Summary of Report Results

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: DUODOPA® Intestinal Gel	**Volume:**	
Name of Active Ingredient: Levodopa-Carbidopa	**Page:**	

Title of Study: A Randomized, Double-Blind, Double-Dummy, Efficacy, Safety, and Tolerability Study of Levodopa-Carbidopa Intestinal Gel in Levodopa-Responsive Parkinson's Subjects Receiving Optimized Treatments with Parkinson Medicinal Products Who Continue to Experience Persistent Motor Fluctuations

Coordinating Investigator: Alberto J. Espay, MD, MSc

Study Sites: 29 sites in the USA, Germany, and New Zealand screened at least 1 subject and 26 sites randomized subjects.

Publications: 5 published abstracts

Studied Period (Years): 2 First Subject First Visit: 06 Jan 2009 Last Subject Last Visit: 26 Oct 2011	**Phase of Development:** 3

Objective: The primary objective of this study was to demonstrate the superiority of treatment with Levodopa-Carbidopa Intestinal Gel (LCIG) over treatment with optimized oral levodopa-carbidopa immediate release (IR) during 12 weeks of treatment. The pharmacokinetic objective was to evaluate the pharmacokinetics of levodopa following administration of LCIG.

Methodology: Study S187-3-001 and Study S187-3-002 were 2 identically designed, Phase 3, 12-week, randomized, double-blind, double-dummy, parallel-group, multicenter studies recruiting subjects from distinct sites. These studies evaluated the efficacy, safety, and tolerability of LCIG in the treatment of levodopa-responsive subjects with advanced PD who had persistent severe motor fluctuations, despite optimized treatment with oral levodopa-carbidopa, concomitant with other available antiparkinsonian medications. Subjects were randomized to either LCIG active gel + placebo capsules or levodopa-carbidopa IR active capsules + placebo gel. Both treatment arms received the percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) procedure for gel administration, active LCIG or placebo gel. Data from these 2 studies were combined for analysis.

Methodology (Continued):

These studies consisted of a Screening Period (open-label treatment with oral levodopa-carbidopa, adjustment for antiparkinsonian medication, and completion of Baseline procedures), a Hospitalization Period for the PEG-J placement, and a double-blind Treatment Period (randomization, initial titration, and study drug treatment for 12 weeks).

Subjects' pre-study levodopa-carbidopa oral medication was converted during the Screening Period to a levodopa-carbidopa 100/25 mg IR tablet formulation in order to standardize their dosing regimen and to ensure compatibility with the study drugs. Subjects were trained on PD symptomatology and completion of the Parkinson's Disease Diary. Subjects were allowed to maintain their pre-study stable antiparkinsonian medications during the Treatment Period.

Number of Subjects (Planned and Analyzed): Approximately 62 subjects across Study S187-3-001 and Study S187-3-002 were planned to be randomized to treatment, 31 subjects to each of the 2 treatment groups. Seventy-one subjects were randomized to treatment, 37 to LCIG + placebo capsules and 34 to LC-oral + placebo gel. Sixty-six subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, at least 30 years of age, with idiopathic Parkinson's disease, according to the United Kingdom Parkinson's Disease Society Brain Bank Criteria, who experienced motor complications despite optimized available therapy and:

- Were levodopa-responsive
- Had an adequate trial of antiparkinsonian therapy (according to the Parkinson's Disease – Treatment Optimization Scale or the specifications in Inclusion Criterion 3, whichever was applicable at the time of the subject's enrollment)
- Had recognizable "Off" and "On" state (motor fluctuations), confirmed by the Parkinson's Disease Diary recordings
- Were experiencing a minimum of 3 hours of "Off" time
- Received Enrollment Steering Committee review and approval of eligibility

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

Study Drug	Formulation	Bulk Lot Numbers (Study S187-3-001)	Bulk Lot Numbers (Study S187-3-002)
LCIG in medication cassette reservoir	Aqueous gel levodopa (20 mg/mL) carbidopa (5 mg/mL)	08F04G07, 08F04G08, 08F08G95, 08F08G96, 08F08G97, 08K25G23, 10B24G21, 10I08G06, 11B09G06	08K25G23, 10B24G21, 10I08G06, 10K02G03

