2.0 Synopsis

AbbVie Inc. and AbbVie GK	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-SLV187 (Levodopa-Carbidopa Intestinal Gel [LCIG])		
Name of Active Ingredient: Levodopa-Carbidopa		

Title of Study:

An Open-Label, Single-Arm, Baseline-Controlled, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of ABT-SLV187 Monotherapy in Subjects with Advanced Parkinson's Disease and Persistent Motor-Complications Despite Optimized Treatment with Available Anti-Parkinsonian Medication

Coordinating Investigator: Miho Murata, MD

Study Sites: 9 sites in Japan, 1 site in South Korea, and 3 sites in Taiwan

Publications: None as of date of this report. Results from this study will be published in the future.

Studied Period (Years): First Subject First Visit: 15 October 2013 Last Subject Last Visit: 03 March 2015	**Phase of Development:** 3

Objectives:

The primary objective of this study was to evaluate the efficacy of ABT-SLV187 (known as Duodopa® and Duopa® in countries where it is marketed) monotherapy over 12 weeks of treatment using the Parkinson's Disease (PD) Diary to assess the "Off" time change from baseline in subjects with advanced PD and persistent motor complications despite optimized treatment with available anti-Parkinsonian medications.

The secondary objective was to assess the safety and tolerability of ABT-SLV187 in this patient population.

Methodology:

This was a Phase 3, open-label, single-arm, baseline-controlled, multicenter study to evaluate the efficacy, safety and tolerability of ABT-SLV187 monotherapy in subjects with advanced PD and persistent motor complications despite optimized treatment with available anti-Parkinsonian medications.

This study consisted of 4 study periods: (i) Screening, (ii) Naso-Jejunum (N-J), (iii) Percutaneous Endoscopic Gastrostomy with Jejunum extension (PEG-J), and (iv) Follow-Up.

Methodology (Continued):

Screening Period (up to 28 + 7 days): Subject eligibility was determined after receiving a written informed consent. Training for subject or their caregiver on completing the PD Diary and concordance testing were performed. The subjects were to be converted from their current levodopa-carbidopa, and/or levodopa-benserazide formulation to the sponsor-supplied levodopa-carbidopa immediate release (LC-IR) tablets. All other anti-Parkinsonian medications were to have been tapered or discontinued according to their individual label and at the discretion of the investigator prior to ABT-SLV187 initiation via N-J.

N-J Period: Subjects were hospitalized for an N-J tube placement. ABT-SLV187 was administered via the NJ-tube to determine the subject response before the PEG-J Period. The N-J tube was to remain in place until PEG-J surgery (or early termination from the study).

PEG-J Period: Subjects were to receive a PEG-J tube placement if a favorable response to the ABT-SLV187 treatment had been obtained during the N-J Period. The ABT-SLV187 treatment via the PEG-J tube was individually optimized with dose titration. ABT-SLV187 was delivered over a full 16-hour period each day, administered as one morning dose, followed by continuous infusion and, if needed, intermittent extra doses. The duration of ABT-SLV187 treatment with the PEG-J infusion system was to be 12 weeks.

Follow-Up Period: Follow-up was to be conducted for safety evaluations 7 days after PEG-J removal.

All subjects who had completed the study and showed persistent clinical benefit as judged by the investigator could participate in an optional extension study and continue ABT-SLV187 treatment without the Follow-Up Period. For the subjects who prematurely discontinued treatment following PEG-J placement or who completed and chose not to participate in the optional extension study, the PEG-J tube was removed following the final assessments at the end of the PEG-J Period, and a follow-up visit was to occur 1 week after the PEG-J removal. For the subjects who prematurely discontinued treatment following N-J placement, a follow-up visit was to occur 1 week after the N-J removal.

Number of Subjects (Planned and Analyzed):

Planned: 32; enrolled (signed informed consent form): 40; treated with ABT-SLV187: 31.

31 subjects analyzed for safety (N-J Period and PEG-J Period);
30 subjects analyzed for efficacy (full analysis set).

Diagnosis and Main Criteria for Inclusion:

Subjects with levodopa-responsive advanced PD who experienced severe motor complications despite optimized treatment with available PD medication and who met the following inclusion criteria were eligible:

- Subjects who had a diagnosis of idiopathic PD according to the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank Criteria;
- Subjects who had 4 or 5 in modified Hoehn & Yahr (H & Y) classification of disease severity at "Off" state as determined by the Unified Parkinson's Disease Rating Scale (UPDRS) Part V at Screening;
- Subjects who had a recognizable "Off" and "On" state (motor fluctuations) as confirmed by the UPDRS Part III (in both "On" and "Off" states), and by the PD Diary;
- Subjects who had a 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;
- Subjects who were male or female at least 30 years of age.

