

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/BLA #: 203952

Drug Name: Levodopa-Carbidopa Intestinal Gel (LCIG)

Indication(s): Treatment of motor fluctuations in patients with advanced Parkinson's disease (PD) (b) (4)

Applicant: AbbVie Inc.

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1 EXECUTIVE SUMMARY

The evidence based on the primary analysis seems to support the efficacy of Levodopa-Carbidopa Intestinal Gel as treatment of motor fluctuations in patients with advanced Parkinson's disease who had continued to experience persistent motor fluctuations despite optimized antiparkinsonian treatment.

The primary efficacy analysis demonstrated a statistically significant LS mean difference in favor of the LCIG group in change of average daily normalized "Off" time of -1.91 hours ($P = 0.0015$), based on Parkinson's Disease Diary data. All sensitivity analyses of the primary endpoint were consistent with the primary analysis. The effect of LCIG was generally consistent across a variety of subgroups defined by demographic and baseline disease characteristics. A statistically significant LS mean difference (improvement) was observed in the average daily normalized "On" time without troublesome dyskinesia (the key secondary efficacy variable) of 1.86 hours ($P = 0.0059$) between the LCIG group and the LC-oral group.

The dropouts were limited (5 out of 71 subjects) and were not included in the primary analysis due to lack of post-baseline diary data. A worst-case type analysis in which the primary endpoint was imputed with the overall mean average baseline "Off" time for the dropouts in the LCIG group, and with the overall mean average "Off" time at Week 12 for those in the LC-oral group still reached statistical significance. All subjects who completed the study had at least 2 valid symptom diary days for Week 12 to derive the primary endpoint. Therefore, missing data was less of a concern.

The use of rescue medication was similar in the LCIG group and the LC-oral group. Extensive sensitivity analyses with respect of rescue medication use showed consistent results with that of the primary analysis.

2 INTRODUCTION

2.1 Overview

AbbVie Inc. resubmitted this New Drug Application (NDA) for Levodopa-Carbidopa Intestinal Gel (LCIG) after receiving a refuse to file letter on January 15, 2013. LCIG is a gel formulation of levodopa and carbidopa, delivered from a medication cassette reservoir via the CADD-Legacy 1400 portable infusion pump into the proximal small intestine through a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). LCIG has been developed for the long-term treatment of motor fluctuations in patients with advanced (b)(4) Parkinson's disease (PD) (b)(4). The LCIG System is currently approved in 41 countries. In many countries, it is marketed under the trade name Duodopa.

The IND number associated with the development of this drug for this indication is 60663. The 2 identically-designed, 12-week Phase 3 studies (Study S187-3-001 and Study S187-3-002) were designed to demonstrate the superiority of LCIG delivered via continuous upper-intestinal infusion over oral levodopa-carbidopa IR capsules adjunctive to background optimized therapy. Efficacy was evaluated by monitoring the change in average daily normalized "Off" time from Baseline to Week 12, based on Parkinson's Disease Diary data. A key secondary efficacy variable was the change from Baseline to Week 12 in average daily normalized "On" time without troublesome dyskinesia. The data from these 2 studies were combined for analysis to constitute a single pivotal study, as agreed in a Type C meeting held on 18 January 2011.

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directory: <\\Cdsesub1\evsprod\NDA203952\0015\m5>.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Key efficacy endpoints were reproduced by this reviewer from raw data. Documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

