

Levodopa-Carbidopa Intestinal Gel Reduces Dyskinesia in Parkinson's Disease in a Randomized Trial

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ABSTRACT: Background: There are limited data regarding the effectiveness of levodopa-carbidopa intestinal gel (LCIG) for dyskinesia.

Objective: Compare the effectiveness of LCIG versus oral optimized medical treatment (OMT) for dyskinesia in patients with advanced Parkinson's disease (PD) using the Unified Dyskinesia Rating Scale (UDysRS).

Methods: This phase 3b, open-label, multicenter, 12-week, interventional study (NCT02799381) randomized 63 LCIG naïve patients with advanced PD (UDysRS ≥ 30) to LCIG (N = 30) or OMT (N = 33) treatment. Dyskinesia impact was assessed at baseline through week 12 using the UDysRS. PD-related motor and non-motor symptoms, and quality of life (QoL) were also assessed.

Results: Dyskinesias measured by UDysRS were significantly reduced in the LCIG group (n = 24; -17.37 ± 2.79) compared with the OMT group (n = 26; -2.33 ± 2.56) after 12 weeks (-15.05 ± 3.20 ; 95% CI, -21.47 to -8.63 ; $P < 0.0001$). At week 12, LCIG versus OMT also

demonstrated significant improvements in "On" time without troublesome dyskinesia ($P = 0.0001$), QoL ($P < 0.0001$), global impression of change ($P < 0.0001$), activities of daily living ($P = 0.0006$), and Unified Parkinson's Disease Rating Scale (UPDRS) Part III ($P = 0.0762$). Treatment-emergent adverse events were reported in 27 (44.3%) patients (LCIG, 18 [64.3%]; OMT, 9 [27.3%]). Serious adverse events occurred in 2 (7.1%) LCIG-treated patients.

Conclusions: LCIG significantly reduced dyskinesia compared with OMT. LCIG showed efficacy for treatment of troublesome dyskinesia in patients with advanced PD while demonstrating benefits in both motor and non-motor symptoms and QoL. © 2021 AbbVie Inc. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson Movement Disorder Society

Key Words: DYSCOVER; dyskinesia; optimized medical treatment; levodopa-carbidopa intestinal gel

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Relevant Conflicts of Interest/Financial Disclosures

E. Freire-Alvarez has received advisory, consulting, and lecture fees from AbbVie Inc., and is an investigator on the DYSCOVER study. E. Kurča was a study investigator. L. Lopez Manzanares has been compensated for advisory services and has received consulting, research grant support, or speaker honoraria from AbbVie, and is an investigator on the

DYSCOVER study. E. Pekkonen is a member of the AbbVie advisory board, and is an investigator on the DYSCOVER study. He has received consulting fees from AbbVie; lecture fees from AbbVie; and travel support from AbbVie. He is a standing member of the MDS Non-Motor Parkinson's Disease Study Group. C. Spanaki has received honoraria for lecturing, advisory fees, educational grants, and travel grants from AbbVie, and is an investigator on the DYSCOVER study. P. Vanni declares no conflicts. Y. Liu, O. Sánchez-Soliño, and L. Barbato are employees of AbbVie and may hold AbbVie stock and/or stock options.

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The combination of levodopa-carbidopa is a mainstay in Parkinson's disease (PD) treatment. Generally, catechol-O-methyl transferase (COMT) inhibitors, monoamine oxidase-B (MAO-B) inhibitors, and dopamine agonists are used simultaneously with levodopa to reduce motor fluctuations. Despite use of optimal oral medications, patients progressively develop persistent motor fluctuations such as wearing-off and delayed "On" time characterized by predictable or unpredictable swings from mobility to immobility.¹ Even with optimal oral treatments, dyskinesias are often challenging to manage.²⁻⁴

