Synopsis

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: An Open-Label, 12-Month Safety and Efficacy Study of Levodopa-Carbidopa Intestinal Gel in Levodopa-Responsive Subjects with Advanced Parkinson's Disease and Severe Motor Fluctuations Despite Optimized Treatment with Available Parkinson's Disease Medications
Coordinating Investigator: Hubert Fernandez, MD
Study Sites: 83 sites in 16 countries worldwide enrolled subjects
Publications: None

Studied Period (Years): 4.5 First Subject First Visit: 30 January 2008 Last Subject Last Visit: 14 June 2012	**Phase of Development:** 3

Objectives: The primary objectives were to evaluate the long-term safety and tolerability of LCIG over 12 months in subjects with advanced levodopa-responsive Parkinson's Disease (PD) with severe motor fluctuations despite optimized treatment with available PD medications.

Methodology: Study S187-3-004 was a Phase 3, open-label, multicenter study of the safety, tolerability, and efficacy of LCIG administered for 12 months in subjects with levodopa-responsive advanced PD with motor fluctuations despite optimized treatment with available PD medications. The study comprised a Screening Period followed by 3 sequential on-treatment periods, as follows: • Screening Period (up to 28 days): determination of subject eligibility and discontinuation of antiparkinsonian disease medications other than levodopa-carbidopa immediate release (LC-oral) prior to nasojejunal (NJ) tube placement. • NJ Test Period (2 to 14 days): first hospitalization period, Baseline assessments, placement of NJ tube, and optimization of LCIG treatment via NJ tube and infusion pump (subject was hospitalized for NJ tube placement but hospitalization was not required for entire duration of LCIG treatment optimization). • Percutaneous Endoscopic Gastrostomy with Jejunal Extension (PEG-J) Period (2 to 14 days): second hospitalization period; placement of PEG-J tube; further optimization of LCIG treatment.

Methodology (Continued):

- Post PEG-J Long-Term Treatment Period (12 months): LCIG administration via a permanent PEG-J tube and infusion pump, with dosage adjusted according to clinical condition. Other antiparkinsonian medication was used at the investigator's discretion after 28 days post-PEG-J placement. The exceptions were apomorphine, any levodopa peripheral decarboxylase inhibitor combination other than levodopa-carbidopa (such as levodopa-benserazide) and controlled release (CR) formulations of levodopa-carbidopa.

Number of Subjects (Planned and Analyzed):

Number of subjects planned: approximately 320 subjects planned; 354 subjects enrolled and allocated to treatment; 354 subject analyzed for safety; 321 subjects analyzed for efficacy.

Diagnosis and Main Criteria for Inclusion:

Subjects with levodopa-responsive advanced PD who experienced severe motor complications despite optimized available therapy who met the following inclusion criteria were eligible: diagnosis of idiopathic PD according to the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank Criteria; recognizable "Off" and "On" state (motor fluctuations) as confirmed by the Parkinson's Disease Diary; minimum of 3 hours per day of "Off" time during a continuous 16-hour interval including the portion of the day during which the subject was awake the majority of the time; and male or female at least 30 years of age. Subjects were to be excluded if they had any of the following: a PD diagnosis was unclear or a suspicion of other Parkinsonian syndromes; undergone surgery for the treatment of PD; any neurological deficit that might have interfered with the study assessments; diagnosed with an acute stroke within the 6 months prior to Baseline; known hypersensitivity to levodopa, carbidopa, or radiopaque material; contraindications to levodopa; sleep attacks or clinically significant impulsive behavior within 3 months prior to screening.

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

All subjects were to receive LCIG, via the NJ tube during the NJ Test Period and delivered to the proximal small intestine via PEG-J during the Post-PEG-J Long-Term Treatment Period. The starting dose was individually determined based on the daily dose of oral levodopa prior to study enrollment. The infusion dose was individually optimized for each subject on the basis of response and potential adverse events. During the Post-PEG-J Long-Term Treatment Period, LCIG was expected to be infused continuously over approximately 16 hours daily with a rate of infusion ranging from 1 to 10 mL/hour (20 to 200 mg of levodopa/hour), in most instances. During initial titration, extra doses may have been administered on an hourly basis at various doses up to 9.9 mL. Subsequently, subjects were allowed to self-administer additional extra doses of LCIG at intervals of no less than 2 hours to address immediate medical needs, such as the rapid deterioration of motor function. If the need for extra doses exceeded 5 per day, the investigator was to consider increasing the maintenance dose.