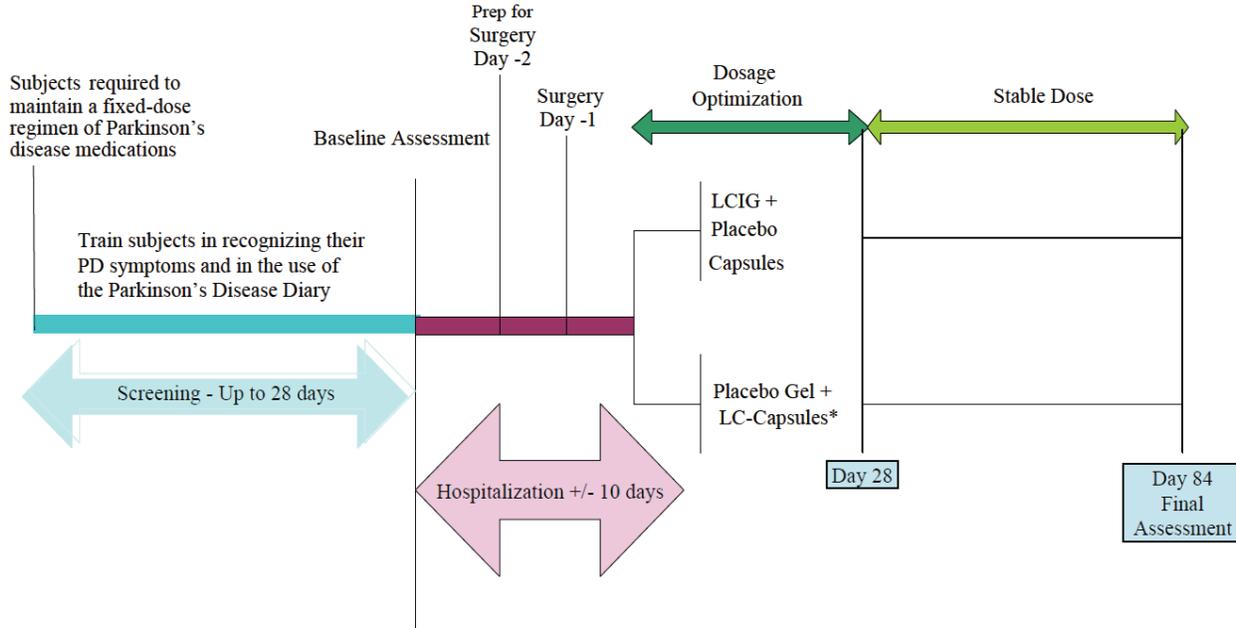
The date of the first visit of the first subject was 06 January 2009 and the date of the last visit of the last subject was 26 October 2011. The original protocols were amended several times, with the last two amendments instituted after the first subject was enrolled. The second to the last amendment dated in July 2010 increased the sample size from 54 to 62. The last protocol amendment was dated March 2011.

The Statistical Analysis Plan (SAP) was submitted on 07 June 2011 for the Agency to review. Subsequently, a covariate of mean daily dose of rescue levodopa on days with non-missing Parkinson's Disease Diary data was added to the ANCOVA model in the primary analysis of change from Baseline to final visit in averaged daily normalized "Off" time. On 07 December 2011, a natural log transformation was planned to be taken on this covariate. After database lock and blind break, the secondary analysis of this primary endpoint using MMRM model replaced the factor for Baseline by Treatment interaction (which was inadvertently specified in the original SAP, as claimed by the sponsor on CSR page 207) with Baseline by Study Week interaction.

Study Design

Study S187-3-001 and Study S187-3-002 were 2 identically-designed, Phase 3, 12-week, randomized, double-blind, double-dummy, parallel-group, multicenter studies. These studies consisted of a Screening Period (open-label treatment with oral levodopa-carbidopa, adjustment for anti-parkinsonian medication, and completion of Baseline procedures), a Hospitalization Period for the PEG-J placement, and a Double-Blind Treatment Period (randomization, dose titration, and study drug treatment for 12 weeks) (Figure 1).

Figure 1. Study Design for Study S187-3-001 and Study S187-3-002



* Levodopa-Carbidopa IR tablets, encapsulated.

Approximately 62 subjects with levodopa-responsive advanced PD who experience severe motor complications (i.e., ≥ 3 hours of "Off" time) despite optimized available therapy were eligible to participate. Eligible subjects were randomly assigned in the ratio 1:1 to receive LCIG + placebo capsules (LCIG group) or placebo gel + levodopa-carbidopa IR capsules (LC-oral group). Distinct sites were used to recruit subjects under each protocol. Randomization was stratified by site.

