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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Application Number(s)	203952
Priority or Standard	Standard
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Division / Office	Division of Neurology Products (DNP) / ODE I
Reviewer Name(s)	Leonard P. Kapcala, M.D.
Review Completion Date	12/5/14
Established Name	Carbidopa and Levodopa Enteral Suspension (CLES)
(Proposed) Trade Name	Duopa
Therapeutic Class	Dopaminergic agonist
Applicant	Abbvie Pharmaceuticals
Formulation(s)	Suspension
Dosing Regimen	Daily intra-intestinal/enteral infusion of CLES over 16 hours while awake
Indication(s)	Treatment of Patients with Advanced Parkinson's disease
Intended Population(s)	Patients with advanced Parkinson's disease taking levodopa and with motor fluctuations

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1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of this NDA. Based upon my review of efficacy and safety, I conclude that carbidopa and levodopa enteral suspension (CLES); Duopa), a combination drug-device product is safe and effective for the indication of treatment of motor fluctuations in patients with advanced Parkinson's disease (PD). CLES is administered via a pump device and percutaneous endoscopic gastrostomy (PEG) via an intestinal/jejunal (J) tube over 16 hours. Initially, CLES is administered in the morning via a bolus infusion, followed by CLES infusion over the following 16 hours with possible extra doses of CLES administered throughout the day at intervals of 2 or more hours,

The sponsor conducted two randomized, double-blinded, active-controlled trials comparing CLES vs oral levodopa/carbidopa (LD/CD) using a double dummy design over 3 months (one month titration period and 2 month maintenance period) in patients with advanced PD who were not adequately controlled with oral LD/CD and other concomitant PD drugs. After seeking agreement from the DNP, the sponsor combined both essentially identical trials into a single trial and analyzed results for efficacy and safety. CLES produced a highly statistically significant (p=0.0015)) effect in the primary analysis of the primary efficacy endpoint, change from baseline in "off" time (normalized to 16 hours, the time during which CLES was infused on a daily basis) compared to the effect produced by oral LD/CD at the end of the trial. The CLES reduction in "off" was 4.04 hours and oral LD/CD reduction was 2.14 hours resulting in an CLES treatment difference reduction of 1.91 hours based upon the ANCOVA model. CLES also produced a highly statistically significant (p=0.0059) effect on a key secondary efficacy endpoint, change from baseline in normalized "on" time without troublesome dyskinesia compared to that produced by oral LD/CD at the end of the trial. The CLES increase in "on" time without troublesome dyskinesia was + 4.11 hours and oral LD/CD increase was + 2.24 hours resulting in an CLES treatment difference increase of 1.86 hours based upon the ANCOVA model. Thus, the efficacy and therapeutic benefit of CLES was demonstrated by showing it significantly decreased "off" time by about 1.9 hours and this reduction in "off" time was related to a complimentary increase in "on" time without troublesome dyskinesia of about 1.9 hours. The mean daily dose of CLES in the maintenance period ranged from 604 mg to 2935 mg and the mean and median daily dose of CLES was 1146 mg and 1022 mg, respectively. The overwhelming majority of patients treated in the controlled trial received a total daily dose of CLES of less than 2000 mg.

Safety was demonstrated from my review of numerous, various analyses of treatment-emergent adverse events (TEAEs), clinical laboratory analytes, orthostatic vital signs, and ECG parameters in the single controlled trial and also in pooled analyses of long-term, open-label trials. CLES caused many adverse reactions typical of the class of medications for PD including sleep attacks and somnolence, hallucinations/psychotic-like behavior, dyskinesia, impulse control disorders, hypotension/orthostatic hypotension as well as hypertension and increases and decreases in

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blood pressure and pulse in some patients. In addition, there were some other adverse reactions of concern that are not class adverse reactions. For example, there were many adverse reactions associated with the procedure/device (some of which were medically serious events such as intestinal obstruction or perforation, peritonitis, sepsis, bleeding, peri-stomal infection/inflammation, etc., and had the potential for a fatal outcome), abdominal pain, and several cases of polyneuropathy. The adverse reactions associated with the procedure/device were not judged to be unique to CLES but were considered to be similar to those associated with chronic PEGs for other reasons/indications. Although the etiology of polyneuropathy occurring during long-term, open label treatment was not clear, it is possible that polyneuropathy was due to levodopa/carbidopa, hydrazine (resulting from carbidopa), and/or various vitamin deficiencies or combinations of these factors. There was an increased risk of depression in the controlled trial with CLES and the incidence of depression was 12 % in the long-term open-label trials and dose-dependent. There were also two suicides and two suicide attempts in the long-term, open-label treatment, but there was no testing assessing the risk of suicidality in the clinical development program and it was not clear whether there was an increased risk for suicidality from CLES treatment. Finally, there was an increased CLES treatment difference incidence in the controlled trial for outliers for various blood pressure and pulse increases and decreases, and for noteworthy laboratory outliers such as increased serum BUN and creatinine phosphokinase (CPK). This outlier risk for BUN and for CPK]and was further increased in elderly patients (≥ 65 years) vs non-elderly patients. Finally, concerns were expressed by the Pharmacology/Toxicology Team regarding its inability to qualify levels of CLES degradant impurities (i.e., hydrazine, (b) (4) (b) (4) and that are mutagenic and carcinogenic. The greatest concern for carcinogenicity was related to hydrazine. However, the clinical importance of these theoretical risks related to these degradants are not known and the Agency consensus is that the potential benefit of this product warrants its approval despite these uncharacterized/unknown risks regarding these degradants. In addition, my review of the Safety Update 2 (consisting of ~ 159 patient-years of additional CLES treatment; 20 % increase in exposure relative to ISS and Safety Update 1 exposures) included in this Complete Response submission did not change the safety profile of Duopa characterized in my initial safety review based upon the review of the ISS and Safety Update 1. As a result of all of my safety reviews, I conclude that these results show that the CLES product is reasonably safe and that these various safety results/findings should be described in the package insert/label.

As a result of my review of efficacy and safety of CLES, I do not have any clinical concerns precluding approval at this time.

In this Complete Response, the sponsor has addressed various issues of concern (e.g., deficiencies) that had been outlined previously by other disciplines (e.g., CMC, DMEPA, Human Factors, CDRH regarding the device) in the Complete Response letter issued on 3/28/14. The consensus of all of the review teams from various disciplines is that the sponsor has adequately addressed all issues of concern/deficiencies outlined in the Complete Response letter. Thus, this NDA appears to be ready to be approved.

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1.2 Risk Benefit Assessment

I have outlined the various safety risks in my summary of safety for CLES. The most important risks associated with CLES treatment are adverse reactions of procedure/device insertion complications, polyneuropathy, hallucinations/psychotic behavior, dyskinesia, depression, and impulse disorder, as well as significant blood pressure changes (decreases and increases), and laboratory evidence of decrease in renal function (e.g., increased BUN outliers) and increase in CPK. There was no clear evidence of risk for rhabdomyolysis. With the exception of procedure/device insertion complications that are unique to CLES treatment (and do not occur with oral medications), these other risks outlined are not clearly different than those for oral levodopa and other various medications (e.g., dopaminergic agonists, COMT inhibitors, MAO-B inhibitors) for PD. It is most relevant to note for this product that the complications of procedure/device insertion from the PEG and J-tube associated with CLES do not appear to be unique to CLES. In addition, the clinical significance of the genotoxic and carcinogenic potential of degradant impurities (hydrazine, (b) (4), and (b) (4)) is unknown in humans. One approach toward possibly limiting this undefined human risk is by limiting the total amount of recommended use of CLES to 2000 mg daily.

In assessing the risk benefit of CLES treatment, it is also important to recognize that the therapeutic benefit of CLES was demonstrated versus an active control, oral LD/CD, in contrast to other drugs that had been evaluated relative to placebo. If the evaluation of CLES efficacy was conducted in a simple design comparing CLES infusion to that of placebo infusion (instead of a double-dummy design comparing it to oral LD/CD, active control), it is likely that the therapeutic benefit of CLES (for decreasing “off” time and increasing “on” time without troublesome dyskinesia) would have been substantially larger, perhaps 3 to 4 hours superior to placebo. Such a huge benefit would be notably larger than that obtained from treatment with any other approved PD drugs evaluated relative placebo.

In view of these considerations outlined above (e.g., magnitude of the treatment effect, it seems that the potential for obtaining this substantial therapeutic effect seen with CLES in this population is worth accepting the various risks that have been outlined. Mean ”off” time was about 7 hours (absolute value) at baseline in patients enrolled in the CLES controlled trial. Patients in controlled trials of other drugs approved for treating advanced PD enrolled patients had less mean “off ” time (e.g., ranging from approximately 5.5 to 6.5 hours) at baseline. It appears that PD patients in the CLES controlled trial had a more advanced stage of disease and may have been more functionally impaired than most patients enrolled in other trials for other drugs approved for advanced stage PD by the DNP. With the exception of the potential risks for procedure/device complications that are unique to CLES (vs other PD drugs), CLES risks for most other adverse reactions appear to be relatively similar to those for other PD drugs. The risk of procedure/device complications associated with CLES is similar to the risk reported in patients who have PEG tubes inserted for other reasons and that the most serious complications are relatively uncommon. The risks associated with CLES treatment seem justified by the potential for a relatively larger therapeutic benefit in a population that may be difficult to treat with other available PD drugs.

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Deep brain stimulation (DBS) is also a potential therapeutic option for patients with advanced PD who are difficult to manage medically. In fact, a screening tool used to characterize whether patients are a legitimate candidate for DBS was initially applied for enrolling patients in the controlled CLES trial. Although patients receiving DBS, may experience significant therapeutic benefit, this benefit is typically limited in duration and patients eventually need to be managed medically. Some risks of DBS are unique to this option and include brain damage with insertion of the DBS device, bleeding and infection. DBS also has the potential for various neuropsychiatric adverse reactions including apathy, hallucinations, compulsive gambling, hypersexuality, cognitive dysfunction, and depression. In comparison, the overall risks of CLES may not necessarily be substantially greater than those of DBS but CLES treatment may have the potential for a longer duration therapeutic benefit (than DBS) and this therapeutic benefit might also be of indefinite duration.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarketing Requirements and Commitments

None

2. Introduction and Regulatory Background

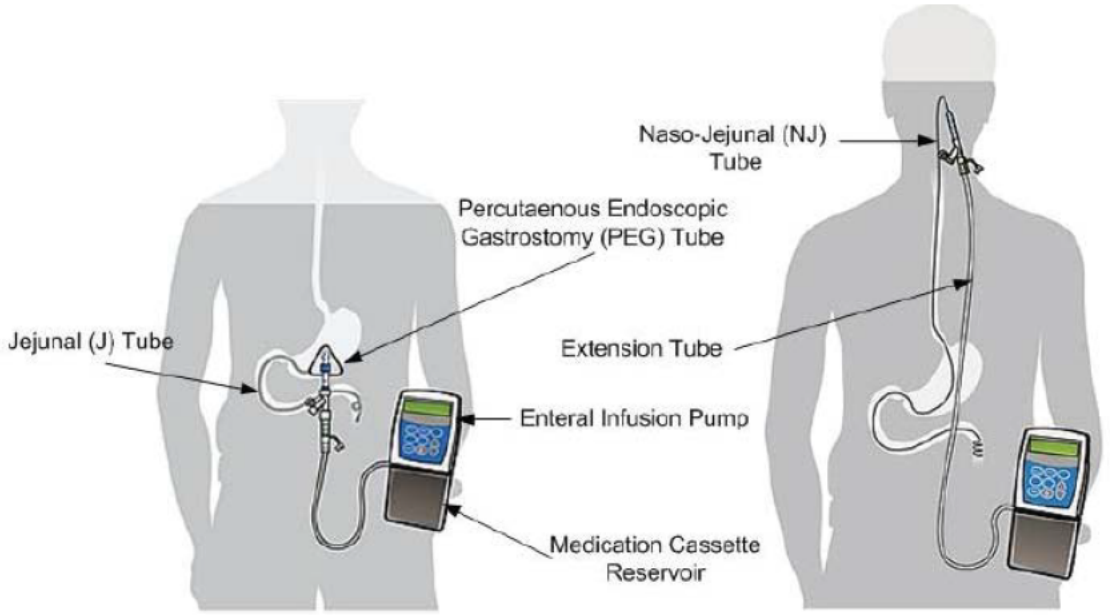
Refer to my original clinical review (3/13/14) for this NDA regarding more detailed and extensive Introductory Information and Regulatory Background.

2.1 Product Information

Product Development Rationale

The carbidopa and levodopa enteral suspension CLES) System is intended for the long-term treatment of motor fluctuations in patients with advanced (b) (4) PD (PD) (b) (4) (b) (4). The System is a combination product comprising the CLES drug product, packaged in a medication cassette reservoir, and the delivery system, a software-driven, ambulatory CADD-Legacy® 1400 infusion pump with accessories and a variety of PEG-J and naso-jejunal tubing products. The CLES drug product is continuously delivered from the medication cassette reservoir via the infusion pump into the patient's proximal small intestine through a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) (Figure 1).

Figure 1 Overview of CLES System



The CLES drug product is a suspension of levodopa (LD = (2S)-2-amino-3-(3,4-dihydroxyphenyl) propanoic acid) and carbidopa (CD = (2S)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid, monohydrate) in an aqueous carmellose sodium (b) (4) [redacted]. In CLES, the concentration of levodopa is 20 mg/mL and carbidopa monohydrate is 5 mg/mL. The therapeutic component of CLES is levodopa, which is a biological precursor of dopamine. Dopamine is a catecholamine neurotransmitter that plays a key role in control of motor function. Carbidopa is a competitive inhibitor of the aromatic amino acid decarboxylase enzyme (AAAD). When co-administered with levodopa, carbidopa reduces peripheral decarboxylation of levodopa. Carbidopa monohydrate contains a hydrazino functional group, which is the most reactive portion of the carbidopa molecule and is the functional group necessary for the compound's inhibitory action on AAAD.

2.2 Summary of Most Recent Regulatory Activity Related to Submission

On November 16, 2012, the Sponsor submitted NDA 203952 for Duopa (CLES) for (b) (4) treatment of advanced PD in patients with motor fluctuations (b) (4) [redacted] On January 15, 2013 the Agency issued a Refuse to File (RTF) letter to the sponsor because of various problems/deficiencies in the format and content of the submission.

On March 14, 2013, a Type A meeting between sponsor and Agency (DNP) was held to discuss addressing problems/deficiencies outlined in the RTF letter. On May 28, 2013, the Sponsor

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resubmitted NDA 203952 as a 505(b)(2) application. The application referenced the Agency's previous findings of safety and efficacy for the reference listed drug, Sinemet® (NDA 017555).

On March 28, 2014, the Agency issued a Complete Response letter to the sponsor outlining problems/issues that needed to be address regarding CMC, the device, and Human Factors. To plan addressing the issues outlined in the Complete Response letter, the sponsor met with the Agency on June 10, 2014. On July 11, 2014, the sponsor submitted a Complete Response (Class 2 ReSubmission) to address the issues outlined in the Complete Response letter.

2.3 Summary of Sponsor's Clinical Development Programs for CLES (Duopa)

US Clinical Development Program

The US clinical development program includes a series of studies that evaluated the safety, efficacy, and pharmacokinetics of the CLES System in the indicated population.

The original program included two Phase 3 pivotal studies of identical design that recruited patients from distinct study sites : Study S187-3-001 and Study S187-3-002 (Randomized, double-blind, double-dummy, multicenter, parallel group studies conducted in the US, Germany, and New Zealand 12-week duration). Study S187-3-001 and Study S187-3-002 were combined as 1 pivotal after obtaining agreement from the Agency because of the sponsor's concerns in the length of time to complete both trials, Study S187-3-001/S187-3-002 prior to database lock, as agreed with the Agency on 18 January 2011. The US clinical development program includes 3 long-term, open-label, single arm, multicenter, Phase 3 trials: Study S187-3-003 (12 months), Study S187-3-004 (CLES initial infusion in 2 to 14 day naso-jejunal (NJ) test period followed by a PEG-J 52-week period), and Study S187-3-005 (for continuation treatment for subjects in Study S187-3-003 and Study S187-3-004 until CLES is commercially available in participating countries). In addition, US clinical development program includes a Phase 1 pharmacokinetic trial.

Development of the CLES System Outside of the US

The CLES System is currently approved outside the US in 41 countries and marketed in many countries under the trade name Duodopa®. The first marketing authorization for CLES in the European Economic Area (EEA) was received in Sweden on 21 January 2004. CLES has been approved in 27 countries in the European Union (EU) and 3 additional countries of the EEA. In addition, 11 national approvals have been granted in the following countries: Albania, Australia, Bosnia and Herzegovina, Canada, Croatia, Israel, Macedonia, Switzerland, Thailand, Turkey, and the Ukraine. The world-wide cumulative exposure to CLES from market introduction 21 January 2004 through 31 March 2014 is estimated to be (b) (4) patient-years (PY).

Six non-IND, Phase 4 postmarketing observational registries or health economics and outcomes research studies (Studies S187-4-001 DAPHNE, S187-4-002, S187-4-004 GLORIA, S187-4-

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005, S187-4-006 RELEVANT, and S187-4-007) have been conducted or are ongoing ex-US to evaluate the long-term safety, effectiveness, and health economic data for subjects treated with CLES. In these studies, (b) (4) subjects have been or are planned to be treated with CLES for durations from 6 months up to a maximum of 16 years. A Phase 2 study conducted in Japan evaluating CLES treatment administered by NJ to subjects with advanced PD has recently concluded. Eight subjects were planned for the study, 6 subjects were treated with CLES, and 5 subjects completed the study. As agreed with the Agency at the Pre-NDA meeting on 07 August 2012, because of the nature of these studies and registries, results from these other studies were not planned to be integrated into the ISS.

3. SAFETY UPDATE 2 (SU-2)

Summary of Clinical Safety

On 28 May 2013, AbbVie submitted a New Drug Application (NDA 203952) for the CLES system in the treatment of motor fluctuations in levodopa-responsive patients with advanced (b) (4) PD (PD) (b) (4) AbbVie submitted the Four-Month Safety Update (Safety Update 1, SU-1) to the Integrated Summary of Safety (ISS) on 20 September 2013 AbbVie has prepared this second Safety Update (SU-2) following receipt of the complete response letter from the Food and Drug Administration (FDA) on 28 March 2014. This SU-2 includes safety information for the patients who continued CLES treatment under open-label conditions subsequent to the data cutoff for the SU-1. The data cutoff dates for the NDA and both safety updates are shown in Table 1. The results presented in this SU-2 are cumulative through these data cutoff dates, unless otherwise noted.

Table 1 Data Cutoff Dates for NDA and Safety Updates

	Data Cutoff Date		
Data Source	**NDA**	**Safety Update 1**	**Safety Update 2**
Ongoing IND Studies	04 May 2012	31 May 2013	31 March 2014
Non-IND Studies			
Pan-Asia Studies	N/A	N/A	31 March 2014
Ex-US Registry Study	30 September 2011	21 January 2013	02 January 2014
Postmarketing Experience	31 May 2012	31 May 2013	31 March 2014

At the time of the data cutoff dates for the SU-1, 2 Investigational New Drug (IND) studies and 1 non-IND study were ongoing. Two additional non-IND studies have started enrollment since the SU-1. In the integrated analysis sets for the United States (US) registration program, no new subjects have been exposed to LCIG, but 203 subjects who were already treated with LCIG have had additional exposure time in ongoing Study S187-3-005. The data updates in this SU-2 are

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derived from the following studies that were either ongoing or commenced since the SU-1 data cutoff date.

At the time of the data cutoff dates for the NDA re-submission, 2 Investigational New Drug (IND) studies and 3 non-IND studies were ongoing, as listed below. No new subjects were exposed to CLES in the ongoing IND studies since the ISS and SU-1, but 203 subjects who were already treated with CLES in the Phase 3 studies had additional exposure time. The additional exposure that contributes to this Safety Update is derived from the following studies that were ongoing at the time of the NDA data cutoff date :

IND Study S187-3-005 (ongoing as of SU-1: open-label extension of Study S187-3-003 and of open-label safety Study S187-3-004 in countries where CLES is not commercially available; 203 subjects were reported as ongoing as of the 31 May 2013 data cutoff for the SU-1. It is intended that this study will continue to follow subjects already enrolled for the foreseeable future or until CLES is marketed in the countries where it is not commercially available for these subjects. No new subjects are intended for enrollment.

IND Study M12-920 (enrollment started but no data available as of the SU-1): Open-label Phase 3b multicenter study in the US to assess the safety and efficacy of LCIG for treatment of non-motor symptoms in subjects advanced PD. Four subjects were enrolled as of the 31 May 2013 data cutoff for the SU-1, but no data were available. Seventeen subjects were enrolled as of the 31 March 2014 data cutoff for this SU-2, and data from all 17 subjects are included in this SU-2.

Non-IND Study S187-4-004 GLORIA (ongoing as of SU-1): Retrospective and prospective registry postmarketing observational study of CLES that follows subjects with advanced PD for 24 months; 243 subjects were enrolled as of the 21 January 2013 data cutoff for SU-1, and 132 additional subjects were enrolled since the SU-1. Enrollment is completed (N = 375) and the anticipated study completion is June 2015.

Non-IND Study M12-921 (started enrollment after SU-1): Open-label, multicenter study in pan-Asia to assess the safety of ABT-SLV187 Monotherapy in subjects with advanced PDs and persistent motor-complications despite optimized treatment with available anti-parkinsonian medication. Six subjects were enrolled as of the 31 March 2014 data cutoff for this SU-2, and data from all 6 subjects are included in this SU-2.

Non-IND Study M12-923 (started enrollment after SU-1): Open-label extension of Studies M12-921 and M12-925. Only 1 subject was enrolled as of the 31 March 2014 data cutoff for this SU-2, and data from this subject is included in this SU-2.

The Sponsor concludes that the data presented in this Safety Update continue to support the conclusions in the submitted NDA that the CLES System can be used in a safe and tolerable manner in the treatment of motor fluctuations in levodopa-responsive patients with advanced (b) (4) PD. No new clinically important or unexpected findings were observed that would affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling or Medication Guide.

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Carbidopa and Levodopa Enteral Suspension System

As described in the ISS, the CLES System was developed to provide symptomatic therapy by continuously delivering the drug product to the proximal small intestine (jejunum) using a portable infusion pump to deliver the gel via a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J, Figure 1). The delivery of CLES directly to the jejunum results in less variability in levodopa and carbidopa plasma concentrations compared to oral dosing and is believed to provide a continuous rather than intermittent stimulation of the dopaminergic receptors in the brain.

The CLES System is intended to address an important unmet medical need for the long-term treatment of motor fluctuations in levodopa-responsive patients with advanced (b) (4) PD (b) (4)

Registration of the CLES System Outside the United States

As reported in the ISS, the CLES System is currently approved in 41 countries. No additional approvals have occurred since the NDA submission. In many countries, it is marketed under the trade name Duodopa®. The first marketing authorization for Duodopa in the European Economic Area (EEA) was received in Sweden on 21 January 2004.CLES has been approved in 27 countries in the European Union (EU) and 3 additional countries in the EEA. Eleven national approvals have been granted in the following countries: Albania, Australia, Bosnia and Herzegovina, Canada, Croatia, Israel, Macedonia, Switzerland, Thailand, Turkey, and Ukraine.

The United States Clinical Development Program

As described in the ISS, the United States (US) registration program for the CLES System consists of a single pivotal study (Study S187-3-001/S187-3-002), an extension Study S187-3-003 (of Study S187-3-001/S187-3-002), an open-label safety Study S187-3-004, an extension Study S187-3-005 (of Study S187-3-003 and Study S187-3-004), and clinical pharmacokinetic Study S187-1-002.

Studies S187-3-003 and S187-3-005 from the US development program contributed additional data for the purposes of this Safety Update to the ISS and SU-1.

Table 2 summarizes clinical studies contributing to the ISS and Safety Updates (SU-1 and SU-2).

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Table 2 Summary of CLES Clinical Studies Included in the Integrated Summary of Safety and/or Safety Updates

Study	Location	Study Type	Number of Subjects	Data Cutoff for the SU-2	Status[a]	How Included in Safety Update
US IND Studies						
S187-1-002[b]	Ex-US	Phase 1 Pharmacokinetic and Safety	19	N/A	Completed	N/A[c]
S187-3-001/ S187-3-002 (combined)	US + Ex-US	Pivotal Phase 3	71	N/A	Completed	Integrated[c]
S187-3-003	US + Ex-US	Extension of Pivotal Study	62	N/A	Completed	Integrated[d]
S187-3-004	US + Ex-US	Open-Label Safety	354	N/A	Completed	Integrated[c]
S187-3-005	US + Ex-US	Extension of Studies S187-3-003 and S187-3-004	262[e]	31 March 2014	Ongoing	Integrated[e]
M12-920	US	Open-Label Safety and Efficacy	17 (36 planned)	31 March 2014	Ongoing	Summarized by Study
Non-IND Studies						
S187-4-001 DAPHNE	Ex-US	HEOR	76	N/A	Completed	N/A[f]
S187-4-002	Ex-US	Registry	100	N/A	Completed	N/A[f]
S187-4-004 GLORIA	Ex-US	Registry	375	02 January 2014	Ongoing	Summarized by Study
S187-4-005	Ex-US	Retrospective	41	N/A	Completed	N/A[f]
S187-4-006 RELEVANT	Ex-US	Registry	541	N/A	Completed	N/A[f]
S187-4-007	Ex-US	Retrospective	135	N/A	Completed	N/A[f]
M12-925	Japan	Open-Label Safety	8	N/A	Completed	N/A[f]
M12-921	Pan-Asia	Open-Label Safety and Efficacy	6 (32 planned)	31 March 2014	Ongoing	Summarized by Study
M12-923	Pan-Asia	Open-Label Safety and Efficacy Extension of Studies M12-921 and M12-925	1 (37 planned)	31 March 2014	Ongoing	Summarized by Study

HEOR = Health Economics Outcome Research; N/A = not applicable; SU-1 = Safety Update 1, SU-2 = Safety Update 2
a. Status of study as of the Safety Update submission.
b. Study S187-1-002 was not conducted under the US IND. The clinical study report was submitted to the Agency 11 November 2011.
c. No new data since the ISS; data are included in the SU-2 cumulative summary.
d. No new data since the SU-1; data are included in the SU-2 cumulative summary.
e. 262 subjects were enrolled per the SU-1; no new subjects enrolled since the SU-1.
f. No new data since the ISS; data were summarized in the ISS.

Overall Summary of Safety

CLES is considered a therapeutic system consisting of the drug, the devices, and the placement procedure for the PEG-J tubing. The analysis sets used in the this Safety Update were designed to systematically evaluate the safety of the treatment system and are consistent with those used in the ISS and SU-1 of the NDA . No new subjects have been added to the Phase 3 datasets since the 04 May 2012 data cutoff date submitted with the NDA on 28 May 2013. All new Phase 3 data in this Safety Update are from additional exposure for 203 subjects who were ongoing as of the SU-1 data cutoff data and contributed additional exposure data to the Open-Label CLES Analysis Set (i.e., Open-Label Levodopa Carbidopa Intestinal Gel-LCIG), the PEG-J Analysis Set, and the All CLES Analysis Set (i.e., All LCIG) (Table 3).

Table 3 Analysis Sets in the ISS and Safety Updates (SU-1 and SU-2)

Analysis Set	Number of Subjects with New Data Since the SU-1[a]	Purpose of Analysis Set
Active-Controlled (N = 71)	0	The safety of LCIG compared with the same active components in the standard oral formulation of levodopa-carbidopa over a 3-month period
Open-Label LCIG (N = 412)	203	The long-term safety associated with open-label LCIG use
All PEG-J (N = 395)	203	The adverse events (AEs) related to PEG-J placement and long-term use of a PEG-J in this advanced PD population that would not necessarily otherwise use this device
3004 (N = 354)	0	The safety associated with nasojejunal (NJ) tube placement
All LCIG (N = 416)	203	The safety of LCIG exposure in blinded or open-label studies, regardless of the LCIG delivery method

ISS = Integrated Summary of Safety; LCIG = levodopa-carbidopa intestinal gel; SU-1 = Safety Update 1; SU-2 = Safety Update 2

a. The new data added to each analysis set since the SU-1 data cutoff date (31 May 2013) from 203 subjects enrolled in IND studies that were ongoing as of the SU-1 cutoff date. These 203 subjects were previously included in the analysis sets, and no new subjects were added to the analysis sets. The data cutoff date for this SU-2 is 31 March 2014.

The safety data in the US registration program are derived from 416 subjects who received CLES. Of these subjects, 212 (51.0%) received CLES for 30 months or longer, compared with 153 subjects (36.8%) who received CLES for at least 30 months in the SU-1.

This Safety Update (SU-2) includes 158.9 additional patient years (PY) of CLES exposure since the ISS and SU-1, resulting in a total of 971.6 PY. Overall, the data presented in this Safety Update support the conclusions in the ISS submitted with the NDA (28 May 2013) and with SU-1 that the CLES System has an acceptable safety and tolerability profile for long-term

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treatment of motor fluctuations in levodopa-responsive patients with advanced (b) (4) PD. **No new clinically important or unexpected findings were observed.**

The SU-2 findings are summarized below for the Open-Label CLES and All PEG-J Analysis Sets. Consistent with the methodology applied in the ISS and SU-1, in order to evaluate and distinguish the incidence of treatment-emergent adverse events (TEAEs) more likely to be related to levodopa carbidopa, route of administration, or underlying PD versus the PEG-J placement procedure and long-term use of PEG-J, all TEAEs with preferred terms (PTs) captured by a "procedure- and device-associated events (CLES specific)" company Medical Dictionary for Regulatory Activities (MedDRA) query (CMQ) were excluded from some TEAE evaluations in the Open-Label CLES Analysis Set. TEAEs that fall within this CMQ, referred to as "procedure- and device-associated AEs of special interest (AESIs)," are summarized separately for the All PEG-J Analysis Set. The cumulative TEAE rates were similar to those reported in the SU-1, even though this Safety Update includes an additional year of data collection with approximately 159 additional patient-years of treatment exposure.

Open-Label CLES Analysis Set

TEAEs, including procedure- and device-associated AESIs, were reported for 93.9 % of subjects, compared with 93.0% of subjects in the SU-1. The cumulative rates of the most common TEAEs (≥ 20% of subjects) were similar to those reported in the SU-1, listed in decreasing order as follows: complication of device insertion, abdominal pain, postoperative wound infection, insomnia, fall, procedural pain, excessive granulation tissue, nausea, constipation, and incision site erythema. Treatment-emergent serious adverse events (TESAEs) were reported for 47.1% of subjects compared with 41.5% of subject in the SU-1. The cumulative rates of the most common SAEs (≥ 2% of subjects) were similar to those reported in the SU-1, listed in decreasing order as follows: complication of device insertion, abdominal pain, peritonitis, pneumonia, PD, weight decreased, fall, hip fracture, polyneuropathy, and device dislocation.

TEAEs, excluding procedure- and device-associated AESIs, were reported for 92.0% of subjects, compared with 90.5% of subjects in the SU-1. The cumulative rates of the most common AEs (≥ 10% of subjects) were similar to those reported in the SU-1, listed in decreasing order as follows: insomnia, fall, nausea, constipation, urinary tract infection, vitamin B_6 decreased, anxiety, dyskinesia, PD, weight decreased, blood homocysteine increased, depression, back pain, orthostatic hypotension, vomiting, diarrhea, and headache. Consistent with the SU-1, the highest incidence of most TEAEs occurred early during treatment, within the first 3 months. TEAEs observed at higher rates after the first 3 months of treatment were urinary tract infection, vitamin B_6 decreased, blood homocysteine increased, polyneuropathy, vitamin B_6 deficiency, and back pain, which is also consistent with the findings in the ISS and SU-1.

Overall, the types of TESAEs that were not procedure- and device-associated AESIs continued to be consistent with the recognized safety profile of levodopa and/or events that may be observed with the underlying disease. TESAEs, excluding procedure- and device-associated AESIs, were reported in 41.5% (171/412) of subjects, including deaths (compared with 35.7% of

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subjects in the SU-1). The most common TESAEs that the investigator classified as treatment-related were the same as those reported in the SU-1 with the addition of hallucination : PD, polyneuropathy, weight decreased, and hallucination.

Deaths were reported for 7 additional subjects in SU-2 subsequent to the SU-1, resulting in a new total of 34 deaths(8.3 %) due to TEAEs (compared with 17 deaths in the ISS and 10 deaths in the SU-1 comprising a total of 27 deaths). The fatal events were considered unrelated or unlikely related to the treatment system by the investigator for each of the 7 additional deaths. Overall, deaths were of varied causes and were generally consistent with what would be expected in an elderly population with chronic disease.

Discontinuations due to TEAEs (including procedure- and device-associated AESIs) were reported for an additional 14 subjects since the SU-1 (including 7 deaths), resulting in a total of 72 (17.5 %) discontinuations due to TEAEs (compared with 14.1% in the SU-1). Of the 14 discontinuation, the events for 2 subjects were considered probably related to the treatment system (dystonia and cellulitis), the event for 1 subject (suicidal ideation) was considered possibly related to the treatment system, and the remaining discontinuations were considered unlikely or not related to the treatment system. Reasons for discontinuation continued to be of a similar nature to those identified in the SU-1, with no unusual patterns observed with extended exposure.

High Dose versus Low Dose CLES

TEAEs reported in ≥ 10% of subjects in the high dose group (≥ 1250 mg/day) with a rate of at least twice that of the low dose group (< 1250 mg/day) were anxiety, weight decreased, and sleep attack.

When the high dose group was further categorized by subjects taking < 2000 mg/day versus ≥ 2000 mg/day, additional PTs that were reported in ≥ 10% of subjects taking ≥ 2000 mg/day with a rate of at least twice that of the low dose group were vomiting, arthralgia, hallucination, decreased appetite, musculoskeletal pain, polyneuropathy, vitamin B_6 deficiency, pain in extremity, fatigue, anemia, laceration, blood homocysteine increased, PD, and dizziness. Many of these events are commonly associated with levodopa treatment, and are generally accepted as having a dose-effect relationship. Disease severity, treatment history and disease progression all contribute to the dose of levodopa required to control symptoms in this advanced PD population. Subjects taking higher doses of CLES may have had more severe underlying PD as their mean oral levodopa dosage required to manage PD symptoms prior to study participation was approximately 50% greater than that of subjects in the low dose group. Subjects in the high dose group also had more polyneuropathy in their medical histories.

<u>All PEG-J Analysis Set</u>

The majority of subjects experienced procedure- and device associated AESIs (75.9% versus 75.2% in the SU-1). As detailed in the ISS, the highest incidence of procedure- and device-associated AESIs occurred during the Titration Period, and this has remained unchanged in this

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SU-2, as the Titration Period was completed for all subjects as of the ISS data cutoff date. The events were generally recognized complications related to the placement of the PEG-J system, and were generally mild or moderate in severity.

In this SU-2, the cumulative rates of the most common procedure and device associated AESIs (≥ 10% of subjects) during the Maintenance Period, were similar to the percentages reported in the SU-1, and are listed in decreasing order as follows: excessive granulation tissue, postoperative wound infection, incision site erythema, procedural site reaction, abdominal pain, complication of device insertion, and post-procedural discharge. The most common events classified as severe events (≥ 1% of subjects) during the Maintenance Period were complication of device insertion, abdominal pain, and device dislocation, and the incidence and prevalence over time continued to remain relatively stable, as observed in the SU-1. The nature of the TEAEs remained consistent with those reported in the SU-1, with no new events identified that could be attributed to long term use of the PEG-J.

Overall, for this SU-2, the types of procedure- and device-related AESIs that were serious and the timing of the TESAEs continue to be reflective of medically recognized risks of the PEG-J procedure, including abdominal pain, pneumoperitoneum, peritonitis, and small intestinal hemorrhage. Six additional subjects had serious procedure- and device-related AESIs since the SU-1, resulting in a cumulative total of 17.2% of subjects with TESAEs (compared with 15.7% in the SU-1). TESAEs involving intestinal perforation and hemorrhage continued to be infrequent (≤ 1.5%) during the clinical studies.

The cumulative rates of the most common serious procedure- and device-associated AESIs (≥ 1.0% of subjects) during the Maintenance Period were similar to those reported in the SU-1 (≤ 1% difference), and are listed in decreasing order as follows: complication of device insertion, abdominal pain, device dislocation, postoperative wound infection, small intestinal obstruction, and device occlusion.

Consistent with the SU-1, the majority of subjects (65/68) with serious procedure- and device-associated AESIs recovered and the events resolved without sequelae.

Postmarketing Experience

The safety profile of the CLES System in the US registration clinical program is similar to that observed in ex-US postmarketing safety data (estimated (b) (4) patient treatment years [PTY] with Duodopa worldwide from 21 January 2004 through 31 March 2014). In addition, procedure- and device-associated AEs in the clinical development program were similar to those reported in the literature for comparable devices.

Sponsor’s Summary Interpretation of SU2

The Sponsor maintains the conclusion that the benefits of the CLES System outweigh the associated risks in the indicated patient population that has very limited treatment options. The

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information contained within this SU-2 does not change AbbVie's previous interpretation of the safety profile for CLES.

Reviewer's Presentation of Specific Information from SU-2

Table 4 shows summary information about new deaths described in this SU-2.

Table 4 New Deaths Reported in Safety Update 2 (SU-2)

Subject	Sex/ Age	LCIG Daily Dose (mg)	Investigator Term (Preferred Term)	Onset – End Day[a]	Relationship to Treatment System[b]
New Deaths Reported Since the SU-1: Study S187-3-005					
107-111	M/66	< 1250	Falling related to PD (fall)	735 – 822	Unrelated
			Subdural hematoma (subdural haematoma)	738 – 822	Unrelated
			Seizures (convulsion)	738 – 822	Unrelated
			Note: Relevant history of cardiac disorder, coronary artery bypass, and stent placement.		
127-102	M/83	< 1250	Respiratory failure (respiratory failure)	1107 – 1107	Unrelated
			Note: Relevant history of multiple vessel angioplasty with stent on left anterior descending coronary artery and left carotid endarterectomy.		
391-006	M/62	< 1250	Acute heart failure (cardiac failure acute)	1466 – 1466	Unlikely
			Note: Relevant history of hypertension, aortic arteriosclerosis, coronary artery arteriosclerosis, myocardial infarction and cardiac chest pain.		
392-009	F/62	< 1250	Cerebral ischemia [other specified disorders of brain vessels] (cerebral ischaemia)	1453 – 1453	Unrelated
			Note: Relevant history of hypertension.		
392-014	M/60	≥ 1250 – 2000	Death – cause unknown (death)	1163 – 1163	Unlikely
396-006	F/70	< 1250	The rupture of cerebral aneurysm (ruptured cerebral aneurysm)	925 – 927	Unrelated
			Note: Relevant history of hypertension.		
502-001	F/67	< 1250	Complications related to Parkinson's disease (confirmed no more detail) (Parkinson's disease)	771 – 771	Unlikely
			Note: Relevant history of advanced Parkinson's disease, asthma, and diabetes.		

Reviewer Comment

- None of these newly reported deaths raised any significant concerns about the safety profile of Duopa.

Table 5 presents information about treatment-emergent serious adverse events (TESAEs) that occurred in at least 1 % of patients during open-label treatment according to low or high dose

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CLES, according to time perspective (i.e., any time, developing in the titration or maintenance periods, and when "persistent"), and according to SU-1 or SU-2.

Table 5 TESAEs ≥ 1% of Subjects Overall by Treatment Period and Dose Group (Open-Label CLES Analysis Set)

	Number (%) of Subjects								
	Titration Period		Maintenance Period[a]		Persistent AEs		Onset Since SU-1[b]	Any Time	
Preferred Term	SU-1 N = 412	SU-2 N = 412	SU-1 N = 378	SU-2 N = 378	SU-1 N = 412	SU-2 N = 412	N = 203	SU-1 N = 412	SU-2 N = 412
N for each dose group									
Low dose: < 1250 mg	155	155	131	131	155	155	78	155	155
High dose: ≥ 1250 mg	257	257	247	247	257	257	125	257	257
Any preferred term	48 (11.7)	48 (11.7)	134 (35.4)	173 (45.8)	20 (4.9)	20 (4.9)	43 (21.2)	171 (41.5)	194 (47.1)
Low dose: < 1250 mg	14 (9.0)	14 (9.0)	42 (32.1)	53 (40.5)	7 (4.5)	7 (4.5)	17 (21.8)	49 (31.6)	60 (38.7)
High dose: ≥ 1250 mg	34 (13.2)	34 (13.2)	106 (42.9)	120 (48.6)	13 (5.1)	13 (5.1)	26 (20.8)	122 (47.5)	134 (52.1)
Complication of device insertion	17 (4.1)	17 (4.1)	14 (3.7)	16 (4.2)	4 (1.0)	4 (1.0)	2 (1.0)	30 (7.3)	32 (7.8)
Low dose: < 1250 mg	5 (3.2)	5 (3.2)	5 (3.8)	5 (3.8)	2 (1.3)	2 (1.3)	0	10 (6.5)	10 (6.5)
High dose: ≥ 1250 mg	12 (4.7)	12 (4.7)	9 (3.6)	11 (4.5)	2 (0.8)	2 (0.8)	2 (1.6)	20 (7.8)	22 (8.6)
Pneumonia	3 (0.7)	3 (0.7)	15 (4.0)	17 (4.5)	1 (0.2)	1 (0.2)	2 (1.0)	18 (4.4)	20 (4.9)
Low dose: < 1250 mg	1 (0.6)	1 (0.6)	5 (3.8)	6 (4.6)	1 (0.6)	1 (0.6)	1 (1.3)	6 (3.9)	7 (4.5)
High dose: ≥ 1250 mg	2 (0.8)	2 (0.8)	10 (4.0)	11 (4.5)	0	0	1 (0.8)	12 (4.7)	13 (5.1)
Abdominal pain	8 (1.9)	8 (1.9)	8 (2.1)	9 (2.4)	0	0	1 (0.5)	16 (3.9)	17 (4.1)
Low dose: < 1250 mg	2 (1.3)	2 (1.3)	3 (2.3)	3 (2.3)	0	0	0	5 (3.2)	5 (3.2)
High dose: ≥ 1250 mg	6 (2.3)	6 (2.3)	5 (2.0)	6 (2.4)	0	0	1 (0.8)	11 (4.3)	12 (4.7)
Parkinson's disease	1 (0.2)	1 (0.2)	9 (2.4)	9 (2.4)	1 (0.2)	1 (0.2)	1 (0.5)	10 (2.4)	10 (2.4)
Low dose: < 1250 mg	0	0	3 (2.3)	3 (2.3)	0	0	1 (1.3)	3 (1.9)	3 (1.9)
High dose: ≥ 1250 mg	1 (0.4)	1 (0.4)	6 (2.4)	6 (2.4)	1 (0.4)	1 (0.4)	0	7 (2.7)	7 (2.7)
Hip fracture	1 (0.2)	1 (0.2)	8 (2.1)	9 (2.4)	1 (0.2)	1 (0.2)	1 (0.5)	9 (2.2)	10 (2.4)
Low dose: < 1250 mg	1 (0.6)	1 (0.6)	2 (1.5)	3 (2.3)	1 (0.6)	1 (0.6)	1 (1.3)	3 (1.9)	4 (2.6)
High dose: ≥ 1250 mg	0	0	6 (2.4)	6 (2.4)	0	0	0	6 (2.3)	6 (2.3)
Weight decreased	2 (0.5)	2 (0.5)	8 (2.1)	9 (2.4)	2 (0.5)	2 (0.5)	2 (1.0)	9 (2.2)	10 (2.4)
Low dose: < 1250 mg	1 (0.6)	1 (0.6)	2 (1.5)	2 (1.5)	1 (0.6)	1 (0.6)	1 (1.3)	3 (1.9)	3 (1.9)
High dose: ≥ 1250 mg	1 (0.4)	1 (0.4)	6 (2.4)	7 (2.8)	1 (0.4)	1 (0.4)	1 (0.8)	6 (2.3)	7 (2.7)
Fall	0	0	6 (1.6)	10 (2.6)	0	0	4 (2.0)	6 (1.5)	10 (2.4)
Low dose: < 1250 mg	0	0	1 (0.8)	3 (2.3)	0	0	2 (2.6)	1 (0.6)	3 (1.9)
High dose: ≥ 1250 mg	0	0	5 (2.0)	7 (2.8)	0	0	2 (1.6)	5 (1.9)	7 (2.7)

Table 5 TESAEs ≥ 1% of Subjects Overall by Treatment Period and Dose

Group (Open-Label CLES Analysis Set (Continued)

	Number (%) of Subjects								
	Titration Period		Maintenance Period[a]		Persistent AEs		Onset Since SU-1[b]	Any Time	
Preferred Term	SU-1 N = 412	SU-2 N = 412	SU-1 N = 378	SU-2 N = 378	SU-1 N = 412	SU-2 N = 412	N = 203	SU-1 N = 412	SU-2 N = 412
Peritonitis	9 (2.2)	9 (2.2)	1 (0.3)	1 (0.3)	4 (1.0)	4 (1.0)	0	10 (2.4)	10 (2.4)
Low dose: < 1250 mg	5 (3.2)	5 (3.2)	1 (0.8)	1 (0.8)	3 (1.9)	3 (1.9)	0	6 (3.9)	6 (3.9)
High dose: ≥ 1250 mg	4 (1.6)	4 (1.6)	0	0	1 (0.4)	1 (0.4)	0	4 (1.6)	4 (1.6)
Device dislocation	3 (0.7)	3 (0.7)	4 (1.1)	6 (1.6)	1 (0.2)	1 (0.2)	2 (1.0)	7 (1.7)	9 (2.2)
Low dose: < 1250 mg	2 (1.3)	2 (1.3)	2 (1.5)	2 (1.5)	1 (0.6)	1 (0.6)	0	4 (2.6)	4 (2.6)
High dose: ≥ 1250 mg	1 (0.4)	1 (0.4)	2 (0.8)	4 (1.6)	0	0	2 (1.6)	3 (1.2)	5 (1.9)
Polyneuropathy	0	0	9 (2.4)	9 (2.4)	0	0	0	9 (2.2)	9 (2.2)
Low dose: < 1250 mg	0	0	1 (0.8)	1 (0.8)	0	0	0	1 (0.6)	1 (0.6)
High dose: ≥ 1250 mg	0	0	8 (3.2)	8 (3.2)	0	0	0	8 (3.1)	8 (3.1)
Pneumoperitoneum	8 (1.9)	8 (1.9)	0	0	1 (0.2)	1 (0.2)	0	8 (1.9)	8 (1.9)
Low dose: < 1250 mg	1 (0.6)	1 (0.6)	0	0	0	0	0	1 (0.6)	1 (0.6)
High dose: ≥ 1250 mg	7 (2.7)	7 (2.7)	0	0	1 (0.4)	1 (0.4)	0	7 (2.7)	7 (2.7)
Pneumonia aspiration	1 (0.2)	1 (0.2)	5 (1.3)	7 (1.9)	0	0	2 (1.0)	6 (1.5)	8 (1.9)
Low dose	0	0	2 (1.5)	3 (2.3)	0	0	1 (1.3)	2 (1.3)	3 (1.9)
High dose	1 (0.4)	1 (0.4)	3 (1.2)	4 (1.6)	0	0	1 (0.8)	4 (1.6)	5 (1.9)
Postoperative wound infection	2 (0.5)	2 (0.5)	4 (1.1)	5 (1.3)	1 (0.2)	1 (0.2)	2 (1.0)	6 (1.5)	7 (1.7)
Low dose: < 1250 mg	0	0	2 (1.5)	2 (1.5)	0	0	0	2 (1.3)	2 (1.3)
High dose: ≥ 1250 mg	2 (0.8)	2 (0.8)	2 (0.8)	3 (1.2)	1 (0.4)	1 (0.4)	2 (1.6)	4 (1.6)	5 (1.9)
Depression	0	0	4 (1.1)	4 (1.1)	0	0	0	4 (1.0)	4 (1.0)
Low dose: < 1250 mg	0	0	0	0	0	0	0	0	0
High dose: ≥ 1250 mg	0	0	4 (1.6)	4 (1.6)	0	0	0	4 (1.6)	4 (1.6)
Back pain	0	0	4 (1.1)	4 (1.1)	0	0	0	4 (1.0)	4 (1.0)
Low dose	0	0	0	0	0	0	0	0	0
High dose	0	0	4 (1.6)	4 (1.6)	0	0	0	4 (1.6)	4 (1.6)
Pulmonary embolism	0	0	4 (1.1)	5 (1.3)	0	0	1 (0.5)	4 (1.0)	5 (1.2)
Low dose	0	0	2 (1.5)	2 (1.5)	0	0	0	2 (1.3)	2 (1.3)
High dose	0	0	2 (0.8)	3 (1.2)	0	0	1 (0.8)	2 (0.8)	3 (1.2)

Table 5 TESAEs ≥ 1% of Subjects Overall by Treatment Period and Dose

Group (Open-Label CLES Analysis Set (Continued)

	Number (%) of Subjects								
	Titration Period		Maintenance Period[a]		Persistent AEs		Onset Since SU-1[b]	Any Time	
Preferred Term	SU-1 N = 412	SU-2 N = 412	SU-1 N = 378	SU-2 N = 378	SU-1 N = 412	SU-2 N = 412	N = 203	SU-1 N = 412	SU-2 N = 412
Constipation	1 (0.2)	1 (0.2)	2 (0.5)	4 (1.1)	0	0	1 (0.5)	3 (0.7)	5 (1.2)
Low dose: < 1250 mg	1 (0.6)	1 (0.6)	0	0	0	0	0	1 (0.6)	1 (0.6)
High dose: ≥ 1250 mg	0	0	2 (0.8)	4 (1.6)	0	0	1 (0.8)	2 (0.8)	4 (1.6)
Death	0	0	4 (1.1)	5 (1.3)	0	0	1 (0.5)	4 (1.0)	5 (1.2)
Low dose	0	0	2 (1.5)	2 (1.5)	0	0	0	2 (1.3)	2 (1.3)
High dose	0	0	2 (0.8)	3 (1.2)	0	0	1 (0.8)	2 (0.8)	3 (1.2)
Anaemia	1 (0.2)	1 (0.2)	2 (0.5)	4 (1.1)	1 (0.2)	1 (0.2)	2 (1.0)	3 (0.7)	5 (1.2)
Low dose: < 1250 mg	0	0	0	0	0	0	0	0	0
High dose: ≥ 1250 mg	1 (0.4)	1 (0.4)	2 (0.8)	4 (1.6)	1 (0.4)	1 (0.4)	2 (1.6)	3 (1.2)	5 (1.9)
Hallucination	0	0	3 (0.8)	5 (1.3)	0	0	2 (1.0)	3 (0.7)	5 (1.2)
Low dose: < 1250 mg	0	0	0	0	0	0	0	0	0
High dose: ≥ 1250 mg	0	0	3 (1.2)	5 (2.0)	0	0	2 (1.6)	3 (1.2)	5 (1.9)
Sepsis	1 (0.2)	1 (0.2)	3 (0.8)	3 (0.8)	1 (0.2)	1 (0.2)	0	4 (1.0)	4 (1.0)
Low dose	1 (0.6)	1 (0.6)	3 (2.3)	3 (2.3)	1 (0.6)	1 (0.6)	0	4 (2.6)	4 (2.6)
High dose	0	0	0	0	0	0	0	0	0
Small intestinal obstruction	0	0	4 (1.1)	4 (1.1)	0	0	0	4 (1.0)	4 (1.0)
Low dose: < 1250 mg	0	0	1 (0.8)	1 (0.8)	0	0	0	1 (0.6)	1 (0.6)
High dose: ≥ 1250 mg	0	0	3 (1.2)	3 (1.2)	0	0	0	3 (1.2)	3 (1.2)
Device occlusion	0	0	3 (0.8)	4 (1.1)	0	0	1 (0.5)	3 (0.7)	4 (1.0)
Low dose: < 1250 mg	0	0	0	0	0	0	0	0	0
High dose: ≥ 1250 mg	0	0	3 (1.2)	4 (1.6)	0	0	1 (0.8)	3 (1.2)	4 (1.6)
Osteoarthritis	0	0	2 (0.5)	4 (1.1)	0	0	1 (0.5)	2 (0.5)	4 (1.0)
Low dose: < 1250 mg	0	0	1 (0.8)	1 (0.8)	0	0	0	1 (0.6)	1 (0.6)
High dose: ≥ 1250 mg	0	0	1 (0.4)	3 (1.2)	0	0	1 (0.8)	1 (0.4)	3 (1.2)
Urinary tract infection	1 (0.2)	1 (0.2)	2 (0.5)	3 (0.8)	0	0	1 (0.5)	3 (0.7)	4 (1.0)
Low dose: < 1250 mg	0	0	0	0	0	0	0	0	0
High dose: ≥ 1250 mg	1 (0.4)	1 (0.4)	2 (0.8)	3 (1.2)	0	0	1 (0.8)	3 (1.2)	4 (1.6)

AESI = adverse event of special interest; LCIG = levodopa-carbidopa intestinal gel; SU-1 = Safety Update 1; SU-2 = Safety Update 2; TESAE = treatment-emergent serious adverse event

a. LCIG exposure up to Day 1980, with 159 subjects (54 low dose, 105 high dose) exposed ≥ 1095 days (Table 9).

b. Onset Since SU-1 = AE onset occurred in ongoing study after SU-1 data cutoff date of 31 May 2013.

Notes: Titration Period = onset during Days 1 through 28; Maintenance Period = onset ≥ Day 29; Persistent = event onset during Titration Period and continued into Maintenance Period with duration ≥ 7 days.

Low dose: mean total daily levodopa dose < 1250 mg during the treatment period.

High dose: mean total daily levodopa dose ≥ 1250 mg during the treatment period.

Reviewer Comment

- There were no significant changes in the incidence of TESAEs in SU-2 vs SU-1. These results support the perspective that the safety profile of DUOPA/LCES remains unchanged from the characterization of this safety profile for TESAEs up to SU-1.

The sponsor analyzed and presented the incidence of all TEAEs in SU-2 vs SU-1. These large tables are not presented.

Reviewer Comment

- There were no substantial changes in the incidence of specific TEAEs observed in SU 2 compared to SU-1.

In SU-2, the sponsor presented (Table 6) medically adjudicated serious procedure- and device-associated adverse events in at least 1 % of patients in the open-label CLES analysis set.

Table 6 Medically Adjudicated Serious Procedure- and Device-Associated Events ≥ 1% of Subjects (Open-Label CLES Analysis Set)

	Number (%) of Subjects[a]							
	Titration Period		Maintenance Period[b]		Persistent AEs		Any Time	
Preferred Term	SU-1 N = 412	SU-2 N = 412	SU-1 N = 378	SU-2 N = 378	SU-1 N = 412	SU-2 N = 412	SU-1 N = 412	SU-2 N = 412
Any preferred term	28 (6.8)	28 (6.8)	35 (9.3)	40 (10.6)	8 (1.9)	8 (1.9)	56 (13.6)	61 (14.8)
Complication of device insertion	17 (4.1)	17 (4.1)	14 (3.7)	16 (4.2)	4 (1.0)	4 (1.0)	30 (7.3)	32 (7.8)
Abdominal pain	7 (1.7)	7 (1.7)	6 (1.6)	7 (1.9)	0	0	13 (3.2)	14 (3.4)
Peritonitis	9 (2.2)	9 (2.2)	1 (0.3)	1 (0.3)	4 (1.0)	4 (1.0)	10 (2.4)	10 (2.4)
Device dislocation	3 (0.7)	3 (0.7)	3 (0.8)	5 (1.3)	1 (0.2)	1 (0.2)	6 (1.5)	8 (1.9)
Pneumoperitoneum	8 (1.9)	8 (1.9)	0	0	1 (0.2)	1 (0.2)	8 (1.9)	8 (1.9)
Postoperative wound infection	2 (0.5)	2 (0.5)	4 (1.1)	5 (1.3)	1 (0.2)	1 (0.2)	6 (1.5)	7 (1.7)
Parkinson's desiease	0	0	4 (1.1)	4 (1.1)	0	0	4 (1.0)	4 (1.0)

SU-1 = Safety Update 1; SU-2 = Safety Update 2

a. Titration Period = onset during Days 1 through 28; Maintenance Period = onset ≥ Day 29; Persistent = event onset during Titration Period and continued into Maintenance Period with duration ≥ 7 days.

b. Exposure was up to Day 1676 for the SU-1 and Day 1980 for the SU-2 (Table 9).

Cross reference: Table 1__2.21.2

Reviewer Comment

There was no significant changes in the incidence of medically adjudicated serious procedure- and device-associated events in SU-2 vs SU-1. These results support the perspective that the safety profile of DUOPA/LCES for these type of events also remains unchanged for the safety profile for these type of events characterized since SU-1.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEONARD P KAPCALA
12/23/2014
Dave,

Here is my review for the NDA resubmission including the Safety Update 2.

GERALD D PODSKALNY
12/24/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203952
Priority or Standard	Standard
Submit Date(s)	5/28/13
Received Date(s)	5/28/13
PDUFA Goal Date	3/28/14
Division / Office	Division of Neurology Products (DNP) / ODE I
Reviewer Name(s)	Leonard P. Kapcala, M.D.
Review Completion Date	2/21/14
Established Name	Levodopa/Carbidopa Intestinal Gel (LCIG)
(Proposed) Trade Name	Duopa
Therapeutic Class	Dopaminergic agonist
Applicant	Abbvie Pharmaceuticals
Formulation(s)	Suspension
Dosing Regimen	Daily intra-intestinal infusion of LCIG over 16 hours while awake
Indication(s)	Treatment of Patients with Advanced Parkinson's Disease
Intended Population(s)	Patients who are not adequately controlled with oral levodopa/carbidopa and other medications for Parkinson's Disease

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that a Complete Response be issued at this time. Based upon my review of efficacy and safety, I conclude that levodopa-carbidopa intestinal gel (LCIG) , a combination drug-device product is safe and effective for the indication of long-term treatment of motor fluctuations in patients with advanced Parkinson's disease (PD). LCIG is administered via a pump device and percutaneous endoscopic gastrostomy (PEG) via a jejunal (J) tube over 16 hours. Initially, LCIG is administered in the morning via a bolus infusion, followed by LCIG infusion over the following 16 hours with possible extra doses of LCIG administered throughout the day at intervals of 2 or more hours,

The sponsor conducted two randomized, double-blinded, active-controlled trials comparing LCIG vs oral levodopa/carbidopa (LD/CD) using a double dummy design over 3 months (one month titration period and 2 month maintenance period) in patients with advanced PD who were not adequately controlled with oral LD/CD and other concomitant drugs. After seeking agreement from the DNP, the sponsor combined both essentially identical trials into a single trial and analyzed results for efficacy and safety. LCIG produced a highly statistically significant (p=0.0015)) effect in the primary analysis of the primary efficacy endpoint, change from baseline in “off” time (normalized to 16 hours, the time during which LCIG was infused on a daily basis) compared to the effect produced by oral LD/CD at the end of the trial. The LCIG reduction in “off” was 4.04 hours and oral LD/CD reduction was 2.14 hours resulting in an LCIG treatment difference reduction of 1.91 hours based upon the ANCOVA model. LCIG also produced a highly statistically significant (p=0.0059) effect on a key secondary efficacy endpoint, change from baseline in normalized “on” time without troublesome dyskinesia compared to that produced by oral LD/CD at the end of the trial. The LCIG increase in “on” time without troublesome dyskinesia was + 4.11 hours and oral LD/CD increase was + 2.24 hours resulting in an LCIG treatment difference increase of 1.86 hours based upon the ANCOVA model. Thus, the efficacy and therapeutic benefit of LCIG was demonstrated by showing it significantly decreased “off” time by about 1.9 hours and this reduction in “off” time was related to a complimentary increase in :on” time without troublesome dyskinesia of about 1.9 hours. The mean daily dose of LCIG in the maintenance period ranged from 604 mg to 2935 mg and \the mean and median daily dose of LCIG was 1146 mg and 1022 mg, respectively.

Safety was demonstrated from my review of numerous, various analyses of treatment-emergent adverse events (TEAEs), clinical laboratory analytes, orthostatic vital signs, and ECG parameters in the single controlled trial and also in pooled analyses of long-term, open-label trials. LCIG caused many adverse reactions typical of the class of medications for PD including sleep attacks and somnolence, hallucinations/psychotic-like behavior, dyskinesia, impulse control disorders, hypotension/orthostatic hypotension as well as hypertension and increases and decreases in blood pressure and pulse, In addition, there were some other adverse reactions of concern that are not class adverse reactions. For example, there were many adverse reactions associated with

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the procedure/device (some of which were medically serious events such as intestinal obstruction or perforation, peritonitis, sepsis, bleeding, peristomal infection/inflammation, etc., and had the potential for a fatal outcome), abdominal pain, and several cases of polyneuropathy. The adverse reactions associated with the procedure/device were not judged to be unique to LCIG but were considered to be similar to those associated with chronic PEGs for other reasons/indications. Although the etiology of polyneuropathy occurring during long-term, open label treatment was not clear, it is possible that polyneuropathy was due to levodopa/carbidopa, hydrazine (resulting from carbidopa), and/or various vitamin deficiencies or combinations of these factors. There was an increased risk of depression in the controlled trial with LCIG and the incidence of depression was 12 % in the long-term open-label trials and dose-dependent. There were also two suicides and two suicide attempts in the long-term, open-label treatment, but there was no testing assessing the risk of suicidality in the clinical development program and it was not clear whether there was an increased risk for suicidality from LCIG treatment. Finally, there was an increased LCIG treatment difference incidence in the controlled trial for outliers for various blood pressure and pulse increases and decreases, and for noteworthy laboratory outliers such as increased serum BUN and creatinine. This outlier risk for BUN and creatinine was further increased in elderly patients (≥ 65 years) vs non-elderly patients. Finally, there are concerns expressed by the Pharmacology/Toxicology Team regarding its inability to qualify levels of LCIG degradant impurities (i.e., hydrazine, (b) (4)) that are mutagenic and carcinogenic, As a result of my safety review, I concluded that these results showed that the LCIG product is reasonably safe and that these various safety results/findings should be described in the package insert/label.

As a result of my review of efficacy and safety of LCIG, I do not have any clinical concerns precluding approval at this time. However, there are significant deficiencies with other disciplines that preclude approval at this time. There are CMC concerns with LCIG related to (b) (4) of the drug product that have yet to be adequately addressed. In addition, there are concerns from DMEPA and the Human Factors review team that the sponsor has not adequately demonstrated that the product can be used safely. The proposed labeling by the sponsor consists of many documents that the various review teams believe should be integrated that additional studies are required to ensure that patients and healthcare providers can use and prescribe the product appropriately. At this time it seems that a comprehension study and human factors study need to be conducted to demonstrate that patients and healthcare providers can comprehend the revised, integrated label and instructions for use document. It is also noteworthy that patients were not permitted to exercise control over LCIG administration with the pump during the controlled trial. Although patients were permitted the opportunity to adjust LCIG treatment during the open-label treatment, the actual patient experience with adjusting LCIG administration in the open-label trial was extremely limited to a small percentage of patients (6 %) who increased the infusion rate of LCIG. Finally, the CDRH reviewer of the pump and related software necessary for operation of the pump has identified several concerns regarding the pump and software that need to be addressed prior to approval.

Thus, it is the consensus of the review teams and the DNP that a Complete Response letter should be issued to address the outstanding deficiencies/inadequacies prior to approval.

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1.2 Risk Benefit Assessment

I have outlined the various safety risks above here in my summary of safety for LCIG. The most important risks associated with LCIG treatment are adverse reactions of procedure/device insertion complications, polyneuropathy, hallucinations/psychotic-like behavior, dyskinesia, depression, and impulse disorder, as well as significant blood pressure changes (decreases and increases), and laboratory evidence of decrease in renal function (e.g., increased BUN and creatinine outliers). With the exception of procedure/device insertion complications that are unique to LCIG treatment (and do not occur with other medications for PD administered orally), these other risks outlined are not clearly different than those for oral levodopa and other various medications (e.g., dopaminergic agonists, COMT inhibitors, MAO-B inhibitors) for PD. It is most relevant to note for this product that the complications of procedure/device insertion from the PEG and J-tube associated with LCIG do not appear to be unique to LCIG. In addition, the clinical significance of the genotoxic and carcinogenic potential of degradant impurities (hydrazine, (b) (4) and (b) (4)) is unknown in humans. One approach toward possibly limiting this undefined human risk is by limiting the total amount of recommended use of LCIG to 2000 mg daily..

In assessing the risk benefit of LCIG treatment, it is also important to recognize that the therapeutic benefit of LCIG was demonstrated versus an active control, oral LD/CD, in contrast to other drugs that had been evaluated relative to placebo. If the evaluation of LCIG efficacy was conducted in a simple design comparing LCIG infusion to that of placebo infusion (instead of a double-dummy design comparing it to oral LD/CD, active control), it is likely that the therapeutic benefit of LCIG would have been substantially larger, perhaps 3 to 4 hours superior to placebo. Such a huge benefit would be vastly larger than that obtained from treatment with any other approved PD drugs evaluated relative placebo.

In view of these considerations outlined above here (e.g., magnitude of the therapeutic benefit in a trial that planned to enroll patients with advanced PD who were somewhat “resistant” to available medical treatment), it seems that the potential for obtaining this substantial therapeutic benefit from LCIG in this population is worth accepting the various risks that have been outlined. Mean ”off” time was about 7 hours (absolute value) at baseline in patients enrolled in the LCIG controlled trial. Considering that patients in controlled trials of many other drugs approved for treating advanced PD enrolled patients had less mean “off ” time (e.g., ranging from approximately 5.5 to 6.5 hours) at baseline, it appears that advanced PD patients in the LCIG controlled trial were somewhat more severe functionally than most patients enrolled in these other trials for other drugs approved by the DNP. With the exception of the potential risks for procedure/device complications that are unique to LCIG (vs other PD drugs), LCIG risks for most other adverse reactions/outcomes are generally quite similar to those for other PD drugs. Given that the risks of procedure/device complications associated with LCIG are not greater than those for PEG and tube for other reasons/indications and that medically serious complications are relatively rare/uncommon, the totality of risks of LCIG treatment seem justified by the potential for a relatively larger therapeutic benefit in a population that is difficult to treat with other available PD drugs.

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Deep brain stimulation (DBS) is also a potential therapeutic option for patients with advanced PD who are difficult to manage medically. In fact, a screening tool used to characterize whether patients are a legitimate candidate for DBS was initially applied for enrolling patients in the controlled LCIG trial. Although patients receiving DBS, may experience significant therapeutic benefit, this benefit is typically limited in duration and patients eventually need to be managed medically. Some risks of DBS are unique to this option and include brain damage with insertion of the DBS device, bleeding and infection. DBS also has the potential for various neuropsychiatric adverse reactions including apathy, hallucinations, compulsive gambling, hypersexuality, cognitive dysfunction, and depression. In comparison, the overall risks of LCIG may not necessarily be substantially greater than those of DBS but LCIG treatment may have the potential for a longer duration therapeutic benefit (than DBS) and this therapeutic benefit might also be of indefinite duration.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I concur with the consensus of review teams (including DRISK) and our division that a REMS is not necessary. Although the sponsor has proposed a REMS with ETASU, the internal consensus is that the risks associated with the PEG and J-Tube are not unique to the LCIG product but are similar to those when a PEG and J-Tube is used for other reasons. This position was presented to the ROC and there was agreement that a REMS was not necessary.

1.4 Recommendations for Postmarketing Requirements and Commitments

I recommend that a 6 month controlled trial (e.g., similar to the 3 month controlled trial submitted to support LCIG approval) be conducted as a Postmarketing Requirement (PMR) to assess the risk for suicidality, depression, vitamin deficiencies, and polyneuropathy. Furthermore, a larger number of patients could be enrolled in this trial than was enrolled in the relatively small (N=71 total patients), 3 month controlled trial.

The following comments outline my rationale for this PMR.

- Two patients who had a history of depression committed suicide and there were two other attempted suicides. Because suicidality was not assessed during clinical trials, it is difficult to know whether there is an increased risk for suicidality. Conducting assessments at baseline and throughout a 6 month controlled trial could help characterize this risk.

- There appeared to be an increased risk for LCIG-induced depression as an adverse reaction in the controlled trial and depression that occurred as an adverse reaction in 12% of patients in pooled, open-label trials (as per 4 Month Safety Update) was dose-dependent for low vs high dose LCIG. Considering that depression is a major risk factor for suicide, characterization of a risk for depression over 6 months treatment and with

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active testing assessing symptoms of depression could be important for characterizing this potential important risk for depression by itself and perhaps LCIG-induced depression contributing to an increased risk for suicidality.

- Systematic testing at baseline and throughout 6 months treatment for vitamin deficiencies (e.g., B12, B6, folic acid) based upon serum measurements of serum B12, B6, folic acid, methlymalonic acid and homocysteine could help clarify whether LCIG increases the risk for certain vitamin deficiencies and the potential role of such deficiencies in causing polyneuropathy. Although some patients had some serum vitamin measurements (baseline and/ or post-baseline) in the 3 month, controlled trial, systematic testing for vitamin deficiencies was not conducted previously in all patients at baseline and at multiple times during the controlled trial (including at the end of the trial).

- The risk for polyneuropathy could be evaluated in this controlled trial conducted over a longer period (6 months) than the original trial. A recent publication reviewing 12 cases of polyneuropathy in LCIG-treated patients showed that 5 patients (42 %) developed polyneuropathy within 6 months of LCIG treatment. Furthermore, active surveillance for polyneuropathy could be conducted by systematically evaluating patients throughout the trial for signs and symptoms of polyneuropathy. In addition, nerve conduction studies could be collected at baseline and at the end of the trial (and possibly at a mid-point in the trial) or could be conducted on an ad hoc basis when systematic assessment for signs and symptoms of polyneuropathy suggest polyneuropathy.

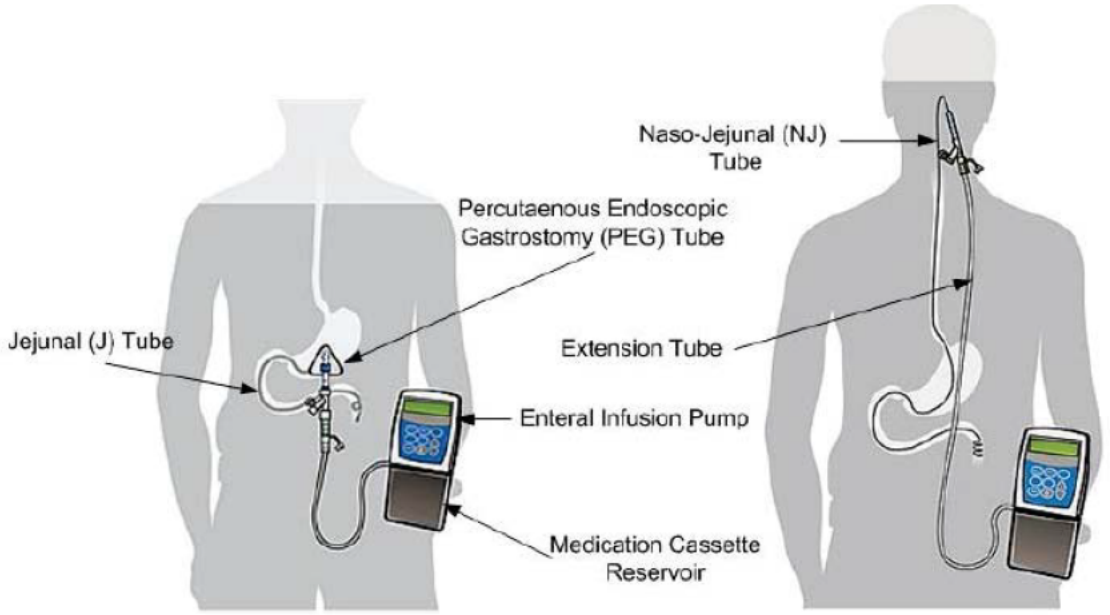
2 Introduction and Regulatory Background

2.1 Product Information

Product Development Rationale

The Levodopa-Carbidopa Intestinal Gel (LCIG) System is intended for the long-term treatment of motor fluctuations in patients with advanced [redacted] (b) (4) Parkinson's disease (PD) [redacted] (b) (4) . The System is a combination product comprising the LCIG drug product, packaged in a medication cassette reservoir, and the delivery system, a software-driven, ambulatory CADD-Legacy® 1400 infusion pump with accessories and a variety of enteral tubing products. The LCIG drug product is continuously delivered from the medication cassette reservoir via the infusion pump into the patient's proximal small intestine through a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) (Figure 1).

Figure 1 Overview of LCIG System



The LCIG drug product is a suspension of levodopa (LD = (2S)-2-amino-3-(3,4-dihydroxyphenyl) propanoic acid) and carbidopa (CD = (2S)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid, monohydrate) in an aqueous carmellose sodium [redacted] (b) (4) . In LCIG, the concentration of levodopa is 20 mg/mL and carbidopa monohydrate is 5 mg/mL. The therapeutic component of LCIG is levodopa, which is a biological precursor of dopamine. Dopamine is a catecholamine neurotransmitter that plays a key role in control of motor function. Carbidopa is a competitive inhibitor of the aromatic amino acid decarboxylase enzyme (AAAD). When co-administered with levodopa, carbidopa reduces peripheral decarboxylation of levodopa. Carbidopa monohydrate contains a hydrazino functional group, which is the most reactive portion of the carbidopa molecule and is the functional group necessary for the compound's inhibitory action on AAAD.

2.2 Currently Available Treatments for Proposed Indications

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease.2 The prevalence of PD is approximately 0.5% to 1% among persons 65 to 69 years of age, increasing to 1% to 3% among persons 80 years of age and older.

The disease is characterized by progressive degeneration of the dopaminergic nigrostriatal system and depletion of dopamine, which results in the core motor symptoms of bradykinesia, rigidity, tremor, and postural instability. Levodopa is the amino acid precursor of dopamine; when levodopa is decarboxylated to dopamine in the brain, depleted striatal dopamine is replenished. The administration of carbidopa with levodopa inhibits its extracerebral

decarboxylation, allowing more levodopa to cross the blood-brain barrier to targeted striatal dopamine receptors. The combination of levodopa-carbidopa in oral tablets is the primary standard and mainstay of treatment in PD.