Test Product, Dose/Strength/Concentration, Mode of Administration, and Lot Number (Continued):			
The LCIG lot numbers are listed below.		*Redacted information - 23May2013*	
Manufacturer	**Study Drug**	**Formulation**	**Bulk Lot Numbers**
▮▮▮▮	LCIG in medication cassette reservoir	Aqueous gel levodopa (20 mg/mL) carbidopa monohydrate (5 mg/mL)	07H20G33, 07H21G36, 07H21G37, 07H22G39, 07H22G40, 07H23G42, 07H23G43, 07H27G48, 07H27G49, 07H28G51, 07H28G52, 07H29G54, 07H29G55, 07H30G57, 07H30G58, 07I18G35, 07I18G36, 07I19G38, 07I19G39, 07I20G41, 07I20G42, 07I23G44, 07I24G47, 07J07G01, 07J08G03, 07J08G04, 07J09G06, 07J09G07, 07J10G09, 07J10G10, 07J11G12, 08A06G09, 08A06G10, 08A07G12, 08A07G13, 08A08G15, 08A08G16, 08A09G18, 08A09G19, 08A13G28, 08A13G29, 08A14G31, 08A14G32, 08A15G34, 08A15G35, 08A16G37, 08A16G38, 08A27G62, 08A27G63, 08A28G65,08A28G66, 08A29G68, 08A29G69, 08A30G71, 08A30G72, 08I01G01, 08I09G06, 08K12G08, 08J19G09, 08L01G01, 08L17G11, 08L15G09, 08L08G05, 09A26G13, 09B02G02, 09F29G18, 09I02G99, 09J21G09, 09J28G12, 09K18G10, 10A13G09, 10A27G23, 10B10G08, 10B17G13, 10D07G03, 10D14G09, 10E10G07, 10F02G02, 10F16G14, 10H04G04, 10H18G15, 10I01G01, 10I22G23, 10J20G12, 10K03G99, 10K17G19, 10L08G07, 10L13G10, 10L20G15, 10L15G12, 11A19G17, 11C02G02, 11C16G13, 11D06G04, 11E04G04, 11E18G15

Levodopa-carbidopa immediate release tablets (LC-oral): Subjects were given a prescription for LC-oral with permission to self-administer their typical nighttime dosage of LC-oral (doses of LC-oral that they took on a regular basis) when their pump was turned off.
Duration of Treatment:
Up to 14 days in the NJ Test Period, and 12 months in the Post PEG-J Long-Term Treatment Period.
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:
Not applicable. All subjects received LCIG.
Criteria for Evaluation
Efficacy:
The efficacy variables included normalized "Off" time, "On" time without troublesome dyskinesia, Unified Parkinson's Disease Rating Scale (UPDRS) total score and subscores of Parts I–III and Part IV (subscore dyskinesia items), Clinical Global Impression-Improvement (CGI-I) scores, and Parkinson's Disease Questionnaire (PDQ-39) Summary Index. The "Off" and "On" times were measured using the self-administered Parkinson's Disease Diary.

Safety:

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

Statistical Methods

Efficacy:

The primary efficacy 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 54 (Endpoint), based on the Full Analysis (FA) data set (all subjects included in the Safety data set who had a baseline efficacy evaluation and at least 1 postbaseline assessment of any efficacy measurement during the Post-PEG Long-Term Treatment Period.)

An average normalized "On" time without troublesome dyskinesia, "On" time without dyskinesia, and "On" time with nontroublesome dyskinesia, using the 3 day average from the Parkinson's Disease Diary data, was calculated for each subject for Baseline through Week 54 (Endpoint).

Safety:

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:

An approximately 4-hour mean decrease in normalized "Off" time was observed as early as 4 weeks post-PEG placement ($P < 0.001$) and was sustained throughout the treatment period, decreasing from 6.77 hours at Baseline to 2.32 hours at Endpoint (–4.44 hours; $P < 0.001$). Statistically significant ($P < 0.05$) mean decreases in "On" time with troublesome dyskinesia were observed at every visit and the mean decrease from Baseline to Endpoint was 0.36 hours ($P = 0.023$). These reductions were consistent with a mean increase from Baseline in normalized "On" time without troublesome dyskinesia (+4.80 hours at Endpoint; $P < 0.001$). This improvement in "On" time without troublesome dyskinesia is mostly attributed to the increase in "On" time without dyskinesia (+3.86 hours at Endpoint, $P < 0.001$) more than "On" time with nontroublesome dyskinesia (+0.95 hours at Endpoint, $P < 0.001$).

