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 Two-Part Extension Study Assessing Safety, Tolerability and Efficacy of ABT-SLV187 in Subjects with Advanced Parkinson's Disease and Persistent Motor-Complications Despite Optimized Treatment with Available Anti-Parkinsonian Medications

Coordinating Investigator: [redacted], MD

Study Sites: Parts 1 and 2: 7 sites in Japan, 1 site in South Korea, and 2 sites in Taiwan, Part 3: 1 site in South Korea

Publications: None as of the date of this report.

Studied Period (Years): First Subject First Visit: 10 March 2014 Last Subject Last Visit: 8 November 2019	**Phase of Development:** 3/Post-Marketing Clinical Study

Objectives:

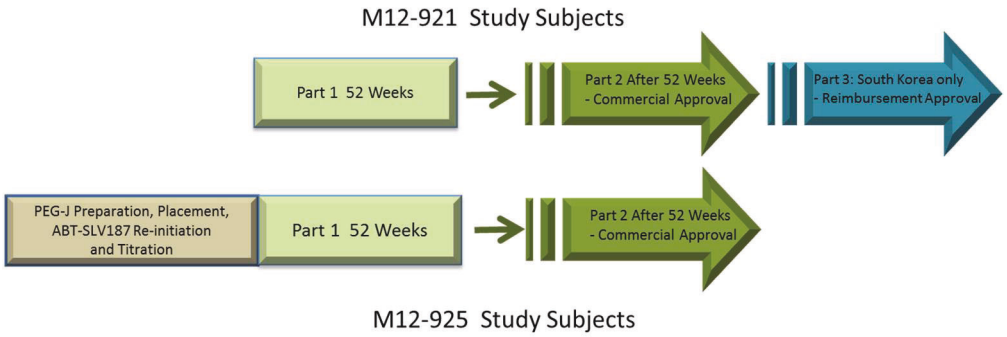
The primary objective of this extension study was to evaluate the long-term safety and tolerability of ABT-SLV187 (known as Duodopa® or Duopa® in countries where it is marketed) in subjects with advanced Parkinson's disease (PD) and persistent motor complications despite optimized treatment with available anti-Parkinsonian disease medications. The secondary objective was to assess the long-term maintenance of efficacy of ABT-SLV187 in these subjects over a period of 12 months.

Methodology:

This is a post-marketing, open-label, multicenter, 3-part study of long-term safety, tolerability and efficacy of ABT-SLV187 in subjects with advanced PD and persistent motor complications despite optimized treatment with available anti-Parkinsonian medications. Study M12-923 enrolled eligible subjects who completed Pan-Asia Study M12-921 or participated in the Japan Study M12-925.

Subjects in Study M12-921 were treated with ABT-SLV187 for 12 weeks through percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) administration and entered Study M12-923 at their current dose. These subjects utilized their final Study M12-921 visit as the Baseline visit of Study M12-923.

Methodology (Continued):



For Study M12-921 subjects, Study M12-923 comprised 3 study periods: (i) Part 1 (52 Weeks), (ii) Part 2 (After 52 weeks until commercial approval), and (iii) Part 3 (South Korea only, until reimbursement approval). In Part 3, this study provided continued access to ABT-SLV187 treatment to 4 subjects from South Korea.

Study M12-925 was designed to treat subjects with a 21-day naso-jejunal (N-J) administration of ABT-SLV187. Upon completion of the study, the N-J tube was removed and subjects resumed their oral PD drug regimen. Subjects who participated in Study M12-925 needed to be prepared for an N-J test period and PEG-J placement for participation in Study M12-923. However, an N-J test period was optional at the principal investigator's (PI) discretion for subjects who completed Study M12-925.

For Study M12-925 subjects, Study M12-923 comprised 3 study periods: (i) Screening, (ii) Part 1: Optional N-J Placement, PEG-J Placement and ABT-SLV187 Initiation/Titration, and Rest of Part 1 (through 52 weeks), (iii) Part 2 (after 52 weeks until commercial approval).

In addition, 1 subject who had already received administration of commercial ABT-SLV187 overseas and was judged by the investigator to require continuous administration of ABT-SLV187 in Japan was also enrolled in the study (Part 1 and Part 2).

Number of Subjects (Planned and Analyzed):

Planned: 37; enrolled (signed informed consent form): 30; treated with ABT-SLV187: 30.

