used rating tool to follow the longitudinal course of PD. It is made up of the following sections: I) Mentation, Behavior, and Mood; II) Activities of Daily Living; III) Motor Examinations; IV) Complications of Therapy sections (including Dyskinesias); and V) Modified Hoehn and Yahr Staging, as well as the Schwab and

England Activities Of Daily Living Scale. These are evaluated by physical examination and observation. Some sections require multiple grades assigned to each extremity.

- The Part I sub-score is the sum of the answers to the 4 questions that comprise Part I, each of which are measured on a 5-point scale (0 – 4). The Part I score will range from 0 – 16. No missing answers will be imputed so the Part I score will be missing if any of the answers are missing.
- The Part II sub-score is the sum of the answers to the 13 questions that comprise Part II, each of which are measured on a 5-point scale (0 – 4). The Part II score will range from 0 – 52. The UPDRS Part II score will be calculated as long as at least 12 questions have been answered. If 1 answer is missing the Part II score will be calculated by multiplying the sum of questions answered by the ratio of the total number of Part II questions to the number of questions answered.
- UPDRS Part III consists of 14 questions. Questions 20 – 26 are multi-part questions in that they are evaluated separately for multiple body parts. For example, Question 24, related to hand movements, is assessed separately for the left and right hand. Counting each of these assessments leads to a total of 27 answers for Part III. The Part III sub-score is the sum of the 27 answers provided to the 14 Part III questions, each of which is measured on a 5-point scale (0 – 4). The Part III score will range from 0 – 108. The UPDRS Part III score will be calculated as long as at least 23 answers have been recorded. If 4 or fewer answers are missing the Part II score will be calculated by multiplying the sum of the answers provided by the ratio of the total number of Part III answers possible (27) to the number of answers provided.
- The total score is the sum of the responses to the 31 questions (44 answers) that comprise Parts I – III of the scale. The total score ranges from 0 – 176 with 176 representing the worst (total) disability, and 0 no disability. The UPDRS Total score will be calculated as long as 38 answers have been recorded. If 6 or fewer answers are missing the Total score will be calculated by multiplying the sum of answers provided by the ratio of the total number of answers possible (44) to the number of answers provided.
- The Part IV Score is the sum of the answers to the 11 questions that comprise Part IV, 4 of which are measured on a 5-point scale (0 – 4) and 7 which are

measured on a 2-point scale (0 – 1). The Part IV score will range from 0 – 23. The UPDRS Part IV score will be calculated as long as at least 10 questions have been answered. If 1 answer (i.e., < 15%) is missing the Part IV score will be calculated by multiplying the sum of questions answered by the ratio of the total number of Part IV questions to the number of questions answered.

- Additionally, Questions 32, 33, and 34 on UPDRS Part IV will be totaled to evaluate dyskinesias. Each of these questions is measured on a 5-point scale (0 – 4). The Part IV dyskinesia score ranges from 0 – 12. No missing answers will be imputed so the Part IV score will be missing if any of the answers are missing.

8.4.3 Clinical Global Impression – Improvement (CGI-I)

The CGI-I is a global assessment by the Investigator of the change in clinical status since the start of treatment. The CGI-I ratings are as follows:

1 = very much improved
2 = much improved
3 = minimally improved
4 = no change
5 = minimally worse
6 = much worse
7 = very much worse

8.4.4 Parkinson's Disease Questionnaire (PDQ-39)

The PDQ-39 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-39 is a self-administered questionnaire that comprises 39 items addressing the following eight domains of health that subjects consider to be adversely affected by the disease:

- Mobility (e.g., fear of falling when walking) – 10 questions

- Activities of daily living (e.g., difficulty cutting food) – 6 questions
- Emotional well-being (e.g., feelings of isolation) – 6 questions
- Stigma (e.g., social embarrassment) – 4 questions
- Social support – 3 questions
- Cognition – 4 questions
- Communication – 3 questions
- Bodily discomfort – 3 questions

Each question is answered on the following 5-point scale: 0 = Never, 1 = Occasionally, 2 = Sometimes, 3 = Often, 4 = Always or Cannot Do At All. The PDQ-39 is scored on a scale of 0 to 100, where lower scores indicate a better perceived health status. Higher scores are consistently associated with the more severe symptoms of the disease such as tremor and stiffness. The domain scores are calculated by first summing the answers to the questions in the domain. The sum is divided by the highest score possible (i.e., number of question multiplied by 4) and the quotient is multiplied by 100 to put the score on a scale from 0 to 100. The Social Support domain has 1 question that cannot be answered if the subject does not have a spouse or partner. If the subject does not have a spouse or partner, the domain score is calculated as if the domain only had two questions. The PDQ-39 summary index (PDQ-39SI) is the sum of all answers divided by the highest score possible (i.e., number of answers multiplied by 4) which is multiplied by 100 to put the score on a 0 to 100 scale. The domain scores will only be calculated if all of the questions are answered. The PDQ-39SI will be calculated as long as no more than 15% (5) of the answers are missing. This enables calculation of the PDQ-39SI even if one or more of the domain scores are not calculated. The highest score possible will be adjusted based on the number of answers provided.

8.5 Safety Analysis Variables

8.5.1 Adverse Events

Adverse event (AE) Investigator terms are assigned to a Lowest Level Term (LLT) and a Preferred Term (PT) and will be classified by High Level Term (HLT), High Level Group

Term (HLGT) to one System Organ Class (SOC), namely the primary SOC, according to the MedDRA thesaurus, Version 14.0.

AE Investigator terms that are related to procedural or device complications may also have a secondary coding. For example, consider the verbatim term "Worsening of Parkinson's disease due to PEG-J dislocation." This AE can be coded as follows:

Primary Coding –

- Lower Level Term: PARKINSONISM AGGRAVATED'
- Preferred Term: 'PARKINSONISM'
- System Organ Class: 'NERVOUS SYSTEM DISORDERS'

Secondary Coding –

- Lower Level Term: 'DEVICE DISLOCATION'
- Preferred Term: 'DEVICE DISLOCATION'
- System Organ Class: 'INJURY, POISONING AND PROCEDURAL COMPLICATIONS'

AE summaries will include the primary as well as the secondary coding.

A detailed description of each AE includes:

- The start and stop date of the event or "Ongoing" at the end of the study.
- Severity (categorized as "Mild," "Moderate" or "Severe"). If severity is missing it will be regarded as "Severe."
- Relationship to the investigational therapeutic system (categorized as "Unrelated," "Unlikely," "Possible" or "Probable").
- Action taken with investigational study medication:
  - Drug discontinued.
  - Drug interrupted.
  - Dosage reduced.

- Dosage increased.
- None/not applicable.

- Outcome of event, which is defined as any one of the following:
  - Recovered/Resolved.
  - Recovered/Resolved with Sequelae.
  - Fatal.
  - Unknown.

  If an adverse event is "Ongoing," the Outcome will be blank.
- Serious, categorized as "Yes" or "No."
- Concomitant treatment/therapy introduced, categorized as "Yes" or "No."
- Led to study termination, categorized as "Yes" or "No."

Missing and/or incomplete dates for AEs are imputed in a manner resulting in the earliest onset within the Treatment Period and the longest duration. However, the Stop Date will not be imputed if the event is reported as "Ongoing."

Technically, this will be done as follows:

For a missing/incomplete start date the minimum of the following will be imputed:

- The maximum of the earliest possible start date and the date of first administration of investigational study drug
- The latest possible start date
- The latest possible stop date

For a missing/incomplete stop date the maximum of the following will be imputed:

- The minimum of the latest possible stop date and the date of last administration of investigational study drug
- The earliest possible stop date
- The earliest possible start date

Here, the earliest (latest) possible date is defined as:

- The date itself if it is possible
- The date of the first (last) day of the month, if month and year are available but the day is missing
- The date of the first (last) day of the year, if year is available but day and month are missing
- A very early (late) date, for example, 01JAN1000 (01JAN3000), if the date is completely missing

From this data the following will be determined and used for presentation in the applicable tables and listings:

- Treatment-Emergent Adverse Events (TEAEs): Defined as AEs which started on or after the Date of the First 3005 LCIG Infusion and within 30 days of the Date of the Last 3005 PEG-J Exposure.
- Treatment-Emergent Serious Adverse Events (TESAEs): Defined as TEAEs regarded by the Investigator as Serious.
- TEAEs that are at least possibly related to the therapeutic system: Defined as TEAEs assessed as having a "Possible" or "Probable" relationship to the investigational therapeutic system and includes those events where the relationship is missing.
- Severe TEAEs: Defined as TEAEs assessed as being "Severe" in intensity and includes those events where the severity is missing.
- TEAEs that led to premature discontinuation: Selected as those events where: "Led to Study Termination" is indicated as "Yes."
- TEAEs with fatal outcome as reported on the "Adverse events" CRF.
- TEAEs in the following categories have been defined as TEAEs of special interest:
    - Procedure and device associated events
    - Polyneuropathy (broad search as well as narrow search)
    - Weight loss

- Cardiovascular fatalities
- Respiratory tract aspiration including aspiration pneumonia/pneumonitis

TEAEs are included in a category of special interest based on their PT and, in the case of cardiovascular fatalities, their outcome. The list of PT's assigned to each category is included as Appendix 12.4. Only TEAEs where an outcome of "Fatal" has been reported on the "Adverse Event" CRF are to be included in the category of cardiovascular fatalities. All events with PT's other than those assigned to the procedure and device associated AESI category will be included in summaries of events that are not procedure and device related.

The percentage of each of the aforementioned AE types will be determined as the number of subjects with at least one mention of the AE type relative to the number of subjects at risk. A subject will be considered at risk if the subject is in the Safety subject sample.

In addition to the aforementioned AE types, AEs reported by the Investigator as related to device complications will also be summarized. Device complications are captured in the DE raw data panel and associated AEs are captured in the AE raw data panel. Investigators link the AEs that are related to device complications by entering an AE number in the DE raw data panel.

The incidence and prevalence of TEAEs during each 3005 Treatment Year will be summarized using the study day intervals described in Section 6.4.9. AE start days and Treatment Period end days will be calculated relative to the start of 3005 LCIG infusion (RFSTDTN) as follows:

AE Start Day = (AE Start Date – Date of First 3005 LCIG Infusion) + 1

Treatment Period End Day = ([Date of Last 3005 PEG-J Exposure + 30 Days] – First Date of 3005 LCIG Infusion) + 1

For summaries of incidence, the count (and numerator for percentage calculations) will be the number of subjects who had their first treatment-emergent occurrence of the PT start

within the study day range for the 3005 Treatment Year. Each subject will be counted at most once within each SOC and PT.

For summaries of prevalence, the count (and numerator for percentage calculations) will be the number of subjects who had a treatment-emergent occurrence of the PT start within the study day range for the 3005 Treatment Year or who had an earlier treatment-emergent occurrence of the PT that had not ended prior to the start of the study day range for the 3005 Treatment Year.

The denominator for both incidence and prevalence percentage calculations will include all subjects whose Treatment Period End Day is within or greater than the study day range for the 3005 Treatment Year.

8.5.2 Safety Laboratory Data

Special tests for vitamin deficiencies (Folic Acid, Vitamin B_6, Vitamin B_{12}, Methylmalonic Acid (MMA), and Homocysteine) were added to the schedule of assessments (Appendix 12.1) with Protocol Amendment 2. Additional clinical laboratory evaluations are to be performed as an element of routine care and are done as a subject's condition mandates. The final visit is the only study visit at which they are one of the scheduled assessments. Abnormal lab results are to be reported, including the Investigator's opinion of whether they are clinically significant. Clinically significant laboratory results are also to be reported as an AE.

Potentially clinically significant (PCS) laboratory values will be identified. A laboratory value will be considered potentially clinically significant if it satisfies the criteria presented in Table 4 and is also more extreme than the subject's corresponding baseline value.

Table 4. Criteria for Identification of Potentially Clinically Significant (PCS) Laboratory Values

Variable (Synonyms)		Medical Condition	S.I. Units		
			Unit	Lower Limit	Upper Limit
Blood Biochemistry					
Alanine aminotransferase (ALT, GPT, SGPT)		Liver toxicity	U/L	NA	> 3 × ULN
Alkaline phosphatase (ALP)		Liver toxicity	U/L	NA	> 400 U/L
Aspartate aminotransferase (AST, GOT, SGOT)		Liver toxicity	U/L	NA	> 3 × ULN
Bilirubin (Total)		Liver toxicity	mcmol/L	NA	> 2 × ULN
Creatinine			mcmol/L	NA	> 177
Creatine phosphokinase (CPK)		Myocardial infarction/ Muscular dystrophy	U/L	NA	> 3 × ULN
Lactate dehydrogenase (LDH)			U/L	NA	> 3 × ULN
Blood urea nitrogen (BUN)			mmol/L	NA	> 10.8
Uric acid	Female		mcmol/L	NA	> 500
	Male		mcmol/L	NA	> 590
Albumin			g/L	< 25	> 70
Calcium (Total)			mmol/L	< 1.75	> 3.0
Total cholesterol			mmol/L	NA	> 12.9
Gamma glutamyl-transferase (GGT)			U/L	NA	> 3 × ULN
Glucose			mmol/L	< 2.78	> 16.0
Potassium			mmol/L	< 3.0	> 6.0
Protein (Total)			g/L	< 45	NA
Sodium			mmol/L	< 126	> 156
Triglycerides			mmol/L	NA	> 5.6

Table 4. Criteria for Identification of Potentially Clinically Significant (PCS) Laboratory Values (Continued)

Variable (Synonyms)		Medical Condition	S.I. Units		
			Unit	Lower Limit	Upper Limit
Blood Biochemistry (continued)					
Hematology					
Eosinophils			%	NA	> 10
Hematocrit (Ejection Volume Fraction)	Female		%	< 30	NA
	Male		%	< 34	NA
Hemoglobin	Female		g/L	< 90	NA
	Male		g/L	< 100	NA
Leukocytes (WBC)			10^9/L	< 2.8	> 16.0
Neutrophils, abs			10^9/L	< 1.2	NA
Thrombocytes (Platelets)			10^9/L	< 95	> 700
Erythocytes (RBC)	Female		10^{12}/L	< 2.0	NA
	Male		10^{12}/L	< 2.5	NA
Lymphocytes			%	NA	> 80
Lymphocytes, abs			10^9/L	< 0.75	NA
Mean corpuscular volume (MCV)			fL	< 60	> 120
Monocytes			%	NA	> 30

8.5.3 Vital Signs and Weight

The measured vital signs include:

- Weight (kg).
- Body Temperature (degrees Celsius) and Route of Measurement.
- Systolic Blood Pressure (SBP [mmHg]), supine and standing.
- Diastolic Blood Pressure (DBP [mmHg]), supine and standing.
- Pulse Rate (bpm), supine and standing.

The following orthostatic vital signs will be calculated based on measurements in the supine and standing positions:

- Orthostatic SBP (mmHg) = Standing SBP – Supine SBP
- Orthostatic DBP (mmHg) = Standing DBP – Supine SBP
- Orthostatic Pulse Rate (bpm) = Standing Pulse Rate – Supine Pulse Rate

See Section 8.2.2 (Other Baseline Characteristics) for the derivations and conversions of the aforementioned variables. At each scheduled visit, preferably by the same observer, supine and standing SBP, DBP, and pulse rate will be measured using the same arm after the subject has been in the position for 2 minutes.

