Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
Duodopa Intestinal Gel</td></tr>
<tr><td>Name of Active Ingredient:
Levodopa-Carbidopa</td></tr>
<tr><td colspan="3">Title of Study: Open-Label, 12-Month Safety and Efficacy Study of Levodopa-Carbidopa Intestinal Gel in Levodopa-Responsive Parkinson's Disease Subjects</td></tr>
<tr><td colspan="3">Coordinating Investigator:
John T. Slevin, MD
University of Kentucky College of Medicine
Kentucky Clinic L-445, 740 South Limestone Street
Lexington, Kentucky 40536-0284</td></tr>
<tr><td colspan="3">Study Sites: Subjects were enrolled at 22 sites in the United States, New Zealand, and Germany.</td></tr>
<tr><td colspan="3">Publications: None</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 15 June 2009
Last Subject Last Visit: 25 October 2012</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="3">Objectives:
The primary objective of this study was to evaluate the long-term safety of the Levodopa-Carbidopa Intestinal Gel (LCIG) over a 12-month period.
A secondary objective was to assess the long-term maintenance of efficacy and health outcome measures.</td></tr>
<tr><td colspan="3">Methodology:
Study S187-3-003 was a Phase 3, 12-month, open-label, multicenter continuation treatment study of the safety, tolerability, and efficacy of LCIG in the treatment of levodopa-responsive Parkinson's disease (PD) subjects with persistent motor fluctuations despite optimized treatment with available PD medications. All subjects received LCIG.
Only subjects who completed 12 weeks of double-blind, double-dummy treatment in Study S187-3-001/S187-3-002 qualified for enrollment in this 12-month continuation treatment study.
In this study, subjects were hospitalized for 2 days at a minimum, and up to 7 days at the discretion of the investigator, to allow for Baseline evaluations and the establishment of the optimum morning and continuous infusion LCIG dose.</td></tr>
</table>

Methodology (Continued):

Scheduled clinic visits occurred as follows:

- Every 4 weeks from Week 4 through Week 52;
- And/or early termination

Subject visit days were to match the target clinic visit days; however, a ± 7-day visit window was allowed as necessary.

Number of Subjects (Planned and Analyzed):

Number of subjects planned: 66 (based on number of subjects who completed Study S187-3-001/S187-3-002)

Number of subjects enrolled: 62

Diagnosis and Main Criteria for Inclusion:

Main Inclusion:

Subjects with levodopa-responsive PD who experienced persistent motor fluctuations despite optimized available therapy were eligible and must have also met the following criteria in order to participate in this study:

1. The subject completed 12 weeks of double-blind, double-dummy treatment in Study S187-3-001/S187-3-002 and, in the opinion of the principal investigator, would have benefitted from long-term treatment with LCIG. No minimum "Off" time was required based on the Parkinson's Disease Diary data at the end of Study S187-3-001/S187-3-002.
2. The subject must have been able to understand the nature of the study and must have provided written informed consent prior to the conduct of any study procedures (including any changes occurring in the subject's current therapeutic regimen).
3. The subject was willing to continue on treatment, and must have continued to meet the inclusion criteria for the preceding study (Study S187-3-001/S187-3-002), with the exception that Enrollment Steering Committee (ESC) review and approval of eligibility was not required for Study S187-3-003.

Exclusion Criteria:

Subjects meeting any of the exclusion criteria listed below at Baseline were to be excluded from participation in the study:

1. Subject was enrolled in another clinical trial.
2. The subject had psychiatric, neurological, or behavioral disorders that could interfere with the ability to give informed consent, or interfere with the conduct of the study.
3. The subject had medical, laboratory, or surgical issues deemed by the investigator to be clinically significant.
4. The subject had an uncooperative attitude or reasonable likelihood for non-compliance with the protocol.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

LCIG was supplied as a suspension of levodopa (20 mg/mL) and carbidopa (5 mg/mL) in an aqueous gel (carboxymethylcellulose) that was dispensed in a medication cassette reservoir containing 100 mL of LCIG. Levodopa-carbidopa intestinal gel was continuously administered through a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) via a portable infusion pump (CADD-Legacy Pump Model 1400) connected to the LCIG medication cassette reservoir.

Subject dosing was determined individually. The LCIG infusion was expected to infuse over approximately16 hours each day with a rate of infusion within the range of 1 to 10 mL/hour (20 to 200 mg of levodopa/hour) in most instances. At night, after disconnecting the pump for sleeping, the tubing was flushed with potable water.

