

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: Levodopa-Carbidopa Intestinal Gel (LCIG)/Carbidopa Levodopa Enteral Suspension (CLES)	Volume:	
Name of Active Ingredient: Levodopa-Carbidopa	Page:	
Title of Study: An Open-label, Randomized 12 Week Study Comparing Efficacy of Levodopa-Carbidopa Intestinal Gel/Carbidopa-Levodopa Enteral Suspension and Optimized Medical Treatment on Dyskinesia in Subjects with Advanced Parkinson's Disease		
Investigator: [REDACTED], MD		
Study Sites: 23 sites in 7 countries where LCIG was commercially available.		
Publications: 1 abstract		
Studied Period (Years): First Subject First Visit: 12 Mar 2017 Last Subject Last Visit: 19 Sep 2019	Phase of Development: 3b	
<p>Objectives:</p> <p>The primary objective of this interventional study was to examine the effect of levodopa-carbidopa intestinal gel (LCIG) treatment relative to that of optimized medical treatment (OMT) on dyskinesia as measured by the Unified Dyskinesia Rating Scale (UDysRS) Total Score.</p> <p>The secondary objective was to assess the effect of LCIG treatment relative to that of OMT on dyskinesia as assessed by Parkinson's disease (PD) Diaries, motor symptoms, motor complications, health-related outcome measures, safety, and tolerability.</p>		

Methodology:

This was a Phase 3b, open-label, randomized, multicenter, 12-week study assessing the efficacy of LCIG treatment compared to OMT on dyskinesia in subjects with advanced PD (aPD). The study consisted of 3 sequential periods: Screening, Treatment, and Follow-Up. The OMT group had the same schedule of visits/procedures throughout the study as the LCIG treatment group, except for visits related to nasojejunal (NJ)/percutaneous endoscopic gastrostomy (PEG) procedures, titration of LCIG, and follow-up period. Investigators were to ensure that subjects were on optimized treatment before randomization. Subjects randomized to LCIG treatment must have discontinued all other anti-PD medications other than amantadine prior to LCIG treatment initiation on Day 1 (Visit [V]4). A temporary NJ tube may have been used initially with the infusion pump to determine the subject response to this method of treatment and to optimize the dose of LCIG before treatment with a permanent PEG with jejunal extension (PEG-J) tube was started. Following optional NJ and/or PEG-J placement on Day 1 and, at the investigator's discretion, the subject may have begun initiation and titration of LCIG infusion on Day 1 once tube placement was confirmed. The dose of LCIG was adjusted to obtain the optimal clinical response for the individual subject. Visit 5 was conducted at Week 2, 14 days after NJ and/or PEG-J insertion. Study activities at V5 (Week 2) had to be completed even if the subject titration was still occurring. For LCIG subjects who elected to discontinue LCIG and not continue with commercially available product, a V9 was conducted 1 week after PEG-J removal and the serious adverse event (SAE)/adverse event (AE) follow-up period was up until 30 days after PEG-J removal. For LCIG treatment subjects who had transitioned to commercial product (Transition Period), the SAE/AE follow-up period was up until 30 days after the transition.

Number of Subjects (Planned and Analyzed):

Total: 60 planned; 63 randomized; 61 analyzed. OMT: 30 planned, 33 randomized, 33 analyzed.
LCIG: 30 planned, 30 randomized, 28 analyzed.