Potentially clinically significant (PCS) vital signs values will be identified. A vital sign value will be considered potentially clinically significant if it satisfies the criteria presented in Table 5 and is also more extreme than the subject's corresponding baseline value.

Table 5. Criteria for Identification of Potentially Clinically Significant (PCS) Vital Sign and Weight Values

Variable	Unit	Very Low (VL)	Very High (VH)
SBP[a]	mmHg	Value ≤ 90 and > 30 decrease from Baseline	Value ≥ 180 and > 40 increase from Baseline
DBP[a]	mmHg	Value ≤ 50 and > 30 decrease from Baseline	Value ≥ 105 and > 30 increase from Baseline
Pulse Rate[a]	bpm	Value ≤ 50 and > 30 decrease from Baseline	Value ≥ 120 and > 30 increase from Baseline
Temperature	°C	NA	Value ≥ 38.3 and ≥ 1.1 increase from Baseline
Orthostatic SBP (Hypotension)	mmHg	Decrease of ≥ 30 in SBP (supine to standing)	NA
Orthostatic DBP (Hypotension)	mmHg	Decrease of ≥ 20 in DBP (supine to standing)	NA
Weight	kg	Decrease of ≥ 7% from Baseline	Increase of ≥ 7% from Baseline

a. Both for supine and standing.

8.5.4 Electrocardiogram (ECG) Data

In Study 3005, single standard 12-lead electrocardiograms (ECGs) are to be performed as an element of routine care and are done as a subject's condition mandates. The final visit is the only study visit at which an ECG is one of the scheduled assessments. All ECGs are to be reviewed by a local reader, who assesses them as "Normal," "Abnormal, not clinically significant," "Abnormal, clinically significant" or "Unknown." Clinically significant abnormalities in the ECG are to be reported as an AE and the subject's ECG is to be repeated at medically appropriate intervals until it stabilizes or returns to acceptable levels. Due to the limited data collected, ECG results and interpretations will be presented as a listing but will not be summarized.

8.5.5 Other Safety Analyses

Other safety data, not previously discussed, include:

- Complications with infusion device
- PEG tube and J tube replacements and average duration
- Sleep attacks
- Minnesota Impulsive Disorders Interview (MIDI)
- Columbia Suicide Severity Rating Scale (C-SSDRS)
- Melanoma check
- Neurological examination

8.5.5.1 Complications with Infusion Device

For each complication related to the infusion device (i.e., tubing kinks, tubing displaced, tubing connector problems, and pump technical difficulties) the following data will be collected in addition to a description of the complication.

- Incident start and stop date
- Type of complication
    - Pump complication

  - Intestinal tube complication
  - PEG-J complication
  - Stoma complication
  - Other complication
- Action taken
  - No action taken
  - Reposition of tube with surgery
  - Reposition of tube without surgery
  - Pump replaced
  - Medication treatment interrupted
  - Medication treatment stopped
  - Other
- Did this complication result in an AE? ("Yes" or "No")
- For complications that resulted in an AE, the AE number(s)

Each device complication will be assigned to a Preferred Term (PT), according to the MedDRA thesaurus, Version 14.0.

The percentage of subjects with a device complication will be determined as the number of subjects with at least one device complication relative to the number of subjects at risk. A subject will be considered at risk if the subject is in the Safety subject sample. Summaries of device complications by action taken will exclude complications where the response for action taken is "No action taken."

The incidence of device complications during each 3005 Treatment Year will be summarized using the study day intervals described in Section 6.4.9. Device complication start days and Treatment Period end days will be calculated relative to the start of 3005 LCIG infusion (RFSTDTN) as follows:

> Device Complication Start Day = (Device Complication Start Date – Date of First 3005 LCIG Infusion) + 1

Treatment Period End Day = ([Date of Last 3005 PEG-J Exposure + 30 Days] – First Date of 3005 LCIG Infusion) + 1

The count (and numerator for percentage calculations) will be the number of subjects who had their first occurrence of the PT start within the study day range for the 3005 Treatment Year. Each subject will be counted at most once within each SOC and PT.

The denominator for percentage calculations will include all subjects whose Treatment Period End Day is within or greater than the study day range for the 3005 Treatment Year.

8.5.5.2 PEG Tube and J Tube Replacements and Average Duration

The date of each PEG tube and J tube placement and removal is recorded on the Device Information eCRF. The number of PEG tube replacements and the number of J tube replacements overall and by 3005 Treatment Year will be summarized.

The number of PEG tube and J tube replacements during each 3005 Treatment Year will be summarized using the study day intervals described in Section 6.4.9. Tube replacement days and Treatment Period end days will be calculated relative to the start of 3005 LCIG infusion (RFSTDTN) as follows:

Tube Replacement Day = (Tube Placement Date – Date of First 3005 LCIG Infusion) +1

Treatment Period End Day = ([Date of Last 3005 PEG-J Exposure + 30 Days] – First Date of 3005 LCIG Infusion) +1

The count (and numerator for percentage calculations) will be the number of subjects who had one or more PEG (or J) tube replacements within the study day range for the 3005 Treatment Year. Each subject will be counted at most once for each 3005 Treatment Year.

The denominator for percentage calculations will include all subjects whose Treatment Period End Day is within or greater than the study day range for the 3005 Treatment Year.

As previously described, Study 3005 is an extension of the previous Studies 3001, 3002, 3003, and 3004. The number of PEG tube and J tube replacements in these previous studies will be retrieved from the relevant study databases and will be summarized.

The average PEG tube and J tube duration (time in place) during Study 3005 will be summarized. For each tube the duration will be calculated as the tube removal date – the tube placement date +1. The average PEG tube and average J tube duration for each subject will then be calculated as the mean of all PEG (J-tube) tubes the subject had exposure to during the study. For tubes already in place at the start of the study (missing placement date), the placement date will be imputed as the date of the first 3005 LCIG infusion (as defined in Section 6.4.1). For tubes remaining in place (missing removal date), the removal date will be imputed as the date of the last 3005 PEG-J exposure (as defined in Section 6.4.1). Due to the imputation of placement and removal dates, the 3005 tube duration will be interpreted as the minimal amount of time the tube was in place.

8.5.5.3 Sleep Attacks

In order to prospectively monitor for the possible development of sleep attacks the following questions will be asked of subjects at each visit:

> Since your last visit (or 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, with or without any previous warning of sleepiness?
>
> - 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?

The summary of sleep attacks will include the incidence of subjects with sleep attacks and the incidence of subjects with "bad outcomes" at Baseline and at any time during the Treatment Period. Summaries of sleep attacks by visit will be considered if the initial results indicate a high incidence of subjects with sleep attacks.

8.5.5.4 Minnesota Impulsive Disorders Interview (MIDI)

In order to monitor for the development of intense impulsive behavior the Minnesota Impulsive Disorder Interview (MIDI) will be administered at each visit. The MIDI is a semi-structured clinical interview assessing pathological gambling, trichotillomania, kleptomania, pyromania, intermittent explosive disorder, compulsive buying, and compulsive sexual behavior. A subject's MIDI screen is positive for a disorder if:

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

The incidence of subjects who report intense impulsive behavior at Baseline and at any time during the Treatment Period will be provided. Summaries of MIDI assessments by

visit will be considered if the initial results indicate a high incidence of subjects with intense impulsive behavior.

8.5.5.5 Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS)[5] is a systematically administered instrument developed to track suicidal adverse events across a treatment study. It was added to the flowchart of study assessments (Appendix 12.1.3) with Protocol Amendment 3. At each study visit, the C-SSRS will collect experience since the last visit. The incidence of subjects with affirmative responses on the C-SSRS at any time during the Treatment Period will be provided.

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

8.5.5.6 Melanoma Check

A comprehensive assessment for the presence of melanoma must be performed at least once a year by a dermatologist experienced with the diagnosis of the condition. If a suspicious lesion is present, a biopsy should be obtained for proper diagnosis. Subjects who have a melanoma present at the start of the study, or who develop one during the course of the study should be discontinued from participation and referred for proper follow-up care.

8.5.5.7 Neurological Examination

At each of the scheduled visits indicated in the flowchart of study assessments a neurological examination will be performed including light touch and pinprick sensation, vibratory sensation, deep tendon reflexes, and strength assessments. Any abnormalities or symptoms identified will be reported as adverse events.

9.0 Statistical Analysis

This section will indicate how the statistical analysis will be performed on the basis of the conventions, definitions and techniques that are described in Section 6.0 through Section 8.0. To each standard table (T), listing (L) or figure (F) a unique code is assigned which is used as a reference in the SAP and indicated on the appropriate table/listing/figure template. For example, a demographics table is assigned the unique code of DMT001, where DM refers to the clinical domain (Demographic Data), T indicates that it is a table and 001 indicates that it is the first table in the DM set of tables. Tables, listings and figures that are referred to are listed in the Appendices, Section 12.2 and Section 12.3.

9.1 Subject Disposition

Subject disposition (DS) will be summarized for all centers/countries combined by means of the default summary statistics described in Section 6.0 (General Definitions, Methods, Naming Conventions and Data Handling).

Subject Samples:	Tables	All subjects consented and Efficacy Sample US Subset
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		Not applicable
Abbreviation:		DS

Standard Presentations

DST001 The primary reason for premature discontinuation after consent, as recorded on the "Study Termination" form, will be presented. The primary reason for premature discontinuation includes:

- Adverse Event
- Lack of Efficacy
- Lost to Follow-up
- Withdrew Consent
- Administrative
- Protocol Violation

The number of subjects who have completed the study and the number whose participation in the study is ongoing will also be presented. The percentage of subjects will be calculated relative to the number of consenting subjects.

DST002 Subject validity/subject sample status will be summarized with the reason for exclusion from the Safety sample. The only reason for exclusion from the safety sample will be that the subject did not infuse any study medication after providing informed consent.

DST003 The number and percentage of subjects prematurely discontinuing in each 3005 treatment year will be summarized.

Standard subject data listings include:

DSL001 A listing of subjects who prematurely discontinued their participation in the study prior to receiving 3005 LCIG.

DSL002 A listing of subjects who discontinued participation after receiving 3005 LCIG will be presented. The relative treatment day of last contact with the subject and the last day of 3005 LCIG infusion, as captured on the "Study Termination" CRF form will be calculated as:

- Relative Treatment Day of Last Contact = (Date of Last Contact – Date of First 3005 LCIG Infusion) + 1
- Relative Treatment Day of Last 3005 LCIG Infusion = (Date of Last 3005 LCIG Infusion – Date of First 3005 LCIG Infusion) + 1

DSL003 Exclusion from the Safety subject sample together with the reason(s) for exclusion will be presented. This listing will include all possible reasons for exclusion per subject.

Study Specific Presentations

Not applicable.

9.2 Major Protocol Deviations

Major protocol deviations (DV) will be summarized for all centers/countries combined.

Subject Samples:	Tables	Safety sample
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		Not applicable
Abbreviation:		DV

Standard Presentations

DVT001 The number of unique subjects presenting with at least one major protocol deviation will be presented. In addition, the number and percentage of subjects allocated to treatment in each major protocol deviation category will be presented. Subjects may have more than one major protocol deviation.

Standard subject data listings include:

DVL001 A by-subject listing of all subjects with one or more major protocol deviations will be presented.

Study Specific Presentations

Not applicable.

9.3 Inclusion/Exclusion Criteria

Only the exceptions are to be listed, that is, subjects with a response to the Inclusion Criteria of "No" and/or subjects with a response to the Exclusion Criteria of "Yes." Subjects with a missing response to Inclusion/Exclusion Criteria will also be presented.

Subject Samples:	Tables	Not applicable
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		Not applicable
Abbreviation:		IE

Standard Presentations

The response (Yes/No) per subject with at least one exception to each of the study specific inclusion/exclusion criteria, will be presented as a subject data listing as follows:

IEL001 Listing of all Inclusion Criteria including a text description of each criterion and the response as either "Yes" or "No" for those subjects with at least one exception.

IEL002 Listing of all Exclusion Criteria including a text description of each criterion and the response as either "Yes" or "No" for those subjects with at least one exception.

Study Specific Presentations

Not applicable.

9.4 Demographic Data and Other Baseline Characteristics

9.4.1 Demographic Data

Subject demographic data (DM), described below, will be summarized and presented for observed data only. All missing data will be presented as part of a missing category, if appropriate.

Subject Samples:	Tables	Safety sample and US Subset
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		Not applicable
Abbreviation:		DM

Standard Presentations

DMT001 Qualitative demographic data, presented by means of default summary statistics, includes:

- Gender: Male or Female.
- Race: American Indian or Alaska Native, Asian, Black of African Heritage or African American, Native Hawaiian or Other Pacific Islander, White. For each subject one or more race categories can be selected.
- Ethnicity: Hispanic or Non-Hispanic.
- Age: $< 65, \geq 65$.
- Country

Quantitative demographic data includes:

- Age (years) presented by default summary statistics.

Standard subject data listings include:

DML001	Standard demographic data will be presented. Missing data will not be imputed for the listing. An incomplete date will be presented, for example, as – Jan 1980, as originally entered in the CRF. The relative day of assessment will be calculated relative to the start of the 3005 LCIG infusion (RFSTDTN) and will be presented for those subjects who received 3005 LCIG infusion.

Study Specific Presentations

Not applicable.

9.4.2 Other Baseline Characteristics

Default summary statistics, described in Section 6.0 (General Definitions, Methods, Naming Conventions and Data Handling), of the baseline subject characteristics will be presented for all countries/centers combined.

Subject Samples:	Tables	Safety sample and US Subset
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		Not applicable
Abbreviation:		SC

Standard Presentations

SCT001 Other subject characteristics (SC) include the following vital signs:

- Systolic Blood Pressure (SBP [mmHg]), supine, standing, and orthostatic
- Diastolic Blood Pressure (DBP [mmHg]), supine, standing, and orthostatic
- Pulse rate (bpm), supine, standing, and orthostatic
- Height (m)
- Weight (kg), overall and by gender
- BMI (kg/m^2)
- Body temperature (degrees Celsius)
- Route of measurement

Standard subject data listings include:

SCL001 The aforementioned vital signs data will be presented by subject. The relative day of the assessment will be calculated relative to the start of 3005 LCIG infusion (RFSTDTN) and will be presented for those subjects who received 3005 LCIG infusion.

Study Specific Presentations

SCT002 Other subject characteristics include the following assessments collected during the Initial Screening Period:

- Duration in years since the first diagnosis of PD
- Diagnosis of bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- Diagnosis of muscular rigidity
- Diagnosis of 4 – 6 Hz resting tremor
- Diagnosis of postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

SCT003 PD medications that were started during the previous study and continue to be used by the subject will be summarized. The primary ATC class (e.g., Dopa and Dopa Derivatives, Dopamine Agonists, COMT Inhibitors, etc.) will be used to group similar medications. Subjects will be categorized according to the number of medication classes used (i.e., 1, 2, 3, or > 3 PD medication classes). Within each group of subjects, the number of subjects using each medication type will be summarized using default summary statistics. The percentage of subjects taking 1, 2, 3, or > 3 PD medications is calculated relative to the total number of subjects considered valid for the specific subject sample, that is, Safety subject sample. The percentage of subjects taking a medication in a specific ATC class is calculated relative to the number of subjects in the 1, 2, 3, > 3 PD medication subgroups.