All subjects received LCIG in this study, delivered to the proximal small intestine through a PEG-J, administered for up to 12 months. In order to maintain the integrity of the blind in the previous studies (Study S187-3-001/S187-3-002), the starting dose of LCIG was based on the subject's optimized oral levodopa-carbidopa dose that the subject was receiving just prior to randomization in Study S187-3-001/S187-3-002. Study S187-3-003 study drug was to be started in the morning of the first day following Study Day 86 of the previous studies (Study S187-3-001/S187-3-002).

The infusion dose was individually optimized for each subject during the study by the investigator based on response and potential adverse events. Extra doses of LCIG could have been used to help control fluctuations in the subject's PD symptoms.

The total dose/day of LCIG was composed of 3 individually adjusted doses: the morning dose, the continuous maintenance dose and extra doses.

Morning Dose

An adjusted morning dose of levodopa-carbidopa was administered as a bolus infusion by the pump to fill the dead space of the intestinal tube and rapidly achieve the therapeutic dose level (over approximately 10 to 30 minutes). The initial dose should have been determined on the basis of the subject's previous oral morning intake of levodopa-carbidopa just prior to randomization in Study S187-3-001/S187-3-002.

The total morning dose was usually 5 to 10 mL, corresponding to 100 to 200 mg levodopa and would usually not exceed 15 mL (300 mg levodopa).

The morning dose could have been increased or decreased by 10 to 20 mg (0.5 to 1.0 mL) daily from Study Day 2 through the day of discharge from the hospital and at study visits but should not have exceeded 300 mg depending on the effectiveness of the previous day's dose.

Subjects were not to be administered a full equivalent of their usual oral morning dose of levodopa-carbidopa in order to minimize the risk of subjects entering a hyperdyskinetic state. The morning dose of LCIG was determined on the basis of a percentage of their usual amount of oral levodopa-carbidopa given at that time.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number (Continued):

Continuous Maintenance Dose

The continuous maintenance dose was adjustable in steps of 2 mg/hour (0.1 mL/hour). The initial dose should have been calculated according to the subject's daily intake of levodopa just prior to randomization in the previous LCIG double-blind, double-dummy study. When supplementary medicines were discontinued, the LCIG dose may have needed adjustment. The continuous maintenance dose was adjusted individually. It was to be kept within a range of 1 to 10 mL/hour (20 to 200 mg levodopa/hour) and was usually 2 to 6 mL/hour (40 to 120 mg levodopa/hour). In exceptional cases, a higher dose may have been needed. During the titration period, the continuous dose could have been titrated in a step-wise fashion that met the clinical needs of the subject.

The continuous maintenance dose was first calculated on the basis of the subject's usual total daily dose of oral levodopa-carbidopa that the subject was receiving immediately prior to randomization in Study S187-3-001/S187-3-002 minus the morning dose. Then 90% of the remaining amount (total daily dose minus the morning dose) was delivered over a 16-hour period in order to minimize the risk of subjects entering a hyperdyskinetic state.

Extra Doses

During initial titration, extra doses may have been administered on an hourly basis at various doses up to 9.9 mL. Subsequently, subjects were allowed to self-administer additional extra doses of LCIG at intervals of no less than 2 hours to address immediate medical needs, such as the rapid deterioration of motor function. Extra doses may have been given as required if the subject became hypokinetic during the day. The extra dose should have been adjusted individually (normally 0.5 to 2.0 mL) during the titration period and remained fixed unless adjusted by the investigator at a subsequent visit. In rare cases, a higher dose may have been needed. If the need for extra doses exceeded 5 per day, the investigator should have considered increasing the maintenance dose. After the initial dose setting, fine adjustments of the morning dose, the continuous maintenance dose, and extra doses could have been made as needed. Extra doses were to be initiated at 1 mL.

Study Drug	Formulation	Bulk Lot Numbers
LCIG in 100 mL medication cassette reservoir	Aqueous gel levodopa (20 mg/mL) carbidopa (5 mg/mL)	08H19G12, 08L02G02, 10B03G03, 10C10G08, 11B02G02, 11B23G16, 11C23G18, 11C30G23, 11I21G19, 11J26G17, 11K16G17, 12B01G01, 12B29G26

Duration of Treatment:

12 months

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Not applicable.