Duration of Treatment: 12 weeks

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

Study Drug	Formulation	Bulk Lot Numbers (Study S187-3-001)	Bulk Lot Numbers (Study S187-3-002)
Placebo gel in medication cassette reservoir	Aqueous gel	08E22G16, 08E28G24, 08K16G10, 09D22G06, 09D22G07, 09D23G08, 09D23G09, 10B21G15, 10B21G16, 10B22G17, 10B28G25, 10I09G09, 10I10G10, 10I10G11, 10I15G98	10I17G17, 10I17G18, 08F03G04, 08F10G17, 08K23G20, 08K23G21, 09D27G10, 09D27G11, 09D28G12, 10B22G17, 10B22G18, 10B28G24, 10B28G25, 10I15G98, 10K01G02, 10K02G05, 10K03G07

Levodopa-carbidopa IR capsules (active control), oral encapsulated tablets, levodopa (100 mg) carbidopa (25 mg), bulk lots 296080, 316043, 346001.

Placebo capsules, oral, bulk lots 295399, 316033, 346000.

Levodopa-carbidopa IR, oral tablets (used during Screening Period for open-label treatment optimization), bulk lots 293525, 308274.

Criteria for Evaluation

Efficacy:

Primary Variable

Change from Baseline to Week 12 (Endpoint) in average daily normalized "Off" time (hours). The Week 12 value was determined on the basis of the 3 consecutive day normalized average of "Off" time from the Parkinson's Disease Diary.

Secondary Variables

- Change from Baseline in average daily normalized "On" time without troublesome dyskinesia ("On" time without dyskinesia and "On" time with non-troublesome dyskinesia) at Week 12.
- Change from Baseline in Parkinson's Disease Questionnaire (PDQ-39) Summary Index at Week 12.
- Clinical Global Impression – Improvement (CGI-I) score at Week 12.
- Change from Baseline in Unified Parkinson's Disease Rating Scale (UPDRS) Part II score at Week 12.
- Change from Baseline in UPDRS Part III score at Week 12.
- Change from Baseline in EuroQual Quality of Life – 5 Dimensions (EQ-5D) Summary Index at Week 12.
- Change from Baseline in Zarit Burden Interview (ZBI) Total score at Week 12.

Criteria for Evaluation (Continued)

Pharmacokinetic:

Plasma concentrations of levodopa, carbidopa, 3-OMD, DHPA, DHPPA, and hydrazine were tabulated by subject, nominal visit week (Week 4 [for samples on Day 28 and Day 29], Week 6 [for samples on Day 42 and Day 43], and Week 12 [for samples on Day 84 and Day 85]) and sampling time relative to start of gel (LCIG or placebo) infusion.

Safety:

The safety and tolerability of LCIG were evaluated with physical and neurological examinations, measurements of vital signs, ECG collections, clinical laboratory assessments, adverse event monitoring, monitoring for sleep attacks, development of melanoma, excessive impulsive behavior, abnormal involuntary movements, and monitoring for complications of the device system.

Statistical Methods

Efficacy:

The primary analysis was performed on the change from Baseline in average daily normalized "Off" time (hours) for the 3 day average "Off" time for the Parkinson's Disease Diary data at Week 12 (Endpoint), based on the Full Analysis (FA) data set (all subjects who had the PEG-J implanted, had a Baseline efficacy evaluation and at least 1 postbaseline efficacy assessment) using last observation carried forward (LOCF) as the imputation method that was applied to the value for "Off" time obtained from the Parkinson's Disease Diary.

The primary analysis was carried out using analysis of covariance (ANCOVA) 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.

Further supportive/sensitivity analyses for the primary efficacy variable were based on alternative imputation schemes using the observed cases data, mixed model repeated measures (MMRM) analysis.

If the null hypothesis for the primary analysis was rejected with statistical significance ($P \leq 0.050$) in favor of the alternative hypothesis that there were larger decreases in "Off" time in the LCIG infusion group compared to the active control group, additional hierarchal testing was to be performed for the key secondary variable and other secondary variables at the 0.050 level, using a similar approach. The claim for superiority was to cease at the point that a secondary variable failed to demonstrate statistical significance at the $P \leq 0.050$ level.

Statistical Methods (Continued)

Efficacy:

Subgroup analyses of the primary efficacy endpoint were performed by gender, age group ($< 65, \geq 65$), and country (US, ex-US). An ANCOVA was used to evaluate treatment-by-subgroup interaction. The factors in the model were treatment, country, subgroup, treatment-by-subgroup interaction with the corresponding Baseline normalized "Off" time as a covariate.

Efficacy analyses were performed on the FA data set, and ANCOVA and MMRM analyses were also performed on the Completers data set (all subjects in the FA who completed the study) and the Resistant Patients data set (all subjects in the FA who met study Inclusion Criteria 3 for confirming "resistant" patients exposed to adequate trials of PD treatment).