Study Specific subject data listings include:

SCL002 A listing of the date and duration of diagnosis as well as results of the 'Diagnosis of Idiopathic Parkinson's Disease' according to the modified UKPDS brain bank criteria will be provided.

SCL003 By-subject and within-subject by ascending start date/relative start day of PD medication use. In SCL003 the relative start and stop day of PD medication use will be calculated relative to the first 3005 LCIG infusion and will be presented for those subjects who were allocated to treatment and received at least one dose of investigational study medication. If the medication is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

SCL004 A listing of the relevant WHO-DD coding information, sorted in the same way as SCL003 will also be provided.

9.5 Medical and Neurological History

Subject Samples:	Tables	Safety sample
	Listings	All subjects consented
	Figures	Not applicable

Subgroups:	Not applicable
Abbreviation:	MH

Standard Presentations

Medical history findings collected on the Medical History and Neurological History CRFs during the Initial Screening Period will be combined and summarized as follows:

MHT001 The number of subjects with at least one medical or neurological history finding will be presented by default summary statistics, where the percentage of subjects is calculated relative to the total number of subjects considered valid for the specific subject sample, for example, Safety subject sample. In addition, the number of subjects with at least one medical or neurological history finding within each primary SOC and PT, will be presented.

Standard subject data listings include:

MHL001 Medical and neurological history findings will be presented by-subject and within-subject by ascending order of start date of each medical history.

MHL002 A listing of the relevant MedDRA coding information, sorted in the same way as MHL001 will also be provided.

Study Specific Presentations

Not applicable.

9.6 Concomitant Medication

Concomitant medication will be presented as the number and percentage of subjects taking concomitant medication according to WHO-DD, 01 March 2011, primary ATC third level subgroup and generic name (corresponds to the first 6 digits of the 11-digit WHO-DD code). For the standard presentation, percentages will be calculated relative to the number of subjects considered valid for the Safety sample.

Subject Samples:	Tables	Safety sample and US Subset
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		Not applicable
Abbreviation:		CM

Standard Presentations

Concomitant medication assigned to the Treatment Period will be summarized as follows:

CMT001 The number of subjects with at least one concomitant medication use in the Treatment Period will be presented by default summary statistics, where the percentage of subjects is calculated relative to the total number of subjects considered valid for the specific subject sample, that is, Safety subject sample. In addition, the number of subjects with at least one concomitant medication use within each ATC third level subgroup and generic name will be presented. The ATC third level subgroups are to be ordered alphabetically/numerically by ATC code and within ATC third level subgroup alphabetically by generic name.

All medications entered on the "Concomitant Medication" CRF form will be presented in subject data listings as follows:

CML001 By-subject and within-subject by ascending start date/relative start day of medication use. In CML001 the relative start and stop day of concomitant medication use will be calculated relative to the start of the first infusion and will be presented for those subjects who were allocated to treatment and received at least one dose of investigational study medication. If the concomitant medication is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

CML002 A listing of the relevant WHO-DD coding information, sorted in the same way as CML001 will also be provided.

Study Specific Presentations

CMT002 The number of subjects with at least one anti-parkinsonian concomitant medication used in the Treatment Period will be presented by time interval (Year 1, Year 2, Year 3, Year 4, Year 5, > Year 5) using default summary statistics, where the percentage of subjects is calculated relative to the total number of subjects considered valid for the specific subject sample, that is, Safety Sample during the given time interval. In addition, the number of subjects with at least one concomitant medication use within each ATC third level subgroup and generic name will be presented. The ATC third level subgroups are to be ordered alphabetically/numerically by ATC code and within ATC third level subgroup alphabetically by generic name.

9.7 Drug Accountability

Subject Samples:	Tables	Not applicable
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		Not applicable
Abbreviation:		DA

Standard Presentations

Not applicable.

Study Specific Presentations

The following subject data listings will be prepared:

DAL001 The number of medication cassettes dispensed and returned will be presented.

9.8 Treatment Exposure

Subject Samples:	Tables	Safety sample and US Subset
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		First LCIG infusion study (3001/3002, 3003 or 3004)
Abbreviation:		EX

Standard Presentations

Not applicable.

Study Specific Presentations

EXT001 The duration of 3005 LCIG exposure, overall duration of LCIG exposure, duration of 3005 PEG-J exposure, and overall duration of PEG-J exposure will be summarized using the same table format. These durations are defined in Section 6.4.1 (General Definitions) and also Section 8.3.2 and will be summarized using the appropriate default summary statistics. The number of subjects exposed will be presented by yearly time intervals (Year 1, Year 2, Year 3, Year 4, Year 5, > Year 5). A subject will be counted within an interval if their duration of exposure extended into the interval for 1 or more days. The total subject-years of exposure will also be presented.

EXT002 The prescribed pump settings for the morning dose and flow rate at the conclusion of the preceding study will be summarized using the appropriate default summary statistics. The summary will not include subjects who enrolled in Study 3005 after completing Study 3003 because the prescribed pump settings were not recorded in that study.

EXT003 The average total daily levodopa dose at the final 3005 visit will be summarized with descriptive statistics for each component as well as for the total levodopa dose. Each subject's total daily levodopa dose at the end of titration in their initial LCIG study (Studies 3001, 3002, 3003 or 3004) will be retrieved from the relevant database. The total daily levodopa dose at the end of initial titration and the change from the end of initial titration to final 3005 visit will be summarized with descriptive statistics.

EXT004 The total daily levodopa dose at the end of initial titration and the change from the end of initial titration to final 3005 visit will be summarized by subgroup for the Safety Sample – US Subset.

Subject data listings include:

EXL001 A listing of treatment exposure data, including the first and last dates of 3005 LCIG infusion will be presented by-subject.

9.9 Efficacy Analyses

Subject Samples:	Tables	Efficacy Sample and US Subset
	Listings	All subject consented
	Figures	Not applicable
Subgroups:		First LCIG infusion study (3001/3002, 3003 or 3004), troublesome dyskinesia at initial LCIG infusion (< 1 hour, > 1 hour), dose of levodopa at initial LCIG infusion (< 1250 mg/day, > 1250 mg/day), and levodopa monotherapy during Study 3005 (yes, no)
Abbreviation:		QS

Standard Presentations

QST001 The average daily normalized "off" time will be summarized at initial LCIG infusion, at 3005 baseline and at 3005 endpoint as well as the change from initial LCIG infusion to 3005 endpoint and the change from 3005 baseline to 3005 endpoint. Descriptive statistics (including n, mean, minimum, maximum and 95% confidence interval) will be calculated.

Statistical tests for within group changes from initial LCIG infusion and from 3005 baseline will be implemented using PROC UNIVARIATE.

For the UNIVARIATE the following SAS® code will be used:

PROC UNIVARIATE data = <SAS®-dataset> cibasic alpha = 0.05;
VAR OFFTIME;
RUN;

The same methods defined above for average daily normalized "off" time will also be used to analyze the following assessments:

1. Change in average daily normalized "on" time without troublesome dyskinesia
2. Change in average daily normalized "on" time with troublesome dyskinesia
3. Change in average daily normalized "on" time with mon-troublesome dyskinesia
4. Change in average daily normalized "on" time without dyskinesia
5. Change in the UPDRS total score, subscores of Parts I – IV and Part IV Questions 32, 33 and 34 (Dyskinesia items)
6. Change in the PDQ-39 summary index and each domain score

Variables derived from the PD Diary and PDQ-39 will be summarized for the Efficacy sample and the US subset of the Efficacy sample. Variables derived from the UPDRS will be summarized for the US subset of the Efficacy sample.

QST002 The change from initial LCIG infusion to 3005 endpoint and from 3005 baseline to 3005 endpoint will be summarized by subgroup in the Efficacy sample – US Subset for the PD Diary variables.

QST003 The CGI score at 3005 endpoint will be summarized using the appropriate default summary statistics for the Efficacy sample.

Subject data listings will include:

QSL001	A listing of Parkinson's Disease Diary data by-subject and within-subject by visit will be presented.
QSL002	A listing of CGI-I scores by-subject and within-subject by visit will be presented.
QSL003	A listing of PDQ-39 responses by subject and within-subject by visit will be presented.
QSL004	A listing of UPDRS responses by subject and within-subject by visit will be presented.

9.10 Pharmacokinetic and Pharmacodynamic Analyses

No pharmacokinetic or pharmacodynamic analyses will be completed.

9.11 Analysis of Safety

9.11.1 Adverse Events

Adverse events (AEs) will be reported on a per-subject basis. This implies that even if a subject reported the same event repeatedly (same event that maps to the same PT), the event will be counted only once. In the latter case, the event will be assigned the worst severity and strongest relationship to the investigational study medication. Except for summaries of prevalence, the presentation of AEs is therefore restricted to the incidence per subject of AEs assigned to the Treatment Period. For summaries of prevalence over time, each event (all events that map to the same PT) will be counted only once per subject for each time period presented.

Subject Samples:	Tables	Safety sample and US subset of safety sample
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		Gender, age category (< 65, ≥ 65), duration of Parkinson's disease (< 10 years, ≥ 10 years), country
Abbreviation:		AE

Standard Presentations

Adverse events will be summarized by default summary statistics, for all centers/countries combined as well as for subjects enrolled at US sites. Percentages will be calculated relative to the total number of subjects considered valid for the subject sample.

The following standard presentations will be produced for all TEAEs in the Safety subject sample.

AET001 Overview of AEs including the number of subjects with:

- At least one TEAE.
- At least one TEAE that is at least possibly drug-related.
- At least one serious TEAE.
- At least one SAE.
- Any AE leading to death.
- A TEAE leading to death.
- A TEAE leading to premature discontinuation.
- At least one severe TEAE.

AET002 Incidence of TEAEs will be presented by primary SOC and PT. The primary SOCs are to be ordered alphabetically. Within each SOC, the PT is also to be ordered alphabetically.

AET003 Incidence of TEAEs will be presented by PT. SOCs will not be presented and PTs will be ordered by decreasing frequency of occurrence.

AET004 Incidence of TESAEs will be presented by primary SOC and PT. The primary SOCs are to be ordered alphabetically. Within each SOC, the PT is also to be ordered alphabetically.

AET005 Incidence of TEAEs leading to premature discontinuation will be presented by primary SOC and PT. The primary SOCs are to be ordered alphabetically. Within each SOC, the PT is also to be ordered alphabetically.

AET006 For each defined category of special interest, incidence of TEAEs will be presented by primary SOC and PT. The primary SOCs are to be ordered alphabetically. Within each SOC, the PT is also to be ordered alphabetically.

AET007 Incidence of TEAEs by strongest relationship. A default frequency table by primary SOC and PT will be presented. The primary SOCs are to be ordered alphabetically. Within each SOC, the PT is also to be ordered alphabetically.

AET008 Incidence of TEAEs that are at least possibly related to treatment will be presented by primary SOC and PT. The primary SOCs are to be ordered alphabetically. Within each SOC, the PT is also to be ordered alphabetically.

AET009 Incidence of TEAEs by maximum severity. A default frequency table by primary SOC and PT will be presented. The primary SOCs are to be ordered alphabetically. Within each SOC, the PT is also to be ordered alphabetically.

In addition, AE data will be listed as follows:

AEL001 All AEs by-subject and within-subject by start date/relative start day of the adverse event. In AEL001 the relative start and stop day of the AE will be calculated relative to the date of the first 3005 LCIG infusion and will be presented for the Safety subject sample. If the AE is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

AEL002 A listing of the relevant MedDRA coding information will be provided as AEL002, sorted in the same chronological order as AEL001.

AEL003	Listing of deaths. AEL003 also includes the general demographic data for each subject who died (gender, age, ethnicity and race).
AEL004	Listing of SAEs. AEL004 lists all subjects with at least one serious adverse event indicating whether the SAE is treatment-emergent or not.
AEL005	Listing of TEAEs leading to study termination. AEL005 will be presented for those subjects valid for the Safety subject sample with at least one adverse event for which the question "Led to Study Termination" is indicated as "Yes."
AEL006	Listing of TEAEs of special interest. A listing will be presented for each AE of special interest category.

Study Specific Presentations

AET010	Incidence of TEAEs that have been linked to a device complication by investigators through the Device Complication CRF. A default frequency table by primary SOC and PT will be presented. The primary SOCs are to be ordered alphabetically. Within each SOC, the PT is also to be ordered alphabetically.
AET011	Incidence of TEAEs within each consecutive 3005 Treatment Year (as defined in Section 6.4.9) will be summarized. A default frequency table by primary SOC and PT will be presented. The primary SOCs are to be ordered alphabetically. Within each SOC, the PT is also to be ordered alphabetically.
AET012	Incidence of TEAEs within subgroups. A default frequency table by primary SOC and PT will be presented for each subgroup category. The primary SOCs are to be ordered alphabetically. Within each SOC, the PT is also to be ordered alphabetically.
AET013	Incidence of TEAEs with a fatal outcome will be presented by primary SOC and PT. The primary SOCs are to be ordered alphabetically. Within each SOC, the PT is also to be ordered alphabetically.
AET014	Prevalence of TEAEs within each consecutive 3005 Treatment Year (as defined in Section 6.4.9) will be summarized. A default frequency table by primary SOC and PT will be presented. The primary SOCs are to be ordered alphabetically. Within each SOC, the PT is also to be ordered alphabetically.

9.11.2 Clinical Laboratory Evaluation

All laboratory tests will be presented in System International (S.I.) units only, unless otherwise specified.

Subject Samples:	Tables	Safety sample
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		Not applicable
Abbreviation:		LB

Standard Presentations

LBT001	For those variables with a PCS criterion (as defined in Table 4) the incidence of marked abnormalities per laboratory parameter will be presented. The percentage per parameter is defined as the ratio of the number of subjects with at least one PCS value occurring at a post-baseline visit and the total number of subjects in the subject sample with a post-baseline measurement of the specified parameter.
LBT002	Summary of quantitative special laboratory parameters for determination of vitamin deficiencies, for all centers/countries combined, using default summary statistics. At each assessed visit, summary statistics will be presented as well as for the change from Baseline at each post-baseline visit.
LBT003	The incidence of values above and below the reference range for the quantitative special laboratory parameters for determination of vitamin deficiencies will be presented. The percentage per parameter is defined as the ratio of the number of subjects with at least one value above (below) the reference range at a post-baseline visit and the total number of subjects in the subject sample with a post-baseline measurement of the specified parameter.

The laboratory test data will be presented in subject data listings as follows:

LBL001	Hematology laboratory test data will be presented by-subject and within-subject by sample collection date and laboratory test, including the relevant reference ranges.
LBL002	Chemistry laboratory test data will be presented by-subject and within-subject by sample collection date and laboratory test, including the relevant reference ranges.
LBL003	Urinalysis laboratory test data will be presented by-subject and within-subject by sample collection date and laboratory test, including the relevant reference ranges.
LBL004	Laboratory test data will be presented by-subject and within-subject by laboratory test. PCS values will be identified and only subjects with one or more PCS values for the laboratory test will be presented.