Patients with advanced PD treated with oral levodopa may develop motor symptoms at the end of each dose (wearing-off), or levodopa-induced dyskinesia. These patients experience persistent motor fluctuations, periods with good motor-system control without troublesome dyskinesia that alternate with unpredictable swings to periods of "Off" time with poor mobility, slowness, and stiffness ("On – Off" phenomenon). These symptoms closely correlate with fluctuating plasma concentrations of levodopa and the corresponding pulsatile concentration of dopamine in the striatum. Plasma levels of orally administered levodopa fluctuate significantly due to its short half-life and the variability in gastric emptying. Motor fluctuations are considered persistent when patients continue to experience them despite having individually optimized treatment, such that no further improvement is expected, regardless of any additional manipulations of levodopa or other antiparkinsonian medication. Treatments that offer continuous levodopa administration result in less variability in levodopa plasma concentration and are believed to provide more continuous dopaminergic stimulation, and, therefore, reduce the frequency and severity of motor fluctuations and dyskinesia.

Pharmacologic treatment options to help achieve sustained dopaminergic stimulation include extended-release levodopa-carbidopa preparations, such as Sinemet® CR, or frequent administration of levodopa-carbidopa immediate release (IR) formulation, adjunct therapy with long-acting dopamine agonists and drugs that act to slow the elimination of levodopa (catechol-*O* methyltransferase [COMT] inhibitors, such as entacapone or tolcapone), or inhibit another metabolic pathway of dopamine (monoamine oxidase inhibitors, such as selegiline or rasagiline). However, these drugs may produce adverse effects that will limit use, and a potential for hepatic injury with tolcapone has resulted in a boxed warning in labeling.

Another drug that is used off label to reduce dyskinesia without worsening parkinsonism is amantadine; however, it is associated with cognitive and other adverse effects that limit its use in patients with advanced PD.

In spite of attempts to optimize their oral PD medication using the drugs described above, many patients with advanced PD continue to experience persistent uncontrollable motor fluctuations. For these patients, currently the only available non-pharmacologic option is deep brain stimulation (DBS). Deep brain stimulation of the subthalamic nucleus or globus pallidus pars interna can provide relief of tremor, bradykinesia, rigidity, "Off" time, and dyskinesia in some patients; DBS can also result in significant improvements in motor function and quality of life. However, not all advanced PD patients are candidates for DBS and the treatment is not effective in all patients. Importantly, DBS may have significant and irreversible side effects. Complications related to the surgical procedure (intracerebral bleeding or stroke), the device (mechanical problems with the system, wires breaking, infection), and the stimulation itself (dysarthria, oculomotor disturbances, depression, and suicide) have been reported.

Because most patients with advanced PD cannot achieve adequate symptom control with available oral medications, and many patients are reluctant to undergo DBS because of the associated risks or are not candidates for the surgery, there remains a significant unmet medical need for patients with persistent motor fluctuations. Motor fluctuations, especially periods of "Off" time and "On" time with troublesome dyskinesia, put the patient at an increased risk of co-morbid complications related to poor mobility.

2.3 Availability of Proposed Active Ingredient in the United States

The original formulation of LD/CD approved in the U.S. was for Sinemet and subsequently a extended release formulation became available. Currently there are generic and proprietary formulations of LD/CD in various strengths of each component.

2.4 Important Safety Issues With Consideration to Related Drugs

There are many class safety issues associated with PD drugs that increase central dopaminergic tone. These safety issues include: somnolence and sleep attacks, hypotension/orthostatic hypotension, dyskinesia, hallucinations and other psychotic-like behavior, hyperprexia and confusion associated with drug discontinuation or dose reduction, impulsive/compulsive disorders, and melanoma.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 60663 for administration of LD/CD as an infusion into the upper intestine was initially submitted to the Agency (to the Division of Neurology Products-DNP) in 2000 (See Table 1)

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Table 1 History of Regulatory Interactions and Guidance Between Agency and Sponsor(s)

Date	Meeting Topic/Regulatory Advice
22 April 1999	Pre-IND meeting
01 October 1999	Request submitted for orphan drug designation
18 January 2000	Orphan drug designation granted
27 July 2000	IND filed
17 January 2001	IND in effect
09 January 2002	Type A Critical Path meeting
30 January 2002	Email correspondence on safety database requirements
10 May 2002	Critical Path teleconference
30 October 2002	Agency advised requirements for long-term safety exposure for Phase 3 studies
24 September 2004	Type A Critical Path meeting
19 December 2005	Type A Protocol Review meeting
17 March 2006	Protocol submitted for Study S187-3-001
26 September 2006	Agency letter with comments on Study S187-3-001 protocol inclusion criteria requiring that treatment had to be optimized.
24 July 2008	Agency letter allowing the sponsor to proceed with ongoing program
15 March 2010	Agency comments on Study S187-3-001 and Study S187-3-002 inclusion criteria required subjects to have had an adequate trial of antiparkinsonian therapy yet failed to achieve therapeutic benefit (instead of PD-TOS criteria).
15 May 2010	Proprietary name request conditionally approved (Duopa™)
18 January 2011	Type C meeting with the Agency to discuss acceleration of the clinical development program. Agreement to combine data from Study S187-3-001 and Study S187-3-002 for analysis as a single study, and that a single well controlled pivotal study of sufficient robustness could form the basis for the NDA submission. Exposure to (b) (4) (b) (4) and possibly hydrazine to be evaluated.
06 April 2011	Final protocol amendments submitted for pivotal Study S187-3-001/S187-3-002
07 June 2011	Request for comment on pivotal Study S187-3-001/S187-3-002 Statistical Analysis Plan
15 November 2011	OCP teleconference to discuss NDA filing strategy: The LCIG System is a combination product (drug, pump, and tubing) that can be submitted as a single marketing application. Tubing elements could be filed as separate 510(k) Premarket Notifications.
30 November 2011	Comments from the Agency on the Statistical Analysis Plan for Study S187-3-001/S187-3-002
08 December 2011	Submission of final Statistical Analysis Plan (v. 4.0) for Study S187-3-001/S187-3-002
20 December 2011	Submission of Type B Pre-NDA meeting request
26 January 2012	Submission of preliminary analysis of the primary efficacy endpoint for Study S187-3-001/S187-3-002
07 August 2012	Type B Pre-NDA meeting. Agency requests additional efficacy and safety analyses, including by levodopa dose, which were completed and are reported in the NDA

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The US clinical development program for the LCIG System was initiated in 2008 with dosing of the first subject in Study S187-3-004. The design of all clinical studies took into account the latest knowledge at the time, including historical precedents of accepted development programs in PD and advice and guidance received from regulatory agencies, as well as established clinical practice for the use of the LCIG System in countries where it is commercially marketed outside of the US. Key communications with the Agency are briefly summarized below and in Table 1 :

- 18 January 2000, LCIG was granted orphan drug designation for the treatment of advanced PD (Designation Number 99-1294).
- 30 October 2002, the Agency informed the sponsor that submission of safety data on at least 300 patients for 6 months and 100 patients for 12 months would be necessary to meet the requirements for long-term safety exposure.
- 18 January 2011, the Agency agreed that the 2 pivotal studies could constitute a single pivotal study (Study S187-3-001/S187-3-002), and that a single, adequate and well-controlled study of sufficient robustness could form the basis for this NDA. The adequacy of the clinical pharmacology development plan was confirmed in this meeting. (b) (4)
- 15 November 2011, the Agency agreed that the LCIG System is considered a combination product (drug, pump, and tubing). A Master Access File (MAF) for the Smiths Medical pump used with LCIG has been submitted, according to *Guidance for Industry and FDA Staff Total Product Life Cycle: Infusion Pump - Premarket Notification [510(k)] Submissions*. Tubing components that are required to administer LCIG will be filed as Premarket Notification 510(k) applications submitted to the Center for Devices and Radiological Health. The LCIG System elements will be cross-labeled to ensure control of its component parts. In addition, there are tubing components currently approved within the US that are compatible with the LCIG System. These tubing components are listed in the proposed US Package Insert for the product and compatibility data are provided in Module 3, Section 3.2.P.2.4 and Section 3.2.P.2.6.
- 30 November 2011, the Agency provided comments on the pivotal study Statistical Analysis Plan and requested 4 additional data sets and analysis on 24 additional variables from the Parkinson's Disease Diary data.
- 07 August 2012, Pre-NDA meeting, agreement with the Agency was reached on multiple points. The Agency requested additional statistical analyses on the pivotal and open-label study data, including subgroup analyses by the mean total dose of levodopa received (< or ≥ 1250 mg/day).

- 16, November, 2012 Sponsor submitted NDA 203952 for Duopa (Levodopa-Carbidopa Intestinal Gel (LCIG)) for (b) (4) treatment of advanced Parkinson's disease (b) (4)
- 15, January, 2013 Refuse to File (RTF) Issued by the Agency (DNP)
- 14, March 2013 Type A meeting held between sponsor and Agency (DNP) to discuss resolutions to the RTF letter
- 28, May, 2013 Sponsor resubmitted NDA 203952 as a 505(b)(2) application. The application will reference the Agency's previous findings of safety and efficacy for the reference listed drug, Sinemet® (NDA 017555).

It is also relevant to note that there were other sponsors for LCIG prior to Abbvie.

2.6 Other Relevant Background Information

Levodopa-Carbidopa Intestinal Gel was granted orphan drug designation on 18 January 2000 (Designation Number 99-1294) for the treatment of advanced PD, with the indication granted for "treatment of (b) (4) Parkinson's disease." This determination was made based on data estimating that after 5 years of therapy, 92,000 patients may suffer from motor fluctuations associated with advanced PD at any time. Since that designation was granted, no relevant published data have contradicted that initial estimate.

The intended indication for this NDA is restricted to advanced PD patients whose disease has progressed such that they experience persistent motor fluctuations that are inadequately controlled with other PD medications. The subject population that was studied in the Phase 3 clinical program included only those whose motor fluctuations were inadequately controlled with levodopa and other adjunctive oral PD medications.

US Clinical Development Program

The US clinical development program includes a series of studies that evaluated the safety, efficacy, and pharmacokinetics of the LCIG System in the indicated population.

The original program included two Phase 3 pivotal studies of identical design that recruitedpatients from distinct study sites : Study S187-3-001 and Study S187-3-002 (Randomized, double-blind, double-dummy, multicenter, parallel group studies conducted in the US, Germany, and New Zealand 12-week duration). Study S187-3-001 and Study S187-3-002 were combined as 1 pivotal after obtaining agreement from the Agency because of the sponsor's concerns in the length of time to complete both trials, Study S187-3-001/S187-3-002 prior to database lock, as agreed with the Agency on 18 January 2011. The US clinical development program also includes 3 long-term, open-label, single arm, multicenter Phase 3 supportive trials : Study S187-3-003 (12 months), Study S187-3-004 (LCIG initial infusion in 2 to 14 day naso-jejunal (NJ) test period followed by a PEG-J 52-week period), and Study S187-3-005 (for continuation treatment for subjects in Study S187-3-003 and Study S187-3-004 until LCIG is commercially available in

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participating countries). In addition, US clinical development program includes a Phase 1 pharmacokinetic trial.

Ex-US Development of the LCIG System

The LCIG System is currently approved ex-US in 41 countries and marketed in many countries under the trade name Duodopa®. The first marketing authorization for LCIG in the European Economic Area (EEA) was received in Sweden on 21 January 2004. LCIG has been approved in 27 countries in the European Union (EU) and 3 additional countries of the EEA. In addition, 11 national approvals have been granted in the following countries: Albania, Australia, Bosnia and Herzegovina, Canada (conditional), Croatia, Israel, Macedonia, Switzerland, Thailand, Turkey, and the Ukraine. The world-wide cumulative exposure to LCIG from market introduction 21 January 2004 through 31 May 2012 is estimated to be (b) (4) patient-years (PY).

Six non-IND, Phase 4 postmarketing observational registries or health economics and outcomes research studies (Studies S187-4-001 DAPHNE, S187-4-002, S187-4-004 GLORIA, S187-4-005, S187-4-006 RELEVANT, and S187-4-007) have been conducted or are ongoing ex-US to evaluate the long-term (b) (4) ty, effectiveness, and health economic data for subjects treated with LCIG. In these studies (b) (4) subjects have been or are planned to be treated with LCIG for durations from 6 months up to a maximum of 16 years. A Phase 2 study conducted in Japan evaluating LCIG treatment administered by NJ to subjects with advanced PD has recently concluded. Eight subjects were planned for the study, 6 subjects were treated with LCIG, and 5 subjects completed the study. As agreed with the Agency at the Pre-NDA meeting on 07 August 2012, because of the nature of these studies and registries, they cannot be integrated into the ISS.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The following is an abstract from the inspection report for the inspections of 3 clinical sites conducted by the Division of Scientific Investigation (DSI).

Three domestic site inspections were requested in support for this NDA which includes protocols S187.3.001 and S187.3.002

II. RESULTS (by protocol/site):

District	Name of CI/Address/ and Site #	Protocol #s and # of Subjects	Inspection Dates	Final Classification
Cincinnati	Alberto Espay, M.D. 260 Stetson Street, Suite 2300 Cincinnati, Oh 4567-0525 Site #41279	Protocol S187-3001/3002 9 subjects	10/28-11/1/2013	Pending (preliminary classification NAI)
Florida	Ramon Rodriguez, M.D. University of Florida Center for Movement Disorder & Neuroretoration 2450 Hall Rd, 4th floor Gainsville, Fl 32607 Site #41267	Protocol S187-3001/3002 7 subjects	11/4-6/2013	Pending (preliminary classification NAI)
Cincinnati	John Slevin, M.D Department of Neurology L-443 Kentucky Clinic University of Kentucky Medical Ctr. Lexington, KY 40536-0284 Site #9339	Protocol S187-3001/3002 7 subjects	8/21-27/13	Pending (preliminary classification NAI)

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; the EIR has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

1. **Alberto Espay, M.D.**
Cincinnati, Ohio, 45267-0525
a. What Was Inspected: At this site, 10 subjects were screened, one subject was reported as a screen failure, nine subjects were randomized into the study, and all nine subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source documents for all subjects were reviewed. The medical records/source documents for all subjects were reviewed including drug accountability records, vital signs, IRB files, monitoring records, inclusion/exclusion criteria, financial disclosure, and adverse events reporting. Source documents for all subjects were compared to case report forms and data listings.

b. General observations/commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Espay. Overall, the medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. However, Subject 107 had adverse events (worsening insomnia, skin irritation, stuffy nose and cold symptoms in study 002. These adverse events continued into the open label for the 003 study and were reported as adverse events for study 003 and inadvertently not submitted for study 002. There were limitations to the inspection.

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c. Assessment of Data Integrity: The data in support of the clinical efficacy and safety at Dr.Espay's site are considered reliable and acceptable in support of the application.

2. **Ramon Rodriguez, M.D.**
Gainsville, FL 32607
a. **What Was Inspected:** At this site, a total of 14 were screened, seven subjects were reported as screen failures and the reason(s) were documented. Seven subjects were randomized into the study, and all seven subjects completed the study, were enrolled in the open label Study 003, and continued in Study 005. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

b. The medical records/source documents for five of the subjects were reviewed. A cursory review of the remaining two subjects was performed and included informed consent, adverse events, concomitant medications, and primary efficacy endpoint. The medical records/source documents for certain subjects were reviewed including drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, use of concomitant medications, and adverse events reporting. Source documents for all subjects were compared to case report forms and data listings.
c. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Rodriguez. The medical records reviewed were found to be in order, organized, and the data verifiable. Except for minor protocol deviations such as vital signs were not always recorded because three subjects refused due to off time, eating and sleeping. One subject did not sign amendment 6 after a protocol and consent revision from amendment 5 to 6. It is not known what the revisions were. However, the sponsor approved the subject to remain under amendment 5 based on the assessments performed. There were no limitations to the inspection.
d. **Assessment of Data Integrity:** The data generated at Dr.Rodriguez's site in support of the clinical efficacy and safety are considered acceptable and may be used in support of the pending application.

3**. John Slavin, M.D.**
Lexington, KY 40536-0284
a. **What Was Inspected:** At this site, a total of 8 subjects were screened, one subject was reported as a screen failure. Seven subjects were randomized into the study, and all completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment. The medical records/source documents for seven subjects were reviewed. The medical records/source documents reviewed included drug accountability records, vital signs, IRB files, monitoring records, sponsor correspondence, inclusion/exclusion criteria, financial disclosure, use of concomitant medications, and adverse events reporting. Source documents for all subjects were compared to case report forms and data listings. There was no evidence of inaccuracy of the data captured. However, the field investigator discussed with the clinical investigator minor discrepancies between the source documents and the data listings. For example, Subject 127-101was documented to have received 400 mg of Sinemet on 3/02/2009 which was corrected to 300 mg on 9/14/1010. This change was not reflected in the data listings. Thus, the impact of the error was minor.

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b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Slevin. The medical records reviewed were found to be in order, organized, and certain data were verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were known limitations to the inspection.
c. **Assessment of Data Integrity:** The data submitted in support of the clinical efficacy and safety at Dr. Slevin's site are considered reliable and appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS
Three clinical investigator sites were inspected in support of this application. The inspections of Drs. Espay, Rodriguez, and Slevin revealed no regulatory violations, and the final classifications for these inspections are noted above as No Action Indicated (NAI). The final classification for all sites will be determined upon review of the establishment inspection reports (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. Overall, the data submitted from these three sites are considered acceptable in support of the pending application.

Reviewer Comments

These 3 Principal Investigators (PIs), who enrolled the largest number of patients in the controlled trial, were selected for inspection. The Office of Scientific Investigations (DSI) did not identify any serious problems with the inspections of these sites.

3.2 Compliance with Good Clinical Practices

Reviewer Comments

The conduct of the clinical trials and the Clinical Development program for LCIG appeared to comply with Good Clinical Practices.

3.3 Financial Disclosures

Reviewer Comments

The sponsor submitted adequate information/forms regarding financial disclosures of investigators in the clinical trials. For 9 Investigators requiring financial disclosure the sponsor submitted more detailed information.

I did not have any concerns for bias in the conduct of the clinical trials and believe that the clinical trials were conducted appropriately and with adequate integrity.

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

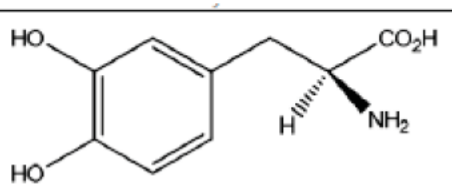
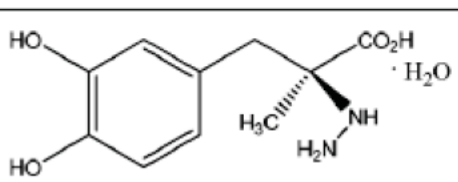
4.1 Chemistry Manufacturing and Controls

CMC Review by Dr. Charles Jewell (Team Leader Martha Heimann)

The following is an abstract of the CMC Review :

Description of the Drug Product(s) and Drug Substance(s)
This drug product is an enteral suspension of levodopa and carbidopa (Figure 2) monohydrate particles in a solution of carmellose sodium in purified water. [redacted] (b) (4) The suspension is packaged in plastic [redacted] (b) (4) bag inside a hard plastic [redacted] (b) (4) container (cassette). This cassette contains approximately 100 g of suspension. The concentration of levodopa is 20 mg/mL, for carbidopa monohydrate 5 mg/mL and for carmellose sodium [redacted] (b) (4) mg/mL. One cassette contains a total of 2000 mg of levodopa, 500 mg of carbidopa monohydrate and [redacted] (b) (4) mg of carmellose sodium. The cassette is designed for use in an administration system which involves an infusion pump that connects to either naso-jejunal (NJ) tubing or percutaneous endoscopic gastrostomy (PEG) tubing which is connected to jejunal (J) tubing. The pump is designed to work with the cassette to deliver a continuous infusion of the enteral suspension directly to the jejunum.

Figure 2 Chemical Name, Structural Formula, Molecular Formula, Molecular Weight

	
Levodopa (S)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid $C_9H_{11}NO_4$ MW: 197.19	Carbidopa Monohydrate (S)-3-(3,4-dihydroxyphenyl)-2-hydrazinyl-2-methylpropanoic acid $C_{10}H_{14}N_2O_4 \cdot H_2O$ MW: 244.24 (as monhydrate)

The pump is programmed to deliver a morning dose (bolus rate higher than the normal infusion rate), the continuous infusion and extra doses (short bursts at a higher than normal infusion rate). The pump has three lock levels for programming. Level 0 and level 1 require passcodes and are designed for original set-up by the physician and for the main health care provider. Level 2 is set for use by the patient, with limited controls. Level 2 allows only stopping and starting the pump, reset of the reservoir volume, starting an extra dose and starting the morning dose. Level 2 does not allow any changes in programming. The morning dose and extra dose mode accelerates the pumping.over the continuous rate during the bolus periods. There is one morning dose and a

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number of extra doses may be allowed, as determined by the physician level programmer. The maximum possible continuous rate is 20 mL/hr. This rate can be varied in level 1. Maximum accessible rate can be programmed in level 0. Continuous dosing can vary from 0.0 mL/hr to 20.0 mL/hr in 0.1 mL/hr increments. The morning dose can be set in 0.1 mL increments to a maximum of 20 mL. The extra dose can be set in 0.1 mL increments to a maximum of 9.9 mL. The rate for an extra dose or morning dose can be as high as 40 mL/hr, the continuous rate plus the fastest rate to achieve the bolus dose. The pump can operate at 125 mL/hr in priming mode.

The control for number of morning doses or extra doses is achieved by locking out a new dose for a set period of time. The morning dose lockout is from 1 to 24 hours in 1 hour increments. The extra dose lockout is from 15 minutes to 24 hours in 15 minute increments.
The drug substances are levodopa and carbidopa monohydrate, both are manufactured for the proposed commercial product by [redacted] (b) (4) and are fully described in DMFs. Both of these drug substances from this manufacturer are approved for use by the Agency in other drug products.

The pump is described completely in a MAF filed with CDRH, and CDRH was consulted by OND to review the MAF with respect to this combination product. The container closure system, the [redacted] (b) (4) cassette, is described in a DMF, but is also adequately described in this application.

The tubing sets (NJ and PEG-J and connecting tubing) recommended by the applicant for use with this product either already have received marketing clearance from CDRH (as feeding tubes) or they are in the process of receiving marketing clearance from CDRH (specially designed tubing sets proposed for marketing by the applicant, based on already cleared feeding tubes). These reviews have been consulted to CDRH.

The proposed combination device is relatively complex to operate and care for. Because of this, both CDER's (DMEPA) and CDRH's Human Factors Evaluation reviewers are involved with assessing the safe and effective usability of this combination of drug product and devices (drug product cassette, infusion pump, connector tubing, NJ and PEG-J tubing sets). Safety and efficacy of the use of levodopa and carbidopa for Parkinson's patients is well understood. The greatest safety concerns for this product are due to complications in using the pump and tubing (pump failures, tubing clogging, improperly positioned internal tubing etc.), thus the need for careful Human Factors evaluation.

This drug product is a stabilized, homogeneous suspension of [redacted] (b) (4) levodopa and carbidopa monohydrate, which represents a novel formulation for these drugs. Carbidopa [redacted] (b) (4) in this formulation compared with solid-oral-dosage forms. The key degradation products are hydrazine, [redacted] (b) (4) and [redacted] (b) (4) The proposed specified limits for these degradation products are at unprecedented levels. The applicant has attempted to justify these levels in light of the benefit/risk of using this drug in advanced Parkinson's patients. The acceptance of this justification is being determined by the non-clinical reviewers of this application.

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While all of the above considerations are interdisciplinary in nature, there are two important deficiencies continuing to be resolved by the applicant which relate directly to chemistry, manufacturing and controls for the drug product. These involve the controls for homogeneity of the drug product and the physiologically relevant quality control dissolution method for this novel product. The Agency CMC reviewers and biopharmaceutical reviewers have been communicating regularly with the applicant with regard to these issues. At this time, the applicant has proposed a reasonable hypothesis for homogeneity issues seen with their product and proposed a logical control strategy for addressing the issue. However, the data necessary to support the hypothesis and proposed control strategy have not been submitted to the NDA. These major amendments might be sufficient to support an "approval" recommendation from CMC, but will not be reviewed in this cycle unless the review clock is extended.

The homogeneity issues involve examples of (b) (4) which have been shown to lower the exposure of levodopa during the morning dose. (b) (4) Based on further study, the applicant now recommends using a (b) (4) as the critical control for homogeneity and thus content uniformity. Although the logic and preliminary data of this change has been discussed with the agency, we are awaiting the confirmatory data to support this finding. Homogeneity needs to be maintained for up to 24 months of frozen storage, followed by up to (b) (4) weeks of refrigerated storage, and up to 24 hours at room temperature to support the proposed use of the product. For the dissolution method, the sponsor needs to demonstrate a method that supports adequate dissolution at conditions that adequately represent the introduction of the drug product suspension directly into the jejunum at a relatively slow steady rate, rather than the originally proposed (b) (4)

Basis for Approvability or Not-Approval Recommendation

Based on deficiencies in drug product homogeneity control and dissolution method, this application is not recommended for approval. In addition, the non-clinical reviewer LuAnn McKinney maintains the unprecedented levels of (b) (4) and (b) (4) has not been adequately qualified for approval of this application. From a chemistry perspective it is not likely that these levels can be controlled using additional quality and manufacturing measures, since they appear to be a natural result of the formulation. The Office of Compliance has not yet issued an overall acceptable recommendation for the manufacturing sites involved in this application through the Establishment Evaluation System. There are pending issues with regard to human factors studies for the drug product administration system. These studies appear incomplete and more studies will be required.

Recommendation and Conclusion on Approvability

A complete response is recommended for this application from the CMC perspective pending resolution of drug product homogeneity issues and recommendations from OC, the non-clinical reviewer, and biopharmaceutics. As of the date of this review, it is still possible that the

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applicant may resolve the CMC deficiencies by amendments that are expected. See deficiencies outlined in the summaries below.

Usability Study, Label, And Labeling Review
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)
DMEPA Acting Team Leader: Julie Neshiewat, PharmD, BCPS
DMEPA Acting Director: Kellie Taylor, PharmD, MPH

This review had the following conclusion and recommendations.

Conclusion & Recommendations
We conclude that the proposed labels, labeling, and product design can be improved to promote the safe use of the product and to clarify information.

Recommendations For The Division
If the Review Division determines that this NDA should be approved, we recommend emphasizing in the labeling that task failures did occur in the usability study and therefore HCPs should be training and evaluating that their patients can safety use the product before prescribing. Labeling changes to the Instructions for Use (IFU) made prior to approval should be evaluated through a labeling comprehension study. In addition, we can provide recommendations for product design changes to consider as a post marketing requirement to help address potential causes of medication errors.

Review by QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

The following outlines deficiencies from the Human Factor Reviewer :

"At this time, the consultant recommends communicating the following deficiencies to the Sponsor: Your human factors study report did not provide analyses and results consistent with best practice to support review of human factors for your combination product submission. As per the deficiencies that follow, we request that you implement mitigations to improve the ability of users to use your product safely and effectively and conduct another human factors study with a minimum of 15 participants, HCPs and patients combined to demonstrate their effectiveness.

1. Only low battery and high pressure alarms were tested your original human factors validation study. We noted that there are other alarms/messages that you have listed in the healthcare providers (HCPs) and patients pump labeling that were not part of the study. If the response and interpretation to these alarms/messages is unique and represent critical user tasks, they should be tested but were not tested in your human factors validation study. Unless there are no critical user tasks associated with these alarms and messages, please include them in your human factors testing of mitigations.

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2. Your original human factors validation study showed multiple task failures for programming the pump, and connecting different pump components. These failures were in addition to the reported other "operational difficulties." We are concerned that these task failures and operational difficulties can lead to suboptimal therapy, dyskinesia, loss of mobility, pain/discomfort. We are most concerned about the following :
a. One HCP accidentally changed Continuous Rate value while changing Morning Dose volume.
b. Two HCPs failed to administer Morning Dose.
c. Five (5/25) HCPs and 14/25 patients experienced failures with critical tasks associated with changing the cassette.
d. Three patients and 6 HCPs did not complete the steps for flushing the PEG-J tubing

You have not explained how these failures and difficulties occurred such that design issues of your product can be ruled out. Therefore, please evaluate the relevant data, develop appropriate mitigations and validate those mitigations via simulated use testing.

3. You provided a supplemental human factors study to evaluate the lock levels, however only 10 HCPs participated in the study. The study was designed to evaluate the HCPs' understanding of the differences between the lock levels. The user tasks associated with setting up lock levels were not evaluated as part of this study. Please provide test results for these tasks or provide justification for the study methodology you followed. Please also clarify the specific patient characteristics for HCPs' determination and setting the lock level for a specific patient.

4. Regarding your supplemental study to evaluate the lock levels, 15 patients were tested to perform Morning Dose and Continuous Rate adjustments. It was not clear if the scenarios in the test were designed to evaluate patient's ability to adjust dose. It was not clear if the patients are only enabled to adjust Morning Dose and Continuous Rate. We note that patient adjustments can be made between a preset prescribed dose and a pre-programming upper limit (+10% of the prescribed dose). Please also describe the minimum and maximum dose that can be prescribed, the adjustments and what parameters can be adjusted relative to the prescribed dose setting, how adjustments can be made, and how the pump tracks adjustments made by patients.

5. Your supplemental study results showed six (6/15) patients failed to inspect for tubing kinks prior to programing adjustments. In addition, some HCPs indicated confusion regarding the table that you provided in the HCP pump labeling that described the function of the different lock levels and whether Morning Dose could be adjusted in LL1. As with the other failures contained in these deficiencies, please evaluate these and develop mitigation strategies for reducing them and test data to demonstrate their effectiveness.

6. Your combined instructions for use for patients included warning statements that have were not included in your human factors testing. Interpreting and abiding by warnings is considered to represent critical tasks for users and therefore should be tested since inability to understand or take note of the warnings could lead to patient harm. Please ensure that these instructions are optimized for safe and effective use, and that they are not simply a combination of two instructions.

7. Please provide screen shots for the HCP programming tasks, and patient dose adjustment tasks.

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Review by CDR Alan Stevens, Reliability and Mechanical Engineering Infusion Pump Team Leader,OMPT/CDRH/ODE/DAGRID/GHDB

This CDRH reviewer of the pump and pump's software identified numerous deficiencies related to the pump's hardware and software necessary for operating the pump that will not be specified here. These various deficiencies preclude approval of this product at this time.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

The following is an abstract from Nonclinical Pharmacology and Toxicology review by Dr. Luann McKinney (and Dr. Lois Freed, Team Leader).

Recommendations

Approvability: No.
Levels of the degradant impurities hydrazine, (b) (4) and (b) (4) are not qualified and the drug product cannot be approved from a pharmacology/toxicology perspective. Approval would be a matter of clinical judgment of the risk of exposure to the degradants and benefit to the patient population.

Additional Non Clinical Recommendations:
To support qualification of the degradants (b) (4) and (b) (4), further characterization of the genotoxic risk would be needed to support the proposed specifications.

4.4 Clinical Pharmacology

Clinical Pharmacology

The following is an abstract from the Clinical Pharmacology review by the review team :

Bei Yu (CP primary reviewer)
Angela Men (CP TL)
Division of Clinical Pharmacology 1

Hongshan Li (PM reviewer)
Atul Bhattaram (PM TL)

RECOMMENDATION
The NDA resubmission is acceptable from a Clinical Pharmacology perspective and the OCP recommends approval for NDA 203952 pending satisfactory agreement with the sponsor on the label.

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PHASE IV COMMITMENT/REQUIREMNT

None.

Biopharmaceutics

The following is the recommendation of the Biopharmaceutics team.

Kelly M. Kitchens, Ph.D. (Primary Reviewer), Angelica Dorantes, Ph.D. (Team Leader)

RECOMMENDATION:
The following proposed dissolution method for the testing of LCIG is acceptable.

USP Apparatus	Rotation Speed	Medium	Volume	Temperature
2 (Paddle)	25 rpm	0.05 M acetate buffer, pH 4.5	500 mL	37°C

However, the dissolution data required for the setting of the dissolution acceptance criteria with the new method are very limited, and therefore critical dissolution data throughout the 15 week stability period under refrigeration conditions at 5ºC are lacking. At this time of the review process, due to lack of critical dissolution data needed for the setting of the dissolution acceptance criteria, from the Biopharmaceutics perspective, a **COMPLETE RESPONSE (CR)** is recommended for NDA 203952 for Levodopa-Carbidopa Intestinal Gel.

The following comments and request for information should be conveyed to the Applicant in the CR letter:
1. Submit the complete dissolution profile data (*individual, mean, SD, profiles*) for each time point for the dissolution testing of the commercial-scale batches. Provide the dissolution data at the following time points: 15, 20, 30, 40, 50, and60 minutes (n=12). The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).

2. We acknowledge your commitment to provide stability data for your drug product under frozen (-20ºC) and refrigeration (5ºC) conditions post-approval. However, for the setting of the specifications of your drug product, you will need to provide data from at least 3 batches at the initial time point and thereafter at 5, 10, and 15 weeks under refrigeration conditions. For this testing, we consider the initial time point when the product is thawed and placed under the 5ºC refrigeration conditions. For the dissolution testing, provide the complete dissolution profile data as described in above Comment 1.

3. In your October 31, 2013 response to our Information Request (IR), you indicated that (b) (4) whereas in your February 7, 2014 IR response, you indicated that

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(b) (4) a 10-fold difference. Clarify this discrepancy (b) (4).

4.4.1 Mechanism of Action

Current evidence indicates that symptoms of PD are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease, apparently because dopamine does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of PD.

Carbidopa inhibits the peripheral decarboxylation of levodopa, thereby increasing the bioavailability of levodopa in the brain

4.4.2 Pharmacodynamics

When levodopa is administered orally, it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect, and these may often be accompanied by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

Carbidopa inhibits the decarboxylation of peripheral levodopa, making more levodopa available for transport to the brain. When co-administered with levodopa, carbidopa increases plasma levels of levodopa and reduces the amount of levodopa required to produce a given response by about 75%. Carbidopa does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system.

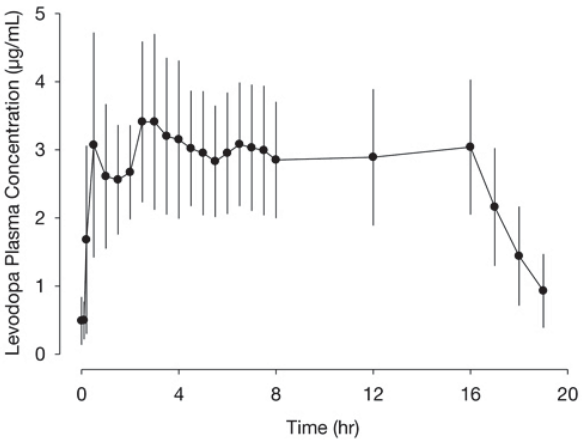
Upper intestinal infusion of Duopa reduces the intra-subject variability in levodopa plasma concentrations compared to oral levodopa-carbidopa treatment. This is believed to result in more consistent dopaminergic stimulation in the brains of Parkinson’s patients, and subsequent improvement in clinical symptoms.

4.4.3 Pharmacokinetics

Absorption and Bioavailability

LCIG is administered via an inserted tube directly into the upper intestine. Levodopa is absorbed quickly and effectively from the intestine through a high-capacity transport system for amino acids. The gastric emptying rate is not believed to influence the absorption from LCIG because it is administered by continuous intestinal infusion. Levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet.

The pharmacokinetics of levodopa and carbidopa with 16-hour intrajejunal infusion of LCIG were evaluated in 18 patients with advanced PD who had been on LCIG therapy for ≥ 30 days. Patients remained on their individualized LCIG doses. The plasma concentrations (mean ± standard deviation) versus time profile for levodopa with LCIG16-hour infusion is presented in the figure below here.



The pharmacokinetic parameters of levodopa and carbidopa with LCIG 16-hour infusion are presented in table below here.

Table Pharmacokinetic Parameters (mean ± SD) of Levodopa and Carbidopa with TRADENAME 16-Hour Infusion

		Analyte	
Pharmacokinetic Parameters (units)		**Levodopa (N = 18)**	**Carbidopa (N = 18)**
Total TRADENAME			
Dose	(mg)	1580 ± 403	395 ± 101
T_{max}	(h)	2.9 ± 2.3	5.7 ± 5.2
C_{max}	(µg/mL)	4.21 ± 1.36	0.371 ± 0.149
C_{min}[a]	(µg/mL)	0.45 ± 0.28	0.10 ± 0.07
C_{avg}	(µg/mL)	2.91 ± 0.84	0.22 ± 0.08
AUC_{0-16}	(µg•h/mL)	46.5 ± 13.3	3.54 ± 1.33
$t_{½}$[b]	(h)	1.5 ± 0.19[c]	--

[a] C_{min} values during the 16 hours of infusion were observed either at time 0 or 5 minutes after start of the infusion and were a result of drug washout during the night.
[b] Harmonic mean ± pseudo-standard deviation.
[c] N = 14.

In the Duopa Phase 1 study, intrajejunal administration of Duopa rapidly achieved therapeutic plasma levels of levodopa and maintained consistent levodopa levels over the course of infusion.

Following termination of infusion, levodopa levels declined rapidly (see figure). The intra-subject variability in levodopa and carbidopa plasma concentrations starting from hour 2 to hour 16 following initiation of infusion was low (13% and 19%, respectively).

In the Duopa double-blind, active-controlled, Phase 3 Study, the intra-subject variability in levodopa and carbidopa plasma concentrations were much lower for patients treated with Duopa(21% and 25%, respectively) than in patients treated with oral levodopa-carbidopa 100/25 mg tablets (Sinemet® tablets over-encapsulated) (67% and 39%, respectively).

A cross-study population pharmacokinetic analysis suggested that Duopa has comparable bioavailability to the oral levodopa-carbidopa 100/25 mg tablets (over-encapsulated Sinemet® tablets). The bioavailability estimate for levodopa from Duopa relative to oral levodopa-carbidopa tablets was 97% (95% confidence interval; 95% to 98%).

Distribution

The volume of distribution of levodopa is moderately small. The partitioning ratio for levodopa between erythocytes and plasma is approximately 1. Levodopa has negligible binding to plasma proteins (about 10% to 30%). Levodopa is transported into the brain by the carrier mechanism for large neutral amino acids.

Carbidopa is approximately 36% bound to plasma protein. Carbidopa does not cross the blood-brain barrier.

Metabolism and Elimination

Levodopa is mainly eliminated via metabolism by the aromatic amino acid decarboxylase (AAAD) and the catechol-O-methyl-transferase (COMT) enzymes. Other routes of metabolism are transamination and oxidation. The decarboxylation of levodopa to dopamine by AAAD is the major enzymatic pathway when no enzyme inhibitor is co-administered. O-methylation of levodopa by COMT forms 3-O-methyldopa. When administered with carbidopa, the elimination half-life of levodopa is approximately 1.5 hours.

Carbidopa is metabolized to two main metabolites (α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid). These 2 metabolites are primarily eliminated in the urine unchanged or as glucuronide conjugates. Unchanged carbidopa accounts for 30% of the total urinary excretion. The elimination half-life of carbidopa is approximately 2 hours.

5 Sources of Clinical Data

The NDA was submitted to the following electronic gateway of the Agency :

\\Cdsesub1\evsprod\NDA203952\0015

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5.1 Tables of Studies/Clinical Trials

Figure 3 provides an overview of the U.S. clinical development program for LCIG.

Figure 3 Overview of U.S. Clinical Development Program for LCIG

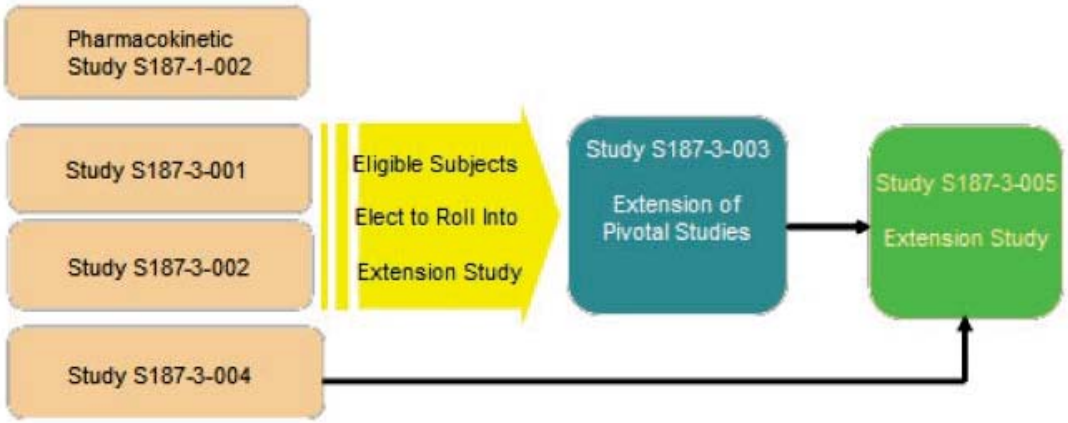

Table 2 shows all relevant trials in the clinical development program for LCIG. Trials S187-3- 001/S187-3-002 were two separate, essentially identical trials that were combined into a single study and is the most important trial in this NDA because it is the main trial supporting the efficacy and safety of LCIG. Other important trials that were conducted to collect long-term safety data were trials were S-187-3-003,-3-004, and -3-005. S187-1002 was a pharmacokinetic (PK) study. All these trials were important one conducted in the U.S. clinical development program. I will not present other non-IND studies that did not provide any significant information to this NDA.

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Table 2 Listing of Clinical Trials

Type of Study	Study ID	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1 PK Safety	S.187.1.002	5.3.3.2	Characterize the PK of levodopa, carbidopa and 3-O-methyldopa following administration of LCIG and evaluate safety of LCIG in subjects with advanced Parkinson's Disease.	Open-label, single arm, multicenter, multiple-dose study (enrolled subjects already on treatment with LCIG)	LCIG delivered to the proximal small intestine through a jejunal extension tube inserted via a PEG-J. The infusion dose was individually optimized. Oral LC IR tablets allowed after infusion termination	18 planned 19 enrolled 18 completed	Advanced Parkinson's Disease	2 days	Complete; Full
Phase 3 Controlled	S187-3-001/S187-3-002	5.3.5.1	Demonstrate the superiority of treatment with LCIG over treatment with optimized oral LC IR during 12 weeks of treatment.	Randomized double-blind, double-dummy, parallel-group, multicenter, active-control study	LCIG (PEG-J)[a] + placebo oral capsules Placebo gel (PEG-J)[a] + LC-oral capsules (100/25 mg LC IR tablets, encapsulated) Dose of LCIG and active control individually optimized by titration.	62 planned LCIG: 37 randomized 35 completed LC-oral: 34 randomized 31 completed	Levodopa-responsive subjects with advanced Parkinson's Disease who had persistent motor fluctuations despite optimized treatment with oral LC and other anti-Parkinson's Disease medications	12 weeks	Complete; Full

Table 2 Listing of Clinical Trials (Continued)

Type of Study	Study ID	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 2 PK	M12-925	5.3.5.1	Evaluate the safety, tolerability, PK, and efficacy of LCIG in advanced Parkinson's Disease Japanese patients with severe motor complications. Evaluate complications of medical devices for naso-jejunum system of LCIG.	Open-label, single arm, baseline-controlled, multicenter study	LCIG delivered to the proximal small intestine through an NJ tube. The infusion dose was individually optimized.	8 planned 8 enrolled 5 completed	Advanced Parkinson's Disease	21 days	Ongoing
Phase 3 Uncontrolled	S187-3-003	5.3.5.2	Evaluate the long-term safety of LCIG over a 12-month period	Long-term open-label, multicenter, single arm, extension study of S187-3-001/S187-3-002	LCIG delivered to the proximal small intestine through PEG-J. The infusion dose was individually optimized by titration.	66 planned[d] 62 enrolled 26 completed (29 subjects ongoing at interim data cut-off on 04 May 2012)	Levodopa-responsive subjects with advanced Parkinson's Disease who had motor fluctuations despite optimized treatment with available Parkinson's Disease medications	12 months	Ongoing
Phase 3 Uncontrolled	S187-3-003	5.3.5.2	Evaluate the long-term safety of LCIG over a 12-month period	Long-term open-label, multicenter, single arm, extension study of S187-3-001/S187-3-002	LCIG delivered to the proximal small intestine through PEG-J. The infusion dose was individually optimized by titration.	66 planned[d] 62 enrolled 26 completed (29 subjects ongoing at interim data cut-off on 04 May 2012)	Levodopa-responsive subjects with advanced Parkinson's Disease who had motor fluctuations despite optimized treatment with available Parkinson's Disease medications	12 months	Ongoing

Table 2 Listing of Clinical Trials (Continued)

Type of Study	Study ID	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Uncontrolled	S187-3-004	5.3.5.2	Evaluate the long-term safety and tolerability of LCIG over 12 months.	Long-term, open-label, multicenter, safety and efficacy	LCIG delivered to the proximal small intestine initially through a temporary NJ tube and then Peg-J. The infusion dose was individually optimized by titration.	320 planned 354 enrolled 272 completed	Levodopa-responsive subjects with advanced Parkinson's Disease who had motor fluctuations despite optimized treatment with available Parkinson's Disease medications	12 months	Complete; Full
Phase 3 Uncontrolled	S187-3-005	5.3.5.2	Provide continued access to LCIG to subjects who participated in a previous open-label study (S187-3-003, S187-3-004)	Long-term, open-label, multicenter, safety and tolerability	LCIG delivered to the proximal small intestine through PEG-J. The infusion dose was individually optimized by titration.	275 planned 220 enrolled 20 completed (transitioned to commercial LCIG) and 179 ongoing as of the 04 May 2012 interim data cut-off date.	Levodopa-responsive subjects with advanced Parkinson's Disease who had motor fluctuations despite optimized treatment with available Parkinson's Disease medications.	Until LCIG is commercially available in countries where subjects are participating.	Ongoing

5.2 Review Strategy

My review strategy focused on reviewing and presenting results of Trial S187-3- 001/S187-3-002 (a randomized, double-blinded, active-controlled trial, double-dummy trial) for efficacy and safety of LCIG. This trial compared results of LCIG delivered via a PEG and J tube with active-controlled treatment with oral LD/CD (e.g., Sinemet). Oral LD/CD (e.g., Sinemet) has been used for treating Parkinson's Disease for many years and is still considered an important and potent therapeutic option. My impressions and conclusions about efficacy and safety from the review of this trial are related to the fact that patients in this trial were randomized to treatment with LCIG or oral LD/CD and treatment was conducted under double-blinded conditions using a double dummy trial design.

Trial S187-3- 001/S187-3-002 used a flexible dosing regimen in which patients were titrated to presumably optimal benefit and minimal problems with tolerability/adverse reactions from their treatment. Because patients were not randomized to fixed-treatment doses, the potential for observing dose-response information for efficacy and safety is limited. Flexible dose studies designs do not typically provide adequate dose-response information for efficacy and safety. Nevertheless, my review will consider assessing for possible dose-related effects based upon additional categorization of patients in both treatment groups to either “low” or “high” dose treatment based upon the mean daily levodopa dose the whole tria of < 1250 mg or ≥ 1250 mg, respectively. All safety analyses were conducted not only to any mean daily levodopa dose but also according to “low” dose, or “high” dose.

Generally. central tendency analyses of clinical laboratory analytes, vital signs, and ECGs generally were not very informative, consequently my review focuses predominantly on presenting outlier results for these safety parameter, particularly those suggesting any safety signals or noteworthy treatment differences related to LCIG (vs oral LD/CD).

Analyses of efficacy and safety data were also made with respect to various subgroups to various intrinsic and extrinsic factors including age, gender, body mass index (BMI), duration of Parkinson's Disease, race, dopaminergic agonist use (in addition to levodopa), and geographic region. My review/interest focused on all of these factors with the exception of BMI and duration of Parkinson's Disease (factors selected by the sponsor) because I did not consider that these factors to have a significant potential for an interaction. My review also included a differential perspective for considering the potential importance of certain subgroups as factors influencing efficacy and safety data and even certain safety data categories. For example, all subgroup factors considered potentially important for one category of safety data (e.g., adverse events) were not necessarily considered as potentially as influential for another category of safety data (e.g., clinical laboratory analytes).

My review for open-label, long-term extension trial safety data focused on a pool of 3 open-label trials (S187-3-003,-3-004, and -3-005. My impressions and conclusions about safety from the review of these pooled data relate to :1) seeking data that help support safety findings observed in the controlled trial; 2) noting safety data/observations from long-term treatment (up to years in

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some patients); 3) noting rare adverse reactions that may be important and possibly related to LCIG treatment and/or the whole product including associated devices and necessary procedures; and 4) noting safety findings suggesting a dose-relationship for patients treated with higher doses of LCIG. Pooled open-label trial data were also reviewed from the perspectives of dose and subgroups.

Data from the Phase 3 studies are analyzed using 5 different analysis sets, described in detail in Table 3, were designed to evaluate the safety and tolerability of LCIG as well as the safety and tolerability of the devices and procedures necessary to administer LCIG, including any temporal relationships to the procedures. Each integrated analysis set contains a significant number of overlapping subjects and the ISS presentation focuses primarily on 3 of the 5 analysis sets: Active-Controlled Analysis Set, Open-Label LCIG Analysis Set, and All PEG-J Analysis Set. The Active-Controlled and Open-Label LCIG Analysis Sets are the primary focus for most safety assessments and the All PEG-J Analysis Set is the primary focus for evaluating AESIs that were Procedure- and Device-Associated Events (CMQ), including an assessment of the temporal relationship to the date of the original PEG-J placement.

The objective of each analysis set, including the 3 key analysis datasets (Active Controlled, Open-Label LCIG, PEG-J) and 2 supportive analysis sets (LCIG, 3004), is described in Table 3.

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Table 3 Objectives for Data Analysis Sets Analyzed for Safety

Analysis Set	N	General Description	Objective of Analysis Set and Treatment Groups
Key Analysis Sets Presented and Discussed within this ISS			
Active-Controlled (i.e., Controlled Study)	71	All subjects who underwent PEG-J placement in combined pivotal Study S187-3-001/S187-3-002. Most of the safety analyses from this analysis set are identical to those presented in the combined Study S187-3-001/S187-3-002 CSR with additional analyses included in this ISS.	Allows a direct comparison of the safety and tolerability over 3 months of the 2 different formulations of the same active compound (levodopa-carbidopa) and discussion of LCIG exposure. The focus in this set is on the non-procedure- and device-associated events.
Open-Label LCIG (i.e., Pooled Open-Label Studies)	412	All subjects in the 3 Phase 3 open-label studies (Studies S187-3-003, S187-3-004, and S187-3-005) who received at least 1 dose of LCIG via an NJ tube and/or PEG-J. This includes 62 subjects enrolled in Study S187-3-003, 26 subjects in Study S187-3-004 who received LCIG via an NJ tube only, and 324 subjects in Study S187-3-004 who received LCIG via an NJ tube followed by PEG-J. All subjects in Study S187-3-005 were included but did not affect the subject count because these subjects rolled over from Study S187-3-003 and Study S187-3-004. Four subjects who enrolled in Study S187-3-004 but failed NJ placement attempts and never received LCIG were not included.	Allows for a temporal evaluation of AEs not associated with the procedure and device from the time of first use of open-label LCIG, regardless of the method of delivery by which subjects received LCIG.
All PEG-J	395	All subjects who underwent PEG-J placement in the Phase 3 Studies S187-3-001/S187-3-002 (N = 71) and S187-3-004 (N = 324) including continuation into the open-label extension Study S187-3-003 and Study S187-3-005.	Allows for the evaluation of AEs related to the procedure and device, including a temporal relationship from the time of first placement of the PEG-J.
Supportive Analysis Sets			
All LCIG	416	All subjects who received at least 1 dose of LCIG in the Open-Label LCIG Analysis Set and in the LCIG group of the Active-Controlled Analysis Set. This includes 37 subjects in Study S187-3-001/S187-3-002 randomized to LCIG, 29 subjects in Study S187-3-001/S187-3-002 randomized to LC-oral once they continued into the open-label extension Study S187-3-003, 26 subjects in Study S187-3-004 who received LCIG via an NJ tube only, and 324 subjects in Study S187-3-004 who received LCIG via an NJ tube followed by PEG-J. Five subjects who received LC-oral in the pivotal Study S187-3-001/S187-3-002 did not roll over into the open-label extension Study S187-3-003 and are not included in this analysis set. Four subjects, who enrolled in Study S187-3-004 but failed NJ placement attempts and never received LCIG, were also not included.	Allows for assessment of LCIG exposure in blinded or open-label studies, regardless of the method of delivery by which subjects received LCIG.
3004	354	All subjects who underwent NJ tube insertion in Study S187-3-004. Most of the safety analyses of this analysis set are identical to those presented in the Study S187-3-004 CSR with additional analyses included in this ISS.	Allows for an evaluation of the safety and tolerability of the NJ (Study S187-3-004 was the only study that utilized the NJ Test Period).

A schematic of the analysis sets discussed in this ISS is provided in Figure 4. Subjects could only enroll into the Phase 3 program by being randomized to LCIG or LC-oral in

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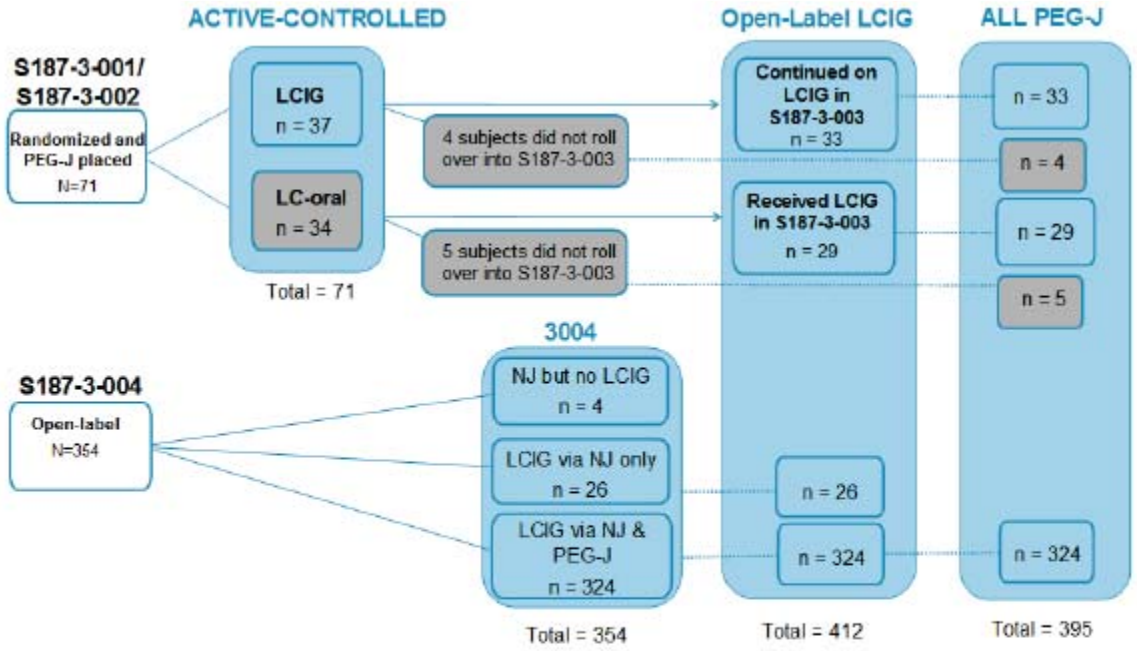
Study S187-3-001/S187-3-002 or by enrolling in the open-label Study S187-3-004 that utilized the NJ Test Period for initial titration.

Figure 4 Key Analysis Sets Discussed Within the ISS



Note: All LCIG Analysis Set is described in Table 7 and Table 8 and not represented in this figure.
Cross reference: Table 2.1__1.2.1, Study S187-3-003 Interim CSR Table 14.1__1.1, Study S187-3-004 CSR Section 10.1

Patients were classified as a low dose user or a high dose user as relevant for each analysis set using the following methods:

● Active-Controlled Analysis Set: each subject's mean total daily dose of levodopa (study drug + levodopa-carbidopa IR tablets) over the entire study was calculated. Each subject was classified as a low dose user(< 1250 mg/day) or high dose user (≥ 1250 mg/day) based on the mean total daily dose.
● Open-Label LCIG Analysis Set:
○ For subjects who received LCIG in Study S187-3-003, the total daily dose of levodopa (LCIG + levodopa-carbidopa IR tablets) on the last titration day in Study S187-3-003 was used to classify each subject as a low dose user (< 1250 mg/day) or high dose user (≥ 1250 mg/day).
○ For subjects who received LCIG in Study S187-3-004: the total daily dose of levodopa (LCIG + levodopa-carbidopa IR tablets) was calculated for each day when the titration card or subject dosing diary is available. The total daily dose on the days when dosing records were not available was imputed from the previous non-missing day. This was done for the entire LCIG treatment period in Study S187-3-004. The mean total daily dose was obtained to classify each subject as a low dose user (< 1250 mg/day) or high-dose user (≥ 1250 mg/day).

● All LCIG Analysis Set:
○ For subjects randomized to the LCIG group in the pivotal Study S187-3-001/S187-3-002 and who did not receive LCIG in Study S187-3-003: the classification of the subject as a low dose or high dose user was the same as that defined for the Active-Controlled Analysis Set.
○ For subjects randomized to the LCIG group in the pivotal study and who received LCIG in Study S187-3-003: the total levodopa dose on the last titration day in Study S187-3-003 was carried forward to the last LCIG infusion day in the study. The mean total daily dose across both the pivotal study and Study S187-3-003 was obtained for each subject and used to classify each subject as a low dose user (< 1250 mg/day) or high dose user (≥ 1250 mg/day).
○ For subjects randomized to LC-oral in the pivotal study and who received LCIG in Study S187-3-003: classification of the subject as a low dose or high dose user was the same as that defined for the Open-Label LCIG Analysis Set.
○ For subjects who received LCIG in Study S187-3-004: classification of the subject as a low dose or high dose user was the same as that defined for the Open-Label LCIG Analysis Set.
No statistical tests were performed for the Open-Label LCIG Analysis Set, the All PEG-J Analysis Set, 3004 Analysis Set, and the All LCIG Analysis Set because each analysis set has only 1 treatment group. The evaluation of these analysis sets focuses on the severity and temporal distribution of AEs related either to LCIG use, devices (NJ or PEG-J), and related procedures. For all safety analyses, Baseline is defined as the last non-missing observation prior to the treatment system exposure start date defined. The final observation is defined as the last non-missing post-Baseline observation.

A Gap Period (number of days) was defined to include data collected after the end date of the treatment system exposure in the analysis. For all analyses, the Gap Period was 1 day for all assessments except TEAEs and device complaints. TEAEs had a 30-day Gap Period while device complications did not have a Gap Period (all device complications are included regardless of time relative to end to "treatment system exposure").
For all safety analyses performed by treatment period, the Titration Period was defined as the first 28 days of treatment system exposure and the Maintenance Period was defined as treatment system exposure on or after Day 29. Safety observations that were persistent are defined as those with onset during the Titration Period that ended during the Maintenance Period with a duration of ≥ 7 days. Safety observations with onset during the Titration Period that were ongoing at the end date of treatment system exposure were also considered persistent.

Additional details for each of the analysis sets used in this ISS are provided in the ISS SAP. Results are summarized in this ISS for all subjects in each analysis set by study drug and delivery system, as appropriate for each analysis set, and by treatment group (LCIG versus LC-oral) for the Active-Controlled Analysis Set. Adverse events related to the procedure and device is summarized for the All PEG-J Analysis Set.

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Table 4 shows the data sets analyzed for efficacy and safety from the Active-Controlled trial.

Table 4 Datasets of All Randomized Patients in Active-Controlled Trial Analyzed for Efficacy and Safety

	Statistic	LCIG + Placebo Capsules (N=37)	Placebo Gel + Levodopa-Carbidopa Capsules (N=34)	All Subjects (N=71)
Number of Subjects in the Safety Data Set	n (%)	37 (100)	34 (100)	71 (100)
Number of Subjects Excluded From the Safety Data Set	n (%)	0	0	0
Reasons for Exclusion:				
PEG not placed	n (%)	0	0	0
Number of Subjects in the Full Analysis Data Set	n (%)	36 (97.3)	33 (97.1)	69 (97.2)
Number of Subjects Excluded From the Full Analysis Data Set	n (%)	1 (2.7)	1 (2.9)	2 (2.8)
Reasons for Exclusion:				
Not in the Safety Data Set	n (%)	0	0	0
No Baseline Efficacy Assessment	n (%)	0	0	0
No Post-Baseline Efficacy Assessment	n (%)	1 (2.7)	1 (2.9)	2 (2.8)
Number of Subjects in the Completers Data Set	n (%)	35 (94.6)	31 (91.2)	66 (93.0)
Number of Subjects Excluded from the Completers Data Set	n (%)	2 (5.4)	3 (8.8)	5 (7.0)
Reasons for Exclusion:				
Did not complete the study	n (%)	2 (5.4)	3 (8.8)	5 (7.0)
Not in the Full Analysis Data Set	n (%)	1 (2.7)	1 (2.9)	2 (2.8)
Number of Subjects in the Resistant Data Set	n (%)	35 (94.6)	33 (97.1)	68 (95.8)
Number of Subjects Excluded from the Resistant Data Set	n (%)	2 (5.4)	1 (2.9)	3 (4.2)
Reasons for Exclusion:				
Did Not Meet Inclusion Criteria #3	n (%)	1 (2.7)	0	1 (1.4)
Not in the Full Analysis Data Set	n (%)	1 (2.7)	1 (2.9)	2 (2.8)

Note: Percentages are based on the number of subjects randomized.
Note: Subjects may be counted in more than one reason for exclusion
Note: No subjects were included in the PD Medication Increase data set, and the No PD Medication Increase data set was the same as the FA data set. Therefore, these data sets are not summarized above.
Source: Table 14.1__1.2

5.3 Discussion of Individual Studies/Clinical Trials

Trial S187-3- 001/S187-3-002 was planned as a result of many interactions between the sponsor and the DNP to attempt to collect efficacy and safety data that would help support the approval of LCIG treatment. During planning of this trial design, consideration focused on the need to have this trial controlled with a comparator (i.e., oral LD/CD) rather than with intestinal infusion of placebo. Use of a placebo was not considered because of the clinical and ethical difficulties of not allowing these patients with relatively severe Parkinson's Disease the important option of concomitant treatment with LD/CD. There were also concerns that use of intestinal infusion of placebo would lead to unblinding of treatment. To facilitate double-blinding of treatment of patients treated with LCIG, the study design required a double dummy approach in which patients randomized to LCIG would also receive oral placebo and patients randomized to oral LCIG would also receive intestinal infusion of placebo. In addition, to the lack of replication of efficacy of Trial S187-3- 001/S187-3-002 from 2 separate trials, other shortcomings of this trial were the relatively small number of patients randomized to each treatment (i.e., 37 to LCIG and 34 to oral LD/CD and the relatively short treatment duration (i.e., 3 months) instead of a long treatment such as 6 months for collecting controlled efficacy and safety data. Three months treatment was considered the minimal duration required by the Division.

Most patients who are participated in the active-controlled trial "rolled over" into a long-term, extension safety trial. In addition, many patients enrolled in the

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The sponsor sought an indication for long-term treatment of motor fluctuations with LCIG in patients with advanced Parkinson's disease. The approach in the active-controlled trial was to seek to enroll patients with motor fluctuations and advanced Parkinson's disease who were inadequately controlled with oral LD/CD and other various Parkinson's disease medications (dopaminergic agonists, MAO-B inhibitors, COMT inhibitors) because these medications were ineffective or patients had experienced adverse reactions/intolerability to these medications.

6.1.1 Methods

Trial Design

Study S187-3-001 and Study S187-3-002 were identically designed randomized,double-blind, double-dummy, multicenter, parallel group studies that recruited subjects from distinct sites. As previously noted, the FDA agreed that the combined data from these 2 studies could constitute a single pivotal study. Additionally, it was agreed that a single pivotal study of sufficient robustness could form the basis for the LCIG System NDA. The combined studies are presented as Study S187-3-001/S187-3-002 and evaluated the efficacy, safety, and tolerability of LCIG in the treatment of levodopa-responsive subjects with advanced PD who had persistent motor fluctuations, despite optimized treatment with oral levodopa-carbidopa and other available antiparkinsonian medications as adjunctive treatment. The study consisted of a Screening Period (open-label treatment with oral levodopa-carbidopa IR capsules, required adjustment for antiparkinsonian medication, and completion of Baseline procedures), a Hospitalization Period for the PEG-J placement, randomization and a Double-Blind Treatment Period (study drug treatment for 12 weeks) including an initial titration following PEG-J placement. Subjects were randomly assigned in a 1:1 ratio to receive either LCIG infusion plus placebo capsules (LCIG group) or placebo gel infusion plus encapsulated levodopa-carbidopa IR tablets (LC-oral group) in a double-blind, double-dummy manner. Beginning at randomization and continuing through the Week 4 Visit, all study drugs were to be optimized for each individual subject on the basis of the investigator's evaluation. After the Week 4 Visit, subjects were to remain on a fixed dose of the study drugs, unless there was an AE that required a clinically indicated dose adjustment, as determined by the investigator.

A schematic of the study design is presented in Figure 5.

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Figure 5 Trial Design for Pivotal Study S187-3-001/S187-3-002

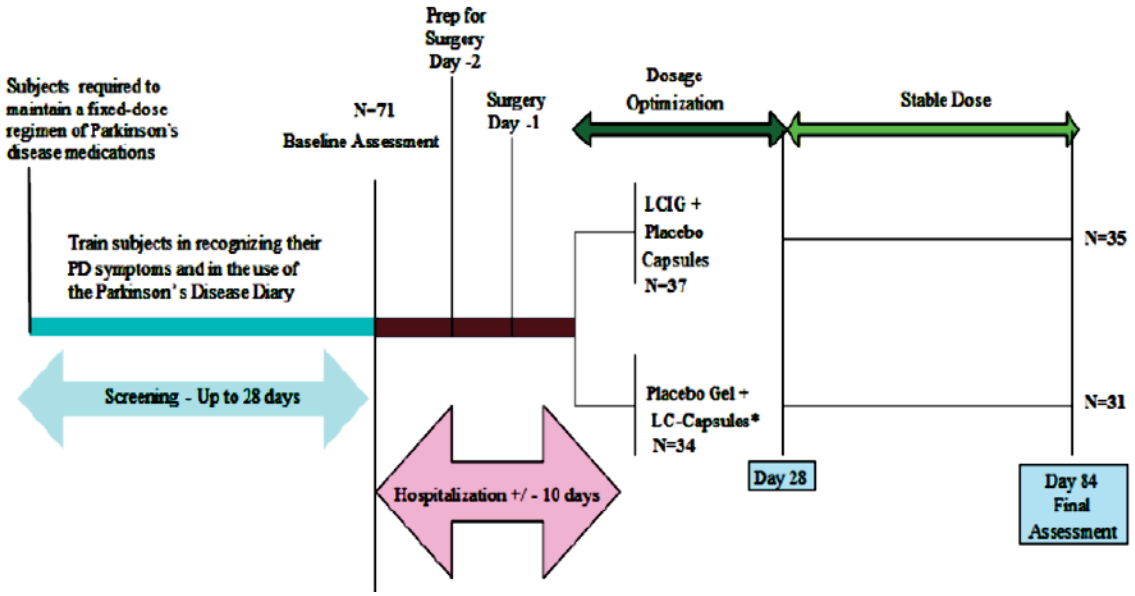

Table 5 shows the schedule of assessments for the controlled trial,

Table 5 Schedule of Assessments

	Screen Periods				Double-Blind Treatment Visits took place ±3 days from the scheduled day, beginning at the Study Day 8 Visit													Follow-Up**
	1		2	3														
Week	Up to 35 days					1	2	3	4	5	6	7	8	9	10	11	12*	13
Day	Up to 28 days	–12 to –3	–2	–1	1	8	15	22	29	36	42 – 43	50	57	64	71	78	85 – 86[k]	92
Hospitalization			X	X	X	X					X						X	
Clinic visit	X		X				X	X	X				X		X			X
Telephone visit										X		X		X		X		
Informed consent	X																	
Eligibility criteria	X		X															
Demographics	X																	
Med/neuro history	X																	
Physical/neuro exam	X																X	
Height	X																	
Weight	X																X	
Melanoma check	X																X	
Vital signs	X		X	X[a]	X[a]	X[a]	X	X	X		X[a]		X		X		X	X
Standard ECG	X								X				X				X	
Holter ECG			X[a]	X[a]	X[a]	X[a]					X[a]							
Clinical labs	X		X[f]								X						X	

Table 5 Schedule of Assessments (Continued)

	Screen Periods				Double-Blind Treatment Visits took place ±3 days from the scheduled day, beginning at the Study Day 8 Visit													Follow-Up**
	1		2	3														
Week	Up to 35 days					1	2	3	4	5	6	7	8	9	10	11	12*	13
Day	Up to 28 days	–12 to –3	–2	–1	1	8	15	22	29	36	42 – 43	50	57	64	71	78	85 – 86[k]	92
Stable dose of levodopa-carbidopa 100/25 IR	X	X	X	X														
Pre-surgical procedures			X	X														
Implantation of upper-intestinal device				X														
Begin randomized treatment					X													
PEG-J follow-up gastroenterologist/ surgeon					X	X												
Removal of upper-intestinal device																	X[j]	
Radiological check of tube placement				X							X						X	
Stoma site inspection					X	X	X	X	X		X		X		X		X	X
Pre-randomization complaints/AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5 Schedule of Assessments (Continued)

AIMS = Abnormal Involuntary Movement Scale; AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; ECG = electrocardiogram; EQ-5D = EuroQol Quality of Life-5 Dimensions; IR = immediate release; MIDI = Minnesota Impulsive Disorders Interview; MMSE = Mini-Mental State Examination; PDQ-39 = Parkinson's Disease Questionnaire; PEG-J = Percutaneous endoscopic gastrostomy – with jejunal extension tube; PD = Parkinson's disease; PK = pharmacokinetic; UPDRS = Unified Parkinson's Disease Rating Scale; ZBI = Zarit Burden Interview

a. Resting Holter ECGs and orthostatic vital sign measurements were collected as follows:
   - Three sets of orthostatic vitals and Holter 12-lead ECGs (collected as close to 30 minute intervals as possible) were collected in the early morning prior to the insertion of the upper-intestinal tube (e.g., at –90, –60, and –30 minutes prior to tube insertion).
   - On Study Day –2 or Study Day –1, 3 sets of orthostatic vital sign measurements and Holter 12-lead ECGs were collected in the early morning prior to the PEG-J placement procedure.
   - On Study Day 1 and Study Day 8, 3 sets of orthostatic vita sign measurements and Holter 12-lead ECGs (collected as close to 30 minute intervals [e.g., at –90, –60, and –30 minutes] as possible) were collected in the early morning prior to the morning oral dose and initiation of the gel infusion; and 3 sets of orthostatic vital sign measurements and Holter 12-lead ECGs (collected as close to 20 minute intervals as possible) at 1, 2, 4, 8, 12, and 16 hours after the initiation of the infusion.
   - On Study Day 42, 3 sets of orthostatic vital sign measurements and 12-lead Holter ECGs (collected as close to 20 minute intervals as possible) were collected at 12 and 16 hours after the initiation of the gel infusion.
   - On Study Day 43, 3 sets of orthostatic vital sign measurements and 12-lead Holter ECGs were collected prior to the morning oral dose and initiation of the gel infusion (collected as close to 30 minute intervals as possible) and at 1, 2, 4, and 8 hours after the initiation of the infusion (collected as close to 20 minute intervals as possible). For time points at which both blood sampling and vital sign/ECG measurements were scheduled, the vital sign/ECG measurements were taken prior to sample collection. Subjects were hospitalized in the afternoon of Study Day 42 and released on Day 43 after completion of study procedures.
   - At Screening and/or early termination, a single, standard 12-lead ECG was performed. On Study Day 29, Study Day 57, and Study Day 86, a single, standard 12-lead ECG was performed as close as possible to 2 hours after the initiation of the gel infusion on that day.

b. For female subjects who were of childbearing potential, a negative urine pregnancy test result was required prior to any radiological procedures and prior to the PEG-J placement procedure, at Week 6, and at Week 12/early termination.

c. Recording in the Parkinson's Disease Diary was to be performed for 3 days prior to PEG-J procedure (Study Day –12 to –3) and during the 3 consecutive days prior to clinic visits (including early termination). A reminder phone call was made 4 days prior to the clinic visit to remind subjects about diary completion.

Open-Label Long-Term Extension Safety Trials

There were 3 open-label, long-term extension trials (S187-3-003,-3-004,-3-005) that collected primarily safety data (adverse events, clinical laboratory analytes, vital signs, ECGs). Only patients who completed 12 weeks of double-blind, double-dummy treatment in Study S187-3-001/S187-3-002 qualified for enrollment in a continuation treatment study. Subjects who received LCIG in the pivotal study continued to receive LCIG, and subjects who received LC-oral in the pivotal study switched to LCIG. Subjects were to be 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 initial establishment of the optimum morning and continuous infusion LCIG dose. The design and conduct of the open-label trials should be considered generally similar. However, in Trial S187-3-004, patients were initially treated patients with a temporary nasojejunal (NJ tube) (2 to 14 days) with the infusion pump (NJ Test Period) to determine if the subject responded favorably to this method of treatment and to optimize the dose of LCIG before treatment with a permanent PEG-J was started. New patients enrolling in an open label trial underwent a brief hospitalization for PEG placement and subsequent LCIG titration. All patients in Trial S187-3-005 were rolled over from Trial S187-3-003 and Trial S187-3-004.

Key Inclusion Criteria
Subjects with PD who experienced motor complications despite optimized available therapy were eligible to participate in the study if they met the following study criteria.

The subject's PD was levodopa-responsive. The subject had to demonstrate some identifiable "On" response, as established through observation by the investigator. Additionally, the subject had to demonstrate severe motor fluctuations in spite of individually optimized treatment, indicating other therapy should be considered.

- The subject's history of antiparkinsonian therapy included the following:
  - Had demonstrated a significant response to levodopa
  - Had an adequate trial of IR levodopa-decarboxylase inhibitor (e.g., Sinemet) or controlled-release levodopa-decarboxylase inhibitor (e.g., Sinemet-CR) administered at a daily dose equivalent to a dose of ≥ 400 mg levodopa
  - Had an adequate trial of a dopaminergic agonist administered concomitantly with levodopa-decarboxylase inhibitor
  - Had an adequate trial of a COMT inhibitor (i.e., entacapone or tolcapone) or an adequate trial of a monoamine oxidase (MAO)-B inhibitor
    An "adequate trial" was defined as a therapeutic attempt in which the subject failed to achieve the therapeutic benefit for reasons of either lack of efficacy or intolerability. The subject had to have been treated for a minimum period of 2 weeks at a minimal dose of at least 33% of the maximally recommended dose in the approved label; or have discontinued the drug either because of an adverse reaction of intolerability following the dosing regimen in the approved label.