Pharmacokinetic:

Statistical analyses of the inter-subject and intra-subject variability in plasma concentrations of levodopa, carbidopa, and 3-OMD were based on a linear mixed effects model for log concentrations with fixed effect (classification) for time and random effects for subject and occasion within subject.

Safety:

Descriptive statistics over time were presented to help detect trends, via changes within the treatment groups or differences between groups. Safety was evaluated using adverse events summarized by MedDRA system organ class and preferred term, and changes in laboratory parameters, ECGs, vital sign measurements, sleep attacks, development of melanoma, excessive impulsive behavior, abnormal involuntary movements, and monitoring for complications of the device system.

Summary/Conclusions

Efficacy Results:

The primary efficacy analysis demonstrated a statistically significant LS mean difference in favor of the LCIG group in change of normalized "Off" time of –1.91 hours ($P = 0.0015$). After 12 weeks of treatment, a clinically relevant greater mean decrease (improvement) from Baseline in the average daily normalized "Off" time was observed in the LCIG group compared to the LC-oral group (LS means, –4.04 hours versus –2.14 hours). The statistically significantly greater mean decrease (improvement) in normalized "Off" time was apparent within the first 4 weeks of LCIG treatment, and was maintained throughout the study duration of 12 weeks, as reflected by the MMRM analysis of the primary efficacy variable. Sensitivity analyses of the primary endpoint were consistent with the primary analysis, affirming the robustness of the primary endpoint findings.

The key secondary efficacy variable demonstrated a statistically significant LS mean difference (improvement) from Baseline in the average daily normalized "On" time without troublesome dyskinesia of 1.86 hours ($P = 0.0059$) between the LCIG group and the LC-oral group (LS mean of change, 4.11 hours versus 2.24 hours). This increase in "On" time without troublesome dyskinesia complemented the decrease in "Off" time observed with the primary efficacy variable. Evaluation of both the primary variable and the key secondary variable using data from the Parkinson's Disease Diary provided consistency in the measurements of change in subjects' motor fluctuations throughout the study.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

The next 3 secondary variables evaluated in hierarchical order, PDQ 39 Summary Index, CGI-I score, and UDPRS Part II score, all demonstrated statistically significant superiority of LCIG treatment over LC-oral treatment. The remaining secondary variables in the hierarchical order, UDPRS Part III score, EQ-5D Summary Index, and ZBI Total score, did not demonstrate a statistically significant difference between treatment groups. In general, the results of the MMRM analyses were consistent with the findings of the ANCOVA for the secondary efficacy variables.

In the analysis of "On" time without dyskinesia, the LS mean of change was an improvement of 3.37 hours for the LCIG group and 1.09 hours for the LC-oral group, with an LS mean difference of 2.28 hours ($P = 0.0142$), in favor of the LCIG group over the LC-oral group. In contrast, the LS mean of change from Baseline in average daily normalized "On" time with non-troublesome dyskinesia was an improvement of 0.81 hours for the LCIG group and 1.54 hours for the LC-oral group (LS mean difference, –0.73 hours [$P = 0.3294$]). When these results were evaluated in the context of the primary efficacy variable, the reduction in "Off" time (LS mean of change, –4.04 hours) for the LCIG group suggested that most of the reduction was concurrent with the increase in "On" time without dyskinesia, whereas the reduction in "Off" time (LS mean of change, –2.14 hours) for the LC-oral group suggested that the majority of the reduction was concurrent with the increase in "On" time with non-troublesome dyskinesia. These results are supported by the overall subject improvement observed in the PDQ-39 Summary Index and the UPDRS Part II score.

Results of efficacy analyses of the Completers data set and the Resistant Patients data set were consistent with the results of the related analyses of the FA data set. Subgroup analysis of gender, age group, or country showed no statistically significant treatment-by-subgroup interaction for any of these subgroups.

Pharmacokinetic Results:

During hour 2 to 16 following initiation of LCIG infusion or administration of the first morning levodopa-carbidopa oral (LC-oral) capsule, the intra-subject variability in levodopa and carbidopa concentrations were much lower for subjects treated with LCIG (21% and 25%, respectively) than for subjects treated with LC-oral (67% and 39%, respectively). Similarly, the inter-subject variability in levodopa and carbidopa concentrations were much lower for subjects treated with LCIG (35% and 31%, respectively) than for subjects treated with LC-oral (93% and 70%, respectively).