9.11.3 Vital Signs

Subject Samples:	Tables	Safety sample
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		Not applicable
Abbreviation:		VS

Standard Presentations

VST001	Summary of quantitative vital signs assessments will be presented, for all centers/countries combined, using default summary statistics. At each assessed visit, summary statistics will be presented as well as for the change from Baseline at each post-baseline visit.
VST002	For each variable with a PCS criterion (as presented in Table 5), the incidence of PCS values will be presented. The percentage per parameter is defined as the ratio of the number of subjects with at least one PCS value occurring at a post baseline visit that is more extreme than their baseline value and the total number of subjects in the subject sample with a post baseline measurement of the specified parameter.

In addition, all vital signs data will be presented as follows:

VSL001 A listing of PCS values together with standard demographic data will be presented by-subject and within-subject by PCS vital signs test criterion by visit.

VSL002 Vital signs data will be presented by-subject and within-subject by vital signs test and visit.

Study Specific Presentations

VST003 For each variable with a PCS criterion (as presented in Table 5), the incidence of PCS values will be presented by visit. For a specific visit, the percentage per parameter is defined as the ratio of the number of subjects with at least one PCS value occurring at a specific post-baseline visit that is more extreme than their baseline value and the total number of subjects in the subject sample with a post baseline measurement of the specified parameter for the visit.

9.11.4 Electrocardiogram (ECG) Evaluations

Subject Samples:	Tables	Not applicable
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		Not applicable
Abbreviation:		EG

Standard Presentations

Standard ECG parameters and any abnormal findings, if applicable, will be presented in subject data listings as follows:

EGL001 ECG data will be presented by-subject and within-subject by visit and parameter and/or findings.

EGL002 ECG data will be presented by-subject and within-subject by parameter. PCS values will be identified and only subjects with one or more PCS values for the parameter will be presented.

9.11.5 Other Safety Analyses

Other safety analyses will include device complications, PEG and J tube replacements and average duration, the sleep attack questions, Minnesota Impulsive Disorder Interview (MIDI), Columbia Suicide Severity Rating Scale (C-SSRS), melanoma check and neurological examination. Device complications will be reported on a per-subject basis. This implies that even if a subject reported the same complication repeatedly (complications that map to the same PT or that result in the same action taken), the complication will be counted only once.

Subject Samples:	Tables	Safety sample and US subset of safety sample
	Listings	All subjects consented
	Figures	Not applicable
Subgroups:		Not applicable
Abbreviation:		DC, DI, PE, QS

Study Specific Presentations

DCT001 The incidence of device complications overall and by complication type will be presented, for all centers/countries combined, using default summary statistics. A table will be produced for all device complications as well as for the subset of device complications that resulted in an AE.

DCT002 The incidence of device complications overall and for each MedDRA PT will be presented, for all centers/countries combined, using default summary statistics. A table will be produced for all device complications as well as for the subset of device complications that resulted in an AE.

DCT003	The incidence of device complications overall and for each MedDRA PT will be summarized within each 3005 Treatment Year (as defined in Section 6.4.9), for all centers/countries combined, using default summary statistics. A table will be produced for all device complications as well as for the subset of device complications that resulted in an AE.
DCT004	The incidence of device complications overall and for each action taken will be presented, for all centers/countries combined, using default summary statistics. A table will be produced for all device complications as well as for the subset of device complications that resulted in an AE.
DCT005	Overview of Device Complications including the number of subjects with: ● At least one device complication ● At least one device complication with action taken of tube replacement (either with or without surgery) ● At least one device complication with an associated adverse event ● At least one device complication with an associated adverse event and action taken of tube replacement (either with or without surgery).
DCT006	Overview of Device Complications (same categories as DCT005) for each 3005 Treatment Year (as defined in Section 6.4.9).
DIT001	A summary of PEG tube replacements will be presented, for all centers/countries combined, using default summary statistics. A similar summary will be presented for J tube replacements.
DIT002	A summary of PEG tube and J tube replacements will be presented for each 3005 Treatment Year (as defined in Section 6.4.9).
DIT003	The average PEG tube and J tube duration in Study 3005 will be summarized with default summary statistics and with the number and percentage of subjects with average durations in 3 month time intervals (≤ 91 days, 92 – 182 days, 183 to 273 days, 274 to 365 days, or > 365 days).
QST001	A summary of sleep attacks will be presented, for all centers/countries combined, using default summary statistics.

QST002	A summary of the development of intense impulsive behavior as assessed by the Minnesota Impulsive Disorders Interview (MIDI) will be presented, for all centers/countries combined, using default summary statistics.
QST003	A summary of suicidal ideation and behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) will be presented, for all centers/countries combined, using default summary statistics.

In addition, the other safety analysis data will be presented as follows:

DCL001	A listing of device complications with the standard demographic data will be presented by-subject.
DIL001	A listing of device information with the standard demographic data will be presented by-subject.
PEL001	A listing of results of melanoma checks with the standard demographic data will be presented by-subject and within-subject by visit.
QSL008	A listing of sleep attack responses with the standard demographic data will be presented by-subject and within-subject by visit.
QSL009	A listing of MIDI responses and positive/negative assessment for impulsive behavior with the standard demographic data will be presented by-subject and within-subject by visit.
QSL010	A listing of C-SSRS responses with the standard demographic data will be presented by-subject and within-subject by visit.

10.0 Changes to Planned Analyses

10.1 Changes to the Analysis as Laid Down in the Protocol and Amendments

The protocol statistical methods (Section 6.2 and Section 13.3) stated that for the analysis of change from baseline in efficacy measures, each subject's baseline will be their baseline measure in the first LCIG study in which they participated (e.g., Studies S187.3.001, S187.3.002 or S187.3.004). To focus the analysis on the maintenance of efficacy during participation in Study 3005, each subject's baseline value for the analysis of change from

baseline in efficacy measures will be the final value in the preceding open-label study. To provide context, the change in each efficacy measure from initial LCIG infusion to 3005 endpoint will also be determined and summarized.

Protocol Section 12.1.4 identifies the following as adverse events of special interest:

- Risks of PEG-J insertion
- Long-term complications of PEG-J
- Device-associated gastrointestinal disorders during long-term therapy

For consistency with current practice throughout the LCIG development program, these 3 categories have been combined into a single category of procedure and device associated events (Duodopa product specific CMQ).

11.0 References

1. SAS® Institute Inc., Cary, North Carolina, United States of America.
2. International Federation of Pharmaceutical Manufacturers Associations (IFPMA). MedDRA – Medical Dictionary for Regulated Activities. Reston, VA.
3. WHO-DD. World Health Organization Collaborating Center for International Drug Monitoring, P.O. Box 26, S-751 03 Uppsala, Sweden.
4. Hauser RA, Freidlander J, Zesiewicz TA, et al. A home diary to assess functional status in patients with Parkinson disease with motor fluctuations and dyskinesia. Clin Neuropharmacol. 2000;23(2):75-81.
5. Columbia-Suicide Severity Rating Scale (C-SSRS) [homepage on the internet]. Columbia University Medical Center. Available from: http//www.cssrs.columbia.edu/.

12.0 Appendices

12.1 Schedules of Assessments

12.1.1 Schedule of Assessments – Amendment 1

Visit	Baseline	Six Monthly Visit	Termination	Follow-up*
Day	Termination Visit of Previous Study (003/004)	+/- 14 Days	----------	Termination Visit + 7 Days
Informed consent	X			
Inclusion/ exclusion	X			
Physical exam	X[A]	X	X	
Weight	X[A]	X	X	
Vital signs	X[A]	X	X	X
12-lead ECG[B]	X[A]	X[B]	X	
Clinical labs[B]	X[A]	X[B]	X	
β-HCG [C]	X[A]	X	X	
Adverse events	X[A]	X	X	X
Concomitant medication	X[A]	X	X	
Sleep attacks	X[A]	X	X	
Melanoma check	X[A]	X[D]	X	
Determination of continued benefit**	X	X		
MIDI	X[A]	X	X	
Complications with infusion device	X[A]	X	X	
Inspection of stoma	X[A]	X	X	X
Assessment of the need to replace PEG-J***	X	X[D]		
Dispensing of study drug	X	Every 6 weeks [E]		

[A] Termination visit assessment from the previous trial will serve as the Baseline Assessment for this item.
[B] Will be done as clinically indicated
[C] For women of childbearing potential
[D] Assessment performed once yearly
[E] Clinical supply visits should take place every 6 weeks ± 1 week.
These visits will take at the hospital pharmacy and are for the sole purpose of dispensing clinical study drug and ancillary supplies.
* This visit needs to be performed only if PEG-J is removed, or if the subject does not continue to receive drug after termination.
**The decision to continue subjects on LCIG treatment will be dependent upon Principle Investigator's clinical judgment.
***On a yearly basis the LCIG system check needs to be evaluated by the study gastroenterologist; frequency of replacement should be in accordance with local practice.

12.1.2 Schedule of Assessments – Amendment 2

Visit	Baseline	6 Monthly Visit	Termination	Follow-up*
Day	Final Assessment in Previous Study	+/– 14 Days	--	Termination Visit + 7 Days
Informed consent	X			
Inclusion/exclusion	X			
Physical exam	X[a]	X	X	
Neurological Exam	X[a]	X	X	
Weight	X[a]	X	X	
Vital signs	X[a]	X	X	X
12-lead ECG	X[a]	X[b]	X	
Clinical labs	X[a]	X[b]	X	
Folic Acid, Vitamins B6, B12, Methylmalonic Acid (MMA), and Homocysteine Levels	X[a]	X	X	
β-HCG[c]	X[a]	X	X	
Adverse events	X[a]	X	X	X
Concomitant medication	X[a]	X	X	X
Sleep attacks	X[a]	X	X	
Melanoma check	X[a]	X[d]	X	
Determination of continued benefit**	X	X		
MIDI	X[a]	X	X	
Complications with infusion device	X[a]	X	X	
Inspection of stoma	X[a]	X	X	X
Assessment of the need to replace PEG-J***	X	X[d]		
Dispensing of study drug	X	Every 6 weeks[e]		
Removal of PEG****			X	

* This visit needs to be performed only if PEG-J is removed, or if the subject does not continue to receive drug after termination.

** The decision to continue subjects on LCIG treatment will be dependent upon Principal Investigator's clinical judgment.

*** On a yearly basis, the LCIG system check needs to be evaluated by the study gastroenterologist; frequency of replacement should be in accordance with local practice.

****For subjects deemed inappropriate for continued treatment by the Investigator, or for subjects who elect not to continue LCIG treatment, the PEG-J will be removed, and a follow-up clinic visit will occur 1 week later.

a. The final assessment in the previous open-label LCIG study will serve as the baseline assessment for this item.

b. Will be done as clinically indicated.

c. For women of childbearing potential.

d. Assessment performed once yearly.

e. Clinical supply visits should take place every 6 weeks ± 7 days. These visits will take place at the hospital pharmacy and are for the sole purpose of dispensing clinical study drug and ancillary supplies.

12.1.3 Schedule of Assessments – Amendment 3

Visit	Baseline	6 Monthly Visit	Termination	Follow-Up*
Day	**Final Assessment in Previous Study**	**+/– 14 Days**	**--**	**Termination Visit + 7 Days**
Informed consent	X			
Inclusion/exclusion	X			
Physical exam	X[a]	X	X	
Neurological Exam	X[a]	X	X	
Weight	X[a]	X	X	
Vital signs	X[a]	X	X	X
12-lead ECG	X[a]	X[b]	X	
Clinical labs	X[a]	X[b]	X	
Folic Acid, Vitamins B_6, B_{12}, Methylmalonic Acid (MMA), and Homocysteine Levels	X[a]	X	X	
β-HCG[c]	X[a]	X	X	
Adverse events	X[a]	X	X	X
Concomitant medication	X[a]	X	X	X
Sleep attacks	X[a]	X	X	
Melanoma check	X[a]	X[d]	X	
Determination of continued benefit**	X	X		
MIDI	X[a]	X	X	
C-SSRS[f]	X[a]	X	X	X
Complications with infusion device	X[a]	X	X	
Inspection of stoma	X[a]	X	X	X
Assessment of the need to replace PEG-J***	X	X[d]		
Dispensing of study drug	X	Every 6 weeks[e]		
Removal of PEG****			X	

* This visit needs to be performed only if PEG-J is removed, or if the subject does not continue to receive drug after termination.

** The decision to continue subjects on LCIG treatment will be dependent upon Principal Investigator's clinical judgment.

*** On a yearly basis, the LCIG system check needs to be evaluated by the study gastroenterologist; frequency of replacement should be in accordance with local practice.

****For subjects deemed inappropriate for continued treatment by the Investigator, or for subjects who elect not to continue LCIG treatment, the PEG-J will be removed, and a follow-up clinic visit will occur 1 week later.

a. The final assessment in the previous open-label LCIG study will serve as the baseline assessment for this item.

b. Will be done as clinically indicated.

c. For women of childbearing potential.

d. Assessment performed once yearly.

e. Clinical supply visits should take place every 6 weeks ± 7 days. These visits will take place at the hospital pharmacy and are for the sole purpose of dispensing clinical study drug and ancillary supplies. When scheduling the 6 weekly drug dispensing visits, the site should always refer back to the baseline visit. Every attempt should be made to bring the subject back on the original targeted dates (± 7 days).

f. The "Already Enrolled Subjects" C-SSRS is to be the first assessment scale administered to the subject. At each subsequent assessment, the "Since Last Visit" C-SSRS scale should be administered. If the subject has previously completed the "Already Enrolled Subjects" scale in Study S187.3.003, the subject should complete the "Since Last Visit" scale at all scheduled time points outlined in Table 2 in this study. For subjects with a C-SSRS completed at their Study S187.3.003 final visit, that Study S187.3.003 final visit C-SSRS assessment will be considered baseline for Study S187.3.005. For all other subjects, the first C-SSRS assessment completed in this study will serve as baseline.

12.1.4 Schedule of Assessments – Amendment 4

Visit	Baseline	6 Monthly Visit	Termination/ Transfer to Commercial	Follow-Up*
Day	**Final Assessment in Previous Study**	**+/– 14 Days**	**--**	**Termination Visit + 7 Days**
Informed consent	X			
Inclusion/exclusion	X			
Physical exam	X[a]	X	X	
Neurological Exam	X[a]	X	X	
Weight	X[a]	X	X	
Vital signs	X[a]	X	X	X
12-lead ECG	X[a]	X[b]	X	
Clinical labs	X[a]	X[b]	X	
Folic Acid, Vitamins B_6, B_{12}, Methylmalonic Acid (MMA), and Homocysteine Levels	X[a]	X	X	
β-HCG[c]	X[a]	X	X	
Adverse events**	X[a]----------X			
Concomitant medication	X[a]	X	X	X
Sleep attacks	X[a]	X	X	
Melanoma check	X[a]	X[d]	X	
Determination of continued benefit***	X	X		
MIDI	X[a]	X	X	
C-SSRS[f]	X[a]	X	X	X
Complications with infusion device	X[a]	X	X	
Inspection of stoma	X[a]	X	X	X
Assessment of the need to replace PEG-J****	X	X[d]		
Dispensing of study drug	X-----Every 6 weeks[e]-----			
Daily Dosing Diary[g]		X	X	
Parkinson's Disease Diary[g]		X	X	
UPDRS[h]		X	X	
PDQ-39[h]		X	X	
Removal of PEG*****			X	

* This visit needs to be performed only if PEG-J is removed, or if the subject does not continue to receive drug after termination.