The gel were delivered via PEG-J over a 16-hour period, administered as one morning dose, followed by continuous infusion for the remainder of the period. Levodopa-carbidopa IR capsules (or matching placebo) were taken daily in the morning at the same time as the morning dose of infused study medication and at multiple times throughout the day. Following the daily discontinuation of the double-blind 16-hour infusion and last double-blind oral dose administration, subjects were permitted to self-administer their routine night-time regimen of oral levodopa-carbidopa IR. Subjects were instructed to complete the Daily Dosing Diary each day of the Treatment Period. Only the doses of oral levodopa-carbidopa 100/25 mg IR tablets taken during the 16-hour daytime period were used to calculate the total daily dose.

Subjects were allowed to take rescue doses of open-label levodopa-carbidopa IR tablets to address immediate serious medical needs. A rescue dose will be any dose of IR tablets taken less than two hours before the morning dose of study medication or any dose taken while the pump is on. However, IR tablets taken on days where the pump was on for less than 12.8 hours (80% of the 16-hour goal for pump duration) were not considered as rescue medication.

There are no interim efficacy analyses planned for this study. A data safety monitoring board (DSMB) reviewed the unblinded safety data only.

Efficacy Endpoints

Primary Variable

The primary variable is the change from baseline in average daily normalized "Off" time (hours), based on the 3 consecutive day average normalized "Off" time for the symptom diary at Week 12. "Off" time was normalized to a 16-hour waking time to account for variation in subjects' sleep time, calculated as (Absolute "off" time / Awake time) * 16.

The amount of average normalized "Off" time is a measurement of the motor fluctuations for a subject. "Off" time was derived from the Parkinson's Disease Diaries. Subjects were to complete the PD Diary for 3 consecutive days prior to clinic visits, noting "Asleep," "Off," "On without dyskinesia," "On with non-troublesome dyskinesia," or "On with troublesome dyskinesia" for each 30-minute interval during their normal waking time in a 24-hour period. The average daily "Off" time were computed using 3 valid symptom diary days (at least 12 awake hours) closest to the clinical visit. For post-baseline visits, the valid symptom diary day must be within 7 days of the clinic visit but not on or after the day of the clinic visit. If only 2 valid symptom diary days are available prior to a clinic visit, data from the 2 days will be used to calculate the average daily "Off" time. If only one valid symptom diary day is available the average daily from the previous week will be averaged with the daily "Off" time from the one valid diary day. Subjects that do not have any valid symptom diary days for a visit or who are completely missing a visit will have the average daily "Off" time set to missing for that visit. Last observation carried forward (LOCF) is applied for the endpoint if a subject is missing Week 12 data.

Key Secondary Variable

Change from baseline in normalized "On" time without troublesome dyskinesia (normalized "On" time without dyskinesia or with non-troublesome dyskinesia), based on the 3 consecutive day average normalized "On" time without troublesome dyskinesia for the symptom diary at Week 12.

Other secondary variables:

- Change from baseline in PDQ-39 Summary Index
- CGI-I score
- Change from baseline in UPDRS Part II score
- Change from baseline in UPDRS Part III score
- Change from baseline in EQ-5D Summary Index score
- Change from baseline in ZBI Total score

3.2.2 Statistical Methodologies

Efficacy Analysis Population

The Full Analysis (FA) population is the primary efficacy analysis set, consisting of all randomized subjects who had the study device implanted and had a baseline efficacy evaluation and data for at least one post-baseline assessment of any efficacy measurement.

Reviewer's note: for the primary endpoint, the analysis only included subjects with at least one post-baseline PD diary data.

Multiplicity Adjustment

Hierarchical testing will be performed for the primary endpoint, the key secondary variable and other secondary variables (in the order listed in previous section) on the FA population at the 0.050 level using a Gatekeeping procedure.

Reviewer's Note: although hierarchal ordering among all those secondary endpoints are specified for the multiple testing procedure, (b) (4)

Analysis of the Primary Endpoint

The primary analysis was carried out using an ANCOVA model including effects for treatment, country, and with the corresponding baseline normalized "off" time and the natural logarithm of the mean daily dose of rescue medication on valid Parkinson's Disease Diary days as covariates.