A population model for levodopa pharmacokinetics from LCIG and oral levodopa-carbidopa immediate release formulation (over-encapsulated sinemet, LC-oral) was developed using available data from this study and from the Phase 1 study (Study S187-1-002). The final levodopa population pharmacokinetic model was a two-compartment model with a transit compartment for absorption, first-order elimination, bioavailability for LCIG relative to LC-oral, different first-order transit absorption rate constants for LCIG versus LC-oral and different residual (intra-subject) variability for LCIG versus LC-oral. Inter-subject variability was estimated for CL, Vc and K_{TR} using exponential models. The residual variability was estimated using a combined additive and proportional error models. Body weight was a statistically significant covariate for the volume of the central compartment (volume of the central compartment allometrically scaled on body weight with an exponent of 1). Levodopa clearance was not found to be statistically significantly correlated with body weight or sex of the subject ($P > 0.01$). Additionally, no statistically significant relationship was found between concomitant use of catechol-O-methyl transferase, entacapone, and levodopa clearance. Age almost reached significance for inclusion as a covariate for levodopa clearance ($P = 0.0057$). The model estimated apparent clearance (CL/F) of levodopa, when co-administered with carbidopa, was 24.8 L/h in subjects with advanced

Parkinson's disease. The apparent steady-state volume of distribution (V_{ss}/F) of levodopa was approximately 130 L for a 70 kg subject. LCIG showed comparable bioavailability to LC-oral with estimated relative bioavailability of 97% (95% bootstrap confidence interval of 95% to 98%). LCIG was absorbed faster than LC-oral, which is consistent with delivery of levodopa/carbidopa directly to the jejunum with LCIG. The first-order absorption transit rate constant was estimated to be 9.2 hr^{-1} for LCIG and 2.4 hr^{-1} for LC-oral. The inter-subject variability was estimated to be 88% for the absorption transit rate constant, 33% for levodopa apparent clearance, and 60% for levodopa central volume of distribution. Administration of LCIG was estimated to be associated with approximately half the intra-subject variability in levodopa concentrations compared to administration of LC-oral in subjects with advanced Parkinson's disease. The estimated proportional residual error (first component of intra-subject variability) was 15% for LCIG versus 29% for LC-oral. The estimated standard deviation of the additive residual error in levodopa concentrations (second component of intra-subject variability) was 0.3 µg/mL for LCIG versus 0.59 µg/mL for LC-oral.

Safety Results:

There were no deaths during the study. A total of 12 of 71 subjects (16.9%) experienced at least 1 treatment-emergent serious adverse event: 5 of 37 (13.5%) subjects in the LCIG group and 7 of 34 (20.6%) subjects in the LC-oral group. Serious adverse events assessed by the investigator as possibly or probably related to the study drug system were experienced in the LCIG group, as follows: 2 events of confusional state and 1 event each of pneumoperitoneum, complication of device insertion, catheter site cellulitis, hypersomnia, delusions, hallucinations, mutism, and psychotic disorder. In the LC-oral group, serious adverse events possibly or probably related to the study drug system included 2 events of pneumonia and 1 event each of neutropenia, abdominal pain, peritonitis, complication of device insertion, postprocedural complication, elevated body temperature, depressed level of consciousness, mental status changes, psychotic disorder, and orthostatic hypotension.

Summary/Conclusions (Continued)

Safety Results (Continued):

A total of 3 of 71 (4.2%) subjects experienced treatment-emergent adverse events that led to study termination. One subject in the LCIG group experienced serious adverse events of psychotic disorder with hallucinations on Day 12 that the investigator assessed as possibly related to study drug treatment and the reason for discontinuation from the study. Two subjects in the LC-oral group discontinued the study prematurely: 1 subject experienced serious adverse events of peritonitis and postprocedural complication (as well as pneumonia and neutropenia) that led to study drug discontinuation on Day 2, and another subject experienced an adverse event of postprocedural discharge that led to study drug discontinuation on Day 9.

Most subjects experienced at least 1 treatment-emergent adverse event during the study (69 of 71 subjects, 97.2%). Adverse events related to the complication of device insertion were the most frequently reported (36 of 71, 50.7%, of subjects across treatment groups, 21 of 37 subjects from the LCIG group and 15 of 34 subjects from the LC-oral group). The next most frequently reported treatment-emergent adverse events were GI related, including abdominal pain (30 of 71, 42.3%, subjects, 19 of 37 subjects from the LCIG group and 11 of 34 subjects from the LC-oral group). Most adverse events were mild or moderate in severity. Severe adverse events were experienced by 19 of 71 subjects, 26.8%. Overall, the incidence of adverse events was noticeably higher in the first 2 weeks of the study (subsequent to the PEG-J procedure) compared to Weeks 3 to 12. A decline in the incidence of adverse events was observed over time.