Improvements in the UPDRS Parts II, III IV, IV of dyskinesia, and Total Score were also statistically significant after 4 weeks of treatment ($P < 0.001$). The improvements were sustained throughout the treatment period with statistically significant ($P < 0.001$) mean decreases from Baseline to Endpoint of 4.4 for Part II (activities of daily living), 7.4 for Part III (motor examinations), 3.5 for Part IV (complications of therapy, including dyskinesia), 1.1 for Part IV subscore of dyskinesia, and 11.7 for Total Score (sum of all questions in Parts I, II and III).

The CGI-I score showed a statistically significant ($P < 0.001$) improvement after 4 weeks of treatment (mean score of 2.18 was close to 'much improved') that was sustained throughout the treatment period. The mean score at Endpoint was 2.10 ($P < 0.001$).

Efficacy Results (Continued):

Improvements in the PDQ-39 Summary Index were statistically significant after 4 weeks of treatment (mean change: −8.8; $P < 0.001$). This effect was sustained throughout the treatment period with a mean decrease from Baseline to Endpoint of 6.9 ($P < 0.001$). Of the 8 domains of the PDQ-39, the social support domain was the only domain that did not show consistent statistically significant mean improvements at every visit.

Improvements in both the EQ-5D Summary Index and the EQ VAS scores were statistically significant after 4 weeks of treatment ($P < 0.001$). The improvements were sustained throughout the treatment period with statistically significant ($P < 0.001$) mean increases from Baseline to Endpoint of 0.064 for EQ-5D Summary Index and 14.0 for EQ VAS.

The mean changes from Baseline in the ZBI total score were small and not statistically significant at any visit.

Although subjects were permitted reintroduction of other PD medications 28 days post-PEG placement, the majority of subjects (> 75%) did not require any additional antiparkinsonian medications other than levodopa-carbidopa therapy.

Pharmacokinetic Results:

Not applicable.

Safety Results:

All 354 subjects in the Safety data set were hospitalized for placement of the NJ tube and the initiation of LCIG titration. The 324 subjects who continued the study after completing the NJ Test Period were hospitalized a second time for PEG-J placement surgery (or the first hospitalization continued into the PEG-J placement) and constitute the Post-PEG Safety data set.

Overall, including both the NJ Test Period and the Post-PEG Long-Term Treatment Period, 350 of the 354 subjects received LCIG for up to 521 days, with a median of 384.0 days. Four subjects (1.1%) did not receive LCIG because the NJ placement was not successful.

Most subjects, 91.2% (323/354), experienced at least 1 treatment-emergent adverse event. Although serious adverse events were reported in 30.5% (108/354) of subjects, the majority of serious adverse events resolved and the subjects continued study treatment. Adverse events resulted in discontinuation from the study for 7.6% (27/354) of subjects.

NJ Test Period

During the NJ Test Period, subjects received LCIG treatment for an average of 5.6 days (median: 6.0 days) during which 46.9% (166/354) of subjects experienced treatment-emergent adverse events. Treatment-emergent adverse events reported for at least 5% of subjects were insomnia (7.9%), complication of device insertion (7.3%), and oropharyngeal pain (6.5%).

No deaths were reported for the NJ Test Period. Six subjects (1.7%) had treatment-emergent serious adverse events. One serious adverse event of syncope was considered at least possibly related to study treatment by the investigator, and the remaining serious adverse events were considered unrelated to study treatment. One serious adverse event of pneumonia resulted in discontinuation from the study and all other serious adverse events resolved. Four additional subjects discontinued from the study because of adverse events that were not serious, and included dysphagia, vomiting, complication of device insertion, QT prolonged, anxiety, and hallucination. Device complications were reported for 25.4% of subjects.

Safety Results (Continued):

Post-PEG Long-Term Treatment Period

During the Post-PEG Long-Term Treatment Period, subjects received LCIG treatment for a median of 379.0 days (mean: 349.9 days) of treatment via the LCIG System. A total of 272 subjects (76.8%) completed the study and 52 subjects (14.7%) discontinued from the Post PEG-Long-Term Treatment Period. The most common primary reasons for discontinuation were adverse event (6.2%), withdrew consent (3.7%), and administrative (3.7%). Although 92.0% (298/324) of subjects experienced treatment-emergent adverse events with the LCIG system, the incidence was highest after the PEG-J surgery and decreased from 65.1% during Week 1 to 17.1% during Week 4. For individual adverse event preferred terms, the incidence rate dropped to less than 5% after the first week. All adverse event preferred terms that were reported for at least 5% of subjects during the first week were device related or gastrointestinal related. The most common adverse events ($\geq$ 10% of subjects) were complication of device insertion (34.9%), abdominal pain (31.2%), procedural pain (20.7%), nausea (16.7%), excessive granulation tissue (16.0%), postoperative wound infection (15.4%), fall (15.1%), constipation (14.5%), insomnia (13.6%), incision site erythema (13.0%), and urinary tract infection (11.4%). These adverse events were mild or moderate for the majority of subjects.