Mean daily dose of rescue levodopa was calculated as total milligram of levodopa taken as rescue dose on valid symptom diary days divided by the number of non-missing symptom diary days in Treatment Period. Before the database was locked, it was discovered on 07 December, 2011 that the mean daily dose of rescue levodopa on days with non-missing symptom diary data for one subject (438001) was 458.3 mg, which is more than 3 times higher than the next highest value. To handle the issue of this large outlier, a natural log transformation was taken on this covariate and the value of 1 will be added to the 0's before taking log transformation.

The assumptions of the ANCOVA models were checked. A test of homoscedasticity was performed with Levene's test. A Shapiro-Wilk test was also performed to check normality. A separate model with an additional term of treatment by country interaction was used to examine the possibility of treatment by country interaction.

Secondary and Sensitivity Analyses of the Primary Efficacy Variable

A secondary analysis of the primary efficacy variable was carried out using a MMRM model, which included Baseline as a fixed-effect covariate; treatment, country, and time as fixed-effect (categorical) factors, and the Baseline by Study Week interaction.

The following sensitivity analyses with respect of rescue medication use were conducted on the primary variable:

- Without the covariate of rescue medication on valid PD Diary days (which was originally the primary analysis in the SAP submitted on 07 June 2011, and changed to sensitivity analysis based on the Agent's comment).
- Replacing the rescue medication covariate with the natural logarithm of mean daily dose of rescue levodopa over the entire Treatment Period.
- Replacing the normalized "Off" time with the average Baseline "Off" time on those days when the subject took at least 1 dose of rescue medication.
- Setting the normalized "Off" time as missing for any PD Diary day that the subject uses rescue medication.

Subgroup Analyses

Key efficacy results were summarized across subgroups defined by gender, race, age (< 65 or ≥ 65 years), country, and duration of Parkinson's disease (< 10 or ≥ 10 years). Analyses with the additional covariates for the primary endpoint were performed. ANCOVA will be used to evaluate treatment by subgroup interaction. The factors in the model were treatment, country, subgroup, treatment by subgroup interaction with baseline normalized "off" time as a covariate. If the interaction *P* value ≤ 0.10, treatment effect will be evaluated within each subgroup stratum within the ANCOVA framework.

Analysis of the Key Secondary Endpoint

The analysis of the key secondary endpoint is the same as that of the primary endpoint.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 71 subjects were randomized at 26 of the sites in the US, Germany, and New Zealand; and 5 of them prematurely discontinued from the study (Table 1). Two randomized subjects discontinued from the study after 2 days of treatment and were excluded from the FA data set due to the lack of post-baseline efficacy assessment.

Table 1. Subject Disposition

	Statistic	LCIG + Placebo Capsules (N=37)	Placebo Gel + Levodopa- Carbidopa Capsules (N=34)	All Subjects (N=71)
Number of Subjects Who Completed the Study	n (%)	35 (94.6)	31 (91.2)	66 (93.0)
Number of Subjects Who Prematurely Terminated the Study	n (%)	2 (5.4)	3 (8.8)	5 (7.0)
Primary Reason for Premature Study Termination:				
Adverse Event	n (%)	1 (2.7)	2 (5.9)	3 (4.2)
Lack of Efficacy	n (%)	0	1 (2.9)	1 (1.4)
Lost to Follow-Up	n (%)	0	0	0
Withdrew Consent	n (%)	0	0	0
Administrative	n (%)	0	0	0
Protocol Violation	n (%)	1 (2.7)	0	1 (1.4)

Source: Table 6 of the CSR.

The overall demographic data and baseline disease characteristics were summarized in Table 2. The treatment groups were balanced for age, sex, and race. Overall, 64.8% of subjects were male and 93.0% were white. Most subjects were enrolled in the United States (73.2%).