Diagnosis and Main Criteria for Inclusion:

Male or female subjects of at least 30 years of age at the time of Visit 3 were eligible for enrollment if they had a diagnosis of advanced levodopa-responsive PD and persistent motor fluctuations, their dyskinesia had not been controlled with optimized medical treatment (defined as UDysRS Total score ≥ 30 at Visit 3), and they were eligible to transfer to commercial treatment of Duodopa after completing the study based on local country requirements. Subjects were excluded if they had predominantly diphasic dyskinesia, had previous surgery for PD, lacked motivation or insufficient language skills to complete the study questionnaires, or had any neurological deficit that might interfere with the study assessments.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:				
Study Drug	Dosage Form	Formulation	Manufacturer	Bulk Lot
100 mL Levodopa (20 mg/mL)-carbidopa monohydrate (5 mg/mL) intestinal gel medication cassette reservoirs	Intestinal Gel	20 mg/mL-5 mg/mg in 100 mL	Fresenius Kabi, Norway	16-005800, 16-005174, 17-007459, 18-005409, 18-007794, 19-002362
Duration of Treatment: 12 weeks of treatment with a 30 days follow-up period for LCIG treatment subjects who had transitioned to commercial product.				
Reference Therapy: Optimized medical treatment				
Dose/Strength/Concentration: Investigator discretion and/or in accordance with approved product label of the prescribed medications				
Mode of Administration: Oral, sublingual, or transdermal				
Criteria for Evaluation				
Efficacy: The between groups comparison of the total score of the UDysRS was chosen for the assessment of the primary efficacy endpoint because it is a validated comprehensive rating tool developed specifically for the assessment of dyskinesia in PD and is endorsed by the International Parkinson and Movement Disorder Society. Containing both patient self-evaluation questions and physician-assessed items to objectively rate dyskinesia and off dystonia, its clinimetric properties are excellent and it has been demonstrated to be superior for detecting treatment effects compared to other available dyskinesia scales. The UDysRS contains 2 primary sections (historical and objective) and each section is divided into 2 parts. The PD Diary tool was used to record Parkinsonian symptoms during "ON," "OFF," or "ASLEEP" along with the severity of the dyskinesia (troublesome or not troublesome). The Parkinson's Disease Questionnaire-8 (PDQ-8) is a disease-specific instrument designed to measure aspects of health that are relevant to subjects with PD. It is a self administered questionnaire used to measure aspects of health that were relevant to subjects with PD, and which may not have been included in general health status questionnaires. The Clinical Global Impression of Change (CGI-C) was used to assess current symptomatology and impact of illness on functioning. The Unified Parkinson's Disease Rating Scale (UPDRS) Part II and Part III assessment was performed to follow the longitudinal course of PD. The Modified Abnormal Involuntary Movement Scale (mAIMS) was also used to assess dyskinesia and emphasizes orofacial dyskinesia. The King's PD Pain Scale is an easily administered clinical PD specific pain scale with a focus on subclassification of nociceptive and neuropathic pain. Besides the UDysRS total score, the historical score, objective score, and scores for Parts I through IV of the UDysRS were assessed separately.				

Criteria for Evaluation (Continued)

Safety:

The following safety evaluations were performed during the study: monitoring of AEs, neurological exams, Columbia Suicide Severity Rating Scale (C-SSRS), Minnesota Impulsive Disorders Interview (MIDI), Sleep Attacks Questionnaire, electrocardiogram, changes in vital signs and weight, physical examinations, clinical laboratory evaluations, and product complaints.

Statistical Methods

Efficacy:

Unless otherwise specified, all efficacy analyses were performed on the intent-to-treat (ITT) data set and comparisons between the OMT and LCIG treatment groups were performed with 2-sided tests at the significance level of 0.050. The primary efficacy variable was the mean change from Baseline to Week 12 for the UDysRS total score. The primary efficacy analysis model was a mixed-effects model repeated measures (MMRM) analysis of the change from Baseline for each post-baseline observation using all observed data. Additional analysis of the primary efficacy variable was analysis of covariance (ANCOVA) of change from Baseline to final UDysRS total score. The ITT data set did not include subjects randomized to LCIG who prematurely discontinued before receiving their first LCIG infusion. To evaluate the impact of not including these subjects in the primary efficacy analysis, a sensitivity analyses was carried out with the same ANCOVA model using all randomized subjects. In this analysis, Baseline Observation Carried Forward (BOCF) was applied to subjects who did not have a post-randomization assessment of UDysRS.