30 subjects analyzed for safety (N-J Period and PEG-J Period);

30 subjects analyzed for efficacy (full analysis set).

In addition, the subject who had already received administration of ABT-SLV187 was enrolled, but not included in the analysis dataset.

Diagnosis and Main Criteria for Inclusion:

The investigator had to confirm that the subjects met all of the Inclusion Criteria and none of the Exclusion Criteria before enrolling in this study.

Inclusion Criteria:

1. Subjects completed 12 weeks of treatment in Study M12-921 who would have benefitted from long-term treatment from ABT-SLV187. Alternatively, subjects who (i) participated in the Phase 2 Study M12-925 (ii) would have, in the opinion of the investigator, benefited from ABT-SLV187 treatment in Study M12-923, (iii) did not discontinue Study M12-925 due to safety reasons, and (iv) met all entry requirements.

Diagnosis and Main Criteria for Inclusion (Continued):

Inclusion Criteria (Continued):

2. The subject must have been able to understand the nature of the study and must provide written informed consent prior to the conduct of any study procedures (including any changes occurring in the subject's current therapeutic regimen).
3. The subject was willing to continue treatment.

Exclusion Criteria:

1. Subjects who were enrolled in another clinical trial.
2. Subjects who had psychiatric, neurological, or behavioral disorders that could have interfered with the ability of subjects to give informed consent, or interfered with the conduct of the study.
3. Subjects who had medical, laboratory, or surgical issues deemed by the investigator to be clinically significant and in the opinion of the PI, would be a contraindication to continued levodopa therapy.
4. Subjects who had uncooperative attitude or reasonable likelihood for non-compliance with the protocol.
5. Subjects who had current significant suicidal ideation as evidenced by answering "yes" to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) completed at the Week 12 Visit of Study M12-921 or at the Baseline Visit for subjects of Study M12-925.
6. Subjects who were considered by the investigator, for any reason, to be an unsuitable candidate to continue to receive ABT-SLV187.

Additional inclusion and exclusion criteria for subjects enrolling from Study M12-925 were included in protocol Appendix D. The subject who had already received administration of ABT-SLV187 overseas had additional inclusion and exclusion criteria. These additional criteria were described in Appendix Y of the Protocol Amendment 3.01 National Center of Neurology and Psychiatry Site – Version 2.

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

Dosing of ABT-SLV187 was to be individually optimized based on the subject's clinical response.

Oral Levodopa-Carbidopa Immediate Release (LC-IR) was utilized for night-time medication and rescue therapy.

For Study M12-921 subjects, ABT-SLV187 (levodopa [20 mg/mL] and carbidopa monohydrate [5 mg/mL]) was delivered to the jejunum through a jejunal extension tube inserted via PEG-J, for long term treatment. ABT-SLV187 was dispensed in a medication cassette reservoir of 100 mL.

ABT-SLV187 was delivered over a full 16-hour period each day, administered as 1 morning dose, followed by continuous infusion and, if needed, intermittent extra doses.

For Study M12-925 subjects, the investigator had the option to initiate ABT-SLV187 through a N-J tube, or through a direct PEG-J.

Extra doses were permitted at intervals of no less than 2 hours, allowing for up to 8 extra doses during the course of a 16-hour treatment period each day, except for the allowance of 1 hour intervals during the titration period. This 16-hour interval corresponded to the hours used to calculate the daily oral doses of levodopa-carbidopa that form the basis for the ABT-SLV187 dose calculation. Study M12-925 subjects were allowed extra doses every hour during the titration period.

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

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, 1ES39M, 1ES92M
LC-IR 100 mg/25 mg tablets	Oral	13-001836, 13-006254, 14-006150, 15-001494, 15-005691, 16-003657 17-008223, 18-005150
100 mL Levodopa (20 mg/mL) carbidopa (5 mg/mL) intestinal gel medication cassette reservoirs	Upper-intestinal infusion	13-003267, 13-003759, 14-006024, 15-001164, 15-003244, 15-004277, 15-006680, 16-001925 17-003301, 18-004786

Duration of Treatment:

This study was extended until ABT-SLV187 was granted marketing authorization in participating countries. Subjects were to participate for a minimum of 52 weeks (Part 1).

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

Not applicable.

Criteria for Evaluation

Safety:

Safety was assessed with 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.

