

2.0 Synopsis

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| AbbVie Inc. and AbbVie GK | Individual Study Table Referring to Part of Dossier: | (For National Authority Use Only) |
| Name of Study Drug: ABT-SLV187 (Levodopa-Carbidopa Intestinal Gel [LCIG]) | Volume: Page: | |
| Name of Active Ingredient: Levodopa-carbidopa | | |
| Title of Study: An Open-Label, Single-Arm, Baseline-Controlled, Multicenter Study to Explore the Safety, Tolerability, Pharmacokinetics, and Efficacy of ABT-SLV187 in Subjects with Advanced Parkinson's Disease | | |
| Investigator: Investigator information is on file at AbbVie | | |
| Study Sites: 5 sites in Japan | | |
| Publications: There were no publications based on this study. | | |
| Studied Period (Years): First Subject First Visit: 13 October 2011 Last Subject Last Visit: 25 July 2012 | Phase of Development: 2 | |
| Objectives: The primary objective of this study was to assess the safety and tolerability of ABT-SLV187 in subjects with advanced Parkinson's Disease (PD). The secondary objectives of this study were as follows: 1. Pharmacokinetic Objective To investigate the pharmacokinetics (PK) of levodopa, carbidopa, and 3-O-methyldopa (3-OMD) following intra-jejunal administration of ABT-SLV187 in advanced PD subjects with severe motor complications, and to compare the within-subject variability of plasma levodopa concentrations following administration of an oral levodopa/carbidopa (L/C) tablet 2. Efficacy To explore the efficacy of ABT-SLV187 in advanced PD subjects with severe motor complications as evaluated by the Treatment Response Scale (TRS) (I) and (II), video scoring, Parkinson's Disease Diary [®] , Unified Parkinson's Disease Rating Scale (UPDRS), modified Hoehn & Yahr (H & Y), Schwab and England Activities of Daily Living Scale, Japanese version of Parkinson's Disease Questionnaire-39 (PDQ-39), Clinical Global Impression rating scale (the Clinical Global Impression-Severity = CGI-S and the Clinical Global Impression-Improvement = CGI-I) and comparing with an oral L/C product 3. Medical Device Complications To investigate the complications of medical devices for the naso-jejunal (NJ) infusion system of ABT-SLV187 (Infusion pump, NJ tube and adaptor), and defects of the ABT-SLV187 cassette and cassette tube | | |

Methodology:

This was a Phase II, open-label, single-arm, baseline-controlled, multicenter study to explore the safety, tolerability, PK and efficacy of ABT-SLV187 in advanced PD subjects with severe motor complications despite optimized oral treatment with anti-PD medications.

Subjects with idiopathic PD were only eligible if they were classified as modified H & Y stage 4 or 5 at OFF state, were responsive to treatment with oral levodopa, had severe motor fluctuations and dyskinesia, and had a minimum daily OFF time of 3 hours during a continuous 16-hour interval as supported by the subject PD-diaries for three consecutive days including the portion of the day during which the subject was awake for the majority of time (e.g. 6 AM to 10 PM).

The study consisted of a Screening Period (maximum 14 days), a Run-in Period (28 days), an ABT-SLV187 Treatment Period (21 days), and a Follow-up Period (7 days).

Screening Period:

In order to confirm the eligibility of subjects for the Run-in Period (the end of the Screening Period), a training and confirmation of the appropriate use of the Parkinson's Disease Diary[®] and the confirmation of the risk/appropriateness to insert a NJ-tube, as well as other evaluations including safety evaluations, were to be conducted. During the final day of the Screening Period, the subjects were to be recorded on video equipment while performing a series of assigned movements, which were to be used by 3 blinded assessors for the evaluation of video assessments and TRS.

Run-in Period:

Subjects were to be converted from their usual anti-PD medications to an individually optimized dose of monotherapy of oral L/C. In order to assure the eligibility of subjects for the ABT-SLV187 Treatment Period, a minimum of 3 hours/day of OFF period and recognizable dyskinesia were to be confirmed from the Parkinson's Disease Diary[®]. Video recordings and PK samplings were to be performed at the end of the Run-in Period.

ABT-SLV187 Treatment Period:

ABT-SLV187 was to be administered via an NJ-tube. At the end of the ABT-SLV187 Treatment Period, video recordings and PK samplings were to be performed.

Follow-up Period:

Follow-up was to be conducted for the safety evaluation after the completion of the ABT-SLV187 Treatment Period.