The secondary efficacy variables were the mean change from Baseline to Week 12 in the following measures:

- "ON" time without troublesome dyskinesia as measured by the PD Diary
- PDQ-8 summary index
- CGI-C Score
- UPDRS Part II Score
- "OFF" time as measured by the PD Diary
- UPDRS Part III Score

Each secondary efficacy variable was analyzed with the same MMRM model as the primary analysis. PD Diary variables were normalized to an averaged 16-hour awake time and the time recorded by the subject on the 3 diaries completed prior to each visit.

Additional efficacy and health outcomes were assessed using: "ON" time with troublesome dyskinesia and "ON" time without dyskinesia as measured by the PD Diary, mAIMS, King's PD Pain Scale, percentage of CGI-C responders, and UDysRS historical score, objective score and Parts I through IV scores. Continuous endpoints were analyzed with the same MMRM model as the primary analysis. Categorical endpoints were analyzed with a Fisher's exact test.

Statistical Methods (Continued)

Safety:

All safety analyses were performed on the safety data set unless otherwise specified. Comparisons between LCIG treatment and OMT groups were performed with 2-sided test at the significance level of 0.050. Unless otherwise specified, the treatment group differences in continuous safety variables (e.g., change from Baseline to final observation on laboratory tests) were assessed using an analysis of variance model with the treatment effect, and the treatment group differences in binary safety variables were evaluated using Fisher's exact test.

The number and percentage of subjects who had AEs were tabulated by primary system organ class and MedDRA preferred term (version 22.0) for both treatment groups. The overall incidence of AEs was summarized as were AEs by severity and relationship to the study drug. Adverse events of special interest (AESIs) defined by prespecified company MedDRA query (CMQ) categories and standardized MedDRA query (SMQ) categories, were summarized by treatment group. AEs were also summarized for the Transition Period.

All laboratory variables were summarized with mean, median, standard deviation, minimum and maximum by treatment group. Shift tables were tabulated for reference range category shifts from Baseline to minimum, maximum and final value for each treatment group. Results for subjects who met potentially clinically significant (PCS) values were summarized.

For each vital sign, weight, and ECG variables, analyses of the mean change from Baseline to each scheduled visit and to the final value were summarized by treatment group and for both treatment groups combined. Results for subjects who met PCS values were summarized.

The number and percentage of subjects with a positive screening on a MIDI module at Baseline, during the Treatment Period, and during the Transition Period were summarized. The number and percentage of subjects with 1 or more affirmative responses to the C-SSRS at Baseline, during the Treatment Period, and during the Transition Period were summarized.

Summary/Conclusions

Efficacy Results:

In this study, LCIG treatment decreased dyskinesia in subjects with aPD, as described below.

Primary Efficacy Endpoint

A statistically significant treatment effect was achieved on the primary efficacy endpoint. The change from Baseline to Week 12 showed that UDysRS total score significantly decreased in the LCIG group compared to the OMT group; LS mean of difference is -15.05 , $P < 0.0001$. The effect was achieved after 2 weeks of treatment and sustained throughout the Treatment Period.

Key Secondary Efficacy Endpoints

All key secondary efficacy endpoints except for the UPDRS Part III (motor examination performed at best "ON" time) score demonstrated statistically significantly greater improvement in PD symptoms for the LCIG group relative to the OMT group after multiplicity adjustment.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

1. Change from Baseline to Week 12 for PD Diary - normalized ON time without troublesome dyskinesia; LS mean of difference is 3.27, $P = 0.0001$.
2. Change from Baseline to Week 12 for PDQ-8 summary index; LS mean of difference is -16.66, $P < 0.0001$.
3. Week 12 CGI-C score; LS mean of difference is -2.11, $P < 0.0001$.
4. Change from Baseline to Week 12 for UPDRS Part II score; LS mean of difference is -5.54, $P = 0.0006$.
5. Change from Baseline to Week 12 for PD Diary - Normalized OFF Time; LS mean of difference is -2.35, $P = 0.0002$.
6. Change from Baseline to Week 12 for UPDRS Part III score; LS mean of difference is -4.05, $P = 0.0762$.