- Treatment-emergent adverse events (TEAEs)
- Clinical labs*
- Vital signs
- ECGs**
- Product quality complaints
- Abnormal findings on neurological exams
- Impulsivity as reported on the Minnesota Impulsive Disorders Interview (MIDI)**
- Sleep attacks as reported in the sleep attack interview**
- Suicidal ideation or behavior reported on the C-SSRS

* Local labs were used for Part 3. Only the central laboratory data were to be entered into the database.

** Not evaluated in Part 3.

Criteria for Evaluation (Continued)

Efficacy (Part 1 and Part 2):

PD Diary variables included average daily normalized "Off" time, "On" time with troublesome dyskinesia and "On" time without troublesome dyskinesia.

Efficacy analyses were performed for the following additional variables.

- 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 (PDQ-39) summary index and domain scores
- Patient Global Impression of Change (PGI-C) score and responder category
- Clinical Global Impression of Change (CGI-C) score

Efficacy evaluation was not performed for the subject who had already received administration of the product overseas.

Statistical Methods

Analysis Datasets:

Data acquired in the Study M12-921 database and the Study M12-923 database were included. The following datasets were used for the statistical analyses.

Oral Study Drug Dataset

The Oral Study Drug dataset included all subjects who took at least 1 dose of oral levodopa-carbidopa study drug in Study M12-923. The Oral Study Drug dataset was used to summarize safety data for all subjects who received oral study drug.

Safety Dataset

The Safety dataset included all Study M12-925 subjects who underwent the N-J or PEG-J placement procedure and all Study M12-921 subjects who received at least 1 infusion of Study M12-923 study drug. The Safety dataset was the primary dataset to summarize safety data.

Full Analysis (FA) Dataset

The Full Analysis (FA) dataset included all subjects who were in the Safety dataset and who had either a) a baseline and a Part 1 measurement for at least 1 of the PD Diary, UPDRS or PDQ-39 efficacy variables or b) a Part 1 measurement for the CGI-C or PGI-C.

The subject who had already received administration of the product overseas was not included in the analysis datasets. Results of this subject are separately presented in Section 16.1__9.2.

Definition of Baseline and Final Visit Values

For Study M12-925 subjects, baseline for a given variable was defined as the last value obtained prior to their first dose of study drug. For Study M12-921 subjects, baseline for a given variable was the last value obtained prior to the first dose of oral study drug in Study M12-921 Screening Period. The final visit value for efficacy analyses was the last non-missing value collected within 1 day after the last Study M12-923 drug infusion, and the final visit value for safety analyses was the last non-missing value collected within 1 day after final ABT-SLV187 device removal.

For subjects who previously completed Study M12-921, the summaries included cumulative data from both Study M12-921 and Study M12-923.

Statistical Methods (Continued)

Statistical Significance of Hypothesis Tests

Unless noted otherwise, all statistical tests were 2-sided, and the null hypothesis was to be rejected at the significance level of $\alpha = 0.050$.

Efficacy Analysis:

Efficacy analyses were performed on the Full Analysis dataset.

For each of the following efficacy variables, summary statistics and a 95% confidence interval was calculated for each scheduled visit using observed values as well as for the last observed value. The last observed value was defined as the last value obtained during the study treatment as the last observation carried forward (LOCF).

For each efficacy variable, the change from baseline to final visit was evaluated with a one-sample t-test, and for the PD Diary, UPDRS and PDQ-39 variables, the change from baseline to each scheduled visit was evaluated with a mixed-effect model repeated measures that included the fixed effects of country and visit, with baseline value as a covariate, and the baseline-by-visit interaction.

Safety Analysis:

The Safety dataset was the primary dataset for the analysis of the safety and tolerability data.

Treatment-emergent AEs were summarized using Preferred Terms (PTs) per primary System Organ Class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Severity and drug-event relationship of treatment-emergent AEs were summarized separately.

Tolerability was assessed by the number of subjects who completed the study.

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

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

For medical device related complaints (device kink, device dislocation, device connection issue, and device difficult to use), a frequency table was presented for the number of subjects reporting complaints.