Subjects were to be hospitalized during the last 2 days of the Run-in Period (Days -2 and -1) and during the entire ABT-SLV187 Treatment Period. The remainder of the study period was to be conducted under out-patient condition; however additional hospitalization was to be permitted, if needed. ABT-SLV187 was to be administered with an infusion pump directly into the proximal jejunum by a NJ tube.

All adverse events reported from the first day of the Run-in Period until 30 days following discontinuation of study drug administration were to be collected, whether solicited or spontaneously reported by the subject. SAEs were to be collected from the time the subject signed the study-specific informed consent until 30 days following discontinuation of study drug administration. The medical device complaint was to be collected starting with the delivery to the investigational site up to the return of used and unused devices to the sponsor.

Number of Subjects (Planned and Analyzed):

Planned: 8; Enrolled: 8; Treated: 6;

Number of Subjects (Planned and Analyzed, Continued):

All 8 subjects enrolled were included in the full safety sample, which was used for analysis of demographics and drug exposure, and evaluation of safety. 6 subjects who had at least one dose of the ABT-SLV187 study medication after the baseline assessment were included in ABT-SLV187 safety sample. Two subjects who prematurely discontinued the study in the Run-in Period, and were not treated with ABT-SLV187, were excluded from the ABT-SLV187 safety sample. The ABT-SLV187 safety sample was used for analysis of demographics and evaluation of safety. 5 subjects who had data for baseline and at least one post-baseline efficacy measurement were included in the full analysis sample (FAS), and 1 subject who prematurely discontinued the study in the ABT-SLV187 Treatment Period and had no post-baseline efficacy measurement was excluded from FAS. The FAS was used for efficacy analysis. Five subjects who completed PK assessments in both the oral L/C and ABT-SLV187 Treatment Periods were included in the PK sample for pharmacokinetic analysis. One subject was excluded from calculation of the summary statistics for the PK parameters of the oral L/C Treatment Period since the subject did not have comparative data for ABT-SLV187 treatment.

Diagnosis and Main Criteria for Inclusion:

Subjects who met all of the inclusion criteria and none of the exclusion criteria were eligible for study participation.

Main Inclusion:

1. Subjects who had a diagnosis of idiopathic PD according to the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank criteria.
2. Subjects whose PD disease stage corresponded to 4 or 5 in the OFF state according to the modified H & Y classification of disease severity.
3. Subjects whose advanced PD was the levodopa-responsive type as judged by the investigator.
4. Subjects who demonstrated severe motor fluctuations in spite of individually optimized available anti-PD treatment and where other therapy options were indicated. Optimized treatment was defined as the maximum therapeutic effect obtained with pharmacological antiparkinsonian therapies when no further improvement was expected regardless of any additional manipulations of oral levodopa and/or other antiparkinsonian medication; this was based on the investigator's best clinical judgment.
5. Subjects who were experiencing a minimum of three hours per day of "OFF" time, as supported by the subject PD-diaries at baseline (diaries were collected for the three days preceding the baseline).

Main Exclusion:

1. Subjects who had an unclear diagnosis of PD or were suspected to have a diagnosis of 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.
2. Subjects who underwent neurosurgery for the treatment of PD (e.g., pallidotomy, deep brain stimulation, fetal tissue transplantation) or any other brain surgery.
3. Subjects who had any neurological deficit that was possible to interfere with the study assessments (e.g. hemiparesis) and/or a diagnosis of an acute stroke within the six months prior to giving voluntary informed consent.
4. Subjects who had known hypersensitivity to levodopa, carbidopa, any other constituent of ABT-SLV187 or oral L/C tablet, or radiopaque material.
5. Subjects for whom the NJ tube placement was a high risk as evaluated by the gastroenterologist or appropriate physician (e.g. an internist, an endoscopic physician, or a surgeon).