Table 2. Demographics

	Statistic	LCIG + Placebo Capsules (N=37)	Placebo Gel + Levodopa- Carbidopa Capsules (N=34)	All Subjects (N=71)	
Age (yrs)	n	37	34	71	
	Mean(SD)	63.7 (9.5)	65.1 (6.8)	64.4 (8.3)	
	Median	64.0	66.0	64.0	
	Min/Max	39/83	45/79	39/83	
Age Category					
	n (%)				
< 65 yrs	n (%)	21 (56.8)	15 (44.1)	36 (50.7)	
>= 65 yrs	n (%)	16 (43.2)	19 (55.9)	35 (49.3)	
Gender					
	n (%)				
Male	n (%)	24 (64.9)	22 (64.7)	46 (64.8)	
Female	n (%)	13 (35.1)	12 (35.3)	25 (35.2)	
Race					
	n (%)				
	American Indian or Alaska Native	n (%)	1 (2.7)	0	1 (1.4)
	*		1 (2.7)	0	1 (1.4)
	Asian	n (%)	1 (2.7)	3 (8.8)	4 (5.6)
	*		1 (2.7)	3 (8.8)	4 (5.6)
	Black, of African Heritage or African American	n (%)	0	0	0
	*		0	0	0
	Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
	*		0	0	0
	White	n (%)	35 (94.6)	31 (91.2)	66 (93.0)
	*		35 (94.6)	31 (91.2)	66 (93.0)
	Country				
n (%)					
Germany		n (%)	7 (18.9)	9 (26.5)	16 (22.5)
New Zealand		n (%)	1 (2.7)	2 (5.9)	3 (4.2)
United States	n (%)	29 (78.4)	23 (67.6)	52 (73.2)	

Source: Table 8 of the CSR.

Subjects in the LCIG group had a shorter duration of Parkinson's disease in comparison to subjects in the LC-oral group (10.02 years versus 11.85 years), a slightly lower mean "Off" time (6.30 hours versus 7.01 hours), and a greater mean "On" time without troublesome dyskinesia (8.69 hours versus 7.82 hours) (Table 3). These numerical differences suggested that subjects in the LCIG group had the potential to be in a slightly less severe disease state at baseline.

Table 3. Baseline Disease Characteristics

Parameter	Subcategory ^a	LCIG + Placebo Capsules	Placebo Gel + L-C Capsules	All Subjects
Total Number of Subjects		N = 37 (35 completed)	N = 34 (31 completed)	N = 71 (66 completed)
MMSE total score, mean (SD)		28.7 (1.4)	28.9 (1.4)	28.8 (1.4)
PD duration (years), mean (SD)		10.02 (4.64)	11.85 (5.58)	10.90 (5.16)
Number of PD medications at Baseline, n (%)	1	6 (16.2)	2 (5.9)	8 (11.3)
	2	12 (32.4)	13 (38.2)	25 (35.2)
	3	8 (21.6)	11 (32.4)	19 (26.8)
	> 3	11 (29.7)	8 (23.5)	19 (26.8)
Baseline "Off" time (hours), mean (SD)	Full Analysis Data Set	N = 36 6.30 (1.70)	N = 33 7.01 (2.06)	N = 69 6.64 (1.90)
Baseline "On" time without troublesome dyskinesia (hours), mean (SD)	Full Analysis Data Set	N = 36 8.69 (1.98)	N = 33 7.82 (2.47)	N = 69 8.27 (2.25)

Source: Table 9 of the CSR.

3.2.4 Results and Conclusions

3.2.4.1 Analyses of the Primary Endpoint

The primary analysis included 66 subjects who had post-baseline PD diary data. All of the 66 subjects had at least 2 valid symptom diary days (at least 12 awake hours) at Week 12. Therefore, the pre-specified LOCF for missing data was not needed for the primary endpoint.