Adverse events of special interest were identified on the basis of ongoing risk management activities in countries where the LCIG System is currently approved for marketing. These adverse events of special interest were identified using MedDRA queries (SMQ or CMQ) and were not based on a temporal relationship of the adverse event to the PEG-J procedure. Overall, a total of 55 of 71 (77.5%) subjects (28 from the LCIG group and 27 from the LC-oral group) experienced at least 1 treatment-emergent adverse event related to long-term complications of the PEG-J, and 40 of 71 (56.3%) subjects (21 from the LCIG group and 19 from the LC-oral group) experienced adverse events relating to risks of PEG-J insertion. Device-associated GI disorders (postprocedural complication and postprocedural hemorrhage) during long-term therapy were reported in 2 of 71 subjects (2.8%) from the LC-oral group. An incidence of 12.7%, 9 of 71 subjects (6 subjects from the LCIG group and 3 subjects from the LC-oral group), was reported for aspiration, and an incidence of 9.9%, 7 of 71 subjects, was reported for weight loss, 1 subject from the LCIG group and 6 from the LC-oral group. Polyneuropathy-related adverse events were reported in 4 of 71 subjects, 5.6%, (1 from the LCIG group and 3 from the LC-oral group). No subject experienced adverse events of cardiovascular fatalities. As a particular MedDRA preferred term might be relevant for more than 1 category of device- and procedure-related adverse events, these categories are not mutually exclusive; a particular adverse event may have been included in more than 1 category.

Summary/Conclusions (Continued)

Safety Results (Continued):

A total of 63 of 71 subjects (88.7%), 34 from the LCIG group and 29 from the LC-oral group, experienced at least 1 device complication (pump complication, intestinal tube complication, PEG-J complication, stoma complication, or other). Actions taken to address the complications included repositioning of the tubing, with or without surgery, and replacement of the tubing, with or without surgery. A total of 53 of 71 subjects (74.6%), 27 LCIG subjects and 26 LC-oral subjects, experienced at least 1 treatment-emergent adverse event linked to device complications. Most of these adverse events were reported within the first 2 weeks following the PEG-J insertion. Overall, the most frequently reported adverse events linked to device complications were complication of device insertion (36 of 71 subjects, 50.7%), abdominal pain (30 of 71 subjects, 42.3%), and procedural pain (21 of 71 subjects, 29.6%).

There were no clinically meaningful differences in change from Baseline to Endpoint values for any hematology, chemistry, or urinalysis variables and no meaningful differences between treatment groups were noted for any of these parameters. Nine subjects met the criteria for very low (VL) or very high (VH) potentially clinically significant (PCS) values in at least 1 hematology parameter during the study, and 7 subjects met the PCS criteria in at least 1 chemistry parameter; most PCS values were for a single time point within each parameter.

Under standard vital sign measurement conditions, no statistically significant or clinically meaningful differences between treatment groups were observed in mean change from Baseline to Week 12 values for systolic or diastolic (supine, standing, orthostatic) blood pressure (SBP, DBP), pulse (supine, standing, orthostatic), temperature, weight, or BMI.

On pharmacokinetic blood collection days when intensive vital sign measurements were collected while subjects were hospitalized, a trend in blood pressure values was noted. Under these conditions, supine and standing systolic and diastolic blood pressure mean values appeared to decrease from Baseline to Hour 2, then increase from Hour 2 to Hour 12 or Hour 16, but did not fully recover to the Baseline value. This trend was not observed with standard vital sign measurements. No notable trends or treatment group differences were observed in pulse, temperature, or weight values collected during the pharmacokinetic blood sampling.

Vital sign PCS values were reported in > 50% of subjects in both treatment groups and included orthostatic SBP (decrease ≥ 30 mmHg in supine to standing) and orthostatic DBP (decrease ≥ 20 mmHg in supine to standing). Overall, the number and percentage of subjects who experienced at least 1 decreased blood pressure-related PCS value was 63 of 71 (89%, 34 LCIG subjects and 29 LC-oral subjects). Adverse events possibly related to vital sign PCS values were reported for 23 subjects, 12 from the LCIG group and 11 from the LC-oral group. In some cases, medication was prescribed to address the adverse events. Most adverse events were assessed by the investigator as mild or moderate in severity. None of the subjects discontinued the study due to the PCS values or the adverse events possibly related to PCS values.