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- The subject had recognizable "Off" and "On" state (motor fluctuations), as confirmed by the Parkinson's Disease Diary recordings prior to the PEG-J procedure. Parkinson's Disease Diaries were collected and evaluated prior to the PEG-J placement procedure.

- The subject had to be experiencing a minimum of 3 hours of "Off" time confirmed by the Parkinson's Disease Diary for each of 3 consecutive days prior to the PEG-J procedure. The "Off" time had to occur during a continuous 16-hour interval, including the portion of the day in which the subject was awake the majority of the time (i.e., 5 AM to 9 PM, 7 AM to 11 PM).

- The subject (or subject's proxy/caregiver) had to be able to complete both the Daily Dosing Diary and the Parkinson's Disease Diary for recording "Off" time. The subject or caregiver had to also be able to demonstrate the ability to operate, manipulate, and care for the infusion pump and tubing.

- The subject had to demonstrate a 75% concordance with the investigator's or qualified designee's assessment of symptoms on the Parkinson's Disease Diary following training. The subject also had to have a 75% or greater compliance rate on the diary completion to qualify for randomization.

- The subject was male or female at least 30 years of age.

Key Exclusion Criteria
Subjects meeting any of the common exclusion criteria at Screening or prior to randomization were to be excluded from participation in the study. The following is key exclusion criterion for this trial.

- The subject for whom the placement of a PEG-J tube for LCIG treatment was contraindicated or the subject would have been considered a high risk for the PEG-J procedure, according to the gastroenterologist's evaluation. Contraindication for PEG-J tube placement included, but was not limited to, the following conditions: pathological changes of the gastric wall, inability to bring the gastric wall and abdominal wall together, blood coagulation disorders, peritonitis, acute pancreatitis, and paralytic ileus.

Active Controlled Trial Treatment (Including Dosing)

Selection of Doses in the Study
Subjects randomized into the study were to have been on optimized oral levodopa-carbidopa IR. After randomization to the equivalent LCIG dose (with placebo capsules) or LC-oral dose capsules (with placebo gel), the subjects were maintained on their previously established stable regimen of antiparkinsonian medications.

Selection and Timing of Dose for Each Subject

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Subject instructions regarding the timing (time of day, interval) of dosing and how to take the dose(s) are described below for the infusion gel and oral treatment. No restrictions were given relating to oral dosing and meals.

During the dose titration from Study Day 2 through the end of titration (up to 14 days), dependent on the effectiveness of the previous day's dose, the dose of the study drugs could have been adjusted up or down once daily. From the end of the dose titration through the Study Week 4 Visit, adjustment to the study drugs was permitted only at the weekly clinic study visits. Following the Study Week 4 Visit, the dose of study drugs was to remain stable for the remaining 8 weeks of the study, and further adjustments were not permitted.

An exception throughout the study was made when a decrease in the study drug was clinically indicated in order to manage side effects (e.g., persistent hyperkinesia). When an adjustment was made to 1 of the study drugs, a concomitant change had to be made to the other study drug to maintain the integrity of the double-blind, double-dummy design of the study.

Only the doses of oral levodopa-carbidopa IR taken during a defined 16-hour day time period were to be used to calculate the total daily dose. This 16-hour period was the same16-hour interval when the study drugs were administered (infusion and oral). The total daily dose calculation was not to include the doses of levodopa-carbidopa that were taken during the night when the continuous infusion was not administered.

Dose Titration
The schedule of oral dosing during the double-blind period was to be based on the oral levodopa-carbidopa IR dosing schedule established prior to double-blind randomization and was to equal 16 hours. For example, if a subject was receiving an oral dose every 3 hours, then the subject was to remain on that same schedule of oral double-blind medication.

The initial dose of oral medication was to match the dose given to the subject prior to randomization. Rescue doses of oral levodopa-carbidopa 100/25 mg IR tablets were administered to address immediate medical needs throughout the day, and were recorded on the inpatient Dose Titration Monitor.

On each subsequent day during titration, both the oral dose and gel infusion dose could be adjusted on the basis of the subject's response to the previous day's treatment and the amount of, if any, rescue medication. If both the investigator and subject were satisfied with the effectiveness of treatment, then no change in the oral dose and gel infusion dose was required.

If clinically indicated, changes in the dose either upward or downward could have been made to further optimize the subject's treatment response. Any adjustments were made equally to both oral and gel infusion dosages. For example, if the daily gel infusion was increased by 5 mL (100 mg levodopa), the oral dose was to have been increased by that same amount.

Required additional oral doses were to be added to the next day's oral dose(s) schedule that most closely corresponded to the time point when the rescue oral dose was needed on the previous

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day. Changes were allowed on a once-daily basis and could only be made at the beginning of each day during dose titration (up to 14 days).

If at any time during titration, the subject developed unsafe dyskinesia or other levodopa-related complications, the gel infusion and oral dose could be paused, if judged absolutely necessary by the investigator, until symptoms had improved to a clinically acceptable level.

Additionally, if at any time during titration the subject developed a prolonged "Off" state that was unsafe or caused the subject unacceptable discomfort, a rescue dose of oral levodopa-carbidopa IR could be administered, if judged necessary by the investigator, until symptoms improved.

In addition to the dosing instructions provided in the protocol, investigators were provided with "Titration Principles," a concise flow chart to guide them through the dosing algorithm decision process.

LCIG (or Placebo) Infusion
Morning Dose
A morning dose was administered as a bolus infusion by the pump to fill the dead space of the intestinal tube and rapidly achieve a therapeutic dose level (over approximately 10 to 30 minutes). This was usually 5 to 10 mL and corresponded to 100 to 200 mg of levodopa.

The total morning dose was not to exceed 15 mL (300 mg levodopa). Subjects were not administered a full equivalent of their usual oral morning dose of levodopa-carbidopa. The starting morning dose of LCIG (or placebo) was calculated at 80% of the subject's usual oral morning dose of the levodopa component of their levodopa-carbidopa 100/25 mg IR tablets, which was established prior to randomization.

The morning dose could have been increased or decreased once daily in the morning from Study Day 2 through the end of initial titration, depending on the effectiveness of the previous day's dose. After completion of initial titration and up to Study Week 4, adjustments to the morning bolus dose were permitted at weekly clinic visits; both upwards and downwards adjustments were allowed.

Note that an additional 3 mL was to be added each day to the morning dose calculation to allow for the priming of the PEG-J tubing that was to be flushed every night.

Continuous Maintenance Dose
The continuous maintenance gel infusion dose could have been adjusted once daily on the basis of the investigator's evaluation of the effectiveness of the previous day's dose and any oral rescue doses. The initial maintenance dose (i.e., the continuous infusion rate for the next 16 hours) was calculated as follows:
Calculation of continuous dose (16-hour day):
● Total oral daily dose minus morning dose and last dose of the day = continuous dose over 16 hours

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● Continuous dose divided by 16 hours = continuous hourly dose.

Only the doses of oral levodopa-carbidopa 100/25 mg IR tablets taken during the 16-hour daytime period were used to calculate the total daily dose. The total daily dose did not include the doses of levodopa-carbidopa that were taken at night when the continuous infusion was not administered.

During treatment, investigator consideration was to be given to instances in which deterioration of treatment response occurred. In the absence of pump alarm notifications, a sudden deterioration in treatment response with recurring motor fluctuations could have been the result of the distal part of the tube becoming displaced from the upper intestine into the stomach. The location of the tube was to be determined radiographically; if necessary, the end of the tube could have been repositioned to the proximal small intestine and the new placement confirmed radiographically.

If a problem developed with the LCIG System and the gel infusion needed to be temporarily discontinued, the subject also had to stop taking the double-blind capsules, in order to maintain the double-blind, double-dummy study design. The investigator was to place the subject on a regimen of oral levodopa-carbidopa 100/25 mg IR tablets (whole tablets) until the problem was resolved and the gel infusion could be resumed the following morning. If the subject was placed on a regimen of oral levodopa-carbidopa 100/25 mg IR tablets, the dose prescribed was to be based on the dose the subject was receiving just prior to randomization and adjusted, as clinically indicated, to stabilize the subject. If the interruption of study drug lasted less than 24 hours, the investigator could have resumed treatment the following morning with the same amount of study drugs (infusion gel and oral) that the subject had been receiving prior to the interruption of the infusion. If the interruption was greater than 24 hours, the investigator was to consult the medical monitor prior to restarting the infusion. Daily dosing and deviations from routine dosing were to be recorded in the Daily Dosing Diary, which was to be completed each day of the study that the subject was not a patient in the hospital.

Oral Levodopa-Carbidopa IR or Placebo Capsules
Morning Oral Dose
The morning dose of oral levodopa-carbidopa 100/25 mg IR or placebo was to be administered at the same time as the morning dose of infusion. The morning dose administered during double-blind treatment was to be equal to the morning dose established prior to randomization.

Remaining Daily Oral Doses
From Study Day 2 through the end of dose titration (up to 14 days), taking into consideration the subject's previous day's response to the study drugs, the investigator could increase or decrease the subject's remaining daily oral study drug dosage (total daily oral dose minus the morning oral dose) at the beginning of each day. After completing dose titration and continuing through the Study Week 4 Visit, the investigator could increase or decrease the subject's remaining daily oral study drug dosage at the weekly clinic visits. Following the Study Week 4 Visit, the dosage of the study drugs was to remain fixed for the remaining 8 weeks of the study and further adjustments were not to occur. An exception to this throughout the study was made when a

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decrease in the study drug was clinically indicated in order to manage side effects (e.g., persistent hyperkinesia).

When an adjustment was made to the oral dose, a concomitant change was to be made to the gel infusion dose. All adjustments to the remaining daily oral study drug dosage (total daily oral dose minus morning oral dose) were to be made in 100/25 mg increments equal to levodopa-carbidopa 100/25 mg IR whole tablets.

At night, the last daily double-blind dose of oral levodopa-carbidopa 100/25 mg IR or placebo capsule was to be 1 single oral levodopa-carbidopa 100/25 mg IR or placebo capsule, to maintain the double-blind double-dummy study design. The last daily dose was to be taken at the same time the pump was disconnected and the tube was to be flushed with potable water.

Rescue Oral Levodopa-Carbidopa Immediate Release Tablets
The subject was allowed to take levodopa-carbidopa rescue tablets, as needed, during the titration period. Subjects were allowed to use 50 mg or one-half tablets of levodopa-carbidopa rescue tablets. Rescue doses were to be the only doses taken during the study when half or partial tablets of levodopa-carbidopa tablets were allowed. Guidance on calculating the levodopa-carbidopa rescue tablets into the subsequent day's dose calculation was provided to the investigator.

During the study, levodopa-carbidopa rescue tablets were to have been used only in case of serious medical needs, such as the rapid deterioration of motor symptoms. A prescription for levodopa-carbidopa rescue tablets was supplied to each subject by the investigator.

Use of levodopa-carbidopa rescue tablets were discouraged unless judged absolutely necessary by the investigator. On assessment days, levodopa-carbidopa rescue tablets were to be avoided, if possible, because of their potential impact on efficacy measures. On final assessment days, at the end of the 12-week, double-blind period, no rescue medication was to be taken unless required to address immediate, serious medical needs. If possible, the medical monitor was to be notified if a subject required rescue medication prior to beginning the final assessments.

All use of rescue medication was to be recorded in the Daily Dosing Diary so that rescue medication use could be monitored during the study.

Post-Infusion Night-Time Treatment
Following the daily discontinuation of the double-blind 16-hour infusion and last double-blind oral dose administration, subjects were permitted to self-administer their routine night-time regimen of oral levodopa-carbidopa IR (doses of oral levodopa-carbidopa IR that they took on a regular basis). These doses, taken after the daily discontinuation of double-blind drug administration and up to 2 hours prior to the administration of the morning dose (gel infusion and oral), were not counted as rescue medication. All oral doses of levodopa-carbidopa IR tablets taken during the night were to be recorded in the Daily Dosing Diary. Subjects were not to use oral levodopa-carbidopa controlled release (CR) as part of their night-time regimen.

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Table 6 Major Protocol Deviations in Active-Controlled Trial

	Statistic	LCIG + Placebo Capsules (N=37)	Placebo Gel + Levodopa-Carbidopa Capsules (N=34)	All Subjects (N=71)
Number of Subjects with at Least One Protocol Deviation	n (%)	9 (24.3)	9 (26.5)	18 (25.4)
Categories of Major Protocol Deviations:				
Subject did not meet entry criteria	n (%)	1 (2.7)	0	1 (1.4)
Subject developed withdrawal criteria during the study but was not withdrawn	n (%)	0	0	0
Subject received the wrong treatment or incorrect dose	n (%)	8 (21.6)	9 (26.5)	17 (23.9)
Subject received excluded concomitant treatment	n (%)	1 (2.7)	1 (2.9)	2 (2.8)

Reviewer Comments

(b) (4)

Regardless of these deficiencies, the sponsor is no longer seeking a specific claim that Duopa is effective in (b) (4) *" patients but simply that Duopa is effective in patients whose Parkinson's disease was able to be controlled with other medications. Thus, these deficiencies are inconsequential to the sponsor's desired claim.*

6.1.2 Demographics

Table 7 Demographics of Active-Controlled Trial

	Statistic	LCIG + Placebo Capsules (N=37)	Placebo Gel + Levodopa-Carbidopa Capsules (N=34)
Age (yrs)	n	37	34
	Mean(SD)	63.7 (9.5)	65.1 (6.8)
	Median	64.0	66.0
	Min/Max	39/83	45/79
Age Category			
< 65 yrs	n(%)	21 (56.8)	15 (44.1)
>= 65 yrs	n(%)	16 (43.2)	19 (55.9)
Gender			
Male	n(%)	24 (64.9)	22 (64.7)
Female	n(%)	13 (35.1)	12 (35.3)
Ethnicity			
Hispanic or Latino	n(%)	2 (5.4)	1 (2.9)
Not Hispanic or Latino	n(%)	35 (94.6)	33 (97.1)
Race			
American Indian or Alaska Native	n(%)	1 (2.7)	0
	*	1 (2.7)	0
Asian	n(%)	1 (2.7)	3 (8.8)
	*	1 (2.7)	3 (8.8)
Black, of African Heritage or African American	n(%)	0	0
	*	0	0
Native Hawaiian or Other Pacific Islander	n(%)	0	0
	*	0	0
White	n(%)	35 (94.6)	31 (91.2)
	*	35 (94.6)	31 (91.2)
Country			
Germany	n(%)	7 (18.9)	9 (26.5)
New Zealand	n(%)	1 (2.7)	2 (5.9)
United States	n(%)	29 (78.4)	23 (67.6)

Table 8 Baseline Characteristics in Active-Controlled Trial

Parameter	Subcategory[a]	LCIG + Placebo Capsules	Placebo Gel + L-C Capsules
Total Number of Subjects		**N = 37 (35 completed)**	**N = 34 (31 completed)**
MMSE total score, mean (SD)		28.7 (1.4)	28.9 (1.4)
PD duration (years), mean (SD)		10.02 (4.64)	11.85 (5.58)
Number of PD medications at Baseline, n (%)	1	6 (16.2)	2 (5.9)
	2	12 (32.4)	13 (38.2)
	3	8 (21.6)	11 (32.4)
	> 3	11 (29.7)	8 (23.5)
Baseline "Off" time (hours), mean (SD)	Full Analysis Data Set	N = 36	N = 33
		6.30 (1.70)	7.01 (2.06)
Baseline "On" time without troublesome dyskinesia (hours), mean (SD)	Full Analysis Data Set	N = 36	N = 33
		8.69 (1.98)	7.82 (2.47)

Reviewer Comments

There were no noteworthy differences in demographic or baseline characteristics for Parkinson's disease between both treatment groups in the controlled trial because they were generally similar.

Table 9 Summary (# and % of Patients) of Concomitant Parkinson's Disease Dopaminergic Drug Classes* and Drug Class Combinations At Baseline According to Treatment in Active-Controlled Trial

Concomitant Dopaminergic Drug Classes	LCIG (N=37)	Oral LD/CD (N=34)
Oral LD/CD alone	6 (16 %)	2 (6 %)
Oral LD/CD + Dopaminergic Agonist	9 (24 %)	13 (38%)
Oral LD/CD + COMT Inhibitor	5 (14 %)	5 (15%)
Oral LD/CD + MAO-B Inhibitor	2 (5 %)	1 (3%)
Oral LD/CD + COMT Inhibitor + MAO-B Inhibitor	2 (5 %)	1 (3 %)
Oral LD/CD + COMT Inhibitor + Dopaminergic Agonist	3 (8 %)	8 (24 %)
Oral LD/CD + MAO-B Inhibitor + Dopaminergic Agonist	3 (8 %)	3 (9 %)
Oral LD/CD + COMT Inhibitor + MAO-B Inhibitor + Dopaminergic Agonist	7 (19 %)	1 (3 %)

*Oral LD/CD (e.g., Sinemet), Dopaminergic Agonist (i.e., ropinirole, pramipexole, or rotigotine), COMT Inhibitor (i.e., entacapone or tolcapone), MAO-B inhibitor (i.e., selegiline, or rasagiline)

Reviewer Comments

At baseline, the percentage of patients were generally similar for various combinations of drugs of Parkinson's disease with the exceptions of 1) oral LD/CD, COMT inhibitor, and dopaminergic agonist; and 2) oral LD/CD, COMT inhibitor, MAO-B inhibitor, and dopaminergic agonist (Table 9). The percentage of patients on oral LD/CD, COMT inhibitor, and dopaminergic agonist for the oral LD/CD group was 3 fold of that for the LCIG group, and the percentage of patients on oral LD/CD, COMT inhibitor, MAO-B inhibitor, and dopaminergic for the LCIG group was about 6 fold of that for the oral LD/CD group. The percentage of patients on 2 drug classes in addition to oral LD/CD was relatively similar for the LCIG group (22 %) and for the oral LD/CD group 35 %. Of interest, there were small percentages (16 % and 6 %) of patients who were only on oral LD/CD alone and not any other concomitant medications for Parkinson's disease at baseline. In addition, the percentage of patients on each drug class alone (e.g., dopaminergic agonist, MAO-B inhibitor, COMT inhibitor) was also quite similar for both treatment groups (percentages not shown).

Table 10 shows the specific concomitant medications for Parkinson's disease at baseline according to treatment group and also according to low or high dose group determined at the end of the trial based upon the mean daily levodopa dose in the trial (low < 1250 mg LD; high ≥ 1250 mg).

Reference ID: 3469235

Table 11 provides perspective about the daily dose of concomitant dopaminergic agonists at baseline.

Table 10 Summary of Specific Concomitant Antiparkinsonian Medications Taken by ≥ 5% of Subjects in Any Group Summarized by ATC 3rd Level Generic Name and by Descending Frequency in the All LCIG Treatment Group (Active-Controlled Analysis Set)

	Number (%) of Subjects					
	LCIG			LC-Oral		
ATC 3rd Level Generic Name	Low Dose N = 27	High Dose N = 10	Any Dose N = 37	Low Dose N = 15	High Dose N = 19	Any Dose N = 34
Any medication	27 (100)	10 (100)	37 (100)	15 (100)	19 (100)	34 (100)
Dopaminergic agents						
Sinemet	27 (100)	10 (100)	37 (100)	15 (100)	19 (100)	34 (100)
Entacapone	13 (48.1)	4 (40.0)	17 (45.9)	4 (26.7)	5 (26.3)	9 (26.5)
Pramipexole	10 (37.0)	2 (20.0)	12 (32.4)	6 (40.0)	6 (31.6)	12 (35.3)
Ropinirole	9 (33.3)	2 (20.0)	11 (29.7)	6 (40.0)	7 (36.8)	13 (38.2)
Rasagiline	7 (25.9)	3 (30.0)	10 (27.0)	3 (20.0)	4 (21.1)	7 (20.6)
Amantadine	6 (22.2)	1 (10.0)	7 (18.9)	8 (53.3)	3 (15.8)	11 (32.4)
Selegiline	7 (25.9)	0	7 (18.9)	0	0	0
Rotigotine	3 (11.1)	0	3 (8.1)	1 (6.7)	0	1 (2.9)
Carbidopa	0	1 (10.0)	1 (2.7)	1 (6.7)	1 (5.3)	2 (5.9)
Tolcapone	1 (3.7)	0	1 (2.7)	3 (20.0)	3 (15.8)	6 (17.6)
Budipine	0	0	0	0	1 (5.3)	1 (2.9)
Apormorphone	0	0	0	1 (6.7)	0	1 (2.9)
Levodopa	0	0	0	1 (6.7)	0	1 (2.9)

ATC = Anatomical Therapeutic Class; LCIG = levodopa-carbidopa intestinal gel; LC-oral = encapsulated levodopa-carbidopa immediate release tablets

Cross reference: Table 2.1__1.4.2.2

Table 11 Daily Dose of Concomitant Dopaminergic Drugs at Baseline as a Percentage of Maximal Recommended Daily Dose* in Active-Controlled Trial

Concomitant Dopaminergic Drug Daily Dose as Percentage of Maximal Dose	**LCIG** (N=22)	**Oral LD/CD** (N=25)
< 50 %	55 %	56 %
< 33 %	45 %	32 %
< 20 %	36 %	12 %

*Maximal recommended daily doses : 4.5 mg for pramipexole; 24 mg for ropinirole immediate-release or extended-release; 8 mg delivered/18 mg total content for rotigotine

Reviewer Comments

Table 11 shows that at baseline that many patients in both treatment groups were on relatively low doses of concomitant dopaminergic agonist relative to the maximally recommended daily dose. These data tend to the support the contention that dosing may not maximized in patients enrolled in the controlled trial. Dosing for dopaminergic agonist is presented because the range for dosing a dopaminergic is quite large in contrast to doses for a COMT inhibitor or MAO-B inhibitor that are relatively fixed.

6.1.3 Subject Disposition

Table 12 shows the disposition of patient in the controlled trial.

Table 12 Disposition of Patients in Active-Controlled Trial

Disposition	Number (%) of Subjects					
	LCIG			LC-oral		
Active-Controlled Analysis Set (Pivotal Study)	Low Dose N = 27	High Dose N = 10	Any Dose N = 37	Low Dose N = 15	High Dose N = 19	Any Dose N = 34
Subjects completed the study	25 (92.6)	10 (100)	35 (94.6)	12 (80.0)	19 (100)	31 (91.2)
Subjects discontinued prematurely	2 (7.4)	0	2 (5.4)	3 (20.0)	0	3 (8.8)
Primary reason for premature discontinuation						
Adverse event	1 (3.7)	0	1 (2.7)	2 (13.3)	0	2 (5.9)
Lack of efficacy	0	0	0	1 (6.7)	0	1 (2.9)
Protocol violation	1 (3.7)	0	1 (2.7)	0	0	0

Reviewer Comments

Few patients (5 % for LCIG and 9 % for oral LD/CD) discontinued prematurely from the controlled trial. Thus, the vast majority of patients randomized and treated completed the whole treatment period (12 weeks) in the controlled trial. One LCIG patient discontinued because of a protocol violation and one in the oral LD/CD group discontinued because of lack of efficacy. ***Because none of the 5 patients who discontinued from the trial had any data collected for the primary efficacy endpoint, the completer dataset is equivalent to the ITT dataset.***

Reference ID: 3469235

6.1.4 Analysis of Primary Endpoint(s)

The primary analysis of the primary efficacy endpoint was the change from baseline in "off" time derived from 24 hours diaries after the data were normalized to 16 hours, the total daily treatment time for LCIG and mainly the time that patients are awake.

The primary efficacy analysis of the primary efficacy endpoint (Table 13) showed a statistically significant LS mean difference (improvement) of nearly 2 hours (i.e., –1.91 hours) from Baseline after 12 weeks of treatment in the average daily normalized "Off" time between the LCIG group and the LC-oral group.

Table 13 Change from Baseline to Endpoint in Average Daily Normalized "Off" Time Based on the Parkinson's Disease Diary, Analysis of Covariance

		Observed Mean (SD) [hours]			Difference from Placebo Gel + Levodopa-Carbidopa Capsules		
Treatment Group	N	Baseline	Endpoint	LS Mean (SE) of Change	LS Mean (SE) of Difference	95% CI	*P* value[a]
Placebo gel + L-C cap[b]	31	6.90 (2.06)	4.95 (2.04)	–2.14 (0.66)			
LCIG + placebo cap[c]	35	6.32 (1.72)	3.05 (2.52)	–4.04 (0.65)	–1.91 (0.57)	(–3.05, –0.76)	0.0015

SD = standard deviation; LS = least square; SE = standard error; CI = confidence interval

a. Two-sided *P* value from ANCOVA model including effects for treatment and country, and covariates of corresponding Baseline and the natural logarithm of the mean daily dose of rescue medication on valid Parkinson's Disease Diary data.

b. Placebo gel + levodopa-carbidopa capsules.

c. LCIG + placebo capsules.

Cross reference: Table 14.2__1.1.1.1

Reviewer Comments

- *The primary analysis of the primary efficacy endpoint (Table 13) showed that Duopa produced a greater decrease in normalized "off" time (nearly 2 hours) compared to the active control treatment (oral LD/CD) and this decrease was highly statistically significant (p=00.15). This is a relatively large effect considering that many other drugs approved for treating advanced Parkinson's disease decrease "off" time by about 1 hour (or even less) and the effect of these drugs is relative to a placebo control in contrast to an active control treatment.*

- *It is also important to note that Dr. Xiang Ling, the Agency Statistical primary reviewer, concurred with the sponsor sponsor's primary analysis of the primary efficacy endpoint,*

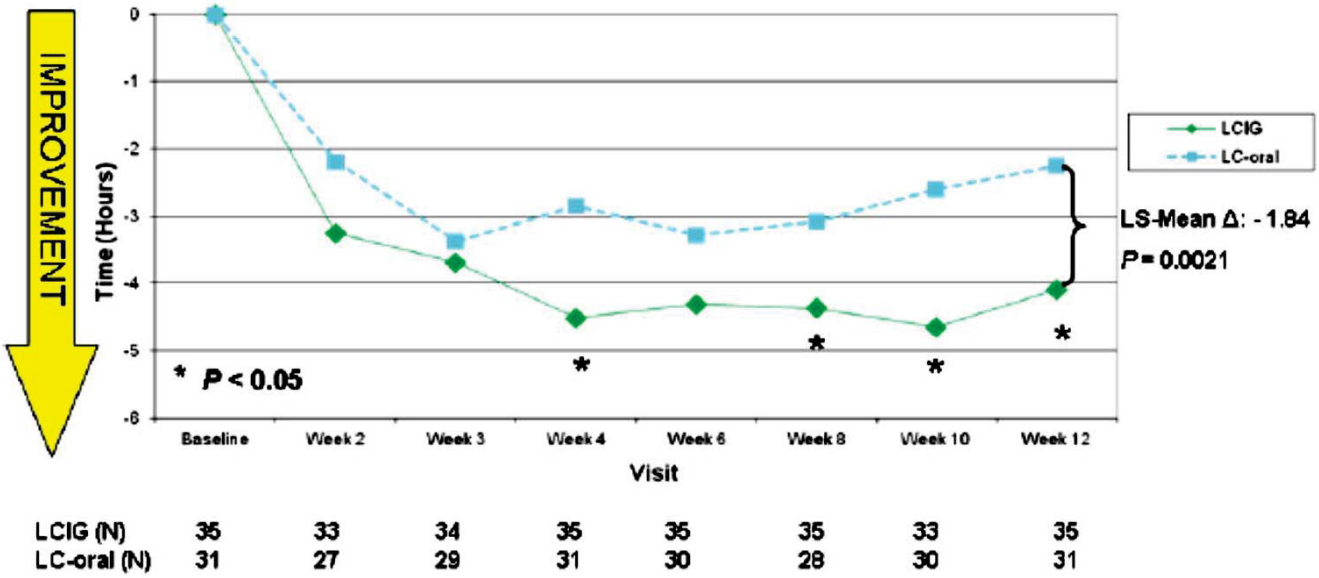
noted that she reproduced the sponsor's results, and concluded that LCIG is effective based upon the primary results and also numerous sensitivity analyses that robustly supported the primary analysis of the primary efficacy endpoint.

The primary efficacy variable was also analyzed using an MMRM analysis. The analysis was based on observed data, i.e., data collected at each time point without carrying forward previous values. The model included Baseline as a fixed-effect covariate; treatment, country, and time as fixed-effect (categorical) factors, and the time-by-treatment and time-by-Baseline interactions. Using this model, treatment effect at the Week 12 endpoint was estimated based on differences between the LS means. The MMRM analysis of the primary efficacy variable showed a statistically significantly greater mean decrease (improvement) from Baseline in the average daily normalized "Off" time in the LCIG group compared to the LC-oral group for Weeks 4, 8, 10, and 12 (Table 14 and Figure 6*).*

Table 14 Change from Baseline in Average Daily Normalized "Off" Time Based on the Parkinson's Disease Symptom Diary Mixed Model Repeated Measures Analysis (FULL ANALYSIS SAMPLE)

	LCIG + Placebo Capsules (N=36)			Placebo Gel + Levodopa-Carbidopa Capsules (N=33)			Treatment Difference		
Study Week	n	Mean (SD)	LS Means (SE)	n	Mean (SD)	LS Means (SE)	LS Means (SE)	95% CI	p-value
Model Estimates									
Week 2	33	-2.71 (2.37)	-3.25 (0.56)	27	-1.81 (2.26)	-2.19 (0.59)	-1.06 (0.61)	(-2.27, 0.15)	0.0855
Week 3	34	-3.00 (2.65)	-3.69 (0.56)	29	-3.03 (2.64)	-3.38 (0.59)	-0.31 (0.61)	(-1.52, 0.90)	0.6124
Week 4	35	-3.72 (2.49)	-4.51 (0.55)	31	-2.53 (2.87)	-2.85 (0.56)	-1.66 (0.57)	(-2.79, -0.52)	0.0049
Week 6	35	-3.52 (3.00)	-4.31 (0.57)	30	-2.97 (2.64)	-3.28 (0.59)	-1.04 (0.61)	(-2.26, 0.18)	0.0941
Week 8	35	-3.56 (2.68)	-4.37 (0.56)	28	-2.70 (2.95)	-3.08 (0.58)	-1.28 (0.59)	(-2.47, -0.10)	0.0346
Week 10	33	-3.92 (2.36)	-4.65 (0.54)	30	-2.14 (2.49)	-2.60 (0.55)	-2.05 (0.55)	(-3.14, -0.95)	0.0004
Week 12	35	-3.27 (3.14)	-4.09 (0.55)	31	-1.96 (2.33)	-2.25 (0.56)	-1.84 (0.57)	(-2.98, -0.70)	0.0021

Figure 6 Change from Baseline in Average Daily Normalized "Off" Time Over Whole Trial Based on Parkinson's Disease Diary Data, Mixed Model Repeated Measures



Note: Mixed Model Repeated Measures analysis of observed data collected at each time point without carrying forward previous values. The model included Baseline as a fixed-effect covariate; treatment, country, and time as fixed-effect (categorical) factors, and treatment by study week, and Baseline by study week interactions, assuming an unstructured covariance matrix.

Cross reference: Table 14.2__1.1.1.1, Table 14.2__1.1.4.1, Figure 14.2__1.1.5

Reviewer Comments

The sensitivity MMRM analysis of the primary efficacy endpoint (Table 14 and Figure 6) shows virtually identical results to that of the primary analysis of that endpoint at the end of the trial. Thus, this analysis supports the robustness of the therapeutic effect of Duopa. With the exception of results at week 3, the numerical treatment difference (LCIG-oral LD/CD) is at least 1 hour from week 1 until the end of the trial and the treatment differences are nominally statistically significant in the last month of the trial (weeks 8-12).

Table 15 shows results for each treatment according to low and high dose categories relative to any dose for the primary analysis of the primary efficacy endpoint.

Table 15 Study S187-3-001/S187-3-002: Subgroup Analysis of Mean Change from Baseline to Endpoint for Average Daily Normalized "Off" by Daily Dose of Levodopa (ANCOVA)

	LC-Oral			LCIG			*P* Value	
Variable	All (N = 31)	Low (n = 12)	High (n = 19)	All (N = 35)	Low (n = 25)	High (n = 10)	Treatment by Subgroup Interaction	Treatment Group Difference
"Off" time, hours								
Baseline mean (SD)	6.90 (2.06)	6.63 (1.94)	7.08 (2.17)	6.32 (1.72)	6.46 (1.87)	5.98 (1.31)		
Endpoint mean (SD)	4.95 (2.04)	4.33 (1.76)	5.33 (2.15)	3.05 (2.52)	2.96 (2.22)	3.27 (3.29)		
LS mean (SE) of change	−2.14 (0.66)	−2.36 (0.79)	−1.85 (0.82)	−4.04 (0.65)	−3.99 (0.70)	−3.77 (0.96)	0.8100	0.0015

Reviewer Comments

Table 15 shows that the treatment difference for low and high dose groups is relatively similar to that of any dose and is approaching 2 hours. Although the numerical treatment difference for low dose LCIG is – 1,63 and for high dose LCIG is -1.92, there was no suggestion of subgroup interaction for dose level (p=0.8100).

Most subjects required rescue medication during the Treatment Period: 36 of 37 (97.3%) subjects in the LCIG group and 31 of 34 (91.2%) subjects in the LC-oral group. The highest percentage of subjects (≥ 85% in each group) used rescue medication during Week 1 when the dose was being titrated. Over the duration of the study, the use of rescue medication declined to less than 42% of subjects in each treatment group at Week 12. The average dose of rescue medication used was less for the LCIG group compared to the LC-oral group at Week 1. At Week 12, the LCIG group required a lower average dose than was required at Week 1, whereas the LC-oral group required more (Table 16).

Table 16 Number of Subjects Using Rescue Medication and Average Dose, Week 1 and Week 12

Treatment Group	N	Number of Subjects Requiring Rescue Mediation	Average Dose of Rescue Medication[a] (mg/day)	
			Levodopa	Carbidopa
Week 1				
Placebo Gel + LC-oral Capsules	34	29 (85.3)	196.6 ± 172.6	49.2 ± 43.2
LCIG + Placebo Capsules	37	32 (86.5)	149.5 ± 87.6	37.4 ±21.9
Week 12				
Placebo Gel + LC-oral Capsules	31	13 (41.9)	210.3 ± 201.3	52.6 ± 50.3
LCIG + Placebo Capsules	35	13 (37.1)	115.3 ± 67.8	28.8 ± 16.9

a. Average dose is mean ± standard deviation.

Cross reference: Table 14.3__1.1.3.1

Various sensitivity analyses were conducted according to the primary analysis for the primary efficacy endpoint to assess the potential influence of rescue oral LD/CD on efficacy. Table 17 presents results of those sensitivity analyses.

Table 17 Secondary and Sensitivity Analyses of the Primary Efficacy Variable, Analysis of Covariance

		Observed Mean (SD) [hours]			Difference from Placebo Gel + Levodopa-Carbidopa Capsules		
Treatment Group	N	Baseline	Endpoint	LS Mean (SE) of Change	LS Mean (SE) of Difference	95% CI	*P* value[a]
Change from Baseline to Endpoint without covariate of rescue medication on valid Parkinson's Disease Diary days							
Placebo gel + L-C cap[b]	31	6.90 (2.06)	4.95 (2.04)	–2.13 (0.66)			
LCIG + placebo cap[c]	35	6.32 (1.72)	3.05 (2.52)	–4.02 (0.65)	–1.89 (0.57)	(–3.03, –0.75)	0.0016
Change from Baseline to Endpoint with covariate of rescue medication over the treatment period							
Placebo gel + L-C cap[b]	31	6.90 (2.06)	4.95 (2.04)	–2.14 (0.66)			
LCIG + placebo cap[c]	35	6.32 (1.72)	3.05 (2.52)	–4.02 (0.65)	–1.88 (0.57)	(–3.03, –0.73)	0.0018
Change from Baseline to Endpoint with values on final Parkinson's Disease Diary days with rescue medication use replaced by average daily normalized "Off" time at Baseline							
Placebo gel + L-C cap[b]	31	6.90 (2.06)	5.44 (1.96)	–1.47 (0.70)			
LCIG + placebo cap[c]	35	6.32 (1.72)	3.46 (2.81)	–3.29 (0.70)	–1.82 (0.61)	(–3.05, –0.60)	0.0042
Change from Baseline to Endpoint excluding values on final Parkinson's Disease Diary days with rescue medication use							
Placebo gel + L-C cap[b]	31	6.90 (2.06)	4.78 (2.02)	–2.52 (0.69)			
LCIG + placebo cap[c]	35	6.32 (1.72)	2.98 (2.73)	–4.30 (0.68)	–1.78 (0.60)	(–2.97, –0.58)	0.0043

SD = standard deviation; LS = least square; SE = standard error; CI = confidence interval

a. Two-sided *P* value from ANCOVA model with factors of treatment and country and covariate of Baseline normalized "Off" time. The model for "Change from Baseline to endpoint with covariate of rescue medication over the entire treatment period" also includes covariate of natural logarithm of mean daily dose of rescue levodopa over the entire treatment period.

b. Levodopa-carbidopa immediate release capsules.

c. Placebo capsules.

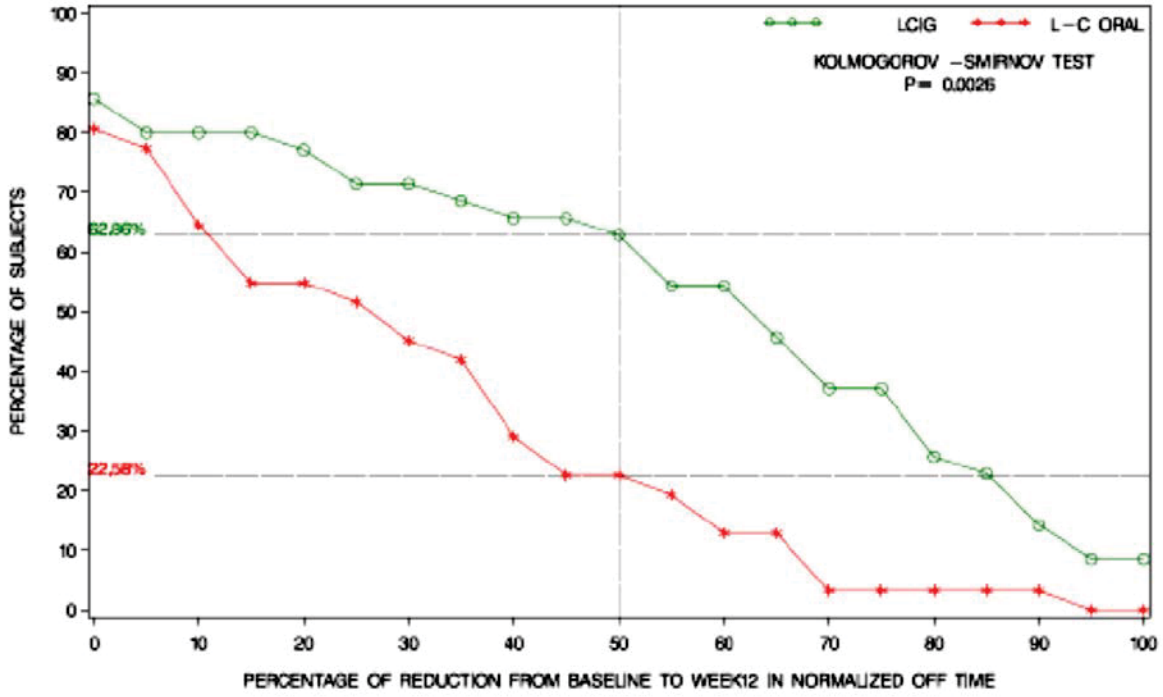
Cross reference: Table 14.2__1.1.3.1, Table 14.2__1.1.2.1, Table 14.2__1.1.2.2, Table 14.2__1.1.2.3

Reviewer Comments

As can be seen in Table 17, there was no statistically significant nor noteworthy effect of oral rescue LD/CD on the LCIG-induced treatment benefit of decreased "off" time based upon the various sensitivity analyses. These results further support the true benefit of LCIG treatment.

Figure 7 shows the percentage of patients who achieved a certain percentage reduction in average daily "normalized" "off" time according to treatment.

Figure 7 Study S187-3-001/S187-3-002: Percentage of Subjects who Achieved at Least a Certain Percent Reduction in Average Daily Normalized "Off" Time at Endpoint



Note: *P* value for test of difference in the distribution between treatment groups using Monte Carlo Exact Kolmogorov-Smirnov Test.

Cross reference: Figure 1.1__5.1

6.1.5 Analysis of Secondary Endpoints(s)

Several secondary efficacy endpoints were also evaluated for change from baseline to the end of the trial (week 12 for completers).

Table 18 shows the results for change from baseline in average daily "normalized" "on" time without troublesome dyskinesia at the end of the controlled trial and Figure 8 shows the effect of treatment on this endpoint over time from baseliue to the end of the trial (week 12).

Table 18 Study S187-3-001/S187-3-002: Change from Baseline to Endpoint in Average Daily Normalized "On" Time Without Troublesome Dyskinesia (ANCOVA)

		Observed Mean (SD) (Hours)			Difference from LC-Oral		
Treatment Group	N	Baseline	Endpoint	LS Mean (SE) of Change	LS Mean (SE) of Difference	95% CI	*P* value
"On" time without troublesome dyskinesia[a]							
LC-oral	31	8.04 (2.09)	9.92 (2.62)	2.24 (0.76)			
LCIG	35	8.70 (2.01)	11.95 (2.67)	4.11 (0.75)	1.86 (0.65)	(0.56, 3.17)	0.0059
Without dyskinesia							
LC-oral	31	5.73 (3.05)	6.65 (4.29)	1.09 (1.05)			
LCIG	35	6.37 (2.71)	9.35 (4.29)	3.37 (1.04)	2.28 (0.90)	(0.47, 4.09)	0.0142
With non-troublesome dyskinesia							
LC-oral	31	2.31 (2.16)	3.27 (3.88)	1.54 (0.86)			
LCIG	35	2.33 (1.81)	2.60 (2.97)	0.81 (0.86)	–0.73 (0.74)	(–2.22, 0.76)	0.3294

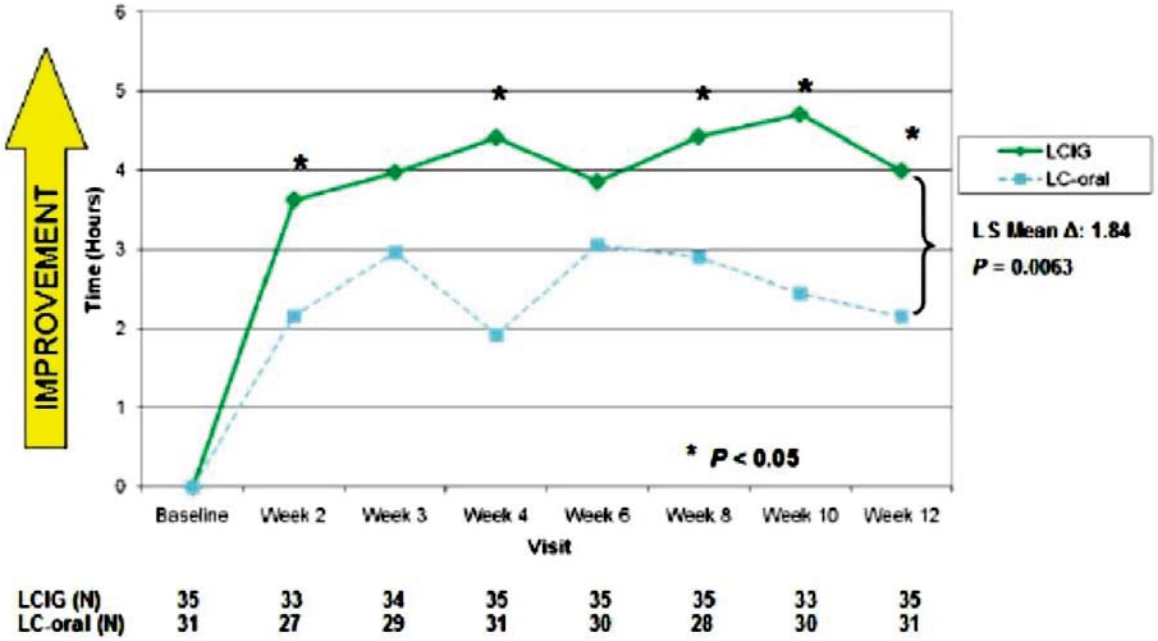
SD = standard deviation; LS = least square; SE = standard error; CI = confidence interval

a. "On" time without troublesome dyskinesia is a composite of "On" time without dyskinesia and "On" time with non-troublesome dyskinesia.

Note: Treatment comparisons are based on an ANCOVA model including effects for treatment and country, and with the corresponding Baseline as a covariate.

Cross reference: Study S187-3-001/S187-3-002 CSR Table 14.2__1.2.1.1, Table 14.2__1.4.1.1, Table 14.2__1.5.1.1

Figure 8 Study S187-3-001/S187-3-002: Change from Baseline in Average Daily Normalized "On" Time Without Troublesome Dyskinesia (MMRM Analysis)



MMRM = Mixed Model Repeated Measures; LS = least square

Notes: Average daily normalized "On" time without troublesome dyskinesia at Baseline: 8.04 hours for LC-oral and 8.70 hours for LCIG.

MMRM analysis of observed data collected at each timepoint (i.e., without carrying forward previous values). The model included Baseline as a fixed-effect covariate; treatment, country, and study week as fixed-effect (categorical) factors, and treatment-by-study week, and Baseline-by-study week interactions, assuming an unstructured covariance matrix.

P value for test of difference between treatment groups.

The time axis was not drawn by scale.

Cross reference: Study S187-3-001/S187-3-002 CSR Figure 7

Reviewer Comments

- *Table 18 shows the effect of LCIG treatment on the change from baseline in "on" time without troublesome dyskinesia, a key secondary efficacy endpoint, and from my perspective most important endpoint for treating patients with motor fluctuations. I note that this is the most important endpoint because an increase in "on" without troublesome dyskinesia is a direct, desirable outcome. A decrease in "off" time is a somewhat indirect outcome measure that may not necessarily be so desirable if the decrease in "off" time was related to an increase in sleep time and or "on" time with troublesome dyskinesia. However, in this case, the LCIG-induced treatment difference for an increase in "on" time without troublesome dyskinesia is 1.86 hours and corresponds to the magnitude*

(about 1 .9 hours) of the treatment difference for the decrease in "off" time. Thus, these effects of LCIG treatment are complimentary and clearly show the LCIG produces a therapeutic benefit by decreasing "off" time and this decrease is related to an increase in "on" time without troublesome dyskinesia. A further subdivision of "one" time without troublesome dyskinesia into "on" time without dyskinesia and "on" time with non-troublesome dyskinesia shows that the LCIG benefit is primarily an increase in "on" time without dyskinesia.

- *Figure 8 shows results for change from baseline in "on" time without troublesome dyskinesia over time throughout the controlled trial from baseline to the end of the trial (week 12). LCIG treatment differences (vs oral LD/CD) are evident throughout the trial and several of these differences are nominally statistically significant ($p < 0.05$), particularly over the last 4 weeks of the trial (weeks 8-12_.*

Table 19 shows results for each treatment and low and high dose subgroups for effects on "on" time without troublesome dyskinesia and also "on" time without troublesome dyskinesia.

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Table 19 Study S187-3-001/S187-3-002: Subgroup Analysis of Mean Change from Baseline to Endpoint for Average Daily Normalized "On" Times by Daily Dose of Levodopa (ANCOVA)

	LC-Oral			LCIG			*P* Value	
Variable	All (N = 31)	Low (n = 12)	High (n = 19)	All (N = 35)	Low (n = 25)	High (n = 10)	Treatment by Subgroup Interaction	Treatment Group Difference
"On" time without troublesome dyskinesia[a], hours								
Baseline mean (SD)	8.04 (2.09)	7.63 (2.21)	8.30 (2.04)	8.70 (2.01)	8.44 (2.19)	9.37 (1.34)		
Endpoint mean (SD)	9.92 (2.62)	10.43 (2.23)	9.60 (2.85)	11.95 (2.67)	12.09 (2.65)	11.60 (2.82)		
LS mean (SE) of change	2.24 (0.76)	2.61 (0.91)	1.80 (0.93)	4.11 (0.75)	4.15 (0.80)	3.44 (1.10)	0.9467	0.0059
Without dyskinesia, hours								
Baseline mean (SD)	5.73 (3.05)	4.87 (2.49)	6.28 (3.30)	6.37 (2.71)	5.70 (2.62)	8.06 (2.23)		
Endpoint mean (SD)	6.65 (4.29)	6.23 (3.83)	6.93 (4.63)	9.35 (4.29)	9.62 (4.24)	8.69 (4.58)		
LS mean (SE) of change	1.09 (1.05)	0.99 (1.23)	0.96 (1.26)	3.37 (1.04)	4.02 (1.08)	1.11 (1.52)	0.1363	0.0142
With non-troublesome dyskinesia, hours								
Baseline mean (SD)	2.31 (2.16)	2.76 (2.13)	2.03 (2.19)	2.33 (1.81)	2.74 (1.84)	1.31 (1.32)		
Endpoint mean (SD)	3.27 (3.88)	4.21 (3.76)	2.68 (3.93)	2.60 (2.97)	2.48 (2.57)	2.91 (3.95)		
LS mean (SE) of change	1.54 (0.86)	2.14 (1.02)	1.11 (1.06)	0.81 (0.86)	0.28 (0.90)	1.97 (1.27)	0.092	0.3294
"On" time with troublesome dyskinesia, hours								
Baseline mean (SD)	1.05 (1.51)	1.73 (1.85)	0.62 (1.09)	0.97 (1.63)	1.10 (1.72)	0.65 (1.44)		
Endpoint mean (SD)	1.13 (1.79)	1.23 (2.05)	1.07 (1.66)	1.00 (2.00)	0.94 (2.18)	1.14 (1.54)		
LS mean (SE) of change	–0.03 (0.52)	–0.20 (0.64)	0.21 (0.65)	–0.11 (0.52)	–0.14 (0.56)	0.27 (0.76)	0.9996	0.8574

SD = standard deviation; BL = Baseline; SE = standard error; Low = < 1250 mg levodopa/day; High = ≥ 1250 mg levodopa/day

a. "On" time without troublesome dyskinesia is a composite of "On" time without dyskinesia and "On" time with non-troublesome dyskinesia.

Notes: Total daily dose of levodopa is from all sources and includes levodopa administered as study drug, rescue tablets, night-time regimen, and replacement tablets.

Interaction test P-value and LS means are based on an ANCOVA model including effects for treatment, subgroup, country, treatment-by-subgroup interaction with the corresponding baseline as covariate. The interaction and main effect *P* values are based on Type II sums of squares.

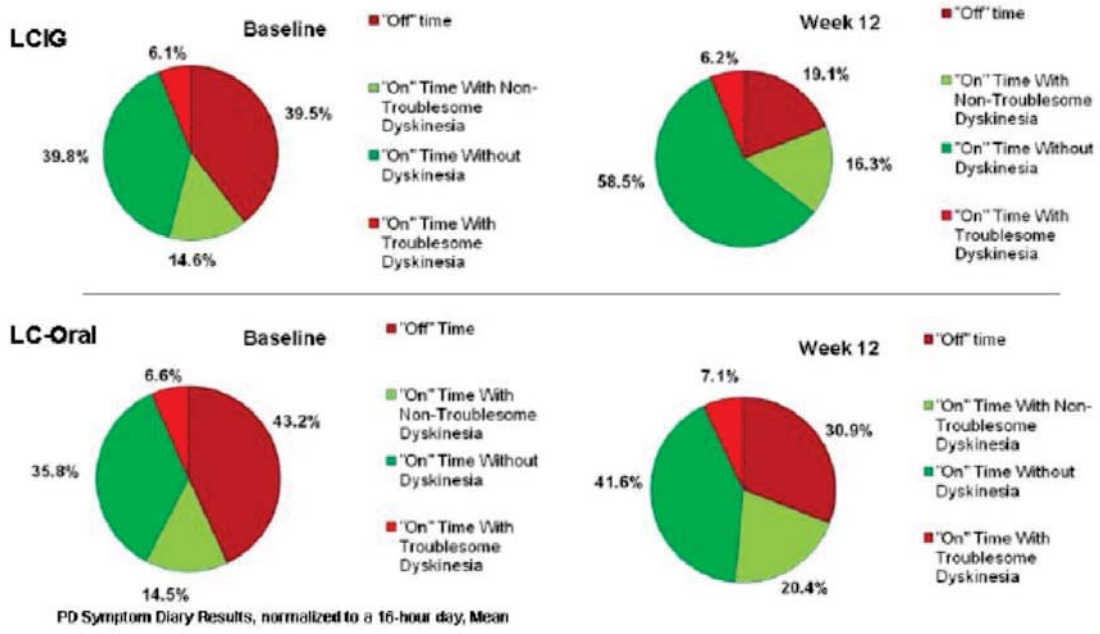
Cross reference: Tables 1.1__1.2.2.1 through Table 1.1__1.2.2.5; Study S187-3-001/S187-3-002 CSR Table 14.2__1.1.1.1, Table 14.2__1.2.1.1, Table 14.2__1.3.1.1, Table 14.2__1.4.1.1, Table 14.2__1.5.1.1

Reviewer Comments

The numerical treatment difference for the LS mean change from baseline for "on" without troublesome dyskinesia is an increase of 1.87 hours for any LCIG dose, 1.54 for low dose LCIG, and 1.64 for high dose LCIG. Not only is the difference for LCIG low and high dose minimal, but there is no suggestion of statistical interaction for this therapeutic benefit based upon dose level. It is also of interest that the change from baseline for "on" time ***with troublesome*** *dyskinesia for LCIG is similar that for oral LD/CD for any dose, low dose, and high dose. Thus, there is no noteworthy numerical treatment difference. Furthermore, statistical analyses shows that there is no statistically significant difference in these LCIG treatment differences for "on" time* ***with troublesome dyskinesia*** *nor a suggestion of any interaction for dose.*

Figure 9 shows the distribution of patient symptoms based upon the Parkinson's disease diary at baseline and at the end of the trial (week 12).

Figure 9 Distribution of Subjects' Symptoms Based on Data from the Parkinson's Disease Diary, at Baseline and at Week 12 (Full Analysis Data Set)



Cross reference: Table 14.2__1.1.8.1, Table 14.2__1.3.5.1, Table 14.2__1.5.5.1, Table 14.2__1.4.5.1

Reviewer Comments

Figure 9 visually illustrates via a pie chart the percentage of "off" time and the various subgroups of "on" time at baseline and at the end of treatment. The most striking changes in

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percentage of diary time for LCIG (vs oral LD/VD) at 12 weeks are the greater decrease in "off" time and the greater increase in "on" time without dyskinesia.

Table 20 shows results for secondary efficacy endpoints.

Table 20 Secondary Efficacy Variables Tested in Hierarchical Order, Analysis of Covariance

		Observed Mean (SD)			Difference from Placebo Gel + Levodopa-Carbidopa Capsules		
Treatment Group	N	Baseline	Endpoint	LS Mean (SE) of Change or Endpoint[a]	LS Mean (SE) of Difference	95% CI	*P* value
Parkinson's Disease Questionnaire (PDQ-39) Summary Index[1]							
Placebo gel + L-C cap[b]	33	38.6 (17.9)	33.6 (16.9)	–3.9 (3.2)			
LCIG + placebo cap[c]	36	35.1 (18.0)	23.7 (17.3)	–10.9 (3.3)	–7.0 (2.8)	(–12.6, –1.4)	0.0155
Clinical Global Impression - Improvement (CGI-I)[2]							
Placebo gel + L-C cap[b]	33	4.6 (0.8)	3.2 (1.4)	3.0 (0.4)			
LCIG + placebo cap[c]	36	4.2 (0.7)	2.3 (1.2)	2.3 (0.4)	–0.7 (0.3)	(–1.4, –0.1)	0.0258
Unified Parkinson's Disease Rating Scale (UPDRS) Part II[3]							
Placebo gel + L-C cap[b]	33	11.8 (7.0)	12.3 (7.0)	1.3 (1.3)			
LCIG + placebo cap[c]	36	11.6 (6.9)	9.1 (6.6)	–1.8 (1.3)	–3.0 (1.1)	(–5.3, –0.8)	0.0086
Unified Parkinson's Disease Rating Scale (UPDRS) Part III[3]							
Placebo gel + L-C cap[b]	33	22.5 (11.7)	18.7 (10.9)	–2.9 (2.4)			
LCIG + placebo cap[c]	36	18.1 (9.9)	16.5 (12.2)	–1.5 (2.4)	1.4 (2.1)	(–2.8, 5.6)	0.5020
EuroQol Quality of Life Scale (EQ-5D) Summary Index[4]							
Placebo gel + L-C cap[b]	32	0.617 (0.181)	0.661 (0.188)	–0.016 (0.043)			
LCIG + placebo cap[c]	36	0.692 (0.151)	0.767 (0.143)	0.054 (0.043)	0.070 (0.038)	(–0.005, 0.146)	0.0670

Reviewer Comments

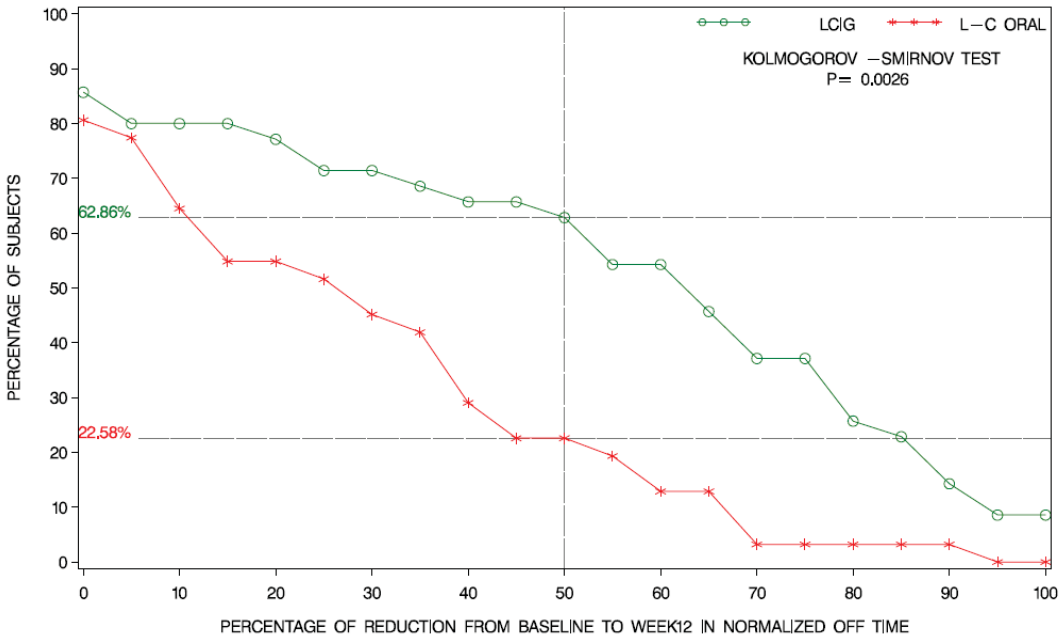
Table 20 shows that the treatment difference for LCIG (vs oral LD/CD) was statistically significant for PDQ-39 (Summary Index), Clinical Global Impression-Improvement (CGI-I),a

and UPDRS Part II-ADL, based upon nominal statistical significance without adjustment for multiplicity. The treatment difference for LCIG's effect on UPDRS Part III-motor score, and EuroQal Qualiity of Life Scale (EQ-SD) Summary Index was not statistically significant. The sponsor noted that this testing was conducted according to a pre-specified hierarchical order for secondary efficacy endpoints.

Responder Analysis

The responder analysis shows that the proportion of subjects with a given percent reduction (ranging from 0% reduction to 100% reduction in 5% increments) in average daily normalized "Off" time at Week 12 was consistently higher in the LCIG group at each threshold than that in the LC-oral group (Figure 10). The greatest difference between treatment groups (~43%) was observed at the 45% threshold: 65.7% of subjects (22/35) in the LCIG group demonstrated ≥ 50% reduction in "Off" time compared with 22.6% of subjects (7/31) in the LC-oral group. Important differences persisted at the 80% threshold with 25.7% of subjects (9/35) in the LCIG group having demonstrated ≥ 80% reduction in "Off" time compared with 3.2% of subjects (1/31) in the LC-oral group. The distribution of treatment group difference in percentage reduction in "Off" time was statistically significantly different ($P = 0.0026$ by Kolmogorov-Smirnov test).

Figure 10 Percentage of Patients Who Achieved at Least a Certain Percent Reduction in Average Daily Normalized "Off" Time at Endpoint in the Controlled Trial



Reviewer Comments

Figure 10 shows that LCIG treatment clearly results in higher percentages of patients for each percentage of reduction from baseline in normalized "off" time.

6.1.6 Other Endpoints

Sensitivity analyses for diary data, especially change from baseline in "off" time and change from baseline in "on" time without troublesome dyskinesia were conducted for absolute 24 hour diary data for comparison with diary data to 16 hours when LCIG was administered. When the normalized Parkinson's Disease Diary data were replaced with absolute data, statistically significantly greater LS mean improvements from Baseline in favor of the LCIG group over the LC-oral group were observed for "Off" time (difference: –2.28 hours; $P = 0.009$), "On" time without troublesome dyskinesia (difference: 1.60 hours; $P = 0.0207$), and "On" time without dyskinesia (difference: 2.19 hours; $P = 0.0255$) (Table 21). These results were consistent with the results of the primary and key secondary efficacy analyses.

Table 21 Study S187-3-001/S187-3-002: Change from Baseline to Endpoint in Average Daily Absolute Parkinson's Disease Diary Data (ANCOVA)

		Observed Mean (SD) (Hours)			Difference from LC-oral		
Treatment Group	N	Baseline	Endpoint	LS Mean (SE) of Change	LS Mean (SE) of Difference	95% CI	*P* Value
"Off" time							
LC-oral	31	7.51 (2.74)	5.48 (2.67)	–2.18 (0.74)			
LCIG	35	6.63 (2.08)	3.14 (2.60)	–4.46 (0.74)	–2.28 (0.65)	(–3.58, –0.98)	0.0009
"On" time without troublesome dyskinesia[a]							
LC-oral	31	8.64 (2.29)	10.62 (2.58)	2.48 (0.79)			
LCIG	35	9.09 (2.26)	12.37 (2.95)	4.08 (0.78)	1.60 (0.67)	(0.25, 2.95)	0.0207
Without dyskinesia							
LC-oral	31	6.24 (3.32)	7.20 (4.61)	1.10 (1.11)			
LCIG	35	6.63 (2.77)	9.62 (4.37)	3.29 (1.11)	2.19 (0.96)	(0.28, 4.11)	0.0255
With non-troublesome dyskinesia							
LC-oral	31	2.41 (2.19)	3.42 (3.91)	1.77 (0.88)			
LCIG	35	2.46 (1.92)	2.75 (3.15)	1.01 (0.88)	–0.77 (0.76)	(–2.29, 0.76)	0.3183
"On" time with troublesome dyskinesia							
LC-oral	31	1.08 (1.55)	1.22 (1.95)	0.04 (0.57)			
LCIG	35	0.99 (1.63)	1.05 (2.16)	–0.07 (0.57)	–0.11 (0.49)	(–1.09, 0.87)	0.8274
"Asleep" time							
LC-oral	31	6.57 (1.74)	6.64 (2.09)	–1.14 (0.58)			
LCIG	35	7.05 (1.91)	6.36 (2.31)	–1.61 (0.59)	–0.47 (0.51)	(–1.49, 0.55)	0.3648

SD = standard deviation; LS = least square; SE = standard error; CI = confidence interval

a. "On" time without troublesome dyskinesia is a composite of "On" time without dyskinesia and "On" time with non-troublesome dyskinesia.

Cross reference: Study S187-3-001/S187-3-002 CSR Table 14

Reviewer Comments

These sensitivity analyses of changes in diary categories based upon absolute diary hours (instead of data "normalized" to a 16 hour period) show similar results as the primary analysis of the primary efficacy endpoint and the analyses of secondary efficacy endpoints. These results support the analyses of "normalized" diary categories. Furthermore, although the treatment difference for the change in sleep time is nearly - 0.5 hours for LCIG, this difference is not statistically significant for a decrease in sleep time.

6.1.7 Subpopulations

Table 22 shows results of analyses for the primary efficacy endpoint for prespecified subgroups (i.e., age, gender, region), and also for post-hoc subgroups (i.e., duration of Parkinson's disease, number of medications for Parkinson's disease at baseline, baseline "off" hours, original vs revised inclusion criterion # 3 address "resistant" patients with Parkinson's disease, Study 1 vs Study 2 before results were combined, average LD daily dose during the controlled trial). This table shows mean "off" time results at baseline, mean change from baseline, LS mean change from baseline, according to treatment (LCIG vs oral LD/CD) and subgroups along with a p value of whether statistical analysis suggested an interaction between the each of the pairs of subgroups. There was not suggestion of an interaction amongst all subgroups as per p values.

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Table 22 Study S187-3-001/S187-3-002: Subgroup Analysis of Change from Baseline to Week 12 in Average Daily Normalized "Off" Time (ANCOVA)

		LCIG				LC-Oral			
Subgroup	Interaction *P* Value	N	Baseline Mean (SD) (Hours)	Mean Change (SD) (Hours)	LS Mean (SE) of Change (Hours)	N	Baseline Mean (SD) (Hours)	Mean Change (SD) (Hours)	LS Mean (SE) of Change (Hours)
Prespecified Analyses									
Age	0.9353								
≥ 65 years		15	6.23 (1.64)	−2.93 (3.58)	−3.76 (0.83)	17	7.29 (2.34)	−2.25 (2.72)	−1.96 (0.74)
< 65 years		20	6.39 (1.82)	−3.53 (2.83)	−4.24 (0.73)	14	6.43 (1.61)	−1.61 (1.78)	−2.34 (0.86)
Gender	0.5892								
Male		24	6.15 (1.47)	−2.96 (2.97)	−3.84 (0.76)	22	7.11 (2.22)	−2.11 (2.30)	−2.16 (0.72)
Female		11	6.70 (2.20)	−3.96 (3.53)	−4.27 (0.82)	9	6.39 (1.61)	−1.59 (2.50)	−1.89 (0.96)
Country	0.8919								
US		28	6.48 (1.67)	−3.14 (3.41)	−3.24 (0.43)	23	6.87 (2.03)	−1.63 (2.04)	−1.39 (0.48)
Non-US		7	5.70 (1.90)	−3.81 (1.72)	−4.59 (0.87)	8	7.00 (2.27)	−2.90 (2.97)	−2.55 (0.81)
Post Hoc Analyses									
PD duration	0.1353								
< 10 years		20	6.05 (1.53)	−2.34 (3.15)	−3.08 (0.74)	14	7.52 (1.81)	−2.15 (1.96)	−1.94 (0.86)
≥ 10 years		15	6.69 (1.93)	−4.53 (2.74)	−4.99 (0.75)	17	6.40 (2.16)	−1.80 (2.64)	−2.07 (0.70)
PD medications at Baseline	0.2369								
1 or 2		16	6.06 (2.20)	−2.49 (4.05)	−3.53 (0.75)	12	7.43 (2.30)	−2.41 (2.78)	−2.45 (0.84)
3 or more		19	6.55 (1.20)	−3.94 (1.99)	−4.54 (0.77)	19	6.57 (1.88)	−1.68 (2.03)	−2.04 (0.77)
Baseline "Off" time, hours	0.6973								
< Median		19	5.14 (0.82)	−2.13 (2.98)	−2.82 (0.79)	14	5.04 (0.82)	−0.68 (1.36)	−1.47 (0.93)
≥ Median		16	7.73 (1.41)	−4.63 (2.83)	−5.51 (0.91)	17	8.44 (1.37)	−3.01 (2.46)	−3.66 (0.81)
Inclusion Criterion 3[a]	0.4895								
Original		19	6.92 (1.79)	−3.70 (3.16)	−4.22 (0.87)	15	6.71 (2.17)	−1.34 (1.84)	−1.94 (0.89)
Revised		16	5.62 (1.37)	−2.77 (3.14)	−3.81 (0.74)	16	7.09 (2.00)	−2.54 (2.63)	−2.35 (0.75)
Study	0.7687								
S187-3-001		17	6.25 (1.38)	−3.24 (2.14)	−3.75 (0.79)	16	6.28 (1.53)	−1.36 (2.21)	−1.70 (0.81)
S187-3-002		18	6.39 (2.03)	−3.31 (3.92)	−4.25 (0.77)	15	7.57 (2.38)	−2.60 (2.35)	−2.55 (0.81)
Daily dose of levodopa[b]	0.8100								
< 1250 mg/day		25	6.46 (1.87)	−3.50 (2.95)	−3.99 (0.70)	12	6.63 (1.94)	−2.30 (2.70)	−2.36 (0.79)
≥ 1250 mg/day		10	5.98 (1.31)	−2.72 (3.67)	−3.77 (0.96)	19	7.08 (2.17)	−1.74 (2.11)	−1.85 (0.82)

SD = standard deviation; LS = least square; SE = standard error; US = United States; PD = Parkinson's disease

a. Original/Revised Inclusion Criterion 3 applied to subjects enrolled prior to/after implementation of Protocol Amendment 6 (Study S187-3-001) and Protocol Amendment 2 (Study S187-3-002). Original criterion was based on the Parkinson's Disease – Treatment Optimization Scale (PD-TOS) score and the revised criterion was based on an adequate trial of protocol-defined antiparkinsonian medications (Resistant patients).

b. Daily dose of levodopa from all sources (study drug, rescue tablets, night-time regimen, and replacement tablets).

Note: The interaction *P* value and LS means are based on an ANCOVA model with the terms of treatment, country and the subgroup variable, and the treatment-by-subgroup variable interaction for all subgroups but "Country," in which case no covariate was included as Country was already specified in the model. Baseline "Off" time was included as a covariate for all subgroup analyses with the exception of the subgroup analysis for "Baseline 'Off' time severity."

Cross reference: Table 1.1__1.2.1, Table 1.1__1.2.2.1

Table 23 and Table 24 show subgroup analyses conducted by the primary statistical reviewer.

Table 23 Change from Baseline in Average Daily Normalized "Off" Time by Demographic Subgroups

	Placebo Gel + Levodopa-Carbidopa Capsules	LCIG + Placebo Capsules
Sex: Female		
N	**9**	**11**
LS mean (SE)	**-1.54 (1.18)**	**-4.01 (0.95)**
Difference in LS means		**-2.47**
p-value		**0.0456**
Sex: Male		
N	**22**	**24**
LS mean (SE)	**-2.78 (0.95)**	**-4.38 (0.98)**
Log difference in LS mean		**-1.60**
Unadjusted p-value		**0.0328**
Age: < 65 years		
N	**14**	**20**
LS mean (SE)	**-1.80 (0.94)**	**-3.74 (0.80)**
Log difference in LS mean		**-1.94**
Unadjusted p-value		**0.0106**
Age: >=65 years		
N	**17**	**15**
LS mean (SE)	**-2.57 (1.04)**	**-4.54 (1.14)**
Log difference in LS mean		**-1.97**
Unadjusted p-value		**0.0462**

Source: FDA reviewer.

Table 24 Change from Baseline in Average Daily Normalized "Off" Time by Duration of Parkinson's Disease Category

	Placebo Gel + Levodopa-Carbidopa Capsules	LCIG + Placebo Capsules
<10 YEARS		
N	**14**	**20**
LS mean (SE)	**-2.75 (0.76)**	**-3.65 (0.59)**
Difference in LS means		**-0.90**
p-value		**0.3070**
>=10 YEARS		
N	**17**	**15**
LS mean (SE)	**-1.91 (0.62)**	**-4.72 (0.73)**
Log difference in LS mean		**-2.81**
Unadjusted p-value		**0.0011**

Source: FDA reviewer

Table 25 shows the statistical results for the treatment difference for the original vs the revised inclusion criterion # 3 that attempted to enroll patients who were "resistant" to medications for Parkinson's disease.

Table 25 Study S187-3-001/S187-3-002: Subgroup Analysis of Change from Baseline to Week 12 in Average Daily Normalized "Off" Time (ANCOVA): Within Stratum Results for Inclusion Criteria #3 (Full Analysis Data Set)

	LCIG		LC-oral		Difference LCIG – LC-Oral		
Inclusion Criterion #3	N	LS Mean (SE)	N	LS Mean (SE)	LS Mean	95% CI	*P*-value[a]
Original	19	-4.22 (0.87)	15	-1.94 (0.89)	-2.28	(-4.39, -0.16)	0.0061
Revised	16	-3.81 (0.74)	16	-2.35 (0.75)	-1.46	(-3.71, 0.79)	0.0912

Note: The LS means are based on an ANCOVA model with the terms of treatment, country and the subgroup variable, the treatment-by-subgroup variable interaction, and covariate of baseline "Off" time. The treatment by Inclusion Criterion #3 interaction *P*-value is 0.4895.

a. The within stratum *P*-values are obtained with SLICE=SUBGROUP option.