** Collection of adverse events is an ongoing and continuous process, not only occurring during site visits.

*** The decision to continue subjects on LCIG treatment will be dependent upon Principal Investigator's clinical judgment.

**** On a yearly basis, the LCIG system check needs to be evaluated by the study gastroenterologist; frequency of replacement should be in accordance with local practice.

*****For subjects deemed inappropriate for continued treatment by the Investigator, or for subjects who elect not to continue LCIG treatment, the PEG-J will be removed, and a follow-up clinic visit will occur 1 week later.

a. The final assessment in the previous open-label LCIG study will serve as the baseline assessment for this item.

b. Will be done as clinically indicated.

c. For women of childbearing potential.

d. Assessment performed once yearly.

e. Clinical supply visits should take place every 6 weeks ± 7 days. These visits may take place at the hospital pharmacy and are for the purpose of dispensing clinical study drug and ancillary supplies. Other assessments may be completed during these visits if required. When scheduling the 6 weekly drug dispensing visits, the site should always refer back to the baseline visit. Every attempt should be made to pick up drug on the original targeted dates (± 7 days).

f. The "Already Enrolled Subjects" C-SSRS is to be the first assessment scale administered to the subject. At each subsequent assessment, the "Since Last Visit" C-SSRS scale should be administered. If the subject has previously completed the "Already Enrolled Subjects" scale in Study S187.3.003, the subject should complete the "Since Last Visit" scale at all scheduled time points in this study. For subjects with a C-SSRS completed at their Study S187.3.003 final visit, that Study S187.3.003 final visit C-SSRS assessment will be considered baseline for the Study S187.3.005. For all other subjects, the first C-SSRS assessment completed in this study will serve as baseline.

g. The Daily Dosing Diary and the Parkinson's Disease Diary will be completed by subjects or their caregivers for the 3 consecutive days prior to each clinic visit at US sites only.

h. The UPDRS and the PDQ-39 will be completed at US sites only.

12.2 List of Tables

SAP Table Code	Table Number	Table Title
DST001	14.1__1.1.1.1	Subject Disposition ALL SUBJECTS CONSENTED
DST003	14.1__1.1.1.2	Number and Percent of Premature Discontinuations by 3005 Treatment Year SAFETY SAMPLE
DST002	14.1__1.1.2	Analysis Samples ALL SUBJECTS CONSENTED
DVT001	14.1__1.1.3	Major Protocol Deviations SAFETY SAMPLE
DMT001	14.1__1.2.1	Demographics SAFETY SAMPLE
SCT001	14.1__1.2.2	Baseline Subject Characteristics SAFETY SAMPLE
SCT002	14.1__1.2.3	Study Specific Subject Characteristics SAFETY SAMPLE
MHT001	14.1__1.3	Medical History SAFETY SAMPLE
CMT002	14.1__1.4.1	Continuing Anti-Parkinsonian Medication Use on the First Day of 3005 SAFETY SAMPLE
CMT002	14.1__1.4.2	Concomitant Anti-Parkinsonian Medication Use by 3005 Treatment Year SAFETY SAMPLE
CMT001	14.1__1.4.3	Concomitant Medications SAFETY SAMPLE
CML001	14.1__1.4.4	Listing of Concomitant Medication: General Findings SAFETY SAMPLE – NARROW POLYNEUROPATHY SUBSET
DST001	14.1__2.1	Subject Disposition EFFICACY SAMPLE – US SUBSET
DMT001	14.1__2.2.1	Demographics EFFICACY SAMPLE – US SUBSET
SCT001	14.1__2.2.2	Baseline Subject Characteristics EFFICACY SAMPLE – US SUBSET
SCT002	14.1__2.2.3	Study Specific Subject Characteristics EFFICACY SAMPLE – US SUBSET
CMT002	14.1__2.3.1	Continuing Anti-Parkinsonian Medication Use on the First Day of 3005 EFFICACY SAMPLE – US SUBSET
CMT002	14.1__2.3.2	Concomitant Anti-Parkinsonian Medication Use by 3005 Treatment Year EFFICACY SAMPLE – US SUBSET
QST001	14.2__1.1.1	Change in Average Daily "Off" Time Based on the Parkinson's Disease Symptom Diary EFFICACY SAMPLE
QST001	14.2__1.1.2	Change in Average Daily "On" Time Without Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary EFFICACY SAMPLE
QST001	14.2__1.1.3	Change in Average Daily "On" Time With Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary EFFICACY SAMPLE

SAP Table Code	Table Number	Table Title
QST001	14.2__1.1.4	Change in Average Daily "On" Time With Non Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary EFFICACY SAMPLE
QST001	14.2__1.1.5	Change in Average Daily "On" Time Without Dyskinesia Based on the Parkinson's Disease Symptom Diary EFFICACY SAMPLE
QST003	14.2__1.2	Clinical Global Impression – Improvement (CGI-I) at Endpoint EFFICACY SAMPLE
QST001	14.2__1.3.1	Change in Parkinson's Disease Questionnaire (PDQ-39) Summary Index EFFICACY SAMPLE
QST001	14.2__1.3.2	Change in Parkinson's Disease Questionnaire (PDQ-39) Mobility Domain Score EFFICACY SAMPLE
QST001	14.2__1.3.3	Change in Parkinson's Disease Questionnaire (PDQ-39) Activities of Daily Living Domain Score EFFICACY SAMPLE
QST001	14.2__1.3.4	Change in Parkinson's Disease Questionnaire (PDQ-39) Emotional Well-Being Domain Score EFFICACY SAMPLE
QST001	14.2__1.3.5	Change in Parkinson's Disease Questionnaire (PDQ-39) Stigma Domain Score EFFICACY SAMPLE
QST001	14.2__1.3.6	Change in Parkinson's Disease Questionnaire (PDQ-39) Social Support Domain Score EFFICACY SAMPLE
QST001	14.2__1.3.7	Change in Parkinson's Disease Questionnaire (PDQ-39) Cognition Domain Score EFFICACY SAMPLE
QST001	14.2__1.3.8	Change in Parkinson's Disease Questionnaire (PDQ-39) Communication Domain Score EFFICACY SAMPLE
QST001	14.2__1.3.9	Change in Parkinson's Disease Questionnaire (PDQ-39) Bodily Discomfort Domain Score EFFICACY SAMPLE
QST001	14.2__2.1.1	Change in Average Daily "Off" Time Based on the Parkinson's Disease Symptom Diary EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.1.2	Change in Average Daily "On" Time Without Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.1.3	Change in Average Daily "On" Time With Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.1.4	Change in Average Daily "On" Time With Non Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary EFFICACY SAMPLE – US SUBSET

SAP Table Code	Table Number	Table Title
QST001	14.2__2.1.5	Change in Average Daily "On" Time Without Dyskinesia Based on the Parkinson's Disease Symptom Diary EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.2.1	Change in Unified Parkinson's Disease rating Scale (UPDRS) Total Score EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.2.2	Change in Unified Parkinson's Disease rating Scale (UPDRS) Part I Score EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.2.3	Change in Unified Parkinson's Disease rating Scale (UPDRS) Part II Score EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.2.4	Change in Unified Parkinson's Disease rating Scale (UPDRS) Part III Score EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.2.5	Change in Unified Parkinson's Disease rating Scale (UPDRS) Part IV Score EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.2.6	Change in Unified Parkinson's Disease rating Scale (UPDRS) Part IV Questions 32, 33 and 34 EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.3.1	Change in Parkinson's Disease Questionnaire (PDQ-39) Summary Index EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.3.2	Change in Parkinson's Disease Questionnaire (PDQ-39) Mobility Domain Score EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.3.3	Change in Parkinson's Disease Questionnaire (PDQ-39) Activities of Daily Living Domain Score EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.3.4	Change in Parkinson's Disease Questionnaire (PDQ-39) Emotional Well-Being Domain Score EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.3.5	Change in Parkinson's Disease Questionnaire (PDQ-39) Stigma Domain Score EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.3.6	Change in Parkinson's Disease Questionnaire (PDQ-39) Social Support Domain Score EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.3.7	Change in Parkinson's Disease Questionnaire (PDQ-39) Cognition Domain Score EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.3.8	Change in Parkinson's Disease Questionnaire (PDQ-39) Communication Domain Score EFFICACY SAMPLE – US SUBSET
QST001	14.2__2.3.9	Change in Parkinson's Disease Questionnaire (PDQ-39) Bodily Discomfort Domain Score EFFICACY SAMPLE – US SUBSET

SAP Table Code	Table Number	Table Title
QST002	14.2__2.4.1	Change in Average Daily "Off" Time Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by the Study of First LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.4.2	Change in Average Daily "On" Time Without Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by the Study of First LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.4.3	Change in Average Daily "On" Time With Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by the Study of First LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.4.4	Change in Average Daily "On" Time With Non Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by the Study of First LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.4.5	Change in Average Daily "On" Time Without Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by the Study of First LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.5.1	Change in Average Daily "Off" Time Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Troublesome Dyskinesia at Initial LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.5.2	Change in Average Daily "On" Time Without Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Troublesome Dyskinesia at Initial LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.5.3	Change in Average Daily "On" Time With Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Troublesome Dyskinesia at Initial LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.5.4	Change in Average Daily "On" Time With Non Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Troublesome Dyskinesia at Initial LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.5.5	Change in Average Daily "On" Time Without Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Troublesome Dyskinesia at Initial LCIG Infusion EFFICACY SAMPLE – US SUBSET

SAP Table Code	Table Number	Table Title
QST002	14.2__2.6.1	Change in Average Daily "Off" Time Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Levodopa Monotherapy in Study S187.3.005 EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.6.2	Change in Average Daily "On" Time Without Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Levodopa Monotherapy in Study S187.3.005 EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.6.3	Change in Average Daily "On" Time With Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Levodopa Monotherapy in Study S187.3.005 EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.6.4	Change in Average Daily "On" Time With Non Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Levodopa Monotherapy in Study S187.3.005 EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.6.5	Change in Average Daily "On" Time Without Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Levodopa Monotherapy in Study S187.3.005 EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.7.1	Change in Average Daily "Off" Time Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Levodopa Dose at Initial LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.7.2	Change in Average Daily "On" Time Without Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Levodopa Dose at Initial LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.7.3	Change in Average Daily "On" Time With Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Levodopa Dose at Initial LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.7.4	Change in Average Daily "On" Time With Non Troublesome Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Levodopa Dose at Initial LCIG Infusion EFFICACY SAMPLE – US SUBSET
QST002	14.2__2.7.5	Change in Average Daily "On" Time Without Dyskinesia Based on the Parkinson's Disease Symptom Diary in Subgroups Determined by Levodopa Dose at Initial LCIG Infusion EFFICACY SAMPLE – US SUBSET

SAP Table Code	Table Number	Table Title
EXT001	14.3__1.1.1.1	Duration of 3005 Levodopa-Carbidopa Intestinal Gel (LCIG) Exposure SAFETY SAMPLE
EXT001	14.3__1.1.1.2	Duration of 3005 PEG-J Exposure SAFETY SAMPLE
EXT001	14.3__1.1.2.1	Overall Duration of Levodopa-Carbidopa Intestinal Gel (LCIG) Exposure SAFETY SAMPLE
EXT001	14.3__1.1.2.2	Overall Duration of PEG-J Exposure SAFETY SAMPLE
EXT001	14.3__1.1.3.1	Duration of 3005 Levodopa-Carbidopa Intestinal Gel (LCIG) Exposure SAFETY SAMPLE – US SUBSET
EXT001	14.3__1.1.3.2	Duration of 3005 PEG-J Exposure SAFETY SAMPLE – US SUBSET
EXT001	14.3__1.1.4.1	Overall Duration of Levodopa-Carbidopa Intestinal Gel (LCIG) Exposure SAFETY SAMPLE – US SUBSET
EXT001	14.3__1.1.4.2	Overall Duration of PEG-J Exposure SAFETY SAMPLE – US SUBSET
EXT002	14.3__1.1.5	Prescribed Dosing Level at the Conclusion of the Previous S187.3.004 Study SAFETY SAMPLE
EXT003	14.3__1.1.6	Dose of Levodopa-Carbidopa Intestinal Gel Administered SAFETY SAMPLE – US SUBSET
EXT004	14.3__1.1.7	Dose of Levodopa-Carbidopa Intestinal Gel Administered in Subgroups Determined by the Study of First LCIG Infusion SAFETY SAMPLE – US SUBSET
AET001	14.3__1.2.1.1	Summary of Adverse Events SAFETY SAMPLE
AET002	14.3__1.2.1.2	Number and Percent of Subjects with Treatment-Emergent Adverse Events SAFETY SAMPLE
AET003	14.3__1.2.1.3	Number and Percent of Subjects with Treatment-Emergent Adverse Events by Descending Frequency SAFETY SAMPLE
AET011	14.3__1.2.1.4	Number and Percent of Subjects with Treatment-Emergent Adverse Events by 3005 Treatment Year SAFETY SAMPLE
AET007	14.3__1.2.1.5	Number and Percent of Subjects with Treatment-Emergent Adverse Events by Strongest Relationship SAFETY SAMPLE
AET008	14.3__1.2.1.6	Number and Percent of Subjects with Treatment-Emergent Adverse Events that are at Least Possibly Related to Treatment SAFETY SAMPLE
AET010	14.3__1.2.1.7	Number and Percent of Subjects with Treatment-Emergent Adverse Events Linked to Device Complications by the Device Complications CRF SAFETY SAMPLE

SAP Table Code	Table Number	Table Title
AET009	14.3__1.2.1.8	Number and Percent of Subjects with Treatment-Emergent Adverse Events by Maximum Severity (Investigator's Judgment) SAFETY SAMPLE
AET014	14.3__1.2.1.9	Prevalence of Treatment-Emergent Adverse Events by 3005 Treatment Year SAFETY SAMPLE
AET013	14.3__1.2.2.1	Number and Percent of Subjects with Treatment-Emergent Adverse Events with Fatal Outcome SAFETY SAMPLE
AET004	14.3__1.2.2.2	Number and Percent of Subjects with Treatment-Emergent Serious Adverse Events SAFETY SAMPLE
AET005	14.3__1.2.2.3	Number and Percent of Subjects with Treatment-Emergent Adverse Events Leading to Study Termination SAFETY SAMPLE
AET006	14.3__1.2.2.4	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Procedure and Device SAFETY SAMPLE
AET011	14.3__1.2.2.5	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Procedure and Device by 3005 Treatment Year SAFETY SAMPLE
AET014	14.3__1.2.2.6	Prevalence of Treatment-Emergent Adverse Events of Special Interest Related to Procedure and Device by 3005 Treatment Year SAFETY SAMPLE
AET006	14.3__1.2.2.7	Number and Percent of Subjects with Treatment-Emergent Serious Adverse Events of Special Interest Related to Procedure and Device SAFETY SAMPLE
AET006	14.3__1.2.2.8	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Procedure and Device Leading to Study Termination SAFETY SAMPLE
AET006	14.3__1.2.2.9	Number and Percent of Subjects with Treatment-Emergent Adverse Events Not Related to Procedure and Device SAFETY SAMPLE
AET011	14.3__1.2.2.10	Number and Percent of Subjects with Treatment-Emergent Adverse Events Not Related to Procedure and Device by 3005 Treatment Year SAFETY SAMPLE
AET014	14.3__1.2.2.11	Prevalence of Treatment-Emergent Adverse Events Not Related to Procedure and Device by 3005 Treatment Year SAFETY SAMPLE
AET006	14.3__1.2.2.12	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Polyneuropathy and Associated Signs and Symptoms (Broad Search) SAFETY SAMPLE