Criteria for Evaluation

Efficacy:

The following efficacy and health outcome measures were assessed by changes from Baseline to Endpoint:

- "Off" time as measured by the Parkinson's Disease Diary
- "On" time without troublesome dyskinesia as measured by the Parkinson's Disease Diary
- Unified Parkinson's Disease Rating Scale (UPDRS) Total Score and Parts I, II, III and IV scores
- Parkinson's Disease Questionnaire (PDQ-39) Summary Index and domain scores
- Clinical Global Impression-Improvement (CGI-I) score
- EuroQol Quality of Life – 5 Dimensions (EQ-5D) Summary Index and Visual Analog Scale (VAS)
- Zarit Burden Interview (ZBI) Total Score

Safety:

The safety and tolerability of LCIG were evaluated with physical and neurological examinations, measurements of vital signs, electrocardiograms (ECGs), clinical laboratory assessments, adverse event monitoring, monitoring for sleep attacks, development of melanoma, excessive impulsive behavior, abnormal involuntary movements, Columbia-Suicide Severity Rating Scale (C-SSRS), and monitoring for complications of the device system.

Statistical Methods

There were 3 main subject data sets of interest.

The All Subjects Consented data set consisted of all subjects who:

- Gave their informed consent and enrolled in Study S187-3-3003.

The Safety data set consisted of all subjects who:

- Were in the All Subjects Consented data set;
- Received at least one Study S187-3-3003 LCIG infusion.

The Full Analysis (FA) data set consisted of all subjects who:

- Were included in the Safety data set;
- Had data for Baseline and at least 1 post-baseline assessment for any efficacy measurement.

All subjects received LCIG in Study S187-3-003. For the statistical analysis, subjects were assigned to a treatment group based on the treatment they had received in the previous double-blind, double-dummy study: either LCIG gel and placebo capsules (the Continuing LCIG treatment group) or placebo gel and levodopa-carbidopa capsules (the LCIG Naïve treatment group). All analyses were exploratory for the purpose of hypothesis generation and no adjustment was made for multiple comparisons.

Statistical Methods (Continued)

Efficacy and Health Outcome:

Descriptive statistics (n, mean, minimum, maximum, and 95% confidence interval) were calculated for the FA data set for each treatment group and overall. Analyses of the change from baseline in the following efficacy and health outcome parameters were prepared:

- "Off" time as measured by the Parkinson's Disease Diary
- "On" time with troublesome dyskinesia as measured by the Parkinson's Disease Diary
- "On" time without troublesome dyskinesia as measured by the Parkinson's Disease Diary
- "On" time with non-troublesome dyskinesia as measured by the Parkinson's Disease Diary
- "On" time without dyskinesia as measured by the Parkinson's Disease Diary
- UPDRS Total Score and Parts I, II, III, IV and Part IV dyskinesia items scores
- CGI-I score
- PDQ-39 Summary Index and domain scores
- EQ-5D Summary Index and VAS
- ZBI score

Safety:

Adverse events were summarized for each treatment group and overall for all centers/countries combined. Additionally, adverse events were summarized during the first 4 weeks of the study for each treatment group. Percentages were calculated relative to the total number of subjects considered valid for the subject sample. Safety was evaluated using adverse events summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT), and changes in laboratory parameters, ECGs, vital sign measurements, sleep attacks, development of melanoma, excessive impulsive behavior, abnormal involuntary movements, C-SSRS, and monitoring for complications of the device system.

Summary/Conclusions

Efficacy Results:

The efficacy results demonstrated that all subjects, independent of previous exposure, derived benefit from treatment with the LCIG System while in Study S187-3-003. Subjects in the Continuing LCIG group (who received LCIG in Study S187-3-001/S187-3-002 and continued on LCIG in this study) demonstrated continued and sustained improvement with long-term treatment. Additionally, subjects in the LCIG Naïve group (who received oral levodopa-carbidopa immediate release (IR) in Study S187-3-001/S187-3-002 and LCIG in this study) demonstrated a greater magnitude of improvement that was sustained during this study based on the PD Diary.

<u>Continuing LCIG Group</u>

A mean decrease in "Off" time of –0.42 hours from a Baseline mean of 2.87 hours was observed at Endpoint. A mean decrease in "On" time with troublesome dyskinesia of –0.58 hours from a Baseline mean of 1.09 hours was observed at Endpoint. The decrease in "Off" time was accompanied by a corollary increase in "On" time without troublesome dyskinesia of 1.00 hour (P = 0.036).