Dyskinesias are among the most troublesome symptoms in advanced PD. Approximately 50% of patients present with dyskinesia 4 to 5 years after treatment initiation and approximately 90% after 9 years.^{1,5} Moderate-to-severe dyskinesia can be painful and impair voluntary movements, thus impacting quality of life (QoL).⁶ Dyskinesias are thought to result from pulsatile stimulation of postsynaptic dopaminergic receptors caused by multiple oral levodopa dosing. In the context of severe neurodegeneration, erratic absorption, unpredictable variability in gastric emptying, and the short levodopa half-life, multiple oral levodopa dosing can result in unstable levodopa levels in plasma and, therefore, unstable dopamine levels in the basal ganglia.⁷⁻¹¹ Thus, dyskinesias in PD may result from drug therapy, specifically levodopa treatment.¹² Dyskinesia treatment options include oral amantadine, continuous subcutaneous apomorphine infusion, and deep brain stimulation (DBS). However, DBS may not be available or suitable for all patients. More treatment options are needed for patients with advanced PD. One option may be continuous levodopa delivery.^{7,13}

Levodopa-carbidopa intestinal gel (LCIG) is continuously delivered to the upper intestine by percutaneous endoscopic gastrostomy with J tube extension (PEG-J) using an external pump. LCIG provides more stable levodopa plasma levels than standard oral levodopa therapy thus decreasing the potential for motor complications and dyskinesia.^{14,15} Clinical trials and observational studies with LCIG have demonstrated marked reductions in "Off" time,¹⁶⁻²² decreased "On" time with dyskinesia,^{19,20} and increased "On" time without troublesome dyskinesia.¹⁶⁻¹⁸ However, these studies assessed dyskinesia using patient PD diaries and/or the motor section (Part IV) of the Unified Parkinson's Disease Rating Scale (UPDRS), both of which are limited in their sensitivity to change and ability to quantify dyskinesia symptoms.

The Unified Dyskinesia Rating Scale (UDysRS) was developed to assess a patient's historical disability of "On" dyskinesia and "Off" dystonia, provide an objective evaluation of severity and distribution of dyskinesia, and provide metric properties to measure several aspects of dyskinesia.²³ There have been no randomized clinical trials designed to compare LCIG effectiveness

on dyskinesia versus optimized medical treatment (OMT) using the UDysRS.

We present data from a randomized, 12-week study in patients with advanced PD specifically designed to evaluate LCIG versus OMT effectiveness on the full spectrum of dyskinesia symptoms using UDysRS and PD diaries. Furthermore, we compared LCIG versus OMT on motor fluctuations, health-related outcomes, safety, and tolerability.

Methods

Study Design

This was a phase 3b, open-label, randomized, multicenter, 12-week study that assessed LCIG versus OMT efficacy on dyskinesia in patients with advanced PD (NCT02799381). Patients were randomized to receive OMT or LCIG. Randomization was stratified by country only. Patients receiving OMT had the same schedule of visits/procedures throughout the study as patients receiving LCIG, except for visits related to nasojejunal (NJ)/PEG procedures, LCIG titration, and follow-up. Investigators ensured that patients were receiving optimized oral treatment before randomization. The study consisted of Screening, Treatment, and Follow-Up periods (Fig. S1).

All anti-PD medications were stable for ≥ 30 consecutive days before visit 3 randomization and baseline assessments. Patients randomized to receive OMT continued their optimal and stable anti-PD medication (including amantadine, if they were taking it) throughout the study. Patients randomized to receive LCIG discontinued all anti-PD medications other than amantadine prior to LCIG treatment initiation on day 1 (visit 4). Patients in both groups treated with amantadine at randomization were required to continue a stable amantadine regimen throughout the study. A temporary, optional NJ tube was placed to determine the patient response to LCIG and to optimize the dose before a permanent PEG-J tube was placed on day 1. The LCIG dose was adjusted to obtain the optimal clinical response for the individual patient (minimized "Off" episodes and "On" time with disabling dyskinesia). Visit 5 was conducted at week 2, 14 days after NJ and/or PEG-J insertion. Patients discontinuing LCIG returned for visit 9, 1 week after PEG-J removal. Adverse events (AEs) and serious AEs (SAEs) were monitored for 30 days following PEG-J removal.