SAP Table Code	Table Number	Table Title
AET006	14.3__1.2.2.13	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Polyneuropathy and Associated Signs and Symptoms (Narrow Search) SAFETY SAMPLE
AET006	14.3__1.2.2.14	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Weight Loss SAFETY SAMPLE
AET006	14.3__1.2.2.15	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Cardiovascular Fatalities SAFETY SAMPLE
AET006	14.3__1.2.2.16	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Aspiration SAFETY SAMPLE
AET012	14.3__1.2.3.1	Number and Percent of Subjects with Treatment-Emergent Adverse Events Subgroup: Gender SAFETY SAMPLE
AET012	14.3__1.2.3.2	Number and Percent of Subjects with Treatment-Emergent Adverse Events Subgroup: Age Category SAFETY SAMPLE
AET012	14.3__1.2.3.3	Number and Percent of Subjects with Treatment-Emergent Adverse Events Subgroup: Duration of Parkinson's Disease SAFETY SAMPLE
AET012	14.3__1.2.3.4	Number and Percent of Subjects with Treatment-Emergent Adverse Events Subgroup: Country SAFETY SAMPLE
AET001	14.3__1.2.4.1	Summary of Adverse Events SAFETY SAMPLE – US SUBSET
AET002	14.3__1.2.4.2	Number and Percent of Subjects with Treatment-Emergent Adverse Events SAFETY SAMPLE – US SUBSET
AET013	14.3__1.2.4.3	Number and Percent of Subjects with Treatment-Emergent Adverse Events with Fatal Outcome SAFETY SAMPLE – US SUBSET
AET004	14.3__1.2.4.4	Number and Percent of Subjects with Treatment-Emergent Serious Adverse Events SAFETY SAMPLE – US SUBSET
AET005	14.3__1.2.4.5	Number and Percent of Subjects with Treatment-Emergent Adverse Events Leading to Study Termination SAFETY SAMPLE – US SUBSET
AET006	14.3__1.2.4.6	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Procedure and Device SAFETY SAMPLE – US SUBSET
AET006	14.3__1.2.4.7	Number and Percent of Subjects with Treatment-Emergent Adverse Events Not Related to Procedure and Device SAFETY SAMPLE – US SUBSET

SAP Table Code	Table Number	Table Title
AET006	14.3__1.2.4.8	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Polyneuropathy and Associated Signs and Symptoms SAFETY SAMPLE – US SUBSET
AET006	14.3__1.2.4.9	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Weight Loss SAFETY SAMPLE – US SUBSET
AET006	14.3__1.2.4.10	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Cardiovascular Fatalities SAFETY SAMPLE – US SUBSET
AET006	14.3__1.2.4.11	Number and Percent of Subjects with Treatment-Emergent Adverse Events of Special Interest Related to Aspiration SAFETY SAMPLE – US SUBSET
AEL003	14.3__2.1	Listing of Subject Deaths SAFETY SAMPLE
AEL004	14.3__2.2	Listing of Serious Adverse Events SAFETY SAMPLE
AEL005	14.3__2.3	Listing of Adverse Events Leading to Study Termination SAFETY SAMPLE
AEL006	14.3__2.4	Listing of Adverse Events of Special Interest Related to Procedure and Device SAFETY SAMPLE
AEL006	14.3__2.5	Listing of Adverse Events of Special Interest Related to Polyneuropathy SAFETY SAMPLE
AEL006	14.3__2.6	Listing of Adverse Events of Special Interest Related to Weight Loss SAFETY SAMPLE
AEL006	14.3__2.7	Listing of Adverse Events of Special Interest Related to Cardiovascular Fatalities SAFETY SAMPLE
AEL006	14.3__2.8	Listing of Adverse Events of Special Interest Related to Aspiration SAFETY SAMPLE
LBT001	14.3__4.1.1	Number and Percentage of Subjects with Potentially Clinically Significant Hematology Laboratory Parameters SAFETY SAMPLE
LBL002	14.3__4.1.2	Listing of Potentially Clinically Significant Hematology Laboratory Parameters SAFETY SAMPLE
LBT001	14.3__4.2.1	Number and Percentage of Subjects with Potentially Clinically Significant Chemistry Laboratory Parameters SAFETY SAMPLE
LBL002	14.3__4.2.2	Listing of Potentially Clinically Significant Chemistry Laboratory Parameters SAFETY SAMPLE
LBT002	14.3__4.3.1	Summary of Quantitative Special Laboratory Parameters for Determination of Vitamin Deficiency SAFETY SAMPLE

SAP Table Code	Table Number	Table Title
LBT003	14.3__4.3.2	Number and Percent of Subjects with Quantitative Special Laboratory Parameters for Determination of Vitamin Deficiency Outside of the Reference Range SAFETY SAMPLE
LBT002	14.3__4.4.1	Summary of Quantitative Special Laboratory Parameters for Determination of Vitamin Deficiency SAFETY SAMPLE – NARROW POLYNEUROPATHY SUBSET
LBT003	14.3__4.4.2	Number and Percent of Subjects with Quantitative Special Laboratory Parameters for Determination of Vitamin Deficiency Outside of the Reference Range SAFETY SAMPLE – NARROW POLYNEUROPATHY SUBSET
LBL002	14.3__4.4.3	Listing of Chemistry Determinations SAFETY SAMPLE – NARROW POLYNEUROPATHY SUBSET
VST001	14.3__5.1.1	Summary of Supine Systolic Blood Pressure (mmHg) SAFETY SAMPLE
VST001	14.3__5.1.2	Summary of Standing Systolic Blood Pressure (mmHg) SAFETY SAMPLE
VST001	14.3__5.1.3	Summary of Orthostatic Systolic Blood Pressure (mmHg) SAFETY SAMPLE
VST001	14.3__5.1.4	Summary of Supine Diastolic Blood Pressure (mmHg) SAFETY SAMPLE
VST001	14.3__5.1.5	Summary of Standing Diastolic Blood Pressure (mmHg) SAFETY SAMPLE
VST001	14.3__5.1.6	Summary of Orthostatic Diastolic Blood Pressure (mmHg) SAFETY SAMPLE
VST001	14.3__5.1.7	Summary of Supine Pulse (bpm) SAFETY SAMPLE
VST001	14.3__5.1.8	Summary of Standing Pulse (bpm) SAFETY SAMPLE
VST001	14.3__5.1.9	Summary of Orthostatic Pulse (bpm) SAFETY SAMPLE
VST001	14.3__5.1.10	Summary of Temperature (Celsius) SAFETY SAMPLE
VST001	14.3__5.1.11	Summary of Weight (kg) SAFETY SAMPLE
VST002	14.3__5.2.1	Number and Percent of Subjects with Potentially Clinically Significant Vital Sign Values SAFETY SAMPLE
VST003	14.3__5.2.2	Number and Percent of Subjects with Potentially Clinically Significant Vital Sign Values by Visit SAFETY SAMPLE
VSL001	14.3__5.2.3	Listing of Potentially Clinically Significant Vital Sign Parameters SAFETY SAMPLE
DCT005	14.3__6.1.1	Overview of Device Complications SAFETY SAMPLE
DCT006	14.3__6.1.2	Overview of Device Complications by 3005 Treatment Year SAFETY SAMPLE

SAP Table Code	Table Number	Table Title
DCT001	14.3__6.1.3	Number and Percent of Subjects with Device Complications by Type SAFETY SAMPLE
DCT002	14.3__6.1.4	Number and Percent of Subjects with Device Complications by MedDRA Preferred Term SAFETY SAMPLE
DCT003	14.3__6.1.5	Number and Percent of Subjects with Device Complications by MedDRA Preferred Term and 3005 Treatment Year SAFETY SAMPLE
DCT004	14.3__6.1.6	Number and Percent of Subjects with Device Complications by Action Taken SAFETY SAMPLE
DCT002	14.3__6.1.7	Number and Percent of Subjects with Device Complications with Action Taken of Tube Replacement by MedDRA Preferred Term SAFETY SAMPLE
DCT001	14.3__6.2.1	Number and Percent of Subjects with Device Complication Related to Adverse Events by Type SAFETY SAMPLE
DCT002	14.3__6.2.2	Number and Percent of Subjects with Device Complication Related to Adverse Events by MedDRA Preferred Term SAFETY SAMPLE
DCT003	14.3__6.2.3	Number and Percent of Subjects with Device Complication Related to Adverse Events by MedDRA Preferred Term and 3005 Treatment Year SAFETY SAMPLE
DCT004	14.3__6.2.4	Number and Percent of Subjects with Device Complication Related to Adverse Events by Action Taken SAFETY SAMPLE
DCT002	14.3__6.3.1	Number and Percent of Subjects with Device Complication by MedDRA Preferred Term SAFETY SAMPLE – US SUBSET
DCT002	14.3__6.3.2	Number and Percent of Subjects with Device Complication Related to Adverse Events by MedDRA Preferred Term SAFETY SAMPLE – US SUBSET
DIT001	14.3__6.4.1.1	Number of PEG Tube Replacements SAFETY SAMPLE
DIT001	14.3__6.4.1.2	Number of J Tube Replacements SAFETY SAMPLE
DIT002	14.3__6.4.2	Number of PEG Tube and J Tube Replacements by 3005 Treatment Year SAFETY SAMPLE
DIT001	14.3__6.4.3.1	Number of PEG Tube Replacements before 3005 Study Start SAFETY SAMPLE
DIT001	14.3__6.4.3.2	Number of J Tube Replacements before 3005 Study Start SAFETY SAMPLE
DIT003	14.3__6.4.4.1	Average PEG Tube Duration in Study 3005 SAFETY SAMPLE
DIT003	14.3__6.4.4.2	Average J Tube Duration in Study 3005 SAFETY SAMPLE

SAP Table Code	Table Number	Table Title
QST001	14.3__7.1	Summary of Sleep Attacks SAFETY SAMPLE
QST002	14.3__7.2	Summary of Minnesota Impulsive Disorder Interview (MIDI) SAFETY SAMPLE
QST003	14.3__7.3	Summary of Columbia Suicide Severity Rating Scale (C-SSRS) SAFETY SAMPLE

12.3 List of Listings

SAP Listing Code	Listing Number	Listing Title
DSL001	16.2__1.1	Listing of Subjects Who Prematurely Terminated the Study Prior to Receiving 3005 LCIG Infusion ALL SUBJECTS CONSENTED
DSL002	16.2__1.2	Listing of Subjects Who Prematurely Terminated the Study After Receiving 3005 LCIG Infusion ALL SUBJECTS CONSENTED
DSL003	16.2__1.3	Listing of Subject Samples ALL SUBJECTS CONSENTED
DVL001	16.2__2.1	Listing of Subjects with Major Protocol Deviations ALL SUBJECTS CONSENTED
IEL001	16.2__3.1	Listing of Subjects with Deviations from Inclusion or Exclusion Criteria ALL SUBJECTS CONSENTED
DML001	16.2__4.1	Listing of Demographics ALL SUBJECTS CONSENTED
SCL001	16.2__4.2	Listing of Baseline Vital Signs ALL SUBJECTS CONSENTED
SCL002	16.2__4.3	Listing of Parkinson's Disease Duration and Diagnosis Data ALL SUBJECTS CONSENTED
MHL001	16.2__4.4	Listing of Medical History: General Findings ALL SUBJECTS CONSENTED
MHL002	16.2__4.5	Listing of Medical History: MedDRA Coding ALL SUBJECTS CONSENTED
SCL004	16.2__4.6	Listing of PD Medication Use Prior to Study Start: General Findings ALL SUBJECTS CONSENTED
SCL005	16.2__4.7	Listing of PD Medication Use Prior to Study Start: WHO-DD Coding ALL SUBJECTS CONSENTED
CML001	16.2__4.8	Listing of Concomitant Medication: General Findings ALL SUBJECTS CONSENTED
CML002	16.2__4.9	Listing of Concomitant Medication: WHO-DD Coding ALL SUBJECTS CONSENTED

SAP Listing Code	Listing Number	Listing Title
DAL001	16.2__5.1	Listing of Cassettes Dispensed, Used and Returned ALL SUBJECTS CONSENTED
EXL001	16.2__5.2	Listing of Study Drug Exposure and Treatment Duration ALL SUBJECTS CONSENTED
EXL002	16.2__5.3	Listing of LCIG Titration in Study 3005 ALL SUBJECTS CONSENTED
QSL001	16.2__6.1	Listing of Parkinson's Disease Symptom Diary ALL SUBJECTS CONSENTED
QSL002	16.2__6.2	Listing of Clinical Global Impression – Improvement (CGI-I) ALL SUBJECTS CONSENTED
QSL003	16.2__6.3	Listing of Parkinson's Disease Quality of Life Questionnaire ALL SUBJECTS CONSENTED
QSL004	16.2__6.4	Listing of Unified Parkinson's Disease Rating Scale (UPDRS) ALL SUBJECTS CONSENTED
AEL001	16.2__7.1	Listing of Adverse Events: General Findings ALL SUBJECTS CONSENTED
AEL002	16.2__7.2	Listing of Adverse Events: MedDRA Coding ALL SUBJECTS CONSENTED
LBL001	16.2__8.1.1	Listing of Hematology Determinations ALL SUBJECTS CONSENTED
LBL002	16.2__8.1.2	Listing of Chemistry Determinations ALL SUBJECTS CONSENTED
LBL003	16.2__8.1.3	Listing of Urinalysis Determinations ALL SUBJECTS CONSENTED
LBL004	16.2__8.1.4	Listing of Abnormal Laboratory Results ALL SUBJECTS CONSENTED
EGL001	16.2__8.2.1	Listing of ECG Assessments by Investigators ALL SUBJECTS CONSENTED
EGL002	16.2__8.2.2	Listing of ECG Assessments by ECG Central Reader ALL SUBJECTS CONSENTED
VSL002	16.2__8.3	Listing of Vital Signs ALL SUBJECTS CONSENTED
QSL008	16.2__8.4	Listing of Sleep Attack Data ALL SUBJECTS CONSENTED
QSL009	16.2__8.5	Listing of Minnesota Impulsive Disorders Interview ALL SUBJECTS CONSENTED
PEL001	16.2__8.6	Listing of Results of Melanoma Checks ALL SUBJECTS CONSENTED