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Continuing LCIG Group (Continued)

The increase in "On" time without troublesome dyskinesia comprised an increase in "On" time without dyskinesia (1.70 hours; $P = 0.030$) and a decrease in "On" time with non-troublesome dyskinesia (–0.70 hours).

The CGI-I, UPDRS Part IV dyskinesia subscore, and UPDRS Part IV score were consistent with improvement. For the CGI-I, the majority of subjects were assessed by the investigator as having been in the top 3 CGI-I scoring categories of 'Very Much Improved' (39.4%), 'Much Improved' (30.3%), and 'Minimally Improved' (15.2%) at Endpoint. A statistically significant mean CGI-I of 2.1 was observed at Endpoint ($P < 0.001$ compared to value of 4 = no change). Improvements in the UPDRS Part IV dyskinesia and Part IV scores were observed throughout treatment with statistically significant mean decreases from Baseline to Endpoint of –0.8 ($P = 0.006$) and –1.6 ($P < 0.001$), respectively. No statistically significant changes were observed for the UPDRS Part I, Part II, Part III, or total scores.

The PDQ-39 summary index showed improvements from Baseline at every visit except Week 52 and Endpoint, but the mean improvements were not statistically significant.

No statistically significant changes were observed for the EQ-5D summary index, EQ-5D VAS score, or ZBI total score.

LCIG Naïve Group

A mean decrease in "Off" time of –2.34 hours from a Baseline mean of 5.18 hours ($P < 0.001$) was observed at Endpoint. This statistically significant decrease from Baseline in "Off" time was observed as early as Week 4 and continued throughout treatment. The reduction in "Off" time at Endpoint was mostly accompanied by an increase in "On" time without troublesome dyskinesia (2.19 hours; $P = 0.005$), but with also a very small increase in "On" time with troublesome dyskinesia (0.15 hours; $P = 0.724$). The increase in "On" time without troublesome dyskinesia comprised an increase in "On" time without dyskinesia (2.62 hours; $P = 0.015$) and a decrease in "On" time with non-troublesome dyskinesia (–0.44 hours).

The CGI-I and UPDRS Part IV score were consistent with improvement. For the CGI-I, the majority of subjects were assessed by the investigator as having been in the top 3 CGI-I scoring categories of 'Very Much Improved' (41.4%), 'Much Improved' (27.6%), and 'Minimally Improved' (13.8%) at Endpoint. A statistically significant mean CGI-I of 2.3 was observed at Endpoint ($P < 0.001$ compared to value of 4 = no change). Statistically significant improvements in the UPDRS Part IV score were observed throughout treatment with a mean decrease from Baseline to Endpoint of –1.4 ($P = 0.022$). No statistically significant changes were observed for the UPDRS Part I, Part II, Part III, Part IV dyskinesia subscore, or total scores at Endpoint.

The PDQ-39 summary index showed improvements from Baseline at every visit and Endpoint, and the improvement was statistically significant at Week 12 (–5.5; $P = 0.018$) and Week 52 (–6.0; $P = 0.031$). The mean decreases ranged from –3.5 (Endpoint) to -6.0 (Week 52).

The EQ-5D summary index showed improvement from Baseline at Week 12 (0.062; $P = 0.043$), but the mean changes were not statistically significant at subsequent visits or at Endpoint. Improvements in the EQ-5D VAS were observed at Week 12 (11.6; $P < 0.001$), but the mean changes were not statistically significant at subsequent visits or at Endpoint.

No statistically significant changes were observed for the ZBI total score.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

In summary, treatment with the LCIG System for 12 months demonstrated clinically meaningful improvement in PD symptoms in subjects with advanced PD. Subjects in the Continuing LCIG group continued to improve and subjects in the LCIG Naïve group demonstrated a significant magnitude of improvement with long-term treatment. The improvement in motor symptoms, as measured by the PD Diary, was observed by a reduction in "Off" time accompanied by increases in "On" time without troublesome dyskinesia. This increase in "On" time without troublesome dyskinesia (comprising mainly an increase in "On" time without dyskinesia) represents important complementary data to the observed decrease in "Off" time. The demonstrated improvement in subjects' motor symptoms was also supported by the results of validated PD scales. The CGI-I and UPDRS Part IV scores demonstrated statistically significant improvements in PD symptoms with the LCIG System. These clinically meaningful results demonstrate the overall improvement in the quality of life that the LCIG System can provide to subjects with advanced PD.