Other Efficacy Variables

In addition, the changes from Baseline to Week 12 in the mAIMS total score and in the King's PD Pain Scale were statistically significantly decreased in the LCIG group compared to the OMT group: LS mean of difference is -5.02, $P = 0.0001$ for mAIMS and LS mean of difference is -11.66, $P = 0.0026$ for King's PD Pain Scale.

For the CGI-C, a higher percentage of subjects were responders at the final evaluation in the LCIG group (18/26 subjects [69.2%]) compared to the OMT group (2/33 subjects [6.1%]).

The changes from Baseline to Week 12 for UDysRS Part I and historical score showed statistically significantly greater reductions for the LCIG group compared to the OMT group, while the difference between groups in the LS mean change was not statistically significant for the UDysRS Part II, Part IV, or objective scores.

Safety Results:

The incidence of treatment-emergent AEs was higher in the LCIG group (64.3%) than in the OMT group (27.3%). The most frequently reported AEs in the LCIG group were fall (17.9%) and procedural pain (10.7%). The most frequently reported AEs in the OMT group were fall and PD (6.1% each). The majority of AEs were nonserious and mild or moderate in severity. Only 1 subject, who was in the LCIG group, had a severe AE (pneumoperitoneum).

Among AESIs, gastrointestinal and gastrointestinal procedure related AEs were the most reported in the LCIG group, with procedural pain being the most commonly reported (10.7%).

No subject in the OMT group experienced SAEs. Two subjects in the LCIG group experienced SAEs, of which one led to study drug discontinuation (pneumoperitoneum). One additional subject in the LCIG group had a non-serious AE of depressive syndrome that led to study drug discontinuation.

No deaths were reported during the Treatment Period or Transition Period. One death from cardiac failure was reported during Screening.

The changes observed in the laboratory values were not clinically meaningfully different between the LCIG and OMT groups.

Summary/Conclusions (Continued)

Safety Results (Continued):

The most common PCS vital sign values were decreases in orthostatic systolic blood pressure ≥ 30 mmHg observed in both groups. The decrease in orthostatic systolic blood pressure ≥ 30 mmHg was not clinically meaningfully different between the LCIG and OMT groups.

There were no clinically meaningful changes in ECGs in the LCIG or OMT groups.

Additional measures of safety were the sleep attack questionnaire, the MIDI, and the Columbia-Suicide Severity Scale. Overall, 2 subjects reported 1 or more sleep attacks during the 12-week Treatment Period in both the OMT and LCIG groups. The number of sleep attacks were higher in the OMT group than in the LCIG group. One subject in the OMT group had a positive screen for the pathological gambling MIDI module during the 12-week Treatment Period. No subject in the LCIG group had a positive screen for any MIDI module. Two subjects in the LCIG group and 3 subjects in the OMT group reported suicidal ideation during the 12-week treatment period. No AE of suicidal ideation were reported.

Conclusions:

Overall, the results of this pivotal study demonstrate clinically meaningful benefit with LCIG treatment in reducing dyskinesia compared to OMT in subjects with aPD.

The primary efficacy endpoint and all key secondary efficacy endpoints met statistical significance except for the UPDRS Part III score after multiplicity adjustment. Additionally, UDysRS Part I and historical score, mAIMS total score, and King's PD Pain Scale total score were significantly improved for the LCIG treatment group compared to the OMT group.

Treatment with LCIG was generally well tolerated. The AEs reported were as expected for the device-related procedure and the patient population with advanced disease treated with levodopa; the majority were assessed as mild or moderate in severity.