Reviewer Comments

- *Table 22 shows that there was no statistically significant interaction for any of the subgroup groups indicating that there did not appear to be a problem with one subgroup vs the other subgroup. Although significant differences are not observed for the LCIG treatment difference in each subgroup, noteworthy LCIG treatment differences are observed for each subgroup regarding the primary efficacy endpoint further supporting the robustness of the therapeutic benefit. Analyses conducted by the primary statistical reviewer and presented in Table 23 show statistically significant treatment differences for each subgroup for age and gender. Table 24 and Table 25 show that LCIG treatment differences for subgroups with less than 10 years duration of Parkinson's disease and for patients enrolled in the controlled trial based upon the revised inclusion criterion # 3 were not statistically significant. However, this is not a problem nor concern because the numbers in each subgroup are relatively small and underpowered for a statistical difference.*

- *In addition, I asked the statistical reviewer to conduct another subgroup analysis in which patients taking domperidone (peripheral dopaminergic antagonist) were excluded from the analysis. My concern was that domperidone is not approved for use in the U.S., and I wanted to see that results were still statistically significant if such patients were excluded. Only 5 patients were taking domperidone in the controlled trial. The analysis of the remaining 61 patients in both treatment groups (LCIG-33; oral LD/CD-28) for the primary efficacy endpoint (change from baseline in normalized "off" time) showed an LCIG treatment effect of – 1.93 hrs that was nearly identical to the primary analysis of all patients and was still highly statistically significant (p=0.0031.*

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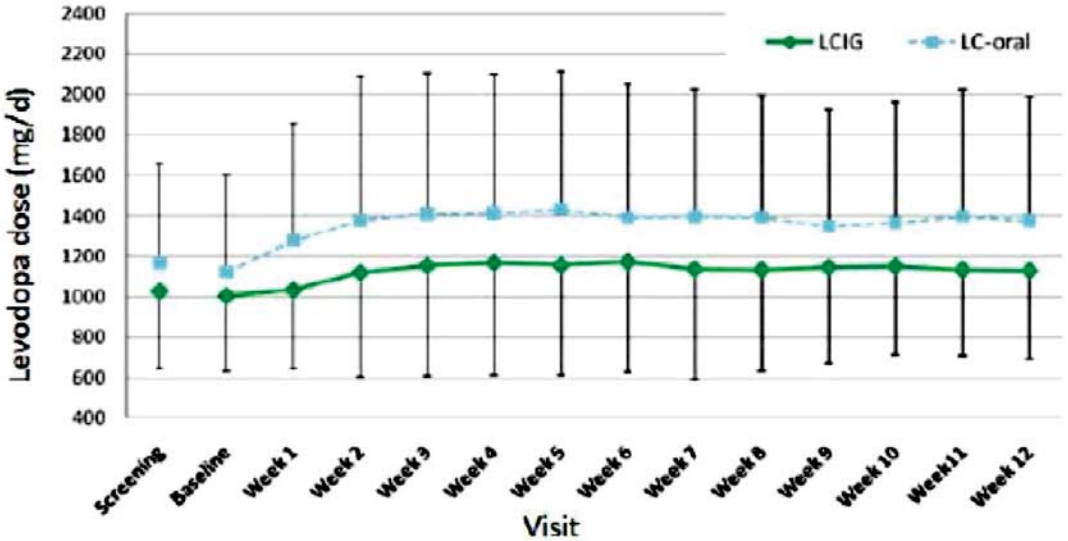
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The following tables and figures provide information relevant to dosing recommendations.

Figure 11 Mean Daily Dose of Levodopa at Screening, Baseline, and Administered as Study Drug in Controlled Trial



	Screening	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
LCIG (N)	37	37	37	36	35	35	34	35	34	33	32	33	35	35
LC-oral (N)	34	34	34	33	31	30	31	31	31	31	30	31	31	31

SD = standard deviation; d = day

Notes: The mean (+ SD) daily dose at Screening and Baseline are from 24-hour oral levodopa-carbidopa. The mean (+ SD) daily dose during the Double-Blind Treatment Period is study drug over approximately 16 hours (does not include levodopa fom levodopa-carbidopa IR rescue tablets and the normal night-time regimen of oral levodopa-carbidopa IR tablets).

The sample includes all 71 subjects who were consented, randomized and had the PEG-J procedure.

Cross reference: Study S187-3-001/S187-3-002 CSR Table 14.1 4.3, Table 14.3 1.1.2.4

Table 26 Descriptive Statistics for Daily Total Levodopa Dosing in LCIG Treatment Group in Maintenance Period of Controlled Trial

Patient ID #	Mean Total Daily Levodopa in Maintenance Period[a]	Mean Total LCIG in Maintenance Period[b]	Mean Total Daily Levodopa with Bolus LCIG in Maintenance Period	Mean Total Daily Levodopa in LCIG Infusion in Maintenance Period	Mean Total Daily Oral Levodopa in Maintenance Period[c]	Mean Total Daily Oral Levodopa Rescue Medication in Maintenance Period[d]	Mean Total Daily Oral Levodopa Bedtime Supplements in Maintenance Period[e]	Mean Total Daily Levodopa Dose Unclassified Tablets in Maintenance Period[f]
N	35	35	35	35	25	21	17	14
Mean (SD)	1181.4 (479.92)	1146.1 (478.34)	134.8 (58.71)	951.3 (462.48)	178.0 (143.45)	116.2 (54.02)	124.3 (66.87)	285.1 (240.24)
Minimum	631.1	603.9	0	413.8	57.1	50.0	50.0	50.0
Quartile 1	881.6	820.0	100.0	640.0	100.0	75.0	75.0	100.0
Median	1030.8	1022.1	160.0	854.3	153.1	100.0	100.0	200.0
Quartile 3	1279.2	1277.4	160.0	1082.7	198.0	145.6	166.7	466.7
Maximum	2942.2	2935.2	273.5	2738.3	800.0	266.7	300.0	800.0

a. All levodopa from LCIG (bolus, infusion and 60 mg allowance for daily tube flush) plus all oral levodopa (including rescue medication, bedtime supplements and unclassified/replacement tablets).
b. All levodopa from LCIG (bolus, infusion and 60 mg allowance for daily tube flush).
c. All oral levodopa including rescue medication, bedtime supplements and unclassified/replacement tablets.
d. Oral levodopa tablets taken during pump operation intervals on days that the total infusion duration was at least 12.8 hours.
e. Oral levodopa tablets not taken during pump operation intervals.
f. Oral levodopa tablets taken during pump operation intervals on days that the total infusion duration was less than 12.8 hours.

Table 27 Five Lowest and Highest Daily Total Levodopa and LCIG Dosing in Individuals in LCIG Treatment Group in Maintenance Period of Controlled Trial

Descriptive Statistic	Total Daily Levodopa Dose	Daily LCIG Dose	Daily Bolus LCIG Dose	Daily LCIG Infusion Dose	Mean Daily Oral Levodopa Dose
5 Lowest Doses	631	604	60	414	0
	636	636	80	416	0
	647	644	93	484	0
	711	672	99	510	0
	737	733	120	512	0
5 Highest Doses	1665	1602	240	1408	111
	1788	1788	246	1568	132
	1951	1901	260	1681	133
	2104	2078	300	1744	161
	2942	2935	334	2738	191

Sponsor's Summary of Phase 3 Support for Dose Selection and Administration Recommendations

The sponsor noted that the 2 most relevant trials were dosing were the controlled 12 trial assessing efficacy and safety under double-blinded, controlled investigation with a comparator and Study S187-3-004, a 12-month, open-label study designed to evaluate the long-term safety and tolerability of LCIG (primary objective), as well as the long-term maintenance of efficacy and health-related outcome measures (secondary objective). Patents in the controlled trial were titrated to their optimal dose through 4 weeks along with their baseline concomitant,

adjunctive medications for Parkinson's disease. In contrast, in Study S187-3-004, all subjects were allocated to open-label treatment with LCIG following discontinuation of antiparkinsonian medications other than oral levodopa-carbidopa IR, leaving subjects on LCIG monotherapy during the 16-hour infusion. If any of the antiparkinsonian medications needed to be tapered over time, this process was completed prior to the initiation of LCIG. In this study, LCIG treatment was initiated via NJ and titrated to an optimal dose prior to the PEG-J procedure. Post-PEG-J, dose adjustments were permitted, based on clinical symptoms. Concomitant antiparkinsonian medications could have been re-introduced 28 days after the PEG-J procedure, at the investigator's discretion. Additionally, the extra dose function could be used., In Study S187-3-004, the majority of subjects (> 75%) achieved "efficacy" while only receiving levodopa-carbidopa throughout the post-PEG treatment period

The sponsor further noted that in the pivotal study, the dose regimen was constrained by the blinded nature of the study. Dose adjustments could only be made once a day and no adjustments to adjunctive antiparkinsonian medications could be made except for safety reasons. Additionally, the extra-dose function could not be utilized. These constraints prolonged the titration period and prevented the investigator from rapidly optimizing LCIG treatment on any given day during titration. Additionally, these restrictions in dose adjustments and background medications prevented the optimal individualization of therapy based on the clinical status of the subject during the maintenance period.

The LCIG dosing regimen employed in Study S187-3-004 allowed more flexibility in dose adjustment and concomitant antiparkinsonian medication use, permitting a greater degree of dose individualization and more rapid titration to optimal dose compared with the pivotal study. The sponsor argued that statistically significant and clinically meaningful improvements in motor function achieved under this open-label/unblinded dosing regimen were similar in magnitude to that achieved in the pivotal study, and were maintained throughout the 54 weeks of treatment while the majority of subjects (> 75%) were receiving only levodopa-carbidopa and contended that the dosing regimen utilized in Study S187-3-004 is the most appropriate method for LCIG dose selection and administration. In this open-label study conducted in 16 countries, the optimized dose was one cassette per day for 82% of patients and two cassettes per day in 18% of patients. Based on this experience, the average daily dose used was 1.18 cassettes ($1 \times 82\% + 2 \times 18\% = 1.18$).

Table 28 summarizes dosing information for levodopa and LCIG in the controlled trial and open-label trial in which detailed dosing information was collected.

The pivotal study demonstrated that LCIG can be safely initiated and titrated without the NJ phase. Eliminating the NJ phase prevents patients from undergoing an additional endoscopic procedure. (b) (4)

Table 28 Study S187-3-001/S187-3-002 and Study S1878-3-004: Summary of Dose Titration and Daily Dose of Levodopa

		Study S187-3-001/3-002		Study S187-3-004	
		LC-Oral (N = 34)	LCIG (N = 37)	LCIG (N = 354)	
				NJ Test	Post-PEG-J
Dose titration days	n	34	37	350	269
	Mean (SD)	8.0 (2.5)	7.1 (2.5)	4.5 (2.15)	3.8 (2.53)
	Min – Max	2 – 16	1 – 15	1 – 14	1 – 15
Total Daily Dose of Levodopa, mg/day					
				Overall Treatment Period	
Baseline oral medication	n	34	37	352	
	Mean (SD)	1123.5 (477.9)	1005.4 (373.6)	1085.78 (590.88)	
	Min – Max	400 – 2200	500 – 2200	62.5 – 3750.0	
Last titration day	n	34	37	338	
	Mean (SD)	1400.0 (698.5)	1127.6 (531.8)	1537.0 (585.22)	
	Min – Max	500 – 3700	460 – 3452	518 – 3768	
Average maintenance dose at Endpoint	n	31	35	317	
	Mean (SD)	1374.1 (615.04)	1131.1 (435.07)	1572.4 (566.14)	
	Min – Max	550 – 2800	597 – 2528	420 – 3620	
Average across entire study duration	n	34	37	350	
	Mean (SD)	1350.6 (617.85)	1117.3 (473.72)	1440.3 (525.40)	
	Min – Max	558.0 – 3096.4	631.8 – 2983.3	412.0 – 3423.6	

Note: The mean (SD) daily dose of levodopa administered as LCIG includes the amount administered during the 16-hour infusion and includes the morning dose, the continuous maintenance dose, any extra doses (Study S187-3-004 only), and dose given during the tube flush that occurs after turning the pump off at the end of the day.

Table 29 shows does-duration information for total daily LD dosing (reflecting primarily LCIG dosing) during long-term treatment (collected mainly during open-label treatment.

Table 29 Summary of Dose-Duration Exposure By Cumulative Total Daily Levodopa Dose Categories (Based Upon Safety Update Cutoff)

TREATMENT DURATION	MEAN TOTAL DAILY DOSE OF LEVODOPA <1000 MG (N=86) n (%)	>=1000 MG (N=330) n (%)	>=1500 MG (N=184) n (%)	>=2000 MG (N=71) n (%)	>=2500 MG (N=23) n (%)	>=3000 MG (N=4) n (%)	ANY DOSE (N=416) n (%)
>= 6 MONTHS	60 (69.8)	291 (88.2)	166 (90.2)	63 (88.7)	20 (87.0)	4 (100)	351 (84.4)
>= 12 MONTHS	58 (67.4)	280 (84.8)	164 (89.1)	63 (88.7)	20 (87.0)	4 (100)	338 (81.3)
>= 18 MONTHS	45 (52.3)	207 (62.7)	115 (62.5)	45 (63.4)	13 (56.5)	4 (100)	252 (60.6)
>= 24 MONTHS	37 (43.0)	170 (51.5)	93 (50.5)	33 (46.5)	7 (30.4)	3 (75.0)	207 (49.8)
>= 30 MONTHS	26 (30.2)	127 (38.5)	71 (38.6)	25 (35.2)	4 (17.4)	1 (25.0)	153 (36.8)
>= 36 MONTHS	16 (18.6)	79 (23.9)	48 (26.1)	16 (22.5)	2 (8.7)	0	95 (22.8)
>= 42 MONTHS	5 (5.8)	46 (13.9)	28 (15.2)	11 (15.5)	2 (8.7)	0	51 (12.3)
>= 48 MONTHS	2 (2.3)	19 (5.8)	12 (6.5)	4 (5.6)	2 (8.7)	0	21 (5.0)

Reviewer Comments

- *Figure 11 shows the mean amount of levodopa received over the whole controlled trial period for each treatment. The approximate mean daily levodopa dose for LCIG patients is slightly less than 1200 mg and the approximate mean levodopa daily for oral LD/CD is about 1409 mg.*

- *Table 26 shows descriptive statistics for daily levodopa dosing for LCIG patients for the various categories of LCIG (i.e.,bolus, infusion) and oral levodopa (i.e., evening supplement, rescue therapy, etc.) for the maintenance period of the controlled trial. The total mean daily levodopa (regardless of source) was 1181 mg (median 1034 mg) and the total LCIG was1146 mg (median 1022 mg). The overwhelming majority of patient receive less than 2000 mg levodopa or LCIG.*

- *Table 27 shows the mean total daily levodopa and the mean total daily LCIG in the maintenance period of the controlled trial for 5 individual patients at the lowest end of daily dosing and at the highest end of daily dosing. Because the LCIG value is only minimally lower than the total daily levodopa value, I will focus on the total daily LCIG of individual patients. The lowest total daily LCIG dose for these 5 individuals ranged from 604 mg to 733 mg. The highest total daily LCIG dose for these other 5 individuals ranged from 1602 mg to 2935 mg. The patient receiving the highest total daily LCIG dose was clearly a marked outlier compared to all other patients. The next highest patient received 2078 mg and the next highest dose after that was 1902 mg. Thus about 95 % of patients received less than a mean total LCIG dose that was less than 2000 mg of LCIG (2000 mg is in a single LCIG cassette.*

- *Table 28 shows various dosing information for LCIG in the controlled trial and one open-label trial (Study3-004) that collected more detailed dosing information. It is noteworthy that the LCIG used in the open-label trial experience was higher than that*

used in the controlled trial experience. In trials of different drugs, the daily dose used in open-label trial design is frequently significantly higher than the dose determined in flexible dosing trial design conducted under double-blinded conditions. It is also noteworthy that patients in the controlled trial continued using their other adjunctive medication for Parkinson's disease in contrast to a substantial number of patients who did not use all or as many other drugs during open-label treatment.

- *Table 29 shows dose-duration exposure data (from the 4Month Safety Update) by cumulative total daily levodopa dose for the clinical trial experience (predominantly derived from open-label treatment). The number of patients who received 2000 -< 2500 mg levodopa daily for 12 months/1 year was 63. The number of patients who received 2500 -< 3000 mg levodopa daily for 12 months/1 year was 20*

- *The controlled trial experience is typically the way that we select and recommend dosing for a drug. Considering that the 95 % of patient used a mean total daily dose of LCIG that was than 2000 mg of levodopa, and many patients in the controlled treatment group that achieved efficacy used less than 1000 mg of LCIG on an average basis during the maintenance period, and that the mean and median dose was close to 1100 mg, I believe that the maximal dose of LCIG should be 2000 mg or one cassette. Furthermore, the long-term, dose-duration exposure and collection of safety experience supports this maximal dose.*

- *Based upon the sponsor's proposed label, the sponsor would allow* (b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The sponsor noted that daily doses of LCIG were stable over time in long-term exposure Study S187-3-004 and did not show any evidence of tolerance effects.

Reviewer Comments

I do not consider efficacy data in an open-label trial to be adequate for addressing the issue of persistence of efficacy or tolerance.

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6.1.10 Additional Efficacy Issues/Analyses

Not applicable. All relevant efficacy analyses were presented in earlier subsections.

7 Review of Safety

Safety Summary

One of the main safety concerns with this LCIG product is the potential for complications related to the whole device (e.g., pump and tubes) administering LCIG and the procedures involved with initially inserting the device and possible replacement or repositioning of tubing. The FDA and the sponsor also agreed that LCIG meets the regulatory definition of a combination product consisting of the drug product in a cassette, an external pump, and PEG-J-tubing. Some examples of potential device or procedure complications include pump malfunction, possible inappropriate/erroneous pump use by patient, caregiver, or healthcare provider and resulting in overdosing of LCIG, intestinal obstruction, and infection (ranging from mild local infection to peritonitis, sepsis, and potentially even death). Presentation of device/procedure complications will be made and will be reviewed in various subsections of section 7. In view of these complications, LCIG treatment via infusion needs to be considered as a total product including not only LCIG but also the associated device and procedures related to the device.

In presenting safety data particularly for adverse events, the sponsor focused on presenting various adverse event perspectives in which adverse events thought to be device or procedure related were excluded from the presentations. The sponsor had evaluated and distinguished the incidence of treatment-emergent adverse events (TEAEs) more likely to be related to levodopa-carbidopa, route of administration, or underlying PD versus the PEG-J placement procedure and long-term use of PEG-J, with all TEAEs with preferred terms (PT) captured by a "procedure- and device-associated events (LCIG specific)" company MedDRA query (CMQ). Thus, some TEAEs were excluded from various TEAE evaluations in the sponsor's Active-Controlled and Open-Label LCIG Analysis Sets. ATEEs that fell within this CMQ, referred to as "procedure- and device-associated AEs of special interest (AESIs)," were also summarized separately for the All PEG-J Analysis Set by the sponsor

Because this exclusionary process/approach seemed somewhat arbitrary, my review focused more than the sponsor on reviewing and presenting all adverse events reported during various treatments irrespective of whether the adverse event might be considered device/procedure related. Given the sponsor's approach, the overwhelming majority of in-text tables of various adverse event perspectives were presentations in which adverse events considered device/procedure related had been excluded. Nevertheless, I have also reviewed data to present and discuss adverse events that I suspect are device/procedure related.

Safety assessments in the US registration clinical program included physical and neurological examinations, vital sign measurements (pulse rate, blood pressure [including the assessment of orthostatic changes] and body temperature), weight, ECG, clinical

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laboratory assessments, and AE monitoring (subjects were queried for AEs at every visit), including assessments for development of sleep attacks, abnormal involuntary movements, melanoma, or excessive impulsive behavior. Complications with the infusion device or product quality complaints defined below (e.g., the tubing system and the pump) were also recorded.

Specific categories of AEs of special interest (AESI) included: procedure- and device-associated events (risks of PEG-J placement, long-term complications of the PEG-J, device-associated GI disorders during long-term therapy), aspiration (including aspiration pneumonia/pneumonitis), clinically significant weight loss, a diagnosis of peripheral polyneuropathy (axonal, demyelinating, or mixed type), and cardiovascular fatalities. Additional details and information on AESI will be presented later.

All safety data (i.e., TEAEs, clinical laboratory analytes, vital signs, ECGs) were evaluated for a time perspective, not only showing TEAEs/abnormalities occurring at any time in the trial, but also in the titration period, in the maintenance period, and when persisting from the titration period into the maintenance period and have a total duration of at least 7 days. In addition, despite the fact that trial design did not randomize patients to a fixed dose of LCIG, all safety data were also analyzed relative to “low” dose and “high” dose LCIG.

It is also important to recognize that an independent Data Safety Monitoring Board (DSMB) was formed to monitor the safety of the US registration clinical program and met on a quarterly basis. The DSMB is composed of 3 members: 1 chairperson, and 2 additional experts. The DSMB members included 2 physicians whose expertise included neurology or gastroenterology, as well as a biostatistician with clinical trial experience. The DSMB reviewed unblinded study safety information during the conduct of the studies. Based on its review, the DSMB provided the sponsor with recommendations regarding study modification, continuation, or termination.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Considering that LCIG is a combination product, the analysis sets used in this ISS were designed to systematically evaluate the following :

1. The safety of LCIG compared with the same active components in the standard oral formulation of levodopa-carbidopa over a 3-month period (Active-Controlled Analysis Set, N = 71),

2. The long-term safety associated with open-label LCIG use (Open-Label LCIG Analysis Set, N = 412),

3. The adverse events (AEs) related to PEG-J placement and long-term use of a

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PEG-J in this advanced PD population that would not necessarily otherwise use this device (All PEG-J Analysis Set, N = 395), and

4. The safety associated with nasojejunal (NJ) tube placement (3004 Analysis Set, N = 354).

5. The safety of LCIG exposure in blinded or open-label studies, regardless of the LCIG delivery method (All LCIG Analysis Set, N = 416).

7.1.2 Categorization of Adverse Events

The following indicates how the sponsor categorized a treatment-emergent adverse event (TEAE) :
Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product (or a system consisting of drug, device, and surgical procedure) and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom (including an adverse event occurring from drug abuse, an AE occurring from drug withdrawal, and any failure of expected pharmacological action), or disease temporally associated with the use of a medicinal product or device, whether or not considered related to the medicinal product or device. AEs that were present before the start of study treatment but worsened during study treatment, including up to 30 days post-treatment, were captured as TEAEs. This standard approach was used in all of the Phase 3 clinical studies in the LCIG program and investigators were trained on this standard procedure for TEAE data collection.

Each TEAE was to be evaluated for duration, severity, seriousness, and causal relationship to the investigational treatment system. The action taken with study drug, the concomitant treatment/therapy introduced, and the outcome, as well as whether the event led to early study termination, were also recorded.

All adverse events presented and analyzed were treatment-emergent (TEAEs) unless otherwise noted. The LCIG System is considered a therapeutic system consisting of the drug, the devices, and the placement procedure for the PEG-J tubing. The analysis sets used in this ISS were designed to systematically evaluate the safety of LCIG and the safety associated with NJ placement, PEG-J placement, and long-term use of a PEG-J in this advanced PD population that otherwise would not necessarily have these devices inserted.
Since the All LCIG Analysis Set comprises the most comprehensive set of subjects who had LCIG infusion in the LCIG System development program, the number and proportion of subjects with AEs over time are described for this analysis set. Otherwise, as requested by the FDA, the Open-Label LCIG Analysis Set consisting of all subjects who received open-label LCIG, which excludes AEs experienced by the subjects during the pivotal study in the Active-Controlled Analysis Set, is summarized and described. Furthermore, events within the procedure- and device-related AESI SMQs/CMQs are excluded from the AE summary tables for the Open-Label LCIG and All LCIG Analysis Sets in appropriate sections to allow a more transparent review of AEs potentially related to the study drug or

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PD (as opposed to the surgical procedure or device/delivery system).

In order to analyze AESIs in the categories of procedure- and device-associated events and respiratory tract aspiration that may be related to the device/delivery system, the All PEG-J Analysis Set is used because it includes all subjects who received PEG-J placement, allows for a clear temporal association of the AE in these categories relative to the date of the PEG-J placement, and excludes subjects who only received treatment though an NJ tube (discontinued during the NJ Test Period of Study S187-3-004 prior to PEG-J placement).

Adverse Events of Special Interest (AESI) and Other AE Evaluations
Adverse events of special interest (AESI) associated with the treatment system included procedure- and device-associated AESI, respiratory tract aspiration AESI, weight loss AESI, polyneuropathy AESI, and cardiovascular fatalities AESI.

The search strategies used to assess AEs potentially related to each AESI are identified in Table 30. Since no standard MedDRA query (SMQ) existed for AEs pertaining to procedure- and device-related events, a company MedDRA query (CMQ) was created to group relevant PTs into the procedure- and device-associated events CMQ. The selection of PTs included in this CMQ was also reviewed by an independent adjudication committee as part of their mandate. This adjudication committee reviewed and adjudicated GI/procedure/device events.

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Table 30 Search Strategy for AESIs

AESI	Search Strategy[a]
Procedure- and device-associated AESI	Procedure- and Device-Associated Events CMQ[b]
Polyneuropathy AESI	Guillain-Barré Syndrome SMQ and Peripheral Neuropathy SMQ
Weight loss AESI	Weight Loss CMQ
Cardiovascular fatalities AESI	Fatal events captured by the Major Adverse Cardiovascular Events [MACE] Myocardial Infarction CMQ
Respiratory tract aspiration AESI	Respiratory Tract Aspiration Including Aspiration Pneumonia/Pneumonitis CMQ

AESI = adverse event of special interest; CMQ = company MedDRA query; SMQ = standardized MedDRA query
a. See Appendix B of the ISS Statistical Analysis Plan (SAP) (Appendix D) for PTs included. SMQs are broad search unless specified otherwise.
b. Duodopa product specific CMQ. The procedure- and device-related CMQ is a combination of 3 CMQs that were previously used in the individual CSRs: risks of PEG placement CMQ, long-term complications of PEG CMQ, and device-associated GI disorders during long-term therapy CMQ.

Within each of the individual CSRs included in this submission, 3 AESIs related to devices (risks of PEG-J placement, long-term complications of PEG, and device-associated GI disorders during long-term therapy) that had previously been employed in postmarketing surveillance were used. The intent was to capture those TEAEs that were specifically related to the placement of the PEG-J versus the long-term complications of the PEG. **However, many of the PTs in the AESI of Risks of PEG Placement captured events that were not temporally related to PEG placement; likewise some events captured in the long-term complications of PEG occurred several days after the initial PEG placement, making them more likely related to the placement of the PEG rather than long-term complications.** As such, the 3 AESIs were combined into 1 AESI CMQ, termed Procedure- and Device-Associated Events. No search terms were dropped during the combination of the 3 original CMQs into the new CMQ, which is also being used in postmarketing surveillance. An aggregate assessment was conducted of the Procedure- and Device-Associated Events CMQ in order to evaluate the incidence and prevalence of AESIs based on their temporal relationship to initial PEG-J placement. In addition, I requested an analysis in which TEAEs were considered procedure/device related when verbatims terms suggested a relationship to the procedure or device.

It is also noteworthy that the sponsor had frequently coded TEAEs to more than one MedDRA preferred term (PT) when a TEAE was experience in the active-controlled trial and was thought

to be related to the procedure/device. For example, a patient experiencing abdominal pain after the PEG placement could have been coded as having a PT for procedure/device complication and also abdominal pain. In addition, some TEAEs (relatively few) were also coded to 3 or even 4 PTs.

The lists of relevant MedDRA PTs for each AESI category was outlined are provided in the Statistical Analysis Plan (SAP) for the ISS .

The sponsor also provided coding dictionaries showing how each verbatim term (VT) was coded to a MedDRA PT and also what VTs were subsumed under each MedDRA PT.

Two separate and independent adjudication committees were formed to evaluate (but not monitor) polyneuropathy and GI/device events.

Other AE Safety Evaluations
Additional AEs were evaluated to correspond with postmarketing surveillance being performed, drug class effects, and as requested by the FDA. The search strategies used to assess other AEs evaluated are identified in Table 31.

Table 31 Search Strategy for Other AE Safety Evaluations

Reason for Evaluation/ AE Category	Search Strategy[a]
Correspond with postmarketing surveillance	
Hepatic events	Drug-Related Hepatic Disorders SMQ
Renal events	Acute Renal Failure SMQ
Malignancies	Malignancies SMQ
Drug class effect	
Sleep attacks	PT of sleep attacks
Impulse control disorder	Abuse Liability CMQ
Melanoma	PT of melanoma
FDA request	
Falls	Falls PT Search Strategy[b]
Orthostatic hypotension	Hypotension/Orthostatic Hypotension PT Search Strategy[c]

CMQ = company MedDRA query; SMQ = standardized MedDRA query; FDA = US Food and Drug Administration;
PT = preferred term
a. See Appendix B of the ISS SAP (Appendix D) for PTs included in CMQ, SMQs, and PT search strategies.
b. The PTs from the SMQ of accidents and injuries were combined with PTs from the SMQ of "hemorrhage terms (excluding laboratory terms)" and other PTs identified from a review of all verbatim reports and PTs in the clinical program that could be potentially related to falls.
c. The PTs identified from a review of all PTs and verbatim reports in the clinical program that could be potentially related to hypotension.

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In addition to AE assessments, the safety evaluations in the LCIG program included additional data collection for sleep attacks, melanoma assessments, assessment of impulsive behavior, and assessment for abnormal involuntary movement scales (AIMS).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As noted previously, the two active-controlled trials were combined for analysis of efficacy and safety data as a single trial. The three open-label, long-term, extension trials were pooled for analyses of open-label data.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The disposition of patients in the controlled trial was presented earlier in Table 12. Here is the disposition of patients in the open-label trials.

Table 32 Disposition of Patients in Open-Label Trials

Open-Label LCIG Analysis Set	Low Dose LCIG N = 155	High Dose LCIG N = 257	All LCIG N = 412
Subjects completed the study	29 (18.7)	69 (26.8)	98 (23.8)
Subjects ongoing at the data cutoff[a]	78 (50.3)	130 (50.6)	208 (50.5)
Subjects discontinued prematurely	48 (31.0)	58 (22.6)	106 (25.7)
Primary reason for premature discontinuation			
Adverse event	12 (7.7)	33 (12.8)	45 (10.9)
Lack of efficacy	5 (3.2)	4 (1.6)	9 (2.2)
Withdrew consent	21 (13.5)	9 (3.5)	30 (7.3)
Administrative[b]	6 (3.9)	8 (3.1)	14 (3.4)
Protocol violation	4 (2.6)	4 (1.6)	8 (1.9)

LCIG = levodopa-carbidopa intestinal gel; LC-oral = encapsulated levodopa-carbidopa immediate release tablets

a. Data cutoff date for Study S187-3-003 and Study S187-3-005 is 04 May 2012.

b. Eleven ongoing subjects in Canada with a minimum of 6 months of LCIG exposure were terminated from Study S187-3-004 early for administrative reasons to allow for timely study closure when the last subject, last visit occurred for the rest of world. All 11 subjects rolled over to Study S187-3-005 after the cutoff date of 04 May 2012.

Notes: Low dose: mean total daily levodopa dose < 1250 mg during the treatment period.
High dose: mean total daily levodopa dose ≥ 1250 mg during the treatment period.

Cross reference: Table 2.1__1.2.1, Table 2.3__1.2.1

Reviewer Comments

Not surprisingly, the most common reason for discontinuing from open-label treatment was adverse event.

7.2.2 Explorations for Dose Response

Throughout the various sections of the review, safety data for adverse events, clinical laboratory analytes, vital sign, and ECGs are analyzed, explored, and reviewed for dose-response based upon “low” dose (mean daily LD dose in the trial < 1250 mg) or “high” dose (≥ 1250 mg). Comments were made about dose response whenever deemed appropriate.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Routine clinical testing seeking information about adverse events, and conducting clinical laboratory testing, and collection of vital sign and ECG was performed at reasonable intervals in the controlled and open-label trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

There was no substantive effort to conduct a metabolic, clearance, or interaction workup in the phase 3 clinical program. Neither did it appear to be necessary to conduct such a workup in the phase 3 clinical program.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The sponsor evaluated adverse events common to drugs in the class that increase

7.3 Major Safety Results

Table 33 provides an overview of serious and non-serious treatment-emergent adverse events (TEAEs), TEAEs causing study discontinuation, and deaths in the controlled and open-label trials.

Reference ID: 3469235

Table 33 Overview of TEAEs (Active-Controlled and Open-Label LCIG Analysis Sets)

	Number (%) of Subjects								
	Active-Controlled Analysis Set						Open-Label LCIG Analysis Set		
	LCIG			LC-Oral					
Subjects with	Low Dose N = 27	High Dose N = 10	Any Dose N = 37	Low Dose N = 15	High Dose N = 19	Any Dose N = 34	Low Dose N = 155	High Dose N = 257	Any Dose N = 412
Any AE	26 (96.3)	9 (90.0)	35 (94.6)	15 (100)	19 (100)	34 (100)	138 (89.0)	241 (93.8)	379 (92.0)
Any AE at least possibly treatment system related[a]	21 (77.8)	8 (80.0)	29 (78.4)	12 (80.0)	17 (89.5)	29 (85.3)	110 (71.0)	212 (82.5)	322 (78.2)
Any severe AE	7 (25.9)	1 (10.0)	8 (21.6)	5 (33.3)	6 (31.6)	11 (32.4)	38 (24.5)	99 (38.5)	137 (33.3)
Any serious AE	3 (11.1)	2 (20.0)	5 (13.5)	4 (26.7)	3 (15.8)	7 (20.6)	38 (24.5)	109 (42.4)	147 (35.7)
Any AE leading to discontinuation from study	1 (3.7)	0	1 (2.7)	2 (13.3)	0	2 (5.9)	12 (7.7)	33 (12.8)	45 (10.9)
Any fatal AE	0	0	0	0	0	0	4 (2.6)	13 (5.1)	17 (4.1)
Deaths[b]	0	0	0	0	0	0	4 (2.6)	14 (5.4)	18 (4.4)

LCIG = levodopa-carbidopa intestinal gel; LC-oral = encapsulated levodopa-carbidopa immediate release tablets; TEAE = treatment-emergent adverse event

Active-Controlled: All data from the 12-week double-blind treatment period in Study S187-3-001/S187-3-002

Open-Label LCIG: all data for all subjects who received open-label LCIG in Studies S187-3-003, S187-3-004 and S187-3-005

a. As assessed by investigator.

b. Includes 1 non-treatment-related death that occurred more than 30 days after PEG-J removal.

Notes: Low dose: mean total daily levodopa dose < 1250 mg during the treatment period.

High dose: mean total daily levodopa dose ≥ 1250 mg during the treatment period.

Cross reference: Table 2.1__2.1, Table 2.3__2.1

7.3.1 Deaths

The following table summarizes deaths in the phase 3 trials. All deaths occurred in the open-label trials during long-term LCIG treatment.

Table 34 All Fatal TEAEs in the Phase 3 Studies

Subject	Sex/Age	Investigator Term (Preferred Term)	Onset – End Day[a]	Relationship to Treatment System[b]
Study S187-3-004				
212-002[4]	M/45	Suicide death by hanging (completed suicide)	370 – 370	Unrelated
		Note: Relevant history of depression, impulse disorder, frontal lobe features, insomnia, and recently separated from wife		
340-001[4]	F/74	Bilateral pleuritis (pleurisy)	22 – 48	Unrelated
		Left pneumonia (pneumonia)	22 – 48	Unrelated
		Septicemia (sepsis)	22 – 48	Unrelated
		Metabolic acidosis (metabolic acidosis)	48 – 48	Unrelated
		Rhabdomyolysis (rhabdomyolysis)	48 – 48	Unrelated
		Septic shock (septic shock)	48 – 48	Unrelated
		Acute renal failure (renal failure acute)	48 – 48	Unrelated
		Note: Relevant history of hypertension		
384-006[4]	F/58	Suicide (completed suicide)	317 – 317	Unrelated
		Note: Relevant history of depression (antidepressant stopped Day –1), sleep disorder, anxiety, and dystonia		
392-016[4]	F/70	Stroke (cerebrovascular accident)	186 – 191	Unrelated
395-008[4]	F/78	Death unknown etiology (death)	172 – 172	Unrelated
		Note: Relevant history of hypertension and chronic pyelonephritis		
435-011[4]	M/76	Patient deceased – cause unknown (death)	174 – 174	Unlikely
		Note: Relevant history of coxarthrosis, total left hip endoprosthesis, hypertension, pacemaker, 3rd degree AV block, osteoporosis with vertebral fractures, ongoing asbestosis; and concurrent SAE of fractured arm (Days 164 – 174)		
447-001[4]	F/82	Cachexia (cachexia)	69 – 124	Unrelated
		Note: Concurrent SAE of hip fracture (Day 69) that required total endoprosthesis		

Table 34 All Fatal TEAEs in the Phase 3 Studies (Continued)

Subject	Sex/Age	Investigator Term (Preferred Term)	Onset – End Day[a]	Relationship to Treatment System[b]
Study S187-3-005				
107-002[5]	M/73	Respiratory arrest (respiratory arrest)	498 – 505	Unrelated
		Note: Subject had a history of focal seizures, developed a pneumonia following a respiratory arrest that occurred 1 day after a hip fracture resulting from a fall; the subject died as a sequelae		
129-002[5]	M/66	Cardiac arrest (cardiac arrest)	491 – 491	Possible
211-002[5]	M/57	Aspiration pneumonia (pneumonia aspiration)	596 – 601	Unrelated
310-001[5]	F/60	Worsening of general condition (general physical health deterioration)	850 – 857	Unlikely
		Multiorgan failure (multi-organ failure)	857 – 857	Unlikely
210-003[5]	F/76	Large left cerebral hemorrhage (cerebral haemorrhage)	1078 – 1084	Unlikely
313-006[5]	M/69	Coronary infarction (myocardial infarction)	539 – 549	Unrelated
382-002[5]	F/75	Acute leukemia (acute leukaemia)	996 – 1109	Unrelated
382-006[5]	M/72	Sudden death (sudden death)	816 – 816	Unrelated
382-008[5]	M/70	Community-acquired pneumonia (pneumonia)	690 – 739	Unrelated
460-006[5]	F/60	Pleural effusion (pleural effusion)	505 – 600	Unlikely
		Pneumonia (pneumonia)	536 – 600	Unlikely

AV = atrioventricular; F = female; M = male; SAE = serious adverse event; TEAE = treatment-emergent adverse event

a. All deaths occurred in subjects initially enrolled in Study S187-3-004. Onset and end days are relative to the start of open-label LCIG treatment.

b. As assessed by the investigator.

Cross reference: Study S187-3-004 CSR Table 14.3__2.3, Study S187-3-005 Interim CSR Table 14.3__2.3, Table 2.3__2.18.5

Reviewer Comments

- *The number (17 in ISS) of patients who died and the adverse events associated with the death did not raise unusual concerns. Considering that this is relatively older population of patients with advanced Parkinson's disease and many other associated diseases/disorders, this fatality rate and causes of fatality seemed reasonable for the population and the total duration of patient treatment and monitoring. The 4 Month Safety Update that included an additional 227 patient-years of LCIG described 10 additional deaths. None of these additional deaths occurring during this substantial additional treatment experience raised any new concerns about LCIG.*

- *However, there are 2 cases of completed suicide about which I would like to provide additional comment. Brief narrative summaries for each cases are presented below here.*

- *Subject 212-0024 (male, 45 years of age), with a relevant medical history of depression, impulse disorder, frontal lobe features since 2004, and insomnia since 2007, attempted suicide by overdose of clonazepam, tramadol, codeine and alcohol on Day 266. He was referred to a psychiatrist who started an antidepressant and noted that the subject had a resolving depressive episode, which had occurred within the context of dissolution of marriage and deteriorating physical function. On Day 271, his total daily levodopa dose was decreased from 2232 mg/day to 1468 mg/day and subsequently decreased further to 1350 mg/day on Day 313. Then, on Day 357, the subject's levodopa dose was increased to 1416 mg/day. However, on Day 370, the subject committed suicide by hanging.*

- *Subject 384-0064 (female, 58 years of age), with relevant history of minor depression since 1997, sleep disorder since 2009 for which she was taking 400 mg of trazodone daily and previous treatment with duloxetine, and anxiety since 2000, committed suicide by hanging on Day 317. She received her highest dose of levodopa on Day 6 (1634 mg/day) that was then decreased to 1472 mg/day on Day 7, and then increased to 1600 mg/day on Day 36. The levodopa dose was decreased to 1440 mg/day on Day 65, then to 1366 mg/day on Day 86, followed by 1273 mg/day on Day 135, then increased to 1352 mg/day on Day 184, and decreased to 1054 mg/day on Day 226. There were no psychiatric symptoms reported at a study visit on Day 297 and, according to the investigator, no known risk factors or previous suicide attempts. The investigator indicated there were no predisposing social circumstances or triggers and that the subject was much improved with study\ medication.*

The first case had a history of depression and was subsequently treated with an antidepressant and had been experiencing a depressive episode related to marriage problems and deteriorating health. It is difficult to consider the potential role of LCIG in this case with confounding factors of depression, personal problems, antidepressant use that can increase the risk for suicide. Although the second case had a history of "minor" depression, the investigator did not suspect that the patient had a significant risk for suicide.

There are some publications that suggest an increased risk for suicidality and completed suicide in patients with PD. One publication (Nazem et al., Movement Disorders, 23: 1573-1579, 2008) noted that active suicidal or death ideation occurs in up to one-third of PD . Regardless of PD, depression is considered a major factor in a subject's risk for suicidal ideation and completed suicide and both patients supposedly had a history of depression. It is also noteworthy that there were 2 additional suicide attempts in the 813 patients-years of LCIG treatment. It is difficult to know whether LCIG treatment played any role in the 2 completed suicides and 2 suicide attempts in this clinical development program. However, it is also noteworthy that there was an increased risk for depression

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in the controlled trial (LCIG 11%, placebo 3 %, Table 48). In addition, the incidence of depression was quite noteworthy at 12 % (Table 54) in the open-label trials (4 Month Safety Update), and this risk for depression was dose-dependent (8 % - low dose, 15 % - high dose).

Given all considerations, it is not possible to conclude that there is an increased risk for suicidality or completed suicide with LCIG treatment. However, LCIG treatment does appear to increase the risk for depression. Considering that depression is a major risk factor in suicide, it may be possible that LCIG increases the risk for depression and thereby indirectly increases the risk for suicide via this relationship. However, it is also possible that LCIG could increase the risk for suicide independent of an increased risk for depression. It is possible that additional insight into the risk for suicide could be obtained by conducting a 6 month controlled trial in the postmarketing period and monitoring patients for the risk for suicidality and depression at baseline and throughout 6 months treatment. I recommend that we make a Postmarketing Requirement for such a trial.

7.3.2 Nonfatal Serious Adverse Events

Treatment-emergent serious adverse events (TESAEs) occurred in the controlled trial and in the open-label trials. Table 35 shows that the incidence of TESAEs was less (~ 14 %) with LCIG than with the control/comparator (oral LD/CD) ~ 21%) and the specific SAEs that occurred in each treatment group as well as according to low and high dose subgroups.

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Table 35 Incidence of TESAEs in Controlled Trial

SYSTEM ORGAN CLASS / MEDDRA 14.0 PREFERRED TERM	LCIG LOW DOSE (N=27) n (%)	LCIG HIGH DOSE (N=10) n (%)	LCIG ALL (N=37) n (%)	LC-ORAL LOW DOSE (N=15) n (%)	LC-ORAL HIGH DOSE (N=19) n (%)	LC-ORAL ALL (N=34) n (%)
ANY ADVERSE EVENT	3 (11.1)	2 (20.0)	5 (13.5)	4 (26.7)	3 (15.8)	7 (20.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
NEUTROPENIA	0	0	0	1 (6.7)	0	1 (2.9)
SUBJ WITH ONE OR MORE EVENTS	0	0	0	1 (6.7)	0	1 (2.9)
CARDIAC DISORDERS						
ATRIAL FIBRILLATION	0	1 (10.0)	1 (2.7)	0	0	0
ATRIAL FLUTTER	0	1 (10.0)	1 (2.7)	0	0	0
SUBJ WITH ONE OR MORE EVENTS	0	1 (10.0)	1 (2.7)	0	0	0
GASTROINTESTINAL DISORDERS						
ABDOMINAL PAIN	0	0	0	1 (6.7)	0	1 (2.9)
PERITONITIS	0	0	0	1 (6.7)	0	1 (2.9)
PNEUMOPERITONEUM	1 (3.7)	0	1 (2.7)	0	0	0
SUBJ WITH ONE OR MORE EVENTS	1 (3.7)	0	1 (2.7)	2 (13.3)	0	2 (5.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
COMPLICATION OF DEVICE INSERTION	1 (3.7)	0	1 (2.7)	1 (6.7)	0	1 (2.9)
SUBJ WITH ONE OR MORE EVENTS	1 (3.7)	0	1 (2.7)	1 (6.7)	0	1 (2.9)
INFECTIONS AND INFESTATIONS						
CATHETER SITE CELLULITIS	0	1 (10.0)	1 (2.7)	0	0	0
PNEUMONIA	0	0	0	1 (6.7)	1 (5.3)	2 (5.9)
SUBJ WITH ONE OR MORE EVENTS	0	1 (10.0)	1 (2.7)	1 (6.7)	1 (5.3)	2 (5.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
FEMUR FRACTURE	0	0	0	1 (6.7)	0	1 (2.9)
POST PROCEDURAL COMPLICATION	0	0	0	1 (6.7)	0	1 (2.9)
SUBJ WITH ONE OR MORE EVENTS	0	0	0	1 (6.7)	0	1 (2.9)
INVESTIGATIONS						
BODY TEMPERATURE INCREASED	0	0	0	0	1 (5.3)	1 (2.9)
SUBJ WITH ONE OR MORE EVENTS	0	0	0	0	1 (5.3)	1 (2.9)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)						
SPINAL HAEMANGIOMA	0	0	0	0	1 (5.3)	1 (2.9)
SUBJ WITH ONE OR MORE EVENTS	0	0	0	0	1 (5.3)	1 (2.9)

Table 35 Incidence of TEASAEs in Controlled Trial (Continued)

SYSTEM ORGAN CLASS / MEDDRA 14.0 PREFERRED TERM	LCIG LOW DOSE (N=27) n (%)	LCIG HIGH DOSE (N=10) n (%)	LCIG ALL (N=37) n (%)	LC-ORAL LOW DOSE (N=15) n (%)	LC-ORAL HIGH DOSE (N=19) n (%)	LC-ORAL ALL (N=34) n (%)	TOTAL (N=71) n (%)	P-VALUE@
NERVOUS SYSTEM DISORDERS								
DEPRESSED LEVEL OF CONSCIOUSNESS	0	0	0	0	1 (5.3)	1 (2.9)	1 (1.4)	
DYSKINESIA	1 (3.7)	0	1 (2.7)	0	0	0	1 (1.4)	
HYPERSOMNIA	1 (3.7)	0	1 (2.7)	0	0	0	1 (1.4)	
PARKINSON'S DISEASE	0	0	0	1 (6.7)	0	1 (2.9)	1 (1.4)	
SUBJ WITH ONE OR MORE EVENTS	2 (7.4)	0	2 (5.4)	1 (6.7)	1 (5.3)	2 (5.9)	4 (5.6)	
PSYCHIATRIC DISORDERS								
CONFUSIONAL STATE	2 (7.4)	0	2 (5.4)	0	0	0	2 (2.8)	
DELUSION	1 (3.7)	0	1 (2.7)	0	0	0	1 (1.4)	
HALLUCINATION	1 (3.7)	0	1 (2.7)	0	0	0	1 (1.4)	
MENTAL STATUS CHANGES	0	0	0	0	1 (5.3)	1 (2.9)	1 (1.4)	
MUTISM	1 (3.7)	0	1 (2.7)	0	0	0	1 (1.4)	
PSYCHOTIC DISORDER	1 (3.7)	0	1 (2.7)	0	1 (5.3)	1 (2.9)	2 (2.8)	
SUBJ WITH ONE OR MORE EVENTS	2 (7.4)	0	2 (5.4)	0	2 (10.5)	2 (5.9)	4 (5.6)	
RENAL AND URINARY DISORDERS								
RENAL CYST	0	0	0	0	1 (5.3)	1 (2.9)	1 (1.4)	
SUBJ WITH ONE OR MORE EVENTS	0	0	0	0	1 (5.3)	1 (2.9)	1 (1.4)	
VASCULAR DISORDERS								
ORTHOSTATIC HYPOTENSION	0	0	0	1 (6.7)	0	1 (2.9)	1 (1.4)	
SUBJ WITH ONE OR MORE EVENTS	0	0	0	1 (6.7)	0	1 (2.9)	1 (1.4)	

NOTE: THE SUM OF THE TOTAL NUMBER OF SUBJECTS REPORTING EACH OF THE PREFERRED TERMS SHOULD BE GREATER THAN OR EQUAL TO THE SYSTEM ORGAN CLASS TOTAL. A SUBJECT WHO REPORTS TWO OR MORE DIFFERENT PREFERRED TERMS WHICH ARE IN THE SAME SYSTEM ORGAN CLASS IS COUNTED ONLY ONCE IN THE SYSTEM ORGAN CLASS TOTAL.

Reviewer Comments

The incidence of TESAEs was less with LCIG(14%) than with oral LD/CD(21%). The only preferred term SAE that occurred in more than one patient was confusional state that occurred in 2 patients treated with LCIG. Most of the isolated events occurring in both treatment groups in the nervous system organ class (e.g., dyskinesia, depressed level of consciousness, hypersomnia), and psychiatric organ class (confusional state, delusion, hallucination, psychotic disorder) are not that unexpected in a population of patients with advanced Parkinson's disease taking often 2 or more dopaminergic drugs.

Table 36 (from the 4 Month Safety Update) shows TESAEs occurring in 48 % of patients during open-label LCIG when the specific preferred term (PT) SAE occurred in one or more patients. TESAEs are presented for different time perspectives (i.e., occurring any time in a trial, onset in the titration period, onset in the maintenance period, onset in the titration period and persisting into the maintenance period and have a total duration of at least 7 days) and also for different doses. TESAEs are presented in descending order of frequency.

Table 36 TESAEs Reported by ≥ 1% of Subjects Overall Presented by 3 Dose Levels and Treatment Period (Open-Label LCIG Analysis Set)

Preferred Term Treatment Period[a]	Low Dose LCIG < 1250 mg/day N = 155	High Dose LCIG ≥ 1250 – 2000 mg/day N = 185	High Dose LCIG ≥ 2000 mg/day N = 72	Any High Dose N = 257	Any Dose LCIG N = 412
Any adverse event	**49 (31.6)**	**78 (42.2)**	**44 (61.1)**	**122 (47.5)**	**171 (41.5)**
Titration Period	14 (9.0)	23 (12.4)	11 (15.3)	34 (13.2)	48 (11.7)
Maintenance Period[b]	42 (32.1)	66 (37.3)	40 (57.1)	106 (42.9)	148 (39.2)
Persistent AEs	7 (4.5)	9 (4.9)	4 (5.6)	13 (5.1)	20 (4.9)
Complication of device insertion	**10 (6.5)**	**16 (8.6)**	**4 (5.6)**	**20 (7.8)**	**30 (7.3)**
Titration Period	5 (3.2)	10 (5.4)	2 (2.8)	12 (4.7)	17 (4.1)
Maintenance Period[b]	5 (3.8)	7 (4.0)	2 (2.9)	9 (3.6)	14 (3.7)
Persistent AEs	2 (1.3)	2 (1.1)	0	2 (0.8)	4 (1.0)
Pneumonia	**6 (3.9)**	**9 (4.9)**	**3 (4.2)**	**12 (4.7)**	**18 (4.4)**
Titration Period	1 (0.6)	2 (1.1)	0	2 (0.8)	3 (0.7)
Maintenance Period[b]	5 (3.8)	7 (4.0)	3 (4.3)	10 (4.0)	15 (4.0)
Persistent AEs	1 (0.6)	0	0	0	1 (0.2)
Abdominal pain	**5 (3.2)**	**6 (3.2)**	**5 (6.9)**	**11 (4.3)**	**16 (3.9)**
Titration Period	2 (1.3)	2 (1.1)	4 (5.6)	6 (2.3)	8 (1.9)
Maintenance Period[b]	3 (2.3)	4 (2.3)	1 (1.4)	5 (2.0)	8 (2.1)
Persistent AEs	0	2 (1.1)	0	0	0
Peritonitis	**6 (3.9)**	**3 (1.6)**	**1 (1.4)**	**4 (1.6)**	**10 (2.4)**
Titration Period	5 (3.2)	3 (1.6)	1 (1.4)	4 (1.6)	9 (2.2)
Maintenance Period[b]	1 (0.8)	0	0	0	1 (0.3)
Persistent AEs	3 (1.9)	1 (0.5)	0	1 (0.4)	4 (1.0)
Parkinson's disease	3 (1.9)	**2 (1.1)**	**5 (6.9)**	**7 (2.7)**	**10 (2.4)**
Titration Period	0	0	1 (1.4)	1 (0.4)	1 (0.2)
Maintenance Period[b]	3 (2.3)	2 (1.1)	4 (5.7)	6 (2.4)	9 (2.4)
Persistent AEs	0	0	1 (1.4)	1 (0.4)	1 (0.2)
Hip fracture	**3 (1.9)**	**2 (1.1)**	**4 (5.6)**	**6 (2.3)**	**9 (2.2)**
Titration Period	1 (0.6)	0	0	0	1 (0.2)
Maintenance Period[b]	2 (1.5)	2 (1.1)	4 (5.7)	6 (2.4)	8 (2.1)
Persistent AEs	1 (0.6)	0	0	0	1 (0.2)

Table 36 TESAEs Reported by ≥ 1% of Subjects Overall Presented by 3 Dose Levels and Treatment Period (Open-Label LCIG Analysis Set) (Continued)

Preferred Term Treatment Period[a]	Low Dose LCIG < 1250 mg/day N = 155	High Dose LCIG ≥ 1250 – 2000 mg/day N = 185	High Dose LCIG ≥ 2000 mg/day N = 72	High Dose LCIG Any High Dose N = 257	Any Dose LCIG N = 412
Polyneuropathy	**1 (0.6)**	**5 (2.7)**	**3 (4.2)**	**8 (3.1)**	**9 (2.2)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	1 (0.8)	5 (2.8)	3 (4.3)	8 (3.2)	9 (2.4)
Persistent AEs	0	0	0	0	0
Weight decreased	**3 (1.9)**	**5 (2.7)**	**1 (1.4)**	**6 (2.3)**	**9 (2.2)**
Titration Period	1 (0.6)	1 (0.5)	0	1 (0.4)	2 (0.5)
Maintenance Period[b]	2 (1.5)	5 (2.8)	1 (1.4)	6 (2.4)	8 (2.1)
Persistent AEs	1 (0.6)	1 (0.5)	0	1 (0.4)	2 (0.5)
Pneumoperitoneum	**1 (0.6)**	**5 (2.7)**	**2 (2.8)**	**7 (2.7)**	**8 (1.9)**
Titration Period	1 (0.6)	5 (2.7)	2 (2.8)	7 (2.7)	8 (1.9)
Maintenance Period[b]	0	0	0	0	0
Persistent AEs	0	1 (0.5)	0	1 (0.4)	1 (0.2)
Device dislocation	**4 (2.6)**	**2 (1.1)**	**1 (1.4)**	**3 (1.2)**	**7 (1.7)**
Titration Period	2 (1.3)	0	1 (1.4)	1 (0.4)	3 (0.7)
Maintenance Period[b]	2 (1.5)	2 (1.1)	0	2 (0.8)	4 (1.1)
Persistent AEs	1 (0.6)	0	0	0	1 (0.2)
Postoperative wound infection	**2 (1.3)**	**2 (1.1)**	**2 (2.8)**	**4 (1.6)**	**6 (1.5)**
Titration Period	0	1 (0.5)	1 (1.4)	2 (0.8)	2 (0.5)
Maintenance Period[b]	2 (1.5)	1 (0.6)	1 (1.4)	2 (0.8)	4 (1.1)
Persistent AEs	0	0	1 (1.4)	1 (0.4)	1 (0.2)
Fall	**1 (0.6)**	**2 (1.1)**	**3 (4.2)**	**5 (1.9)**	**6 (1.5)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	1 (0.8)	2 (1.1)	3 (4.3)	5 (2.0)	6 (1.6)
Persistent AEs	0	0	0	0	0
Pneumonia aspiration	**2 (1.3)**	**2 (1.1)**	**2 (2.8)**	**4 (1.6)**	**6 (1.5)**
Titration Period	0	0	1 (1.4)	1 (0.4)	1 (0.2)
Maintenance Period[b]	2 (1.5)	2 (1.1)	1 (1.4)	3 (1.2)	5 (1.3)
Persistent AEs	0	0	0	0	0

Table 36 TESAEs Reported by ≥ 1% of Subjects Overall Presented by 3 Dose Levels and Treatment Period (Open-Label LCIG Analysis Set) (Continued)

Preferred Term Treatment Period[a]	Low Dose LCIG < 1250 mg/day N = 155	High Dose LCIG ≥ 1250 – 2000 mg/day N = 185	High Dose LCIG ≥ 2000 mg/day N = 72	High Dose LCIG Any High Dose N = 257	Any Dose LCIG N = 412
Depression	**0**	**2 (1.1)**	**2 (2.8)**	**4 (1.6)**	**4 (1.0)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	0	2 (1.1)	2 (2.9)	4 (1.6)	4 (1.1)
Persistent AEs	0	0	0	0	0
Back pain	**0**	**2 (1.1)**	**2 (2.8)**	**4 (1.6)**	**4 (1.0)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	0	2 (1.1)	2 (2.9)	4 (1.6)	4 (1.1)
Persistent AEs	0	0	0	0	0
Pulmonary embolism	**2 (1.3)**	**2 (1.1)**	**0**	2 (0.8)	**4 (1.0)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	2 (1.5)	2 (1.1)	0	2 (0.8)	4 (1.1)
Persistent AEs	0	0	0	0	0
Death	**2 (1.3)**	**1 (0.5)**	**1 (1.4)**	**2 (0.8)**	**4 (1.0)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	2 (1.5)	1 (0.6)	1 (1.4)	2 (0.8)	4 (1.1)
Persistent AEs	0	0	0	0	0
Sepsis	**4 (2.6)**	**0**	**0**	**0**	**4 (1.0)**
Titration Period	1 (0.6)	0	0	0	1 (0.2)
Maintenance Period[b]	3 (2.3)	0	0	0	3 (0.8)
Persistent AEs	1 (0.6)	0	0	0	1 (0.2)
Small intestinal obstruction	**1 (0.6)**	**2 (1.1)**	**1 (1.4)**	**3 (1.2)**	**4 (1.0)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	1 (0.8)	2 (1.1)	1 (1.4)	3 (1.2)	4 (1.1)
Persistent AEs	0	0	0	0	0

Reviewer Comments

The most common TESAEs (≥ 2 % after rounding % off) during open-label treatment and presented in descending order included : complication of device insertion, pneumonia, abdominal pain, peritonitis, Parkinson's disease, hip fracture, polyneuropathy , weight decreased, pneumoperitoneum, device dislocation, postoperative wound infection, fall, and pneumonia aspiration. The vast majority of TESAEs occurring during open-label treatment developed in the maintenance period that was sustained over a long period. There was no clear dose-dependent relationship for developing a TESAE amongst the 3 dose levels categorized in the presentation.

7.3.3 Dropouts and/or Discontinuations

The following table describes TEAEs that led to premature discontinuation in the controlled trial.

Table 37 TEAEs that Led to Discontinuation from the Study(Active-Controlled Analysis Set)

Subject ID, Sex/Age/Race	Analysis Set/ Dose Category	TEAE Investigator Term (Preferred Term)	Onset – End Day, Outcome	Severity, Relationship to Treatment System	Serious
119-103[2] F/55/White	Low dose LCIG	Hallucinations (Hallucination)	12 – Ongoing unknown	Moderate Possible	Yes
		Psychosis (Psychotic disorder)	12 – Ongoing unknown	Moderate Possible	Yes
210-101[2] F/67/White	Low dose LC-oral	Peritonitis: procedure complication after the event (peritonitis AND postprocedural complication)	2 – 270 Recovered/ resolved	Severe Probable	Yes
436-105[1] F/79/White	Low dose LC-oral	Stoma dysfunction, leakage-no culture done (Post procedural discharge)	5 – 10 Recovered/ resolved	Severe Possible	No

F = female; M = male; TEAE = treatment-emergent adverse event

Notes: Low dose: mean total daily levodopa dose < 1250 mg during the treatment period.
High dose: mean total daily levodopa dose ≥ 1250 mg during the treatment period.

Cross reference: Study S187-3-001/S187-3-002 CSR Table 14.3__2.2

Reviewer Comments

Hallucinations/psychotic disorder in an LCIG-treated patient is not an unexpected TEAE in this population undergoing drug treatment with one or more drugs increasing central dopaminergic , tone. Neither would be unusual for a patient developing such adverse reaction to discontinue prematurely from a trial. The 2 patients in the oral LD/CD treatment group who discontinued prematurely from the controlled trial did so because of complications related to the device/procedure. Neither is this surprising, particularly considering that these complications were considered to be severe.

Table 38 TEAEs Causing Study Discontinuation in Open-Label Trials TEAEs that Led to Discontinuation from the Study for > 1 Subject by 3 Dose Levels and Treatment Period (Open-Label LCIG Analysis Set in 4 Month Safety Update)

	Number (%) of Subjects				
		High Dose LCIG			
Preferred Term Treatment Period[a]	Low Dose LCIG < 1250 mg/day N = 155	≥ 1250 – 2000 mg/day N = 185	≥ 2000 mg/day N = 72	Any High Dose N = 257	Any Dose LCIG N = 412
Any adverse event	**16 (10.3)**	**30 (16.2)**	**12 (16.7)**	**42 (16.3)**	**58 (14.1)**
Titration Period	4 (2.6)	8 (4.3)	1 (1.4)	9 (3.5)	13 (3.2)
Maintenance Period[b]	12 (9.2)	23 (13.0)	11 (15.7)	34 (13.8)	46 (12.2)
Persistent AEs	3 (1.9)	6 (3.2)	1 (1.4)	7 (2.7)	10 (2.4)
Complication of device insertion	**5 (3.2)**	**5 (2.7)**	**0**	**5 (1.9)**	**10 (2.4)**
Titration Period	2 (1.3)	3 (1.6)	0	3 (1.2)	5 (1.2)
Maintenance Period[b]	3 (2.3)	2 (1.1)	0	2 (0.8)	5 (1.3)
Persistent AEs	1 (0.6)	1 (0.5)	0	1 (0.4)	2 (0.5)
Abdominal pain	**2 (1.3)**	**2 (1.1)**	**0**	**2 (0.8)**	**2 (0.5)**
Titration Period	1 (0.6)	1 (0.5)	0	1 (0.4)	2 (0.5)
Maintenance Period[b]	1 (0.8)	1 (0.6)	0	1 (0.4)	2 (0.5)
Persistent AEs	0	0	0	0	0
Pneumonia	**1 (0.6)**	**2 (1.1)**	**1 (1.4)**	**3 (1.2)**	**4 (1.0)**
Titration Period	0	1 (0.5)	0	1 (0.4)	1 (0.2)
Maintenance Period[b]	1 (0.8)	1 (0.6)	1 (1.4)	2 (0.8)	3 (0.8)
Persistent AEs	0	0	0	0	0
Death	**2 (1.3)**	**1 (0.5)**	**1 (1.4)**	**2 (0.8)**	**4 (1.0)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	2 (1.5)	1 (0.6)	1 (1.4)	2 (0.8)	4 (1.1)
Persistent AEs	0	0	0	0	0
Myocardial infarction	**0**	**2 (1.1)**	**1 (1.4)**	**3 (1.2)**	**3 (0.7)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	0	2 (1.1)	1 (1.4)	3 (1.2)	3 (0.8)
Persistent AEs	0	0	0	0	0
Fall	**0**	**1 (0.5)**	**1 (1.4)**	**2 (0.8)**	**2 (0.5)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	0	1 (0.6)	1 (1.4)	2 (0.8)	2 (0.5)
Persistent AEs	0	0	0	0	0
Dyskinesia	**1 (0.6)**	**1 (0.5)**	**0**	**1 (0.4)**	**2 (0.5)**
Titration Period	0	1 (0.5)	0	1 (0.4)	1 (0.2)
Maintenance Period[b]	1 (0.8)	0	0	0	1 (0.3)
Persistent AEs	0	1 (0.5)	0	1 (0.4)	1 (0.2)
Completed suicide	**0**	**2 (1.1)**	**0**	**2 (0.8)**	**2 (0.5)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	0	2 (1.1)	0	2 (0.8)	2 (0.5)
Persistent AEs	0	0	0	0	0
Abdominal discomfort	**1 (0.6)**	**1 (0.5)**	**0**	**1 (0.4)**	**2 (0.5)**
Titration Period	1 (0.6)	1 (0.5)	0	1 (0.4)	2 (0.5)
Maintenance Period[b]	0	0	0	0	0
Persistent AEs	1 (0.6)	1 (0.5)	0	1 (0.4)	2 (0.5)

AE = adverse event; LCIG = levodopa-carbidopa intestinal gel; TEAE = treatment-emergent adverse event

a. Titration Period = onset during Days 1 through 28; Maintenance Period = onset ≥ Day 29; Persistent = event onset during Titration Period and continued into Maintenance Period with duration ≥ 7 days.

b. N = 131 for < 1250 mg/day, 177 for ≥ 1250 – 2000 mg/day, 70 for ≥ 2000 mg/day, 247 for any high dose.

Cross reference: Tables 1__2.4.1.3.1 through 1__2.4.1.3.4, Tables 1__2.19.1.3.1 through 1__2.19.1.3.4

7.3.4 Significant Adverse Events

Significant adverse events are presented in other subsections in this section (Major Safety Results) and subsection 7.4.1 (Common Adverse Events).

7.3.5 Submission Specific Primary Safety Concerns

The sponsor conducted many various and detailed analyses for various potential safety concerns including adverse events of special interest (AESI) such as procedure/device-associated events, polyneuropathy events, weight loss events, cardiovascular fatality events, and respiratory tract aspiration events, and other safety events of interest including hepatic events, renal events, malignancies, drug class events (i.e., sleep attacks, impulse control disorders, melanoma), falls, events possibly related to orthostatic hypotension. The evaluation for these events of interest was primarily made through search for various designated PT events as outlined in section 7.1.2 Categorization of Adverse Events. There was an evaluation of LCIG toxins/carcinogens/impurities.

I will not present analyses for many of these events of interest (i.e., weight loss events, cardiovascular fatality events, respiratory tract aspiration events, hepatic events, renal events, malignancies, melanoma), events possibly related to falls, and events possibly related to orthostatic hypotension) because there was no clear suggestion of a relationship to LCIG treatment and I considered that no important information was obtained from these various analyses. However, I will present some information related to some of these events of interest including LCIG procedure/device-associated events, polyneuropathy, LCIG toxins/carcinogens/impurities, malignancies, sleep attacks, impulsive behavior,

Procedure/Device-Associated Events

The following tables and figures present information regarding procedure-device associated events in the controlled and open-label trials.

Reference ID: 3469235

Table 39 Incidence of TEAE Of Medically Reviewed Procedure/Device Associated Events By Time Perspective (Active-Controlled Analysis Set)

SYSTEM ORGAN CLASS / PREFERRED TERM	ANY TIME LCIG (N=37) n (%)	ANY TIME LC-ORAL (N=34) n (%)	TITRATION PERIOD LCIG (N=37) n (%)	TITRATION PERIOD LC-ORAL (N=34) n (%)	MAINTENANCE PERIOD LCIG (N=35) n (%)	MAINTENANCE PERIOD LC-ORAL (N=31) n (%)	PERSISTENT AEs LCIG (N=37) n (%)	PERSISTENT AEs LC-ORAL (N=34) n (%)
ANY ADVERSE EVENT	28 (75.7)	27 (79.4)	27 (73.0)	26 (76.5)	9 (25.7)	6 (19.4)	4 (10.8)	5 (14.7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS								
NEUTROPENIA	0	1 (2.9)	0	1 (2.9)	0	0	0	0
SUBJ WITH >=1 EVENTS	0	1 (2.9)	0	1 (2.9)	0	0	0	0
GASTROINTESTINAL DISORDERS								
ABDOMINAL DISCOMFORT	1 (2.7)	1 (2.9)	1 (2.7)	1 (2.9)	0	0	0	0
ABDOMINAL DISTENSION	2 (5.4)	1 (2.9)	2 (5.4)	1 (2.9)	0	0	0	0
ABDOMINAL PAIN	19 (51.4)	11 (32.4)	19 (51.4)	11 (32.4)	0	0	1 (2.7)	1 (2.9)
ABDOMINAL PAIN UPPER	0	2 (5.9)	0	2 (5.9)	0	0	0	0
FLATULENCE	5 (13.5)	4 (11.8)	5 (13.5)	4 (11.8)	0	0	0	0
PERITONITIS	0	1 (2.9)	0	1 (2.9)	0	0	0	1 (2.9)
PNEUMOPERITONEUM	4 (10.8)	1 (2.9)	4 (10.8)	1 (2.9)	0	0	1 (2.7)	1 (2.9)
SUBJ WITH >=1 EVENTS	21 (56.8)	15 (44.1)	21 (56.8)	15 (44.1)	0	0	2 (5.4)	1 (2.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
ADVERSE DRUG REACTION	1 (2.7)	0	1 (2.7)	0	0	0	0	0
COMPLICATION OF DEVICE INSERTION	21 (56.8)	15 (44.1)	21 (56.8)	15 (44.1)	0	0	2 (5.4)	1 (2.9)
IMPAIRED HEALING	1 (2.7)	0	1 (2.7)	0	0	0	1 (2.7)	0
MEDICAL DEVICE SITE REACTION	1 (2.7)	0	0	0	1 (2.9)	0	0	0
SUBJ WITH >=1 EVENTS	21 (56.8)	15 (44.1)	21 (56.8)	15 (44.1)	1 (2.9)	0	2 (5.4)	1 (2.9)
INFECTIONS AND INFESTATIONS								
CATHETER SITE CELLULITIS	1 (2.7)	0	1 (2.7)	0	0	0	0	0
INCISION SITE CELLULITIS	1 (2.7)	1 (2.9)	1 (2.7)	0	0	1 (3.2)	0	0
POST PROCEDURAL INFECTION	0	1 (2.9)	0	1 (2.9)	0	0	0	0
POSTOPERATIVE WOUND INFECTION	4 (10.8)	8 (23.5)	3 (8.1)	6 (17.6)	2 (5.7)	3 (9.7)	2 (5.4)	2 (5.9)

Table 39 Incidence of TEAE Of Medically Reviewed Procedure/Device Associated Events By Time Perspective (Active-Controlled Analysis Set) (Continued)

SYSTEM ORGAN CLASS / PREFERRED TERM	ANY TIME LCIG (N=37) n (%)	ANY TIME LC-ORAL (N=34) n (%)	TITRATION PERIOD LCIG (N=37) n (%)	TITRATION PERIOD LC-ORAL (N=34) n (%)	MAINTENANCE PERIOD LCIG (N=35) n (%)	MAINTENANCE PERIOD LC-ORAL (N=31) n (%)	PERSISTENT AEs LCIG (N=37) n (%)	PERSISTENT AEs LC-ORAL (N=34) n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS								
INCISION SITE COMPLICATION	0	1 (2.9)	0	1 (2.9)	0	0	0	0
INCISION SITE ERYTHEMA	7 (18.9)	4 (11.8)	3 (8.1)	3 (8.8)	4 (11.4)	1 (3.2)	1 (2.7)	1 (2.9)
POST PROCEDURAL COMPLICATION	0	1 (2.9)	0	1 (2.9)	0	0	0	1 (2.9)
POST PROCEDURAL CONSTIPATION	0	1 (2.9)	0	1 (2.9)	0	0	0	0
POST PROCEDURAL DISCHARGE	4 (10.8)	3 (8.8)	3 (8.1)	2 (5.9)	1 (2.9)	1 (3.2)	1 (2.7)	0
POST PROCEDURAL DISCOMFORT	0	1 (2.9)	0	0	0	1 (3.2)	0	0
POST PROCEDURAL HAEMORRHAGE	0	1 (2.9)	0	0	0	1 (3.2)	0	0
POSTOPERATIVE ILEUS	2 (5.4)	0	2 (5.4)	0	0	0	0	0
PROCEDURAL NAUSEA	0	1 (2.9)	0	1 (2.9)	0	0	0	0
PROCEDURAL PAIN	11 (29.7)	12 (35.3)	9 (24.3)	12 (35.3)	2 (5.7)	1 (3.2)	1 (2.7)	1 (2.9)
PROCEDURAL SITE REACTION	2 (5.4)	2 (5.9)	2 (5.4)	2 (5.9)	0	0	0	1 (2.9)
SUBJ WITH >=1 EVENTS	18 (48.6)	19 (55.9)	16 (43.2)	19 (55.9)	5 (14.3)	3 (9.7)	3 (8.1)	4 (11.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS								
MUSCLE SPASMS	1 (2.7)	0	1 (2.7)	0	0	0	0	0
MUSCULOSKELETAL PAIN	1 (2.7)	1 (2.9)	1 (2.7)	1 (2.9)	0	0	0	0
PAIN IN EXTREMITY	0	1 (2.9)	0	1 (2.9)	0	0	0	0
SUBJ WITH >=1 EVENTS	2 (5.4)	1 (2.9)	2 (5.4)	1 (2.9)	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS								
HYPOVENTILATION	1 (2.7)	0	1 (2.7)	0	0	0	1 (2.7)	0
OROPHARYNGEAL PAIN	1 (2.7)	0	1 (2.7)	0	0	0	0	0
SUBJ WITH >=1 EVENTS	2 (5.4)	0	2 (5.4)	0	0	0	1 (2.7)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS								
DERMATITIS ALLERGIC	1 (2.7)	0	1 (2.7)	0	0	0	0	0
EXCESSIVE GRANULATION TISSUE	2 (5.4)	0	0	0	2 (5.7)	0	0	0
SUBCUTANEOUS EMPHYSEMA	1 (2.7)	0	1 (2.7)	0	0	0	0	0
SUBJ WITH >=1 EVENTS	4 (10.8)	0	2 (5.4)	0	2 (5.7)	0	0	0

NOTE: MEDDRA VERSION IS 14.0. NOTE: THE SUM OF THE TOTAL NUMBER OF SUBJECTS REPORTING EACH OF THE PREFERRED TERMS SHOULD BE GREATER THAN OR EQUAL TO THE SYSTEM ORGAN CLASS (SOC) TOTAL. A SUBJECT WHO REPORTS TWO OR MORE DIFFERENT PREFERRED TERMS WHICH ARE IN THE SAME SOC IS COUNTED ONLY ONCE IN THE Total.