Safety Results:

The results from Study S187-3-003 provide support for the continued safety and tolerability of the LCIG System in subjects who previously completed the double-blind, double-dummy Study S187-3-001/S187-3-002. Sixty-two subjects received at least 1 dose of LCIG in this study. A total of 55 subjects (88.7%) completed the study. Seven subjects (11.3%) prematurely discontinued from the study. The primary reasons for premature discontinuation were adverse events for 3 subjects, withdrew consent for 3 subjects, and lack of efficacy for 1 subject. The mean number of days on treatment in this study was 349.6 days (range: 31 to 384 days) for the Continuing LCIG group and 316.2 days (range: 7 to 425 days) for the LCIG Naïve group. On Day 1 of titration and the last titration day, the total daily dose of levodopa was lower for the LCIG Continuing group (mean: 1,115.5 mg/day and 1,330.3 mg/day) compared to the LCIG Naïve group (mean: 1,278.3 mg/day and 1,652.6 mg/day).

The tolerability of the LCIG System is supported by the low rate of premature discontinuations due to adverse events in the study.

- A total of 3/62 subjects (4.8%) experienced at least 1 adverse event leading to premature discontinuation from the study. One subject experienced an adverse event of bipolar disorder on Study Day 1 that was considered moderate and unlikely related to study treatment by the investigator, 1 subject experienced a serious adverse event of renal mass on Study Day 2 that was considered severe and unlikely related to study treatment by the investigator, and another subject experienced serious adverse events of complication of device insertion and intestinal perforation on Study Day 38 that were considered severe and probably related to study treatment by the investigator.

To evaluate the impact of LCIG initiation in the LCIG Naïve group, adverse events with onset during the first 4 weeks were summarized separately for the Continuing LCIG and LCIG Naïve groups. The adverse events reported during Weeks 1 to 4 were comparable between groups. The start of LCIG in the LCIG Naïve group did not seem to result in additional adverse events.

Summary/Conclusions (Continued)

Safety Results (Continued):

- Eighteen (54.5%) subjects in the Continuing LCIG group and 15 subjects (51.7%) in the LCIG Naïve group reported at least 1 adverse event during Weeks 1 to 4. The most frequently reported adverse events during Weeks 1 to 4 were fall (8.1%), incision site erythema (6.5%), depression and insomnia (4.8% each).
- The most frequently reported (≥ 3 subjects) treatment-related adverse events during Weeks 1 to 4 were incision site erythema reported by 4 subjects (3 Continuing LCIG and 1 LCIG Naive) and fall reported by 3 subjects (all Continuing LCIG).
- The only SOCs reported by at least 2 subjects in the LCIG Naïve group and at a greater frequency in the LCIG Naïve group were psychiatric disorders (6 LCIG Naïve subjects, 3 Continuing LCIG subjects) and renal and urinary disorders (2 LCIG Naïve subjects, 1 Continuing LCIG subject). The only PT reported by at least 2 subjects in the LCIG Naïve group and at a greater frequency in the LCIG Naïve group during Weeks 1 to 4 was insomnia.
- Adverse events potentially associated with levodopa (e.g., dyskinesia, hallucinations, and orthostatic hypotension) did not occur with a clinically meaningful increased incidence during the first 4 weeks in the LCIG Naïve group.

The safe use of the LCIG System is supported by additional results observed in the study of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

- A total of 59/62 subjects (95.2%) experienced 1 or more adverse events. A majority of these adverse events were mild to moderate in severity. Overall, the most frequently reported (> 10%) adverse events were incision site erythema (29.0%), fall and decreased vitamin B_6 (21.0% each), post-operative wound infection (17.7%), constipation, insomnia, nausea, and urinary tract infection (14.5% each), PD, post-procedural discharge, procedural pain, and seborrheic keratosis (12.9% each), arthralgia, increased blood homocysteine, dyskinesia, and freezing phenomenon (11.3% each).
- There were no deaths during this study.
- A total of 14/62 subjects (22.6%) experienced at least 1 TESAE. The most frequently reported TESAEs were complication of device insertion (3 subjects, 4.8%), abdominal pain, asthenia, and pneumonia (2 subjects each, 3.2%). Of these serious adverse events, complication of device insertion (2 subjects) and asthenia and pneumonia (1 subject each) were considered severe. Five subjects reported serious adverse events assessed by the investigator as possibly or probably related to study treatment. Of these 5 subjects, more than 1 subject reported TESAEs considered at least possibly related to study treatment of complication of device insertion (n = 3) and abdominal pain (n = 2); all other at least possibly related TESAEs were reported by 1 subject each. Ten of the subjects recovered without sequelae; SAEs were ongoing (or outcome was not known) for 3 subjects and 1 subject recovered with sequelae of paranoia.