Subjects were excluded if they met any of the following criteria:

- Subjects who had an unclear diagnosis of PD or were suspected to have other Parkinsonian syndromes such as secondary Parkinsonism (caused by drugs, toxins, infectious agents, vascular disease, trauma, brain neoplasm), Parkinson's plus syndromes (e.g., multiple system atrophy, progressive supranuclear palsy) or other neurodegenerative diseases that might mimic the symptoms of PD;
- Subjects who had undergone neurosurgery for the treatment of PD;
- Subjects who had any neurological deficit that might have interfered with the study assessments (e.g., hemiparesis);
- Subjects who had known hypersensitivity to levodopa, carbidopa, or radiopaque material; contraindications to levodopa (e.g., narrow angle glaucoma, pheochromocytoma, Cushing's syndrome, and melanoma);
- Subjects for whom the placement of a PEG-J tube for ABT-SLV187 treatment was contraindicated or was considered a high risk for the PEG-J procedure according to the gastroenterology evaluation.

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

Subject dosing of ABT-SLV187 was to be determined individually. The total daily dose of ABT-SLV187 was composed of a morning dose, a continuous maintenance dose, and extra doses. The starting total daily dose of ABT-SLV187 infusion was based on the daily dose of LC-IR calculated from the 16-hour daily dose the day before initiation. The rate of ABT-SLV187 infusion was expected to be within the range of 1 to 10 mL/hour (20 to 200 mg of levodopa/hour) in most instances and ran over a period of 16 consecutive hours.

ABT-SLV187 was administered with an infusion pump directly into the proximal jejunum by an N-J tube during the N-J Period, and then by a PEG-J tube during the PEG-J Period. ABT-SLV187 was to be delivered over a full 16-hour period each day, administered as one morning dose, followed by continuous infusion and, if needed, intermittent extra doses.

Oral LC-IR tablets may only have been used to supplement at night, after the 16-hour ABT-SLV187 dosing period. Oral LC-IR tablets should not have been used during the day, except as rescue medication for device related complications resulting in the interruption with ABT-SLV187 treatment.

The bulk lot numbers are listed below.

Study Drug	Route of Administration	Bulk Lot Numbers
LC-IR 100 mg/10 mg tablets	oral	1EP80M 1ER10M
LC-IR 100 mg/25 mg tablets	oral	13-006254 13-001836
100 mL Levodopa (20 mg/mL) carbidopa (5 mg/mL) intestinal gel medication cassette reservoirs	upper-intestinal infusion	13-003267 13-003759 14-006024

Duration of Treatment:

The duration of ABT-SLV187 treatment during the N-J test period was variable, but not expected to last more than 5 days, although in rare instances it might take longer.

The duration of ABT-SLV187 treatment with the PEG-J infusion system was to be 12 weeks.

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

Not applicable.

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the change from baseline to Week 12 in the mean daily "Off" time (hours) as measured by the PD Diary.

Secondary efficacy variables included the following:

- Change from baseline in PD Diary mean daily "Off" time (hours) at additional time points
- Change from baseline in PD Diary mean daily "On" time without troublesome dyskinesia ("On" time without dyskinesia or with non-troublesome dyskinesia), and "On" time with troublesome dyskinesia
- Clinical Global Impression of Change (CGI-C) scores
- Patient Global Impression of Change (PGI-C) scores
- Change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) total score, Parts I to IV scores and dyskinesia item score
- Change from baseline in the Parkinson's Disease Questionnaire-39 (PDQ-39) total score and domain scores

Safety:

Safety was assessed with the adverse event (AE) monitoring, clinical laboratory assessments, vital sign measurements, physical and neurological examinations, resting 12-lead electrocardiogram (ECG), Product Quality Complaints (PQCs), Columbia-Suicide Severity Rating Scale (C-SSRS), and the monitoring for the development of sleep attacks, melanoma, or excessive impulsive behavior.

Statistical Methods

Efficacy:

Efficacy analysis was performed on the Full Analysis (FA) data set (all subjects who had undergone the PEC-J procedure and had a) both a baseline and a PEG-J Period measurement for at least one of the PD Diary, UPDRS or PDQ-39 efficacy variables, or b) a PEG-J Period measurement for the CGI-C or PGI-C).