Table 40 Incidence Of TEAE Of Medically Reviewed Procedure/Device Associated Events By Time Perspective (Open-Label Lcig Analysis Set)

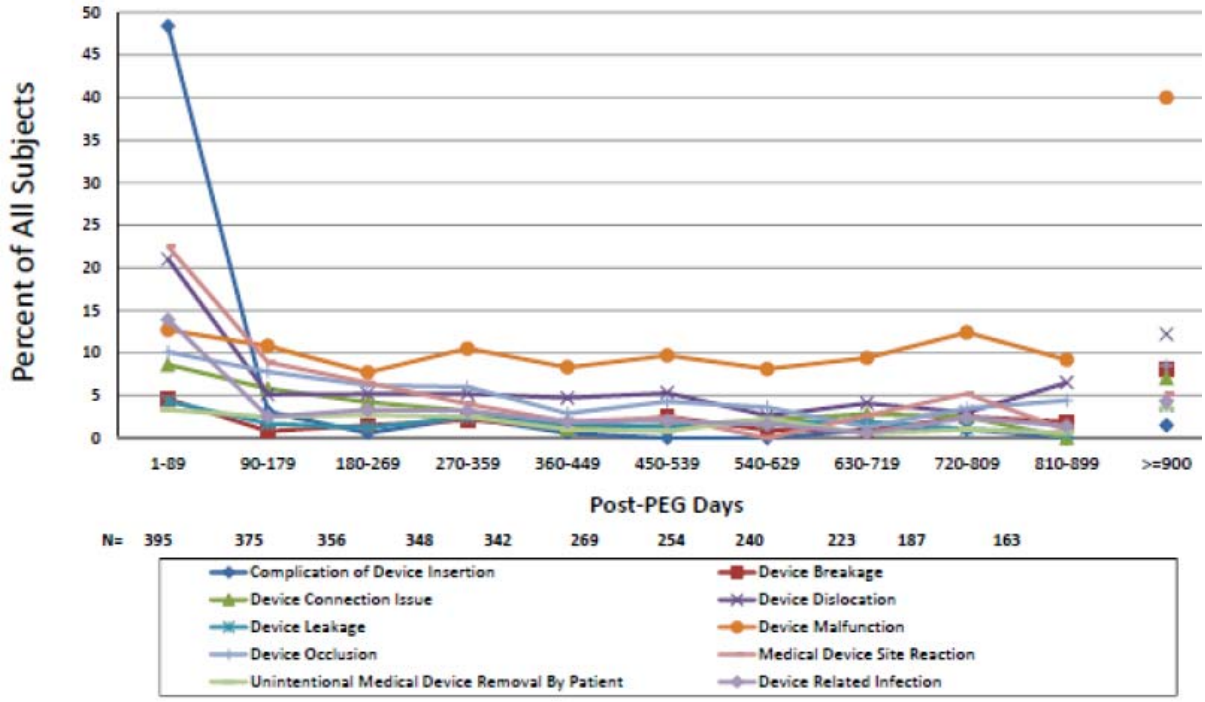
SYSTEM ORGAN CLASS PREFERRED TERM	------- ANY TIME ------- ISS (N=412) n (%)	SU (N=412) n (%)	--- TITRATION PERIOD --- ISS (N=412) n (%)	SU (N=412) n (%)	-- MAINTENANCE PERIOD -- ISS (N=378) n (%)	SU (N=378) n (%)	---- PERSISTENT AEs ---- ISS (N=412) n (%)	SU (N=412) n (%)
ANY ADVERSE EVENT	268 (65.0)	278 (67.5)	194 (47.1)	191 (46.4)	198 (52.4)	220 (58.2)	73 (17.7)	71 (17.2)

Table 41 New Incidence of Device Complaints with an Overall Incidence ≥ 10% During Days 1 Through 28 - ISS All PEG-J Analysis Set

Device Complaints	Days 1 - 28 (%)
Complication of Device Insertion	48.4
Medical Device Site Reaction	14.7
Device Dislocation	12.7
Device Related Infection	11.4
Device Connection Issue	4.6
Device Malfunction	3.8
Device Occlusion	2.5
Unintentional Medical Device Removal By Patient	2.3
Device Leakage	1.8
Device Breakage	1.5

Cross reference: ISS Table 2.4__2.19.2.1

Figure 12 New Incidence Over Time of Device Complaints PTs with an Overall Occurrence ≥ 10% in the Safety Update: All PEG-J Analysis Set



Note: Data ≥ 900 days includes PEG exposure up to Day 1668, with 100 subjects exposed ≥ 1095 days.
Cross reference: Safety Update Figure 7, Table 2__2.19.2.1, and Table 2__2.19.2.2

The following information describes the frequency of PEG and J-Tube replacement,

Table 42 Number of PEG Tube and J-Tube Replacements (All PEG-J Analysis Set)

Number of PEG Tube Replacements	Number (%) of Subjects N = 395
0	339[a] (85.8)
1	42 (10.6)
2	9 (2.3)
3	3 (0.8)
4	1 (0.3)
Number of J-Tube Replacements	
0	223[a] (56.5)
1	80 (20.3)
2	46 (11.6)
3	26 (6.6)
4	8 (2.0)
5	6 (1.5)
6	0
7	2 (0.5)
8	1 (0.3)
9	2 (0.5)

Figure 13 Time to First PEG Tube Replacement (Kaplan-Meier for All PEG-J Analysis Set)

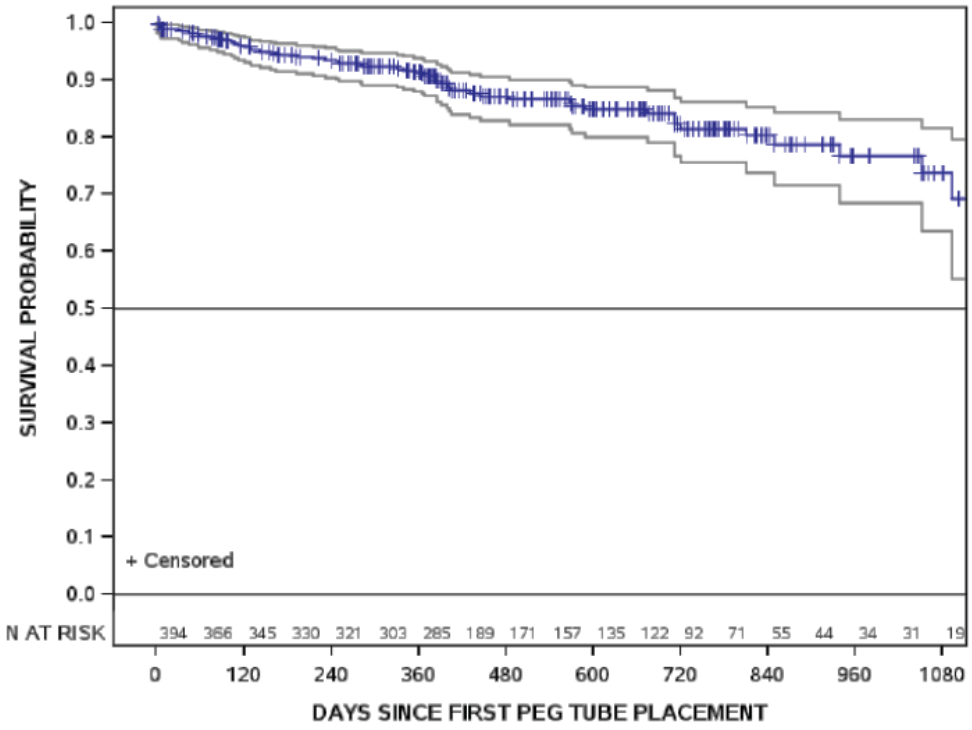
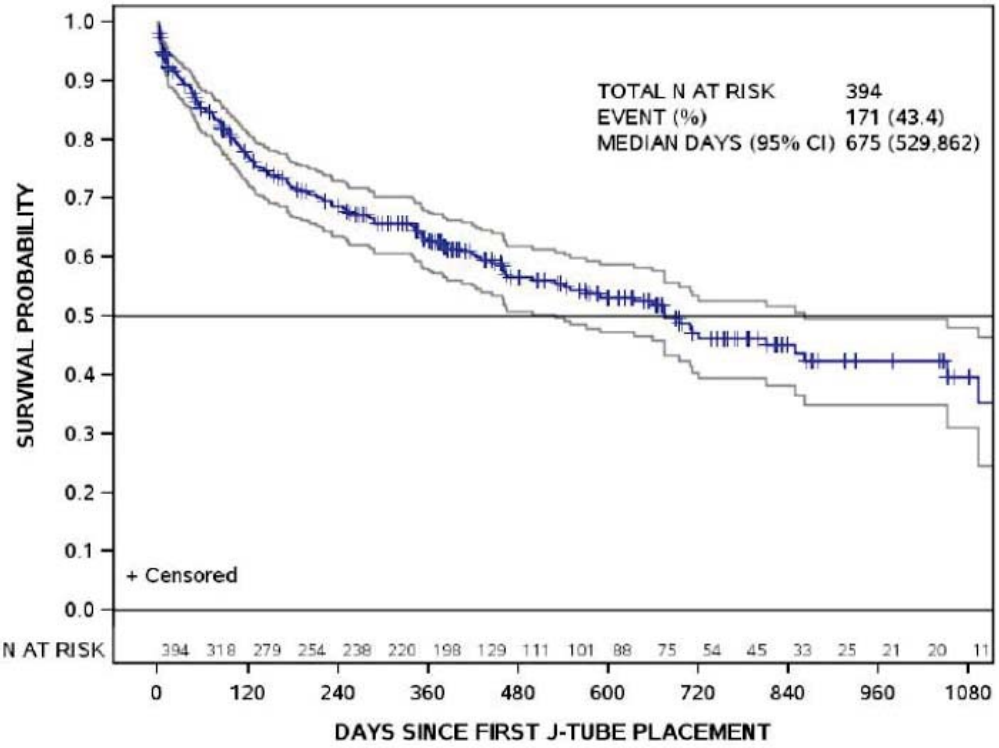


Figure 14 Time to First J-Tube Replacement (Kaplan-Meier for All PEG-J Analysis Set)



Serious Procedure/Device_Associated TEAEs in PEG-J Analysis Dataset

The procedure- and device-associated AESI identified 55 patients (Table 43) in the PEG-J Analysis Set with SAEs potentially related to the placement of the PEG-J and/or the long-term complications of the PEG-J. Most of these serious TEAEs occurred in the open-label treatment experience. An additional medical review performed on these SAEs and other categories of SAEs identified a total of 59 subjects with SAEs potentially related to the placement of the PEG-J and/or the long-term complications of the PEG-J. The sponsor presented results of analysis of the procedure- and device-associated AESIs and discussed them below, followed by a discussion of the medical review.

Table 43 Serious Procedure- and Device-Associated AESIs > 1 Subject by Treatment Period (All PEG-J Analysis Set)

	Number (%) of Subjects			
Preferred Term	Titration Period N = 395	Maintenance Period N = 382	Persistent AEs N = 395	Any Time N = 395
Any preferred term	32 (8.1)	30 (7.9)	8 (2.0)	55 (13.9)
Complication of device insertion	19 (4.8)	11 (2.9)	3 (0.8)	29 (7.3)
Abdominal pain	9 (2.3)	6 (1.6)	0	14 (3.5)
Peritonitis	10 (2.5)	1 (0.3)	4 (1.0)	11 (2.8)
Pneumoperitoneum	9 (2.3)	0	1 (0.3)	9 (2.3)
Device dislocation	3 (0.8)	3 (0.8)	1 (0.3)	6 (1.5)
Postoperative wound infection	2 (0.5)	4 (1.0)	1 (0.3)	6 (1.5)
Device occlusion	0	4 (1.0)	0	4 (1.0)
Small intestinal obstruction	0	4 (1.0)	0	4 (1.0)
Post procedural complication	3 (0.8)	0	2 (0.5)	3 (0.8)
Unintentional medical device removal	0	2 (0.5)	0	2 (0.5)
Acute abdomen	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.5)
Gastrointestinal hemorrhage	0	2 (0.5)	0	2 (0.5
Ileus paralytic	1 (0.3)	1 (0.3)	0	2 (0.5)
Intestinal ischaemia	0	2 (0.5)	0	2 (0.5)
Intestinal obstruction	0	2 (0.5)	0	2 (0.5)
Intestinal perforation	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.5)
Small intestinal hemorrhage	0	2 (0.5)	0	2 (0.5)

Serious procedure- and device-associated AESIs in the All PEG-J Analysis Set were reported in 13.9% (55/395) of subjects over a total of 590.2 patient years with a mean exposure of 546 days . All serious procedure- and device-associated AESIs reported in more than 1 subject are summarized by treatment period in Table 43. Overall, serious procedure- and device-associated AESIs were reported in 8.1% (32/395) of subjects during the 28-day Titration Period and in 7.9% (30/382) of subjects during the long-term Maintenance Period, which included exposure to PEG-J from Day 29 up to a maximum of Day 1276. The most common SAEs that occurred during the Titration Period or the Maintenance Period or persisted from the Titration Period to the Maintenance Period are summarized as follows :

● Titration Period (Days 1 – 28): Serious procedure- and device-associated AESIs reported in ≥ 1% of subjects in the Titration Period were complication of device insertion (4.8%), peritonitis (2.5%), abdominal pain (2.3%), and pneumoperitoneum (2.3%).

● Maintenance Period (Day 29 up to Day 1276): Serious procedure- and device-associated AESIs reported in ≥ 1% of subjects in the Maintenance Period were complication of device insertion (2.9%), abdominal pain (1.6%), postoperative wound infection (1.0%), device occlusion (1.0%), and small intestinal obstruction (1.0%).

● Titration Period versus Maintenance Period: Any comparisons between the Titration Period and the Maintenance Period must take into consideration the hospitalization and PEG-J surgery during the Titration Period, and the difference in duration between the treatment periods (Titration Period was 28 days, Maintenance Period was up to 1276 days, including 180 subjects with overall exposure to PEG-J for ≥ 540 days).

- Greater Incidence in Titration Period: PTs reported in ≥ 1% of subjects in the Titration Period at a rate at least twice that of the Maintenance Period were peritonitis (2.5% versus 0.3%) and pneumoperitoneum (2.3% versus 0%).

- Greater Incidence in Maintenance Period: PTs reported in ≥ 1% of subjects in the Maintenance Period at a rate at least twice that of the Titration Period were postoperative wound infection (1.0% versus 0.5%), device occlusion (1.0% versus 0%), and small intestinal obstruction (1.0% versus 0%).

● Persistent SAEs (onset during Titration Period with a duration ≥ 7 days and extended into the Maintenance Period or ongoing at the end date of the treatment system): A subset of SAEs reported in the Titration Period persisted into the Maintenance Period and the overall percentage of subjects with persistent SAEs was 2.0% (8/395). The SAEs that began during the Titration Period persisted into the Maintenance Period for 2 of the 3 subjects with post procedural complication, and for less than half of the subjects for other PTs reported in more than 2 subjects during the Titration Period.

LCIG Gastrointestinal Device Safety Adjudication Committee

The sponsor had convened an LCIG Gastrointestinal Device Safety Adjudication Committee (LGDAC) to review adverse events associated with LCIG and the PEG and J-Tube placements procedures to assess the risks of this product related to the procedure/device.

Adjudication Committee Members and Affiliation

1. (b) (4)

2. (b) (4)

3. (b) (4)

4. (b) (4)

The following represents the conclusions of that committee.

Conclusions of LCIG Gastrointestinal Device Safety Adjudication Committee (LGDAC) Report

"Percutaneous endoscopic gastrostomy (PEG) has become the modality of choice for providing enteral access to patients who require long-term enteral nutrition. Although generally considered safe, PEG tube placement can be associated with many potential complications. PEG-J-tubes can add to the complication rate and repositioning requirements of these tubes.

"Infusion of medication via a PEG-J combination is a novel therapeutic approach although PEG-J combination with infusion pump is commonly used for constant enteral feedings. Medications are also delivered via the PEG-J-tube although rarely by constant infusion.

The LGDAC committee extensively reviewed the comprehensive database of information provided from studies 3.001/3.002, 3.003, 3.004 and 3.005. The committee developed protocols based on their extensive knowledge to carefully adjudicate the SAE and AE reported events linked to device events. The entire database was queried based on the CMQ/PMQ and adverse events felt by the committee to be device events (Des) but not coded as such were added to the analysis. Additional review was undertaken of pneumonia events as subjects were felt to be high risk for periprocedure pneumonitis.

The process was labor intensive and required at a minimum concordance of 2 out of 3 voting members of the committee. There was notable agreement amongst the experts and consensus was reached in the majority of adjudicated events. None of the major SAE's were considered anticipated by the committee confirming that adjudication was concordant. An extensive literature review was undertaken and the committee reached consensus on best practices to recommend as a guidance document with use of the existing PEG-J technology.

As study 3.005 remains the only ongoing study, this evaluation stands as comprehensive, with the findings not likely to change substantially. Further refinement and subset analysis are planned as the data sets are finalized.

After adjudication, and given the length of exposure of these subjects to the PEG- J-tubes (590.2 patient years of exposure) , the committee found rates of Adverse Events to be either lower than expected or consistent with ranges quoted in the literature. Tube survival was longer than expected. Importantly, there was no series of events or sentinel event(s) that should limit clearance of the device since it compares favorably with existing technology and clinical use of

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PEG and PEG-J. The committee has developed a consensus of recommendations that will potentially reduce the risk of peritonitis and post-procedure surgical intervention.

These Parkinson's Disease subjects were considered a unique population in that the majority of PEG and PEG-J subjects in the literature had even more limited mobility that this population. This mobility may lead to increased risk of tube dislocations but in fact the risk of tube dislocation appeared much lower than anticipated.

The PD subjects have special considerations with a documented increased rate of gastroparesis and swallow dysfunction that predisposes to aspiration and pneumonic events. The committee took this into consideration in their review and was satisfied that there were no excess cases of pneumonia over expected incidence.

These studies represent the largest database on enteral tubes collected with a median exposure to PEG tubes of 383 days. The data set is more comprehensive and detailed than any previously reported and has been exhaustively reviewed and adjudicated. The committee recommends adoption of the current PEGJ/ pump/drug system concurrently with implementation of the *Consensus Recommendations for Best Practice* guidelines as outlined in this report by incorporating these into the (b) (4) PEG-J training system and the Study Reference Manual."

Division of Gastroenterology and Inborn Errors Products (DGIEP) Consult

A consult was made to the DGIEP posing several questions regarding LCIG treatment with the device and associated procedures.

The most important question posed in our consult was :

"Please evaluate whether you consider the adverse events/complications associated with the PEG (initial insertion and/or chronic use) to be similar to those associated with a PEG used for other reasons or whether you conclude that there are some unique safety issues associated with a PEG for Duopa treatment. We are especially interested in knowing whether chronic use of the PEG for administering Duopa is associated with unique safety issues/concerns."

The following is a quotation abstracted from the DGIEP consult provided by Juli Tomaino, M.D. (Primary Reviewer) and Jessica J. Lee, M.D. (Team Leader).

"Response Overall, the types of AEs reported in the clinical trials are consistent with safety issues associated with the use of PEG or PEG-J tubes for other indications. The most common indications are head and neck cancers, neurologic disorders (motor neuron diseases such as ALS), Parkinson's Disease, Alzheimer Syndrome, and stroke.[10] Indications for jejunal rather than gastric feedings include cancers of the esophagus, stomach, pancreas, metastatic cancers, gastroparesis, and patients at high risk of aspiration.[5] The complications of the placement and continued use of PEG and PEG-J tubes are similar across the indications.[5,6,10,11] The placement of PEG and PEG-J tubes are most frequently indicated for patients who cannot meet their enteral nutritional requirements

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and the PEG-J is used for feeding. Common AEs related to enteral feeding are diarrhea and abdominal distention and are often caused by the introduction of hyperosmolar formula into the intestine.[14] However, based on the proposed labeling, the rate of infusion of Duopa is very slow (b) (4) **These slow infusion rates will unlikely alter the motility of a healthy small intestine in an adult patient. One study showed that healthy volunteers were able to tolerate a duodenal infusion of Osmolite at a rate of 340 ml/hr. without developing diarrhea.**

However, placement of the PEG-J tube specifically for Duopa administration is unique for this patient population since this patient population would not otherwise require placement of a PEG-J. This reviewer is in agreement with the conclusion of the GI adjudication committee that since this patient population may be more mobile than the majority of adult patients who require PEG or PEG-J placement, these patients may be at high risk for complications of tube migration or breakage due to increased mobility. Since there is an increased morbidity (17%) and mortality (0.5%)[8] associated with the placement of a PEG-J, this reviewer recommends that the intended population be carefully selected (i.e., patient population who are most likely to gain clinical benefit from continuous infusion of Duopa).

Reviewer Comments

- *Table 39 presents the incidence of procedure/device related TEAEs observed in the controlled trial after verbatim terms were specifically medically reviewed to ascertain whether the investigator suspected that the TEAE was related to the procedure device. The incidence of these TEAEs is similar for LCIG and oral LD/CD for all time perspectives as would be expected if the TEAE was actually related to the procedure device and not related to LCIG because both groups of patients had the same procedure and device (considering the control group had the PEG and J-Tube also while receiving placebo treatment in the double-dummy trial design. This table also shows the incidence of specific TEAEs that were considered procedure/device related. The open-label trial experience (Table 40) as observed in the ISS and in the 4 Month Safety Update show similar incidence for procedure/device-related events for all time perspective after medical review of the verbatim terms for the events.*

- *Table 41 shows the incidence for categories of procedure/device-related events occurring in the first 28 days of PEG-J-Tube placebo in the all PEG-J set (consisting mostly of open-label trial data). The most common category for about half of the patients was complication of device insertion. The next most common categories were medical device site reaction, device dislocation, and device-related infection.*

- *Figure 12 shows the new incidence of device complaints over time in the all PEG-J analysis set. For the first 3 months, the highest incidence complaint is complication of device insert for almost half of patients and then the next two most common events are medical device site reaction and device dislocation. This pattern is fairly similar to the*

one suggested by the analyses of events in the first 28 days. Over time (at 3 month intervals) the new incidence of these various device-related events appears to be relatively stable. The category that appears highest over the whole observation period after 3 months is device malfunction. The reason that the incidence of device malfunction appears to increase from 900 day and long (as do some other categories) is that the reporting window is much longer 678 days.

- *Table 42 shows the number of PEG and J-Tube replacements in the all PEG analysis set. Approximately 14 % of patients required PEG replacement and approximately 43 % of patients require J-Tube replacement. For the vast majority of patient requiring a PEG replacement, only 1 or 2 PEG replacements was needed, For the vast majority of patient requiring a J-Tube replacement, only 1 to 3 J-Tube replacements was needed. Figure 13 shows the Kaplan –Meier analysis for time to first PEG replacement over 1080 days. Figure 14 shows the Kaplan –Meier analysis for time to first J-Tube replacement over 1080 days.*

- *Table 43 shows the incidence of serious procedure/device-related TEAEs according to time perspective of in the PEG analysis set.*

- *I am also concerned that the TEAE table for the controlled trial experience may overestimate the incidence of various TEAEs because the sponsor has frequently coded events occurring in the controlled trial to more than one preferred term (PT) (and also in some cases to more than 2 PTs). I believe the sponsor should review all TEAEs in the controlled trial and code the event to an appropriate term that most appropriately describes the event at the highest integrated level. For example, if the event is assessed as a device/procedure complication it should be coded solely as that and not to other terms to describe the event. I also believe that it may be useful in the label to have another table that describes more specifically the type of device/procedure event (e.g., PEG replacement, J0Tube dislocation, incisions infection, etc. and also a specific adverse body manifestation that may have been experienced (e.g., abdominal pain, nausea, abdominal distention, etc.).*

- ***After review of all this information, I agree with the assessment of the LCIG Gastrointestinal Device Safety Adjudication Committee (LGDAC) and the DGIEP consult that procedure/device related TEAEs associated with LCIG are not unique for this treatment but overall appear to be similar in nature and incidence/rate to information reported in the published literature.***

Polyneuropathy

Methodological Approach for Evaluating Polyneuropathy

An Adjudication Committee consisting of 3 neurologists with expertise in peripheral neuropathy,

(b) (4)

(b) (4)

) was established to review peripheral neuropathy cases. The Adjudication Committee received the case material, did individual reviews, and then met by conference call for adjudication. At each call, cases were discussed and a completed final review form was completed by the Chair. Material from the review forms was transferred to an excel spreadsheet for the final analysis.

Cases of polyneuropathy were identified in the AEGIS safety database and Clinical Database of the above studies. Cases were identified using version 14.0 of the appropriate MedDRA Standardized Medical Query (SMQ). Abbott was responsible for tracking the cases identified in the AEGIS safety database and Clinical Database, receipt of event documents from the investigative site, and processing and updating the documents for review by the committee. Abbott compiled documents pertaining to each event as identified by review of the database for the MedDRA terms.

For the initial review, all cases within the 3.001 and 3.002 studies were reviewed as blinded cases. Following completion of the study and database lock, these cases were unblinded to gain greater understanding of any potential relationship to LCIG. Abbott provided the committee with an estimate of total LCIG exposure for each subject.

The daily dose was based on the pump setting for morning dose +infusion rate*16 hours. Moreover, this estimate of dose did not include any nighttime oral levodopa use or rescue levodopa use. The committee was informed that this daily calculation could overestimate or underestimate the true daily dose if the subject did not use LCIG for 16 hours or if bolus doses were used. A sample calculation is provided as follows:

All pertinent event information was compiled by Abbott and sent to each member of the Review Committee in batches as available. Each committee member reviewed the supplied information prior to meetings and completed the Individual Case review for Postmarketing or Clinical Case Forms.

The adjudication committee requested primary data where possible such as examination details, nerve conduction/EMG reports, and primary lab data. In some cases this was not possible, and the adjudication committee relied upon the statements of the Investigators. Each case required the completion of an Individual Review Form completed by the committee members and a Final Review Form completed by the Chair. Review of all cases focused on description of the type of neuropathy, likely etiology and potential causality. To document an accurate, independent, and unbiased evaluation of the events, the Review Committee was provided with the Individual Event Review forms that were completed for each identified case.

Peripheral polyneuropathy was diagnosed using clinical criteria. Specifically, the diagnosis was based on the reported presence of symmetrical sensory and motor symptoms and abnormalities on the clinical examination with a distal to proximal distribution. Typical sensory symptoms included paresthesias, numbness and pain. Weakness was the primary motor symptom.

Examination abnormalities include deficits in vibration perception, pin perception, touch perception and proprioception; clinically evident weakness; and loss or diminution of reflexes. The clinical diagnosis was supported by neurophysiological abnormalities documented on electromyography and nerve conduction studies when available. The presence of neurophysiological abnormalities was not a requirement for the diagnosis of a peripheral polyneuropathy. Some consideration was given to the clinical opinion of the treating physician but the final conclusion was based on the clinical judgment of the members of the evaluating committee. If insufficient information was available to make a clinical diagnosis, the conclusion of the committee was "insufficient data."

The majority of cases were reviewed by all 3 committee members. All cases were reviewed by at least two committee members. All opinions and conclusions of the adjudication committee were unanimous.

Results

The adjudication committee reviewed eighty-six (86) cases in which, using prespecified search criteria, a neuropathy was identified as an adverse event (AE). Using these criteria, of those eighty-four (86) identified cases, nineteen (19) cases met criteria for a generalized polyneuropathy, three (3) did not meet criteria for a generalized polyneuropathy, and, sixty-two (64) cases there were insufficient data to come to a definitive conclusion as to whether a neuropathy was present or not. The relatively large proportion of cases that had insufficient data is at least in part related to the broad search criteria that including search terms such as aphasia, dysarthria, dysphagia, bulbar palsy, which are unlikely to be features of a generalized polyneuropathy (for a complete list of terms, see Charter).

Of those 19 cases that met criteria for peripheral neuropathy, the onset of the neuropathy could be determined in 14 cases. Of these cases, 1 case was acute, 7 cases were subacute, and 6 cases were chronic.

Of the 19 confirmed neuropathy cases, eight (8) were mild, ten (10) cases were moderate, and one (1) case was severe.

Polyneuropathy Assessment

The following shows the Summary and Conclusions of the Polyneuropathy Adjudication Committee..

"Summary overview
Based on this review, by 3 independent experts, LCIG appears associated with a generalized polyneuropathy. The onset is characteristically subacute or chronic; the severity mild to moderate; and the phenotype sensory or sensorimotor. In cases with sensorimotor neuropathy, sensory features are more prominent and more severe. In some cases, motor involvement was only shown by nerve conduction studies and not clinically. The neurophysiology is typically consistent with an axonal polyneuropathy. The majority of cases were associated with vitamin deficiency. There are a small number of exceptions to this characteristic description.]

Risk and issues

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The judgment of the Adjudication Committee is that the risk of a peripheral neuropathy in patients exposed to LCIG is greater than would be expected in a comparable population, and most likely greater than would be seen in a comparable Parkinson's disease population treated with levodopa (see Introduction).

While the adjudication is not designed to assess risk, the findings suggest that patients with underlying vitamin deficiencies or at risk for vitamin deficiencies would be at greater risk for developing a peripheral neuropathy from LCIG.

Further, it is likely that patients with a pre-existing neuropathy (including those associated with Parkinson's disease with and without prior oral therapy with levodopa) or diseases that make one prone to neuropathy such as diabetes would be at greater risk for developing drug-induced neuropathy. This final assessment is based on experience, not this data set.
In any given patient, even with possible risk factors, the use of LCIG should be based on a clinical assessment of risk-benefit ratio.

The adjudication is also not designed to assess causality. While the risk of neuropathy in LCIG recipients appears greater than that in comparable populations, it is not possible to determine whether this is due to factors related to levodopa itself, the delivery system, hydrazine, the intervention, or other factors acting alone or in combination.

These are all topics for a future prospective study.

Approach to monitoring and treatment.
Based on this assessment, the Adjudication Committee suggests the following approach to monitoring and treatment of LCIG candidates and recipients:

For an LCIG candidate's evaluation prior to initiation of therapy:
☐Baseline laboratory assessments could include plasma values for B6, B12, folic acid, homocysteine, and MMA.
☐Based on the laboratory data, vitamin supplementation may be warranted. Careful dose selection is needed as excess B6 can cause a PN itself. In patients with pre-existing PN, LCIG should be treatment with carefully weighed for a favorable benefit-risk ratio.

For an LCIG recipient:
☐Because vitamin status can change after therapy starts, consider measuring B6, B12, folate, MMA and homocysteine at regular intervals such as every 3 months. Depending on the values, vitamin supplementation may be needed.
☐In patients with existing PN, careful monitoring is suggested to detect worsening PN before it becomes symptomatic. This should include a detailed history, neurological examination and neurophysiological studies as clinically indicated

For Peripheral Neuropathy in an LCIG recipient:

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- In patients with subacute or chronic PN, the decision to continue or stop LCIG should depend on the individual patient's clinical picture. If deficient or marginal laboratory values as detailed above are determined, vitamin supplementation is recommended.

- In patients with acute PN, LCIG should be stopped, and oral levodopa should be reinstituted. Specific conditions if present should be treated.

- Further diagnostic evaluation and treatment should follow local standards for the treatment of a peripheral neuropathy.

- In the cases to date, there is no evidence that IV Ig treatment had any effect on the neuropathy. Given associated costs and risks, it is not recommended that this treatment be given unless a condition normally treated with IV Ig, such as Guillain-Barré syndrome is suspected.

Preventive measures

- See above under or serial measurements while on drug. We emphasize that the above approach to monitoring and therapy is based on review of predominantly retrospective, cross-sectional data and our clinical judgment. It should be considered expert-opinion. There is insufficient data, in particular, prospective and longitudinal data for an evidence-based opinion."

Reviewer Comments

- *The Adjudication Committee concluded that :*
  the risk of a peripheral neuropathy in patients exposed to LCIG is greater than would be expected in a comparable population, and most likely greater than would be seen in a comparable Parkinson's disease population treated with levodopa," The Committee did not believe that there was a dose relationship for LCIG and polyneuropathy. Although I believe that there is a risk for polyneuropathy associated with LCIG treatment and I recognize that it is possible that this risk may be greater than that for this population using oral LD/CD, I am not necessarily convinced that this risk is definitely greater than the risk for this population using oral LD/CD. A very recent publication (Caravolo et al., Movement Disorders : 28 : 1391-1397, 2013) not referenced by this Committee's report described the risk of polyneuropathy in a cross sectional study of patients with PD. This publication reported that 19.40 % of 144 PD patients treated for 3 or more years with oral LD/CD exhibited neuropathy based upon an abnormal parameter in nerve conduction studies and clinical signs or symptoms of neuropathy. The percentage of patients with a diagnosis of neuropathy was 6.80 % in 103 PD patients treated for less than 3 years with oral LD/CD, 4.82 % in 83 patients not exposed to oral LD/CD, and 8.76 % in 137 control subjects without PD. The authors noted that the greatest risk factor for neuropathy was the duration of exposure to oral LD and age was also a noteworthy risk factor.

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I believe that it is possible that the risk of polyneuropathy associated with LCIG treatment may be related to oral LD itself, hydrazine, associated vitamin deficiencies (e.g., B12, B6,, folic acid) and possible a combination of these factors. Treatment with isoniazid which exposes subjects to hydrazine is a well-recognized cause of neuropathy, presumably from causing a functional B6 deficiency.

- *Although there were no cases of polyneuropathy with this PT in the controlled trial there was one patient in the controlled trial who was treated with oral LD/CD who had a TEAE categorized as peripheral neuropathy. There were however, many cases of TEAEs categorized as polyneuropathy in the pooled, open-label trials. The incidence of polyneuropathy was 12 % (24 patients) in the 4 Month Safety Update. All these patients developed polyneuropathy in the maintenance period. The incidence of polyneuropathy was dose-dependent : approximately 2 % for LCIG mean daily dose of < 1250 mg, & for LCIG mean daily dose of > 1250 mg - < 2000 mg, and 13 % for LCIG mean daily dose of ≥ 2000 mg. I interpret this dose-dependence as suggestive of a causal role of LCIG.*

- *Although many patients had associated vitamin deficiency, (B12, B6, or folic acid) it was not clear that the vitamin deficiency was caused by LCIG because vitamin levels were not systematically measured at baseline and throughout the controlled trial or pooled, open-label trials. I agree with the Polyneuropathy Adjudication Committee that it was not possible to conclude whether LCIG caused vitamin deficiencies and whether vitamin deficiencies played a causal role in the development of polyneuropathy.*

- *Polyneurapathy associated with LCIG treatment and its relationship to vitamin deficiency could possibly be investigated in a postmarketing controlled trial of 6 months duration.*

- *If this product is approved, it may be desirable to monitor vitamin levels before and periodically after treatment and to include these recommendations in the label, as was recommended by the Polyneuropathy Adjudication Committee.*

Toxins/Carcinogens/Impurities with LCIG Treatment

Hydrazine

Hydrazine is a degradation product of carbidopa that is reasonably suspected to be a human carcinogen based on tumor findings in animal studies; thus presenting a theoretical risk to patients. Several lines of evidence suggest that this risk is low and have been described in detail in a sponsor analysis of safety risks related to hydrazine.

Carbidopa in LCIG is stable (b) (4) and has a relatively low degradation rate to hydrazine during (b) (4) The use of (b) (4) (b) (4) limits hydrazine formation prior to use by patients. Hydrazine is carcinogenic in rodents and appears to act via an indirect or epigenetic mechanism of action. From rat

carcinogenicity studies, the highest non-tumor dose is approximately 8-fold higher and the threshold tumor dose is approximately 40-fold higher than the theoretical maximum hydrazine exposure from a single LCIG cassette. Higher multiples of the theoretical maximum hydrazine exposure from a single LCIG cassette is achieved based on mouse and hamster carcinogenicity studies.

Hydrazine is also a metabolite of isoniazid and there is considerable scientific literature devoted to evaluating its mechanistic role in isoniazid toxicities. While the carcinogenicity of isoniazid is well described in animals and a causal role for hydrazine has been proposed, an association with higher cancer rates in human patients has not been established. Multiple epidemiological studies have been reported for patients taking isoniazid for either therapeutic or prophylactic reasons and have failed to identify a causal link to cancer in humans. The epidemiology studies cited in this review represent data from a total of more than 38,000 patients treated with isoniazid for approximately 1 year up to several years, with post-treatment or retrospective follow-up durations of 9 to 24 years post-treatment. Many of these studies used a placebo controlled design and isoniazid doses were described as within the therapeutic range (4 to 7 mg/kg). While it might be argued that a longer follow-up period is necessary to detect a signal for cancer, the consistency across studies of the absence of a relationship between isoniazid and a higher cancer rate in humans supports the absence of a treatment-effect relationship.

Under Amendment 7 of LCIG Study S187-3-001 and Amendment 3 of LCIG Study S187-3-002, additional PK samples were collected to allow for characterization of the plasma exposure to hydrazine in subjects treated with LCIG (and oral levodopa-carbidopa capsules, LC-oral). Blood samples were collected over the 16-hour LCIG infusion period. Plasma hydrazine concentration data were available from 16 subjects; 11 of those subjects were randomized to LCIG and 5 subjects were randomized to LC-oral. Ten of 11 subjects on LCIG and 3 of 5 subjects on LC-oral did not have measurable hydrazine levels in plasma at any time point (levels were less than the lower limit of quantitation [LLOQ] of (b) (4) ng/mL). In the 1 LCIG subject (Subject 111-102) who had detectable levels, the plasma concentrations were much lower than mean hydrazine plasma concentrations reported in patients taking isoniazid. Based on the assay limit of quantitation, hydrazine exposure (AUC) in the subjects treated with LCIG is more than 38-fold lower than hydrazine plasma exposure (AUC) reported with isoniazid use.

The subject with detectable plasma hydrazine levels (Subject 111-102, LCIG treatment) had TEAEs of abdominal pain, complication of device insertion, pollakiuria, flatulence, and falls. These adverse events were all mild or moderate in severity, nonserious, and did not lead to study discontinuation. The AE of flatulence was ongoing and the remaining AEs resolved during the controlled study.

In the clinical trials, 5.3% of subjects in the Open-Label LCIG Analysis Set experienced malignancies. Analysis of the postmarketing pharmacovigilance data for Duodopa has not identified a signal for cancer occurrence having a causal relationship to treatment. A review of the 22 neoplasms reported in the postmarketing database did not reveal any clustering of cancer types.

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Given the small number of reports during LCIG therapy and the background rate of these malignancies in this elderly population, there is no evidence of causality between LCIG exposure and malignancy. In addition to malignancies, no clear evidence was observed for the association of hydrazine exposure and hepatic, renal, and peripheral neurotoxicity.

The sponsor further noted that the cumulative weight of evidence points to the findings of cancer in animals treated with hydrazine as having an uncertain translation to human. The dosing margins derived from the animal studies indicate that at the theoretical maximum level of hydrazine in LCIG the daily amount of hydrazine given and LCIG patient is 8- to 40-fold lower than the highest tumor free dose animals. In combination with the lack of evidence for an increased cancer rate in isoniazid patients having hydrazine exposure via metabolite formation at levels that are at least 40-fold higher than exposures observed in LCIG, hydrazine appears to represent a small component of risk for LCIG patient.

(b) (4) and (b) (4) Exposure

Both (b) (4) and (b) (4) are both metabolites of carbidopa and degradation products of carbidopa in LCIG. Both (b) (4) and (b) (4) were tested in a 4-week rat toxicity study at doses that were 9-fold and 8-fold higher, respectively, than doses a patient would be exposed to from use of 1 LCIG cassettes daily. These doses were found to be well tolerated and without evident signs of toxicity. No human data regarding adverse health outcomes has been reported for either (b) (4) or (b) (4)

Under Amendment 7 of Study S187-3-001 and Amendment 3 of Study S187-3-002, additional PK samples were collected to allow for characterization of the plasma exposure to (b) (4) and (b) (4) in subjects treated with LCIG (and oral levodopa-carbidopa capsules, LC-oral). Blood samples were collected on Study Day 42 at 12 and 16 hours post-infusion initiation and on Study Day 43, prior to the morning oral dose and initiation of intestinal gel infusion, at 0 (pre-dose), 1, 2, 4, and 8 hours after initiation of intestinal gel infusion. The data from the 2 days together characterize the exposure for the entire 16 hours of treatment with LCIG, since all subjects were on stable doses of LCIG starting Week 4 of treatment. (b) (4) and (b) (4) plasma concentration data were available from 16 subjects; 11 of those subjects were randomized to LCIG and 5 subjects were randomized to LC-oral.

In subjects treated with LCIG (and LC-oral), systemic exposure to (b) (4) and (b) (4) as measured by plasma concentrations at steady-state, were low (b) (4) to non-measurable (less than the lower limit of quantitation of (b) (4) ng/mL; (b) (4)). Based on observed (b) (4) concentrations, exposure (AUC0-16) of (b) (4) in subjects treated with LCIG was less than 9% of that of carbidopa. Exposure (AUC0-16) of (b) (4) in subjects treated with LC-oral was less than 5% of that of carbidopa. The pharmacokinetic sampling was not optimized for characterizing the exposure from LC-oral since fluctuations in exposure with oral administration may require more frequent sampling for adequate determination of the (b) (4)/carbidopa exposure ratio with LC-oral. Based on the limit of quantitation of (b) (4) and lack of measurable concentrations in the majority of samples in Study S187-3-001/S187-3-002, exposure (AUC0-16) of (b) (4) in subjects treated with

LCIG (and LC-oral) was estimated to be less than 5% of that of carbidopa.

The comparable levels of (b) (4) and (b) (4) exposure in subjects treated with LCIG and LC-oral suggests there is a negligible concern for added (b) (4) and (b) (4) exposures due to degradation with LCIG relative to exposure endogenously generated as metabolites from LC-oral.

Reviewer Comments

There are potential concerns about the carcinogenicity and mutagenicity of these substances that are present as degradants of carbidopa. Our nonclinical pharmacologists/toxicologists are not able to qualify the amounts of these substances and have suggested that the approvability could rest on the risk benefit ratio. I believe that it may be acceptable to consider that these substances are acceptable with a maximum LCIG daily dose of 2000 mg daily and that limiting this dose might also limit the unknown/undefined risk in humans.. This product has demonstrated a relative large magnitude of therapeutic benefit in a population that is relatively difficult to manage. Considering that this product is not likely to be used by patients who can be managed adequately with oral medications, I believe that it may be possible to approve this product because the benefits outweigh the risks. The worldwide use of approximately 9000 patient-years suggest that the use of this product has not been that common despite its approval in many countries.

It may also be noteworthy that there has not been any serious suspicion for malignancy during the clinical development program in which safety data have been collected during 807 patient-years of treatment. Although one patient exhibited measurable levels of hydrazine several other patients did not. One concern could also be a carcinogenic risk locally in the intestines but there has not been a suggestion of such a risk based upon the current experience.

Malignancies

To compare LCIG malignancy rates with the published United States (US) and global background rates, the sponsor calculated the incidence rates for developing any malignancy and specific malignancies by patient-years of LCIG treatment (incidence rate per 100,000) . The results obtained are crude incidence rates, an overall average rate of disease not accounting for possible confounding factors. Consequently, a direct comparison to the literature is not possible because the published incidence rates are always age-adjusted to a standard population and comparison to crude incidence rates could be misleading. Additionally, the published rates for developing any malignancy do not include non-melanoma skin cancers since non-melanoma skin cases are not typically reported to cancer registries. To make a more direct comparison with the assumption that the LCIG data are representative of the population, the sponsor calculated the 1 year age-adjusted rate per 100,000. The crude rates were age-adjusted to the 2000 US standard population utilizing the age-specific weights obtained from the Surveillance, Epidemiology, and End Results (SEER) Program. The rates for any malignancy were calculated including and excluding non-melanoma skin cancer.

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The background incidence cancer rates for comparison were obtained from the Surveillance Research Program of the National Cancer Institute (NCI), which manages the SEER Program in the US. The SEER program is an authoritative source of information on cancer incidence and survival in the US. SEER collects and publishes these statistics from population-based registries covering 28% of the US population. The global background incidence rates were obtained from the GLOBOCAN (2012) project of the International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization. The background incidence rates for specific and all malignancies reported in SEER and in GLOBOCAN are age-adjusted to the 2000 US standard population and the world standard population respectively.

There are 3 major components used to calculate age-adjusted rates: the number of cases reported in the population, and a "standard" population. A rate (new cases or deaths per 100,000 population in 1 year) is first computed for each age group (crude rate). Adjustment is accomplished by multiplying the age-specific rates of disease by age-specific weights. The weights used in the age-adjustment of cancer data are the proportion of the 2000 US population within each age group and are standard weights. The weighted rates are then summed across the age groups to give the age-adjusted rate. Additional details on calculation of age-adjusted rates are publicly available on the SEER website.

The crude and the age-adjusted rates of malignancies for the *LCIG program (Table 44) is* compared to the background rates of age-adjusted rates obtained from SEER and GLOBOCAN. The sponsor concluded that the rates of malignancy in the LCIG Phase 3 program (Table 45) were relatively comparable to that of these estimates and the literature. The sponsor further noted that despite the fact that the rates of some malignancies are slightly higher than in the LCIG program compared to global rates, it is important to note that 32% of subjects in the LCIG Phase 3 program came from the US where the rates of these malignancies are higher than the global rates. The crude and the age-adjusted rates of malignancies for the LCIG program (
Table 44) was compared to the background rates of age-adjusted rates obtained from SEER and GLOBOCAN. The sponsor concluded that the rates of malignancy in the LCIG Phase 3 program were relatively comparable to that of these estimates and the literature. The sponsor further noted that despite the fact that the rates of some malignancies are slightly higher than in the LCIG program compared to global rates, it is important to note that 32% of subjects in the LCIG Phase 3 program came from the US where the rates of these malignancies are higher than the global rates. The sponsor commented that the number of basal cell carcinomas and squamous cell carcinomas are difficult to estimate because these cases are not required to be reported to the cancer registries and that other common cancers seen in the general population did not occur in the LCIG program. Hydrazine, a breakdown product of carbidopa is known to cause lung, liver, and breast tumors in animals, and therefore has a theoretical risk of malignancies in humans. However, the overall risk of malignancy with LCIG was comparable to that of the background rates in the US and globally, and those cancers seen in animals studies related to hydrazine were not seen in higher frequencies in the LCIG program. Given the totality of the data, the sponsor concluded that there is no signal for an increased risk of malignancy with LCIG.

Reference ID: 3469235

Table 44 Malignancies During Selected Age Intervals by Sex and Dose Group (Open-Label LCIG Analysis Set)

Preferred Term	Sex	Dose Group	Birth to 39 years	40 to 49 years	50 to 59 years	60 to 69 years	70 years and older	Birth to Death
			n/N (%)					
Any malignancy	Male	Low	0/3	0/4	0/14	1/33 (3.0)	3/19 (15.79)	4/73 (5.48)
		High	0/1	1/17 (5.9)	0/38	10/67 (14.93)	5/47 (10.64)	16/170 (9.41)
		Any	0/4	1/21 (4.8)	0/52	11/100 (11.0)	8/66 (12.12)	20/243 (8.23)
	Female	Low	0/0	0/2	0/11	2/38 (5.26)	1/31 (3.23)	3/82 (3.66)
		High	0/0	0/3	1/24 (4.2)	3/34 (8.8)	1/26 (3.8)	5/87 (5.7)
		Any	0/0	0/5	1/35 (2.9)	5/72 (6.94)	2/57 (3.51)	8/169 (4.73)
Any malignancy excluding non-melanoma skin cancers[a]	Male	Low	0/3	0/4	0/14	0/33	1/19 (5.7)	1/73 (1.4)
		High	0/1	0/17	0/38	2/67 (3.0)	1/47 (2.1)	3/170 (1.8)
		Any	0/4	0/21	0/52	2/100 (2.0)	2/66 (3.0)	4/243 (1.6)
	Female	Low	0/0	0/2	0/11	1/38 (2.6)	1/31 (3.2)	2/82 (2.4)
		High	0/0	0/3	0/24	1/34 (2.9)	1/26 (3.8)	2/87 (2.3)
		Any	0/0	0/5	0/35	2/72 (2.8)	2/57 (3.5)	4/169 (2.4)
Any 2 malignancies	Male	Low	0/3	0/4	0/14	0/33	1/19 (5.3)	1/73 (1.4)
		High	0/1	0/17	0/38	1/67 (1.5)	2/47 (4.3)	3/170 (1.8)
		Any	0/4	0/21	0/52	1/100 (1.0)	3/66 (4.5)	4/243 (1.6)
	Female	Low	0/0	0/2	0/11	1/38 (2.6)	1/31 (3.2)	2/82 (2.4)
		High	0/0	0/3	0/24	0/34	0/26	0/87
		Any	0/0	0/5	0/35	1/72 (1.4)	1/57 (1.8)	2/169 (1.2)
Any 2 malignancies excluding non-melanoma skin cancers[a]	Male	Low	0/3	0/4	0/14	0/33	0/19	0/73
		High	0/1	0/17	0/38	1/67 (1.5)	0/47	1/170 (0.6)
		Any	0/4	0/21	0/52	1/100 (1.0)	0/66	1/243 (0.4)
	Female	Low	0/0	0/2	0/11	0/38	1/31 (3.2)	1/82 (1.2)
		High	0/0	0/3	0/24	0/34	0/26	0/87
		Any	0/0	0/5	0/35	0/72	1/57 (1.8)	1/169 (0.6)
Acute leukaemia	Male	Low	0/3	0/4	0/14	0/33	0/19	0/73
		High	0/1	0/17	0/38	0/67	0/47	0/170
		Any	0/4	0/21	0/52	0/100	0/66	0/243
	Female	Low	0/0	0/2	0/11	0/38	0/31	0/82
		High	0/0	0/3	0/24	0/34	1/26 (3.8)	1/87 (1.1)
		Any	0/0	0/5	0/35	0/72	1/57 (1.8)	1/169 (0.6)
Basal cell carcinoma	Male	Low	0/3	0/4	0/14	1/33 (3.0)	1/19 (5.3)	2/73 (2.7)
		High	0/1	1/17 (5.9)	0/38	7/67 (10.4)	3/47 (6.4)	11/170 (6.5)
		Any	0/4	1/21 (4.8)	0/52	8/100 (8.0)	4/66 (6.1)	13/243 (5.3)
	Female	Low	0/0	0/2	0/11	2/38 (5.3)	0/31	2/82 (2.4)
		High	0/0	0/3	1/24 (4.2)	0/34	0/26	1/87 (1.1)
		Any	0/0	0/5	1/35 (2.9)	2/72 (2.8)	0/57	3/169 (1.8)

Table 44 Malignancies During Selected Age Intervals by Sex and Dose Group (Open-Label LCIG Analysis Set) (Continued)

Preferred Term	Sex	Dose Group	Birth to 39 years	40 to 49 years	50 to 59 years	60 to 69 years	70 years and older	Birth to Death
			n/N (%)					
Colon cancer	Male	Low	0/3	0/4	0/14	0/33	0/19	0/73
		High	0/1	0/17	0/38	1/67 (1.5)	0/47	1/170 (0.6)
		Any	0/4	0/21	0/52	1/100 (1.0)	0/66	1/243 (0.4)
	Female	Low	0/0	0/2	0/11	0/38	1/31 (3.2)	1/82 (1.2)
		High	0/0	0/3	0/24	0/34	0/26	0/87
		Any	0/0	0/5	0/35	0/72	1/57 (1.8)	1/169 (0.6)
Keratoacanthoma	Male	Low	0/3	0/4	0/14	0/33	0/19	0/73
		High	0/1	0/17	0/38	0/67	1/47 (2.1)	1/170 (0.6)
		Any	0/4	0/21	0/52	0/100	1/66 (1.5)	1/243 (0.4)
	Female	Low	0/0	0/2	0/11	0/38	0/31	0/82
		High	0/0	0/3	0/24	0/34	0/26	0/87
		Any	0/0	0/5	0/35	0/72	0/57	0/169
Lentigo maligna stage unspecified	Male	Low	0/3	0/4	0/14	0/33	0/19	0/73
		High	0/1	0/17	0/38	1/67 (1.5)	0/47	1/170 (0.6)
		Any	0/4	0/21	0/52	1/100 (1.0)	0/66	1/243 (0.4)
	Female	Low	0/0	0/2	0/11	0/38	0/31	0/82
		High	0/0	0/3	0/24	0/34	0/26	0/87
		Any	0/0	0/5	0/35	0/72	0/57	0/169
Lung adenocarcinoma	Male	Low	0/3	0/4	0/14	0/33	0/19	0/73
		High	0/1	0/17	0/38	0/67	0/47	0/170
		Any	0/4	0/21	0/52	0/100	0/66	0/243
	Female	Low	0/0	0/2	0/11	0/38	1/31 (3.2)	1/82 (1.2)
		High	0/0	0/3	0/24	0/34	0/26	0/87
		Any	0/0	0/5	0/35	0/72	1/57 (1.8)	1/169 (0.6)
Malignant melanoma	Male	Low	0/3	0/4	0/14	0/33	0/19	0/73
		High	0/1	0/17	0/38	0/67	0/47	0/170
		Any	0/4	0/21	0/52	0/100	0/66	0/243
	Female	Low	0/0	0/2	0/11	0/38	0/31	0/82
		High	0/0	0/3	0/24	1/34 (2.9)	0/26	1/87 (1.1)
		Any	0/0	0/5	0/35	1/72 (1.4)	0/57	1/169 (0.6)
Peripheral T-cell lymphoma unspecified	Male	Low	0/3	0/4	0/14	0/33	0/19	0/73
		High	0/1	0/17	0/38	1/67 (1.5)	0/47	1/170 (0.6)
		Any	0/4	0/21	0/52	1/100 (1.0)	0/66	1/243 (0.4)
	Female	Low	0/0	0/2	0/11	0/38	0/31	0/82
		High	0/0	0/3	0/24	0/34	0/26	0/87
		Any	0/0	0/5	0/35	0/72	0/57	0/169

Table 44 Malignancies During Selected Age Intervals by Sex and Dose Group (Open-Label LCIG Analysis Set) (Continued)

Preferred Term	Sex	Dose Group	Birth to 39 years	40 to 49 years	50 to 59 years	60 to 69 years	70 years and older	Birth to Death
			n/N (%)					
Prostate cancer	Male	Low	0/3	0/4	0/14	0/33	1/19 (5.3)	1/73 (1.4)
		High	0/1	0/17	0/38	0/67	1/47 (2.1)	1/170 (0.6)
		Any	0/4	0/21	0/52	0/100	2/66 (3.0)	2/243 (0.8)
	Female	Low	0/0	0/2	0/11	0/38	0/31	0/82
		High	0/0	0/3	0/24	0/34	0/26	0/87
		Any	0/0	0/5	0/35	0/72	0/57	0/169
Rectal cancer	Male	Low	0/3	0/4	0/14	0/33	0/19	0/73
		High	0/1	0/17	0/38	1/67 (1.5)	0/47	1/170 (0.6)
		Any	0/4	0/21	0/52	1/100 (1.0)	0/66	1/243 (0.4)
	Female	Low	0/0	0/2	0/11	0/38	0/31	0/82
		High	0/0	0/3	0/24	0/34	0/26	0/87
		Any	0/0	0/5	0/35	0/72	0/57	0/169
Renal cell carcinoma	Male	Low	0/3	0/4	0/14	0/33	0/19	0/73
		High	0/1	0/17	0/38	0/67	0/47	0/170
		Any	0/4	0/21	0/52	0/100	0/66	0/243
	Female	Low	0/0	0/2	0/11	1/38 (2.6)	0/31	1/82 (1.2)
		High	0/0	0/3	0/24	0/34	0/26	0/87
		Any	0/0	0/5	0/35	1/72 (1.4)	0/57	1/169 (0.6)
Squamous cell carcinoma/ Squamous cell carcinoma of skin	Male	Low	0/3	0/4	0/14	0/33	2/19 (10.5)	2/73 (2.7)
		High	0/1	0/17	0/38	0/67	2/47 (4.3)	2/170 (1.2)
		Any	0/4	0/21	0/52	0/100	4/66 (6.1)	4/243 (1.6)
	Female	Low	0/0	0/2	0/11	0/38	0/31	0/82
		High	0/0	0/3	0/24	2/34 (5.9)	0/26	2/87 (2.3)
		Any	0/0	0/5	0/35	2/72 (2.8)	0/57	2/169 (1.2)

LCIG = levodopa-carbidopa intestinal gel;

a Non-melanoma skin cancers excluded were basal cell and squamous cell carcinoma/squamous cell carcinoma of skin, keratoacanthoma, and lentigo maligna stage unspecified.

Notes: Low dose: mean total daily levodopa dose < 1250 mg during the treatment period.

High dose: mean total daily levodopa dose ≥ 1250 mg during the treatment period.

Cross reference: SU Table 1__2.18.7

Table 45 Age-Adjusted Malignancies Incidence Rates (Open-Label LCIG Analysis Set) Per 100,000 Persons (All Ages and Genders)

Preferred Term	Both Sexes
Any malignancy	1083.61
Any malignancy excluding non-melanoma skin cancers[a]	262.54
Any 2 malignancies	220.09
Any 2 malignancies excluding non-melanoma skin cancers[a]	131.27
Acute leukaemia	44.41
Basal cell carcinoma	689.80
Colon cancer	65.63
Keratoacanthoma	44.41
Lentigo maligna stage unspecified	21.23
Lung adenocarcinoma	44.41
Malignant melanoma	21.23
Peripheral T-cell lymphoma unspecified	21.23
Prostate cancer	146.90
Rectal cancer	21.23
Renal cell carcinoma	21.23
Squamous cell carcinoma/Squamous cell carcinoma of skin	220.09

a. Non-melanoma skin cancers excluded were basal cell and squamous cell carcinoma/squamous cell carcinoma of skin, keratoacanthoma, and lentigo maligna stage unspecified.
Cross reference: SU Table 1__2.12.8

Sleep Attacks

In the Phase 3 studies, results from the Sleep Attack Questionnaire were summarized for the Open-Label LCIG Analysis Set.

Active-Controlled Analysis Set

In the Active-Controlled Analysis Set, sleep attack was reported as a TEAE in 1 subject (Subject 115-101, high dose) in the LC-oral group and no subjects in the LCIG group. The sleep attack AE for Subject 115-101 occurred during the Maintenance Period (Day 35), was mild in severity, was not serious, and did not lead to discontinuation from the study. On the Sleep Attack Questionnaire, no subject in the LCIG group reported sleep attacks at Baseline or during LCIG treatment. In the LC-oral group, 1 subject (Subject 449-102) reported sleep attacks on the questionnaire at Baseline although sleep attacks were not noted as part of the medical history and 1 subject (Subject 115-101) reported 1 sleep attack at Week 5. The sleep attack at Week 5 was preceded by drowsiness, with no consequences, and was reported as a TEAE that resolved the same day. No other sleep attacks were reported in the Active-Controlled Analysis Set. Only 1 subject in the Active-Controlled Analysis Set (Subject 104-108 in LC-oral group) had reported sleep attacks in the medical history, and

this subject had no sleep attacks during treatment.

Open-Label LCIG Analysis Set
In the Open-Label LCIG Analysis Set, 34 subjects (8/155 [5.2%] low dose, 26/257 [10.1%] high dose) had TEAEs of sleep attack .The AEs of sleep attack were mild in severity for the majority of subjects (27 mild, 5 moderate, 2 severe) and considered at least possibly related to study treatment for 20 of the 34 subjects. No AEs of sleep attack required medication.

One subject (Subject 201-0055, high dose) had an SAE of sleep attack that occurred on Day 596, was considered unlikely related to study treatment, and subsequently resolved. No AEs of sleep attack resulted in discontinuation from the study. On the Sleep Attack Questionnaire, 9 of the 412 subjects (2.2%) reported at Baseline that they had at least 1 sleep attack during the previous 3 months. During open-label LCIG treatment, with an overall mean exposure of 512.2 days, 42 subjects (10.2%) reported sleep attacks: 12 (7.7%) in the low dose group and 30 (11.7%) in the high dose group.

Reviewer Comments

It was not unexpected that some patient developed sleep attacks during LCIG treatment because sleep attacks are considered a class adverse reaction for drugs that increase central dopaminergic tone, as LCIG does. A risk for sleep attack and class labeling language will need to be described in the label as is done for other drugs treating Parkinson's disease.

MIDI Assessment of Intense Impulsive/Compulsive Behavior

The MIDI was used as a validated assessment of intensive impulsive behavior in the Active-Controlled, In this Analysis Set at Baseline, 2 subjects (1/37 in the LCIG group and 1/34 in the LC-oral group) reported compulsive behavior on the MIDI). Two different subjects, both in the LC-oral group, reported compulsive sexual behavior during the treatment period. No compulsive behavior was reported in the LCIG group during treatment. There were no TEAEs reported for these subjects related to the compulsive behavior.

In the Open-Label LCIG Analysis Set (N = 412; 155 low dose LCIG, 257 high dose LCIG), during the 3 months prior to Baseline, 2 subjects (1 [0.6%] low dose, 1 [0.4%] high dose, 0.5% overall) had compulsive buying, 2 subjects (1 [0.6%] low dose, 1 [0.4%] high dose, 0.5% overall) had pathological gambling, and 12 subjects (5 [3.2%] low dose, 7 [2.7%] high dose; 2.9% overall) had compulsive sexual behavior. During open-label LCIG treatment, with an overall mean exposure of 512.2 days in the Open-Label LCIG Analysis Set, 17 subjects had compulsive behavior reported on the MIDI: 6 subjects (1.5%) had pathological gambling (2 [1.3%] low dose, 4 [1.6%] in the high dose), 3 subjects (0.7%) had compulsive buying (0 low dose, 3 [1.2%] high dose), and 12 subjects (2.9%) had compulsive sexual behavior (2 [1.3%] low dose, 10 [3.9%] high dose) in their MIDI assessment. Two subject (Subject 201-010 and Subject 349-001) had both pathological gambling and compulsive sexual behavior, and 1 subject (Subject 112-003) had pathological gambling, compulsive buying, and compulsive sexual

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behavior, as summarized in Table 46. Seven of the 17 subjects had compulsive-related TEAEs, and 3 subjects (Subjects 104-001, 112-003, and 442-001) had a medical history of compulsion.

Table 46 TEAEs Related to Impulse Control Disorder for Subjects with Positive MIDI Results Postbaseline (Open-Label LCIG Analysis Set)

Intense Impulsive Behavior	Subject, Sex/Age	LCIG Dose	Impulse Control Disorder History	MIDI Result		TEAE Related to Impulse Control Disorder
				Positive Baseline	Positive Postbaseline	
Pathological Gambling	101-007, M/65	High	None	No	Day 35	None
	112-003, M/58	High	Yes	No	Days 254, 331, 415, 583	Impulsive behaviour (Days 168–255, 256+), Agitation (Days 168–258), Restlessness (Day 381–381)
	201-010, M/56	High	None	No	Days 134, 225	Impulsive behavior (85+), Dopamine dysregulation syndrome (Days 146–386, 617–896)
	201-014, M/67	High	None	No	Day 134	Impulse-control disorder (Days 85+)
	349-001, M/63	Low	None	Yes	Days 44, 142	Pathological gambling (Days 70+)
	421-006, M/69	Low	None	No	Days 130, 291	Pathological gambling (Days 217–307)
Compulsive Buying	112-003, M/58	High	Yes	No	Day 415	Impulsive behaviour (Days 168–255, 256+), Agitation (Days 168–258), Restlessness (Day 381–381)
	129-002, M/65	High	None	No	Days 136, 219	None
	310-001, F/58	High	None	No	Day 303	Compulsive shopping (Days 170 – 857)
Compulsive Sexual Behavior	104-001, M/46	High	Yes	Yes	Days 38, 1130	None
	106-001, M/60	High	None	No	Days 31, 49	None
	112-003, M/58	High	Yes	No	Days 415	Impulsive behaviour (Days 168–255, 256+), Agitation (Days 168–258), Restlessness (Day 381–381)
	128-004, M/61	High	None	No	Days 132, 300, 595	Impulsive Behavior (124+)
	201-010, M/56	High	None	Yes	Days 36, 134, 225, 302, 386	Impulsive Behavior (85+), Dopamine dysregulation syndrome (Days 146–386, 617–896)
	213-101, F/62	Low	None	No	Day 180[b]	None
	312-003, F/64	High	None	No	Day 42	None
	349-001, M/63	Low	None	Yes	Day 44	Pathological gambling (Days 70+)
	421-005, M/66	High	None	Yes	Day 33	None
	436-103, M/54	High	None	No	Days 89[a], 252[a], 362[a]	None
	440-001, M/60	High	None	No	Day 37	None
	442-001, M/77	High	Yes	No	Days 37, 133, 212, 302, 381	None

Of the 12 subjects with a positive postbaseline MIDI result but no history of compulsive disorders and no positive MIDI result at Baseline, 2 were in the low dose group and 10 were in the high dose group. This is consistent with an increased risk of impulsive control disorders with higher doses of oral levodopa reported by Weintraub et al.

The possibility that patients may experience intense urges to gamble, increased sexual urges, other intense urges, and the inability to control these urges is listed as a precaution in the oral carbidopa-levodopa label. These disorders may lead to significant impairments in psychosocial functioning, interpersonal relationships, physical health and quality of life. In a study of over 3,000 PD patients, Weintraub et al (2010) determined that dopamine agonist treatment in PD is associated with 2- to 3.5-fold increased odds of having an impulse control disorder. Weintraub et al also noted some association between levodopa dose and impulse control disorder in patients taking levodopa but not a dopamine agonist: on univariate analysis of the 991 patients not on a dopamine agonist, the median levodopa equivalent dosage was higher in patients with an impulse control disorder than in patients without an impulse control disorder (621 mg versus 461 mg, respectively).

Reviewer Comments

Based upon the MIDI, the frequency of reporting compulsive behavior was not increased in LCIG patients (3 %) compared to oral LD/CD patients 3 %) in the controlled trial but was similar. In addition, 2 other patients in the oral LD/CD group reported compulsive sexual behavior. Thus, LCIG did not appear to cause an increased risk for impulsive/compulsive behavior. Furthermore, the identification of several patients with impulsive/compulsive behavior in the open-label, long-term treatment experience was not surprising. Several patients with a positive MIDI results for impulsive behavior also had a TEAE of impulsive/compulsive behavior. This class adverse reaction for dopaminergic drugs will also need to be described in the LCIG label.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following tables show the frequency of TEAEs in the controlled and open-label trials at various frequency (i.e., incidence) thresholds. Results are also presented according to time perspectives and dose perspectives.

Controlled Trial Common Adverse Events

Yellow highlights of the number of patients and incidence for LCIG in the various tables indicate when the incidence of LCIG is at least 5 % greater than the respective incidence for oral LD/CD in the controlled trial. Tables.

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Table 47 TEAEs Reported by ≥ 5% of Subjects in Any Treatment Group At Any Time AND Where Incidence in Patients on Any Dose of LCIG is Greater than Incidence in Patients on Any Dose of LC-Oral in Any Time Period Presented by Time Perspectives (Active-Controlled Analysis Set)

	Number (%) of Subjects							
	Titration Period		Maintenance Period		Persistent AEs		Any Time	
Preferred Term	LCIG N = 37	LC-oral N = 34	LCIG N = 35	LC-oral N = 31	LCIG N = 37	LC-oral N = 34	LCIG N = 37	LC-oral N = 34
Any preferred term	32 (86.5)	31 (91.2)	25 (71.4)	26 (83.9)	17 (45.9)	21 (61.8)	35 (94.6)	34 (100)
Complication of device insertion	21 (56.8)	15 (44.1)	0	0	2 (5.4)	1 (2.9)	21 (56.8)	15 (44.1)
Abdominal pain	19 (51.4)	11 (32.4)	0	0	1 (2.7)	1 (2.9)	19 (51.4)	11 (32.4)
Nausea	9 (24.3)	4 (11.8)	3 (8.6)	4 (12.9)	0	1 (2.9)	11 (29.7)	7 (20.6)
Constipation	8 (21.6)	7 (20.6)	0	1 (3.2)	4 (10.8)	3 (8.8)	8 (21.6)	7 (20.6)
Incision site erythema	3 (8.1)	3 (8.8)	4 (11.4)	1 (3.2)	1 (2.7)	1 (2.9)	7 (18.9)	4 (11.8)
Flatulence	6 (16.2)	4 (11.8)	0	0	1 (2.7)	0	6 (16.2)	4 (11.8)
Dyskinesia	2 (5.4)	3 (8.8)	3 (8.6)	2 (6.5)	2 (5.4)	2 (5.9)	5 (13.5)	4 (11.8)
Pneumoperitoneum	4 (10.8)	1 (2.9)	0	0	1 (2.7)	1 (2.9)	4 (10.8)	1 (2.9)
Post procedural discharge	3 (8.1)	2 (5.9)	1 (2.9)	1 (3.2)	1 (2.7)	0	4 (10.8)	3 (8.8)
Depression	1 (2.7)	0	3 (8.6)	1 (3.2)	0	0	4 (10.8)	1 (2.9)
Hiatus hernia	3 (8.1)	2 (5.9)	0	0	3 (8.1)	2 (5.9)	3 (8.1)	2 (5.9)
Oedema peripheral	1 (2.7)	0	2 (5.7)	0	0	0	3 (8.1)	0
Upper respiratory tract infection	0	0	3 (8.6)	0	0	0	3 (8.1)	0
Dizziness	3 (8.1)	1 (2.9)	0	1 (3.2)	0	0	3 (8.1)	2 (5.9)
Anxiety	2 (5.4)	0	1 (2.9)	1 (3.2)	1 (2.7)	0	3 (8.1)	1 (2.9)
Confusional state	3 (8.1)	1 (2.9)	0	1 (3.2)	1 (2.7)	0	3 (8.1)	1 (2.9)
Atelectasis	3 (8.1)	0	0	0	1 (2.7)	0	3 (8.1)	0
Oropharyngeal pain	3 (8.1)	0	0	0	1 (2.7)	0	3 (8.1)	0
Hypertension	1 (2.7)	0	2 (5.7)	0	1 (2.7)	0	3 (8.1)	0
Abdominal distension	2 (5.4)	1 (2.9)	0	0	0	0	2 (5.4)	1 (2.9)
Diarrhoea	2 (5.4)	1 (2.9)	0	0	0	0	2 (5.4)	1 (2.9)
Dyspepsia	2 (5.4)	0	0	1 (3.2)	1 (2.7)	0	2 (5.4)	1 (2.9)
Pyrexia	2 (5.4)	0	0	0	0	0	2 (5.4)	0
Postoperative ileus	2 (5.4)	0	0	0	0	0	2 (5.4)	0
Bacterial test positive	0	0	2 (5.7)	0	0	0	2 (5.4)	0
White blood cells urine positive	0	0	2 (5.7)	0	0	0	2 (5.4)	0
Hallucination	1 (2.7)	1 (2.9)	1 (2.9)	0	1 (2.7)	0	2 (5.4)	1 (2.9)
Psychotic disorder	1 (2.7)	1 (2.9)	1 (2.9)	0	1 (2.7)	1 (2.9)	2 (5.4)	1 (2.9)
Sleep disorder	1 (2.7)	0	1 (2.9)	0	1 (2.7)	0	2 (5.4)	0
Excessive granulation tissue	0	0	2 (5.7)	0	0	0	2 (5.4)	0
Rash	1 (2.7)	0	1 (2.9)	0	1 (2.7)	0	2 (5.4)	0

Table 48 TEAEs Reported by ≥ 5% of Subjects on Any Dose in Any Time Period AND Where Subjects on Any Dose of LCIG > Subjects on Any Dose of LC-Oral in Any Time Period Presented by Dose Group (Active-Controlled Analysis Set)

	Number (%) of Subjects					
	LCIG			LC-Oral		
Preferred Term	**Low Dose N = 27**	**High Dose N = 10**	**Any Dose N = 37**	**Low Dose N = 15**	**High Dose N = 19**	**Any Dose N = 34**
Any preferred term	26 (96.3)	9 (90.0)	35 (94.6)	15 (100)	19 (100)	34 (100)
Complication of device insertion	14 (51.9)	7 (70.0)	21 (56.8)	7 (46.7)	8 (42.1)	15 (44.1)
Abdominal pain	13 (48.1)	6 (60.0)	19 (51.4)	5 (33.3)	6 (31.6)	11 (32.4)
Nausea	8 (29.6)	3 (30.0)	11 (29.7)	1 (6.7)	6 (31.6)	7 (20.6)
Constipation	6 (22.2)	2 (20.0)	8 (21.6)	3 (20.0)	4 (21.1)	7 (20.6)
Incision site erythema	6 (22.2)	1 (10.0)	7 (18.9)	2 (13.3)	2 (10.5)	4 (11.8)
Flatulence	5 (18.5)	1 (10.0)	6 (16.2)	1 (6.7)	3 (15.8)	4 (11.8)
Dyskinesia	4 (14.8)	1 (10.0)	5 (13.5)	2 (13.3)	2 (10.5)	4 (11.8)
Pneumoperitoneum	3 (11.1)	1 (10.0)	4 (10.8)	1 (6.7)	0	1 (2.9)
Post procedural discharge	4 (14.8)	0	4 (10.8)	1 (6.7)	2 (10.5)	3 (8.8)
Depression	4 (14.8)	0	4 (10.8)	0	1 (5.3)	1 (2.9)
Hiatus hernia	2 (7.4)	1 (10.0)	3 (8.1)	2 (13.3)	0	2 (5.9)
Oedema peripheral	2 (7.4)	1 (10.0)	3 (8.1)	0	0	0
Upper respiratory tract infection	2 (7.4)	1 (10.0)	3 (8.1)	0	0	0
Dizziness	2 (7.4)	1 (10.0)	3 (8.1)	0	2 (10.5)	2 (5.9)
Anxiety	2 (7.4)	1 (10.0)	3 (8.1)	1 (6.7)	0	1 (2.9)
Confusional state	3 (11.1)	0	3 (8.1)	0	1 (5.3)	1 (2.9)
Atelectasis	1 (3.7)	2 (20.0)	3 (8.1)	0	0	0
Oropharyngeal pain	2 (7.4)	1 (10.0)	3 (8.1)	0	0	0
Hypertension	3 (11.1)	0	3 (8.1)	0	0	0
Abdominal distension	2 (7.4)	0	2 (5.4)	0	1 (5.3)	1 (2.9)
Diarrhoea	2 (7.4)	0	2 (5.4)	1 (6.7)	0	1 (2.9)
Dyspepsia	2 (7.4)	0	2 (5.4)	1 (6.7)	0	1 (2.9)
Pyrexia	2 (7.4)	0	2 (5.4)	0	0	0
Postoperative ileus	2 (7.4)	0	2 (5.4)	0	0	0
Bacterial test positive	1 (3.7)	1 (10.0)	2 (5.4)	0	0	0
White blood cells urine positive	1 (3.7)	1 (10.0)	2 (5.4)	0	0	0
Hallucination	2 (7.4)	0	2 (5.4)	1 (6.7)	0	1 (2.9)
Psychotic disorder	2 (7.4)	0	2 (5.4)	0	1 (5.3)	1 (2.9)
Sleep disorder	2 (7.4)	0	2 (5.4)	0	0	0
Excessive granulation tissue	1 (3.7)	1 (10.0)	2 (5.4)	0	0	0
Rash	2 (7.4)	0	2 (5.4)	0	0	0

Table 49 TEAEs Reported by ≥ 5% of Subjects on Any Dose in Any Treatment Group During the Titration Period AND Where Subjects on Any Dose of LCIG > Subjects on Any Dose of LC-Oral During the Titration Period Presented by Dose Group (Active-Controlled Analysis Set)

	Number (%) of Subjects					
	LCIG			LC-Oral		
Preferred Term	**Low Dose N = 27**	**High Dose N = 10**	**Any Dose N = 37**	**Low Dose N = 15**	**High Dose N = 19**	**Any Dose N = 34**
Any preferred term	24 (88.9)	8 (80.0)	32 (86.5)	14 (93.3)	17 (89.5)	31 (91.2)
Complication of device insertion	14 (51.9)	7 (70.0)	21 (56.8)	7 (46.7)	8 (42.1)	15 (44.1)
Abdominal pain	13 (48.1)	6 (60.0)	19 (51.4)	5 (33.3)	6 (31.6)	11 (32.4)
Nausea	7 (25.9)	2 (20.0)	9 (24.3)	0	4 (21.1)	4 (11.8)
Constipation	6 (22.2)	2 (20.0)	8 (21.6)	3 (20.0)	4 (21.1)	7 (20.6)
Flatulence	5 (18.5)	1 (10.0)	6 (16.2)	1 (6.7)	3 (15.8)	4 (11.8)
Pneumoperitoneum	3 (3.11)	1 (10.0)	4 (10.8)	1 (6.7)	0	1 (2.9)
Insomnia	2 (7.4)	2 (20.0)	4 (10.8)	3 (20.0)	0	3 (8.8)
Hiatus hernia	2 (7.4)	1 (10.0)	3 (8.1)	2 (13.3)	0	2 (5.9)
Post procedural discharge	3 (11.1)	0	3 (8.1)	1 (6.7)	1 (5.3)	2 (5.9)
Dizziness	2 (7.4)	1 (10.0)	3 (8.1)	0	1 (5.3)	1 (2.9)
Confusional state	3 (11.1)	0	3 (8.1)	0	1 (5.3)	1 (2.9)
Atelectasis	1 (3.7)	2 (20.0)	3 (8.1)	0	0	0
Oropharyngeal pain	2 (7.4)	1 (10.0)	3 (8.1)	0	0	0
Abdominal distension	2 (7.4)	0	2 (5.4)	0	1 (5.3)	1 (2.9)
Diarrhoea	2 (7.4)	0	2 (5.4)	1 (6.7)	0	1 (2.9)
Dyspepsia	2 (7.4)	0	2 (5.4)	0	0	0
Vomiting	2 (7.4)	0	2 (5.4)	0	1 (5.3)	1 (2.9)
Pyrexia	2 (7.4)	0	2 (5.4)	0	0	0
Postoperative ileus	2 (7.4)	0	2 (5.4)	0	0	0
Anxiety	1 (3.7)	1 (10.0)	2 (5.4)	0	0	0

Table 50 TEAEs Reported by ≥ 5% of Subjects on Any Dose in Any Treatment Group During the Maintenance Period AND Where Subjects on Any Dose of LCIG > Subjects on Any Dose of LC-Oral During the Maintenance Period Presented by Dose Group (Active-Controlled Analysis Set)

	Number (%) of Subjects					
	LCIG			LC-Oral		
Preferred Term	**Low Dose N = 25**	**High Dose N = 10**	**Any Dose N = 35**	**Low Dose N = 12**	**High Dose N = 19**	**Any Dose N = 31**
Any preferred term	19 (76.0)	6 (60.0)	25 (71.4)	10 (83.3)	16 (84.2)	26 (83.9)
Fall	2 (8.0)	2 (20.0)	4 (11.4)	2 (16.7)	1 (5.3)	3 (9.7)
Incision site erythema	3 (12.0)	1 (10.0)	4 (11.4)	0	1 (5.3)	1 (3.2)
Upper respiratory tract infection	2 (8.0)	1 (10.0)	3 (8.6)	0	0	0
Dyskinesia	3 (12.0)	0	3 (8.6)	1 (8.3)	1 (5.3)	2 (6.5)
Depression	3 (12.0)	0	3 (8.6)	0	1 (5.3)	1 (3.2)
Oedema peripheral	1 (4.0)	1 (10.0)	2 (5.7)	0	0	0
Procedural pain	1 (4.0)	1 (10.0)	2 (5.7)	0	1 (5.3)	1 (3.2)
Bacterial test positive	1 (4.0)	1 (10.0)	2 (5.7)	0	0	0
White blood cells urine positive	1 (4.0)	1 (10.0)	2 (5.7)	0	0	0
Headache	2 (8.0)	0	2 (5.7)	0	1 (5.3)	1 (3.2)
Excessive granulation tissue	1 (4.0)	1 (10.0)	2 (5.7)	0	0	0
Hypertension	2 (8.0)	0	2 (5.7)	0	0	0

Table 51 Persistent TEAEs Reported by ≥ 5% of Subjects on Any Dose in Any Treatment Group From the Titration Period to the Maintenance Period AND Where Subjects on Any Dose of LCIG > Subjects on Any Dose of LC-Oral From the Titration Period to the Maintenance Period Presented by Dose Group (Active-Controlled Analysis Set)

	Number (%) of Subjects					
	LCIG			LC-Oral		
Preferred Term	**Low Dose N = 27**	**High Dose N = 10**	**Any Dose N = 37**	**Low Dose N = 15**	**High Dose N = 19**	**Any Dose N = 34**
Any preferred term	11 (40.7)	6 (60.0)	17 (45.9)	9 (60.0)	12 (63.2)	21 (61.8)
Constipation	2 (7.4)	2 (20.0)	4 (10.8)	1 (6.7)	2 (10.5)	3 (8.8)
Hiatus hernia	2 (7.4)	1 (10.0)	3 (8.1)	2 (13.3)	0	2 (5.9)
Insomnia	1 (3.7)	2 (20.0)	3 (8.1)	0	0	0
Complication of device insertion	2 (7.4)	0	2 (5.4)	1 (6.7)	0	1 (2.9)

Reviewer Comments

- *Table 47 of "common" TEAEs indicated that there were several TEAEs that were relatively common and notably more frequent with LCIG treatment than with oral LD/CD treatment in the controlled trial. There were many TEAEs occurring* ***at any time*** *in the controlled trial in the LCIG group* ***with an incidence of at least 7 % greater than oral LD/CD****. These TEAEs presented in descending order of the treatment difference (LCIG % - oral LD/CD %) included abdominal pain, complication of device insertion, nausea, pneumoperitoneum, depression, hypertension, peripheral edema, upper respiratory tract infection, atelectasis, oropharyngeal pain, and incisional site erythema. Many of these TEAEs (i.e., abdominal pain, complication of device insertion, nausea, pneumoperitoneum, \ atelectasis, and oropharyngeal pain) notably more frequent with LCIG treatment were similarly common in the titration period. The only TEAEs occurring in the maintenance period and have an LCIG treatment difference incidence of at least 7 % were incision site erythema and upper respiratory tract infection. Although there was some "persistent" TEAEs (i.e., onset in titration period and perisisting into the maintenance period and having a duration of at least 7 days), that were more frequent with LCIG treatment than with oral LD/CD., none of these persistent TEAEs occurred with a notably increased frequency for LCIG compared to oral LD/CD.*

- *Table 48 presented the incidence of TEAEs occurring with a frequency of at least 5 %* ***at any time*** *in the "any dose" group in the controlled trial and also according to low and high dose groups for each treatment. Only three TEAEs (complication of device insertion, abdominal pain, and atelectasis) appeared to stand out as occurring notably more frequently in the high dose group compared to the low dose group. Of interest, complication of device insertion and abdominal pain occurred in the any dose LCIG group with the greater treatment difference in the any time analysis and also in the titration period analysis.*

- *Table 49 showed that TEAEs developing notably more frequently with LCIG than oral LD/CD in the titration period and also occurring notably more frequently in the high dose group were complication of device insertion, abdominal pain, pneumoperitoneum, and atelectasis.*

- *In contrast to dosed-dependent analyses for any time and for the titration period, Table 50 did not suggest a dose-dependent risk for TEAEs for LCIG treatment for TEAEs developing in the maintenance period. Neither did Table 51 suggest a dose-dependent effect for TEAEs considered "persistent" with LCIG treatment.*

Open-Label Trial Common Adverse Events

The following tables present common adverse events during open-label treatment based upon the 4 Month Safety Update (4MSU).