SAP Listing Code	Listing Number	Listing Title
DCL001	16.2__8.7	Listing of Device Complications ALL SUBJECTS CONSENTED
DIL001	16.2__8.8	Listing of Pump and Tube Information ALL SUBJECTS CONSENTED
SCL001	16.2__8.9	Listing of LCIG System Checks ALL SUBJECTS CONSENTED
INL001	16.2__8.10	Listing of Stoma Site Inspections ALL SUBJECTS CONSENTED
IML001	16.2__8.11	Listing of Radiological Tube Placement Checks ALL SUBJECTS CONSENTED
HUL001	16.2__8.12	Listing of Hospitalizations ALL SUBJECTS CONSENTED
CBL001	16.2__8.13	Listing of Determination of Continued LCIG Benefit ALL SUBJECTS CONSENTED
NEL001	16.2__8.14	Listing of Neurological Examination Results ALL SUBJECTS CONSENTED
QSL010	16.2__8.15	Listing of Columbia Suicide Severity Rating Scale (C-SSRS) Responses ALL SUBJECTS CONSENTED

12.4 List of MedDRA Preferred Terms for Adverse Events of Special Interest

1. Procedure and device associated events (Duodopa Product Specific CMQ 80000111).

Code	Preferred Term
10000059	Abdominal discomfort
10060923	Abdominal hernia obstructive
10060924	Abdominal injury
10000081	Abdominal pain
10000084	Abdominal pain lower
10000087	Abdominal pain upper
10000099	Abdominal wall abscess
10066337	Abdominal wound dehiscence
10000647	Acute abdomen
10069773	Administration related reaction

Code	Preferred Term
10049555	Anal haemorrhage
10002243	Anastomotic ulcer
10002244	Anastomotic ulcer haemorrhage
10002248	Anastomotic ulcer perforation
10003445	Ascites
10004542	Bezoar
10067442	Bloody peritoneal effluent
10069801	Cardiac complication associated with device
10053183	Catheter site cellulitis
10068607	Catheter site erosion
10056520	Catheter site infection
10070776	Chemical burn of gastrointestinal tract
10050399	Chronic gastrointestinal bleeding
10009900	Colitis ulcerative
10052931	Colon fistula repair
10009995	Colonic fistula
10010000	Colonic obstruction
10057078	Colonic pseudo-obstruction
10010004	Colonic stenosis
10064538	Complication of device insertion
10010151	Complication of device removal
10057798	Computerised tomogram abdomen abnormal
10012575	Device breakage
10069872	Device chemical property issue
10069873	Device colour issue
10069869	Device component issue
10065066	Device connection issue
10069870	Device damage
10070691	Device deployment issue
10070692	Device deposit issue
10069845	Device-device incompatibility
10069853	Device difficult to use
10064684	Device dislocation

Code	Preferred Term
10012578	Device expulsion
10070614	Device extension damage
10012579	Device extrusion
10056871	Device failure
10059875	Device ineffective
10070617	Device infusion issue
10012586	Device interaction
10068444	Device intolerance
10070618	Device inversion
10069868	Device issue
10070305	Device kink
10012587	Device leakage
10063829	Device malfunction
10069871	Device material issue
10069879	Device material opacification
10067161	Device misuse
10064685	Device occlusion
10069880	Device physical property issue
10064687	Device related infection
10069802	Device related sepsis
10063371	Device therapy
10068139	Device toxicity
10013474	Distal ileal obstruction syndrome
10056361	Distal intestinal obstruction syndrome
10070470	Drug administered in wrong device
10056586	Drug delivery device implantation
10056590	Drug delivery device removal
10013828	Duodenal fistula
10013830	Duodenal obstruction
10013832	Duodenal perforation
10050094	Duodenal stenosis
10013836	Duodenal ulcer
10013839	Duodenal ulcer haemorrhage

Code	Preferred Term
10013855	Duodenal ulcer, obstructive
10013849	Duodenal ulcer perforation
10013850	Duodenal ulcer perforation, obstructive
10069807	Duodenal ulcer repair
10013864	Duodenitis
10013865	Duodenitis haemorrhagic
10064826	Duodenoenterostomy
10014896	Enterocolitis haemorrhagic
10056991	Enterocolonic fistula
10051425	Enterocutaneous fistula
10057005	Enterostomy
10057074	Enterostomy closure
10062570	Enterovesical fistula
10062532	Erosive duodenitis
10063655	Erosive oesophagitis
10071039	Excessive dietary fibre intake
10063560	Excessive granulation tissue
10068515	Exposure to contaminated device
10056661	Feeding tube complication
10067143	Fistula discharge
10071275	Functional gastrointestinal disorder
10061138	Fungal peritonitis
10065713	Gastric fistula
10071259	Gastric fistula repair
10017788	Gastric haemorrhage
10058035	Gastric ileus
10070994	Gastric mucosa erythema
10017807	Gastric mucosal hypertrophy
10061164	Gastric mucosal lesion
10067855	Gastric occult blood positive
10017815	Gastric perforation
10061970	Gastric stenosis
10017822	Gastric ulcer

Code	Preferred Term
10017826	Gastric ulcer haemorrhage
10017829	Gastric ulcer haemorrhage, obstructive
10051348	Gastric ulcer helicobacter
10017835	Gastric ulcer perforation
10017836	Gastric ulcer perforation, obstructive
10017840	Gastric ulcer, obstructive
10057348	Gastric ulcer surgery
10057572	Gastric varices haemorrhage
10017860	Gastritis atrophic
10017865	Gastritis erosive
10017866	Gastritis haemorrhagic
10053768	Gastroduodenal haemorrhage
10017886	Gastroduodenal ulcer
10048712	Gastroduodenitis haemorrhagic
10017873	Gastro-enterostomy
10017928	Gastrointestinal angiodysplasia
10017929	Gastrointestinal angiodysplasia haemorrhagic
10017944	Gastrointestinal disorder
10061171	Gastrointestinal disorder postoperative
10053074	Gastrointestinal disorder therapy
10060709	Gastrointestinal erosion
10017877	Gastrointestinal fistula
10071258	Gastrointestinal fistula repair
10017955	Gastrointestinal haemorrhage
10052105	Gastrointestinal hypomotility
10061172	Gastrointestinal injury
10059028	Gastrointestinal ischaemia
10061173	Gastrointestinal motility disorder
10056995	Gastrointestinal mucosal disorder
10017980	Gastrointestinal mucosal necrosis
10017982	Gastrointestinal necrosis
10061974	Gastrointestinal obstruction
10018001	Gastrointestinal perforation

Code	Preferred Term
10018007	Gastrointestinal stenosis
10065718	Gastrointestinal stoma complication
10065712	Gastrointestinal stoma necrosis
10070840	Gastrointestinal tract irritation
10053050	Gastrointestinal tube insertion
10061459	Gastrointestinal ulcer
10056743	Gastrointestinal ulcer haemorrhage
10057161	Gastrointestinal ulcer management
10061975	Gastrointestinal ulcer perforation
10017882	Gastro-jejunostomy
10018044	Gastroparesis postoperative
10067091	Gastropleural fistula
10068792	Gastrosplenic fistula
10050056	Gastrostomy failure
10059766	Haemorrhagic ascites
10067786	Haemorrhagic erosive gastritis
10061213	Iatrogenic injury
10065728	Ileal fistula
10021305	Ileal perforation
10021307	Ileal stenosis
10021309	Ileal ulcer
10021310	Ileal ulcer perforation
10021312	Ileitis
10021319	Ileojejunal bypass
10021328	Ileus
10021333	Ileus paralytic
10021335	Ileus spastic
10063860	Implant site induration
10063869	Implant site ulcer
10049660	Incision site abscess
10067990	Incision site blister
10064109	Incision site cellulitis
10059048	Incision site complication

Code	Preferred Term
10065615	Incision site erythema
10059241	Incision site haematoma
10051100	Incision site haemorrhage
10065616	Incision site infection
10065614	Incision site oedema
10058043	Incision site pain
10059386	Incision site pruritus
10068945	Incorrect dose administered by device
10021784	Infected skin ulcer
10071647	Infectious peritonitis
10065464	Infusion site haemorrhage
10054995	Infusion site ulcer
10069803	Injury associated with device
10070773	Intentional medical device removal by patient
10068575	Intestinal anastomosis complication
10022642	Intestinal dilatation
10022647	Intestinal fistula
10051095	Intestinal fistula infection
10052991	Intestinal fistula repair
10069829	Intestinal haematoma
10059175	Intestinal haemorrhage
10022657	Intestinal infarction
10022680	Intestinal ischaemia
10022687	Intestinal obstruction
10022694	Intestinal perforation
10071197	Intestinal polyp haemorrhage
10022699	Intestinal stenosis
10022714	Intestinal ulcer
10061248	Intestinal ulcer perforation
10061249	Intra-abdominal haemorrhage
10066127	Ischaemic pancreatitis
10065719	Jejunal fistula
10023172	Jejunal gangrene

Code	Preferred Term
10062027	Jejunal operation
10023174	Jejunal perforation
10023176	Jejunal stenosis
10023177	Jejunal ulcer
10023178	Jejunal ulcer perforation
10023180	Jejunostomy
10023694	Laparoscopy abnormal
10052534	Large intestinal haemorrhage
10062062	Large intestinal obstruction
10023794	Large intestinal obstruction reduction
10023799	Large intestinal ulcer
10061262	Large intestinal ulcer haemorrhage
10023804	Large intestine perforation
10066768	Localized intraabdominal fluid collection
10050953	Lower gastrointestinal haemorrhage
10026712	Mallory-Weiss syndrome
10051399	Mechanical ileus
10057075	Meconium plug syndrome
10059108	Medical device change
10057281	Medical device complication
10053683	Medical device discomfort
10070765	Medical device entrapment
10049812	Medical device implantation
10059057	Medical device pain
10052971	Medical device removal
10062680	Medical device site reaction
10069699	Mesenteric traction syndrome
10028084	Mucocutaneous ulceration
10061297	Mucosal erosion
10061298	Mucosal haemorrhage
10067993	Mucosal necrosis
10028124	Mucosal ulceration
10061876	Obstruction

Code	Preferred Term
10029957	Obstruction gastric
10052400	Oedematous pancreatitis
10030172	Oesophageal haemorrhage
10070818	Oesophageal irritation
10030178	Oesophageal obstruction
10030181	Oesophageal perforation
10030194	Oesophageal stenosis
10030201	Oesophageal ulcer
10030202	Oesophageal ulcer haemorrhage
10052488	Oesophageal ulcer perforation
10030210	Oesophageal varices haemorrhage
10030219	Oesophagitis haemorrhagic
10049098	Oesophagitis ulcerative
10030860	Operative haemorrhage
10033645	Pancreatitis
10033647	Pancreatitis acute
10033649	Pancreatitis chronic
10033650	Pancreatitis haemorrhagic
10033654	Pancreatitis necrotizing
10033657	Pancreatitis relapsing
10069846	Patient-device incompatibility
10062065	Perforated ulcer
10034649	Peritoneal abscess
10067011	Peritoneal cloudy effluent
10061343	Peritoneal disorder
10058095	Peritoneal haematoma
10034666	Peritoneal perforation
10034674	Peritonitis
10062070	Peritonitis bacterial
10065326	Peritonitis helminthic
10034681	Peritonitis pneumococcal
10034684	Peritonitis syphilitic
10053418	Peritonitis viral

Code	Preferred Term
10048299	Pneumoperitoneum
10068676	Pneumoretroperitoneum
10053174	Post procedural cellulitis
10058046	Post procedural complication
10068620	Post procedural constipation
10057585	Post procedural diarrhea
10057751	Post procedural discharge
10054126	Post procedural discomfort
10061489	Post procedural fistula
10063188	Post procedural haematoma
10051077	Post procedural haemorrhage
10067268	Post procedural infection
10066592	Post procedural myocardial infarction
10063645	Post procedural oedema
10066590	Post procedural pneumonia
10063909	Post procedural pulmonary embolism
10066593	Post procedural sepsis
10066591	Post procedural stroke
10066415	Post procedural swelling
10051182	Postoperative abscess
10054048	Postoperative ileus
10061468	Postoperative wound complication
10036410	Postoperative wound infection
10050173	Prepyloric stenosis
10057765	Procedural complication
10066962	Procedural nausea
10064882	Procedural pain
10036769	Procedural site reaction
10066963	Procedural vomiting
10069889	Product adhesion issue
10054981	Prophylaxis against gastrointestinal ulcer
10049863	Puncture site abscess
10063677	Puncture site infection

Code	Preferred Term
10061926	Purulence
10037569	Purulent discharge
10038063	Rectal haemorrhage
10069839	Respiratory complication associated with device
10039003	Reversal of ileojejunal bypass
10040102	Seroma
10040893	Skin necrosis
10040943	Skin ulcer
10050377	Skin ulcer haemorrhage
10052535	Small intestinal haemorrhage
10041101	Small intestinal obstruction
10041103	Small intestinal perforation
10062263	Small intestinal stenosis
10061550	Small intestinal ulcer haemorrhage
10041133	Small intestine ulcer
10042070	Stitch abscess
10042128	Stomatitis
10050396	Subileus
10042618	Surgical procedure repeated
10044522	Traumatic haematoma
10053476	Traumatic haemorrhage
10067979	Traumatic liver injury
10044546	Traumatic ulcer
10045285	Ulcer
10061577	Ulcer haemorrhage
10070772	Unintentional medical device removal by patient
10046274	Upper gastrointestinal haemorrhage
10056091	Varices oesophageal
10069840	Vascular complication associated with device
10058042	Wound abscess
10054108	Wound evisceration
10048038	Wound infection
10065240	Wound infection bacterial

Code	Preferred Term
10065242	Wound infection fungal
10065243	Wound infection helminthic
10059444	Wound infection pseudomonas
10059442	Wound infection staphylococcal
10065241	Wound infection viral
10070469	Wrong device dispensed
10070468	Wrong device used
10061582	X-ray gastrointestinal tract abnormal
10059691	X-ray with contrast lower gastrointestinal tract
10059705	X-ray with contrast lower gastrointestinal tract abnormal
10048210	X-ray with contrast upper gastrointestinal tract

2. Polyneuropathy: include Guillain-Barre syndrome SMQ (20000131) and peripheral neuropathy SMQ (20000034).

Guillain-Barre Syndrome SMQ (20000131)

Code	Preferred Term	Narrow Search (N)
10057645	Chronic inflammatory demyelinating polyradiculoneuropathy	N
10061811	Demyelinating polyneuropathy	N
10018767	Guillain-Barre syndrome	N
10049567	Miller Fisher syndrome	N
10049460	Abasia	
10001052	Acute respiratory distress syndrome	
10051224	Akinaesthesia	
10059978	Albumin CSF increased	
10002948	Aphasia	
10003084	Areflexia	
10003549	Asthenia	
10003591	Ataxia	
10070439	Autoimmune neuropathy	
10003840	Autonomic nervous system imbalance	
10061666	Autonomic neuropathy	