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

Test Product: ABT-SLV187
Dose/Strength/Concentration: The total daily dose of ABT-SLV187 was composed of the morning dose, the continuous maintenance dose, and the extra dose which were individually adjusted. Subject dosing of ABT-SLV187 was to be determined individually. The starting dose on the first day of the ABT-SLV187 Treatment Period (Day 1) was to be based on the daily dose of the oral levodopa component from the oral L/C tablet taken at baseline (Day -1). The infusion dose was to be optimized individually for each subject during the study by the investigator based on the subject's symptoms (the efficacy and safety).
Mode of Administration: ABT-SLV187 was to be administered with an infusion pump directly into the proximal jejunum by a naso-jejunal tube. Morning dose and subsequent continuous maintenance dose were to be administered for 16 hours a day. During this period, extra dose could be administered, if necessary.
Batch Number/Bulk Lot Number: 5713-01/10J27G18

Duration of Treatment:

Oral L/C tablet for 28 days in the Run-in Period, followed by ABT-SLV187 via medical devices (infusion pump, NJ tube and adaptor) directly into the proximal jejunum for 21 days in the ABT-SLV187 Treatment Period

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

Reference Therapy: Standard Therapy: Oral L/C Tablet
Dose/Strength/Concentration: Subject dosing of the oral L/C tablet was to be determined individually and optimally. Six times daily (excl. night time administration).
Mode of Administration: Oral administration.
Batch Number/Bulk Lot Number: RY8A/1EN14M and RYXA/1EN41M

Criteria for Evaluation

Efficacy:

1. Video Assessment and Treatment Response Scale (TRS)
 - a. Video Assessment (UPDRS Nos. 20, 23, 25, 27, 29, 30 & 31, and Goetz Dyskinesia Rating Scale)
 - b. Treatment Response Scale (I): Primary Efficacy Measurement
 - c. Treatment Response Scale (II)
2. Parkinson's Disease Diary[©]
3. Unified Parkinson's Disease Rating Scale (UPDRS)
4. Modified Hoehn and Yahr
5. Schwab and England activities of daily living scale
6. Japanese version of Parkinson's Disease Questionnaire 39 (PDQ-39)
7. Clinical Global Impression (CGI):
 - a. Clinical Global Impression-Severity (CGI-S)
 - b. Clinical Global Impression-Improvement (CGI-I)

Criteria for Evaluation (Continued)

Pharmacokinetic:

Values for the pharmacokinetic parameters of levodopa, carbidopa, and 3-OMD were determined using non-compartmental methods.

For Day-1,

- The maximum observed plasma concentration (C_{max}), time of C_{max} (T_{max}), and the minimum observed plasma concentration (C_{min}), were determined for the 0-12 hour interval relative to administration of first morning oral L/C dose (interval covering administration of 4 doses of oral L/C).
- Additionally, the C_{max} and C_{min} values were calculated for the 2-12 hour interval relative to administration of first morning oral L/C dose.
- The area under the plasma concentration-time curve (AUC) for the 0-12 hour interval (AUC_{0-12}) as well as the AUC for the 2-12 hour interval (AUC_{2-12}) were calculated by the linear-up log-down trapezoidal rule.
- The average plasma concentration (C_{avg}) for the 0-12 hour and 2-12 hour intervals were calculated by dividing the AUC for these time intervals by the respective duration.
- The degree of fluctuation (DFL) for the 2-12 hour interval relative to administration of first morning oral L/C dose (DFL_{2-12}) was determined as $(C_{max}-C_{min})/C_{avg}$ using the parameters calculated for the 2 to 12 hour interval.
- Dose-normalized values for AUC were calculated by dividing AUC_{0-12} by the total dose of the parent drug (levodopa dose for levodopa and 3-OMD parameters, and carbidopa dose for carbidopa parameters) during the 0-12 hour interval relative to administration of first morning oral L/C dose (total of 4 oral L/C doses).
- For 3-OMD, the metabolite to parent ratios (M/P) for AUC_{0-12} were calculated.

For Day 21,

- C_{max} , T_{max} , AUC, C_{min} , and C_{avg} were calculated for the 0-12 hour as well as the 0-16 hour intervals relative to initiation of infusion of ABT-SLV187.
- Additionally, the C_{max} , C_{min} , C_{avg} , AUC and DFL were calculated for the 2-12 hour and the 2-16 hour intervals relative to initiation of infusion of ABT-SLV187.
- Dose-normalized AUC values were calculated by dividing the AUC_{0-12} and AUC_{0-16} by the total parent dose during the corresponding time intervals relative to initiation of ABT-SLV187 infusion.
- Additionally, the total dose during the 0-16 hour interval was divided by body weight and used to normalize the AUC_{0-16} .
- For 3-OMD, the M/P ratios for AUC_{0-12} and AUC_{0-16} were calculated.

The inter- and intra- subject coefficient of variation for plasma concentrations of levodopa, carbidopa, and 3-OMD were estimated for the 2-12 hour intervals on Days -1 and 21 and for the 2-16 hour interval on Day 21.