Table 52 TEAEs Reported by ≥ 5% of Subjects Any Time Presented by Treatment Period (Open-Label LCIG Analysis Set)

	Number (%) of Subjects							
	Titration Period		Maintenance Period[a]		Persistent AEs		Any Time	
Preferred Term	ISS N = 412	Safety Update N = 412	ISS N = 378	Safety Update N = 378	ISS N = 412	Safety Update N = 412	ISS N = 412	Safety Update N = 412
Any adverse event	305 (74.0)	304 (73.8)[b]	327 (86.5)	338 (89.4)	201 (48.8)	200 (48.5)	379 (92.0)	383 (93.0)
Complication of device insertion	113 (27.4)	113 (27.4)	38 (10.1)	44 (11.6)	15 (3.6)	15 (3.6)	132 (32.0)	137 (33.3)
Abdominal pain	85 (20.6)	85 (20.6)	40 (10.6)	47 (12.4)	5 (1.2)	5 (1.2)	108 (26.2)	113 (27.4)
Insomnia	44 (10.7)	44 (10.7)	43 (11.4)	57 (15.1)	26 (6.3)	26 (6.3)	80 (19.4)	94 (22.8)
Postoperative wound infection	26 (6.3)	24 (5.8)	60 (15.9)	77 (20.4)	16 (3.9)	14 (3.4)	75 (18.2)	90 (21.8)
Procedural pain	59 (14.3)	59 (14.3)	24 (6.3)	33 (8.7)	2 (0.5)	2 (0.5)	77 (18.7)	84 (20.4)
Fall	20 (4.9)	20 (4.9)	63 (16.7)	76 (20.1)	2 (0.5)	2 (0.5)	74 (18.0)	86 (20.9)
Nausea	35 (8.5)	35 (8.5)	51 (13.5)	58 (15.3)	5 (1.2)	5 (1.2)	77 (18.7)	83 (20.1)
Excessive granulation tissue	3 (0.7)	3 (0.7)	70 (18.5)	80 (21.2)	3 (0.7)	3 (0.7)	71 (17.2)	81 (19.7)
Incision site erythema	27 (6.6)	27 (6.6)	42 (11.1)	57 (15.1)	19 (4.6)	19 (4.6)	65 (15.8)	77 (18.7)
Constipation	37 (9.0)	37 (9.0)	43 (11.4)	51 (13.5)	13 (3.2)	13 (3.2)	69 (16.7)	76 (18.4)
Urinary tract infection	6 (1.5)	6 (1.5)	52 (13.8)	62 (16.4)	3 (0.7)	3 (0.7)	55 (13.3)	65 (15.8)
Anxiety	22 (5.3)	22 (5.3)	31 (8.2)	41 (10.8)	8 (1.9)	8 (1.9)	49 (11.9)	59 (14.3)
Parkinson's disease	13 (3.2)	13 (3.2)	38 (10.1)	47 (12.4)	5 (1.2)	5 (1.2)	47 (11.4)	55 (13.3)
Procedural site reaction	17 (4.1)	17 (4.1)	33 (8.7)	47 (12.4)	9 (2.2)	9 (2.2)	42 (10.2)	55 (13.3)
Weight decreased	11 (2.7)	11 (2.7)	38 (10.1)	46 (12.2)	11 (2.7)	11 (2.7)	47 (11.4)	53 (12.9)
Depression	12 (2.9)	12 (2.9)	32 (8.5)	41 (10.8)	10 (2.4)	10 (2.4)	44 (10.7)	51 (12.4)
Dyskinesia	15 (3.6)	15 (3.6)	32 (8.5)	41 (10.8)	10 (2.4)	10 (2.4)	42 (10.2)	51 (12.4)
Vitamin B_6 decreased	2 (0.5)	2 (0.5)	35 (9.3)	48 (12.7)	2 (0.5)	2 (0.5)	37 (9.0)	50 (12.1)
Blood homocysteine increased	2 (0.5)	2 (0.5)	31 (8.2)	43 (11.4)	2 (0.5)	2 (0.5)	33 (8.0)	45 (10.9)
Orthostatic hypotension	13 (3.2)	13 (3.2)	25 (6.6)	30 (7.9)	5 (1.2)	5 (1.2)	37 (9.0)	42 (10.2)
Back pain	3 (0.7)	3 (0.7)	36 (9.5)	39 (10.3)	0	0	38 (9.2)	41 (10.0)
Postprocedural discharge	10 (2.4)	9 (2.2)	29 (7.7)	33 (8.7)	6 (1.5)	5 (1.2)	38 (9.2)	41 (10.0)
Vomiting	19 (4.6)[c]	19 (4.6)	24 (6.3)	26 (6.9)	2 (0.5)	2 (0.5)	38 (9.2)	40 (9.7)
Headache	20 (4.9)	20 (4.9)	21 (5.6)	24 (6.3)	4 (1.0)	4 (1.0)	38 (9.2)	39 (9.5)
Diarrhoea	8 (1.9)	8 (1.9)	31 (8.2)	32 (8.5)	2 (0.5)	2 (0.5)	36 (8.7)	37 (9.0)
Sleep attacks	9 (2.2)	9 (2.2)	26 (6.9)	27 (7.1)	4 (1.0)	4 (1.0)	34 (8.3)	35 (8.5)
Dyspepsia	10 (2.4)	10 (2.4)	19 (5.0)	22 (5.8)	3 (0.7)	3 (0.7)	29 (7.0)	32 (7.8)
Arthralgia	6 (1.5)	6 (1.5)	18 (4.8)	26 (6.9)	3 (0.7)	3 (0.7)	24 (5.8)	32 (7.8)
Hallucination	5 (1.2)	5 (1.2)	22 (5.8)	25 (6.6)	2 (0.5)	2 (0.5)	25 (6.1)	28 (6.8)
Oropharyngeal pain	25 (6.1)[d]	25 (6.1)[d]	4 (1.1)	5 (1.3)	1 (0.2)	1 (0.2)	26 (6.3)	27 (6.6)
Pain in extremity	8 (1.9)	8 (1.9)	16 (4.2)	18 (4.8)	4 (1.0)	4 (1.0)	24 (5.8)	26 (6.3)
Decreased appetite	4 (1.0)	4 (1.0)	20 (5.3)	23 (6.1)	2 (0.5)	2 (0.5)	23 (5.6)	26 (6.3)
Dizziness	8 (1.9)	8 (1.9)	14 (3.7)	20 (5.3)	1 (0.2)	1 (0.2)	21 (5.1)	26 (6.3)
Musculoskeletal pain	10 (2.4)	10 (2.4)	13 (3.4)	16 (4.2)	3 (0.7)	3 (0.7)	22 (5.3)	25 (6.1)
Pneumonia	7 (1.7)	7 (1.7)	13 (3.4)	18 (4.8)	3 (0.7)	3 (0.7)	20 (4.9)	25 (6.1)
Polyneuropathy	0	0	17 (4.5)	24 (6.3)	0	0	17 (4.1)	24 (5.8)
Vitamin B_6 deficiency	0	0	16 (4.2)	22 (5.8)	0	0	16 (3.9)	22 (5.3)
Fatigue	8 (1.9)	8 (1.9)	12 (3.2)	15 (4.0)	3 (0.7)	3 (0.7)	19 (4.6)	22 (5.3)
Laceration	2 (0.5)	2 (0.5)	18 (4.8)	19 (5.0)	1 (0.2)	1 (0.2)	20 (4.9)	21 (5.1)
Incision site pain	13 (3.2)	13 (3.2)	9 (2.4)	9 (2.4)	0	0	21 (5.1)	21 (5.1)

Table 53 TEAEs Reported by ≥ 5% of Subjects on Any Dose Any Time Presented by Dose Group (Open-Label LCIG Analysis Set)

	Number (%) of Subjects					
	Low Dose N = 155		High Dose N = 257		Any Dose N = 412	
Preferred Term	ISS	Safety Update	ISS	Safety Update	ISS	Safety Update
Any adverse event	139 (89.0)	142 (91.6)	241 (98.3)	241 (93.8)	379 (92.0)	383 (93.0)
Complication of device insertion	39 (25.2)	40 (25.8)	93 (36.2)	97 (37.7)	132 (32.0)	137 (33.3)
Abdominal pain	35 (22.6)	36 (23.2)	73 (28.4)	77 (30.0)	108 (26.2)	113 (27.4)
Insomnia	27 (17.4)	34 (21.9)	53 (20.6)	60 (23.3)	80 (19.4)	94 (22.8)
Postoperative wound infection	29 (18.7)	32 (20.6)	46 (17.9)	58 (22.6)	75 (18.2)	90 (21.8)
Procedural pain	22 (14.2)	24 (15.5)	55 (21.4)	60 (23.3)	77 (18.7)	84 (20.4)
Fall	22 (14.2)	26 (16.8)	52 (20.2)	60 (23.3)	74 (18.0)	86 (20.9)
Nausea	26 (16.8)	27 (17.4)	51 (19.8)	56 (21.8)	77 (18.7)	83 (20.1)
Excessive granulation tissue	17 (11.0)	19 (12.3)	54 (21.0)	62 (24.1)	71 (17.2)	81 (19.7)
Incision site erythema	16 (10.3)	19 (12.3)	49 (19.1)	58 (22.6)	65 (15.8)	77 (18.7)
Constipation	19 (12.3)	23 (14.8)	50 (19.5)	53 (20.6)	69 (16.7)	76 (18.4)
Urinary tract infection	20 (12.9)	24 (15.5)	35 (13.6)	41 (16.0)	55 (13.3)	65 (15.8)
Anxiety	12 (7.7)	13 (8.4)	37 (14.4)	46 (17.9)	49 (11.9)	59 (14.3)
Parkinson's disease	9 (5.8)	12 (7.7)	38 (14.8)	43 (16.7)	47 (11.4)	55 (13.3)
Procedural site reaction	12 (7.7)	20 (12.9)	30 (11.7)	35 (13.6)	42 (10.2)	55 (13.3)
Weight decreased	9 (5.8)	11 (7.1)	38 (14.8)	42 (16.3)	47 (11.4)	53 (12.9)
Depression	10 (6.5)	13 (8.4)	34 (13.2)	38 (14.8)	44 (10.7)	51 (12.4)
Vitamin B_6 deficiency	4 (2.6)	5 (3.2)	12 (4.7)	17 (6.6)	16 (3.9)	22 (5.3)
Fatigue	5 (3.2)	6 (3.9)	14 (5.4)	16 (6.2)	19 (4.6)	22 (5.3)
Laceration	5 (3.2)	5 (3.2)	15 (5.8)	16 (6.2)	20 (4.9)	21 (5.1)
Incision site pain	7 (4.5)	7 (4.5)	14 (5.4)	14 (5.4)	21 (5.1)	21 (5.1)

Table 54 TEAEs (≥ 5 %) in Open-Label Trials According to 3 Dose Subgroups

Preferred Term Treatment Period[a]	Low Dose LCIG < 1250 mg/day N = 155	High Dose LCIG ≥ 1250 – 2000 mg/day N = 185	High Dose LCIG ≥ 2000 mg/day N = 72	Any High Dose N = 257	Any Dose LCIG N = 412
Any adverse event	**142 (91.6)**	**170 (91.9)**	**71 (98.6)**	**241 (93.8)**	**383 (93.0)**
Titration Period	110 (71.0)	135 (73.0)	59 (81.9)	194 (75.5)	304 (73.8)
Maintenance Period[b]	118 (90.1)	153 (86.4)	67 (95.7)	220 (89.1)	338 (89.4)
Persistent AEs	68 (43.9)	89 (48.1)	43 (59.7)	132 (51.4)	200 (48.5)
Complication of device insertion	**40 (25.8)**	**62 (33.5)**	**35 (48.6)**	**97 (37.7)**	**137 (33.3)**
Titration Period	32 (20.6)	52 (28.1)	29 (40.3)	81 (31.5)	113 (27.4)
Maintenance Period[b]	12 (9.2)	20 (11.3)	12 (17.1)	32 (13.0)	44 (11.6)
Persistent AEs	4 (2.6)	7 (3.8)	4 (5.6)	11 (4.3)	15 (3.6)
Abdominal pain	**36 (23.2)**	**46 (24.9)**	**31 (43.1)**	**77 (30.0)**	**113 (27.4)**
Titration Period	28 (18.1)	35 (18.9)	22 (30.6)	57 (22.2)	85 (20.6)
Maintenance Period[b]	12 (9.2)	20 (11.3)	15 (21.4)	35 (14.2)	47 (12.4)
Persistent AEs	2 (1.3)	1 (0.5)	2 (2.8)	3 (1.2)	5 (1.2)
Insomnia	**34 (21.9)**	**44 (23.8)**	**16 (22.2)**	**60 (23.3)**	**94 (22.8)**
Titration Period	14 (9.0)	19 (10.3)	11 (15.3)	30 (11.7)	44 (10.7)
Maintenance Period[b]	21 (16.0)	28 (15.8)	8 (11.4)	36 (14.6)	57 (15.1)
Persistent AEs	7 (4.5)	15 (8.1)	4 (5.6)	19 (7.4)	26 (6.3)
Postoperative wound infection	**32 (20.6)**	**40 (21.6)**	**18 (25.0)**	**58 (22.6)**	**90 (21.8)**
Titration Period	6 (3.9)	13 (7.0)	5 (6.9)	18 (7.0)	24 (5.8)
Maintenance Period[b]	28 (21.4)	33 (18.6)	16 (22.9)	49 (19.8)	77 (20.4)
Persistent AEs	2 (1.3)	9 (4.9)	3 (4.2)	12 (4.7)	14 (3.4)
Procedural pain	**24 (15.5)**	**40 (21.6)**	**20 (27.8)**	**60 (23.3)**	**84 (20.4)**
Titration Period	14 (9.0)	31 (16.8)	14 (19.4)	45 (17.5)	59 (14.3)
Maintenance Period[b]	12 (9.2)	14 (7.9)	7 (10.0)	21 (8.5)	33 (8.7)
Persistent AEs	0	2 (1.1)	0	2 (0.8)	2 (0.5)
Nausea	**27 (17.4)**	**36 (19.5)**	**20 (27.8)**	**56 (21.8)**	**83 (20.1)**
Titration Period	13 (8.4)	18 (9.7)	4 (5.6)	22 (8.6)	35 (8.5)
Maintenance Period[b]	17 (13.0)	23 (13.0)	18 (25.7)	41 (16.6)	58 (15.3)
Persistent AEs	2 (1.3)	2 (1.1)	1 (1.4)	3 (1.2)	5 (1.2)
Fall	**26 (16.8)**	**35 (18.9)**	**25 (34.7)**	**60 (23.3)**	**86 (20.9)**
Titration Period	6 (3.9)	10 (5.4)	4 (5.6)	14 (5.4)	20 (4.9)
Maintenance Period[b]	23 (17.6)	31 (17.5)	22 (31.4)	53 (21.5)	76 (20.1)
Persistent AEs	0	2 (1.1)	0	2 (0.8)	2 (0.5)
Excessive granulation tissue	**19 (12.3)**	**51 (27.6)**	**11 (15.3)**	**62 (24.1)**	**81 (19.7)**
Titration Period	0	3 (1.6)	0	3 (1.2)	3 (0.7)
Maintenance Period[b]	19 (14.5)	50 (28.2)	11 (15.7)	61 (24.7)	80 (21.2)
Persistent AEs	0	3 (1.6)	0	3 (1.2)	3 (0.7)
Incision site erythema	**19 (12.3)**	**36 (19.5)**	**22 (30.6)**	**58 (22.6)**	**77 (18.7)**
Titration Period	10 (6.5)	9 (4.9)	8 (11.1)	17 (6.6)	27 (6.6)
Maintenance Period[b]	13 (9.9)	29 (16.4)	15 (21.4)	44 (17.8)	57 (15.1)
Persistent AEs	7 (4.5)	7 (3.8)	5 (6.9)	12 (4.7)	19 (4.6)
Constipation	**23 (14.8)**	**34 (18.4)**	**19 (26.4)**	**53 (20.6)**	**76 (18.4)**
Titration Period	9 (5.8)	20 (10.8)	8 (11.1)	28 (10.9)	37 (9.0)
Maintenance Period[b]	18 (13.7)	20 (11.3)	13 (18.6)	33 (13.4)	51 (13.5)
Persistent AEs	5 (3.2)	5 (2.7)	3 (4.2)	8 (3.1)	13 (3.2)
Urinary tract infection	**24 (15.5)**	**30 (16.2)**	**11 (15.3)**	**41 (16.0)**	**65 (15.8)**
Titration Period	2 (1.3)	2 (1.1)	2 (2.8)	4 (1.6)	6 (1.5)
Maintenance Period[b]	23 (17.6)	29 (16.4)	10 (14.3)	39 (15.8)	62 (16.4)
Persistent AEs	1 (0.6)	1 (0.5)	1 (1.4)	2 (0.8)	3 (0.7)
Anxiety	**13 (8.4)**	**29 (15.7)**	**17 (23.6)**	**46 (17.9)**	**59 (14.3)**
Titration Period	8 (5.2)	10 (5.4)	4 (5.6)	14 (5.4)	22 (5.3)
Maintenance Period[b]	6 (4.6)	22 (12.4)	13 (18.6)	35 (14.2)	41 (10.8)
Persistent AEs	3 (1.9)	4 (2.2)	1 (1.4)	5 (1.9)	8 (1.9)

Table 54 TEAEs (≥ 5 %) in Open-Label Trials According to 3 Dose Subgroups (Continued)

Preferred Term Treatment Period[a]	Low Dose LCIG < 1250 mg/day N = 155	High Dose LCIG ≥ 1250 – 2000 mg/day N = 185	High Dose LCIG ≥ 2000 mg/day N = 72	Any High Dose N = 257	Any Dose LCIG N = 412
Parkinson's disease	**12 (7.7)**	**23 (12.4)**	**20 (27.8)**	**43 (16.7)**	**55 (13.3)**
Titration Period	1 (0.6)	6 (3.2)	6 (8.3)	12 (4.7)	13 (3.2)
Maintenance Period[b]	11 (8.4)	20 (11.3)	16 (22.9)	36 (14.6)	47 (12.4)
Persistent AEs	1 (0.6)	1 (0.5)	3 (4.2)	4 (1.6)	5 (1.2)
Procedural site reaction	**20 (12.9)**	**20 (10.8)**	**15 (20.8)**	**35 (13.6)**	**55 (13.3)**
Titration Period	5 (3.2)	8 (4.3)	4 (5.6)	12 (4.7)	17 (4.1)
Maintenance Period[b]	17 (13.0)	16 (9.0)	14 (20.0)	30 (12.1)	47 (12.4)
Persistent AEs	2 (1.3)	5 (2.7)	2 (2.8)	7 (2.7)	9 (2.2)
Weight decreased	**11 (7.1)**	**25 (13.5)**	**17 (23.6)**	**42 (16.3)**	**53 (12.9)**
Titration Period	3 (1.9)	5 (2.7)	3 (4.2)	8 (3.1)	11 (2.7)
Maintenance Period[b]	9 (6.9)	22 (12.4)	15 (21.4)	37 (15.0)	46 (12.2)
Persistent AEs	3 (1.9)	5 (2.7)	3 (4.2)	8 (3.1)	11 (2.7)
Depression	**13 (8.4)**	**29 (15.7)**	**9 (12.5)**	**38 (14.8)**	**51 (12.4)**
Titration Period	4 (2.6)	6 (3.2)	2 (2.8)	8 (3.1)	12 (2.9)
Maintenance Period[b]	10 (7.6)	24 (13.6)	7 (10.0)	31 (12.6)	41 (10.8)
Persistent AEs	3 (1.9)	6 (3.2)	1 (1.4)	7 (2.7)	10 (2.4)
Dyskinesia	**19 (12.3)**	**19 (10.3)**	**13 (18.1)**	**32 (12.5)**	**51 (12.4)**
Titration Period	5 (3.2)	8 (4.3)	2 (2.8)	10 (3.9)	15 (3.6)
Maintenance Period[b]	16 (12.2)	13 (7.3)	12 (17.1)	25 (10.1)	41 (10.8)
Persistent AEs	3 (1.9)	6 (3.2)	1 (1.4)	7 (2.7)	10 (2.4)
Vitamin B_6 decreased	**19 (12.3)**	**20 (10.8)**	**11 (15.3)**	**31 (12.1)**	**50 (12.1)**
Titration Period	0	0	2 (2.8)	2 (0.8)	2 (0.5)
Maintenance Period[b]	19 (14.5)	20 (11.3)	9 (12.9)	29 (11.7)	48 (12.7)
Persistent AEs	0	0	2 (2.8)	2 (0.8)	2 (0.5)
Blood homocysteine increased	**14 (9.0)**	**19 (10.3)**	**12 (16.7)**	**31 (12.1)**	**45 (10.9)**
Titration Period	1 (0.6)	0	1 (1.4)	1 (0.4)	2 (0.5)
Maintenance Period[b]	13 (9.9)	19 (10.7)	11 (15.7)	30 (12.1)	43 (11.4)
Persistent AEs	1 (0.6)	0	1 (1.4)	1 (0.4)	2 (0.5)
Orthostatic hypotension	**14 (9.0)**	**20 (10.8)**	**8 (11.1)**	**28 (10.9)**	**42 (10.2)**
Titration Period	5 (3.2)	5 (2.7)	3 (4.2)	8 (3.1)	13 (3.2)
Maintenance Period[b]	9 (6.9)	15 (8.5)	6 (8.6)	21 (8.5)	30 (7.9)
Persistent AEs	2 (1.3)	2 (1.1)	1 (1.4)	3 (1.2)	5 (1.2)
Back pain	**13 (8.4)**	**21 (11.4)**	**7 (9.7)**	**28 (10.9)**	**41 (10.0)**
Titration Period	1 (0.6)	1 (0.5)	1 (1.4)	2 (0.8)	3 (0.7)
Maintenance Period[b]	12 (9.2)	20 (11.3)	7 (10.0)	27 (10.9)	39 (10.3)
Persistent AEs	0	0	0	0	0
Postprocedural discharge	**10 (6.5)**	**19 (10.3)**	**12 (16.7)**	**31 (12.1)**	**41 (10.0)**
Titration Period	1 (0.6)	4 (2.2)	4 (5.6)	8 (3.1)	9 (2.2)
Maintenance Period[b]	9 (6.9)	15 (8.5)	9 (12.9)	24 (9.7)	33 (8.7)
Persistent AEs	0	2 (1.1)	3 (4.2)	5 (1.9)	5 (1.2)
Vomiting	**12 (7.7)**	**14 (7.6)**	**14 (19.4)**	**28 (10.9)**	**40 (9.7)**
Titration Period	7 (4.5)	7 (3.8)	5 (6.9)	12 (4.7)	19 (4.6)
Maintenance Period[b]	6 (4.6)	11 (6.2)	9 (12.9)	20 (8.1)	26 (6.9)
Persistent AEs	1 (0.6)	0	1 (1.4)	1 (0.4)	2 (0.5)
Headache	**11 (7.1)**	**20 (10.8)**	**8 (11.1)**	**28 (10.9)**	**39 (9.5)**
Titration Period	6 (3.9)	11 (5.9)	3 (4.2)	14 (5.4)	20 (4.9)
Maintenance Period[b]	7 (5.3)	12 (6.8)	5 (7.1)	17 (6.9)	24 (6.3)
Persistent AEs	2 (1.3)	2 (1.1)	0	2 (0.8)	4 (1.0)
Diarrhoea	**11 (7.1)**	**19 (10.3)**	**7 (9.7)**	**26 (10.1)**	**37 (9.0)**
Titration Period	0	6 (3.2)	2 (2.8)	8 (3.1)	8 (1.9)
Maintenance Period[b]	11 (8.4)	15 (8.5)	6 (8.6)	21 (8.5)	32 (8.5)
Persistent AEs	0	2 (1.1)	0	2 (0.8)	2 (0.5)
Sleep attacks	**8 (5.2)**	**19 (10.3)**	**8 (11.1)**	**27 (10.5)**	**35 (8.5)**
Titration Period	3 (1.9)	3 (1.6)	3 (4.2)	6 (2.3)	9 (2.2)
Maintenance Period[b]	6 (4.6)	16 (9.0)	5 (7.1)	21 (8.5)	27 (7.1)
Persistent AEs	1 (0.6)	2 (1.1)	1 (1.4)	3 (1.2)	4 (1.0)

Table 54 TEAEs (≥ 5 %) in Open-Label Trials According to 3 Dose Subgroups (Continued)

Preferred Term Treatment Period[a]	Low Dose LCIG < 1250 mg/day N = 155	High Dose LCIG ≥ 1250 – 2000 mg/day N = 185	High Dose LCIG ≥ 2000 mg/day N = 72	Any High Dose N = 257	Any Dose LCIG N = 412
Dyspepsia	**11 (7.1)**	**13 (7.0)**	**8 (11.1)**	**21 (8.2)**	**32 (7.8)**
Titration Period	6 (3.9)	2 (1.1)	2 (2.8)	4 (1.6)	10 (2.4)
Maintenance Period[b]	5 (3.8)	11 (6.2)	6 (8.6)	17 (6.9)	22 (5.8)
Persistent AEs	3 (1.9)	0	0	0	3 (0.7)
Arthralgia	**9 (5.8)**	**13 (7.0)**	**10 (13.9)**	**23 (8.9)**	**32 (7.8)**
Titration Period	1 (0.6)	2 (1.1)	3 (4.2)	5 (1.9)	6 (1.5)
Maintenance Period[b]	8 (6.1)	11 (6.2)	7 (10.0)	18 (7.3)	26 (6.9)
Persistent AEs	1 (0.6)	1 (0.5)	1 (1.4)	2 (0.8)	3 (0.7)
Hallucination	**7 (4.5)**	**11 (5.9)**	**10 (13.9)**	**21 (8.2)**	**28 (6.8)**
Titration Period	2 (1.3)	2 (1.1)	1 (1.4)	3 (1.2)	5 (1.2)
Maintenance Period[b]	7 (5.3)	9 (5.1)	9 (12.9)	18 (7.3)	25 (6.6)
Persistent AEs	1 (0.6)	1 (0.5)	0	1 (0.4)	2 (0.5)
Oropharyngeal pain	**9 (5.8)**	**12 (6.5)**	**6 (8.3)**	**18 (7.0)**	**27 (6.6)**
Titration Period	8 (5.2)	12 (6.5)	5 (6.9)	17 (6.6)	25 (6.1)
Maintenance Period[b]	1 (0.8)	1 (0.6)	3 (4.3)	4 (1.6)	5 (1.3)
Persistent AEs	0	1 (0.5)	0	1 (0.4)	1 (0.2)
Pain in extremity	**7 (4.5)**	**11 (5.9)**	**8 (11.1)**	**19 (7.4)**	**26 (6.3)**
Titration Period	2 (1.3)	2 (1.1)	4 (5.6)	6 (2.3)	8 (1.9)
Maintenance Period[b]	5 (3.8)	9 (5.1)	4 (5.7)	13 (5.3)	18 (4.8)
Persistent AEs	1 (0.6)	0	3 (4.2)	3 (1.2)	4 (1.0)
Decreased appetite	**6 (3.9)**	**10 (5.4)**	**10 (13.9)**	**20 (7.8)**	**26 (6.3)**
Titration Period	1 (0.6)	1 (0.5)	2 (2.8)	3 (1.2)	4 (1.0)
Maintenance Period[b]	5 (3.8)	10 (5.6)	8 (11.4)	18 (7.3)	23 (6.1)
Persistent AEs	1 (0.6)	0	1 (1.4)	1 (0.4)	2 (0.5)
Dizziness	**6 (3.9)**	**12 (6.5)**	**8 (11.1)**	**20 (7.8)**	**26 (6.3)**
Titration Period	1 (0.6)	3 (1.6)	4 (5.6)	7 (2.7)	8 (1.9)
Maintenance Period[b]	5 (3.8)	9 (5.1)	6 (8.6)	15 (6.1)	20 (5.3)
Persistent AEs	0	0	1 (1.4)	1 (0.4)	1 (0.2)
Musculoskeletal pain	**4 (2.6)**	**12 (6.5)**	**9 (12.5)**	**21 (8.2)**	**25 (6.1)**
Titration Period	1 (0.6)	6 (3.2)	3 (4.2)	9 (3.5)	10 (2.4)
Maintenance Period[b]	4 (3.1)	6 (3.4)	6 (8.6)	12 (4.9)	16 (4.2)
Persistent AEs	0	1 (0.5)	2(2.8)	3 (1.2)	3 (0.7)
Pneumonia	**7 (4.5)**	**14 (7.6)**	**4 (5.6)**	**18 (7.0)**	**25 (6.1)**
Titration Period	2 (1.3)	5 (2.7)	0	5 (1.9)	7 (1.7)
Maintenance Period[b]	5 (3.8)	9 (5.1)	4 (5.7)	13 (5.3)	18 (4.8)
Persistent AEs	1 (0.6)	2 (1.1)	0	2 (0.8)	3 (0.7)
Hallucination	**7 (4.5)**	**11 (5.9)**	**10 (13.9)**	**21 (8.2)**	**28 (6.8)**
Titration Period	2 (1.3)	2 (1.1)	1 (1.4)	3 (1.2)	5 (1.2)
Maintenance Period[b]	7 (5.3)	9 (5.1)	9 (12.9)	18 (7.3)	25 (6.6)
Persistent AEs	1 (0.6)	1 (0.5)	0	1 (0.4)	2 (0.5)
Oropharyngeal pain	**9 (5.8)**	**12 (6.5)**	**6 (8.3)**	**18 (7.0)**	**27 (6.6)**
Titration Period	8 (5.2)	12 (6.5)	5 (6.9)	17 (6.6)	25 (6.1)
Maintenance Period[b]	1 (0.8)	1 (0.6)	3 (4.3)	4 (1.6)	5 (1.3)
Persistent AEs	0	1 (0.5)	0	1 (0.4)	1 (0.2)
Pain in extremity	**7 (4.5)**	**11 (5.9)**	**8 (11.1)**	**19 (7.4)**	**26 (6.3)**
Titration Period	2 (1.3)	2 (1.1)	4 (5.6)	6 (2.3)	8 (1.9)
Maintenance Period[b]	5 (3.8)	9 (5.1)	4 (5.7)	13 (5.3)	18 (4.8)
Persistent AEs	1 (0.6)	0	3 (4.2)	3 (1.2)	4 (1.0)
Decreased appetite	**6 (3.9)**	**10 (5.4)**	**10 (13.9)**	**20 (7.8)**	**26 (6.3)**
Titration Period	1 (0.6)	1 (0.5)	2 (2.8)	3 (1.2)	4 (1.0)
Maintenance Period[b]	5 (3.8)	10 (5.6)	8 (11.4)	18 (7.3)	23 (6.1)
Persistent AEs	1 (0.6)	0	1 (1.4)	1 (0.4)	2 (0.5)
Dizziness	**6 (3.9)**	**12 (6.5)**	**8 (11.1)**	**20 (7.8)**	**26 (6.3)**
Titration Period	1 (0.6)	3 (1.6)	4 (5.6)	7 (2.7)	8 (1.9)
Maintenance Period[b]	5 (3.8)	9 (5.1)	6 (8.6)	15 (6.1)	20 (5.3)
Persistent AEs	0	0	1 (1.4)	1 (0.4)	1 (0.2)

Table 54 TEAEs (≥ 5 %) in Open-Label Trials According to 3 Dose Subgroups (Continued)

Preferred Term Treatment Period[a]	Low Dose LCIG < 1250 mg/day N = 155	High Dose LCIG ≥ 1250 – 2000 mg/day N = 185	High Dose LCIG ≥ 2000 mg/day N = 72	Any High Dose N = 257	Any Dose LCIG N = 412
Musculoskeletal pain	**4 (2.6)**	**12 (6.5)**	**9 (12.5)**	**21 (8.2)**	**25 (6.1)**
Titration Period	1 (0.6)	6 (3.2)	3 (4.2)	9 (3.5)	10 (2.4)
Maintenance Period[b]	4 (3.1)	6 (3.4)	6 (8.6)	12 (4.9)	16 (4.2)
Persistent AEs	0	1 (0.5)	2(2.8)	3 (1.2)	3 (0.7)
Pneumonia	**7 (4.5)**	**14 (7.6)**	**4 (5.6)**	**18 (7.0)**	**25 (6.1)**
Titration Period	2 (1.3)	5 (2.7)	0	5 (1.9)	7 (1.7)
Maintenance Period[b]	5 (3.8)	9 (5.1)	4 (5.7)	13 (5.3)	18 (4.8)
Persistent AEs	1 (0.6)	2 (1.1)	0	2 (0.8)	3 (0.7)
Polyneuropathy	**3 (1.9)**	**12 (6.5)**	**9 (12.5)**	**21 (8.2)**	**24 (5.8)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	3 (2.3)	12 (6.8)	9 (12.9)	21 (8.5)	24 (6.3)
Persistent AEs	0	0	0	0	0
Vitamin B_6 deficiency	**5 (3.2)**	**9 (4.9)**	**8 (11.1)**	**17 (6.6)**	**22 (5.3)**
Titration Period	0	0	0	0	0
Maintenance Period[b]	5 (3.8)	9 (5.1)	8 (11.4)	17 (6.9)	22 (5.8)
Persistent AEs	0	0	0	0	0
Fatigue	**6 (3.9)**	**9 (4.9)**	**7 (9.7)**	**16 (6.2)**	**22 (5.3)**
Titration Period	2 (1.3)	4 (2.2)	2 (2.8)	6 (2.3)	8 (1.9)
Maintenance Period[b]	4 (3.1)	6 (3.4)	5 (7.1)	11 (4.5)	15 (4.0)
Persistent AEs	1 (0.6)	2 (1.1)	0	2 (0.8)	3 (0.7)
Laceration	**5 (3.2)**	**10 (5.4)**	**6 (8.3)**	**16 (6.2)**	**21 (5.1)**
Titration Period	1 (0.6)	0	1 (1.4)	1 (0.4)	2 (0.5)
Maintenance Period[b]	4 (3.1)	10 (5.6)	5 (7.1)	15 (6.1)	19 (5.0)
Persistent AEs	1 (0.6)	0	0	0	1 (0.2)
Incision site pain	**7 (4.5)**	**8 (4.3)**	**6 (8.3)**	**14 (5.4)**	**21 (5.1)**
Titration Period	3 (1.9)	6 (3.2)	4 (5.6)	10 (3.9)	13 (3.2)
Maintenance Period[b]	5 (3.8)	2 (1.1)	2 (2.9)	4 (1.6)	9 (2.4)
Persistent AEs	0	0	0	0	0

AE = adverse event; AESI = adverse event of special interest; LCIG = levodopa-carbidopa intestinal gel; TEAE = treatment-emergent adverse event

a. Titration Period = onset during Days 1 through 28; Maintenance Period = onset ≥ Day 29; Persistent = event onset during Titration Period and continued into Maintenance Period with duration ≥ 7 days.

b. N = 131 for < 1250 mg/day, 177 for ≥ 1250 – 2000 mg/day, 70 for > 2000 mg/day

Cross reference: Safety Update Tables 1__2.4.1.1.1 through 1__2.4.1.1.4, Tables 1__2.19.1.1.1 through 1__2.19.1.1.4

Reviewer Comments

- *Table 52 presents results for TEAEs for any dose of LCIG in the whole open-label trial period, in the titration period, in the maintenance period, and when considered "persistent" and compares frequencies in the ISS vs the 4MSU. The incidence of TEAEs occurring in each time perspective is quite similar for the ISS analysis and the 4MSU. Of interest, the 2 most frequent TEAEs (complication of device insertion and abdominal*

pain) in the open-label experience were also the most common TEAEs in the LCIG any dose group in the controlled trial.

- *Table 53 shows common TEAEs (occurring in ≥ 5 % patients of patients at any dose) according to low and high dose subgroups. The incidence of all TEAEs in this table were more frequent in the high dose subgroup than in the low dose subgroup with the exception of postoperative wound infection and urinary tract infection.*

- *An additional dose-dependent analysis of 3 subgroups (mean daily LD : < 1250 mg, ≥ 1250 mg - < 2000 mg, > 2000 mg) presented in Table 54 showed that the highest dose subgroup (≥ 2000 mg) was frequently associated with the highest incidence of TEAEs for many TEAEs (e.g., some of the most common : complication of device insertion, abdominal pain, postoperative wound infection, procedural pain, nausea, fall, incision site erythema, constipation, and anxiety.) In many instances, the dose-dependent increases were monotonic and the increase in the incidence in the highest dose subgroup (compared to the middle dose subgroup) was quite substantial. In some instances, the high dose group (≥ 1250 mg) was greater than the low dose group < 1250 mg).*

- *Results of open-label, long-term treatment did not suggest a risk of medically serious adverse events possibly related to LCIG treatment that was different than the results of the controlled trial experience. However, the open-label treatment did suggest that the incidence of many TEAEs was dose-dependent, particularly at daily dosing at ≥ 2000 mg daily for LD. Despite the fact that these TEAEs were observed in the open-label treatment experience, dose-dependent increases in the incidence suggests that they were caused by LCIG.*

7.4.2 Laboratory Findings

Central tendency analyses (e.g., mean analyte change from baseline) did not suggest any clear effects of LCIG treatment. Consequently, laboratory analyses presented here will focus on outlier analyses. Results from only the controlled trial will be presented because results from the open-label trials were not noteworthy.

The following tables show outliers for clinical laboratory analytes for hematology and chemistry.

Active Controlled Trial

Table 55 Hematology Variables for Which ≥ 1 Subject Met the Sponsor PCS Criteria Any Time During Treatment (Active-Controlled Analysis Set)

	n/N Subjects (%)[a]					
	LCIG			LC-Oral		
Hematology Variable/ PCS Criterion	Low Dose N = 27	High Dose N = 10	Any Dose N = 37	Low Dose N = 15	High Dose N = 19	Any Dose N = 34)
Eosinophils > 10%	1/25 (4.0)	1/10 (10.0)	2/35 (5.7)	1/13 (7.7)	0/19	1/32 (3.1)
Hemoglobin < 90 g/L	1/25 (4.0)	0/10	1/35 (2.9)	0/14	0/19	0/33
Hematocrit fraction < 30%	2/25 (8.0)	0/10	2/35 (5.7)	0/13	0/19	0/32
Absolute lymphocyte count < 0.75×10^9/L	1/25 (4.0)	1/10 (10.0)	2/35 (5.7)	2/13 (15.4)	2/19 (10.5)	4/32 (12.5)

LCIG = levodopa-carbidopa intestinal gel; LC-oral = encapsulated levodopa-carbidopa immediate release tablets

a. Results are presented for any time during treatment. Assessments were performed at Week 6, Week 12, and Final.

Reviewer Comments

Table 55 shows results of some hematology outliers according to the sponsor's criteria for potentially clinically significant. The only outlier abnormalities that I note may have some significance is the increased percentage of LCIG patients at any dose with a markedly low hematocrit compared to the control patients who did not have any such outliers. These are only 2 patients and this occurred in the low dose LCIG group. This may be something to note in the label in the section on laboratory analyses,

Chemistry Analytes

The follow are some sponsor tables of outliers abstracted from the NDA.

Table 56 Chemistry Variables for Which ≥ 10% of Subjects Exhibited Shifts from Baseline to Final Value (Active-Controlled Analysis Set)

	n/N Subjects (%)											
	LCIG						LC-Oral					
	Low Dose N = 27		High Dose N = 10		Any Dose N = 37		Low Dose N = 15		High Dose N = 19		Any Dose N = 34	
Chemistry Variable	Low/ Normal to High	Normal/ High to Low	Low/ Normal to High	Normal/ High to Low	Low/ Normal to High	Normal/ High to Low	Low/ Normal to High	Normal/ High to Low	Low/ Normal to High	Normal/ High to Low	Low/ Normal to High	Normal/ High to Low
ALT	0/25	0/23	1/10 (10.0)	0/9	1/35 (2.9)	0/32	0/13	1/12 (8.3)	0/19	2/17 (11.8)	0/32	3/29 (10.3)
AST	0/25	0/25	1/10 (10.0)	0/10	1/35 (2.9)	0/35	0/14	0/12	0/19	1/19 (5.3)	0/33	1/31 (3.2)
Bicarbonate	2/19 (10.5)	0/23	2/10 (20.0)	0/10	4/29 (13.8)	0/33	1/13 (7.7)	1/12 (8.3)	2/17 (11.8)	1/18 (5.6)	3/30 (10.0)	2/30 (6.7)
BUN	2/15 (13.3)	0/19	1/9 (11.1)	0/9	3/24 (12.5)	0/28	0/5	0/6	0/15	0/17	0/20	0/23
Calcium	0/24	1/25 (4.0)	0/9	1/10 (10)	0/33	2/35 (5.7)	0/13	2/14 (14.3)	0/19	0/19	0/32	2/33 (6.1)
Cholesterol	1/17 (5.9)	0/22	0/8	1/9 (11.1)	1/25 (4.0)	1/31 (3.2)	0/6	0/13	0/14	0/18	0/20	0/31
CPK	2/20 (10.0)	0/25	1/9 (11.1)	0/10	3/29 (10.3)	0/35	0/12	0/14	1/17 (5.9)	0/19	1/29 (3.4)	0/33
LDH	2/24 (8.3)	0/24	1/10 (10.0)	0/10	3/34 (8.8)	0/34	1/14 (7.1)	0/14	0/19	0/19	1/33 (3.0)	0/33
Non-fasting glucose	1/24 (4.2)	0/25	1/8 (12.5)	0/10	2/32 (6.3)	0/35	0/14	0/14	2/16 (12.5)	0/19	2/30 (6.7)	0/33
Potassium	0/25	0/24	0/10	0/10	0/35	0/34	0/14	2/14 (14.3)	0/19	1/19 (5.3)	0/33	3/33 (9.1)
Total protein	0/25	2/25 (8.0)	0/10	3/10 (30.0)	0/35	5/35 (14.3)	0/14	2/13 (15.4)	0/19	0/19	0/33	2/32 (6.3)
Triglycerides	1/23 (4.3)	0/25	0/10	0/10	1/33 (3.0)	0/35	0/14	0/14	3/18 (16.7)	0/18	3/32 (9.4)	0/32
Uric acid	0/24	0/22	0/10	0/10	0/34	0/32	0/14	1/14 (7.1)	0/19	4/18 (22.2)	0/33	5/32 (15.6)

Table 57 Chemistry Variables for Which ≥ 1 Subject Met the Sponsor PCS Criteria by Treatment Period and Dose (Active-Controlled Analysis Set)

	n/N Subjects (%)[a]					
	LCIG			LC-Oral		
Chemistry Variable/ PCS Criterion	Low Dose N = 27	High Dose N = 10	Any Dose N = 37	Low Dose N = 15	High Dose N = 19	Any Dose N = 34
CPK > 3 × ULN	1/25 (4.0)	2/10 (20.0)	3/35 (8.6)	0/14	0/19	0/33
BUN > 10.8 mmol/L	1/19 (5.3)	1/9 (11.1)	2/28 (7.1)	0/6	0/17	0/23
Non-fasting glucose > 16 mmol/L	0/25	0/10	0/35	0/14	1/19 (5.3)	1/33 (3.0)
Uric acid > 500 µmol/L	1/25 (4.0)	0/10	1/35 (2.9)	0/14	0/19	0/33

Reviewer Comments

- *Regarding the outlier shifts (relative to the "normal" reference range) in Table 56, I will only comment on analytes where there was a shift in more than one LCIG patient and the % was greater for LCIG any dose than for oral LD/CD any dose. Most notably, any dose LCIG patients exhibited a shift from low or normal at baseline to high at the final study visit in 13 % of patients compared to 0 % for the control oral LD/CD. The shifts from low-normal to high for CPK, LDH, and bicarbonate were only slightly greater than the % shift for respective patients in the control group.*

- *Table 57 shows incidence results for outliers (during the controlled trial) that the sponsor deemed potentially clinically significant/markedly abnormal. The increased incidence in BUN and CPK deserved comment because they occurred in more than one patient in the LCIG group and the incidence was greater than that for the control group. The incidence of a markedly increase results at any time in the trial for the any dose LCIG group was 7 % for BUN and 8 % for CPK. For BUN, there was one patient in the low dose group and one in the high dose group. For CPK, there were 2 patients in the high dose group and one in the low dose group. However, this small sample size makes it difficult to conclude about dose-dependence. There did not appear to be any clear cases of rhabodmyolysis or muscle disorders in the LCIG patients in the controlled trial. The incidence of markedly increased CPK (i.e., > 3 X ULN) was 2 % in the open-label trial experience.*

- *Because of the potential importance of the seemingly increased risk for BUN, this observation in Table 56 stimulated me to explore and present additional outlier analyses not only for BUN but also for serum creatinine to try to understand the potential effect on renal function.*

Reference ID: 3469235

Table 58 Incidence (Rounded off %) of Increased Values (Relative to Normal Reference Range) for BUN and Creatinine in Controlled Trial According to Treatment and Dose Groups

Time Perspective for Each Clinical Laboratory Abnormality	**LCIG %** N = 37 Randomized to Any Dose (Low Dose = 27; High Dose = 10)			**Oral LD/CD %** N=34 Randomized to Any Dose (Low Dose = 15; High Dose = 19)		
	LD	HD	Any Dose	LD	HD	Any Dose
Increased BUN						
Baseline	20	0	14	25	0	15
6 Week	20	0	20	7	11	9
12 Weeks	20	13	18	8	6	7
Any Visit	28	20	26	7	11	9
Final Visit	28	10	17	7	5	6
Increased Creatinine						
Baseline	0	0	0	7	11	9
6 Week	4	0	3	0	6	3
12 Weeks	4	0	3	0	6	4
Any Visit	4	0	3	0	5	3
Final Visit	4	0	3	0	5	3

Yellow highlight emphasizes notable difference from respective control group

Table 59 Incidence (Rounded Off %) of Markedly Increased BUN and Creatinine According to Treatment and Dose in Controlled Trial

Time Perspective for Each Clinical Laboratory Abnormality	**LCIG %** N = 37 Randomized to Any Dose (Low Dose = 27; High Dose = 10)			**Oral LD/CD %** N=34 Randomized to Any Dose (Low Dose = 15; High Dose = 19)		
	LD	**HD**	**Any Dose**	**LD**	**HD**	**Any Dose**
Increased BUN						
Baseline	7	0	5	13	5	9
6 Week	8	10	9	0	0	0
12 Weeks	8	0	6	0	0	0
Any Visit	12	10	11	0	0	0
Final Visit	8	0	6	0	0	0
Increased Creatinine						
Baseline	0	0	0	0	0	0
6 Week	0	0	0	0	0	0
12 Weeks	4	0	2	0	0	0
Any Visit (Not conducted)						
Final Visit	4	0	3	0	0	0

Yellow highlight emphasizes notable difference from respective control group

Table 60 Shift (Rounded Off %) for BUN and Creatinine from Low or Normal at Baseline to High (relative to Reference Range) at Visit According to Treatment and Dose in Controlled Trial

Time Perspective for Each Clinical Laboratory Abnormality	**LCIG %**			**Oral LD/CD %**		
	LD	**HD**	**Any Dose**	**LD**	**HD**	**Any Dose**
Increased BUN						
6 Week	0	11	4	0	7	5
12 Weeks	13	15	14	0	0	0
Final Visit	13	11	13	0	0	0
Increased Creatinine						
6 Week	4	0	3	0	0	0
12 Weeks	4	0	3	0	0	0
Final Visit	4	0	3	0	0	0

Yellow highlight emphasizes notable difference from respective control group

Table 61 Incidence of Increased BUN According to Age Subgroups for Any Dose for All Treatments in Controlled Trial

	ALL DOSES			
	< 65 YEARS		>= 65 YEARS	
VISIT CRITERIA#	LCIG (N=21) n/N_OBS (%)	LC-ORAL (N=15) n/N_OBS (%)	LCIG (N=16) n/N_OBS (%)	LC-ORAL (N=19) n/N_OBS (%)
BASELINE				
LOW	0/21	0/15	0/16	0/19
HIGH	2/21 (9.5)	2/15 (13.3)	3/16 (18.8)	3/19 (15.8)
WEEK 6				
LOW	0/20	0/14	0/15	0/18
HIGH	3/20 (15.0)	0/14	4/15 (26.7)	3/18 (16.7)
WEEK 12				
LOW	0/19	0/13	0/14	0/16
HIGH	2/19 (10.5)	0/13	4/14 (28.6)	2/16 (12.5)
ANY VISIT POST BASELINE				
LOW	0/20	0/15	0/15	0/18
HIGH	3/20 (15.0)	0/15	6/15 (40.0)	3/18 (16.7)
FINAL VISIT DURING ENTIRE TREATMENT PERIOD				
LOW	0/20	0/15	0/15	0/18
HIGH	2/20 (10.0)	0/15	4/15 (26.7)	2/18 (11.1)

Reviewer Comments

- *In Table 58, the incidence of increased BUN (relative to the normal reference range) was notably higher for any dose LCIG (vs any dose oral LD/CD) at 6 and 12 weeks, any visit and the final visit. There was no suggestion for dose-response of LCIG. However, there is no treatment difference for creatinine for LCIG from any time perspective. In the open-label trial experience, the incidence for an increased value was 6 % for BUN and 1 % for creatinine.*

- *When one assessed the incidence of markedly increased BUN (i.e., > 10 mmol/L for < 65yo and > 9.5 for 65 or older) in , Table 59, this incidence was notably increased for any dose LCIG vs the control, oral LD/CD also at 6 and 12 weeks, any visit and the final visit. Neither was there a suggestion for LCIG dose-response. The sponsor had showed that the treatment differences at 6 weeks and at any visit were statistically significant ($p < 0.05$). In this analysis, there was an increased incidence of markedly increase creatinine for LCIG (any dose) at 12 weeks/final visit. However, this was based on only 1 patient who had received low dose LCIG.*

- *Results of shift table analyses (Table 60) were also considered because in a shift table analysis one can exclude patients who may have had an increased value of BUN or creatinine from the analysis time when the post-treatment value is elevated by considering only patients with a low or normal value at baseline in the analysis. In this*

analysis, the incidence of increased BUN was observed at the 12 week/final visit analysis. The magnitude of the increased % in this shift analysis was somewhat lower than the incidence analysis but this increased % was still notably increased compared to the incidence for the control group for any dose (0 %). In addition, there was no suggestion of dose response for the high dose LCIG group. In the shift analysis for creatinine, the incidence of an increased creatinine was observed at 12 weeks/ final visit and thus the treatment difference relative to oral LD/CD was small at 3 % but this difference was only based upon one patient with a shift to an increased creatinine value.

- *Table 61 presents analyses for an increased incidence in BUN according to age Subgroup (i.e., < 65 yo vs ≥ 65 yo) according to treatment and time perspective. The treatment difference (LCIG % - oral LD/CD %) is increased for the older patients in the any visit and final visit analysis. These results suggest that the risk for increased BUN may be higher in older patients. Analyses of age subgroups in patients with an increased post-treatment creatinine were not useful because there was only one patient with an increased value in each treatment group, There was no suggestion of subgroup difference for a risk of increased BUN or creatinine based upon gender subgroup analyses.*

- *I conclude from these analyses that there is an increased risk for BUN with LCIG treatment and this increased risk may be higher in patients 65 years and old. It is not so clear that there is an increased risk for increased creatinine. These results raise the question of whether some pre-renal mechanism might be involved with this increased risk because with a renal mechanism one would expect both BUN and creatinine to be increased. Regardless, these noteworthy outlier results should at least be described in the Duopa label in the laboratory section.*

Special Laboratory Evaluations

Vitamin B6 and vitamin B12 deficiencies are reported to be risk factors for polyneuropathy and special chemistry parameters (vitamin B6, vitamin B12, MMA, folic acid, and homocysteine) were added by amendment to the Phase 3 protocols after enrollment was initiated. Therefore, few subjects had Baseline measurements. AESI of polyneuropathy were presented and associated special laboratory results special chemistry analytes. .

Approximately 48% of subjects (34 of 71 subjects) in the Active-Controlled Analysis Set had vitamin B12 assessments at both Baseline and at least 1 post-Baseline visit. No clinically important mean changes from Baseline or statistically significant differences between treatment groups (LCIG versus LC-oral) were observed in special chemistry parameters. Although a mean decrease from Baseline to final visit in vitamin B12 of – 903 pmol/L was observed in the low dose LCIG group, the median change from Baseline to final visit was an increase of 13 pmol/L. The large mean decrease was largely due to an outlier at Baseline (Subject 136-102 was taking vitamin B12 supplements and had a Baseline value of 14485 pmol/L); the mean change from Baseline excluding this subject from the analysis was an increase of 45 pmol/L. No special

Reference ID: 3469235

chemistry results were below the normal range and the categorical shifts relative to the normal reference range were unremarkable.

Table 62 Abnormal Shift Results (Number of Patients and %) for Special Laboratory Analytes (Vitamin and Related Metabolites) From Baseline to Final Visit According to Treatment in Controlled Trial

Baseline Categorical Result	Final Visit Result			
	LCIG (N = 37)		Oral LD/CD (N = 34)	
	Low	High	Low	High
Serum Folic Acid				
Low-Normal		0		0
Normal-High	0		0	
Serum Homocysteine				
Low-Normal		5 (39 %)		0
Normal-High	0		0	
Serum Methylmalonic Acid (MMA)				
Low-Normal		0		1 (11 %)
Normal-High	0		0	
Serum B12				
Low-Normal		3 (17 %)		0
Normal-High	0		0	
Serum B6				
Low-Normal		0		0
Normal-High	0		0	

Less than 13% of subjects (52 of 412 subjects) in the Open-Label LCIG Analysis Set had vitamin B12 assessments at both Baseline and at least 1 post-Baseline visit. For subjects included in this analysis set from Study S187-3-003, the Baseline value in the Open-Label LCIG Analysis Set was taken after 12 weeks of LCIG or LC-oral treatment. Additionally, the standard deviations were generally large relative to the mean changes from Baseline, limiting interpretation of the central tendencies.

The sponsor provided the following brief summaries for these special chemistry analytes in the open-label trials.

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● Vitamin B6: Mean changes from Baseline ranged from 3 to 70 pmol/L for low dose and 12 to 52 pmol/L for the high dose group, with mean changes of 56.63 pmol/L for the low dose group and 32 pmol/L for the high dose group at the final visit. Individual shifts from low or normal at Baseline to high at final visit were observed for 24 % (7/29) of subjects. Individual shifts from high or normal at Baseline to low at final visit were observed for 20 % (4/20) of subjects.

● Vitamin B12: Mean changes from Baseline were 26 pmol/L for the low dose group and –1.13 pmol/L for the high dose group at Week 12 with subsequent mean increases from Baseline at each dose level at every visit. The mean changes from Baseline to final visit were 69 pmol/L for the low dose group and 67 pmol/L for the high dose group. Individual shifts from low or normal at Baseline to high at final visit were observed for 9 % (4/47) of subjects. Individual shifts from high or normal at Baseline to low at final visit were observed for 2.0% (1/51) of subjects. Table 63 presents results for patients who had baseline serum B12 measurements along with results of various special laboratory tests.

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Table 63 Vitamin B12: Subjects with Baseline Assessments (Normal : > 500; Low : ≥ 148 - < 500; Markedly Low : < 148) All Subjects Who Received LCIG Using Baseline Prior to Any LCIG Exposure in Open-Label Trials (All LCIG Analysis Sets)

	Vitamin B_{12} Value at Baseline[a]		
	Normal ≥ 500 pmol/L	Low-Normal < 500 pmol/L and ≥ 148 pmol/L	Low < 148 pm
Number of subjects with Baseline[a] B_{12}	6	51	1
Baseline homocysteine and/or MMA	N = 6	N = 49[b]	N = 1
> ULN	1	28	1
Vitamin B_6 at Baseline[a]	N = 2	N = 24	N = 1
< LLN	1	10	1
> ULN	1	2	0
Vitamin B_{12} Supplement	N = 6	N = 51	N = 1
No	0	33	0
Yes	6	18	1
Started prior to Baseline[a]	6	11	0
Started after Baseline[a]	0	7	1
Vitamin B_{12} value at Final	N = 6	N = 45	N = 1
Low, < 148 pmol/L	0	1	0
Low-normal, < 500 pmol/L and ≥ 148 pmol/L	3	35[c]	1
Normal, ≥ 500 pmol/L	3	9[d]	0
Polyneuropathy TEAE per independent adjudication committee[e]	0	1	1
TEAE in the Polyneuropathy AESI[f]	4	6	1

AESI = adverse event of special interest; LCIG = levodopa-carbidopa intestinal gel; LLN=lower limit normal range; MMA = methylmalonic acid;; ULN=upper limit normal range
a. Baseline was defined as the last measurement prior to any LCIG exposure.
b. N = 45 for homocysteine; N = 46 for MMA.
c. 10 of the 35 subjects were taking vitamin B supplements.
d. 7 of the 9 subjects were taking vitamin B supplements.
e. Subject 401-0144 and Subject 500-003 were determined by the Neuropathy Evaluation Committee to meet criteria for a generalized polyneuropathy event.
f. Subjects with TEAE preferred term in the category of polyneuropathy AESI: normal vitamin B12 at Baseline (Subjects 114-1033, 136-102, 148-101, 502-001), low-normal vitamin B12 at Baseline (Subjects 104-108, 126-1033, 146-105, 446-103, 500-003, 502-002), low vitamin B12 at Baseline (Subject 401-0144). The TEAEs for 4 of these 11 subjects were coded to PTs more likely indicative of neuropathy (Table 77): Guillain-Barré Syndrome for Subject 401-0144, mononeuropathy for Subject 502-001, and polyneuropathy for Subject 104-108 and Subject 446-103.

● MMA: Mean changes from Baseline ranged from 0.09 to –0.01 µmol/L for the low dose group and –0.18 to –0.08 µmol/L for the high dose group, with mean changes of –0.58 µmol/L for the low dose group and –0.10 µmol/L for the high dose group at the final visit. No individual shifts from low or normal at Baseline to high at final visit or from high or normal at Baseline to low at final visit were observed.

● Folic acid: Mean changes from Baseline ranged from 2.13 to 43.20 nmol/L for low dose and –13.95 to 29.28 nmol/L for the high dose group, with mean changes of 18.512 nmol/L for the low dose group and 12.894 nmol/L for the high dose group at the final visit. No individual shifts from high or normal at Baseline to low at final visit were observed.

● Homocysteine: Mean changes from Baseline ranged from 1.27 to 6.40 µmol/L for the low dose group and 1.90 to 15.41 µmol/L for the high dose group, with mean changes of 2.65 µmol/L for the low dose group and 1.31 µmol/L for the high dose group at the final visit. Individual shifts from low or normal baseline values to high values at final visit were observed for 52 % (12/23) of subjects. No individual shifts from high or normal at Baseline to low at final visit were observed.

The interpretation of vitamin B12 levels is complicated by the limitations of current assay techniques, as a low serum vitamin B12 level does not always indicate vitamin B12 deficiency and a normal vitamin B12 level does not always exclude a deficiency. Individuals with low or borderline levels of vitamin B12 and elevated levels of homocysteine or MMA can be defined as having "metabolically significant" vitamin B12 deficiency. Of subjects who had special lab measurements prior to any LCIG infusion, the majority (87.9%, 51/58) had vitamin B12 Baseline values that were considered low-normal (≥ 148 and < 500 pmol/L), including 28 subjects with elevated homocysteine or MMA, suggesting a relative B12 deficiency. Six subjects (10.3%) had normal values (≥ 500 pmol/L) at Baseline, and 1 subject (1.7%) had a low Baseline value (< 148 pmol/L). The majority of subjects with normal values at the final assessment were taking supplemental vitamin B (3 of 3 subjects with normal Baseline, 6 of 9 subjects with low-normal Baseline). The majority of subjects with low-normal values at the final assessment were not taking supplemental vitamin B (0 of 3 subjects with normal Baseline, 21 of 35 subjects with low-normal Baseline). The subject (Subject 401-0144) with low vitamin B12 at Baseline started taking vitamin B12 during the study and the vitamin B12 levels increased from 145 pmol/L at Baseline to 248 pmol/L at the final assessment. This subject, with a history of hypothyroidism and vitamin B12 deficiency, had polyneuropathy, as determined by the Neuropathy Evaluation Committee, which was reported as an AE of Guillain-Barré Syndrome by the investigator. The committee determined that one additional subject (Subject 500-003) with vitamin B12 assessments at Baseline had evidence of a generalized polyneuropathy with the AE of paraesthesia that was mild in severity. This subject, with a history of hypothyroidism and vitamin B12 deficiency, had baseline metabolic B12 deficiency (low-normal vitamin B12 with elevated homocysteine) and a low vitamin B6 despite treatment with subcutaneous injection of vitamin B12 for approximately 1 year prior to study start. At the final lab assessed, B12 was still low-normal but the homocysteine and vitamin B6 normalized.

Reviewer Comments

It is not possible to draw any conclusions that LCIG treatment resulted in any clear abnormalities of these special analytes,

7.4.3 Vital Signs

Vital sign (VS) analyses presented here will focus on outlier analyses that appeared to be informative. However, some central tendency results will be presented as figures because that approached also seemed most informative. . Results from only the controlled trial will be presented because results from the open-label trials were not considered noteworthy.

Active Controlled Trial

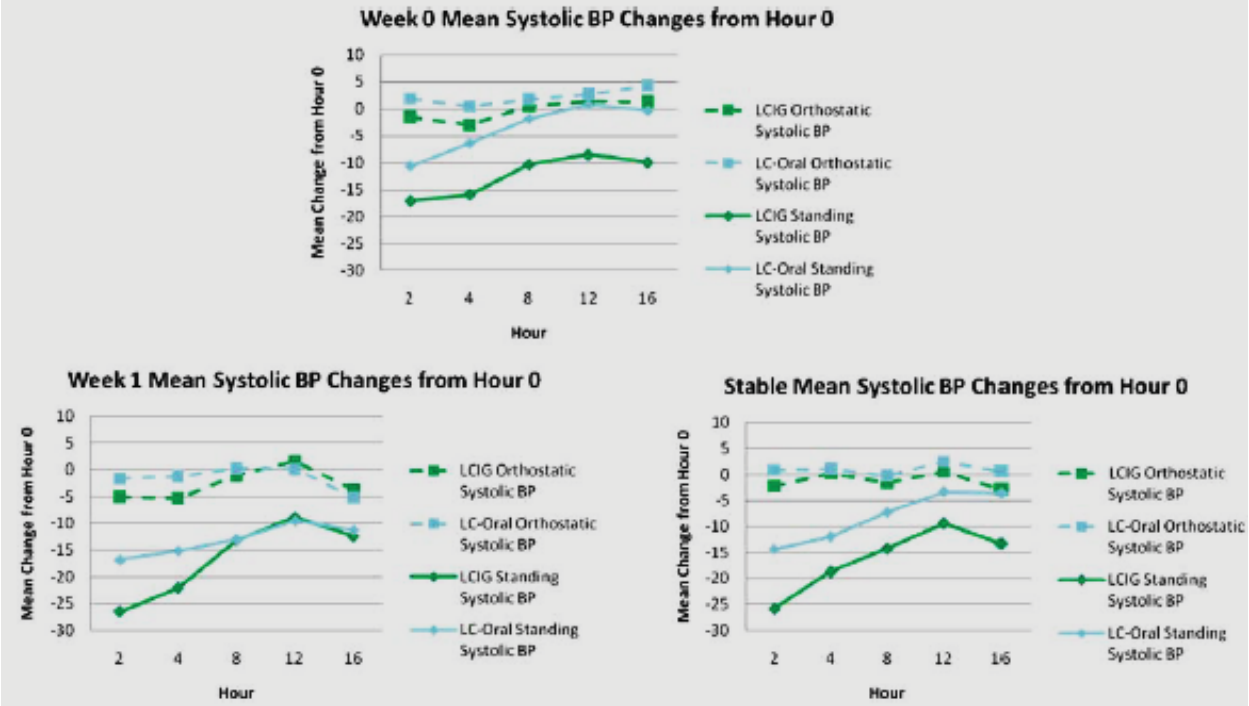
Active-Controlled Analysis Set
In the Active-Controlled Analysis Set, no statistically significant differences in mean changes from Baseline between LCIG and LC-oral were observed. Blood pressure at Baseline was taken from the 3 sets of measurements prior to placement of the study device, and these measurements were not obtained at any specific time relative to levodopa-carbidopa IR dosing on that day. It is likely that subjects took oral levodopa-carbidopa IR on the same day prior to Baseline assessments, as the study drug titration for LCIG and LC-oral did not begin until the day after device placement.

As demonstrated in the graphs below, there are numerically greater blood pressure decreases in the LCIG group compared with the LC-oral. Blood pressure was measured at Hours 0, 1, 2, 8, 12, and 16, relative to study drug administration on the first day of dosing (Week 0), and Weeks 1 and 6, where Hour 0 was the measurements taken just prior to the morning dose after subjects had been off study drug treatment during the night. On the first day of dosing, the mean SBP and DBP values decreased from Hour 0 to Hour 2 (standing SBP: –17.1 mmHg for LCIG, –10.6 for LC-oral; standing DBP: –10.3 mmHg for LCIG, –5.2 mmHg for LC-oral), and then increased without fully recovering to the Hour 0 values by the last assessment at Hour 16.

These results are graphically *displayed for SBP in Figure 15, and* the results for DBP followed the same trend. These observations are consistent with the known effect of levodopa on blood pressure in unmedicated conditions, such as patients being off medication overnight. This trend was more pronounced for LCIG than for LC-oral, and the differences between treatment groups were greater at Weeks 0 and 1 compared with when subjects were on a stable dosage. The changes in mean orthostatic SBP and DBP were less pronounced than changes in standing SBP and DBP, showing more recovery to the values observed at Hour 0, but the results were also less consistent (i.e., increases from Hour 0 were observed for LC-oral at many time points). The differences in the orthostatic blood pressure between LCIG and LC-oral were small and considered unlikely to be clinically significant.

Reference ID: 3469235

Figure 15 Systolic Blood Pressure Changes from Hour 0 on Day 1, Week 1, and on Stable Dosage (Active-Controlled Analysis Set)



A review of orthostatic blood pressure by dose level indicated that the largest decreases in orthostatic blood pressure were observed in the high dose LCIG group, **with the greatest decreases occurring during the first 4 hours for orthostatic SBP, and at later time points for DBP**, even on a stable dosage (Figure 16, Figure 17). A dose effect with slightly greater decreases in orthostatic blood pressure at higher dosages of LC-oral has been documented.