No deaths were considered possibly or probably related to study treatment by the investigator. Seven deaths resulting from treatment-emergent adverse events were considered unrelated (n = 6) or unlikely related (n = 1) to study treatment: 1 cerebrovascular accident, 1 cachexia, 1 multiple complications resulting from pneumonia, 2 completed suicides, and 2 unknown etiologies. The 2 subjects who completed suicides were 45 and 58 years of age with histories of depression. One of these subjects stopped antidepressant medication the day before NJ tube placement, and the other subject had recently separated from his wife. The remaining 5 deaths were reported in subjects who were at least 70 years of age.

Serious adverse events were reported in 32.4% (105/324) of subjects and the majority of these events resolved and the subjects continued study treatment.

Adverse events that led to discontinuation from the study were reported for a total of 22 subjects (6.8%). Complication of device insertion was the only adverse event that resulted in discontinuation from the study for more than 1% of subjects (1.9% [6/324]).

Safety Results (Continued):

Complication of device insertion was the only serious adverse event reported for more than 5% of subjects (6.5%). Other serious adverse events reported in at least 2% subjects were abdominal pain (3.1%), peritonitis (2.8%), polyneuropathy (2.8%), pneumoperitoneum (2.5%), and PD (2.5%). For 17 of the 21 subjects with serious adverse events coded to complication of device insertion, the same adverse events were also coded to serious adverse events of abdominal pain (n = 5), peritonitis (n = 6), and pneumoperitoneum (n = 6), because all device-related adverse events were double coded to both a device-related preferred term and a preferred term that was descriptive of the adverse event presentation. For the majority of subjects with serious adverse events of complication of device insertion (14/21), abdominal pain (6/10), peritonitis (7/9), and pneumoperitoneum (8/8), the serious adverse events occurred within 1 week of PEG-J placement. Serious adverse events coded to these preferred terms resolved for all but 1 subject (complication of device insertion), and led to discontinuation from the study for 4 subjects (3 abdominal pain, 1 peritonitis).

Device complications were reported for 87.0% of subjects as an intestinal tube complication (n = 165), pump complication (n = 116), PEG-J complication (n = 114), stoma complication (n = 116), or other (n = 114). Adverse events were linked to device complications for 68.5% (222/324) of subjects. Overall, the most frequently reported adverse events linked to device complications were complication of device insertion (33.6%), abdominal pain (26.5%), and procedural pain (20.4%).

No consistent or clinically important trends were observed in mean changes from Baseline or individual subject shifts to values outside the normal range for any clinically laboratory variables.

Although the predefined criteria for low orthostatic blood pressure was met for more than 15% of subjects (24.7% for SBP, 18.2% for DBP), orthostatic hypotension was not chronic for most subjects, and only 2 subjects had both low orthostatic SBP and DBP at the last assessment. Orthostatic hypotension was reported as an adverse event for 7.7% (25/324) of subjects and none of these adverse events led to discontinuation from the study.

Although 29.0% of subjects experienced a weight loss of at least a 7%, the average BMI at Baseline was 24.79 kg/m^2 for the study population. Of the 8 subjects with serious adverse events in the company MedDRA query for weight loss, no BMI values of less than 19 kg/m^2 were reported.

Five subjects had ECG results that were assessed by the investigator as clinically significant changes from Baseline and reported as an adverse event, including 1 subject who required pacemakers. None of these adverse events resulted in discontinuation from the study.

Conclusions:

The results of this study provide evidence for the safety, tolerability, and efficacy of LCIG continuous infusion treatment. LCIG treatment demonstrated statistically significant and clinically meaningful improvement in subjects with advanced PD who had motor fluctuations despite optimized treatment with oral levodopa-carbidopa and other available anti-PD medications. Improvements in motor symptoms, a reduction in "Off" time and complementary increase in "On" time without troublesome dyskinesia, combined with improvement in health-related and quality-of-life outcome measures of the PDQ-39, CGI-I, and UPDRS, demonstrated the totality of symptomatic improvement with LCIG treatment. The adverse events reported were as expected for the device-related procedure and the patient population with advanced disease treated with levodopa; the majority were assessed as mild or moderate in severity and observed to decline over time. Overall, the statistically significant and clinically meaningful efficacy results, together with the acceptable safety and tolerability findings, constitute a positive benefit-risk profile for LCIG. The data from this study indicate that the LCIG system has the potential to provide significant long-term benefits to patients with advanced PD and limited therapeutic options.

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