Safety:

Adverse events, clinical laboratory tests, vital signs, electrocardiogram, physical examination, neurological examination and medical device complaints.

Statistical Methods

Efficacy:

Efficacy analysis was performed on the Full Analysis Sample (FAS).

The primary efficacy analysis of this study was to compare the efficacy of intra-jejunal administration of ABT-SLV187 at the end of the ABT-SLV187 Treatment Period (Day 21) with that of administration of the oral L/C tablet at the baseline (Day -1) based on the percentage of ratings in the interval -1 to +1 (“mild OFF” to “ON with mild dyskinesia”) in TRS I. The TRS I was to be calculated by averaging the results of video assessment by three raters. Summary statistics including a 95% confidence interval were to be provided to summarize the primary efficacy parameter. A comparison of the primary efficacy parameter between the end of the ABT-SLV187 Treatment Period and the baseline was to be carried out using a paired t-test at a two-sided significance level of 5%. Descriptive statistics including a 95% confidence interval were to be provided.

Secondary efficacy analyses were to include the change from baseline (Day -1) to the end of the ABT-SLV187 Treatment Period (Day 21) for the following: TRS II, daily "Off" time in the Parkinson's Disease Diary[®], UPDRS total score and sub-scores, PDQ-39 total score and CGI-S/CGI-I scores.

Pharmacokinetic:

Descriptive statistics were provided for each parameter. For each of the three compounds, an analysis was performed on dose normalized AUC_{0-12} and on DFL_{2-12} . A point estimate and 95% confidence interval for the central value of the ratio of the ABT-SLV187 AUC_{0-12} to the oral L/C tablet AUC_{0-12} was provided by exponentiation of the geometric mean of the observed ratios and the endpoints of a 95% confidence interval obtained for the mean difference of logarithms from the one-sample t-statistic. For each of the oral L/C tablet regimen and ABT-SLV187, a repeated measures analysis was performed on the logarithm of concentration during Hours 2-12 relative to the first dose or beginning of infusion. Within this framework, point estimates for the intra-subject and inter-subject components of the total variance of the logarithm of concentration were obtained, and from these corresponding estimates of coefficients of variation for untransformed concentration were derived.

Safety:

The safety sample was used for the analysis of the safety and tolerability data.

Treatment emergent AEs were to be summarized using Preferred Terms per primary System Organ Class and per High Level Term according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus. Severity and event relationship with the standard product (Oral L/C Tablet) to be used during the Run-in Period or the ABT-SLV187 therapeutic system (three components: drug, devices and naso-jejunal tube insertion procedures) were to be summarized separately.

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

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

For product quality complaints, a frequency table was to be presented.

Summary/Conclusions

Efficacy Results:

A total of 8 Japanese subjects with PD aged 58–72 years with disease duration of approximately 15 years were enrolled in the study. Two subjects prematurely discontinued the study in the Run-in Period and 6 subjects were treated with study drug. Out of 6 subjects, 1 subject (Subject [REDACTED]) prematurely discontinued the study due to AEs (somatic hallucination; delusion; and hallucination, auditory [severe, possibly related with study drug, serious, each]) in the ABT-SLV187 Treatment Period and 5 subjects completed the study. The full safety sample consisting of 8 subjects who were enrolled in the study was used for the analyses of demographic and baseline characteristics and the FAS consisting of 5 subjects who completed the study was used for the analyses of efficacy parameters.

The efficacy results of the study are summarized below.