Figure 16 Orthostatic Systolic Blood Pressure Changes from Hour 0 on Day 1 and Stable Dosage (Active-Controlled Analysis Set)

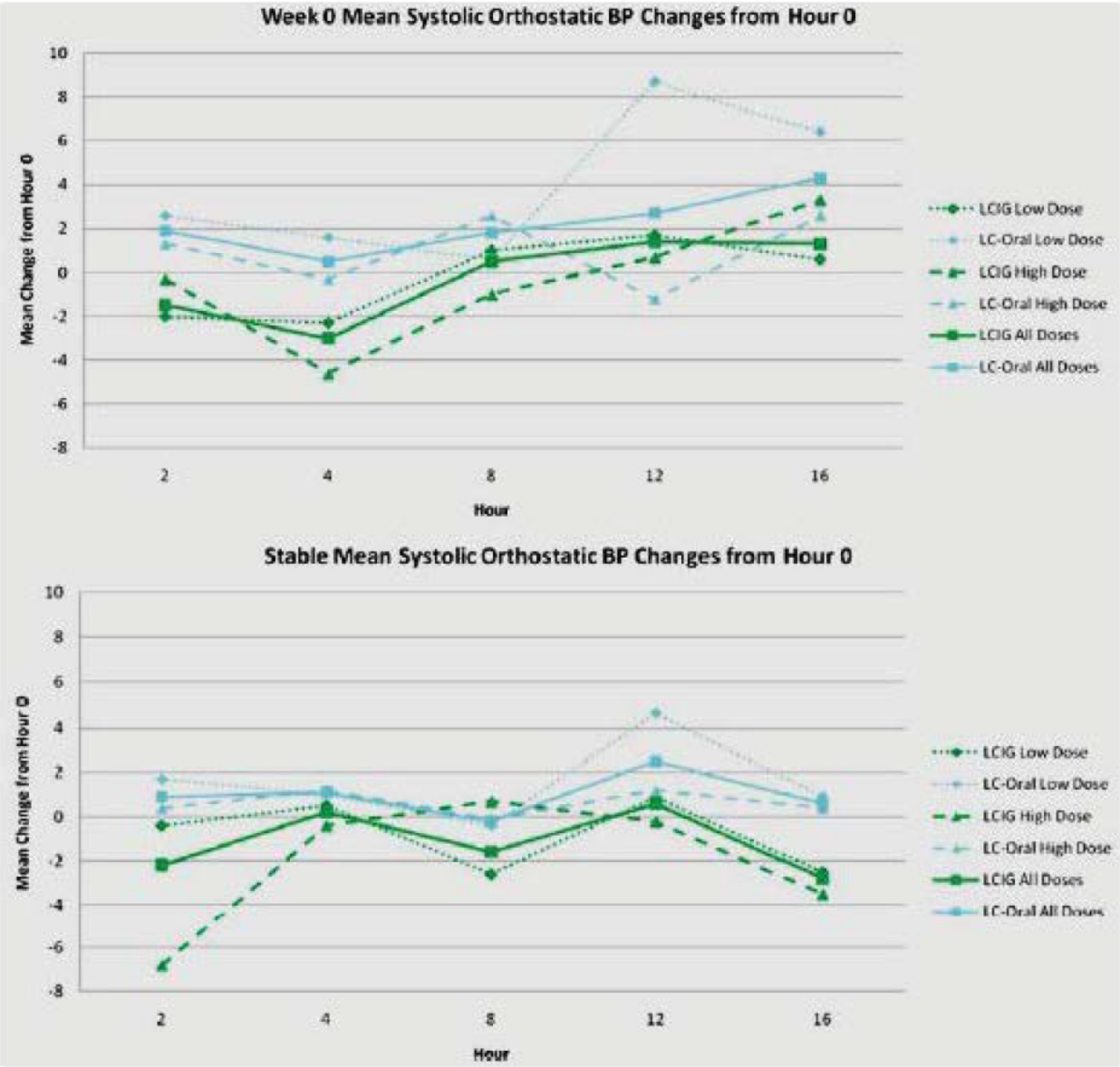
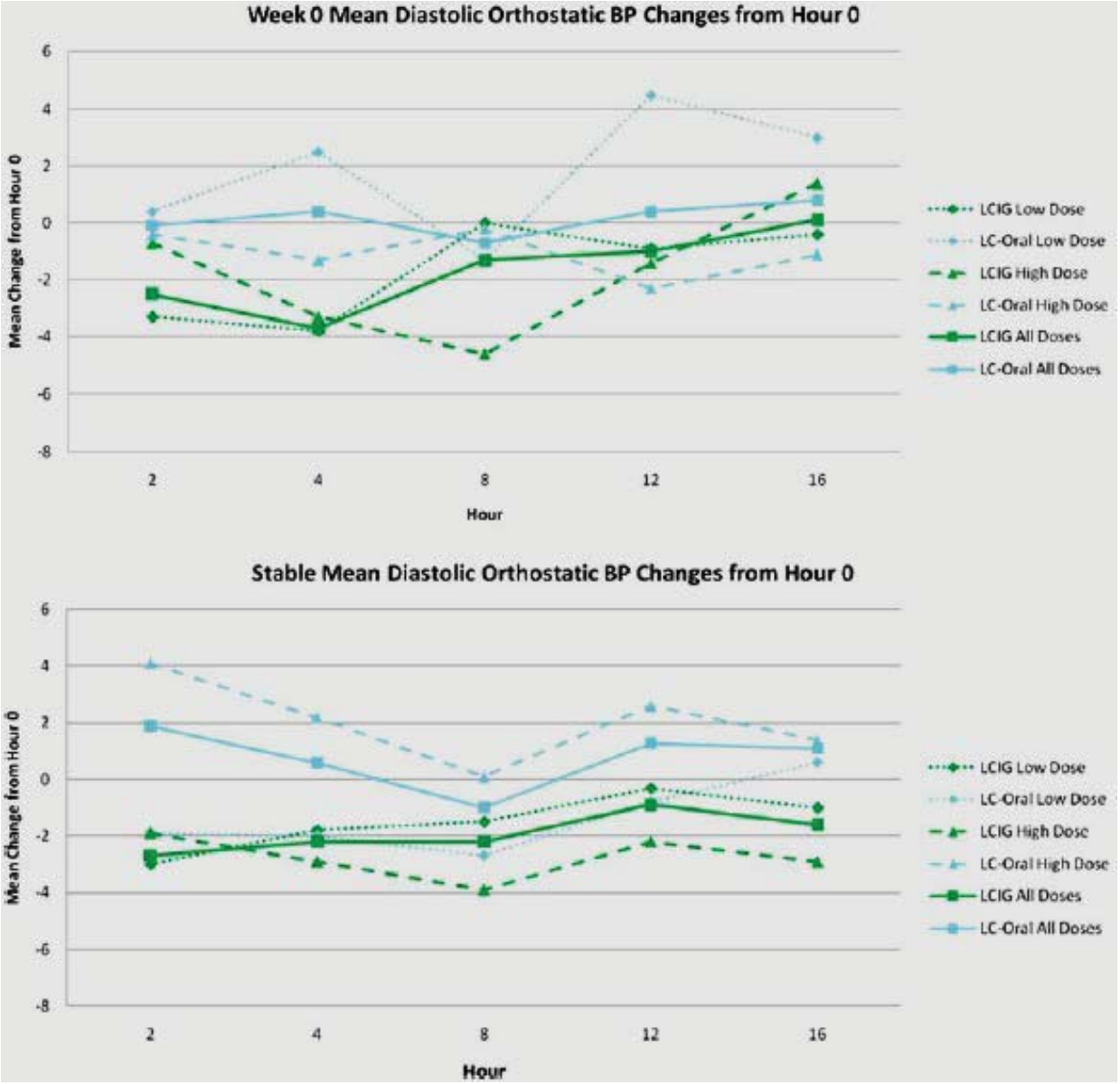


Figure 17 Orthostatic Diastolic Blood Pressure Changes from Hour 0 on Day 1 and Stable Dosage (Active-Controlled Analysis Set)



Reviewer Comments

- *The most striking observation in Figure 15 during ntensive orthostatic VS monitoring over 16 hours at the start of the trial is that LCIG (any dose) decreased the mean standing SBP by approximately 6 mm Hg (starting at 1 hour after start of LCIG infusion compared to mean oral LD/CD (any dose) standing SBP and this notable mean difference was sustained ranging from ~ 6-8 mm Hg throughout the rest of the monitoring up to 16 hours. As recognized by the sponsor, the greatest SBP decrease from*

baseline for both treatments occurred relatively early (e.g., 2-4 hours) after starting the infusion. Although the changes from baseline for mean orthostatic SBP for both treatments are relatively small over the 16 hour infusion period, it appears that the LCIG changes are slightly negative (representing decreases) toward the early part of the infusion and that this mean difference is apparent over the rest of the infusion but that mean difference between LCIG (vs oral LD/CD) becomes smaller at later time points over the 16 hours.

At week one, the pattern for standing SBP and orthostatic SBP is generally similar to that at day 0 (when the infusion was initiated) with the exception that from 8-16 hours mean results for standing SBP are essentially superimposed for both treatments.

At week 6 (when patients have entered the maintenance period after 4 week of treatment titration), the pattern for standing SBP and orthostatic SBP is relatively similar to that on day 0. Thus, it appears that these LCIG SBP changes persist with more prolonged treated and that there does not appear to be any pharmacodynamic tolerance to these VS changes.

- *Figure 16 is somewhat similar to Figure 15 and shows mean results for orthostatic SBP changes for LCIG and oral LD/CD over 16 hours infusion at week 0 (first dosing day) according to dose (i.e., any dose, low dose, high dose). The most striking observations in this figure are that the changes are greatest for all LCIG dose perspective and these changes are negative (i.e., decreases) and most evident between 2-4 hours after starting the infusion. In contrast, the mean changes for all dose perspectives of oral LD/CD are positive and relatively similar over the whole 16 hours. It is also quite noteworthy that the greatest changes for LCIG treatment occur in the high dose subgroup at 4-12 hours.*

- *Figure 17 is similar to Figure 16 and presents mean results for SBP when LCIG and oral LD/CD dosing is stable (week 6). The most striking observation in this figure is that the orthostatic decrease in SBP is greatest for the high dose LCIG and this difference occurs at 2 hours after starting the infusion.*

Outliers

The following tables present outlier analyses for VS conducted by this sponsor and also tables conducted by this reviewer based upon the sponsor's tables.

Reference ID: 3469235

Table 64 Vital Sign Variables for Which ≥ 1 Subject Met the Sponsor PCS Criteria at Any Visit (Active-Controlled and Open-Label LCIG Analysis Sets)

	n/N Subjects (%)								
	Active-Controlled Analysis Set N = 71						Open-Label LCIG Analysis Set N = 412		
	LCIG			LC-Oral					
Vital Sign Variable/ PCS Criterion	Low Dose N = 27	High Dose N = 10	All N = 37	Low Dose N = 15	High Dose N = 19	All N = 34	Low Dose N = 155	High Dose N = 257	All N = 412
Orthostatic BP									
DBP ≥ 20 mmHg decrease	21/27 (77.8)	5/10 (50.0)	26/37 (70.3)	9/15 (60.0)	12/19 (63.2)	21/34 (61.8)	24/154 (15.6)	54/257 (21.0)	78/411 (19.0)
SBP ≥ 30 mmHg decrease	20/27 (74.1)	7/10 (70.0)	27/37 (73.0)	10/15 (66.7)	13/19 (68.4)	23/34 (67.6)	34/154 (22.1)	75/257 (29.2)	109/411 (26.5)
DBP – Low, ≤ 50 mmHg and > 30 mmHg decrease									
Standing	10/27 (37.0)	2/10 (20.0)	12/37 (32.4)	7/15 (46.7)	8/19 (42.1)	15/34 (44.1)	3/154 (1.9)	14/257 (5.4)	17/411 (4.1)
Supine	5/27 (18.5)	1/10 (10.0)	6/37 (16.2)	3/15 (20.0)	4/19 (21.1)	7/34 (20.6)	1/154 (0.6)	13/257 (5.1)	14/411 (3.4)
DBP – High, ≥ 105 mmHg and > 30 mmHg increase									
Standing	3/27 (11.1)	0/10	3/37 (8.1)	0/15	0/19	0/34	4/154 (2.6)	8/257 (3.1)	12/411 (2.9)
Supine	1/27 (3.7)	1/10 (10.0)	2/37 (5.4)	2/15 (13.3)	0/19	2/34 (5.9)	1/154 (0.6)	6/257 (2.3)	7/411 (1.7)
SBP – Low, ≤ 90 mmHg and > 30 mmHg decrease									
Standing	9/27 (33.3)	5/10 (50.0)	14/37 (37.8)	9/15 (60.0)	9/19 (47.4)	18/34 (52.9)	14/154 (9.1)	38/257 (14.8)	52/411 (12.7)
Supine	9/27 (33.3)	2/10 (20.0)	11/37 (29.7)	4/15 (26.7)	6/19 (31.6)	10/34 (29.4)	7/154 (4.5)	14/257 (5.4)	21/411 (5.1)
SBP – High, ≥ 180 mmHg and > 40 mmHg increase									
Standing	5/27 (18.5)	0/10	5/37 (13.5)	2/15 (13.3)	3/19 (15.8)	5/34 (14.7)	2/154 (1.3)	0/257	2/411 (0.5)
Supine	5/27 (18.5)	1/10 (10.0)	6/37 (16.2)	2/15 (13.3)	2/19 (10.5)	4/34 (11.8)	4/154 (2.6)	3/257 (1.2)	7/411 (1.7)
Pulse – High, ≥ 120 bpm and > 30 bpm increase									
Standing	1/27 (3.7)	1/10 (10.0)	2/37 (5.4)	0/15	0/19	0/34	0/153	1/257 (0.4)	1/410 (0.2)
Supine	1/27 (3.7)	1/10 (10.0)	2/37 (5.4)	0/15	2/19 (10.5)	2/34 (5.9)	0/153	0/257	0/410
Pulse – Low, ≤ 50 bpm and > 30 bpm decrease									
Standing	0/27	1/10 (10.0)	1/37 (2.7)	0/15	1/19 (5.3)	1/34 (2.9)	0/153	0/257	0/410
Supine	0/27	0/10	0/37	0/15	0/19	0/34	0/153	2/257 (0.8)	2/410 (0.5)
Weight, kg									
≥ 7% increase	0/24	1/10 (10.0)	1/34 (2.9)	0/12	0/19	0/31	23/122 (18.9)	31/228 (13.6)	54/350 (15.4)
≥ 7% decrease	3/24 (12.5)	1/10 (10.0)	4/34 (11.8)	3/12 (25.0)	4/19 (21.1)	7/31 (22.6)	27/122 (22.1)	91/228 (39.9)	118/350 (33.7)
Temperature, ≥ 38.3 °C, ≥ 1.1 °C increase	0/25	0/10	0/35	0/14	0/19	0/33	1/151 (0.7)	1/257 (0.4)	2/408 (0.5)

DBP = diastolic blood pressure; LCIG = levodopa-carbidopa intestinal gel; PCS = potentially clinically significant; SBP = systolic blood pressure

n/N = number of subjects with PCS value/number of subjects with post-Baseline values for the respective parameter

Notes: Low dose: mean total daily levodopa dose < 1250 mg during the treatment period.
High dose: mean total daily levodopa dose ≥ 1250 mg during the treatment period.

Cross reference: Table 2.1__4.2.1.1, Tables 2.3__4.2.1.1 through 2.3__4.2.1.3

Table 65 Vital Sign Variables for Which ≥ 1 Subject Met the Sponsor PCS Criteria by Treatment Period (Active-Controlled Analysis Set)

	n/N Subjects (%)							
	Titration Period		Maintenance Period		Persistent		Any Time	
	LCIG N = 37	LC-oral N = 34	LCIG N = 35	LC-oral N = 31	LCIG N = 37	LC-oral N = 34	LCIG N = 37	LC-oral N = 34
Orthostatic BP								
DBP ≥ 20 mmHg decrease	19/37 (51.4)	16/34 (47.1)	20/35 (57.1)	14/31 (45.2)	0/35	0/31	26/37 (70.3)	21/34 (61.8)
Low dose	17/27 (63.0)	7/15 (46.7)	16/25 (64.0)	7/12 (58.3)	0/25	0/12	21/27 (77.8)	9/15 (60.0)
High dose	2/10 (20.0)	9/19 (47.4)	4/10 (40.0)	7/19 (36.8)	0/10	0/19	5/10 (50.0)	12/19 (63.2)
SBP ≥ 30 mmHg decrease	22/37 (59.5)	18/34 (52.9)	20/35 (57.1)	19/31 (61.3)	3/35 (8.6)	0/31	27/37 (73.0)	23/34 (67.6)
Low dose	17/27 (63.0)	7/15 (46.7)	15/25 (60.0)	8/12 (66.7)	3/25 (12.0)	0/12	20/27 (74.1)	10/15 (66.7)
High dose	5/10 (50.0)	11/19 (57.9)	5/10 (50.0)	11/19 (57.9)	0/10	0/19	7/10 (70.0)	13/19 (68.4)
DBP – Low, ≤ 50 mmHg and > 30 mmHg decrease								
Standing	9/37 (24.3)	9/34 (26.5)	6/35 (17.1)	6/31 (19.4)	0/35	0/31	12/37 (32.4)	15/34 (44.1)
Low dose	8/27 (29.6)	5/15 (33.3)	5/25 (20.0)	2/12 (16.7)	0/25	0/12	10/27 (37.0)	7/15 (46.7)
High dose	1/10 (10.0)	4/19 (21.1)	1/10 (10.0)	4/19 (21.1)	0/10	0/19	2/10 (20.0)	8/19 (42.1)
Supine	1/37 (2.7)	5/34 (14.7)	5/35 (14.3)	2/31 (6.5)	0/35	0/31	6/37 (16.2)	7/34 (20.6)
Low dose	1/27 (3.7)	3/15 (20.0)	4/25 (16.0)	0/12	0/25	0/12	5/27 (18.5)	3/15 (20.0)
High dose	0/10	2/19 (10.5)	1/10 (10.0)	2/19 (10.5)	0/10	0/19	1/10 (10.0)	4/19 (21.1)
SBP – High, ≥ 180 mmHg and > 40 mmHg increase								
Standing	3/37 (8.1)	4/34 (11.8)	3/35 (8.6)	3/31 (9.7)	0/35	0/31	5/37 (13.5)	5/34 (14.7)
Low dose	3/27 (11.1)	2/15 (13.3)	3/25 (12.0)	2/12 (16.7)	0/25	0/12	5/27 (18.5)	2/15 (13.3)
High dose	0/10	2/19 (10.5)	0/10	1/19 (5.3)	0/10	0/19	0/10	3/19 (15.8)
Supine	4/37 (10.8)	4/34 (11.8)	5/35 (14.3)	2/31 (6.5)	0/35	0/31	6/37 (16.2)	4/34 (11.8)
Low dose	3/27 (11.1)	2/15 (13.3)	5/25 (20.0)	2/12 (16.7)	0/25	0/12	5/27 (18.5)	2/15 (13.3)
High dose	1/10 (10.0)	2/19 (10.5)	0/10	0/19	0/10	0/19	1/10 (10.0)	2/19 (10.5)
Pulse – High, ≥ 120 bpm and > 30 bpm increase								
Standing	1/37 (2.7)	0/34	1/35 (2.9)	0/31	0/35	0/31	2/37 (5.4)	0/34
Low dose	0/27	0/15	1/25 (4.0)	0/12	0/25	0/12	1/27 (3.7)	0/15
High dose	1/10 (10.0)	0/19	0/10	0/19	0/10	0/19	1/10 (10.0)	0/19
Supine	1/37 (2.7)	2/34 (5.9)	1/35 (2.9)	0/31	0/35	0/31	2/37 (5.4)	2/34 (5.9)
Low dose	0/27	0/15	1/25 (4.0)	0/12	0/25	0/12	1/27 (3.7)	0/15
High dose	1/10 (10.0)	2/19 (10.5)	0/10	0/19	0/10	0/19	1/10 (10.0)	2/19 (10.5)
DBP – High, ≥ 105 mmHg and > 30 mmHg increase								
Standing	2/37 (5.4)	0/34	1/35 (2.9)	0/31	0/35	0/31	3/37 (8.1)	0/34
Low dose	2/27 (7.4)	0/15	1/25 (4.0)	0/12	0/25	0/12	3/27 (11.1)	0/15
High dose	0/10	0/19	0/10	0/19	0/10	0/19	0/10	0/19
Supine	0/37	1/34 (2.9)	2/35 (5.7)	2/31 (6.5)	0/35	0/31	2/37 (5.4)	2/34 (5.9)
Low dose	0/27	1/15 (6.7)	1/25 (4.0)	2/12 (16.7)	0/25	0/12	1/27 (3.7)	2/15 (13.3)
High dose	0/10	0/19	1/10 (10.0)	0/19	0/10	0/19	1/10 (10.0)	0/19
SBP – Low, ≤ 90 mmHg and > 30 mmHg decrease								
Standing	13/37 (35.1)	14/34 (41.2)	10/35 (28.6)	13/31 (41.9)	0/35	0/31	14/37 (37.8)	18/34 (52.9)
Low dose	9/27 (33.3)	8/15 (53.3)	7/25 (28.0)	5/12 (41.7)	0/25	0/12	9/27 (33.3)	9/15 (60.0)
High dose	4/10 (40.0)	6/19 (31.6)	3/10 (30.0)	8/19 (42.1)	0/10	0/19	5/10 (50.0)	9/19 (47.4)
Supine	5/37 (13.5)	7/34 (20.6)	8/35 (22.9)	6/31 (19.4)	0/35	0/31	11/37 (29.7)	10/34 (29.4)
Low dose	4/27 (14.8)	3/15 (20.0)	7/25 (28.0)	2/12 (16.7)	0/25	0/12	9/27 (33.3)	4/15 (26.7)
High dose	1/10 (10.0)	4/19 (21.1)	1/10 (10.0)	4/19 (21.1)	0/10	0/19	2/10 (20.0)	6/19 (31.6)

Table 65 Vital Sign Variables for Which ≥ 1 Subject Met the Sponsor PCS Criteria by Treatment Period (Active-Controlled Analysis Set) (Continued)

	n/N Subjects (%)							
	Titration Period		Maintenance Period		Persistent		Any Time	
	LCIG N = 37	LC-oral N = 34	LCIG N = 35	LC-oral N = 31	LCIG N = 37	LC-oral N = 34	LCIG N = 37	LC-oral N = 34
Pulse – Low, ≤ 50 bpm and > 30 bpm decrease								
Standing	0/37	1/34 (2.9)	1/35 (2.9)	1/31 (3.2)	0/35	0/31	1/37 (2.7)	1/34 (2.9)
Low dose	0/27	0/15	0/25	0/12	0/25	0/12	0/27	0/15
High dose	0/10	1/19 (5.3)	1/10 (10.0)	1/19 (5.3)	0/10	0/19	1/10 (10.0)	1/19 (5.3)
Supine	0/37	0/34	0/35	0/31	0/35	0/31	0/37	0/34
Low dose	0/27	0/15	0/25	0/12	0/25	0/12	0/27	0/15
High dose	0/10	0/19	0/10	0/19	0/10	0/19	0/10	0/19
Weight, kg								
≥ 7% increase	0/2	0/3	1/34 (2.9)	0/30	0/2	0/2	1/34 (2.9)	0/31
Low dose	0/2	0/1	0/24	0/11	0/2	0/0	0/24	0/12
High dose	0/0	0/2	1/10 (10.0)	0/19	0/0	0/2	1/10 (10.0)	0/19
≥ 7% decrease	1/2 (50.0)	0/3	3/34 (8.8)	7/30 (23.3)	0/2	0/2	4/34 (11.8)	7/31 (22.6)
Low dose	1/2 (50.0)	0/1	2/24 (8.3)	3/11 (27.3)	0/2	0/0	3/24 (12.5)	3/12 (25.0)
High dose	0/0	0/2	1/10 (10.0)	4/19 (21.1)	0/0	0/2	1/10 (10.0)	4/19 (21.1)
Temperature								
≥ 38.3 °C, ≥ 1.1 °C increase	0/33	0/26	0/34	0/31	0/32	0/24	0/35	0/33
Low dose	0/24	0/11	0/24	0/12	0/23	0/9	0/25	0/14
High dose	0/9	0/15	0/10	0/19	0/9	0/15	0/10	0/19

DBP = diastolic blood pressure; LCIG = levodopa-carbidopa intestinal gel; LC-oral = encapsulated levodopa-carbidopa immediate release tablets; PCS = potentially clinically significant; SBP = systolic blood pressure

n/N = number of subjects with PCS value/number of subjects with post-Baseline values for the respective parameter

Notes: Titration Period = onset during Days 1 through 28; Maintenance Period = onset ≥ Day 29; Persistent = event onset during Titration Period and continued into Maintenance Period with duration ≥ 7 days.

Low dose: mean total daily levodopa dose < 1250 mg during the treatment period.

High dose: mean total daily levodopa dose ≥ 1250 mg during the treatment period.

Cross reference: Table 2.1__4.2.1.1

Table 66 Treatment Difference (LCIG % - Oral LD/CD %) of At Least 5 % (≥ 5 %) for Vital Sign Outliers According to Position and Time Perspective

VS Outlier Change from Baseline by Position	Any Visit In Whole Trial	Final Visit in Whole Trial	Any Visit in Titration Period	Final Visit in Titration Period	Any Visit in Mainten-ance Period	Final Visit in Mainten-ance Period	Persistent from Titration Period into Mainten-ance Period
Systolic Blood Pressure-SBP							
Standing Increase ≥ 20 mm Hg		6 %	10 %				
Orthostatic Increase ≥ 20 mm Hg		7 %					
Orthostatic Increase ≥ 40 mm Hg					7 %		
Orthostatic Decrease ≥ 20 mm Hg			5 %	16 %			
Diastolic Blood Pressure-DBP							
Supine Increase ≥ 10 mm Hg				7 %			
Supine Increase ≥ 20 mm Hg	6 %		8 %	5 %			
Standing Increase ≥ 10 mm Hg	8 %						
Orthostatic Increase ≥ 10 mm Hg				10 %			
Orthostatic Increase ≥ 20 mm Hg				5 %			
Orthostatic Decrease ≥ 10 mm Hg				6 %			8 %
Orthostatic Decrease ≥ 20 mm Hg				5 %			
Pulse							
Supine Increase ≥ 15 BPM			5 %				7 %
Supine Increase ≥ 30 BPM	14 %						
Standing Increase ≥ 15 BPM				11 %			

Reviewer Comments

- *Table 64 shows results of a sponsor outlier analyses when any patient met the sponsor's potentially clinical significant (i.e., markedly abnormal) threshold at any visit in the controlled trial and also in the open-label trials. Data in this table are not selected upon necessarily showing that the incidence for LCIG treatment was greater than the incidence in the control group (oral LD/CD). Considering results where there is treatment difference for LCIG (i.e., LCIG % - oral LD/CD %), there is a greater incidence for orthostatic DBP decrease of ≥ 20 mm Hg, orthostatic SBP decrease of ≥ 20 mm Hg, high standing DBP (≥ 105 mm Hg and ≥ 30 mm Hg increase), high supine SBP (≥ 180 mm Hg and ≥ 40 mm Hg increase), and high pulse (≥ 120 BPM and > 30 BPM increase), There is no dose-dependent effect of LCIG for these outliers. The incidence of these specific outliers that were increased for LCIG in the controlled trial was less in the open-label trials. These results further support the impression that LCIG treatment can be associated with significant effects (decreases or increase sin BP) on SBP, DBP, and also on pulse.*

- *Table 65 shows VS outlier abnormalities as per the sponsor's potentially clinically according to treatment, dose perspective, and various time perspectives in the controlled trial. The noteworthy findings are related to an increased incidence of LCIG % (vs oral LD/CD) of at least 5 %from a specific time perspective. Because outlier results for any time have been reported, I will focus on presenting noteworthy outliers for the other time perspectives. In the titration period, the noteworthy outliers where LCIG % is greater than oral LD/CD % are orthostatic DBP decrease of ≥ 20 mm Hg for low dose,, orthostatic SBP decrease of ≥ 30 mm Hg for any dose, and high standing DBP (≤ 50 mm Hg and ≥ 30 mm Hg decrease) for any dose and low dose.*

  For the maintenance period, outliers more frequent for LCIG than for oral LD/CD were orthostatic DBP decrease of ≥ 20 mm Hg for any dose and low dose, low supine DBP (≥ 105 mm Hg and ≥ 30 mm Hg increase) for any dose and low dose, high supine SBP (≥ 180 mm Hg and ≥ 40 mm Hg increase) for any dose, and low supine SBP (≤ 90 mm Hg and ≥ 30 mm Hg decrease).

  There were no noteworthy outliers from the "persistent" time perspective.

- *Table 66 shows results of outliers (based upon DNP recommendations) according to treatment (any dose), and time perspective in the controlled trial Outliers were presented in this table only when the treatment difference (LCIG % -oral LD/CD %) was ≥ 5 %. The largest number of outliers for SBP, DBP, and pulse occurred at the final visit in the titration period (e.g. typically at the end of week 4). Outliers represented both increase and decreases in VS and different positional perspectives. The largest LCIG treatment differences (≥ 10 %) were orthostatic SBP decrease of ≥ 20 mm Hg, orthostatic DBP increase of ≥ 10 mm Hg, standing pulse increase of ≥ 15 BPM at the final visit in the*

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titration period, standing SBP increase of ≥ 20 mm Hg at any visit in the titration period, and supine pulse increase of ≥ 30 BPM.

- *Altogether, all these analyses depicted in these figures and tables support the importance of the increased risk for these various VS changes associated with LCIG treatment and should be described in the label. Although a greater risk for VS changes may occur in the titration period, notable VS changes can also occur later after achieving a stable dose in a maintenance phase of LCIG treatment.*

7.4.4 Electrocardiograms (ECGs)

Some outlier analyses will be presented. Central tendency analyses (e.g., ECG parameter changes from baseline) did not show substantive changes and were not considered to be very informative for presentation. Results from only the controlled trial will be presented because results from the open-label trials were not noteworthy.

Active Controlled Trial

The following table presents outlier results for ECG parameters when at least one patient met the potentially clinical significant outlier criterion in the active-controlled trial and the open-label trials.

Table 67 ECG Variables for Which ≥ 1 Subject Met the PCS Criteria (Active-Controlled and Open-Label LCIG Analysis Sets)

	Analysis Sets								
	Active-Controlled N = 71						Open-Label LCIG N = 412		
	LCIG			LC-Oral					
Vital Sign Variable/PCS Criterion	Low Dose n/N Subjects (%) N = 27	High Dose n/N Subjects (%) N = 10	All n/N Subjects (%) N = 37	Low Dose n/N Subjects (%) N = 15	High Dose n/N Subjects (%) N = 19	All n/N Subjects (%) N = 34	Low Dose n/N Subjects (%) N = 155	High Dose n/N Subjects (%) N = 257	All n/N Subjects (%) N = 412
QTcB									
≥ 450 msec	3/25 (12.0)	1/10 (10.0)	4/35 (11.4)	1/12 (8.3)	0/18	1/30 (3.3)	38/144 (26.4)	58/251 (23.1)	96/395 (24.3)
≥ 480 msec	1/25 (4.0)	0/10	1/35 (2.9)	0/12	0/18	0/30	5/144 (3.5)	14/251 (5.6)	19/395 (4.8)
≥ 500 msec	1/25 (4.0)	0/10	1/35 (2.9)	0/12	0/18	0/30	3/144 (2.1)	3/251 (1.2)	6/395 (1.5)
≥ 30 msec increase	1/25 (4.0)	0/10	1/35 (2.9)	2/12 (16.7)	1/18 (5.6)	3/30 (10.0)	23/144 (16.0)	55/251 (21.9)	78/395 (19.7)
≥ 60 msec increase	0/25	0/10	0/35	0/12	0/18	0/30	3/144 (2.1)	2/251 (0.8)	5/395 (1.3)
QTcF									
≥ 450 msec	2/25 (8.0)	0/10	2/35 (5.7)	0/12	0/18	0/30	24/144 (16.7)	31/251 (12.4)	55/395 (13.9)
≥ 480 msec	1/25 (4.0)	0/10	1/35 (2.9)	0/12	0/18	0/30	3/144 (2.1)	5/251 (2.0)	8/395 (2.0)
≥ 500 msec	0/25	0/10	0/35	0/12	0/18	0/30	1/144 (0.7)	0/251	1/395 (0.3)
≥ 30 msec increase	1/25 (4.0)	0/10	1/35 (2.9)	0/12	0/18	0/30	21/144 (14.6)	47/251 (18.7)	68/395 (17.2)
≥ 60 msec increase	0/25	0/10	0/35	0/12	0/18	0/30	2/144 (1.4)	2/251 (0.8)	4/395 (1.0)
PR Interval									
≤ 120 msec	1/25 (4.0)	0/10	1/35 (2.9)	0/12	0/18	0/30	8/148 (5.4)	3/251 (1.2)	11/399 (2.8)
≥ 220 msec	0/25	0/10	0/35	0/12	0/18	0/30	10/148 (6.8)	19/251 (7.6)	29/399 (7.3)
Heart Rate									
≤ 50 bpm and > 30 bpm decrease from Baseline	0/25	0/10	0/35	0/12	0/18	0/30	0/148	1/252 (0.4)	1/400 (0.3)
≥ 120 bpm and > 30 bpm increase from Baseline	0/25	0/10	0/35	0/12	0/18	0/30	1/148 (0.7)	0/252	1/400 (0.3)

Reviewer Comments

Markedly abnormal ECG parameter outlier results presented in Table 67 do not suggest any reason for concern. In the controlled trial, the only result in which there are 2 or more patient outliers and the incidence of outliers for LCIG (any dose) is greater than that for oral LD?CD is for QTcB ≥ 450 msecs. There is not an increased incidence of outliers for LCIG treatment for important issues (e.g., QTc ≥ 30 or 60 msecs increase or > 500 msecs) in more than a single LCIG patient.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose-dependency of adverse events was addressed in the earlier various analyses of adverse events particularly in section 7.4.1 (Common Adverse Events) for the controlled trial and open-label trials.

7.5.2 Time Dependency for Adverse Events

Time-dependency of adverse events was addressed in the earlier various analyses of adverse events particularly in section 7.4.1 (Common Adverse Events) for the controlled trial and open-label trials. Time-dependency was considered from the perspective of having a TEAE onset at any time in the trial, onset in the titration period, onset in the maintenance period, and onset in the titration period and persisting into the maintenance period and having a total duration of at least 7 days.

7.5.3 Drug-Demographic Interactions

Intrinsic Factors
The following intrinsic factors were evaluated in the subgroup analyses:
● Gender (male, female),
● Age (< 65 years; ≥ 65 years),
● Race (white and other for Active-Controlled Analysis Set; white, Asian, and other for the Open-Label LCIG and All PEG-J Analysis Sets),
● Baseline BMI (< 25 kg/m2; ≥ 25 kg/m2).

The sponsor evaluated subgroup analyses for all TEAEs, TESAEs, TEAEs leading to study discontinuation, AESIs , other AE categories evaluated, clinical laboratory evaluations, vital signs, and core ECG variables. No consistent clinically meaningful trends were observed in the subgroup analyses by dopamine use.

No clinically important trends emerged in the evaluation of duration of Parkinson's disease (< 10 years; ≥ 10 years).

The sponsor concluded that no clinically important trends emerged in the evaluation of intrinsic factors that would affect the overall safety profile of LCIG. Nevertheless, the sponsor noted that SAE of fall was more common (≥ 2-fold) in subjects who were ≥ 65 (1.4% [3/211]) versus < 65 years of age (0.5% [1/201]), in subjects with a BMI < 25 kg/m2 (1.3% [3/229]) versus ≥ 25 kg/m2 (0.6% [1/178]), and in subjects with Parkinson's disease for ≥ 10 years (1.2% [3/253]) versus < 10 years (0.6% [1/159]). Hip fractures were also more common in subjects who were ≥ 65 (4.3% [9/211]) versus < 65 years of age (0% [0/201]) and in subjects with a BMI < 25 kg/m2 (3.1% [7/229]) versus ≥ 25 kg/m2 (1.1% [2/178]).

Regional Subgroup Analyses

Reference ID: 3469235

The sponsor also conducted subgroup analyses according to geographic region of patients in a trial. The sponsor noted that results of analyses by country/region revealed a higher incidence in North America versus other regions; however, this trend was not observed for SAEs and discontinuations due to AEs.

The categorization of countries for the subgroup analyses by region are shown below, followed by a summary of results :

● For the Active-Controlled Analysis Set
○ United States (US): N = 52
○ Ex-US: Germany and New Zealand; N = 19

● For the Open-Label LCIG and All PEG-J Analysis Sets, the countries were grouped into the following regions:
○ North America (NA): Canada and the US
● N = 143 for Open-Label LCIG Analysis Set
● N = 142 for PEG-J Analysis Set
○ Israel, Oceania Countries, and Western Europe (IOE): Israel, Australia, New Zealand, Germany, Finland, Italy, Netherlands, Portugal, Spain, and the United Kingdom
● N = 173 for Open-Label LCIG Analysis Set
● N = 166 for PEG-J Analysis Set
○ Asia and Central Europe (ACE): Thailand, Czech Republic, Poland, and Russia
● N = 96 for Open-Label LCIG Analysis Set
● N = 87 for PEG-J Analysis Set

The following tables illustrate the incidence of TEAEs and some TESAEs from the open-label trial experience presented in the ISS and also in the 4 Month Safety Update. Regional results from the active-controlled trial are not presented because most patients in that trial were from the U.S. and there were relatively few patients (N=19) from outside the U.S.

Reference ID: 3469235

Table 68 TEAEs Reported by ≥ 5% of All Subjects and ≥ 2-fold Higher in North America Versus IOE and/or ACE Any Time (Open-Label LCIG Analysis Set)

	Number (%) of Subjects					
	NA N = 143		IOE N = 173		ACE N = 96	
Preferred Term	ISS	SU	ISS	SU	ISS	SU
PTs ≥ 2-fold higher in North America versus both IOE and ACE						
Abdominal pain	62 (43.4)	64 (44.8)	37 (21.4)	38 (22.0)	9 (9.4)	11 (11.5)
Incision site erythema	42 (29.4)	49 (34.3)	20 (11.6)	21 (12.1)	3 (3.1)	7 (7.3)
Constipation	42 (29.4)	46 (32.2)	17 (9.8)	19 (11.0)	10 (10.4)	11 (11.5)
Nausea	40 (28.0)	45 (31.5)	24 (13.9)	25 (14.5)	13 (13.5)	13 (13.5)
Parkinson's disease	27 (18.9)	33 (23.1)	16 (9.2)	18 (10.4)	4 (4.2)	4 (4.2)
Anxiety	26 (18.2)	33 (23.1)	17 (9.8)	19 (11.0)	6 (6.3)	7 (7.3)
Dyskinesia	25 (17.5)	33 (23.1)	14 (8.1)	15 (8.7)	3 (3.1)	3 (3.1)
Post procedural discharge	27 (18.9)	29 (20.3)	6 (3.5)	6 (3.5)	5 (5.2)	6 (6.3)
Diarrhoea	23 (16.1)	24 (16.8)	11 (6.4)	11 (6.4)	2 (2.1)	2 (2.1)
Oropharyngeal pain	22 (15.4)	23 (16.1)	3 (1.7)	3 (1.7)	1 (1.0)	1 (1.0)
Blood homocysteine increased	17 (11.9)	24 (16.8)	12 (6.9)	14 (8.1)	4 (4.2)	7 (7.3)
Decreased appetite	16 (11.2)	19 (13.3)	5 (2.9)	5 (2.9)	2 (2.1)	2 (2.1)
Dizziness	16 (11.2)	19 (13.3)	5 (2.9)	6 (3.5)	0	1 (1.0)
Arthralgia	15 (10.5)	21 (14.7)	5 (2.9)	7 (4.0)	4 (4.2)	4 (4.2)
Musculoskeletal pain	14 (9.8)	15 (10.5)	7 (4.0)	9 (5.2)	1 (1.0)	1 (1.0)
Abdominal distension	14 (9.8)	15 (10.5)	1 (0.6)	1 (0.6)	3 (3.1)	3 (3.1)
Fatigue	13 (9.1)	14 (9.8)	6 (3.5)	7 (4.0)	0	1 (1.0)
Pneumoperitoneum	14 (9.8)	14 (9.8)	4 (2.3)	4 (2.3)	1 (1.0)	1 (1.0)
Incision site pain	14 (9.8)	14 (9.8)	7 (4.0)	7 (4.0)	0	0
Dystonia	9 (6.3)	13 (9.1)	5 (2.9)	5 (2.9)	2 (2.1)	2 (2.1)
Muscle spasms	8 (5.6)	13 (9.1)	4 (2.3)	5 (2.9)	1 (1.0)	1 (1.0)
Neck pain	11 (7.7)	13 (9.1)	3 (1.7)	4 (2.3)	0	0
Upper respiratory tract infection	10 (7.0)	13 (9.1)	2 (1.2)	4 (2.3)	1 (1.0)	1 (1.0)
Dysphagia	5 (3.5)	12 (8.4)	4 (2.3)	5 (2.9)	1 (1.0)	1 (1.0)
Freezing phenomenon	9 (6.3)	12 (8.4)	0	0	1 (1.0)	1 (1.0)
Excoriation	8 (5.6)	11 (7.7)	2 (1.2)	2 (1.2)	1 (1.0)	1 (1.0)

Table 68 TEAEs Reported by ≥ 5% of All Subjects and ≥ 2-fold Higher in North America Versus IOE and/or ACE Any Time (Open-Label LCIG Analysis Set) (Continued)

	Number (%) of Subjects					
	NA N = 143		IOE N = 173		ACE N = 96	
Preferred Term	ISS	SU	ISS	SU	ISS	SU
PTs ≥ 2-fold higher in North America versus both IOE and ACE (continued)						
Contusion	6 (4.2)	10 (7.0)	5 (2.9)	5 (2.9)	1 (1.0)	1 (1.0)
Micturition urgency	6 (4.2)	10 (7.0)	0	0	0	0
Seborrhoeic keratosis	8 (5.6)	10 (7.0)	1 (0.6)	1 (0.6)	0	0
Cough	7 (4.9)	9 (6.3)	3 (1.7)	3 (1.7)	1 (1.0)	1 (1.0)
Dry mouth	9 (6.3)	9 (6.3)	0	0	0	0
Flatulence	9 (6.3)	9 (6.3)	0	0	3 (3.1)	3 (3.1)
Hypoaesthesia	6 (4.2)	9 (6.3)	1 (0.6)	1 (0.6)	2 (2.1)	2 (2.1)
Paraesthesia	7 (4.9)	9 (6.3)	3 (1.7)	4 (2.3)	1 (1.0)	1 (1.0)
Abdominal pain upper	7 (4.9)	8 (5.6)	1 (0.6)	1 (0.6)	1 (1.0)	1 (1.0)
Asthenia	8 (5.6)	8 (5.6)	0	0	0	1 (1.0)
Confusional state	7 (4.9)	8 (5.6)	2 (1.2)	3 (1.7)	0	0
Gastrointestinal stoma complication	7 (4.9)	8 (5.6)	1 (0.6)	1 (0.6)	2 (2.1)	2 (2.1)
Muscular weakness	7 (4.9)	8 (5.6)	0	0	0	1 (1.0)
Musculoskeletal stiffness	8 (5.6)	8 (5.6)	2 (1.2)	2 (1.2)	0	0
Nasopharyngitis	6 (4.2)	8 (5.6)	1 (0.6)	1 (0.6)	2 (2.1)	2 (2.1)
Joint swelling	6 (4.2)	8 (5.6)	1 (0.6)	1 (0.6)	0	0
PTs ≥ 2-fold higher in North America versus either IOE or ACE						
Complication of device insertion	66 (46.2)	69 (48.3)	49 (28.3)	50 (28.9)	17 (17.7)	18 (18.8)
Fall	36 (25.2)	46 (32.2)	36 (20.8)	38 (22.0)	2 (2.1)	2 (2.1)
Procedural pain	36 (25.2)	41 (28.7)	18 (10.4)	18 (10.4)	23 (24.0)	25 (26.0)
Urinary tract infection	27 (18.9)	34 (23.8)	25 (14.5)	26 (15.0)	3 (3.1)	5 (5.2)
Procedural site reaction	24 (16.8)	28 (19.6)	10 (5.8)	14 (8.1)	8 (8.3)	13 (13.5)
Depression	22 (15.4)	27 (18.9)	18 (10.4)	19 (11.0)	4 (4.2)	5 (5.2)
Orthostatic hypotension	20 (14.0)	23 (16.1)	14 (8.1)	16 (9.2)	3 (3.1)	3 (3.1)
Weight decreased	20 (14.0)	22 (15.4)	20 (11.6)	24 (13.9)	7 (7.3)	7 (7.3)
Vomiting	20 (14.0)	21 (14.7)	10 (5.8)	11 (6.4)	8 (8.3)	8 (8.3)

Table 68 TEAEs Reported by ≥ 5% of All Subjects and ≥ 2-fold Higher in North America Versus IOE and/or ACE Any Time (Open-Label LCIG Analysis Set) (Continued)

	Number (%) of Subjects					
	NA N = 143		IOE N = 173		ACE N = 96	
Preferred Term	ISS	SU	ISS	SU	ISS	SU
PTs ≥ 2-fold higher in North America versus either IOE or ACE (continued)						
Vitamin B6 decreased	13 (9.1)	19 (13.3)	22 (12.7)	25 (14.5)	2 (2.1)	6 (6.3)
Dyspepsia	15 (10.5)	16 (11.2)	13 (7.5)	15 (8.7)	1 (1.0)	1 (1.0)
Dyspnoea	10 (7.0)	12 (8.4)	8 (4.6)	8 (4.6)	0	0
Laceration	11 (7.7)	12 (8.4)	9 (5.2)	9 (5.2)	0	0
Polyneuropathy	4 (2.8)	10 (7.0)	12 (6.9)	12 (6.9)	1 (1.0)	2 (2.1)
Pain in extremity	8 (5.6)	9 (6.3)	13 (7.5)	14 (8.1)	3 (3.1)	3 (3.1)
Basal cell carcinoma	4 (2.8)	9 (6.3)	6 (3.5)	6 (3.5)	1 (1.0)	1 (1.0)
Oedema peripheral	4 (2.8)	9 (6.3)	5 (2.9)	5 (2.9)	2 (2.1)	3 (3.1)
Gastrooesophageal reflux disease	6 (4.2)	8 (5.6)	6 (3.5)	7 (4.0)	0	0
Abdominal discomfort	7 (4.9)	8 (5.6)	2 (1.2)	2 (1.2)	7 (7.3)	8 (8.3)

ACE = Asia (Thailand) and Central Europe (Czech Republic, Poland, and Russia); AESI = adverse event of special interest; IOE = Israel, Oceania Countries (Australia and New Zealand), and Western Europe (Germany, Finland, Italy, Netherlands, Portugal, Spain, and the United Kingdom); ISS = Integrated Summary of Safety;
LCIG = levodopa-carbidopa intestinal gel; LC-oral = encapsulated levodopa-carbidopa immediate release tablets;
NA = North America (US and Canada); PT = preferred term; SU = Safety Update

Cross reference: Safety Update Table 1__2.8.1.1.1, Table 21; ISS (R&D/12/077) Table 2.3__2.8.1.1.1

Table 69 TESAEs Reported by > 2 Subjects in a Region and ≥ 2-fold Difference Between North America Versus Other Regions Any Time (Open-Label LCIG Analysis Set)

	Number (%) of Subjects					
	NA N = 143		IOE N = 173		ACE N = 96	
Preferred Term	ISS	SU	ISS	SU	ISS	SU
PTs ≥ 2-fold higher in North America versus Other Regions						
Abdominal pain	11 (7.7)	13 (9.1)	2 (1.2)	2 (1.2)	1 (1.0)	1 (1.0)
Hip fracture	6 (4.2)	6 (4.2)	3 (1.7)	3 (1.7)	0	0
Pneumoperitoneum	5 (3.5)	5 (3.5)	3 (1.7)	3 (1.7)	0	0
Fall	2 (1.4)	4 (2.8)	2 (1.2)	2 (1.2)	0	0
Small intestinal obstruction	4 (2.8)	4 (2.8)	0	0	0	0
Asthenia	3 (2.1)	3 (2.1)	0	0	0	0
Pneumonia aspiration	2 (1.4)	3 (2.1)	1 (0.6)	3 (1.7)	0	0
Postoperative wound infection	3 (2.1)	3 (2.1)	1 (0.6)	1 (0.6)	2 (2.1)	2 (2.1)
Orthostatic hypotension	2 (1.4)	3 (2.1)	0	0	0	0
PTs ≥ 2-fold higher in Other Regions versus North America						
Depression	1 (0.7)	1 (0.7)	3 (1.7)	3 (1.7)	0	0
Polyneuropathy	1 (0.7)	1 (0.7)	7 (4.0)	7 (4.0)	1 (1.0)	1 (1.0)
Device dislocation	2 (1.4)	2 (1.4)	4 (2.3)	4 (2.3)	0	1 (1.0)
Weight decreased	1 (0.7)	2 (1.4)	4 (2.3)	6 (3.5)	1 (1.0)	1 (1.0)

ACE = Asia (Thailand) and Central Europe (Czech Republic, Poland, and Russia); AESI = adverse event of special interest; IOE = Israel, Oceania Countries (Australia and New Zealand), and Western Europe (Germany, Finland, Italy, Netherlands, Portugal, Spain, and the United Kingdom); ISS = Integrated Summary of Safety;
LCIG = levodopa-carbidopa intestinal gel; LC-oral = encapsulated levodopa-carbidopa immediate release tablets;
NA = North America (US and Canada); PT = preferred term; SU = Safety Update
Cross reference: Safety Update Table 1__2.8.1.2.1; ISS (R&D/12/077) Table 2.3__2.8.1.2.1

Reviewer Comments

- *Table 68 presents results for regional subgroup analyses of common TEAEs (≥ 5 % of all patients) in the open-label trial experience presented in the ISS and the 4Month Safety Update. Regional subgroup analyses of the active-controlled trial are not presented because most of the patients were in the U.S. and relatively few patients (N=19) from outside the U.S. were included in that trial. Many TEAEs (including several medically serious type of events) were much more frequent in North America compared to both the*

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IOE and ACE subgroups. The threshold for presenting these more frequent TEAEs in North America was that they were at least 2 fold higher than the incidence ***in both other regions****.*

The second part of the table also shows many TEAEs (several also medically serious) that were at least 2 fold higher than the incidence ***in either of the other 2 regions.***

It is also of interest that the incidence of TEAEs for several events in the IOE subgroup was notably more frequent than the incidence in the ACE subgroup. Several examples of this observation include complication of device insertion, abdominal pain, procedural pain, incision site erythema, dyskinesia, diarrhea, urinary tract infection, depression, orthostatic hypotension, and weight decreased.

- *Table 69 shows results of analyses of TESAEs that had at least a 2 fold higher incidence f than the incidence in both other regional subgroups or in either regional subgroup. The most striking differences for much more common TESAEs in North America are for abdominal pain, hip fracture, and pneumoperitoneum.*

- *These results are not that surprising because I had a suspicion that such results might be observed and we had recommended to the sponsor how to combine regional subgroups. My a priori hypothesis would have been that various TEAEs (primarily based upon subjective reporting) would be most frequent in patients from North America than both other regional subgroups. In addition, I would have hypothesized that the incidence of various TEAEs in the IOE subgroup was also greater than the incidence of various TEAEs in the ACE regional subgroup. My suspicion for these regional subgroup differences in TEAEs is based upon previous experience in which this phenomenon has been observed. Although I cannot state with certainty the reason for these regional subgroup differences in the incidence of TEAEs, I believe that it is more likely related to cultural differences/practices in collecting adverse event data than to intrinsic biological differences in the patient populations. If there had been significant numbers of patient studied in the active-controlled trial, I would have expected possibly seeing such regional subgroup differences in the incidence of TEAEs in North America vs outside of North America. I also would have expected the frequencies of TEAEs to be more common in each treatment group in patients from North America vs patients from outside of North America.*

7.5.4 Drug-Disease Interactions

The sponsor evaluated subgroup analyses for the effect of the duration of Parkinson's disease (< 10 years; ≥ 10 years). The sponsor conducted these subgroup analyses for all TEAEs, TESAEs, TEAEs leading to study discontinuation, AESIs , other AE categories evaluated, clinical laboratory evaluations, vital signs, and core ECG variables. No consistent clinically meaningful trends were observed in the subgroup analyses by dopamine use.

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No clinically important trends emerged in the evaluation of duration of Parkinson's disease (< 10 years; ≥ 10 years).

7.5.5 Drug-Drug Interactions

The effect of a drug-drug interaction was evaluated in subgroup analyses of dopamineric agonist usage (user; non-user). The sponsor conducted these subgroup analyses for all TEAEs, TESAEs, TEAEs leading to study discontinuation, AESIs , other AE categories evaluated, clinical laboratory evaluations, vital signs, and core ECG variables.

No consistent clinically meaningful trends were observed in the subgroup analyses by dopamine use.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Refer to review related to hydrazine/carcinogens/impurities and malignancies in 7.3.5 Submission Specific Primary Safety Concerns

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was no significant information provided regarding overdose or withdrawal and rebound.

The sponsor noted that no SMQ exists for impulse control disorder; however, many of the PTs relevant to this syndrome are located within the CMQ of abuse liability. A total of 27 subjects had TEAEs related to impulse control disorder, and the incidence was generally higher in the high dose group, as summarized in Table 70The TEAEs were all mild to moderate in severity., One subject (Subject 149-002) had an SAE of illicit substance abuse and 1 subject (Subject 435-014) discontinued study drug because of agitation. Both of these AEs were reported as recovered/resolved.

Reference ID: 3469235

Table 70 Summary of Adverse Events in the Abuse Liability CMQ Related to Impulse Control Disorder (Open-Label LCIG Analysis Set)

	Number (%) of Subjects		
Preferred Term	Low Dose LCIG N = 155	High Dose LCIG N = 257	Any Dose LCIG N = 412
Agitation	2 (1.3)	9 (3.5)	11 (2.7)
Compulsions	0	1 (0.4)	1 (0.2)
Compulsive shopping	0	2 (0.8)	2 (0.5)
Dopamine dysregulation syndrome	0	2 (0.8)	2 (0.5)
Impulse control disorder	0	2 (0.8)	2 (0.5)
Impulsive behaviour	0	5 (1.9)	5 (1.2)
Libido increased	0	1 (0.4)	1 (0.2)
Pathological gambling	2 (1.3)	0	2 (0.5)
Restlessness	0	2 (0.8)	2 (0.5)
Stereotypy	0	2 (0.8)	2 (0.5)
Substance abuse	0	1 (0.4)	1 (0.2)

Reviewer Comments

The sponsor believes that LCIG treatment is associated with an increased risk for impulsive behavior because it contains levodopa but does not believe that the risk for impulsive behavior related to levodopa use is distinctly different than that for oral levodopa tablets or dopaminergic agonists in general. Furthermore, the sponsor did not conclude that there is an abuse potential for LCIG treatment that is independent of a risk that may be linked to potential abuse to facilitate impulsive behavior. I concur with the sponsor's perspective on abuse liability.

7.7 Additional Submissions / Safety Issues

The sponsor submitted a 4 Month Safety Update (4MSU) as had been planned. Because no new patients were enrolled in any trials for LCIG treatment, the 4MSU provided additional safety information based upon increased treatment exposure related to patients who were continuing in open-label treatment subsequent to the data cut-off for the NDA submission.

The data cutoff dates for the Safety Update are at least a year after the data cutoff dates for the NDA, as shown in . The results presented in this Safety Update are cumulative through these data cutoff dates, unless otherwise noted.

Reference ID: 3469235

Table 71 Data Cutoff Dates for NDA and Safety Update

	Data Cutoff Date	
Data Source	NDA	Safety Update
Ongoing IND Studies	04 May 2012	31 May 2013
Non-IND Studies	30 September 2011	21 January 2013
Postmarketing Experience	31 May 2012	31 May 2013

In the Open-Label LCIG Analysis Set, the mean duration of LCIG exposure is 713.1 days (804.4 PY) compared with 512.2 days (577.8 PY) in the ISS. In the All LCIG Analysis Set, the mean duration of LCIG exposure is 713.6 days (812.7 PY) compared with 514.6 days (586.1 PY) in the ISS. Thus, the 4MSU provided additional information on the safety experience based upon approximately 227 additional patient-years of LCIG treatment. In the US registration program, 351 subjects have been exposed to LCIG for at least 6 months (180 days), including 338 subjects exposed for at least 1 year (365 days), 252 subjects for at least 1.5 years (18 months), 207 subjects for at least 2 years (24 months), and 153 subjects for at least 2.5 years (30 months). Consistent with the ISS, the mean duration of exposure and the total PY were greater in subjects on a high dose of LCIG (high dose group) compared with those on a low dose of LCIG (low dose group) in both the Open-Label LCIG Analysis Set (Table 72) and All LCIG Analysis Set. There were no changes in individual dose group assignments since the ISS. Because the differences in safety experience were related to additional open-;label treatment, the 4MSU focused on presenting results relative to the Open-Label LCIG Analysis Set.

A notetworthy difference between the ISS and 4MSU was that some additional dose-related information was presented in the 4MSU because some TEAE data were analyzed into 3 levodopa daily dose groups according to an average dose of < 1250 mg, 1250 mg- < 2000 mg, and ≥ 2000 mg, so that the "high dose" group (≥ 1250 mg) presented in the ISS was further subdivided into two additional groups (≥ 1250 - < 2000 mg, and ≥ 2000 mg).

The sponsor concluded that the additional data analyzed for the 4MSU Update did not differ substantially with safety results presented in the ISS and noted that the additional safety data furthered confirms that the benefits of LCIG outweigh the risks associated with its use.

Reviewer Comments

I concur with the sponsor's conclusion that the additional safety information/results presented in the 4MSU did not substantially differ from safety information/results presented in the ISS.

Table 72 Duration of LCIG Exposure (Open-Label LCIG Analysis Set)

	Low Dose		High Dose				Any Dose	
				Safety Update				
Duration Interval[a]	ISS N = 155	Safety Update N = 155	ISS N = 257	Any High Dose N = 257	≥ 1250 – 2000 mg/day N = 185	≥ 2000 mg/day N = 72	ISS N = 412	Safety Update N = 412
By Number of Days[b], n (%)								
1 to 14	24 (15.5)	24(15.5)	8 (3.1)	8 (3.1)	6 (3.2)	2 (2.8)	32 (7.8)	32 (7.8)
15 to 29	0	0	5 (1.9)	5 (1.9)	5 (2.7)	0	5 (1.2)	5 (1.2)
30 to 59	3 (1.9)	3 (1.9)	5 (1.9)	5 (1.9)	2 (1.1)	3 (4.2)	8 (1.9)	8 (1.9)
60 to 89	5 (3.2)	5 (3.2)	3 (1.2)	3 (1.2)	2 (1.1)	1 (1.4)	8 (1.9)	8 (1.9)
90 to 179	4 (2.6)	4 (2.6)	5 (1.9)	5 (1.9)	3 (1.6)	2 (2.8)	9 (2.2)	9 (2.2)
180 to 364	18 (11.6)	1 (0.6)	34 (13.2)	13 (5.1)	12 (6.5)	1 (1.4)	52 (12.6)	14 (3.4)
365 to 539	41 (26.5)	25 (16.1)	82 (31.9)	59 (23.0)	42 (22.7)	17 (23.6)	123 (29.9)	84 (20.4)
540 to 729	24 (15.5)	22 (14.2)	44 (17.1)	30 (11.7)	16 (8.6)	14 (19.4)	68 (16.5)	52 (12.6)
≥ 730	36 (23.2)	N/A	71 (27.6)	N/A	N/A	N/A	107 (26.0)	NA
730 – 899	N/A	19 (12.3)	N/A	30 (11.7)	23 (12.4)	7 (9.7)	N/A	49 (11.9)
900 – 1094	N/A	22 (14.2)	N/A	36 (14.0)	27 (14.6)	9 (12.5)	N/A	58 (14.1)
≥ 1095	N/A	30 (19.4)	N/A	63 (24.5)	47 (25.4)	16 (22.2)	N/A	93 (22.6)
By Number of Months/Years[c], n (%)								
≥ 6 mo (≥ 180 days)	119 (76.8)	119 (76.8)	231 (89.9)	231 (89.9)	167 (90.3)	64 (88.9)	350 (85.0)	350 (85.0)
≥ 1 year ≥ 365 days)	101 (65.2)	118 (76.1)	197 (76.7)	218 (84.8)	155 (83.8)	63 (87.5)	298 (72.3)	336 (81.6)
≥ 18 mo (≥ 540 days)	60 (38.7)	93 (60.0)	115 (44.7)	159 (61.9)	113 (61.1)	46 (63.9)	175 (42.5)	252 (61.2)
≥ 2 years (≥ 730 days)	36 (23.2)	71 (45.8)	71 (27.6)	129 (50.2)	97 (52.4)	32 (44.4)	107 (26.0)	200 (48.5)
≥ 30 months (≥ 900 days)	N/A	52 (33.5)	N/A	99 (38.5)	74 (40.0)	25 (34.7)	N/A	151 (36.7)

	Low Dose		High Dose				Any Dose	
				Safety Update				
Duration Interval[a]	ISS N = 155	Safety Update N = 155	ISS N = 257	Any High Dose N = 257	≥ 1250 – 2000 mg/day N = 185	≥ 2000 mg/day N = 72	ISS N = 412	Safety Update N = 412
Summary Statistics								
Mean ± SD, days	456.3 ± 323.34	660.3 ± 459.81	546 ± 314.56	745.0 ± 438.60	750.2 ± 441.15	731.5 ± 434.76	512.2 ± 320.46	713.1 ± 448.03
Median (min – max), days	389 (1 – 1219)	666.0 (1 – 1611)	446 (3 – 1284)	736.0 (3 – 1676)	771.0 (3 – 1676)	636.0 (8 – 1669)	422.5 (1 – 1284)	685.5 (1 – 1676)
Total PY	193.6	280.2	384.2	524.2	380.0	144.2	577.8	804.4

ISS = Integrated Summary of Safety; LCIG = levodopa-carbidopa intestinal gel; max = maximum; min = minimum; N/A = not applicable; PY = patient years; SD = standard deviation

a. Data cutoff date for ongoing studies was 04 May 2012 for ISS and 31 May 2013 for Safety Update.

b. Categories are mutually exclusive.

c. Categories are not mutually exclusive.

Reviewer Comments

The 4MSU did not suggest any new safety risks that had not been recognized in review of the ISS data analyses provided with the sponsor's NDA submission.

8 Postmarket Experience

The LCIG System is currently approved in 41 countries. In many countries, it is marketed under the trade name Duodopa®. The first marketing authorization for Duodopa in the European Economic Area (EEA) was received in Sweden on 21 January 2004. LCIG has been approved in 27 countries in the EU and 3 countries in the EEA. Eleven national approvals have been granted in the following other countries: Albania, Australia, Bosnia and Herzegovina, Canada (conditional), Croatia, Israel, Macedonia, Switzerland, Thailand, Turkey, and the Ukraine.

Annual patient years of treatment (PTY) and cumulative PTY are provided in *Table 73 by* country and year. There were (b) (4) PTY with Duodopa worldwide from 21 January 2004 through 31 October 2012. The sponsor reviewed the Postmarketing safety database for LCIG relative to the safety data collected in NDA 203952 and safety events of interest and concluded the safety profile is generally similar.

Table 73 Estimated PTY of Postmarketing Exposure to Levodopa-Carbidopa by Country and Year

Country	2004	2005	2006	2007	2008	2009	2010	2011	2012[a]	Total
Germany										(b) (4)
Netherlands										
Italy										
Spain										
Sweden										
Belgium										
Finland										
Norway										
United Kingdom										
France										
Denmark										
Austria										
Slovenia										
Czech Republic										
Ireland										
Romania										
Australia										
Greece										
Switzerland										
Saudi Arabia										
Slovakia										
Israel										
Bulgaria										
Hungary										
Croatia										
Luxemburg										
Portugal										
Albania										
United Arab Emirates										
Turkey										
Total										

Reviewer Comments

The postmarketing review did not suggest any previously unrecognized risks from LCIG treatment.

9 Appendices

9.1 Literature Review/References

The sponsor provided a comprehensive literature review for LCIG that was a systematic literature review in which it synthesized AE data from sources including prospective and retrospective studies with blinded or open-label designs, case-control studies, case series, and case reports. Specific AEs that were discussed in this review were selected based on the preferred terms reported from the LCIG Phase 3 program and grouped by incidence. Common TEAEs were defined as events that were reported in 10% or more of subjects in the LCIG group of the active-controlled analysis set or open-label analysis set; less common TEAEs were reported in less than 10% of subjects. Other areas of discussion included AESIs, TEAEs reported in the literature and not seen in the Phase 3 clinical program, TEAEs reported in the Phase 3 clinical studies but not reported in the literature, and TEAEs in the published literature leading to discontinuation of treatment.

The most common adverse events in the active-controlled analysis set and the open-label LCIG analysis set (excluding procedure- and device-associated AESIs) include insomnia, nausea, falls, constipation, anxiety, depression dyskinesias, orthostatic hypotension, worsening of Parkinson's disease, and weight decreased.

Less common TEAEs in the active-controlled and the open-label LCIG analysis sets (excluding procedure- and device-associated AESIs) include psychotic disorders, delusions, agitation, muscle spasms, dysarthria, syncope, memory impairment, dizziness, somnolence, restless legs syndrome, diarrhoea, anorexia, decubitus ulcer, subdural haematoma, cardiac arrest, atrial fibrillation, and myocardial infarction.

TEAEs identified in the published literature that were not observed during the clinical program included pica, trichotillomania, and status epilepticus. Common TEAEs reported in the clinical program and not identified in the published literature included flatulence, urinary tract infection, sleep attacks, oropharyngeal pain, dyspepsia, pain in extremity, and musculoskeletal pain.

The incidence of TEAEs reported in the LCIG group of the active-controlled analysis set and the open-label analysis set were either lower than, or comparable to, AEs reported in the published literature across all the aforementioned categories. Nausea was the only AE where the incidence rate in the literature, reported from 1 published study, was notably less (about half) than that reported in LCIG clinical program.

However, nausea is known to be associated with levodopa treatment and underlying PD, and the higher rate seen in the clinical program was likely reflective of these subjects being in a controlled, prospective clinical trial. Additionally, the sponsor noted that rates of AESIs, including polyneuropathy, weight loss, respiratory tract aspiration including aspiration

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pneumonia or pneumonitis, cardiovascular fatalities, and procedure- and device-related events were comparable between the published LCIG literature and the US clinical program.

The LCIG Phase 3 program represents the largest database on levodopa-carbidopa intestinal gel in patients with advanced PD. The prospective data are more comprehensive and detailed than any previously reported. Moreover, no published studies were identified with a comparable double-blind design as seen with the pivotal Studies S187.3.001/S187.3.002. However, despite this limitation, rates of AESIs and all\ other TEAEs in the published literature were consistent with those seen in the clinical program. Therefore, this comprehensive integrative systematic literature review demonstrates that the published literature does not differ remarkably from the clinical trial results included in the 505(b)(2) application for LCIG with respect to the type or incidence of AEs, nor does it affect the benefit/risk balance for this product.

Reviewer Comments

The sponsor's literature search did not suggest any previously unrecognized risks from LCIG treatment.

9.2 Labeling Recommendations

Labeling recommendations are not being provided at this time because the plan is to issue a Complete Response for primarily because of CMC concerns and also the fact that the sponsor has not demonstrated from its human factors investigation that the safe use of this product has been adequately established.

9.3 Advisory Committee Meeting

Not applicable because there is no need for such a meeting.

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/s/

LEONARD P KAPCALA

03/11/2014

Dave,
Here is my clinical review (that you have seen) for your signature. Please let me know if any questions. Thanx.
Len

GERALD D PODSKALNY

03/13/2014

Cross-Discipline Team Leader Review

Date	03/11/2014
From	Gerald D. Podskalny DO, MPHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA-203952 (0000)
Applicant	AbbVie
Date of Submission	11/16/2012 with resubmission 05/28/2013
PDUFA Goal Date	03/28/2014
Proprietary Name / Established (USAN) names	Duopa (carbidopa levodopa [redacted] (b) (4))
Dosage forms / Strength	20 mg/mL levodopa and 5 mg/mL carbidopa 100 gram cassette
Proposed Indication(s)	1. Advanced Parkinson's Disease
Recommended:	***Complete Response***

1. Introduction

The reference listed drug for this 505(b)(2) application is Sinemet (carbidopa levodopa) tablets (NDA No. 017555. The Office of Orphan Products granted Orphan Development designation to levodopa carbidopa intestinal gel (LCIG) on January 18, 2000. The Office of Combination Products agreed that the LCIG System is a combination product (drug, pump, and tubing) and CDER would have jurisdiction on November 15, 2011. The first submission of the NDA was on November 16, 2012. The review team identified several filing review deficiencies in the CMC and Clinical sections, leading to a Refuse to File action. The Sponsor resubmitted the NDA on May 28, 2013 that was accepted for standard review. The PDUFA goal date for this NDA is March 28, 2013.

Table 1: List of Review for NDA 203952

Discipline	Primary Review	Secondary Review/Memo/Sign-off	Recommendation
Chemistry	Charles Jewel PhD	Olen Stephens, Ph.D. Acting Branch Chief Branch I, Division I ONDQA	Complete response based on Biopharm deficiencies in dissolution
Biopharmacology	Kelly M. Kitchens, Ph.D.	Richard Lostritto, Ph.D.	**Complete Response additional dissolution information needed**
Clinical Pharmacology	Bei Yu Ph.D.	Angela Men, MD, Ph.D.,	Adequate no recommendations
Pharmacometrics	Hongshan Li, Ph.D.	Atul Bhattaram, Ph.D.	Adequate no recommendations
Pharmacology Toxicology Review	LuAnn McKinney, DVM, DACVP	Lois M. Freed, PhD Pharm/Tox Supervisor (memo)	Adequate no recommendations
Clinical	Leonard Kapcala, M.D.	Gerald Podskalny, DO, MPHS (review)	**Complete response efficacy supported no safety concerns**

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Biostatistics	Xiang Ling, Ph.D.	Kun Jin, Ph.D., Team Leader Kooros Mahjoob, Ph.D., Director	Support the efficacy of Levodopa- Carbidopa Intestinal Soln.
Gastroenterology Consult (DGIEP)	Julie Tomaino, MD, MSCR	Jessica J. Lee, MD, MMSc	Adequate-no recommendations
CDRH Reliability and Mechanical Engineering	CDR Alan Stevens, Reliability and Mechanical Engineering Infusion Pump Team Leader,OMPT/CDRH/ ODE/DAGRID/GHDB		**Complete Response recommended retest pump performance and safety**
CDRH Human Factors	QuynhNhu Nguyen Biomedical Engineer/Human Factors Reviewer CDRH/ODE/ DAGRID	Ron Kaye Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID	**Complete response recommended repeat HF studies**
DMEPA Human Factors, label review	Julie Neshiewat, Pharm D, BCPS	Kellie Taylor, Pharm D, MPH, DMEPA Acting Director	**Complete response recommended repeat user comprehension studies**
Patient Labeling/REMS	Robin Duer, MBA, BSN, RN, Senior Patient Labeling Reviewer	Melissa Hulett, MSBA, BSN, RN, Team Leader LaShawn Griffiths, MSHS-PH, BSN, RN, Associate Director for Patient Labeling DMPP	Review deferred
Controlled Substance Staff	Katherine Bonson, Ph.D., Pharmacologist	Silvia Calderon, Ph.D., Team Leader Michael Klein, Ph.D., Director	LCIG does not have abuse potential
Proprietary Name Review	Sue (Liu) Liu, Pharm D, DMEPA	Irene Z. Chan, Pharm D. BCPS Carol Holquist, RPh Director	Duopa- Granted
PeRC Review	None		OOPD granted orphan designation 1/18/2000
Clinical Site Inspections OSI/DGCPC/GCPAC	Antoine El-Hage, Ph.D.	Susan Thompson, M.D. Team Leader Kassa Ayalew, M.D., M.P.H. Acting Branch Chief	3 sites inspected all NAI

2. Background

Carbidopa and levodopa (CD/LD) is a fixed combination oral tablets (Sinemet). Sinemet tablets contain carbidopa and levodopa in 1:4 (25/100 mg), 1:5 (25/250) or 1:10 (10/100) ratios. Extended release carbidopa and levodopa (Sinemet CR) tablets are only available in a fixed 1:4 ratio (25/100 mg and 50/200 mg). Selection of the fixed carbidopa to levodopa ratios

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was based on the belief that approximately 75 mg/day of carbidopa was needed to inhibit enough circulation aromatic amino acid decarboxylase inhibitor (AADC) to allow levodopa to escape peripheral decarboxylation and enter the brain. The surviving nigral neurons in the Pars Compacta are capable of converting the exogenous levodopa to dopamine. As the loss of nigral neurons progresses, the symptoms of Parkinson's disease (PD) also worsen. The ability of nigral neurons to convert levodopa to dopamine, store and release dopamine also decreases with progression of PD.

The ability to store and release exogenously sourced dopamine in a physiologic manner may explain why the pharmacodynamic profile of levodopa not follow the pharmacokinetic (PK) profile. The pharmacodynamic response to levodopa changes with disease progression. The half-life of levodopa (oral tablets) remains 1.5 hours throughout the disease course. However, in early Parkinson's disease, effect a single oral dose of carbidopa levodopa on motor symptoms may last 6 hours. The long pharmacodynamic effect of levodopa is due to the ability of the remaining nigral neurons to convert levodopa to dopamine, store and physiologically release dopamine. Over time, nigral neurons continue to be lost and the pharmacodynamic effect of levodopa becomes progressively shorter. Eventually, the duration of action from a single dose of carbidopa and levodopa starts to mimic the plasma half-life of levodopa lasting1.5 hours. Glial cell may become the primary cells that convert levodopa to dopamine in the brain from levodopa that is available in extracellular fluid. The shortened pharmacodynamic effect of levodopa in patients with advanced Parkinson's disease is the reason for developing a continuous levodopa delivery system. Continuous (non-pulsatile) delivery of levodopa may less the severity of dyskinesia and "off" time, in patients with advanced PD.

The LCIG Administration System was first approved internationally in 2004 It is currently marketed in 25 countries globally, including the European Union Member States (total-41 countries), under the trade name Duodopa and is in clinical trials in 15 other countries. The Sponsor estimates, over (b) (4) patients received treatment with LCIG. If the market potential of 10 years, in 41 countries is considered, the number of patients treated with this product is small, compared to other medication approved for the treatment of PD.

