Synopsis

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

Title of Study: A Pharmacokinetic Study of Levodopa and Carbidopa Intestinal Gel in Subjects with Advanced Parkinson's Disease

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Study Site: Quintiles Research Unit, Uppsala, Sweden; Klinikum Bremerhaven Reinkenheide, Bremerhaven, Germany

Publications: None.

Studied Period (Years): First Subject First Visit: 07 April 2010 Last Subject Last Visit: 30 September 2010	**Phase of Development:** 1

Objectives:

The objectives of this study were 1) to characterize the pharmacokinetics of levodopa, carbidopa and 3-O-methyldopa (3-OMD) metabolite following administration of levodopa-carbidopa intestinal gel (LCIG) in subjects with advanced Parkinson's disease, and 2) to evaluate the safety of LCIG in subjects with advanced Parkinson's disease.

Methodology:

The multicenter, multiple-dose, open-label study was conducted in subjects with advanced Parkinson's disease. Subjects who were already on a stable dose of LCIG were screened for the study and remained on their individualized LCIG dose during the study.

Subjects who were on approximately 16- or 24-hour LCIG infusion regimen per day were enrolled. Subjects were confined in the clinic for two days. They reported to the clinic one day prior to the pharmacokinetic (PK) sample collection day for baseline assessment and stayed in the clinic until the last blood sample was collected. A radiological check of tube placement was done at baseline. If there was an indication that the tube was displaced, the tube was repositioned to the original placement as needed prior to the PK day.

Subjects who were on 16-hour infusion per day remained on their normal 16-hour infusion regimen. At baseline, oral levodopa-carbidopa immediate release (IR) was allowed after discontinuation of the pump for up to 3 hours prior to the start of the pump on the PK sampling day.

Methodology (Continued):

Subjects who received infusion of more than 16 hours per day prior to the study start had their pumps turned off after 16 hours of infusion on the day prior to the PK sampling day and the PK sampling day. No dosage adjustment (morning dose and continuous flow rate) was done. To compensate for the remaining 8 hours without LCIG infusion, oral levodopa-carbidopa IR was given for up to three hours prior to the start of the pump on the PK day. The oral dosing regimen was determined by the investigator based on the subject's condition. On the PK day, all subjects received their individualized dose of LCIG for 16 hours. The administration of any extra doses of LCIG was discouraged during the PK day except when it was deemed absolutely needed. Oral levodopa-carbidopa was not allowed until the last PK sample was collected. Had it become necessary to provide levodopa-carbidopa medication after the pump was turned off and before the last blood sample was to be obtained at 19 hours, a blood sample was to be collected prior to administration of levodopa-carbidopa medication and no other PK samples were to be collected thereafter. After the collection of the last PK sample, the subjects resumed their original levdodopa-carbidopa regimens.

Whole blood samples for the determination of levodopa, 3-OMD, and carbidopa were collected via an indwelling catheter or by direct venous puncture on the PK sampling day immediately prior to the initiation of LCIG infusion in the morning and at the following time points after the initiation of infusion: 5 minutes, immediately after the end of the morning dose (if the end of the morning dose was at 5 or 30 minutes, only one sample was taken at the specified time point), every 30 minutes up to 8 hours (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8 hours), 12, 16 (immediately after flushing the tube), 17, 18, and 19 hours. The blood samples were collected in 6 mL potassium edentate anticoagulant-containing collection tubes.

Plasma concentrations of levodopa, 3-OMD and carbidopa were determined using a validated liquid chromatography method with tandem mass spectrometric detection at PPD, Middleton, WI. The lower limits of quantitation (LLOQ) for levodopa, 3-OMD and carbidopa were established at 10 ng/mL, 50 ng/mL and 0.5 ng/mL, respectively, using 200 µL plasma aliquots. Samples were analyzed between the dates of 04 August 2010 and 10 November 2010.

Number of Subjects (Planned and Analyzed):

Planned: 18; Entered: 19; Completed: 18; Evaluated for Safety: 19;
Evaluated for Pharmacokinetics: 18
For the 19 subjects who participated in the study, the mean age was 65 years (ranging from 47 to 78 years), the mean weight was 66 kg (ranging from 45 to 93 kg) and the mean height was 1.7 m (ranging from 1.5 to 1.9 m).

Diagnosis and Main Criteria for Inclusion:

Subjects were male and female volunteers aged 30 years or older. Subjects in the study had advanced Parkinson's disease and were undergoing treatment with LCIG for at least 30 days. Otherwise, the subjects were judged to be in general good health based on the results of medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), serum/urine biochemistry and hematology. Females were either post-menopausal or surgically sterile. If of childbearing potential, they had a negative serum β-human chorionic gonadotropin (β-HCG) and used an accepted form of contraception.

Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:

	Regimen			
Dosage Form	**LCIG**	**LCIG, 100 mL**	**LCIG, 100 mL**	**LCIG, 100 mL**
Strength (Levodopa + Carbidopa)	20 mg/mL + 5 mg/mL	20 mg/mL + 5 mg/mL	20 mg/mL + 5 mg/mL	20 mg/mL + 5 mg/mL
Lot (Batch) Number	10H01G01	10F21G17	10B01G01	10C21G15

Duration of Treatment:

Subjects underwent treatment for 2 days.

Criteria for Evaluation

Pharmacokinetic: The pharmacokinetic parameter values of levodopa, 3-OMD and carbidopa were estimated using noncompartmental methods. These included the maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), the minimum observed plasma concentration (C_{min}), the average plasma concentration (C_{avg}), the apparent terminal phase elimination rate constant (β), terminal phase elimination half-life ($t_{½}$), and the area under the plasma concentration-time curve (AUC) from time 0 to time 16 hours (AUC_{0-16}), peak trough fluctuation (PTF) and dose-normalized pharmacokinetic parameter values. The AUC from time 0 to time 24 hours (AUC_{0-24}) and the apparent oral clearance (CL/F) were calculated for levodopa, and the metabolite to parent ratios (M/P) for C_{max} and AUC_{0-16} were calculated for 3-OMD. The intra-subject coefficient of variation in the 2- to 16-hour infusion interval was also calculated.

Safety: Safety was evaluated based on assessments of adverse events, vital signs, orthostatic vital signs, ECGs and laboratory tests.

Statistical Methods

Pharmacokinetic: An estimate of the coefficient of variation was obtained for concentrations in the interval beginning at 2 hours after the beginning of infusion until the end of the 16-hour infusion using a repeated measures analysis. Summary statistics of the pharmacokinetics parameters of levodopa, carbidopa and 3-OMD were calculated.

Safety: An adverse event that began during a unique treatment or that already existed before the start of that unique treatment but worsened during the treatment was considered as treatment-emergent for that unique treatment.

Safety (Continued):

Adverse events were counted on a per-subject basis, i.e., counting subjects rather than events. This means that if a subject suffered the same adverse event repeatedly during the applicable study period, the event was counted only once for that period. Repeated events per subject were summarized according to the following rule: if a subject suffered the same adverse event more than once, the event was assigned the worst severity, the closest relationship to the treatment system and the earliest starting date. Only treatment-emergent adverse events were summarized.

For each unique treatment, treatment-emergent adverse events were summarized per primary system organ class (SOC), per the Medical Dictionary for Regulatory Activities (MedDRA) high level term (HLT) name by primary SOC and per preferred term (PT) by HLT and primary SOC. Severity and drug-event relationship of treatment-emergent adverse events were summarized separately.

Data for vitals signs and orthostatic changes in blood pressure and pulse rate were summarized. A frequency table was presented for markedly abnormal vital sign values.

Laboratory variables, including changes from baseline, were summarized. A frequency table was presented for markedly abnormal values.

Summary tabulations of ECG parameter data were done by descriptive statistics for central tendency and by categorical analyses. All ECG parameters were summarized by measurement time.

The number and percentage of subjects with QTc interval values > 450 and ≤ 480 ms, > 480 and ≤ 500 ms, and > 500 ms were tabulated. The number and percentage of subjects with one or more QTc change scores > 30 and ≤ 60 ms, and > 60 ms were presented. Results of the Holter waveform interpretation were also summarized.

Summary/Conclusions:

Pharmacokinetic Results:

Mean ± standard deviation (SD) pharmacokinetic parameters of levodopa, 3-OMD and carbidopa after administration of LCIG are presented in the following table.

Pharmacokinetic Parameters (units)		Analyte: Levodopa (N = 18)	Analyte: 3-OMD (N = 18)	Analyte: 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}	(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]	--	--
$t_{½}$[a]	(h)	1.5 ± 0.19[c]	--	--
CL/F[b]	(L/h)	30.7 ± 7.52[c]	--	--
M/P (C_{max})	(%)	--	462 ± 82	--
M/P (AUC_{0-16})	(%)	--	597 ± 109	--
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. Harmonic mean ± pseudo-standard deviation; evaluations of $t_{½}$ were based on statistical tests for β.

b. Parameter was not tested statistically.

c. N = 14.

Safety Results: LCIG was generally well-tolerated. No clinically significant ECG or laboratory changes were observed during the course of the study. No deaths or serious adverse events were reported during the study.

Safety Results (Continued): Three out of nineteen (3/19, 15.8%) subjects reported at least one treatment-emergent adverse event. The treatment-emergent adverse events reported by one or more subjects who received LCIG were headache (2/19, 11%), migraine, dizziness and vomiting (each 1/19, 5%). The adverse events of migraine, vomiting and dizziness all occurred in a single subject. Of these treatment-emergent adverse events, headache, migraine and vomiting were assessed by the investigator as unrelated to study drug and moderate in severity. No treatment-emergent adverse events were assessed by the investigator as severe.