Interim Analysis

The first interim analysis was performed when all subjects had either prematurely discontinued or completed 24 weeks of cumulative ABT-SLV187 treatment through PEG-J (12 weeks of treatment in Study M12-923 for continuing Study M12-921 subjects and 24 weeks of treatment in PEG-J period for Study M12-925 subjects). The second interim analysis was performed when all subjects had either prematurely discontinued or completed 52 weeks of cumulative ABT-SLV187 treatment (12 weeks of treatment in Study M12-921, 40 weeks of treatment in Study M12-923 for continuing Study M12-921 subjects and 52 weeks of treatment in PEG-J period for Study M12-925 subjects). The third interim analysis occurred either after premature discontinuation in Part 1 and Part 2 or after completion of ABT−SLV187 treatment in the Part 2.

Summary/Conclusions

Efficacy Results:

A total of 30 Asian subjects aged 45 to 77 years (median: 61.5 years) with a mean PD duration of approximately 12 years were enrolled and treated with ABT-SLV187. Of these 30 subjects, 28 subjects had N-J and PEG-J placement and were treated with ABT-SLV187 for 12 weeks prior to entering this extension study; 2 subjects enrolled from Study M12-925 had PEG-J placement and were treated with ABT-SLV187 in Study M12-923 without undergoing the optional N-J period. All 30 subjects entered the PEG-J treatment period and were included in the Full Analysis dataset for efficacy evaluations.

All efficacy variables are reported in the third interim clinical study report. No efficacy data are presented in the final clinical study report.

Pharmacokinetic Results:

Not applicable

Safety Results:

Thirty subjects were enrolled and received at least 1 dose of ABT-SLV187. All these subjects were included in the safety dataset. The mean exposure to ABT-SLV187 was 7.1 days (range: 3 to 14 days) in the N-J test period and 835.4 days (range: 184 to 1816 days) in the PEG-J period. Twenty-two subjects completed study treatment, and 8 subjects discontinued study treatment. Primary reasons for discontinuation included adverse event (4 subjects), and withdrew consent, subject noncompliant, lack of efficacy and other reason (1 subject, each).

Treatment-Emergent Adverse Events (TEAEs)

All subjects treated with ABT-SLV187 experienced at least 1 TEAE. The most common TEAEs (≥ 10%) were excessive granulation tissue (23 [76.7%]), nasopharyngitis (16 [53.3%]), incision site pain (15 [50.0%]), constipation (13 [43.3%]), incision site erythema (10 [33.3%]), diarrhea (9 [30.0%]), fall (8 [26.7%]), weight decreased, vitamin B_6 deficiency, and dyskinesia (7 [23.3%] each), nausea, tinea pedis, and procedural pain (6 [20.0%] each), dental caries, vomiting, and blood homocysteine increased, back pain, insomnia, and rash (5 [16.7%] each), abdominal pain, pyrexia, body tinea, conjunctivitis, stoma site infection, contusion, decreased appetite, and eczema (4 [13.3%] each), and anaemia, abdominal distension, toothache, device dislocation, body tinea, catheter site infection, incision site rash, stoma site erythema, blood pressure increased, vitamin B_6 decreased, catheter site discharge, arthralgia, headache, "hallucination, visual," epistaxis, oropharyngeal pain, pneumonia aspiration, dermatitis contact, hypertension, and orthostatic hypotension (3 [10.0%] each). The highest incidence for most TEAEs occurred early (within the first 12 weeks) and decreased over time. In general, the profile in Japanese subjects was similar to that of the overall study population, whereas fewer events were reported for Taiwanese and South Korean subjects with the ethnicity subgroup analyses. This could be due to the imbalance in the sample size of these ethnicity subgroups.

All of the subjects (30 [100.0%]) 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 excessive granulation tissue (23 [76.7%]), incision site pain (15 [50.0%]), incision site erythema (10 [33.3%]), procedural pain, vitamin B_6 deficiency, and dyskinesia (6 [20.0%] each), weight decreased (5 [16.7%]), constipation and stoma site infection (4 [13.3%] each), and catheter site discharge, device dislocation, pyrexia, catheter site infection, incision site rash, stoma site erythema, decreased appetite, and pneumonia aspiration (3 [10.0%] each). Most of the reported TEAEs were mild or moderate in severity. Severe TEAEs were reported for 6 subjects.

Summary/Conclusions (Continued)

Safety Results (Continued):

During the PEG-J period, the incidence of any TEAE was highest during the first 12 weeks of the study (100.0%) and decreased over time. The most common procedure and procedure related AEs occurred most frequently within the first week (abdominal pain, complication of device insertion, incision site pain, and procedural pain) and/or within the first 12 weeks (excessive granulation tissue and incision site erythema).