The primary efficacy endpoint was the mean change from baseline to final PEG-J Period visit in average daily normalized "Off" time as measured by the PD Diary. The FA dataset was used for the primary efficacy analysis after deleting all PD Diaries that a subject completed after starting a concomitant PD medication during the PEG-J Period. A one-sample t-test was used for the primary analysis.

Statistical Methods (Continued)

Efficacy (Continued):

The following additional analyses of PD Diary "Off" time were performed.

- A one-sample t-test similar to the primary analysis was performed after excluding all subjects who did not remain on ABT-SLV187 monotherapy throughout the entire PEG-J Period.
- A one-sample t-test similar to the primary analysis was performed including all PD Diaries regardless if they were completed after the subject had used a concomitant PD medication during the PEG-J Period.
- The mean change from baseline to each scheduled visit up to Week 12 was estimated using a mixed model repeated measures (MMRM). The model included the fixed effects of ethnicity and visit, with baseline value as a covariate and the baseline-by-visit interaction. Type III Sums-of-Squares and Least Squares means were used for statistical inferences.

The t-test analyses for the mean change from baseline to final PEG-J Period visit and the MMRM analysis prepared for PD Diary average daily normalized "Off" time were to be performed for the following additional continuous efficacy variables.

- PD Diary average daily normalized "On" time without troublesome dyskinesia ("On" time without dyskinesia or with non-troublesome dyskinesia)
- PD Diary average daily normalized "On" time with troublesome dyskinesia
- UPDRS total score, Parts I to IV scores, and dyskinesia item score
- PDQ-39 summary index and domain scores

Hierarchical analyses of secondary efficacy endpoints (PD Diary "On" time without troublesome dyskinesia and "On" time with troublesome dyskinesia; PDQ-39 summary index total score and domain scores; CGI-C scores; PGI-C scores; and UPDRS total score and subscores) were to be performed if the primary hypothesis had been demonstrated with a statistically significant ($P \leq 0.050$) mean decrease in average daily normalized "Off" time. Testing was to be stopped at the point that a secondary analysis failed to demonstrate statistical significance.

The primary efficacy endpoint results were summarized across subgroups defined by gender, age (< 65 years or ≥ 65 years), and ethnicity.

Safety:

Treatment-emergent adverse events (TEAEs) were summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA).

Laboratory variables, including changes from baseline, were summarized. Shift tables were presented according to the reference ranges (low, normal, or high). A frequency table was presented for potentially clinically significant (PCS) abnormal values.

Vitals signs and ECG parameters, including changes from baseline, were summarized. A frequency table was presented for PCS abnormal values.

For PQCs, a frequency table was presented. A frequency table was presented for sleep attacks, excessive impulsive behavior, and suicidal ideation or behavior on the C-SSRS.

Summary/Conclusions

Efficacy Results:

A total of 31 Asian subjects aged 45–83 years (mean: 61.6 years) with a mean PD duration of approximately 12 years were enrolled and treated with ABT-SLV187. Of these 31 subjects, 30 entered the PEG-J treatment period, and 30 were included in the Full Analysis dataset for efficacy evaluations.

Primary Efficacy Variable: The primary efficacy analysis demonstrated a statistically significant mean change of –4.64 hours ($P < 0.001$) from baseline after 12 weeks of treatment in the average daily normalized "Off" time. Analysis with MMRM for subjects remaining on ABT-SLV 187 monotherapy showed consistent statistically significant ($P < 0.001$) mean changes from baseline at all analyzed time points, with mean changes of –4.53 hours on Week 2, –4.02 hours on Week 4, –5.08 hours on Week 6, –4.74 hours on Week 8, –5.09 hours on Week 10, and –5.03 hours on Week 12. Similar results were found with analyses of the average daily absolute "Off" time.

Results of subgroup analyses demonstrated that the observed improvement in average daily normalized "Off" time was independent of age, gender, and ethnicity:

- Gender (male: –4.43 hours, $P < 0.001$; female: –4.79 hours, $P < 0.001$);
- Age (< 65 years: –4.79 hours, $P < 0.001$; ≥ 65 years: –4.31 hours, $P = 0.010$), and;
- Ethnicity (Japanese: –4.37 hours, $P < 0.001$; Korean: –5.71 hours, $P = 0.018$; Taiwanese: –5.00 hours, $P = 0.155$).

Secondary Efficacy Variable: Positive results from the following secondary efficacy variables (except UPDRS) at Week 12, analyzed in hierarchical order, provide supportive evidence for the efficacy and benefits of treatment with ABT-SLV187.