Patients

This study was conducted at 23 movement disorder specialist sites in seven countries where LCIG was commercially available. Eligible patients were aged ≥ 30 years, had a diagnosis of advanced levodopa-responsive PD, and had persistent motor fluctuations, with dyskinesia not controlled with OMT (defined as

UDysRS total score ≥ 30 as determined from limited data from previous studies^{24,25}). While there were no other dyskinesia-specific inclusion criteria, PD Diary concordance testing data were required, including ≥ 1 interval of “On” time with dyskinesia. Patients were excluded if they had predominantly diphasic dyskinesia, had undergone previous surgery for PD (eg, DBS), or had a Mini-Mental State Examination score < 24 .

All patients provided written informed consent prior to the study. The study protocol was approved by the institutional review boards/ethics committees at all centers in all the participating countries. This study was conducted in accordance with the Good Clinical Practice guideline as defined by the International Council on Harmonisation, the Declaration of Helsinki, and all applicable federal and local regulations and institutional review boards.

Efficacy Assessments

The primary efficacy endpoint was the mean change from baseline to week 12 in UDysRS total scores. The UDysRS is a validated comprehensive historical and objective measure of dyskinesia in PD. Scores range from 0 to 104, with a lower score indicating less dyskinesia.²³ The UDysRS contains four parts; the historical disability section composed of Part I (“On”-dyskinesia impact) and Part II (“Off”-dystonia impact) as perceived by the patient. Part III (objective impairment) and Part IV (disability) evaluate the specific problems caused by dyskinesia and are assessed by the physician. Dyskinesia severity was scored via videotape by a central rater blinded to the study protocol and hypothesis. All patients had external pumps during scoring, with patients in the OMT group wearing dummy pumps. Key ranked secondary efficacy endpoints (tested in a hierarchical order) were the mean change from baseline to week 12 in: “On” time without troublesome dyskinesia (measured by patients’ responses in the PD Diary),²⁶ Parkinson’s Disease Questionnaire-8 (PDQ-8) summary index score,²⁷ Clinical Global Impression of Change (CGI-C) score,²⁸ UPDRS²⁹ Part II score, “Off” time (PD Diary), and UPDRS Part III score (measured at best “On” time). Additional efficacy assessments included: UDysRS subdomain scores (Part I-IV, Historical, and Objective), normalized “On” time without dyskinesia and “On” time with troublesome dyskinesia (PD Diaries), the modified Abnormal Involuntary Movement Scale (mAIMS),²⁸ and the King’s PD Pain Scale (KPPS).³⁰ Data collected from PD diaries were normalized to an average 16-hour awake time and the time recorded for the three diaries before each visit.

Safety

Safety and tolerability were assessed using AE monitoring, neurological examinations, clinical laboratory

tests, ECG tracings, vital sign monitoring, Columbia Suicide Severity Rating Scale, Minnesota Impulsive Disorders Interview, and the Sleep Attacks Questionnaire.

Analysis

An estimated enrollment of 60 patients randomized 1:1 would provide $>85\%$ power to determine the primary endpoint, assuming a 10-point treatment difference in UDysRS total score between groups, at a two-sided significance level of 0.05. The intent-to-treat population (ITT; $N = 60$) was used for all efficacy analyses and consisted of all patients randomized to either OMT or LCIG treatment groups who received ≥ 1 dose of study drug following PEG-J placement in the LCIG group. Two-sided statistical tests were used with a significance level of $\alpha = 0.05$, unless otherwise noted. We used a mixed-effects model repeated-measures (MMRM) analysis of change from baseline for each postbaseline observation and included fixed categorical effects for treatment, country, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline score and baseline score-by-visit interaction. Each key ranked secondary endpoint was analyzed using the same MMRM model and was tested in a fixed sequence for multiplicity control until a secondary variable failed to demonstrate significance at the 0.05 level.

The safety dataset ($N = 61$) was used for all baseline and safety assessments and consisted of all patients randomized to either OMT or LCIG groups who had study device (NJ and/or PEG-J) placement. AEs were tabulated by primary system organ class and MedDRA preferred term (version 22.0).