Four out of nineteen (4/19, 21%) subjects reported other adverse advents not considered as treatment-emergent since these events had onset prior to the start of the study drug on Study Day 1. These adverse events were dystonia, spasmodic dysphonia, headache, excessive granulation tissue and blood thyroid stimulating hormone decreased. These adverse events were assessed by the investigator as possibly or unrelated to study drug and ranged from moderate to severe.

One subject was discontinued from the study prior to dosing due to non-compliance to the inclusion-exclusion criteria.

Mean systolic and diastolic supine blood pressure decreased from a mean of 152/86 mmHg to a mean of 120/66 mmHg at 3.5 hours post-dose. This was the maximal reduction from baseline. Mean systolic supine blood pressures were above 120 mmHg for the remainder of the study. Only small mean differences from baseline in orthostatic change pressures were observed. The observed mean values of both SBP and DBP were elevated at baseline and a reduction in mean values was seen in the subsequent 2 to 3 hours after the initiation of the LCIG infusion. The values did not return to the higher pre-dose levels during the course of the study. The mean data indicate that the largest effect on blood pressure occurred around 3.5 hours post-dose. Importantly, no adverse events related to this decrease in blood pressure were reported. There was a single subject who had an adverse event of dizziness related to a decrease in blood pressure occurring on Day 2 (24-hour time-point). Only small changes in mean pulse were seen and a compensatory increase in heart rate did not occur following the initiation of the LCIG infusion. A possible explanation for the reduction of blood pressure observed is that a higher baseline mean on Day 1 may have occurred as a reaction to study conditions at the time of measurement. Conditions that may have contributed to an elevation in baseline blood pressures include a treatment protocol outside the subject's normal daily dosing routine, as well as the subject's anticipation of study procedures. Per the protocol, LCIG on the Study Day could not be started until completion of all baseline study procedures, and oral levodopa-carbidopa could not be taken within 3 hours of the start of infusion. In an elderly patient population, the changes in normal routine and study conditions may have led to increased anxiety and a subsequent increase in blood pressure at baseline. Other factors that may have contributed to observed changes in blood pressure include influence of circadian rhythm, ingestion of meals and the use of concomitant medications. Three subjects had a diagnosis of hypertension, and five subjects were receiving concomitant medications that may reduce blood pressure including calcium channel blockers, beta-blockers, angiotensin II receptor antagonists, ACE inhibitors, and nitrates. There is no clear temporal pattern of the individual markedly abnormal blood pressure values in relation to the start of dosing. The markedly abnormal values also did not show a relationship to drug concentration for either levodopa or carbidopa levels. In patients with severe Parkinson's disease, some degree of autonomic dysfunction is common. Autonomic dysfunction as well as concomitant medications may have further contributed to the observed changes in blood pressure and may also contribute to the individual markedly abnormal vital sign values. It is a recognized effect of levodopa that blood pressure decreases may occur.

Safety Results (Continued): While Levodopa may be contributing to the blood pressure changes observed it is difficult to determine the extent of the effect due to the study conditions described and the lack of a control arm.

The safety profile as observed in the 19 investigated subjects corresponds well with the knowledge that has been obtained with LCIG in countries where it is marketed.

Conclusions:

The average total daily LCIG dose was 1580 mg for levodopa and 395 mg for carbidopa on the PK assessment day of the study. LCIG administration resulted in mean C_{avg} of 2.9 µg/mL for levodopa, 17.1 µg/mL for 3-OMD and 0.22 µg/mL for carbidopa. The within-subject coefficient of variation in levodopa, 3-OMD and carbidopa concentrations over the 2 to 16 hours time interval relative to starting LCIG infusion was low (13%, 6% and 19%, respectively).

Three out of nineteen (3/19, 15.8%) subjects reported at least one treatment-emergent adverse event. The treatment-emergent adverse events reported by one or more subjects who received LCIG were headache (2/19, 11%), migraine, dizziness and vomiting (each 1/19, 5%). Mean systolic and diastolic supine blood pressure decreased from a mean of 152/86 mmHg to a mean of 120/66 mmHg at 3.5 hours post-dose. No adverse events associated with this mean decrease in blood pressure were observed. One subject experienced a low blood pressure associated with an adverse event of dizziness occurring on Day 2. Of these treatment-emergent adverse events, headache, migraine and vomiting were assessed by the investigator as unrelated to study drug and moderate in severity. No treatment-emergent adverse events were assessed by the investigator as severe.

No deaths or serious adverse events were reported during the study.

The safety profile of LCIG as it was obtained in this study corresponds well with the experience with marketed Duodopa®. Adverse events are either due to the medical devices or are well known side effects of oral levodopa-carbidopa.

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