- PD Diary "On" time: A statistically significant mean increase (improvement) of 5.58 hours ($P < 0.001$) from baseline in the average daily normalized "On" time without troublesome dyskinesia was observed. There was a mean change (improvement) of –1.00 hour ($P = 0.032$) from baseline in the average daily normalized "On" time with troublesome dyskinesia.
- PDQ-39: A statistically significant mean change (improvement) of –12.0 ($P < 0.001$) from baseline in the summary index total score was observed. There were statistically significant ($P < 0.001$) mean changes (improvements) from baseline in the domain scores of mobility (–19.2), activities of daily living (–16.0), cognition (–14.0), and bodily discomfort (–17.8).
- CGI-C: Twenty-four of 29 (82.8%) subjects had "Much improved" or "Very much improved" responses on CGI-C. Nine of 29 (31%) subjects had "Very much improved" response. The results showed statistically significant difference from the null hypothesis of a score of 4 (no change) ($P < 0.001$).
- PGI-C: CGI-C and PGI-C responses were well correlated. Twenty-three of 29 (79.3%) subjects had "Much improved" or "Very much improved" responses on PGI-C. Eight of 29 (27.6%) subjects had "Very much improved" response. The results showed statistically significant difference from score of 4 (no change) ($P < 0.001$).
- UPDRS: No statistically significant change from baseline to final visit results was observed for UPDRS Part II score or Part III score; the hierarchical testing ceased at this point.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

In summary, treatment with ABT-SLV187 demonstrated statistically significant and clinically beneficial effects on improvements in PD symptoms. The improvement in motor symptoms observed by a reduction in "Off" time was accompanied by an increase in "On" time without dyskinesia, and a decrease in "On" time with troublesome dyskinesia, as assessed by the PD Diary data. This improvement in motor symptoms was reinforced by improvements measured by validated PD Quality of Life (QoL) and clinical scales widely used and accepted for evaluating clinical symptoms and activities of daily living. The PDQ-39 summary index, CGI-C, and PGIC all demonstrated statistically significant improvements with the ABT-SLV187 treatment. These findings demonstrate the efficacy and beneficial effects of treatment with ABT-SLV187 in levodopa-responsive subjects with advanced PD and persistent motor complications.

Pharmacokinetic Results:

Not applicable

Safety Results:

Safety During the Screening Period

Thirty-three enrolled subjects with advanced PD received at least 1 dose of oral LC-IR tablets in the screening period. Adverse events were reported for 16 (48.5%) subjects in the oral study drug dataset. Three (9.1%) subjects had mild AEs (nausea, dystonia aggravation, vomiting) judged by the investigator as possibly related to oral levodopa-carbidopa. There were no deaths, SAEs, or AE leading to discontinuation of study treatment during the Screening period.

Safety During Treatment with ABT-SVT187 (N-J and PEG-J Periods)

Thirty-one enrolled subjects had N-J placement, received at least 1 dose of ABT-SLV187, and were included in the safety dataset. The mean exposure to ABT-SLV187 was 6.9 days (range: 3 to 14 days) in the N-J test period, and 81.5 days (range: 18 to 87 days) in the PEG-J Period. For subjects in the PEG-J dataset, it took 5.6 days (range: 2 to 11 days) to reach stable morning, continuous, and extra doses.

Treatment-Emergent Adverse Events

All subjects treated with ABT-SLV187 experienced at least 1 TEAE. The most common TEAEs (> 10%) were incision site pain (13 [41.9%]), excessive granulation tissue (10 [32.3%]), constipation (7 [22.6%]); diarrhea, fall, nasopharyngitis (6 [19.4%] each); blood homocysteine increased, dyskinesia, procedural pain (5 [16.1%] each); and incision site erythema (4 [12.9%]). The profile of TEAEs during the PEG-J Period was similar to that of the overall treatment period (N-J and PEG J Periods). In general, the profile in Japanese subjects was similar to that of the overall study population, whereas fewer events were reported for Taiwanese and Korean subjects with the ethnicity subgroup analyses. This could be due to the imbalance in the sample size of these ethnicity subgroups.

Most of the subjects (30 [96.8%]) reported TEAEs that were judged by the investigator as having a reasonable possibility of being related to the ABT-SLV187 therapeutic system. The most common (> 10%) possibly related TEAEs were primarily related to the procedure: incision site pain (13 [41.9%]), excessive granulation tissue (10 [32.3%]), procedural pain (5 [16.1%]); dyskinesia, and incision site erythema (4 [12.9%] each).

Most of the reported TEAEs were mild or moderate. Severe TEAEs were reported for 2 (6.5%) subjects; all were also serious.