Based on the clinical and postmarketing safety experience and given the interventional nature of the administration of the LCIG System, underlying disease being studied and the known risks of levodopa-carbidopa, the following were examined to further assess the safety and tolerability of the LCIG System: device complications and adverse events of special interest (AESI) categories of procedure- and device-associated events, respiratory tract aspirations (including aspiration pneumonia/pneumonitis), weight loss, polyneuropathy, and cardiovascular fatalities.

Summary/Conclusions (Continued)

Safety Results (Continued):

As described in the Statistical Analysis Plan (SAP), TEAEs were included in one or more of the AESI categories based on their MedDRA PT. Results support the safe administration of LCIG via the PEG-J delivery system.

- Device complications were reported by 50 subjects (80.6%). Among these, 31 subjects (50.0%) experienced intestinal tube complications most of which were device occlusion (21 subjects) or device dislocation (17 subjects), 27 subjects (43.5%) experienced stoma complications most of which were medical device site reactions (19 subjects), 34 subjects (54.8%) experienced pump complications a majority of which were device malfunctions (32 subjects), 22 subjects (35.5%) experienced PEG complications most of which were a device connection issue (5 subjects), device dislocation or complication of device insertion (4 subjects each), and 10 subjects (16.1%) experienced other complications most of which were device connection issues (4 subjects), device breakage (3 subjects), or medical device site reactions (2 subjects). The most frequently reported actions taken for intestinal tube complications were "other" (14 subjects), for stoma complications were no action taken (20 subjects), for pump complications were pump replaced (33 subjects), for PEG complications were "other" (11 subjects), and for other complications were "other" (7 subjects).
- Treatment-emergent AEs linked to device complications were experienced by 33 subjects (53.2%). The most frequently reported adverse events linked to device complications were incision site erythema (27.4%), post-operative wound infection (16.1%), post-procedural discharge (12.9%), excessive granulation tissue (9.7%), complication of device insertion and procedural pain (8.1% each), and procedural site reaction (6.5%). The majority of the TEAEs linked to device complication were mild or moderate in severity. One subject discontinued the study prematurely due to complication of device insertion.
- In the category of Procedure and Device-Associated Events, 35 subjects (56.5%) experienced at least 1 adverse event. The most frequently reported (> 10%) adverse events were incision site erythema (29.0%), post-operative wound infection (17.7%), post-procedural discharge (12.9%), and procedural pain (12.9%). Four subjects experienced serious AESIs and 1 subject experienced AESIs that resulted in premature discontinuation.
- In the category of Aspiration, 6 subjects (9.7%) had at least 1 TEAE. None of these subjects underwent endoscopy for tube replacement or repositioning during the study. The most frequently reported TEAEs related to aspiration were pneumonia and hypoxia (2 subjects each, 3.2%). One subject reported an adverse event of dysphagia that was considered possibly related to study treatment. Two subjects reported severe AESIs (pneumonia aspiration and hypoxia in 1 subject and pneumonia in 1 subject). Three subjects reported serious AESIs (pneumonia aspiration and hypoxia in 1 subject and pneumonia in 2 subjects). No subjects discontinued the study due to an aspiration AESI.
- In the category of Weight Loss, 7 subjects (11.3%) had at least 1 TEAE. Treatment-emergent AEs related to weight loss included weight decreased (5 subjects, 8.1%), decreased appetite (3 subjects, 4.8%), and dysphagia (1 subject, 1.6%). Among the 7 subjects reporting an event within the weight loss AESI category, most (6 subjects) experienced an event that was considered at least possibly related to study treatment by the investigator. No subjects reported TESAEs or discontinued the study due to a weight loss AESI.