- Primary Efficacy Variable: Mean values of the "Normal" states on TRS I by video assessment at baseline and the end of ABT-SLV187 treatment were $62.67 \pm 18.166\%$ and $78.0 \pm 8.692\%$, respectively. Mean increase (improvement) in the "Normal" state on TRS I from baseline to the end of ABT-SLV187 treatment was 15.33% (95% CI: -2.37 to 33.04%), however, this improvement did not achieve statistical significance ($P = 0.074$).
- Mean changes in the "Off" state and the "Dyskinesia" state on TRS I by video assessment from baseline to the end of ABT-SLV187 treatment were -15.33% (95% CI: -31.52 to 0.86%) and 0.00% (95% CI: -5.85 to 5.85%), respectively. Mean changes in the "Normal" state, the "Off" state and the "Dyskinesia" state on TRS II by video assessment from baseline to the end of ABT-SLV187 treatment were 14.67% (95% CI: -8.49 to 37.82%), -15.33% (95% CI: -38.49 to 7.82%) and 0.67% (95% CI: -1.18 to 2.52%), respectively. None of these observed changes were statistically significant.
- Mean changes in the "Off" time, the "On" time without dyskinesia plus time with non-troublesome dyskinesia and the "On" time without dyskinesia plus time with non-troublesome dyskinesia plus time with troublesome dyskinesia (Total "On" time) by Parkinson's Disease Diary[®] assessment from baseline to the end of ABT-SLV187 treatment was -1.02 hours (95% CI: -5.65 to 3.61 hours), 0.76 hours (95% CI: -3.71 to 5.24 hours) and 1.02 hours (95% CI: -3.61 to 5.65 hours), respectively. None of these observed changes were statistically significant.
- To address possible bias due to a lack of study drug compliance in a subject (Subject 201) on Day20 due to displacement of the NJ-tube, a sensitivity analysis for Parkinson's disease diary[®] was repeated after excluding the data of the subject from the dataset, in addition to items defined to be evaluated in the study protocol. The results indicate that the mean change in the "Off" time from baseline to the end of ABT-SLV187 treatment was -2.68 hours (95% CI: -3.51 to -1.84 hours), and the decrease (improvement) was statistically significant ($P = 0.002$). The mean change in the "On" time without dyskinesia plus time with non-troublesome dyskinesia from baseline to the end of ABT-SLV187 treatment was 2.35 hours (95% CI: 1.28 to 3.43 hours) and the increase (improvement) was statistically significant ($P = 0.006$). The mean change in the "On" time without dyskinesia plus time with non-troublesome dyskinesia plus time with troublesome dyskinesia (Total "On" time) from baseline to the end of ABT-SLV187 treatment was 2.68 hours (95% CI: 1.84 to 3.51 hours) and the increase (improvement) was statistically significant ($P = 0.002$). The issue did not influence other efficacy parameters.
- Mean changes from baseline to the end of ABT-SLV187 treatment in all other items defined to be evaluated in the study protocol for assessment of PD were small and no statistically significant change was observed.

Summary/Conclusions

Efficacy Results (Continued):

No significant difference was observed in the results of the "Normal" states on TRS 1 by video assessment, a primary endpoint of this exploratory clinical study, from the 5 completed subjects, as well as other variables by video assessment. In contrast, significant improvements in "Off" time and "On" time without troublesome dyskinesia in the Parkinson's Disease Diary[®] evaluation were observed in a sensitivity analysis excluding the data of the one subject for whom the NJ tube was not in the proper location for drug delivery from the dataset.

Although video scoring has an advantage that it can be performed in a blinded manner, it did not provide consistent results among the 3 evaluation committee members. Despite of the training provided to minimize the inter-rater variability prior to the evaluation, inconsistency in the evaluation remained. The Kraemer κ coefficient for concordance on TRS I was 0.220 and results were considered to be with large variability among the assessments by three neurologists designated for the study. The result was also different from patient's and physician's disease evaluation. Based on these observations, it was concluded that Parkinson's Disease Diary[®] would be a more appropriate efficacy measurement for the phase 3 study.

Pharmacokinetic Results:

The average total study drug daily doses during the oral L/C and ABT-SLV187 Treatment Periods were 1230 mg and 1370 mg, respectively, for levodopa, and 123 mg and 342 mg, respectively, for carbidopa. The higher dose of carbidopa during the ABT-SLV187 Treatment Period was due to the lower levodopa:carbidopa ratio in ABT-SLV187 (4:1) compared to oral L/C tablets (10:1).

Oral L/C (10/1) administration resulted in mean C_{avg} of 2.37 $\mu\text{g/mL}$ for levodopa, 0.079 $\mu\text{g/mL}$ for carbidopa and 7.36 $\mu\text{g/mL}$ for 3-OMD. The within-subject coefficient of variation in levodopa, carbidopa and 3-OMD concentrations over the 2 to 12 hours time interval relative to the first morning dose was 38%, 29% and 7%, respectively. In comparison, intrajejunal administration of ABT-SLV187 (L/C, 4/1) resulted in mean C_{avg} of 2.87 $\mu\text{g/mL}$ for levodopa, 0.172 $\mu\text{g/mL}$ for carbidopa and 9.80 $\mu\text{g/mL}$ for 3-OMD. The within-subject coefficient of variation in levodopa, carbidopa and 3-OMD concentrations over the 2 to 12 hours time interval relative to initiation of infusion was 10%, 20% and 7%, respectively. The within-subject coefficient of variation in levodopa, carbidopa and 3-OMD concentrations over the 2 to 16 hours time interval relative to initiation of infusion was 10%, 21% and 7%, respectively.