Results

Patient Disposition and Baseline Measurements

Overall, 96 patients were screened from 27 sites in seven countries, and 63 patients from 23 sites were randomized into the OMT ($N = 33$) and LCIG groups ($N = 30$; Fig. S2). In the OMT group, 4 patients discontinued prematurely. Primary reasons for discontinuation (patients could have multiple reasons) were withdrawn consent ($n = 3$) and “other” ($n = 1$; Fig. S2). In the LCIG group, 5 patients prematurely discontinued, primarily due to withdrawn consent ($n = 3$), AE ($n = 1$), and “other” ($n = 1$). Demographic characteristics were balanced between groups (Table 1). Patients receiving OMT were 48.5% female ($n = 16$) and on average were 68.7 ± 7.20 years of age, with 12.77 ± 6.370 years since PD diagnosis. Patients receiving LCIG were 57.1% female ($n = 16$) and were on average 69.3 ± 6.99 years of age with 12.67 ± 4.159 years since PD diagnosis. At baseline,

13.1% of patients were taking 1 PD medication (L-dopa and dopa derivatives), 31.1% were taking 2, 36.1% were taking 3, and 19.7% were taking >3. The daily levodopa dose for both groups remained stable from week 2 to the end of the treatment period; OMT (876.7 ± 365.04 mg at week 2 to 912.4 ± 371.17 mg at week 12) and LCIG (1211.5 ± 374.89 mg at week 2 to 1215.0 ± 403.40 mg at week 12). At baseline, and throughout the treatment period, 8 (28.6%) LCIG-treated patients and 11 (33.3%) OMT-treated patients were receiving concomitant amantadine.

Primary Endpoint

The least squares (LS) mean \pm standard error (SE) change from baseline in UDysRS total scores—the primary study endpoint—significantly decreased by week 2 and was sustained through week 12 for LCIG (-17.37 ± 2.79 , $P < 0.0001$) versus OMT (-2.33 ± 2.56 , $P = 0.3663$; Fig. 1). At week 12, the LS mean UDysRS total score was significantly different for LCIG and OMT groups (MMRM difference: -15.05 ± 3.20 ; 95% confidence interval [CI], -21.47 to -8.63 ; $P < 0.0001$; Table S1). This analysis was supported by both analysis of covariance (ANCOVA) compared with the final visit (-14.5 ± 3.16 ; 95% CI, -20.87 to 8.17 ; $P < 0.0001$) and the prespecified sensitivity analysis, using ANCOVA with baseline observation carried forward for all randomized patients who did not have postbaseline UDysRS assessments (-12.8 ± 3.02 ; 95% CI, -18.84 to -6.71 ; $P < 0.0001$; Table S1).

Key Ranked Secondary Endpoints

Normalized hours/day of “On” time without troublesome dyskinesia at week 12 showed a significant LS mean \pm SE increase with LCIG (3.15 ± 0.69) versus OMT (-0.12 ± 0.63 ; MMRM difference, 3.27 ± 0.78 ; 95% CI, 1.71 to 4.83 ; $P = 0.0001$; Fig. 2A and Table S2). These increases were achieved at week 2 and lasted through week 12 (Fig. 2A). At week 12, patient QoL was significantly improved with LCIG (-21.62 ± 3.47 ; $P < 0.0001$) versus OMT (-4.95 ± 3.11 ; $P = 0.1167$) as measured by the PDQ-8 Summary Index (MMRM difference, -16.66 ± 3.89 ; 95% CI, -24.48 to -8.85 ; $P < 0.0001$; Fig. 2B and Table S2). Compared with baseline assessments, LCIG (2.48 ± 0.28 ; $P < 0.0001$) also significantly improved CGI-C scores at week 12 compared with OMT (MMRM difference, -2.11 ± 0.33 ; 95% CI, -2.78 to -1.44 ; $P < 0.0001$; Table S2), with improvement maintained through week 12 (Fig. 2C). For the CGI-C, a higher percentage of patients were responders (“much”, “very much”, or “minimally” improved) after 12 weeks with LCIG (17/27 [68.0%]) versus OMT (2/33 [6.9%]; data not shown). At week 12, UPDRS Part II scores