Seven subjects (4 in the LCIG group and 3 in the LC-oral group) experienced PCS values for pulse, supine or standing, ≥ 120 bpm and > 30 bpm increase from Baseline, or ≤ 50 and > 30 bpm decrease from Baseline. Eleven subjects (4 in the LCIG group and 7 in the LC-oral group) experienced PCS values for decreased weight loss (≥ 7%) and 1 subject (LCIG group) experienced a PCS value for weight gain (≥ 7%).

Summary/Conclusions (Continued)

Safety Results (Continued):

Standard 12-lead ECG and Holter 12-lead ECG measurements were collected during the study. The standard ECG tracing for 1 subject in the LC-oral group was assessed by the investigator as shifting from normal at Baseline to abnormal, clinically significant at Week 4 (Endpoint). Two subjects (both from the LCIG group) met the criteria for PCS ECG values, 1 subject for PR interval < 120 msec and 1 subject for QTcB and QTcF > 480 msec.

The Holter ECG collections and evaluation identified new onset abnormal ECG waveform interpretations that appeared to be evenly distributed across treatment groups. New onset abnormal ECG waveforms of prolonged QTcF were identified in a total of 11 subjects, 5 of 37 subjects in the LCIG group and 6 of 34 subjects in the LC-oral group. Potentially clinically significant Holter QTcF intervals (maximum > 450 msec and ≤ 480 msec) were identified in 6 subjects (4 of 37 subjects in the LCIG group and 2 of 34 subjects in the LC-oral group) at stable dose and Week 12. One subject (LCIG group) met the PCS criteria for QTcF maximum change from Baseline > 30 msec and ≤ 60 msec at stable dose and Week 12. A total of 26 subjects (13 from each group) met the PCS criteria of QTcB > 450 msec and ≤ 480 msec at stable dose and 11 subjects (7 from the LCIG group and 4 from the LC-oral group) met these criteria at Week 12. No QTcF from any subject was greater than 480 msec by Holter ECG.

No clinically meaningful changes from Baseline or treatment group differences in sleep attacks, intense impulsive behavior, AIMS total score, evidence of melanoma, or neurological examination results were noted.

Conclusions:

In this study, LCIG treatment for 12 weeks provided a clinically meaningful and statistically significant improvement in motor fluctuations in subjects with advanced PD. LCIG jejunal infusion resulted in less fluctuation in plasma levodopa concentrations relative to treatment with oral levodopa-carbidopa. Pharmacokinetic analysis indicated the intra-subject variability in levodopa concentrations was much lower for subjects treated with LCIG (21%) than for subjects treated with LC-oral (67%) during hours 2 to 16 of treatment on sampling days. The benefit of the continuous levodopa infusion and the associated low fluctuations in plasma levodopa concentrations were manifested in a greater reduction in "Off" time and increase in "On" time experienced by the subjects in the LCIG group relative to subjects in the LC-oral group. Efficacy with LCIG was demonstrated by a statistically and clinically significant decrease in "Off" time (LS mean, –4.04 hours and improvement over LC-oral of –1.91 hours) and complementary increase in "On" time (LS mean, 4.11 hours and improvement over LC-oral of 1.86 hours) without troublesome dyskinesia. Other efficacy assessments demonstrated statistically and clinically significant improvement with LCIG on subjects' activities of daily living and quality of life parameters.

Adverse events attributed to the drug product were consistent with the known safety profile of oral levodopa-carbidopa. Complications of the procedure and the device component of the LCIG System were consistent with and expected for PEG-J placement. Most adverse events were related to the PEG-J placement; the incidence of adverse events decreased over time and adverse events were mostly mild or moderate in severity. The LCIG System has the potential to address a significant unmet medical need in this patient population with limited therapeutic options. The data acquired in this study provide strong evidence for the efficacy, safety, and tolerability of the LCIG System. The efficacy data from multiple analyses demonstrated the robustness of the results and superiority of the LCIG System over LC-oral

Summary/Conclusions (Continued)

Conclusions (Continued):

administration in the treatment of persistent motor fluctuations in subjects with advanced PD. Overall, the statistically significant and clinically meaningful efficacy results, together with the tolerability and acceptable safety findings observed in the study, constitute a positive benefit-risk profile for the LCIG System.

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