The primary efficacy analysis demonstrated a statistically significant LS mean difference (improvement) of -1.91 hours (P = 0.0015) from Baseline after 12 weeks of treatment in the average daily normalized "Off" time between the LCIG group and the LC-oral group (LS mean of change, -4.04 hours versus -2.14 hours)

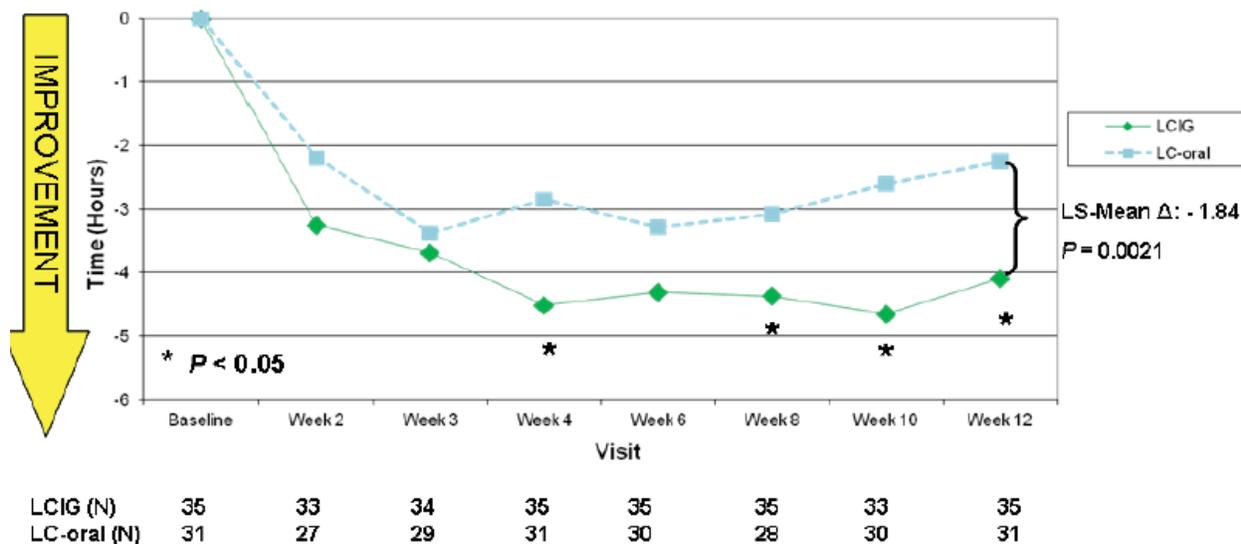
Table 4. Change from Baseline to Endpoint in Average Daily Normalized "Off" Time

Treatment Group	N	Observed Mean (SD) [hours]		LS Mean (SE) of Change	Difference from Placebo Gel + Levodopa-Carbidopa Capsules		
		Baseline	Endpoint		LS Mean (SE) of Difference	95% CI	P value
Placebo gel + L-C cap ^b	31	6.90 (2.06)	4.95 (2.04)	-2.14 (0.66)			
LCIG + placebo cap ^c	35	6.32 (1.72)	3.05 (2.52)	-4.04 (0.65)	-1.91 (0.57)	(-3.05, -0.76)	0.0015

Source: Table 10 of the CSR, confirmed by the reviewer.

The MMRM analysis of the primary efficacy variable showed a statistically significant LSmean difference (improvement) of -1.84 hours (P=0.0021) from Baseline in the average daily normalized "Off" time in the LCIG group compared to the LC-oral group for Weeks 12 (Figure 2).

Figure 2. Change from Baseline in Average Daily Normalized "Off" Time by Visit



Source: Figure 6 of the CSR, confirmed by the reviewer.

The use of rescue medication on valid diary days was similar in the two groups (Table 5). About 68% of the subjects did not use rescue medication at Week 12 and about 35% did not use rescue medication during the whole treatment period. The sensitivity analysis of ANCOVA without the covariate of rescue medication, which was the originally proposed primary analysis, yielded an estimated difference of -1.89 (P=0.0016), consistent with that of the primary analysis. All other pre-specified sensitivity analyses with respect of rescue medication use showed consistent

results, indicating that the subjects' use of rescue medication did not influence the measurement of the primary variable, the improvement in "Off" time.