Code	Preferred Term	Narrow Search (N)
10003882	Axonal neuropathy	
10049848	Balance disorder	
10071641	Bell's phenomenon	
10004846	Biopsy peripheral nerve abnormal	
10049509	Brain stem auditory evoked response abnormal	
10006542	Bulbar palsy	
10007947	Central nervous system function test abnormal	
10051290	Central nervous system lesion	
10054937	Central nervous system mass	
10010947	Coordination abnormal	
10061093	Cranial nerve disorder	
10011314	Cranial nerve palsies multiple	
10061908	Cranial nerve paralysis	
10064338	CSF immunoglobulin increased	
10011562	CSF oligoclonal band present	
10011573	CSF protein abnormal	
10011575	CSF protein increased	
10059703	CSF test abnormal	
10067502	Decreased vibratory sense	
10012305	Demyelination	
10012725	Diaphragmatic paralysis	
10013033	Diplegia	
10013886	Dysaesthesia	
10013887	Dysarthria	
10013950	Dysphagia	
10050256	Dysstasia	
10014431	Electromyogram abnormal	
10015727	Extensor plantar response	
10051267	Facial paresis	
10017577	Gait disturbance	
10068912	Genital hypoaesthesia	
10020937	Hypoaesthesia	
10020939	Hypoaesthesia eye	

Code	Preferred Term	Narrow Search (N)
10057371	Hypoaesthesia oral	
10051780	Hypoaesthesia teeth	
10021021	Hypokinesia	
10021089	Hyporeflexia	
10071552	Hyporesponsive to stimuli	
10021118	Hypotonia	
10067068	Intranasal hypoaesthesia	
10051660	Intranasal paraesthesia	
10057332	Loss of proprioception	
10025000	Lumbar puncture abnormal	
10061296	Motor dysfunction	
10065579	Multifocal motor neuropathy	
10028289	Muscle atrophy	
10028372	Muscular weakness	
10029175	Nerve conduction studies abnormal	
10056677	Nerve degeneration	
10029192	Nerve stimulation test abnormal	
10029323	Neuromyopathy	
10071579	Neuronal neuropathy	
10029331	Neuropathy peripheral	
10030875	Ophthalmoplegia	
10033712	Papilloedema	
10033775	Paraesthesia	
10033780	Paraesthesia mucosal	
10058469	Paraesthesia of genital female	
10052544	Paraesthesia of genital male	
10057372	Paraesthesia oral	
10033799	Paralysis	
10033809	Paralysis flaccid	
10033885	Paraparesis	
10033892	Paraplegia	
10033985	Paresis	
10061911	Paresis cranial nerve	

Code	Preferred Term	Narrow Search (N)
10034580	Peripheral motor neuropathy	
10067633	Peripheral nerve lesion	
10058530	Peripheral nerve palsy	
10034591	Peripheral nervous system function test abnormal	
10054808	Peripheral paralysis	
10056673	Peripheral sensorimotor neuropathy	
10034620	Peripheral sensory neuropathy	
10034701	Peroneal nerve palsy	
10059923	Pharyngeal hypoaesthesia	
10036105	Polyneuropathy	
10036111	Polyneuropathy idiopathic progressive	
10036800	Progressive bulbar palsy	
10037114	Pseudobulbar palsy	
10049680	Quadriparesis	
10037714	Quadriplegia	
10037779	Radiculopathy	
10038254	Reflexes abnormal	
10038669	Respiratory arrest	
10038695	Respiratory failure	
10070833	Respiratory muscle weakness	
10038708	Respiratory paralysis	
10062162	Sensorimotor disorder	
10040026	Sensory disturbance	
10048871	Sensory integrative dysfunction	
10061567	Sensory level abnormal	
10040030	Sensory loss	
10041466	Speech disorder	
10061551	Spinocerebellar disorder	
10058560	Tandem gait test abnormal	
10068008	Trigeminal nerve paresis	
10049788	Trigeminal palsy	
10045380	Ulnar neuritis	
10045555	Unresponsive to stimuli	

Code	Preferred Term	Narrow Search (N)
10059101	Vibration test abnormal	
10050040	VIIth nerve paralysis	
10047641	VIth nerve paralysis	
10071044	VIth nerve paresis	

Peripheral Neuropathy SMQ (20000034)

Code	Preferred Term	Narrow Search (N)
10066699	Acute polyneuropathy	N
10002027	Amyotrophy	N
10070439	Autoimmune neuropathy	N
10003882	Axonal neuropathy	N
10004846	Biopsy peripheral nerve abnormal	N
10067502	Decreased vibratory sense	N
10061811	Demyelinating polyneuropathy	N
10018767	Guillain-Barre syndrome	N
10051307	Ischaemic neuropathy	N
10057332	Loss of proprioception	N
10049567	Miller Fisher syndrome	N
10065579	Multifocal motor neuropathy	N
10028570	Myelopathy	N
10029175	Nerve conduction studies abnormal	N
10029223	Neuralgia	N
10029240	Neuritis	N
10071579	Neuronal neuropathy	N
10029331	Neuropathy peripheral	N
10034580	Peripheral motor neuropathy	N
10034591	Peripheral nervous system function test abnormal	N
10056673	Peripheral sensorimotor neuropathy	N
10034620	Peripheral sensory neuropathy	N
10036105	Polyneuropathy	N
10064135	Polyneuropathy chronic	N
10036111	Polyneuropathy idiopathic progressive	N

Code	Preferred Term	Narrow Search (N)
10068886	Radiation neuropathy	N
10062162	Sensorimotor disorder	N
10040026	Sensory disturbance	N
10040030	Sensory loss	N
10067722	Toxic neuropathy	N
10003084	Areflexia	
10056339	Autonomic failure syndrome	
10061666	Autonomic neuropathy	
10070237	Burning feet syndrome	
10006784	Burning sensation	
10013886	Dysaesthesia	
10014431	Electromyogram abnormal	
10017062	Formication	
10017577	Gait disturbance	
10068912	Genital hypoaesthesia	
10020937	Hypoaesthesia	
10021089	Hyporeflexia	
10021118	Hypotonia	
10027910	Mononeuritis	
10062203	Mononeuropathy	
10027918	Mononeuropathy multiplex	
10061296	Motor dysfunction	
10028289	Muscle atrophy	
10028372	Muscular weakness	
10056677	Nerve degeneration	
10062284	Neuromuscular toxicity	
10029323	Neuromyopathy	
10029332	Neuropathy vitamin B6 deficiency	
10029350	Neurotoxicity	
10033775	Paraesthesia	
10067633	Peripheral nerve lesion	
10058530	Peripheral nerve palsy	
10071663	Peripheral nerve paresis	

Code	Preferred Term	Narrow Search (N)
10034699	Peroneal muscular atrophy	
10034701	Peroneal nerve palsy	
10064964	Phrenic nerve paralysis	
10054786	Skin burning sensation	
10068015	Temperature perception test decreased	
10052492	Tinel's sign	
10045380	Ulnar neuritis	

3. Weight loss (CMQ 80000109).

Code	Preferred Term
10000159	Abnormal loss of weight
10002647	Anorexia and bulimia syndrome
10002649	Anorexia nervosa
10060961	Appetite disorder
10005895	Body mass index decreased
10006895	Cachexia
10061428	Decreased appetite
10012775	Diet refusal
10013950	Dysphagia
10014062	Eating disorder
10061832	Eating disorder symptom
10050366	Fear of eating
10053050	Gastrointestinal tube insertion
10052592	Gastrostomy tube insertion
10063743	Hypophagia
10021577	Inadequate diet
10061273	Malnutrition
10026820	Marasmus
10028155	Multi-vitamin deficiency
10065026	Nutritional condition abnormal
10029861	Nutritional support
10051284	Parenteral nutrition

Code	Preferred Term
10050086	Poor weight gain neonatal
10041954	Starvation
10048828	Underweight
10056814	Weight abnormal
10047894	Weight decrease neonatal
10047895	Weight decreased
10049040	Weight fluctuation
10047897	Weight gain poor
10047901	Weight loss diet

4. Cardiovascular fatalities: major adverse cardiovascular events (MACE) MI CMQ (80000076) and the outcome of the AE was fatal.

Code	Preferred Term
10051592	Acute coronary syndrome
10000891	Acute myocardial infarction
10054015	Agonal rhythm
10002388	Angina unstable
10003225	Arteriospasm coronary
10005468	Blood creatine phosphokinase abnormal
10005470	Blood creatine phosphokinase increased
10005472	Blood creatine phosphokinase MB abnormal
10005474	Blood creatine phosphokinase MB increased
10007515	Cardiac arrest
10049993	Cardiac death
10007548	Cardiac enzymes increased
10007617	Cardio-respiratory arrest
10007625	Cardiogenic shock
10050329	Coronary angioplasty
10052086	Coronary arterial stent insertion
10011077	Coronary artery bypass
10048631	Coronary artery dissection
10011084	Coronary artery embolism

Code	Preferred Term
10052895	Coronary artery insufficiency
10011086	Coronary artery occlusion
10053261	Coronary artery reocclusion
10056489	Coronary artery restenosis
10011089	Coronary artery stenosis
10011091	Coronary artery thrombosis
10059025	Coronary bypass thrombosis
10011101	Coronary endarterectomy
10011105	Coronary ostial stenosis
10049887	Coronary revascularisation
10013428	Dissecting coronary artery aneurysm
10051177	Electrocardiogram Q wave abnormal
10014390	Electrocardiogram ST segment abnormal
10014392	Electrocardiogram ST segment elevation
10049225	Electrocardiogram ST-T segment elevation
10066846	In-stent coronary artery restenosis
10061216	Infarction
10070909	Metabolic cardiomyopathy
10028596	Myocardial infarction
10028600	Myocardial ischaemia
10051624	Myocardial reperfusion injury
10033697	Papillary muscle infarction
10065608	Percutaneous coronary intervention
10066592	Post procedural myocardial infarction
10058144	Postinfarction angina
10036759	Prinzmetal angina
10058151	Pulseless electrical activity
10061501	Scan myocardial perfusion abnormal
10040560	Shock
10049768	Silent myocardial infarction
10049418	Sudden cardiac death
10042434	Sudden death
10058268	Troponin I increased

Code	Preferred Term
10058267	Troponin increased
10058269	Troponin T increased
10049060	Vascular graft occlusion
10047284	Ventricular asystole
10071186	Ventricular dyssynchrony
10047290	Ventricular fibrillation
10047294	Ventricular flutter
10065341	Ventricular tachyarrhythmia
10047302	Ventricular tachycardia

5. Respiratory tract aspiration including aspiration pneumonia/pneumonitis (CMQ 80000103).

Code	Preferred Term
10066728	Acute interstitial pneumonitis
10069351	Acute lung injury
10001029	Acute pulmonary oedema
10001052	Acute respiratory distress syndrome
10001053	Acute respiratory failure
10002974	Apnoea
10002977	Apnoeic attack
10003497	Asphyxia
10003504	Aspiration
10050777	Aspiration bronchial
10003530	Aspiration tracheal
10003531	Aspiration tracheal abnormal
10003598	Atelectasis
10006102	Bradypnoea
10064913	Bronchial disorder
10006438	Bronchial irritation
10006440	Bronchial obstruction
10056695	Bronchial oedema

Code	Preferred Term
10066820	Bronchial secretion retention
10051547	Bronchial ulceration
10067182	Bronchial wall thickening
10049413	Bronchoalveolar lavage
10063078	Bronchoalveolar lavage abnormal
10006469	Bronchopneumonia
10053582	Bronchopneumopathy
10053420	Bronchopulmonary disease
10006479	Bronchoscopy
10006480	Bronchoscopy abnormal
10008589	Choking
10008590	Choking sensation
10057482	Dependence on respirator
10060865	Duodenogastric reflux
10013950	Dysphagia
10013968	Dyspnoea
10013969	Dyspnoea at rest
10013971	Dyspnoea exertional
10067450	Endotracheal intubation
10063349	Endotracheal intubation complication
10052591	Enteral nutrition
10015894	Extubation
10056661	Feeding tube complication
10016985	Forced expiratory volume abnormal
10016987	Forced expiratory volume decreased
10017000	Foreign body aspiration
10017505	Functional residual capacity abnormal
10017508	Functional residual capacity increased
10053050	Gastrointestinal tube insertion
10064069	Gastrointestinal tube removal
10017885	Gastrooesophageal reflux disease
10052592	Gastrostomy tube insertion
10020591	Hypercapnia

Code	Preferred Term
10020910	Hyperventilation
10020952	Hypocapnia
10021079	Hypopnoea
10021133	Hypoventilation
10021143	Hypoxia
10062530	Increased bronchial secretion
10062717	Increased upper airway secretion
10061257	Jaw disorder
10024378	Leukocytosis
10024738	Lobar pneumonia
10057260	Lower respiratory tract inflammation
10025080	Lung consolidation
10025082	Lung disorder
10025102	Lung infiltration
10026882	Mastication disorder
10049783	Mendelson's syndrome
10056652	Middle lobe syndrome
10058525	Nasal aspiration
10059841	Nasopharyngeal reflux
10049235	Nocturnal dyspnoea
10061877	Obstructive airways disorder
10056992	Oesophagobronchial fistula
10067472	Organising pneumonia
10031123	Orthopnoea
10058982	PCO2 abnormal
10034181	PCO2 decreased
10034193	Peak expiratory flow rate abnormal
10034195	Peak expiratory flow rate decreased
10067353	Pharyngeal disorder
10070912	Pharyngeal dyskinesia
10035664	Pneumonia
10035669	Pneumonia aspiration
10060946	Pneumonia bacterial

Code	Preferred Term
10035730	Pneumonia primary atypical
10035742	Pneumonitis
10035745	Pneumonitis chemical
10062087	PO2 abnormal
10035768	PO2 decreased
10059184	Poor dental condition
10066590	Post procedural pneumonia
10036790	Productive cough
10037368	Pulmonary congestion
10037660	Pyrexia
10053307	Radiography guided aspiration
10067869	Reflux laryngitis
10062102	Removal of foreign body
10038330	Removal of foreign body from larynx
10038333	Removal of foreign body from oesophagus
10059390	Removal of foreign body from respiratory tract
10038334	Removal of foreign body from throat
10038647	Respiration abnormal
10038661	Respiratory acidosis
10038664	Respiratory alkalosis
10038669	Respiratory arrest
10038678	Respiratory depression
10038681	Respiratory depth decreased
10038682	Respiratory depth increased
10038683	Respiratory disorder
10038687	Respiratory distress
10038695	Respiratory failure
10052251	Respiratory tract congestion
10068956	Respiratory tract inflammation
10038731	Respiratory tract irritation
10070774	Respiratory tract oedema
10039109	Rhonchi
10050419	Sputum culture

Code	Preferred Term
10051612	Sputum culture positive
10041807	Sputum discoloured
10041812	Sputum increased
10042241	Stridor
10042444	Suffocation feeling
10043089	Tachypnoea
10044291	Tracheal obstruction
10063968	Upper airway resistance syndrome
10052252	Upper respiratory tract congestion
10049590	Upper respiratory tract inflammation
10070841	Upper respiratory tract irritation
10069555	Use of accessory respiratory muscles
10047924	Wheezing