TABLE 1 Baseline demographics and disease characteristics

Characteristic	OMT (N = 33)	LCIG (N = 28)
Sex, n (%)		
Female	16 (48.5)	16 (57.1)
Male	17 (51.5)	12 (42.9)
Age, years	68.7 \pm 7.20	69.3 \pm 6.99
BMI, kg/m ²	25.2 \pm 4.42	24.5 \pm 4.24
PD duration (time since diagnosis), years	12.77 \pm 6.370	12.67 \pm 4.159 ^a
MMSE total score ^b	27.85 \pm 1.661	28.14 \pm 1.715
UDysRS total score	51.2 \pm 11.56 ^c	53.2 \pm 12.24 ^a
“Off” time, hours ^d	4.0 \pm 2.99 ^c	4.8 \pm 2.41 ^a
“On” time without dyskinesia, hours ^d	5.2 \pm 3.58 ^c	3.8 \pm 2.94 ^a
“On” time without troublesome dyskinesia, hours ^d	9.7 \pm 3.57 ^c	8.8 \pm 2.88 ^a
“On” time with troublesome dyskinesia, hours ^d	2.3 \pm 3.12 ^c	2.4 \pm 1.75 ^a
PDQ-8 summary index	43.4 \pm 15.81 ^c	45.1 \pm 20.46 ^a
UPDRS Part II score	18.4 \pm 6.44	18.3 \pm 6.35 ^a
UPDRS Part III score ^e	25.4 \pm 10.91	26.3 \pm 6.66 ^a

Note: Data are presented as mean \pm SD, unless otherwise noted.

Abbreviations: OMT, optimized medical treatment; LCIG, levodopa-carbidopa intestinal gel; BMI, body mass index; PD, Parkinson's disease; MMSE, Mini-Mental State Examination; UDysRS, Unified Dyskinesia Rating Scale; PDQ-8, Parkinson's Disease Questionnaire-8; UPDRS, Unified Parkinson's Disease Rating Scale; SD, standard deviation.

^an = 27.

^bPatients must have an MMSE score \geq 24.

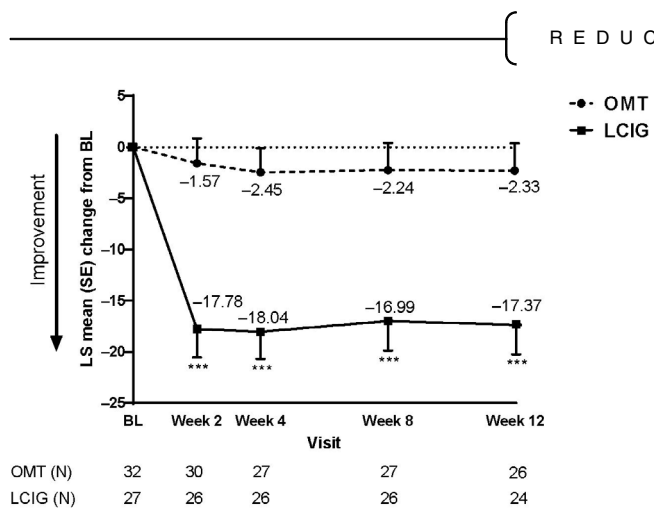
^cn = 32.

^dDerived from PD Diaries and normalized to 16-hour waking day.

^eUPDRS Part III (motor examination) was measured during the “On” state.

(activities of daily living) were significantly improved for LCIG (-5.33 ± 1.28) versus OMT (0.21 ± 1.16 ; MMRM difference, -5.54 ± 1.52 ; 95% CI, -8.59 to -2.49 ; $P = 0.0006$; Fig. 2D and Table S2).