Levodopa and carbidopa bioavailability appeared to be comparable (as indicated by the comparable dose-normalized levodopa AUC values) after administration of oral L/C tablets and jejunal administration of ABT-SLV187. ABT-SLV187 resulted in approximately 2.2-fold higher exposure of carbidopa than administration of oral L/C tablets, consistent with the difference in carbidopa dose in the two products. Nasojejunal infusion of ABT-SLV187 resulted in a 5.5-fold lower mean degree of fluctuation in levodopa plasma concentrations compared to oral administration of L/C tablets. Similarly, the within-subject variability in levodopa plasma concentrations was approximately 4-fold lower for nasojejunal infusion of ABT-SLV187 than for levodopa-carbidopa (10:1) tablets.

Overall, with ABT-SLV187 jejunal infusion and individually titrated doses, levodopa and carbidopa exposures were comparable between Japanese subjects (as characterized in the present study) and Caucasian subjects (as characterized in Study S-187-1-002). Intrajejunal infusion of ABT-SLV187 in Japanese and Caucasian subjects resulted in comparable values of mean C_{avg} for levodopa (2.92 $\mu\text{g/mL}$ and 2.91 $\mu\text{g/mL}$, respectively), and carbidopa (0.175 $\mu\text{g/mL}$ and 0.221 $\mu\text{g/mL}$, respectively). The mean C_{avg} for 3-OMD, an inactive metabolite of levodopa, was lower in Japanese subjects compared to Caucasians (10.3 $\mu\text{g/mL}$ and 17.1 $\mu\text{g/mL}$, respectively).

Summary/Conclusions

Pharmacokinetic Results (Continued):

The mean for dose-normalized levodopa AUC during the 16-hour infusion was 17% higher in Japanese subjects than previously observed in Caucasian subjects. The mean for levodopa AUC divided by the body weight normalized dose was 8% lower for Japanese subjects than previously observed in Caucasian subjects. The dose-normalized AUC for carbidopa was 11% lower in Japanese subjects than in Caucasian subjects. The mean for carbidopa AUC divided by the body weight normalized dose was 29% lower in Japanese subjects than in Caucasian subjects. These small observed numerical differences in levodopa and carbidopa exposures between Japanese and Caucasians are not clinically relevant given that ABT-SLV187 doses are individually titrated to optimal effect in patients with PD.

Safety Results:

Run-in Period

Mean extent of exposure to oral L/C tablet during the 28 days of the Run-in Period was 25.1 days (range: 4–29 days).

The safety results in Run-in Period of the study are summarized below.

- Seven out of the 8 subjects (87.5%) enrolled in the study experienced at least one AE. AEs assessed as at least possibly related (i.e., probably related or possibly related) to study drug or device by the investigator and AEs caused by study drug were reported in 5 subjects (62.5%) each. AEs leading to discontinuation of the study drug were reported in 1 subject (12.5%). There were no deaths, AEs leading to death, SAEs, severe AEs, or AE of special interest in the Run-in Period.
- The most frequently reported AEs in the Run-in Period were constipation and insomnia (3 subjects each, 37.5%), and nausea (2 subjects, 25.0%). The AEs reported are common conditions associated with Parkinson's disease or are known adverse events associated with oral levodopa-carbidopa.
- All AEs reported in the Run-in Period were assessed as mild or moderate in severity by the investigator.
- One AE leading to discontinuation of study was reported in Subject 301 in the Run-in Period of the study. The subject experienced Parkinson's disease (Reported AE: Parkinson's disease aggravated, moderate, probably not related, non-serious). The subject discontinued the study prior to the participation in ABT-SLV187 Treatment Period due to the AE and withdrawal of informed consent after 4 days of administration of L/C tablets in the period. The events were treated with medications and the subject recovered from the event by the end of the study.
- No AESIs were observed in the Run-in Period.

ABT-SLV187 Treatment Period

Mean extent of exposure to ABT-SLV187 during the 21 days of the ABT-SLV187 Treatment Period was 18.7 days (range: 8–21 days).

The safety results in ABT-SLV187 Treatment Period of the study are summarized below.