Summary/Conclusions (Continued)

Safety Results (Continued):

- In the category of Polyneuropathy, 16 subjects (25.8%) had at least 1 TEAE. The most frequently reported TEAEs related to polyneuropathy were polyneuropathy (6 subjects, 9.7%), asthenia (3 subjects, 4.8%), and hypoaesthesia and paraesthesia (2 subjects each, 3.2%). Two of the 16 subjects experienced events that were either serious or severe. One subject experienced TESAEs (asthenia [2 events]) that were considered severe and unrelated to study treatment. The second subject experienced a TESAE (asthenia) that was considered moderate and possibly related to study treatment by the investigator. No subjects discontinued the study due to a polyneuropathy AESI.
- No cardiac-related deaths were reported.

The LCIG System was generally safe and well tolerated throughout the duration of the study, as also evaluated by clinical laboratory, vital signs, ECG results, sleep attacks, impulsive behavior, abnormal involuntary movement, melanoma checks, neurological exams, and the C-SSRS.

- No consistent or clinically important trends were observed for any clinical laboratory variables. Potentially clinically significant (PCS) hematology values were reported for 4 subjects (decreased lymphocytes [2 subjects], decreased hematocrit [2 subjects], and decreased hemoglobin [1 subject]). PCS chemistry values were reported for 5 subjects (increased blood urea nitrogen [BUN] [3 subjects] and increased gamma-glutamyl transferase [GGT] [2 subjects]).
- There were no clinically meaningful changes from Baseline in vital signs. The most frequently (> 10% overall) reported PCS vital signs were decreased orthostatic systolic blood pressure (SBP) (30.6%), decreased orthostatic diastolic blood pressure (DBP) (22.6%), decreased standing SBP (17.7%), increased weight (26.7%), and decreased weight (16.7%). Overall, a total of 6 subjects (9.7%) experienced an adverse event of orthostatic hypotension.
- No clinically meaningful changes were observed over time in ECG assessments. None of the abnormal ECG assessments were considered clinically significant by the investigator. PCS ECG values were reported for 2 subjects (decreased PR interval [1 subject] and increased PR interval [1 subject]).
- There were no clinically meaningful changes from Baseline in sleep attacks, or impulsive behavior as measured by the Minnesota Impulsive Disorders Interview (MIDI), or abnormal involuntary movement as measured by the Abnormal Involuntary Movement Scale (AIMS) total score. There were no cases of melanoma. Most neurological examination results were reported as normal.
- There were no reports of suicidal ideation or behavior during the study, as measured by the C-SSRS.

Overall, results from this study support the safety and tolerability of the LCIG System in advanced PD.

Conclusions:

In this study, LCIG treatment for 12 months provided a clinically meaningful improvement in subjects' "Off" time and "On" time without troublesome dyskinesia. Improvement in these efficacy measures that subjects in the Continuing LCIG group experienced in the previous study was maintained and further enhanced with long-term treatment in this study. Subjects in the LCIG Naïve group demonstrated a greater improvement in these efficacy measures after conversion to LCIG in this study. The improvements observed over time in this study occurred without exacerbating "On" time with troublesome dyskinesia. The benefit of the LCIG System also translated into improvement in the overall clinical status of these subjects with advanced PD. The safety profile of the LCIG System was similar to that observed in the previous study. Most subjects experienced at least 1 treatment-emergent adverse event during the study (59 of 62 subjects, 95.2%) and most adverse events were mild or moderate in severity. The adverse events reported were as expected for long-term use of the device and this advanced PD patient population treated with levodopa.

The key results from this study demonstrated the positive effects of the LCIG System:

- Efficacy with LCIG for the Continuing LCIG group and LCIG Naïve group was demonstrated by clinically meaningful decreases in "Off" time (–0.42 hours and –2.34 hours), and complementary increases in "On" time without troublesome dyskinesia (1.00 hour and 2.19 hours).
- Other efficacy assessments demonstrated clinically meaningful improvement in subjects' clinical status.
- Safety results were consistent with the safety profile of the LCIG System observed in Study S187-3-001/S187-3-002.
- No clinically meaningful differences in adverse events were observed between the Continuing LCIG group and LCIG Naïve group.
- The tolerability of the LCIG System was demonstrated by the low rate of premature discontinuations due to adverse events from this long-term study.

The LCIG System has the potential to address a significant unmet need in this patient population with limited therapeutic options. Data collected in this study provide support for the efficacy, safety, and tolerability of the LCIG System in the treatment of persistent motor fluctuations in subjects with advanced PD.

Date of Report: 15Aug2013