Patients treated with LCIG versus OMT had significantly reduced LS mean \pm SE “Off” time at week 12 (MMRM difference, -2.35 ± 0.58 ; 95% CI, -3.51 to -1.19 ; $P = 0.0002$). This effect was achieved by week 2 and maintained through week 12 (Fig. 2E and Table S2). UPDRS Part III scores (motor examination) were significantly improved in the LCIG versus OMT groups at weeks 2 ($P = 0.0345$) and 8 ($P = 0.0014$) but were insignificantly reduced at week 12 as the last variable in the ranked MMRM did not reach significance (MMRM difference, -4.05 ± 2.24 ; 95% CI, -8.55 to 0.44 ; $P = 0.0762$; Fig. 2F and Table S2).



MMRM difference of LCIG vs OMT: -15.05 ± 3.20 ; 95% CI, -21.47 to -8.63 ; $P < 0.0001$.

FIG. 1. Unified Dyskinesia Rating Scale total scores. LS mean change from baseline in UDysRS total scores in the OMT and LCIG treatment groups. The UDysRS total score ranges from 0 to 104 with a lower score indicating less dyskinesia. Asterisks indicate statistical significance compared with baseline in a mixed-effects model repeated measures at the $P < 0.0001$ (***) level. Error bars represent SE. BL, baseline; CI, confidence interval; LCIG, levodopa-carbidopa intestinal gel; LS, least squares; MMRM, mixed-effect model repeated measures; OMT, optimized medical treatment; SE, standard error; UDysRS, Unified Dyskinesia Rating Scale.

Additional Efficacy Assessments

There were significant reductions for LCIG versus OMT in UDysRS Part I ($P < 0.0001$), Part III ($P = 0.0172$), and the historical score ($P < 0.0001$), while the groups showed numerical, but not statistically significant reductions for all the other UDysRS parts including Part II ($P = 0.1408$), Part IV ($P = 0.4084$), and the objective score ($P = 0.0646$; Table S3). Treatment with LCIG versus OMT also showed significant improvements in LS mean \pm SE “On” time without dyskinesia (MMRM difference, 2.69 ± 1.13 ; 95% CI, 0.42 to 4.96; $P = 0.0212$) and numerical improvement in “On” time with troublesome dyskinesia (MMRM difference, -0.93 ± 0.50 ; 95% CI, -1.92 to 0.07 ; $P = 0.0670$; Table S4). mAIMS scores were significantly decreased for LCIG versus OMT (mAIMS total score MMRM difference, -5.02 ± 1.19 ; 95% CI, -7.41 to -2.62 ; $P < 0.0001$). KPPS total scores were significantly improved at week 12 with LCIG (-14.16 ± 3.42) versus OMT (-2.50 ± 3.12 ; MMRM difference, $P = 0.0026$) primarily driven by improvements in musculoskeletal ($P = 0.0044$), fluctuation-related ($P = 0.0376$), and nocturnal ($P = 0.0119$) pain KPPS subdomains (Table S5).

Safety and Tolerability

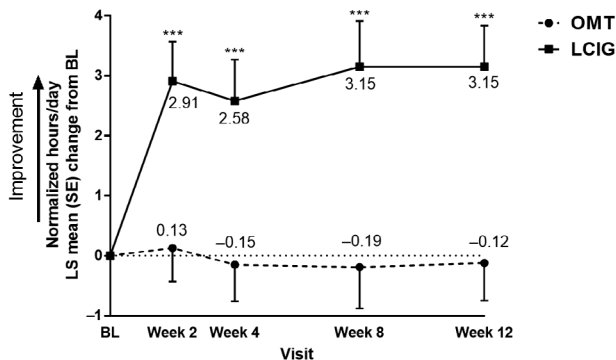
Overall, 64.3% of patients ($n = 18$) in the LCIG group and 27.3% of patients ($n = 9$) in the OMT group reported treatment-emergent AEs (Table 2). The most frequently reported AEs in the LCIG group were falling (17.9%) and procedural pain (10.7%). In the

OMT group the most frequently reported AEs were falling and PD symptoms (6.1% each). Most AEs were rated mild or moderate in severity by the investigators. Among AEs of special interest, gastrointestinal and gastrointestinal procedure-related AEs were the most reported in LCIG-treated patients, with procedural pain being the most common (10.7%). One patient in the OMT group experienced vitamin B6 deficiency. No patient in the OMT group experienced SAEs; however, 2 patients (7.1%) in the LCIG group experienced SAEs. Overall, two study drug discontinuations (both from the LCIG group) included AEs (patients could have multiple reasons for discontinuation), of which there was one SAE (pneumoperitoneum), and one non-serious AE of depressive syndrome. The one SAE of pneumoperitoneum was potentially related to PEG-J placement and was the only severe AE reported.