- Four out of the 6 subjects (66.7%) treated with the study drug experienced at least one AE. AEs assessed by the investigator as at least possibly related (i.e., probably related or possibly related) to study drug or device, and AEs caused by study drug were reported in 3 subjects (50.0%) each, and AEs caused by NJ tube insertion were reported in 1 subject (16.7%). AEs of special interest were reported in 2 subjects and SAEs, severe AEs, SAEs assessed as possibly related to study drug or device by the investigator, AEs leading to discontinuation of study drug were reported in 1 subject (16.7%) each. There were no deaths or AEs leading to death in the ABT-SLV187 Treatment Period.

Summary/Conclusions

Safety Results (Continued):

- The most frequently reported AEs in the ABT-SLV187 Treatment Period were fall and dyskinesia (2 subjects each, 33.3%); all other AEs were reported in 1 subject. The AEs reported were common conditions associated with Parkinson's disease or are known adverse events associated with oral levodopa-carbidopa.
- The majority of AEs were assessed as mild or moderate in severity by the investigator. Only 1 subject (Subject [REDACTED]) experienced 3 severe AEs (somatic hallucination; delusion; and hallucination, auditory [possibly related with study drug, serious, each]) in the ABT-SLV187 Treatment Period.
- Three subjects (50.0%) experienced AEs which were assessed by the investigator as probably related or possibly related to study drug, device or NJ-tube insertion in ABT-SLV187 Treatment Period. AEs caused by study drug and those caused by NJ tube insertion were reported in 3 subjects (50.0%) and 1 subject (16.7%), respectively. Dyskinesia was observed in 2 subjects and one was assessed as probably related to study drug and the other was assessed as possibly related to study drug; all other AEs assessed as probably related or possibly related to study drug, device or NJ-tube insertion were reported in 1 subject each. No AEs were assessed by the investigator as probably related or possibly related to the device. Three AEs (thirst, nausea, and decreased appetite) occurred in 1 subject (Subject [REDACTED]) and were all assessed by the investigator as probably related to both study drug and NJ-tube insertion.
- A device associated gastrointestinal disorder TEAE and a clinically significant weight loss was observed in 1 subject each in the study. Subject [REDACTED] experienced stomatitis in the ABT-SLV187 Treatment Period and it was considered as a device associated gastrointestinal disorder TEAE, and Subject [REDACTED] experienced decreased appetite in the ABT-SLV187 Treatment Period and it was considered as a clinically significant weight loss.
- Two out of the 6 subjects (33.3%) treated with the study drug reported at least one POCs. POCs related to NJ-tube insertion were reported in 2 subjects (33.3%), and those related to cassettes were reported in 1 subject (16.7%). No complaint-related adverse events were reported in the study.
- Three SAEs were reported in Subject [REDACTED] in the ABT-SLV187 Treatment Period of the study. This subject had hallucination and delusion as past medical histories, and experienced somatic hallucination; delusion; and hallucination, auditory as SAE with hospitalization in the ABT-SLV187 Treatment Period, and they were assessed as severe and possibly related to study drug by the investigator. The subject discontinued the study due to the AEs and withdrawal of informed consent after 8 days of administration of study drug. The events were treated with medications and the subject recovered from the events by the end of the study.
- None of the mean changes in clinically laboratory variables, vital sign measurements or ECG findings from baseline to the end of ABT-SLV187 treatment were statistically significant, and no consistent or clinically important trends were observed.
- Shifts from PCS normal value or PCS high value at baseline to PCS low value at the final laboratory test of the study for total protein were reported in 2 subjects. Shifts from PCS normal value or PCS low value at baseline to PCS high value at the final laboratory test of the study for CK/CPK and homocysteine were reported in 2 subjects each. Subject [REDACTED] who discontinued the study due to the AEs and withdrawal of informed consent had anemia, ongoing AE at the end of the study, as relevant concurrent adverse event with low PCS hematocrit, hemoglobin or RBC count. No blood biochemistry or urinalysis laboratory abnormalities, or abnormalities in special laboratory parameters were reported as adverse events.

Summary/Conclusions

Safety Results (Continued):

- Low PCS standing SBP, orthostatic SBP and orthostatic DBP were observed in 1 subject each and the values improved during study treatment. Subject [REDACTED] had low PCS standing SBP and orthostatic SBP, and orthostatic hypotension as relevant concurrent adverse event. No other vital sign abnormalities were reported as adverse events.
- There were no PCS ECG findings reported in the study.