Safety Results (Continued):

Adverse Events of Special Interest Searched with Standardized MedDRA Query

A total of 28 (90.3%) subjects had at least 1 AESI. The most common (> 10%) AESIs were primarily GI and GI procedure-related: incision site pain (13 [41.9%]), excessive granulation tissue (10 [32.3%]), procedural pain (5 [16.1%]), and incision site erythema (4 [12.9%]). The majority of the AESIs were mild to moderate in severity. Analyses of polyneuropathy (broad search), weight loss, aspiration, and GI and GI procedure-related AESIs showed overall incidences of 1 (3.2%), 4 (12.9%), 7 (22.6%), and 27 (87.1%), respectively. Only 1 AESI (pneumonia aspiration) in the aspiration category resulted in study discontinuation.

Product Quality Complaints

A total of 25 (80.6%) subjects had any PQCs, and 21 (67.7%) subjects had any PQCs that resulted in an AE. The most common (> 10%) preferred terms reported for subjects with PQCs were medical device site reaction (16 [51.6%]), device difficult to use (10 [32.3%]), complication of device insertion (5 [16.1%]), and device related infection (4 [12.9%]). No PQC events resulted in study discontinuation, except for 1 death due to sepsis.

Deaths, SAEs, and AEs Leading to Discontinuations

There was 1 death due to sepsis, the death was judged by the investigator as having no reasonable possibility of being related to the study drug.

Serious TEAEs were reported for 4 (12.9%) subjects, including the subject who died. The serious adverse events (SAEs) for 2 subjects (severe femur fracture, pneumonia aspiration, sepsis, and disseminated intravascular coagulation for 1 subject; and mild melaena for another) were judged by the investigator as having no reasonable possibility of being related to the study drug. The SAEs for another 2 subjects (severe pneumonia aspiration, device kink, device dislocation, and gastrointestinal perforation for 1 subject; and moderate abdominal pain and constipation for another) were judged by the investigator as having a reasonable possibility of being related to the study drug therapeutic system. All the SAEs resolved except the sepsis event leading to death; and the concurrent pneumonia aspiration and disseminated intravascular coagulation events were ongoing at the time of death.

Pneumonia aspiration and sepsis were the only TEAEs that resulted in study discontinuation for 1 (3.2%) subject.

Clinical laboratory results

There were no clinically meaningful mean changes from baseline, or consistent shifts from normal values at baseline, for hematology, clinical chemistry, and urinalysis variables. Among subjects with identified PCS hematology values, relevant concurrent AEs were only observed for low hemoglobin and low hematocrit in 1 subject (moderate anemia), low hematocrit in 1 subject (mild tarry stool), and high WBC count in 1 subject (severe aspiration pneumonia). None of the subjects discontinued the study due to the PCS values.

Safety Results (Continued):

Vital signs, ECGs, and Other Safety Observations

No clinically meaningful mean changes from baseline for vital sign variables or 12-lead ECG data were observed. Among subjects with identified PCS vital sign values, relevant concurrent AEs were only observed for low body weight in 3 subjects (mild weight loss), low blood pressure in 2 subjects (mild blood pressure decreased), and high blood pressure in 1 subject (mild hypertension). None of the subjects discontinued the study due to the PCS values or the AEs that were possibly related to the PCS vital sign values. Results of 12-lead ECGs were clinically unremarkable.

No noteworthy findings were found with assessments for MIDI, sleep attacks, any suicidal ideation or behavior with C-SSRS responses, or melanoma checks.

Overall, ABT-SLV187 was safe and well tolerated throughout the duration of this study. The results from this study support the safety and tolerability of ABT-SLV187 in subjects with advanced PD.

Conclusions:

ABT-SLV187 has the potential to address a significant unmet medical need in advanced PD patient population, where limited therapeutic options are available.

Improvements in motor symptoms, a reduction in "Off" time and complementary increase in "On" time without troublesome dyskinesia, combined with improvement in QoL and clinical scales including the PDQ-39, CGI-I, and PGI-C, demonstrated the beneficial effects of symptomatic improvement with ABT-SLV187. The adverse events reported were generally those expected for the device-related procedure and those expected for the patient population with advanced PD treated with levodopa or levodopa-carbidopa. The majority of events were mild or moderate in severity.

The statistically significant and clinically meaningful efficacy results, together with the tolerability and acceptable safety findings observed in the study, provide evidence of a positive benefit-risk profile for treatment with ABT-SLV187 in levodopa-responsive subjects with advanced PD and persistent motor complications.