Table 5. Number of Tablets of Rescue Medication Taken on Valid Diary Days

Study Week Categories for Levodopa Tablets	Statistic	LCIG + Placebo Capsules (N=35)	Placebo Gel + Levodopa-Carbidopa Capsules (N=31)
Week 12	n	35	31
Tablets per Day = 0	n (%)	24 (68.6)	21 (67.7)
0 < Tablets per Day <= 0.5	n (%)	3 (8.6)	4 (12.9)
0.5 < Tablets per Day <= 1	n (%)	5 (14.3)	4 (12.9)
1 < Tablets per Day <= 2	n (%)	3 (8.6)	1 (3.2)
2 < Tablets per Day <= 3	n (%)	0	0
3 < Tablets per Day <= 4	n (%)	0	0
4 < Tablets per Day <= 5	n (%)	0	0
5 < Tablets per Day <= 6	n (%)	0	0
6 < Tablets per Day <= 7	n (%)	0	0
Tablets per Day > 7	n (%)	0	1 (3.2)
Treatment Period	n	35	31
Tablets per Day = 0	n (%)	11 (31.4)	12 (38.7)
0 < Tablets per Day <= 0.5	n (%)	20 (57.1)	11 (35.5)
0.5 < Tablets per Day <= 1	n (%)	2 (5.7)	7 (22.6)
1 < Tablets per Day <= 2	n (%)	2 (5.7)	0
2 < Tablets per Day <= 3	n (%)	0	0
3 < Tablets per Day <= 4	n (%)	0	0
4 < Tablets per Day <= 5	n (%)	0	1 (3.2)
5 < Tablets per Day <= 6	n (%)	0	0
6 < Tablets per Day <= 7	n (%)	0	0
Tablets per Day > 7	n (%)	0	0

Source: Table 14.3__1.1.3.3 of CSR.

Subgroup analyses were performed by the sponsor for subgroups of age, sex, and country. None of the treatment-by-covariate interactions were statistically significant.

3.2.4.2 Analyses of Secondary Endpoints

Results of the ANCOVA of the key secondary efficacy variable demonstrated a statistically significantly LS mean difference (improvement) of 1.86 hours, P = 0.0059, in the average daily normalized "On" time without troublesome dyskinesia in the LCIG group compared to the LC-oral group (Table 6).

Table 6. Change from Baseline in "On" Time Without Troublesome Dyskinesia

Treatment Group	N	Observed Mean (SD) [hours]		LS Mean (SE) of Change	Difference from Placebo Gel + Levodopa-Carbidopa Capsules		
		Baseline	Endpoint		LS Mean (SE) of Difference	95% CI	P value
Placebo gel + L-C cap ^a	31	8.04 (2.09)	9.92 (2.62)	2.24 (0.76)			
LCIG + placebo cap ^b	35	8.70 (2.01)	11.95 (2.67)	4.11 (0.75)	1.86 (0.65)	(0.56, 3.17)	0.0059

Source: Table 12 of the CSR, confirmed by the reviewer.

The ANCOVA analyses performed in hierarchical order for the other secondary efficacy variables demonstrated statistically significant results for the PDQ-39 Summary Index,

CGI-I score, and UPDRS Part II score. Statistically significant results were not obtained for the UPDRS Part III score, EQ-5D Summary Index, or the ZBI Total score. Results of the MMRM analyses were consistent, in general, with the findings of the ANCOVA for these secondary efficacy variables.

3.2.4.3 Reviewer’s Results

The reviewer confirmed the sponsor’s results presented in this review. In addition, the reviewer conducted the following analyses for the primary endpoint.

The data was combined from 2 identical studies. Including the studyid as an additional factor in the ANCOVA model yielded consistent result with the primary analysis. The p-value was 0.0016.

Examination of the interaction of treatment by duration of Parkinson's Disease category was specified in SAP but was not included in the study report. The reviewer conducted the analysis and the result showed that the interaction was not statistically significant (P value=0.135). Results of subgroup analyses were presented in Section 4.