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

Conclusions:

The current study provides exploratory data for the pharmacokinetics, safety, tolerability, and efficacy of ABT-SLV187 in subjects with advanced PD.

The pharmacokinetics of ABT-SLV187 was evaluated by comparing levodopa, carbidopa and 3-OMD pharmacokinetic parameters after administration of oral L/C tablets and ABT-SLV187. The average total study drug daily doses during the oral L/C and ABT-SLV187 treatment periods was 1230 mg and 1370 mg, respectively, for levodopa, and 123 mg and 342 mg, respectively, for carbidopa. Oral L/C (10/1) administration resulted in mean C_{avg} of 2.37 $\mu\text{g/mL}$ for levodopa, 0.079 $\mu\text{g/mL}$ for carbidopa and 7.36 $\mu\text{g/mL}$ for 3-OMD. The within-subject coefficient of variation in levodopa, carbidopa and 3-OMD concentrations over the 2 to 12 hours time interval relative to the first morning dose was 38%, 29% and 7%, respectively. In comparison, intrajejunal administration of ABT-SLV187 (L/C, 4/1) resulted in mean C_{avg} of 2.87 $\mu\text{g/mL}$ for levodopa, 0.172 $\mu\text{g/mL}$ for carbidopa and 9.80 $\mu\text{g/mL}$ for 3-OMD. The within-subject coefficient of variation in levodopa, carbidopa and 3-OMD concentrations over the 2 to 12 hours time interval relative to initiation of ABT-SLV187 infusion was 10%, 20% and 7%, respectively. The within-subject coefficient of variation in levodopa, carbidopa and 3-OMD concentrations over the 2 to 16 hours time interval relative to initiation of ABT-SLV187 infusion was 10%, 21% and 7%, respectively.

Levodopa and carbidopa bioavailability appeared to be comparable after administration of oral L/C tablets and jejunal administration of ABT-SLV187. ABT-SLV187 resulted in approximately 2.2-fold higher exposure of carbidopa than administration of oral L/C tablets, consistent with the difference in carbidopa dose in the two products. Nasojejunal infusion of ABT-SLV187 resulted in a 5.5-fold lower mean degree of fluctuation in levodopa plasma concentrations compared to oral administration of L/C tablets. Similarly, the within-subject variability in levodopa plasma concentrations was approximately 4-fold lower for nasojejunal infusion of ABT-SLV187 than for oral levodopa-carbidopa (10:1) tablets.

Overall, ABT-SLV187 intrajejunal infusion resulted in low fluctuations and smaller intra-subject variability in levodopa and carbidopa concentrations for the majority of the treatment duration in patients with advanced PD.

Conclusions(Continued):

The potential benefit of an improved pharmacokinetic profile of levodopa due to continuous intra-jejunal administration of ABT-SLV187 on its efficacy was evaluated. For efficacy evaluation, video scoring and patient diary evaluation were introduced in this study. No significant difference was observed in the results of the "Normal" states on TRS 1 by video assessment, a primary endpoint of this exploratory clinical study, from the 5 completed subjects, as well as other variables by video assessment. However, significant improvements in "Off" time and "On" time without troublesome dyskinesia in the Parkinson's Disease Diary[®] evaluation were observed in a sensitivity analysis excluding the one subject for whom the NJ tube was not in the proper location for drug delivery. Although video scoring has an advantage that it can be performed in a blinded manner, it did not provide consistent results among the 3 evaluation committee members. The Kraemer κ coefficient for concordance on TRS I was 0.220 and results were considered to be with large variability among the assessments by three neurologists designated for the study. The result was also different from patient's and physician's disease evaluation. Based on these observations, it was concluded that Parkinson's Disease Diary[®] would be a more appropriate efficacy measurement for the phase 3 study. The most frequently reported AEs in ABT-SLV187 Treatment Period were fall and dyskinesia, which are AEs common conditions associated with Parkinson's disease or are known adverse events associated with oral levodopa-carbidopa. The majority of AEs were assessed as mild or moderate in severity and observed to decline over time. Overall, clinically meaningful efficacy results together with the acceptable safety and tolerability findings constitute a positive benefit-risk profile for ABT-SLV187 to be confirmed in the phase 3 study.

The data from this study indicate that the ABT-SLV187 has the potential to provide benefits to patients with advanced PD and limited therapeutic options in the future.