Adverse Events of Special Interest (AESI) Searched with Standardized MedDRA Query and Company MedDRA Queries

All subjects (30 [100%]) had at least 1 AESI. Analyses of polyneuropathy (broad search), weight loss, aspiration, and and gastrointestinal (GI) and GI procedure-related AESIs showed overall incidences of 4 (13.3%), 8 (26.7%), 11 (36.7%), and 30 (100.0%) subjects, respectively. The most common (≥ 10%) AESIs were primarily GI and GI procedure-related; excessive granulation tissue (23 [76.7%]), incision site pain (15 [50.0%]), incision site erythema (10 [33.3%]), procedural pain (6 [20.0%]), abdominal pain and stoma site infection (4 [13.3%] each), and device dislocation, catheter site infection, and stoma site erythema (3 [10.0%] each). Most of the AESIs were mild to moderate in severity. Three subjects who had AESIs in the GI and GI procedure-related category resulted in study discontinuation and/or death.

Product Quality Complaints (PQC)

All of 30 (100.0%) subjects had PQC that resulted in an AE. The most common (≥ 10%) PTs reported for subjects with PQCs were medical device site reaction (29 [96.7%]), medical device change (26 [86.7%]), device malfunction (18 [60.0%]), device difficult to use (13 [43.3%]), device breakage (12 [40.0%]), device dislocation, device kink, and device occlusion (10 [33.3%] each), complication of device insertion, and device issue (9 [30.0%] each), device leakage (6 [20.0%]), device colour issue, device connection issue, and device related infection (5 [16.7%] each), and device use error (4 [13.3%]).

Deaths, Serious Adverse Events (SAEs), and AEs Leading to Discontinuations

Two deaths were reported in the study. One subject had TEAEs of intestinal obstruction (recurrent), shock, and sepsis that led to death during the study treatment. These fatal TEAEs were judged by the investigator as having no reasonable possibility of being related to the study treatment system. The other subject died due to non-TEAE of drowning after discontinuation of the study treatment. The drowning was judged by the investigator as having no reasonable possibility of being related to the study treatment system.

Serious TEAEs were reported for 13 (43.3%) subjects. Pneumonia aspiration was reported in 3 subjects (10.0%). Subdural hematoma was reported in 2 subject (6.7%). All other serious TEAEs were reported in 1 subject (3.3%) each. Serious TEAEs considered to have a reasonable possibility of being related to the treatment system by the investigator were reported for 7 subjects: Parkinson's disease psychosis, pneumonia aspiration, delirium, abdominal pain, constipation, pneumoperitoneum, ileus, excessive granulation tissue, device kink, device dislocation, gastrointestinal perforation, and peritonitis. Three subjects had serious TEAEs that led to discontinuation and/or death. TEAEs that led to discontinuation were reported in 4 (13.3%) subjects. One of these subjects had TEAEs resulted in death.

Summary/Conclusions (Continued)

Safety Results (Continued):

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. Relevant concurrent AEs were only observed for potentially clinically significant (PCS) low hematocrit in 1 subject (mild melaena and anemia), PCS high white blood cell (WBC) count in 2 subjects (severe pneumonia aspiration; mild nasopharyngitis), and PCS low WBC count in 1 subject (mild leukopenia). None of the subjects discontinued the study due to the PCS values. Among subjects with identified PCS chemistry values, relevant concurrent AE was observed for low sodium in 1 subject (mild hyponatremia). None of the subjects discontinued the study due to the PCS values.

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. Relevant concurrent AEs were observed for PCS weight loss in 8 subjects (mild to moderate weight decreased), PCS low blood pressure in 2 subjects (mild blood pressure decreased), and PCS 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 report supported the safety and tolerability of ABT-SLV187 in subjects with advanced PD.

Conclusions:

Improvements in motor symptoms, a reduction in "Off" time and complementary increase in "On" time without troublesome dyskinesia, combined with improvement in quality of live (QoL) and PDQ-39, 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, along with the tolerability and acceptable safety findings observed in this study, provided evidence of a positive benefit-risk profile for long-term treatment with ABT-SLV187 in levodopa-responsive subjects with advanced PD and persistent motor complications.