There were 5 (2 assigned to the LCIG group and 3 to the LC-oral group) dropouts excluded from the primary analysis due to lack of post-baseline diary data. The reviewer conducted a worst-case type analysis in which the primary endpoint was imputed with the overall mean average baseline "Off" time for the dropouts in the LCIG group, and with the overall mean average "Off" time at Week 12 for those in the LC-oral group. The analysis yielded an estimated difference of -1.65 (P=0.0046), consistent with that of the primary analysis.

3.3 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender and Age

The analysis results for the primary endpoint by demographic subgroups were in Table 7. The treatment effect was generally consistent across the subgroups. Most subjects are white and from the U.S.; therefore, no statistical comparisons were performed for race and region subgroups.

Table 7. Change from Baseline in Average Daily Normalized "Off" Time by Demographic Subgroups

	Placebo Gel + Levodopa-Carbidopa Capsules	LCIG + Placebo Capsules
Sex: Female		
N	9	11

	Placebo Gel + Levodopa-Carbidopa Capsules	LCIG + Placebo Capsules
LS mean (SE)	-1.54 (1.18)	-4.01 (0.95)
Difference in LS means		-2.47
p-value		0.0456
Sex: Male		
N	22	24
LS mean (SE)	-2.78 (0.95)	-4.38 (0.98)
Difference in LS means		-1.60
p-value		0.0328
Age: < 65 years		
N	14	20
LS mean (SE)	-1.80 (0.94)	-3.74 (0.80)
Difference in LS means		-1.94
p-value		0.0106
Age: >=65 years		
N	17	15
LS mean (SE)	-2.57 (1.04)	-4.54 (1.14)
Difference in LS means		-1.97
p-value		0.0462

Source: FDA reviewer.

4.2 Other Special/Subgroup Populations

The treatment effect seems larger for the subgroup of subjects with longer duration of Parkinson's disease (Table 8).

Table 8. Change from Baseline in Average Daily Normalized "Off" Time by Duration of Parkinson's Disease Category

	Placebo Gel + Levodopa-Carbidopa Capsules	LCIG + Placebo Capsules
<10 YEARS		
N	14	20
LS mean (SE)	-2.75 (0.76)	-3.65 (0.59)
Difference in LS means		-0.90
p-value		0.3070
>=10 YEARS		
N	17	15
LS mean (SE)	-1.91 (0.62)	-4.72 (0.73)
Difference in LS means		-2.81
p-value		0.0011

Source: FDA reviewer.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The primary analysis is ANCOVA. All model assumptions were met. The dropouts were limited (5 out of 71 subjects) and were not included in the primary analysis as they did not have any post-baseline diary data. A worst-case type analysis in which the primary endpoint was imputed with the overall mean average baseline "Off" time for the dropouts in the LCIG group, and with the overall mean average "Off" time at Week 12 for those in the LC-oral group still reached statistical significance. All subjects who completed the study had at least 2 valid symptom diary days for Week 12 to derive the primary endpoint. Therefore, missing data was less of a concern.

The use of rescue medication was similar in the LCIG group and the LC-oral group. Extensive sensitivity analyses with respect of rescue medication use showed consistent results with that of the primary analysis.

5.2 Collective Evidence

The primary efficacy analysis demonstrated a statistically significant LS mean difference in favor of the LCIG group in change of average daily normalized "Off" time of -1.91 hours ($P = 0.0015$), based on Parkinson's Disease Diary data. All sensitivity analyses of the primary endpoint were consistent with the primary analysis. The effect of LCIG was generally consistent across a variety of subgroups defined by demographic and baseline disease characteristics. A statistically significant LS mean difference (improvement) was observed in the average daily normalized "On" time without troublesome dyskinesia (the key secondary efficacy variable) of 1.86 hours ($P = 0.0059$) between the LCIG group and the LC-oral group.

5.3 Conclusions and Recommendations

The evidence based on the primary analysis seems to support the efficacy of Levodopa-Carbidopa Intestinal Gel as treatment of motor fluctuations in patients with advanced Parkinson's disease who had continued to experience persistent motor fluctuations despite optimized antiparkinsonian treatment.

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/s/

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I concur with the review.

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I concur with the review.