This application relies on the results of a single pivotal Phase 3 clinical trial (combination of study S187-3-001 and study S187-3-002 into one pivotal study), the Agency's finding of efficacy for oral Sinemet and three long-term Phase 3 supportive studies, plus a human pharmacokinetic study.

3. CMC/Device

This is combination device-drug product. The drug portion of the product is a stabilized, homogenous enteral suspension of carbidopa monohydrate and levodopa in carmellose sodium (b) (4) in purified water delivered by continuous jejunal infusion. The final drug product is housed in a (b) (4) bag that is incased in a hard (b) (4) cassette. Each cassette holds 100 grams of suspension that contains approximately 2000 mg levodopa, 500 mg of carbidopa (4:1) and (b) (4) mg of carmellose sodium. The final mixture results in 20 mg/mL of levodopa and 5 mg/mL of carbidopa monohydrate. The CMC/ONDQA reviewer comments that the composition of the product is actually a

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suspension (b) (4) The viscosity of the product is obtained by (b) (4)

(b) (4)

The drug substances are carbidopa monohydrate (DMF (b) (4)) and levodopa (DMF (b) (4)) both supplied by (b) (4) The application contained letters of authorization to the respective (Drug Master Files). The DMF for both drug substances are adequate with pending stability amendments).

Drug product delivery is by continuous infusion over 16 hours controlled by the CADD-Legacy 1400 ambulatory enteral infusion pump (Smith Medical). The Smith medical device Master File (MAF (b) (4)) was reviewed by CDRH at the request of the Division of Neurology Products. The drug product flows through extension tubing that is connects to a jejunal tube (permanent configuration) or naso-gastric tube (temporary configuration). The applicant included several marketed jejunal tubes that require different insertion techniques [(standard PEG and 2-port through the PEG jejunal tube (PEG-J tube)] in the NDA. Compatibility testing was conducted for the device components including the naso-jejunal, PEG and PEG-J tubes included in the NDA. FDA review of the Sponsor's data found the non-proprietary tubes are compatible with LCIG. Prior to NDA approval, the sponsor plans to submit proprietary naso-jejunal and PEG-J tubing stets with connectors in a separate 510K to CDRH. Approval of the 510K is contingent upon approval of this NDA. The enteral medication cassette reservoir manufactured by (b) (4)) is covered under the Device Master File is adequate.

The programming features of the CADD 1400 enteral infusion pump are described the Human Factors section of this review.

The applicant proposes up to 24 months stored frozen and (b) (4) weeks stored refrigerated, however; CMC (at FDA) is not ready to make such a recommendation until additional (b) (4) dissolution and further stability data is received and evaluated.

The Dr. Jewell described two critical deficiencies in his review and also noted, the levels of hydrazine and two other degredants were higher than the specified limits allow. I will describe Dr. Jewell's concerns about the levels of hydrazine and of the other two degredants however; the issue is described in greater detail in the Pharmacology Toxicology section of this review.

The first CMC deficiency involves problems with homogeneity of the drug product (b) (4)

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(b) (4)

Dr. Jewell concluded that the sponsor's explanation of the root cause for (b) (4) is "logical" but there is insufficient information to support approval at this time. The Sponsor submitted a CMC Addendum on January 30, 2014, and committed to testing 3 batches of drug product comparing batched made using the new manufacturing control and plan to evaluate the new batches (b) (4). However, the sponsor must show that the new controls adequately address the problem (b) (4) and simply proposing new methods do not adequately address the concerns. The Sponsor must show that homogeneity of the solution is maintained for up to 24 months under frozen conditions, followed by (b) (4) weeks refrigerated conditions, and up to 24 hours at room temperature.

Degradation Products

The key carbidopa degradation products are hydrazine, (b) (4) and (b) (4) Dr. Jewell notes in his review; (b) (4). As a consequence, the proposed specification limits for these "degradation products are at unprecedented levels". The applicant has attempted to justify these levels in light of the benefit/risk of using this drug in advanced Parkinson's patients. Dr. Jewell raised the issue that is discussed in detail in the non-clinical section of this review.

CMC Reviewer's Recommendations to the Sponsor:

1. Provide updated control measures (e.g., (b) (4) for homogeneity control of drug product (e.g., (b) (4). Provide supporting stability data to verify that the new quality measures are effective in controlling drug product homogeneity and demonstrate the prevention of low levodopa exposure with initiation of morning dose.
2. Provide updated drug product stability data with new drug product dissolution data using the improved dissolution method.
3. Change all references from (b) (4) to "levodopa-carbidopa enteral suspension" in the application and labeling.
4. The comparability protocol is not accepted (b) (4)

Facility inspection update

Inspections of the drug manufacturing facilities listed in the application are complete and their status is **Acceptable**.

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Table 2: List of manufacturing Facilities Listed in the NDA

Establishment Name	FEI Number	Responsibilities	Profile Code	Facts Assignment ID	Inspection Start-End Date	Recent Milestone	Recent EER Compliance Status
(b) (4)		DS manufacturing, (b) (4) and testing	CSN	Not applicable	Not applicable	OC Recommendation	AC
		Drug substance (b) (4) Testing	CTL	Not applicable	Not applicable	OC Recommendation	AC
Smith Medical ASD Inc., 1265 GREY FOX RD. ST. PAUL, MN 55112	2183502		DKA			OC Recommendation	AC
(b) (4)		Drug Product Manufacturing, Packaging, Testing	SES	(b) (4)	(b) (4)	Assigned inspection to IB	AC

Biopharmacology Review

The Sponsor did not submit dissolution method development information, data supporting the methods discriminating ability, and the dissolution test or its acceptance criteria, in the NDA. (b) (4)

The Biopharmacology reviewer advised the Sponsor that their rationale for omitting dissolution profile information from the NDA submission was not adequate and it not consistent with CMC regulation (21 CFR 314.50). The Biopharmacology reviewer requested the Sponsor submit dissolution testing information on July 1, 2013 with a response requested by September 17, 2013.

Table 3:Dissolution Method (submitted September 17, 2013) (Biopharmacology review)

USP Apparatus	Rotation Speed	Medium	Volume	Temperature
(b) (4) [redacted]				

Biopharmacology review team did not agree with the Sponsor's dissolution test method (Table 3) parameters and recommended the company revise their dissolution method to include more testing conditions and/or apparatus designed to simulate the physiological conditions for product administration in the G.I. tract. The Sponsor was asked to submit the dissolution data and profiles for freshly prepared product, and for the thawed product, after freezing, by December 13, 2013.

The Sponsor submitted results from a comparison of three dissolution methods on December 13, 2013, (Table 4). The method using Apparatus 2 with a slower rotation speed was selected by the Sponsor. The Sponsor's justification was based on method A's ability to discriminate product produced with [redacted] (b) (4) levodopa and product intentionally produced at the extremes of the product's viscosity limits. The Sponsor's method selection and justification was acceptable to the Biopharmacology reviewer.

Table 4:Revised Dissolution Method (submitted December 13, 2013) (Biopharmacology)

USP Apparatus	Rotation Speed	Medium	Volume	Temperature
2 (Paddle)	25 rpm	0.05 M acetate buffer, pH 4.5	500 mL	37°C

Table 5: Proposed Dissolution Acceptance Criteria (submitted December 13, 2013) (Biopharmacology)

Table 7. Tentative Acceptance Criteria

Test	Limits	Time point	Q according to (b) (4)
[redacted] (b) (4)			

The Biopharmacology reviewer had concerns about the proposed dissolution acceptance criteria and communicated them to the Sponsor. In Table 5, the Sponsor proposed (b) (4) [redacted]

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(b) (4)

Dr. Kitchens (FDA Biopharmacology reviewer) advised the Sponsor that the proposed dissolution acceptance criteria are not supported by the provided dissolution data, and the acceptance criteria for batch release and stability testing should be the same.

Dr. Kitchens requested additional information January30, 2014, asking the Sponsor to provide the age(s) of the LCIG batch used for the dissolution methods development. The sponsor was also asked to submit a proposal for dissolution acceptance criteria with a specification time point where Q= (b) (4) % dissolution occurs. The acceptance criteria should use the dissolution data generated from all of the test batches using the new dissolution method. The Sponsor was asked to provide information that accounts for the expected (b) (4) over the shelf-life of the product.

The Sponsor submitted new batch information for the experimental batches used for the dissolution method development to the NDA on February 7, 2014. The dissolution data for 10 commercial-scale batches were also submitted to support the proposed dissolution acceptance criteria. Additional data also demonstrated that carbidopa monohydrate met assay specifications (b) (4) over the (b) (4) week expiration period.

However, the dissolution data required for the setting of the dissolution acceptance criteria using the new method was limited to the dissolution values for the 40 minute time point, which was insufficient. Complete multipoint dissolution profile data for dissolution testing is needed to set dissolution acceptance criteria. Critical dissolution data through week 15 of stability testing under refrigeration conditions at 5ºC was also lacking.

Biopharmacology Recommendations:
The following comments and request for information should be conveyed to the Applicant in the CR letter:

1. Submit the complete dissolution profile data (*individual, mean, SD, profiles*) for each time point for the dissolution testing of the commercial-scale batches. Provide the dissolution data at the following time points: 15, 20, 30, 40, 50, and 60 minutes (n=12). The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).

2. We acknowledge your commitment to provide stability data for your drug product under frozen (-20ºC) and refrigeration (5ºC) conditions post-approval. However, for the setting of the specifications of your drug product, you will need to provide data from at least 3 batches at the initial time point and thereafter at 5, 10, and 15 weeks under refrigeration conditions. For this testing, we consider the initial time point when the product is thawed and placed under the 5ºC refrigeration conditions. For the dissolution testing, provide the complete dissolution profile data as described in above Comment 1.

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3. In your October 31, 2013 response to our Information Request (IR), you indicated that [redacted] (b) (4) hereas in your February 7, 2014 IR response, you indicated that [redacted] (b) (4) a 10-fold difference. Clarify this discrepancy [redacted] (b) (4)

CDRH Reliability and Mechanical Engineering Review
CDR Alan Stevens, Reliability and Mechanical Engineering Infusion Pump Team Leader, OMPT/CDRH/ODE/DAGRID/GHDB. CDR Stevens recommends a Complete Response based on the need for additional hazards testing and additional information about the software function.

CADD-Legacy 1400 Pump Features and Programing
The CADD-Legacy 1400 Pump is a modification to the existing FDA Cleared CADD-Legacy PCA Pump System (K982839) and Medication Cassette Reservoir (K846772). The CADD-Legacy 1400 Pump System was developed as a specific enteral medication system. Prior to launching the CADD-Legacy 1400 Pump System, changes were made to the CADD-Legacy PCA System pump hardware, labeling, and software to modify features and capabilities that address the needs for enteral delivery of medication.
The CADD-Legacy 1400 Pump is supplied with the following accessories:

- Remote Dose Cord
- Pump Pouch
- Protective Cassette
- Battery Door

The medication is delivered directly to the proximal small intestine (the duodenum and/or jejunum) via a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J), requiring endoscopic insertion. A temporary naso-jejunal (NJ) tube will be used initially with the infusion pump to determine if the subject responds favorably to LCIG continuous enteral infusion treatment and to transition the patient from oral CD/LD to of LCIG before long-term treatment with a PEG-J tube is started.

A healthcare provider programs the device. There are 3 programming access levels referred to as "Lock Levels". Lock Level zero (LL0) is only assessed by the programmer.

- Lock Level 0 (LL0): All dose changes and programming are possible to make dosing changes (morning dose bolus, continuous flow rate, or extra bolus dose). In addition, changes to the continuous infusion rate, dose lockout times for the morning dose and the extra bolus doses can be made within the manufacturer's set limits.

- Lock Level 1 (LL1): The dose can be adjusted by the patient up and down between a preset prescribed dose to a pre-programmed upper limit (+10% of the prescribed dose). The default lockout time for morning dose is 20 hours.

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- Lock Level 2 (LL2): No dose changes by the patient are possible, the morning dose, continuous infusion rate and bolus dose (dose and lock out times) can only be delivered as programmed.

CDRH Safety Engineering Review Comments

The request for a Reliability and Mechanical Engineering Infusion Pump consult review CDRH was completed by CDR Alan Stevens Team Leader, OMPT/CDRH/ODE/DAGRID/GHDB. His review indicates there are deficiencies that may impact the ability to use the device safely to deliver LCIG.

The Division requested CDRH Infusion Pump Team conduct a Reliability and Mechanical Engineering consult review of the information pump information submitted in the NDA (Module 3). The review noted several deficiencies including some that require additional investigation or information from the sponsor. The information requested in items #1, #6 and #7 are required to complete the CDRH review therefore; they are **Complete Response issues**.

1. Please address the following issues regarding the CADD-Legacy Model 1400 delivery rate, delivery accuracy and dose accuracy specifications and testing:

    a. System delivery accuracy and bolus accuracy specifications listed in the submission are (b) (4) However, the design verification testing for the CADD-Legacy Model 1400 pump state that acceptance criteria for therapy accuracy and dose accuracy are (b) (4) and (b) (4) respectively. Please clarify the correct accuracy specifications.

    b. The design verification report (DVT-1258R-000) states that the Dose Volume accuracy specification should be updated to (b) (4) It is not clear if this recommendation was followed. Please verify the Dose Volume accuracy specification and provide the supporting data. Further, verify that the test conditions reflect the conditions the user is going to experience with respect to the pump, cassette, tubing configuration, drug temperature, etc.

    c. Verify that infusion delivery rate and demand dose specifications are adequate for the drug dosing (e.g. minimum infusion rate, maximum infusion rate, and infusion rate increments). For example, if the maximum labeled infusion rate in the drug labeling is 10mL/hr, justification for the device specification exceeding this rate would be needed to assure that potential risks associated with a higher rate are adequately addressed.

    d. Testing has not bracketed the infusion rates (e.g. minimum and maximum) to verify adequate performance throughout the programmable range. Provide updated testing to verify delivery accuracy at minimum and maximum programmable rates.

2. Drug labeling indicates that neuroleptic malignant syndrome (NMS) is associated with abruptly reduced / discontinued drug dosage or therapy. In the device hazard analysis,

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there is a stated assumption that the onset of Parkinson's symptoms due to infusion delivery at an incorrect rate is detectable by the patient soon enough for the patient to stop the potentially harmful activity and adjust the dosage for improved response. Please address the following:

a. What timeframe is required for onset of NMS and how are device malfunctions adequately handled to reduce the risk of NMS onset.
b. With respect to occlusion detection, the system specifications provide the time to occlusion detection. Verify that these times are acceptable to mitigate harm from NMS.
c. The occlusion detection verification testing results are measured against an acceptable pressure range, while the system specifications are provided in time to detection. Verify that the system specification time-to-detection is derived from the design verification tests using LCIG.
d. The occlusion detection alarm specification is 26psi +/-14psi. Describe is the practical effect of having a high pressure alarm that is tripped at 12 psi. Additionally, provide justification for the deviation in pressure alarm of 28 psi.

3. There appears to be inconsistencies in the system specifications listed in the submission with the drug delivery requirements or device verification testing. For example, the time-to-occlusion alarm identifies time for (b) (4) infusion rate. However, the device specification for maximum infusion rate is 20 mL/hr. Also, as mentioned, the delivery accuracy specification does not match the design verification test criteria. Address the inconsistencies and also verify that all system specifications listed in the instructions for use are accurate with respect to the CADD-Legacy Model 1400 pump system for infusion of Levodopa-Carbidopa Intestinal Gel.

4. The device operating temperature specification is 2C to 40C. Verify that this is consistent with the acceptable temperature exposure specifications during administration of the drug.

5. (b) (4)

6. We have conducted a review of the software documentation. Please provide the following software documentation for the current release version:

a. Provide the software revision history document.

b. Identify any remaining unresolved anomalies and include the following information for each:
   i. A description of the anomaly from a symptom point of view and how it is manifested.
   ii. The location in the code where the anomaly occurs.
   iii. A description of how to fix the code.
   iv. A search of the software source code for other possible instances of the anomaly. For example, if the problem was an off-by-one error in an array, provide evidence that all arrays were checked for off-by-one errors.
   v. Provide evidence that a coupling analysis was performed to identify all parts of the software that accessed the errant code and that no problems would arise because of accessing this code.
   vi. Provide evidence that the anomalies are corrected, or provide an acceptable rationale for why the anomaly could not result in harm if it occurs.
   vii. Provide evidence that the corrected, final finished production software was re-tested and that no new anomalies are found.

c. Provide a static analysis report for the current release version. The report should include the following:
   i. Identify the static analysis tools used.
   ii. Describe the implementation of the tool(s) for the analysis of the software.
   iii. Describe the results of the testing, including any alerts / defects identified.
   iv. Provide a detailed explanation for the acceptability of each alert / defect such that we are able to agree that it will not occur during use of the device, or does not pose a risk to health.
   v. Provide an overall analysis and conclusion of the results.

7. We have conducted a review of device hazards that can cause the drug infusion to occur at an incorrect rate. Column one and two in the following table identifies the causes and hazard controls from the device hazard analysis documentation (MAF (b) (4), Amendment 3, VOL 6 TAB 10B CADD Legacy 1400 Pump Hazard Analysis). <u>Column 3 identifies additional information needed to complete our review. Please address the deficiencies identified in column 3.</u>

<u>Table 6: Pump Hazard Analysis</u>

Hazard - Infusion delivery occurs at an incorrect rate		
Cause	**Control**	**Deficiency**
(b) (4)		

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CDRH Human Factors Review

Quynh Nhu Nguyen, Biomedical Engineer/Human Factors Reviewer completed the CDRH Human Factors (HF) review for the HF study submitted in the NDA. AbbVie submitted a human factors study report to IND 60663 on July 10, 2012. The Division consulted CDRH HF to review the report and provide comments for the scheduled Type B meeting. "*CDRH HF review identified four deficiencies including a request for Abbvie to further optimize the device, and to perform a focused HF/usability validation study demonstrating that representative users can use the device without patterns of preventable use errors/failures that can result in patient harm. These deficiencies were provided to CDER on August 29, 2012*". The CDRH HF review team held a teleconference with representatives from AbbVie on September 17, 2012 CDRH HF. CDRH HF advised AbbVie to provide the following information in their HF study final report (from the CDRH-HF review):

- Further elaboration is needed on what happened after task failures, and the possible clinical impact of these user actions, and if needed, a discussion of what could be changed in the user interface to address those failures
- Further discussion on test results of the alarm tasks
- Further discussion on lock level functions and capabilities. CDRH HF team recommended that to assess user's ability to operate the different lock levels (amount of user access) additional HF testing should be conducted with at least 15 representative users.

The Sponsor submitted an updated HF study report that included a response to CDRH's request for additional information about task failures and discussion of alarms tested in the NDA. The study report also included a supplemental HF test results for assessing physician's knowledge on the differences between the three lock levels, and assessing patients' ability to adjust dose for lock level 1. The CDRH HF review of this information identified several concerns regarding the study methodology and results. The sponsor included a Patient Instructions for Use (IFU) document in the labeling section of the NDA. However, the DMEPA reviewer noted (b) (4) [redacted] After internal discussions involving DMEPA, the CDRH engineering and HF, CMC, Combination products and Patient Labeling, it was decided that the overall product instructions for use and the pump patient information needed to be combined. At the request of the review Division, the sponsor submitted (on 01/28/2014) a single Patient IFU (b) (4) [redacted] The CDRH HF reviewer's provided comments and recommendations pertaining to the revised Patient IFU (below). The issue of greatest concern was that the new Patient IFU contained revised warnings and caution statements that were not tested in representative patients.

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***CDTL note**- It is my opinion that the bolded statements (below) are deficiencies that have the potential to cause harm.

CDRH HF Recommendations for the Sponsor.

Your human factors study report did not provide analyses and results consistent with best practice to support review of human factors for your combination product submission. As per the deficiencies that follow, we request that you implement mitigations to improve the ability of users to use your product safely and effectively and conduct another human factors study with a minimum of 15 participants, HCPs and patients combined to demonstrate their effectiveness.

1. Only low battery and high pressure alarms were tested your original human factors validation study. We noted that there are other alarms/messages that you have listed in the healthcare providers (HCPs) and patients pump labeling that were not part of the study. If the response and interpretation to these alarms/messages is unique and represent critical user tasks, they should be tested but were not tested in your human factors validation study. Unless there are no critical user tasks associated with these alarms and messages, please include them in your human factors testing of mitigations.
2. **Your original human factors validation study showed multiple task failures for programming the pump, and connecting different pump components. These failures were in addition to the reported other "operational difficulties." We are concerned that these task failures and operational difficulties can lead to suboptimal therapy, dyskinesia, loss of mobility, pain/discomfort. We are most concerned about the following: a. One HCP accidentally changed Continuous Rate value while changing Morning Dose volume.**
   b. **Two HCPs failed to administer Morning Dose**.
   c. Five (5/25) HCPs and 14/25 patients experienced failures with critical tasks associated with changing the cassette.
   d. **Three patients and 6 HCPs did not complete the steps for flushing the PEG-J tubing**

   You have not explained how these failures and difficulties occurred such that design issues of your product can be ruled out. Therefore, please evaluate the relevant data, develop appropriate mitigations and validate those mitigations via simulated use testing.
3. You provided a supplemental human factors study to evaluate the lock levels, however only 10 HCPs participated in the study. The study was designed to evaluate the HCPs' understanding of the differences between the lock levels. **The user tasks associated with setting up lock levels were not evaluated as part of this study. Please provide test results for these tasks or provide justification for the study methodology you followed. Please also clarify the specific patient characteristics for HCPs'** determination and setting the lock level for a specific patient.
4. Regarding your supplemental study to evaluate the lock levels, 15 patients were tested to perform Morning Dose and Continuous Rate adjustments**. It was not clear if the scenarios in the test were designed to evaluate patient's ability to adjust dose. It was not clear if the patients are only enabled to adjust Morning Dose and Continuous Rate.** We note that patient adjustments can be made between a preset

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prescribed dose and a pre-programming upper limit (+10% of the prescribed dose). Please also describe the minimum and maximum dose that can be prescribed, the adjustments and what parameters can be adjusted relative to the prescribed dose setting, how adjustments can be made, and how the pump tracks adjustments made by patients.

5. Your supplemental study results showed six (6/15) patients failed to inspect for tubing kinks prior to programing adjustments. In addition, some HCPs indicated confusion regarding the table that you provided in the HCP pump labeling that described the function of the different lock levels and whether Morning Dose could be adjusted in LL1. As with the other failures contained in these deficiencies, please evaluate these and develop mitigation strategies for reducing them, and test data to demonstrate their effectiveness.
6. **Your combined instructions for use for patients included warning statements that have were not included in your human factors testing. Interpreting and abiding by warnings is considered to represent critical tasks for users and therefore should be tested since inability to understand or take note of the warnings could lead to patient harm. Please ensure that these instructions are optimized for safe and effective use, and that they are not simply a combination of two instructions.**
7. Please provide screen shots for the HCP programming tasks, and patient dose adjustment tasks.

DMEPA Review of The Human Factors Study Julie Neshiewat, Pharm D, BCPS Division of Medication Error Prevention and Analysis (DMEPA) conducted a Usability Study, Label, and Labeling Review.

Dr. Neshiewat, the DMEPA reviewer, identified deficiencies similar to those described in the CDRH HF review. DMEPA recommended a comprehension study rather than a repeat HF study (limited cohort) to reevaluate for improved comprehension instructions and performance of the tasks. In her review, Dr. Neshiewat notes that the HF assessment was conducted after minimal training representing a "worst case scenario" and that additional training would reduce the potential for errors. Dr. Neshiewat also points out that not all of the deficiencies affected the performance of critical tasks or that other mechanisms (alarms) would signal a problem to the patient. Also, only a few healthcare providers were responsible for most of the programming errors. DMEPA's recommendations to reassess changes made to the Patient Instructions for Use are extensive and they appear in the DMEPA review. The Sponsor also proposed combining the [redacted] (b) (4) DMEPA agrees with the Sponsor's proposal they anticipate these revisions can also be assessed by a comprehension study rather than repeating a HF study. The combined provider guided was not be formally reviewed by the Agency this cycle because it was submitted to the NDA late in the review cycle, after the DMEPA and CDRH-HF reviews were already complete.

DMEPA's Recommendation

"We recommend the Applicant combine the two instructional materials for HCPs into one document, address inconsistent information, and remove instructions associated with features of the pump that the Applicant does not intend for HCPs to use. We do not anticipate that combining the two documents will warrant other human factors simulated use study given that

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all critical tasks associated with programming the pump were already evaluated in the usability study".

CDTL Comment:
DMEPA's agrees with CDRH HF about the need to reassess the instructions and Warnings provided in the revised (combined) Patient IFU. However, they have different opinions regarding the type of assessment needed to evaluate the revised instructions. CDRH HF believes repeat HF testing in a small cohort (n=15 patients) is required and DMEPA believes that a comprehension study would be adequate to assess the revised Patient IFU.

The CDRH HF comments (bold text) to the sponsor are critical issues from a clinical perspective. Failure to correctly program the morning dose may lead to patients never achieving the "on" state or experiencing a lengthy delay before reaching the "on" state. Improper or incomplete flushing of the PEG-J tube may lead to clogging of the tube and a need to change the jejunal tube component. It may also lead to improvised attempts to unclog the tube causing additional complications. Comment #4 indicates the Sponsor did not test programming adjustments patients are permitted to make under Lock Level 1. Patients enrolled in the pivotal efficacy trial were all programmed to Lock Level 2 (no changes permitted by patients) and the Sponsor disabled the extra-dose feature, therefore; none of the dosing adjustment features that patients are permitted to make in Lock Level 1 were tested in clinical trial or in HF studies. In addition, very few patients in the open label studies adjusted their programmed dose of LCIG according to the sponsor. I agree with DMEPA's position that not all of the deficiencies occurred in critical tasks or they would come to the attention of the patient by other means, such as the sounding of an alarm for kinked tubing. From a clinical perspective, critical task failures like those that may result in dosing errors, such as missing the morning dose or equipment failure. Patients will perform critical tasks including increasing the infusion rate in Lock level 1 and administration of the morning dose. It is likely patients and caregivers will need to refer to the Patient IFU for instructions on how to complete critical pump functions. There is no way to assure that patients will receive repeated instruction or that they will be able to resolve failures on their own. The Sponsor should assess the patient's ability to complete tasks affected by the changes in the Patient IFU in a repeat human factors study. Assessment of comprehension alone, will not adequately evaluate the ability of patients to complete these task as directed considering they have advance PD and impaired motor functions.

4. Nonclinical Pharmacology/Toxicology

There were no new impurities derived from levodopa that required qualification. However, carbidopa is associated with known impurities. Hydrazine, (b) (4) and (b) (4) are degradation impurities of carbidopa. The Sponsor did not conduct qualification studies for hydrazine because hydrazine has been shown to be carcinogenic in rodents and potentially carcinogenic in humans. As Drs. McKinney and Freed note in their review and memo: "*The sponsor was also asked to address the high levels of hydrazine in LCIG and the proposed specification limits for two additional degredants,* (b) (4) *and* (b) (4) *(Meeting Minutes, dated February 18, 2011)".*

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The Sponsor submitted information from the following studies to support qualification of carbidopa impurities and nonclinical assessment of local irritation caused by LCIG infusion into the duodenum/jejunum.

- local (GI) toxicity studies in mini-pig, including dose-ranging/MTD studies and pivotal 4-week studies.
- in vitro genotoxicity (Ames, chromosomal aberration) assays for (b) (4) and (b) (4)
- Four week oral toxicity studies of (b) (4) and (b) (4) in rat.

The proposed shelf-life limit for three carbidopa degradants, (b) (4) ((b) (4) relative to carbidopa monohydrate), (b) (4) ((b) (4) relative to carbidopa monohydrate, and hydrazine ((b) (4) µg per g of LCIG) exceed the qualification thresholds ((b) (4), (b) (4), and (b) (4), respectively) for the shelf-life limits. Hydrazine is a genotoxic carcinogen; therefore, the expected limit would be ≤1.5 µg/day.

Results of Local Irritation Studies.
The results of two four-week local irritation studies in the mini-pig were included in the Toxicology section of the submission. The doses studied roughly approximate the dose of LCIG administered to patients. Several animals were observed to have behavioral abnormalities, in some cases severe, resulting in injury. Diazepam was administered to allow completion of the study. Histologic examination was limited to the duodenum. The sponsor concluded the results suggested only mild inflammation in male animals in red areas of the duodenal mucosa near or slightly distal to the cannula tip in animals in control and drug-treated groups. Microscopically, these findings correlated with minimal or slight congestion and minimal or slight increases in inflammatory cells. Drs. Freed and McKinney agreed, from these results it did not did not appear that LCIG induced local tissue toxicity

The Results of In Vitro Genetic Toxicology Study Results (b) (4) and (b) (4)
Based on the result in vitro studies:

- (b) (4) and (b) (4) were not mutagenic in bacteria
- (b) (4) was clastogenic in human peripheral blood lymphocytes
- (b) (4) was clastogenic in human peripheral blood lymphocytes.

Qualifications of Carbidopa Related Impurities:

<u>Hydrazine</u>
The sponsor acknowledges that hydrazine is an animal carcinogen, and potential human carcinogen. They also acknowledge the levels of Hydrazine in LCIG will never meet limits in humans set in ICH documents. The Sponsor argues that the safety margin calculated from published carcinogenicity data in rat (safety margin>4.2), mouse (safety margin>3.9) provides a higher safety margin compared to maximum human exposure to the maximum dose of hydrazine from LCIG, at the proposed shelf life limit of (b) (4) mg/day based on mg/m^2 calculation. Dr. Freed points out; the studies described in the publication cited by the Sponsor did not collect plasma levels, leaving no means to bridge between these studies. The studies were also conducted more than 20 years apart.

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The Sponsor's PK analysis in patients was also limited, only a single patient had detectable hydrazine levels and safety margins based on such limited data are likely to be unreliable. Despite these limitations, Dr. Freed points out that even if the available data is used for mouse and rat, it still leaves no safety margin between the levels associated with increased tumors in liver (rat, hamster) or lung (mouse) tumors and the highest plasma level of hydrazine detected in the single patient. As mentioned earlier, hydrazine is a genotoxic carcinogen therefore; the expected daily dose limit would be ≤1.5 µg/day. Dr. Freed cites a recently published report that suggests the daily limit for hydrazine should actually be as low as 0.736 µg/day for a 60-kg person.

CDTL Comment:
The Sponsor argues that hydrazine levels in human PK studies of isoniazid are greater than with LCIG however; the recommended dosing interval for isoniazid is three times a week for up to 1-year. Even if the levels of hydrazine associated with isoniazid is greater than with LCIG, it does not provided evidence that increased levels of hydrazine from the high doses of carbidopa in LCIG is not associated with an increased risk for carcinogenicity in humans.

[redacted] (b) (4) and [redacted] (b) (4)
The Sponsor completed a 4-week toxicity study of [redacted] (b) (4) and [redacted] (b) (4) in rat and a PK study (Drug Metabolism Memo 01) to estimate the exposure of rats to [redacted] (b) (4) and [redacted] (b) (4) in an attempt to bridge to a published report of a 2-year study of carbidopa in rat [redacted] (b) (4) Dr. McKinney pointed out the duration of the 28-day study was insufficient because 90-day bridging studies are typically required to qualify an impurity in a product intended for chronic use however; the study was otherwise adequate. In rat, the [redacted] (b) (4) AUC at [redacted] (b) (4) mg/kg (highest plasma level) was [redacted] (b) (4) ng*hr/mL and [redacted] (b) (4) was only detected in was [redacted] (b) (4) µg*hr/mL (C_{max} = [redacted] (b) (4) µg/mL). In the Sponsor's PK study in rat, the carbidopa highest dose administered was 100 mg/kg. The highest dose of carbidopa administered to animals in [redacted] (b) (4) study was only 10mg/kg making it unlikely that animals in the 2-year study al had sufficient exposure to [redacted] (b) (4) or [redacted] (b) (4)

Human PK study
The sponsor stated that both [redacted] (b) (4) and [redacted] (b) (4) are in vivo metabolites of carbidopa and referenced published reports by [redacted] (b) (4) The Sponsor conducted a PK study in a subset of patients (described in the Clinical Pharmacology section of this review) to detect levels [redacted] (b) (4) and [redacted] (b) (4) in patients treated with LCIG and oral LC. [redacted] (b) (4) was detected in a single patient (1 /11) in the LCIG group at a level near the lower limit of quantification, and no patients (0/5) in the group treated with oral LC. [redacted] (b) (4) was detected in plasma of 7/11 patients receiving LCIG and 4/5 patients receiving oral LC tablets. Based on this limited data the Sponsor concluded plasma levels of [redacted] (b) (4) following LCIG and oral LC were [redacted] (b) (4)% and [redacted] (b) (4)%, respectively, relative to carbidopa. However, the majority of the [redacted] (b) (4) level from LCIG are attributed to the absorbed degredants and not formed as a metabolite of carbidopa.

Dr. Freed notes: *"These data demonstrate that* [redacted] (b) (4) *is likely to be a circulating metabolite in humans. However, T_{max} for* [redacted] (b) (4) *in patients on LCIG was earlier than that for carbidopa, indicating that the higher circulating levels of* [redacted] (b) (4) *following LCIG resulted*

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from absorption of degredants (b) (4) *The data do not support the sponsor's claim that* (b) (4) *is a metabolite of carbidopa in vivo in humans".*

Dr. Freeds Comment and Recommendation:
"I concur with Dr. McKinney's conclusions regarding hydrazine and that the 4-week oral toxicity study was not of sufficient duration to qualify either (b) (4) *or* (b) (4) *Although the sponsor's data confirm that* (b) (4) *is a human metabolite of carbidopa in vivo, they also suggest that LCIG may result in higher exposure (~2-fold) to* (b) (4) *than would be obtained from metabolism. The actual levels of* (b) (4) *(or* (b) (4)*) in the LCIG administered in the clinical study are unknown, suggesting that higher exposures could result. Therefore, it is unclear whether or not* (b) (4) *should be considered qualified based on its being a metabolite. As Dr. McKinney notes,* (b) (4) *does not appear to be a metabolite of carbidopa in vivo in humans or in rat".*

Recommendations
There are concerns regarding the high shelf-life limits proposed for three degredants in LCIG, but the greatest concern is the potential for exposure of patients to substantial amounts of hydrazine, a known genotoxic animal carcinogen and possible human carcinogen. Considering the seriousness of the indication, if the LCIG product is considered to be of sufficient therapeutic benefit to warrant approval, I would suggest that the sponsor be asked to explore possible strategies for lowering the amounts of degredants formed under the conditions of storage and use.

CDTL Comment:
I concur with Drs. Freed and McKinney that of the three degredants, hydrazine is of greatest concern. Current estimates of the levels of (b) (4) and (b) (4) are low however, the data is limited and estimates of their levels in patients taking LCIG are not completely reliable. Hydrazine is carcinogenic to animals, however, the risk to humans cannot be excluded but it also has not been observed. The hydrazine levels patients receive in LCIG far exceed levels provided by oral LC.

Postmarketing experience provided some, albeit limited assurance that chronic use of LCIG has not been associated with in increased risk for cancer. Given the limited therapeutic options in patients with advanced PD (duration > 10 years), LCIG may provide another effective therapeutic option. The dosing regimen studied in the pivotal clinical trials, gave no more than 500 mg of the carbidopa component daily, for a maximum of 16 hours/day in patients with advanced PD. These patients were required to have at least 3 hours of off time but the mean was 6-7 hours per day despite "optimized" oral PD medication regimen. The study population had advance disease and disability and I agree that the potential benefits seem to outweigh the potential risks. However, I concur with Dr. Freed, in recommending the sponsor explore methods that would limit the formation of hydrazine.

Dr. Kapcala' s review the sponsor's comparison of cancer rates from the U.S. SEER database and Globscan, to the age adjusted cancer rates for patients enrolled in open-label studies of LCIG. The rate for reported malignancy was not significantly different between patients receiving open-label LCIG and the comparison group. The rates for colon, liver and lung were

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not elevated compared to published reports and the rate in the Sponsor's reference databases. However, this type of analysis does not provide reassurance that the risk for cancer associated with hydrazine from LCIG is low. The LCIG clinical studies program is small and only the most common malignancies would be observed. There were no cases of liver cancer reported in the open label trial population and only two cases of colon and lung cancer. Patients in the open-label studies received a relatively brief exposure to LCIG, and they were observed for a relatively brief duration. These are just two examples of factors that limit the ability to draw conclusions from this type of analysis.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

There are no unresolved Clinical Pharmacology issues. The Office of Clinical Pharmacology recommendations Approval for this application and no postmarketing studies were recommended.

The LCIG formulation is a suspension of 20 mg/mL levodopa and 5 mg/mL carbidopa (CD) monohydrate in water. One medication cassette reservoir supplies up to 2000 mg levodopa and 500 mg of carbidopa. The total daily dose consists of morning dose, the continuous maintenance dose and the doses that can be provided by the extra dose function of the pump. (b) (4)

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Table 7: PK Parameters in subjects receiving LCIG

Table 1. Study S187-1-002: Pharmacokinetic Parameters (Mean ± SD) of Levodopa, 3-OMD, and Carbidopa with LCIG 16-Hour Infusion

Pharmacokinetic Parameters (units)		Analyte		
		Levodopa (N = 18)	3-OMD (N = 18)	Carbidopa (N = 18)
Total LCIG Dose (Day 1)	(mg)	1580 ± 403	--	395 ± 101
T_{max}	(h)	2.85 ± 2.31	8.38 ± 5.77	5.70 ± 5.22
C_{max}	(µg/mL)	4.21 ± 1.36	19.0 ± 5.66	0.371 ± 0.149
C_{min}[a]	(µg/mL)	0.447 ± 0.282	15.1 ± 4.85	0.103 ± 0.0667
C_{avg}	(µg/mL)	2.91 ± 0.836	17.1 ± 4.99	0.221 ± 0.0834
AUC_{0-16}	(µg•h/mL)	46.5 ± 13.3	273 ± 79.8	3.54 ± 1.33
AUC_t	(µg•h/mL)	51.2 ± 14.9	316 ± 90.3	4.05 ± 1.65
AUC_{0-24}	(µg•h/mL)	53.8 ± 17.2[c]	--	--
$t_{1/2}$[b]	(h)	1.5 ± 0.19[c]	--	--
CL/F	(L/h)	30.7 ± 7.52[c]	--	--
AUC_{0-16}/Dose	(ng•h/mL/mg)	29.7 ± 5.86	175 ± 40.2	9.22 ± 3.67
AUC_{0-24}/Dose	(ng•h/mL/mg)	34.3 ± 7.78[c]	--	--

a. C_{min} values during the 16 hours of infusion were observed either at time 0 or 5 minutes after start of the infusion and were a result of drug washout prior to establishment of infusion.

b. Harmonic mean ± pseudo-standard deviation.

c. N = 14.

Levodopa from LCIG reaches its Tmax at (median) of 2.5 hours, and it maintains consistent levodopa levels over the course of the infusion. Following termination of infusion, levodopa levels declined rapidly with average half-life of 1.5 hours.

Levodopa is absorbed in the proximal small intestine by active transport. The active transport mechanism is competitive, with neutral amino acids competing for uptake. Food, especially a diet rich in protein can reduce the levodopa uptake from the small intestine. Once absorbed levodopa is converted to dopamine by peripheral AADC however, dopamine does not cross the blood brain barrier. Dopamine is degraded by catecholamine –O- methyl transferase [(COMT) forms 3-O-Methyldopa] and Monoamine oxidase.

The plasma concentration appears to be consistent for both levodopa and carbidopa after an initial rise in level that is likely caused by the morning (bolus) dose (see figures 8 and 9).

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Table 8: Mean Plasma Levodopa Concentration Time Profile in Patients Receiving LCIG 16-hour Infusion

Figure 2. Mean Plasma Concentration versus Time Profiles of Levodopa with LCIG 16-hour Infusion, Linear Scale

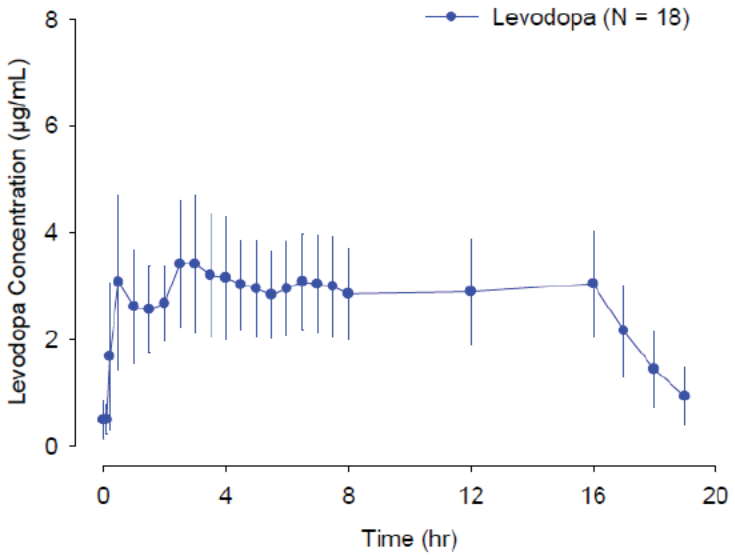
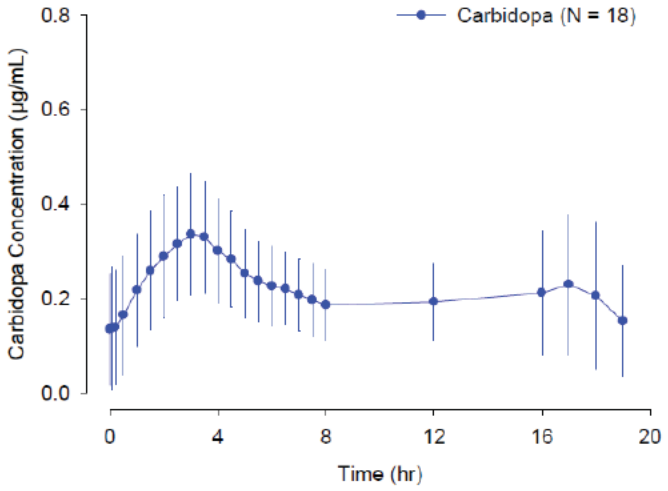


Table 9: Mean Plasma Carbidopa Concentration Time Profile in Patients Receiving LCIG 16-hour Infusion

Figure 6. Mean Plasma Concentration versus Time Profiles of Carbidopa with LCIG 16-hour Infusion, Linear Scale



Carbidopa, Hydrazine, [redacted] (b) (4) and [redacted] (b) (4) [redacted] Levels

The sponsor measured patient samples for the presence of hydrazine, [redacted] (b) (4) and [redacted] (b) (4) Plasma concentrations of hydrazine, [redacted] (b) (4) and [redacted] (b) (4) were determined at the Drug Analysis Department, Abbott Laboratories, using a validated liquid chromatography with

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tandem mass spectrometry method. The methods and quality control validations for each compound was acceptable.

Clinical Pharmacology Reviewer's Comments:
Hydrazine is a degradation product of carbidopa in LCIG, it is a known animal carcinogen and genotoxin whose formation is pH- and temperature- sensitive. Only one subject with LCIG had detectable levels (in 5 out of 7 samples) of hydrazine, measurable hydrazine concentrations ranged from (b) (4) ng/mL (value of AUC (b) (4) was (b) (4) ng.hr/mL). Two of 5 subjects treated with LC-oral showed measurable hydrazine concentra s (b) (4) and (b) (4) ng/mL) only at 1 time point in the 16-hour sampling interval.

(b) (4) (and possibly (b) (4)) is a metabolite of carbidopa. After oral administration of LC, (b) (4) is below the level of quantification, and the median Tmax of (b) (4) is greater than that of CD (6 hr vs., 1.5 hr); indicating (b) (4) is as a metabolite of CD. After LCIG administration, however, while majority of (b) (4) is below the level of quantification, the median Tmax of (b) (4) is less than that of CD (1 hr vs., 2 hr), indicating that the (b) (4) is also a degredant impurity from LCIG is formed and absorbed along with CD from LCIG.

Pharmacometrics Review
Although the sponsor executed two active controlled Phase III studies (Studies 3001 and 3002), total only 30 patients in the PK analysis subset completed Study 3001 with half patients on LCIG and half on LC capsules (the active control), and total only 20 patients completed Study 3002 with 12 patients on LCIG and 8 patients on LC capsules. Clinical data collected for those 50 patients of the Phase III controlled studies are not sufficient for a reasonable exposure-response analysis.

Pharmacokinetic Model
Data from Studies S187-1-002 and S187-3-001/S187-3-002 was used to generate a population model for levodopa pharmacokinetics from LCIG and oral levodopa-carbidopa immediate release formulation (over encapsulated Sinemet at the oral carbidopa levodopa). The Model was created using a nonlinear mixed effects modeling approach with NONMEM software. The final model underwent internal evaluation using the data from the above studies and external evaluation using available pharmacokinetic data from Study S187-3- 004.

The bioavailability estimate for levodopa from LCIG relative to oral levodopa-carbidopa tablets was 97% (95% confidence interval; 95% to 98%) based on the Sponsor's Population PK analysis performed in a subset of patients enrolled in studies S187-1-002, S197-3-001, S187-3-002, and S187-3-004. The intra-subject variability of levodopa plasma concentration (ISVLPC) of LCIG is smaller than the ISCLPC of the oral formulation based on Population PK analysis (2.3% vs., 4.1%).

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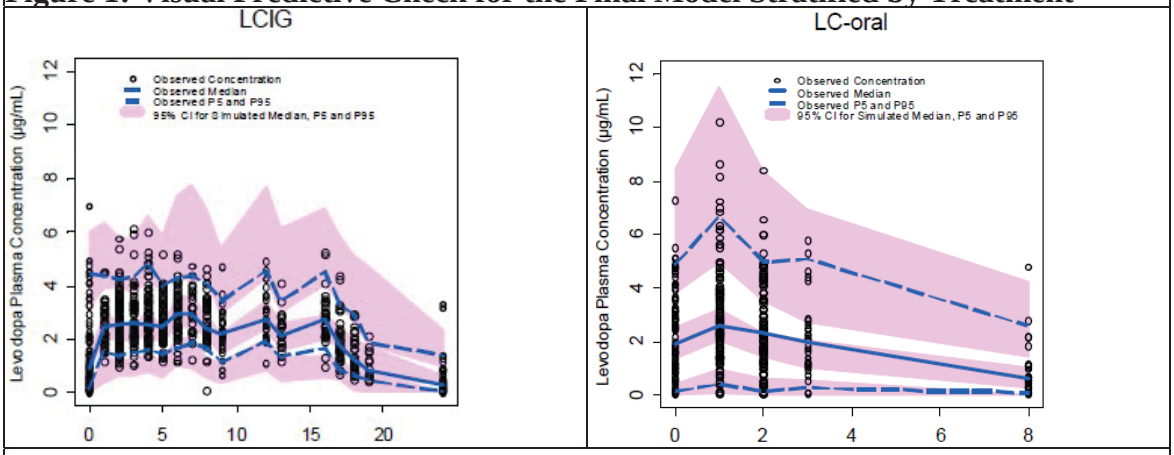
Figure 1: Visual Predictive Check for the Final Model Stratified by Treatment



Source: Page 60 of sponsor's population pharmacokinetics report.

Conclusion:
"*The levodopa population pharmacokinetic model was robust and replicated the features of the data from which it was built in simulations. In addition, the model performed well in external evaluation and was able to adequately predict levodopa plasma concentrations for a study of LCIG that was not utilized in model development.*"

The Pharmacometrics reviewer did not find levodopa clearance was significantly affected by gender or body weight or use of the COMT inhibitor entacapone. Clearance was affected by age but it was not statistically significant so it was not included in the PK model. There were few Non-Caucasians enrolled in the study and only Caucasians were included in the PK subset.

Thorough Qt Study:
A Thorough QT Study was not required for this 505(b)(2) application.

5. Clinical Microbiology

Vinayak B. Pawar, Ph.D., submitted a Microbiology review (July 31, 2013). The application did into contain microbiological data for this nonsterile drug product Levodopa-Carbidopa Intestinal Solution.

6. Clinical/Statistical- Efficacy

Xiang Ling, Ph.D. Division of Biometrics I and Dr. Len Kapcala, MD were the primary Statistical and Clinical reviewers for this application. There were no unresolved issues and both reviewers concluded the pivotal study provided demonstrated a statistically significant superiority of LCIG over oral LC. I concur with their findings.

The U.S. clinical development program includes a Phase 1 pharmacokinetic study, pivotal studies S187-3-001 and S187-3-002 were combined as 1 pivotal Study S187-3-001/S187-3-002 prior to database lock, as agreed with the Agency on 18 January 2011 (Table 1). The clinical development program also includes 3 long-term Phase 3 supportive studies.

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The Sponsor proposed two separate studies (b) (4) Type C meeting was granted by the Agency on January 18, 2011, at the Sponsor's request. The Sponsor proposed combining identical studies S187-3-001 and S187-3-002 into a single study under a revised protocol because of difficulty recruiting patients into the separate studies. (b) (4) The agency also rescinded Fast Track Designation because the patient population studied in the single trial would resemble the population studied for other drugs approved to the treatment of patients PD experiencing "off" time.

The Pivotal Efficacy Study in the LCIG U.S. Development Program N=71		
Study S187-3-001/Study S187-3-002	Randomized, double-blind, double-dummy, multicenter, parallel group studies conducted in the US, Germany, and New Zealand	12-week duration

In the combined pivotal Study S187-3-001/S187-3-002, the key study inclusion criteria required subjects to be levodopa-responsive and to have had an adequate trial of antiparkinsonian therapy as measured by the Parkinson's Disease - Treatment Optimization Scale (PD-TOS), or as described by the Agency communication dated 15 March 2010, to have recognizable "Off" and "On" states (motor fluctuations), and to be experiencing a minimum of 3 hours of "Off" time.

The mean age of patients enrolled in both treatment arms was approximately 64 years. Patients had PD for an average of 10-11 years. Most patients were using two or more anti-PD medications at the time of enrollment but experienced a mean "Off" time of 6-7 hours per day. Overall, the active control study population was approximately two-thirds male and one–third female. This male predominance is consistent with the prevalence of PD which preferentially affects males in the same proportion.

Although 71 patients were enrolled, 66 patients were included in the ITT population and these same patients formed the Completer group. Three patients (n=2 placebo, n= 1 LCIG), withdrew prematurely because of an adverse event. One patients in the placebo group withdrew prematurely because of "lack of efficacy" and another patient was withdrawn because of protocol violation (took prohibited medication).

The **primary efficacy endpoint**, the change in normalized "Off" time (Baseline to Endpoint) Parkinson's Disease Diary The **primary efficacy analysis** was carried out using analysis of covariance (ANCOVA) with the main effects of treatment and country with baseline normalized "Off" time and natural logarithm of mean daily dose of rescue levodopa on days with non-missing symptom diary data as covariates. The same ANCOVA model was used for the analysis of the secondary endpoints.

The **key secondary efficacy endpoint**, the change in normalized "On" time without troublesome dyskinesia (Baseline to Endpoint). This is another diary parameter that the

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review division considers a complement of the same endpoint the Parkinson's Disease Patient Diary.

Other secondary variables: (for hierarchical analysis)

- Change from baseline in PDQ-39 Summary Index
- CGI-I score
- Change from baseline in UPDRS Part II score
- Change from baseline in UPDRS Part III score
- Change from baseline in EQ-5D Summary Index score
- Change from baseline in ZBI Total score

In the LCIG group, **the mean total daily dose of levodopa** was 1117.2 mg (range 632-2983 mg/day) and the mean daily dose of carbidopa was 279.3 (range=158-746 mg/day).

Efficacy Results

The primary efficacy analysis demonstrated a statistically significant LS mean difference(improvement) of –1.91 hours ($P = 0.0015$) from Baseline after 12 weeks of treatment in the average daily normalized "Off" time between the LCIG group and the LC-oral group (LS mean of change, –4.04 hours versus –2.14 hours). The effect of LCIG was consistent across important sub groups (age, gender) and duration of illness. The results of a secondary analysis of the primary efficacy variable using a MMRM model which included Baseline as a fixed-effect covariate; treatment, country, and time as fixed-effect (categorical) factors, and the Baseline by Study Week interaction, was also positive. The effect was consistent in the planned sensitivity analyses as well.

7. Safety

Exposure in the U.S. Development Program

Phase 1 Pharmacokinetic Study		
Study S187-1-002	Open-label, multidose, multicenter study in subjects already on a stable dose of LCIG infusion via PEG-J for at least 30 days	2-day duration
Pivotal Study in original U.S. Development Plan N=71		
Study S187-3-001/Study S187-3-002	Randomized, double-blind, double-dummy, multicenter, parallel group studies conducted in the US, Germany, and New Zealand	12-week duration
Long-term Phase 3 Supportive Studies N=412		
Study S187-3-003	Open-label, multicenter, single arm, continuation treatment of Study S187-3-001/S187-3-002	12-month duration, ongoing
Study S187-3-004	Open-label, multicenter, single arm, with LCIG initial infusion in 2 to 14 day naso-jejunal (NJ) test period followed by a PEG-J 52-week period	54-week duration
Study S187-3-005	Open-label, multicenter, single arm, continuation treatment for subjects in Study S187-3-003 and Study S187-3-004 until LCIG is commercially available in participating countries	Ongoing

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All PEG-J Analysis Set N=395		
All PEG-J	The dataset is **not** mutually exclusive .All subjects who underwent PEG-J placement in the Phase 3 Studies S187-3-001/S187-3-002 (N = 71) and in study S187-3-004 (N = 324) and including continuation into the open-label extension studies S187-3-003 and S187-3-005. The All PEG-J analysis dataset was created for the evaluation of device- and procedure-associated adverse events, including a temporal relationship from the time of first placement of the PEG-J	Completed

The safety database for the U.S. development program included 416 patients with advanced PD. The pivotal study a flexible dose the mean total daily dose of levodopa in the LCIG group was 1164 mg/day (604-2935 mg/day levodopa) and in the active control, LC-oral group, the mean total daily levodopa dose was 1409 mg/day. On the basis of interim data, in open-label Study S187-3-003, the mean total daily dose of levodopa was 1481 mg/day at the end of titration. In Study S187-3-004, the mean total daily dose of levodopa was 1572 mg/day at Week 54. The completed studies ranged from 12 weeks up to 54 weeks in duration, and including the exposure in ongoing extension Study S187-3-003 and Study S187-3-005, subjects received LCIG up to 3.5 years. The Sponsor empaneled a data safety monitoring board (DSMB) who had access to only unblinded safety data.

There were two pools of data, the first, pool included safety data from the active control study. The data from the three open-label trials formed the second data pool. The All PEG-J analysis dataset was created using the controlled and open label datasets in an attempt to capture the procedure related adverse reactions in a separate data pool. The All PEG-J analysis dataset does not include any unique sources of data that is not included in the two safety data pools.

There were no deaths in the active control study. Eighteen deaths were reported in the Open-Label LCIG analysis set (N = 412). Two patients committed suicide (both subjects, ages 45 and 58, had pre-existing relevant histories of depression). A 45-year-old male patient had a history of impulse control disorder and prior suicide attempt. A 58-year-old female only had a history of minor depression prior to committing suicide. Depression with or without self-injury was more frequent in the LCIG treated group (n=4) compared to 1 patient in the active control group. The remaining deaths were attributed to comorbid illness or illness associated with immobility (e.g., pneumonia, falls with fracture and cardiovascular disease) caused by advanced PD.

The frequency of nonfatal, serious adverse events was lower in the LCIG treat group compared to the group treated with oral carbidopa and levodopa. The events were similar to nonfatal, serious events (e.g., psychosis, hallucination, hypotension and dyskinesia) reported in clinical trial involving patients with advanced PD.

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Table 10: Adverse Reactions in the Active Control Trial (>1 person reporting the event) in the LCIG Group) CDTL Table

	LCIG + PBO CAP (N = 37)			*PBO GEL + LC CAP (N = 34)*			
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*	*Risk Diff (per hundred)*
Abdominal pain	21	19	51.35	11	11	32.35	19
Complication of device insertion	38	21	56.76	19	15	44.12	12.64
Nausea	14	11	29.73	9	7	20.59	9.14
Atelectasis	3	3	8.11	0	0	0	8.11
Hypertension	3	3	8.11	0	0	0	8.11
Oedema peripheral	3	3	8.11	0	0	0	8.11
Oropharyngeal pain	3	3	8.11	0	0	0	8.11
Upper respiratory tract infection	3	3	8.11	0	0	0	8.11
Depression	4	4	10.81	1	1	2.94	7.87
Pneumoperitoneum	4	4	10.81	1	1	2.94	7.87
Incision site erythema	8	7	18.92	5	4	11.76	7.15
Bacterial test positive	2	2	5.41	0	0	0	5.41
Excessive granulation tissue	2	2	5.41	0	0	0	5.41
Postoperative ileus	2	2	5.41	0	0	0	5.41
Pyrexia	2	2	5.41	0	0	0	5.41
Rash	2	2	5.41	0	0	0	5.41
Sleep disorder	2	2	5.41	0	0	0	5.41
White blood cells urine positive	2	2	5.41	0	0	0	5.41
Anxiety	3	3	8.11	2	1	2.94	5.17
Confusional state	3	3	8.11	2	1	2.94	5.17
Flatulence	6	6	16.22	4	4	11.76	4.45

Table 11: SMQ Analysis (narrow search) Events (events in the LCIG group >1) CDTL Table

	LCIG + PBO CAP (N = 37)			*PBO GEL + LC CAP (N = 34)*			
SMQ (Narrow Search)	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*	*Risk Diff (per hundred)*
(1) Depression and suicide/self-injury	5	5	13.51	1	1	2.94	10.57
(2) Depression (excl suicide and self injury)	5	5	13.51	1	1	2.94	10.57
(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	60	24	64.86	46	20	58.82	6.04

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(2) Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic *	4	3	8.11	1	1	2.94	5.17
(1) Haemodynamic oedema, effusions and fluid overload *	3	3	8.11	1	1	2.94	5.17
(1) Cardiac arrhythmias	2	1	2.7	0	0	0	2.7
(2) Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)	2	1	2.7	0	0	0	2.7
(3) Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias)	2	1	2.7	0	0	0	2.7
(4) Supraventricular tachyarrhythmias	2	1	2.7	0	0	0	2.7

* after SMQ name indicates SMQ with narrow terms only. Broad search will yield the same results.
Number in parenthesis before SMQ name represents SMQ level.

Table 12: Adverse Reactions in Open Label Studies (events ≥ 5%) CDTL Table

	LCIG (N = 412)		
PT	*Events*	*Number of subjects*	*Proportion (X100=%)*
Complication of device insertion	299	161	0.39
Abdominal pain	200	133	0.32
Procedural pain	119	97	0.24
Insomnia	154	94	0.23
Nausea	155	89	0.22
Constipation	131	86	0.21
Fall	164	80	0.19
Postoperative wound infection	134	80	0.19
Excessive granulation tissue	109	72	0.17
Incision site erythema	95	70	0.17
Urinary tract infection	110	64	0.16
Orthostatic hypotension	88	55	0.13
Anxiety	83	54	0.13
Parkinson's disease	78	51	0.12
Weight decreased	74	50	0.12
Depression	69	47	0.11
Dyskinesia	73	47	0.11
Procedural site reaction	74	45	0.11
Headache	60	44	0.11
Vomiting	69	43	0.1
Post procedural discharge	56	41	0.1
Back pain	64	40	0.1

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Vitamin B6 decreased	54	39	0.09
Diarrhoea	56	38	0.09
Blood homocysteine increased	57	36	0.09
Sleep attacks	55	35	0.08
Dyspepsia	36	31	0.08
Musculoskeletal pain	40	31	0.08
Oropharyngeal pain	33	30	0.07
Arthralgia	49	29	0.07
Pain in extremity	41	29	0.07
Decreased appetite	38	28	0.07
Hallucination	36	28	0.07
Dizziness	31	26	0.06
Flatulence	29	23	0.06
Pneumoperitoneum	24	23	0.06
Laceration	27	22	0.05
Pneumonia	22	22	0.05
Abdominal distension	22	21	0.05
Fatigue	27	21	0.05
Incision site pain	25	21	0.05
Abdominal discomfort	30	20	0.05

Table 13: Exploratory SMQ Analysis (narrow search) in Open Label Studies (events ≥ 5%) CDTL Table

	LCIG (N = 412)		
SMQ (Narrow Search)	*Events*	*Number of subjects*	*Proportion (%)*
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	825	233	0.57
(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	719	214	0.52
(1) Extrapyramidal syndrome	245	108	0.26
(1) Accidents and injuries	282	104	0.25
(2) Parkinson-like events	134	70	0.17
(1) Oropharyngeal disorders *	92	61	0.15
(1) Depression and suicide/self-injury	87	58	0.14
(2) Depression (excl suicide and self-injury)	83	56	0.14
(2) Haemorrhage terms (excl laboratory terms) *	80	55	0.13
(1) Haemorrhages	81	55	0.13
(2) Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic *	79	52	0.13
(2) Dyskinesia	77	49	0.12
(2) Gastrointestinal nonspecific dysfunction	59	45	0.11

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(1) Gastrointestinal perforation, ulceration, haemorrhage or obstruction	74	43	0.1
(1) Psychosis and psychotic disorders	61	39	0.09
(1) Peripheral neuropathy	39	30	0.07
(2) Gastrointestinal nonspecific inflammation	47	29	0.07
(1) Malignancies *	43	28	0.07
(1) Haemodynamic oedema, effusions and fluid overload *	36	27	0.07
(3) Malignant tumours *	41	27	0.07
(2) Malignant or unspecified tumours *	41	27	0.07
(1) Hypertension	34	24	0.06
(1) Embolic and thrombotic events *	23	20	0.05
(2) Skin malignant tumours	25	19	0.05
(1) Skin neoplasms, malignant and unspecified	25	19	0.05
(2) Dystonia	32	19	0.05

* after SMQ name indicates SMQ with narrow terms only. Broad search will yield the same results.
Number in parenthesis before SMQ name represents SMQ level.

Division of Gastroenterology & Inborn Errors Products Consult

The Sponsor's analysis of safety includes information specific to endoscopic procedure for device insertion, and device related adverse reactions. The Division consulted the Division of Gastroenterology & Inborn Errors Products (Primary reviewer-Julie Tomaino, MD, MSCR)

The Sponsor empaneled the LCIG Gastrointestinal Device Safety Adjudication Committee (LGDAC). The purpose of the LGDAC was to review, evaluate, and adjudicate the LCIG gastrointestinal (GI) and device-related safety data from study S187.3.001/3.002 (controlled) and studies S187.3.003, S187.3.004, and S187.3.005 (open label). The goals of the LGDAC were to:

- Classify what AEs associated with device events (DEs) are clinically meaningful;
- Categorize expectedness, severity, and the time course of AEs;
- Propose strategies that may decrease the incidence, severity, and/or duration of events;

The LGDAC included three GI specialists (voting members) and a fourth non-voting executive secretary (not an employee of Abbott).

To facilitate analysis of procedure and device related adverse events, adverse events (AEs) were double-coded to more than 1 preferred term (PT) in the procedure- and device-associated adverse events of special interest. The majority of AEs reflecting complications of device insertion were also coded to one or more of the following PTs that described event presentation: abdominal pain, abdominal discomfort, abdominal distension, flatulence, or pneumoperitoneum. AEs of complication of device insertion and abdominal pain were double-coded to both of these PTs for the majority of patients with these events (109 of 156 patients with complication of device insertion, 109 of 135 patients with abdominal pain). Other non-serious AEs that were double coded to the PT of complication of device insertion included abdominal discomfort, abdominal pain upper, duodenal ulcer, duodenal ulcer

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hemorrhage, erosive duodenitis, gastritis erosive, gastrointestinal hemorrhage, peritonitis, pneumoperitoneum, and small intestine ulcer. *"Therefore, the percentage of PEG-related AEs reported during the clinical trials may appear higher than those reported in the literature because of the double coding used by the sponsor in the analysis of the safety data"*.

Dr. Tomaino, noted the largest difference between the groups is for reports of abdominal pain: 19 (51.4%) patients who received LCIG + placebo capsule vs. 11 (32.4%) patients who received placebo gel + Levodopa-Carbidopa capsules. Since both treatment arms underwent placement of a PEG-J, this difference suggests that the increase in abdominal pain may be related to the direct infusion of the drug into the jejunum compared to administration of oral capsules. However, the small sample size makes causality difficult to establish.

G.I. Consultant Conclusions:
The procedure- and device-related adverse events identified by the sponsor appear to be consistent with the type of complications that are known to be associated with the placement and continued use of percutaneous endoscopic gastrostomy (PEG) and percutaneous endoscopic gastrostomy with jejunal extension (PEG-J).

Dr. Tomaino, agreed with the following conclusions and recommendations of the GI adjudication committee .

- Because this patient population may be more mobile than the majority of adult patients who require PEG or PEG-J placement, these patients may be at high risk for complications of tube migration or breakage due to increased mobility.

- The outer bolster should not be released and the tube should not be moved within 72 hours of placement to reduce leakage of stomach contents and allow the tract to heal.

- "To ensure that the G-tube bolster is not too tight to the abdominal wall, the G-tube should be gently rotated less than 90 degrees clockwise and counter clockwise without over-twisting to avoid potential displacement of the J-tube."

- The "*Consensus Recommendations for Best Practice*" should be communicated to prescribers and patients.

Depression:
There were more patients with reported depression in the LCIG group compared to placebo. SMQ analysis using narrow search criteria indicates a greater risk (risk difference) for depression in patients treated with LCIG compared to oral levodopa. There were two completed suicide. One of the patients who committed suicide was a 48-year-old male in the open label study, had a history of previous suicide attempt and depression. He also suffered from an impulse control disorder. A second patient committed suicide; she was a58-year-old female with a history of depression and anxiety. She was treated with oral antidepressants and anxiolytics but had no other psychiatric illness or previous suicide attempt. The increased frequency of depression in the LCIG group compared to the LC group in the controlled study and the high proportion of patients in the open label study who reported depression as an

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adverse event suggests there is an increased risk for depression in patients treated with LCIG. Depression and suicide is already described briefly in the Warnings section of the Sinemet label. We may consider expanding on the warning in the LCIG label.

Neuropathy:
Postmarketing cases of polyneuropathy have been reported in patients treated with LCIG[1]. The sponsor was asked to treat neuropathy as an adverse event of special interest during our pre-submission, Type C meeting. The characteristics and time to onset was similar between clinical studies and postmarketing events with the highest incidence of polyneuropathy at or after 360 days of treatment in the clinical group and with a median time to onset of 285 days in the postmarketing data. The sponsor included laboratory assessments of vitamin B12, folate, vitamin B6 and Methyl Malonic Acid (MMA) at baseline and periodically during the active control trial. There was no laboratory data clearly linking a nutritional or specific B12 or B6 vitamin deficiency to cases of neuropathy but most cases of neuropathy had low levels of one or the other.

The Sponsor empaneled a committee of neuromuscular specialists to adjudicate events that met case criteria for polyneuropathy. The committee consisted of three neurologists who specialized in the diagnosis and treatment of neuromuscular disorders. The criteria were sufficiently broad and were bases on MedDRA standardized queries for Guillain-Barré Syndrome and peripheral neuropathy or Abbott's customized query to capture cases of neuropathy.

Nineteen patients met criteria for peripheral neuropathy, the onset of the neuropathy could be determined in 14 cases. Of these cases, 1 case was acute, 7 cases were subacute, and 6 cases were chronic. Seven patients were classified as mild neuropathy, 10 as moderate and 1 as severe neuropathy. The onset of acute and subacute cases had an onset of between approximately 200 and 390 days. Cases of chronic neuropathy started with in 81 to 395 days.

The panel recommended close clinical monitoring for signs of developing polyneuropathy. They recommended testing for B6, B12, folate and MMA levels prior to starting LCIG and every 3 months on treatment but it is not clear that any of these laboratory tests are predictive of neuropathy. They recommend that patients who develop neuropathy stop LCIG and switch to oral LC. However, recent publications suggest that even oral levodopa may be associated with neuropathy[2]

CDTL Comment:
There are no clinical safety issues that prevent approval of the application. The safety concerns related to hydrazine, depression and neuropathy can be addressed in labeling. The adverse events related the PEG-J procedures are similar to those experienced by patients who have the procedure for reasons other than LCIG therapy. There are no recommended Postmarketing Commitments and Requirements. I recommend postmarketing surveillance for depression/suicidality and neuropathy through pharmacovigilance monitoring by the Sponsor.

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[1] (Santos-Garcia, de la Fuente-Fernandez, & Valldeoriola, 2012)
[2] (Ceravolo, Cossu, & Bandettini di Poggio, 2013)

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In the revised version of his review, Dr. Kapcala, recommended a Postmarketing Requirement for a 6-month controlled trial to study safety in patients taking LCIG or a comparator. Polyneuropathy was diagnosed in the clinical trials population after 6 months of treatment. The controlled study population was small because of difficulty recruiting patients making a larger study less feasible. If patients were treated previously with oral levodopa and carbidopa, prior to treatment with LCIG, it may confound the study results. Such a trial would also require stratification or exclusion criteria based on risk factors for neuropathy such as diabetes, low B12 and B6 and collagen vascular and rheumatologic disease, increasing the necessary sample size. Repeated nerve conduction studies with needle EMG is uncomfortable and painful, likely causing participants to withdraw from the proposed trial prematurely. It may be ethically difficult to justify delivering electrical shocks for nerve conduction studies needle EMG at several time points during the study. It may also cause a large percentage of patients with no signs of neuropathy to withdraw from the study prematurely.

The data provided in the NDA indicates that abnormal levels of B12, folate, MMA or B6 do not identify patients who are destined to develop neuropathy from LCIG. A 6-month study would miss more than half the cases of neuropathy and the laboratory data alone is not predictive of neuropathy.

Depression is already described in the Sinemet (reference list drug) label. Although I agree with changing the Warning statement to clearly state the potential for increased risk associated with levodopa and carbidopa, new controlled study information is unlikely to significantly change the statement in Warnings.

8. Advisory Committee Meeting

An Advisory Committee was not held for this application.

9. Pediatrics

Pediatric studies under PREA are not required for this Orphan designated product.

10. Other Relevant Regulatory Issues

Controlled Substances Staff Consult:
The sponsor submitted abuse potential assessment for Carbidopa and Levodopa in the NDA. The Division consulted the CSS to review this information.

<u>CSS Conclusion:</u>
"Based on all information submitted by the Sponsor to date, and in consideration of the lack of abuse-related signals for levodopa/carbidopa in epidemiological data in the medical literature, CSS has concluded that Dudopa does not have abuse potential".

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Clinical Site Inspections by OSI
Office of Scientific Investigations inspected three clinical study sites (selected because high enrollment) for study S187.3.001and S187.3.002 (merged). All three sites were domestic sites that enrolled a combined total of 23 patients. All three sites were classified as No Action Indicated following inspection.

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Financial disclosures:
The sponsor disclosed the names of investigators who received compensation or grant awards that exceed the reporting threshold. Dr. Kapcala notes that none of the investigators were likely to have affected the outcome of the pivotal efficacy study

11. Labeling

Proprietary Name Review:

In September, DMEPA notified Abbvie that:

> *"We have completed our review of the proposed proprietary name,* ***Duopa*** *and have concluded that it* ***is acceptable****."*

Patient Labeling Review
LaShawn Griffiths, MSHS-PH, BSN, RN, Associate Director for Patient Labeling, Office of Medical Policy Initiatives, Division of Medical Policy Programs (DMPP)

Due to outstanding clinical deficiencies, DNP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

DMEPA Carton and Container Labeling Review
Dr. Neshiewat reviewed the carton and container labeling and has an extensive list of recommendations. Labeling was not discussed with the sponsor because of deficiencies that preclude approval of the application this cycle. The comments from Dr. Neshiewat will be conveyed to the Sponsor prior to the End of Review meeting.

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12. Recommendations/Risk Benefit Assessment

Complete Response. Review of this application identified multiple deficiencies in, the CMC (b) (4), Biopharmaceutics (dissolution specification) and the CDRH Safety Engineering reviews. In addition, changes made to the Patient IFU need to be reassessed in human factors or labeling comprehension studies. The Sponsor submitted labeling changes combining the (b) (4) into a single document (unsolicited). The combined document was submitted to the NDA after the primary DMEPA and CDRH HF review were complete. The combined Pump Operators Manual will not be reviewed this cycle. The sponsor will be made aware of potential issues in the revised Pump Operator document during the End of Review meeting (if requested) or early in the next review cycle.

The was pivotal study provides substantial evidence of effectiveness of LCIG for reducing off time in patients with advanced PD experiencing at least 3 hours of off time per day. The safety concerns of depression/suicidality and neuropathy will be addressed in labeling. The procedure related adverse reactions are consistent with those reported in patients who have PEG tubes inserted to other reasons.

The potential risks associated with high levels of hydrazine are worrisome but do not preclude approval in a population of advanced PD with limited treatment options, such as Deep Brain Stimulation that may also pose substantial risk to patients related to the procedure and infection. However, given the potential for an increased risk for carcinogenicity and lack of conclusive evidence in humans, patients with less advanced PD should not be encouraged to use LCIG. In addition, providers should be discouraged from prescribing one cassette per day (2000 mg levodopa component) delivered over 16 hours in a single day. The sponsor states that (b) (4) However, the sponsor should be encouraged to explore methods, such as (b) (4)

Risk Benefit Assessment

The benefit to patient with advanced PD experiencing significant daily off time appears to be substantial and the results demonstrate robust p-values with internal consistency across most of the secondary endpoints. The potential risk associated with increased levels of hydrazine as a human carcinogen remains a safety concern however; this risk is considered in setting of a population experiencing substantial impairment in mobility and limited treatment options.

The Sponsor's request for a REMS with an ETASU (b) (4)

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(b) (4) There was no justification in the REMS document or in evidence in the safety data, that the PEG-J procedure poses an increased risk for adverse reactions that is greater than the risk associated with feeding tube insertion. The REMS Oversight Committee (ROC) agreed with the division that a REMS with or without an ETASU is not recommended for this application.

The primary clinical reviewer Dr. Kapcala, recommended a Postmarketing Requirement for a 6-month, controlled safety study. However; the study is unlikely to provide definitive information for the safety issues of concern therefore, I do not recommend requiring a Postmarketing safety study as described by Dr. Kapcala, at this time. None of the other review disciplines requested postmarketing studies at this time.

Comments will be conveyed to the applicant in the regulatory action letter.

Reference ID: 3468986

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/s/

GERALD D PODSKALNY
03/11/2014