Discussion

This is the first randomized clinical trial showing that LCIG versus OMT significantly reduces dyskinesia in patients with advanced PD. The primary objective was to measure dyskinesia using the validated and highly sensitive UDysRS, which includes both historical and objective clinical assessments of dyskinesia.²³ Most LCIG studies have primarily utilized only patient diaries or patient-reported UPDRS Part IV (motor complications) scores to measure dyskinesia without blind evaluation of objective disability.¹⁶⁻²¹ LCIG versus OMT treatment significantly reduced UDysRS total scores through week 12, thus meeting the primary endpoint. Scores in two of the four UDysRS parts significantly improved including ON-dyskinesia (Part I), impairment (Part III), and the composite historical score (sum of Part I and Part II). Compared with the OMT group, the LCIG group had numerical reductions in UDysRS Part II (OFF-Dystonia), Part IV (Disability), and the composite objective score (sum of Part III and IV). To date the only LCIG study assessing dyskinesia using the UDysRS is a smaller open-label study of Hungarian patients with advanced PD treated with LCIG for 12 months.³¹ UDysRS total score reductions in this study were similar to those in the Hungarian study; however, direct comparisons are confounded by the varied assessment periods (12 weeks vs. 1 year) and different statistical analyses used.³¹ The minimal clinically important difference has only been calculated for UDysRS Parts I-III.^{32,33} The differences at week 12 for LCIG versus OMT for UDysRS Parts I-III were -8.75 , -1.60 , and -3.45 , respectively, and the calculated minimal clinically important differences are -2.1 , -1.8 , and -2.32 ^{32,33}; therefore, both UDysRS Parts I and III reached both statistical and clinically meaningful differences.

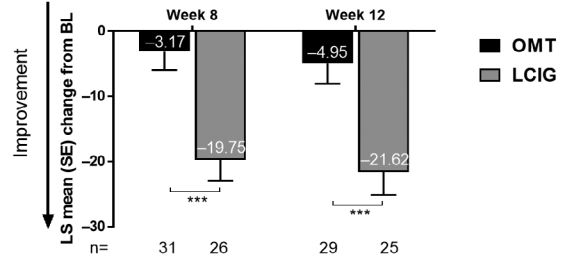
(A) Normalized "On" Time Without Troublesome Dyskinesia



OMT (N)	32	29	28	28	28
LCIG (N)	27	25	24	25	25

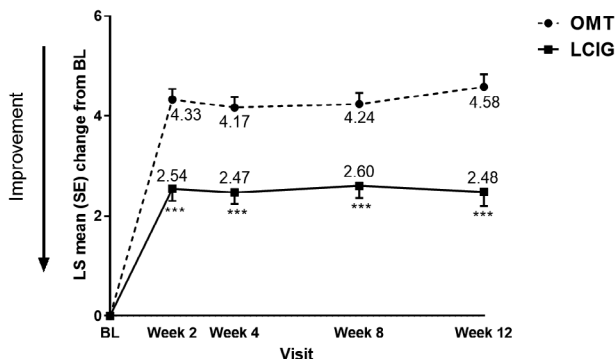
MMRM difference of LCIG vs OMT: 3.27 ± 0.78 ; 95% CI, 1.71 to 4.83; $P = 0.0001$.

(B) PDQ-8 Summary Index Scores



MMRM difference of LCIG vs OMT: -16.66 ± 3.89 ; 95% CI, -24.48 to -8.85 ; $P < 0.0001$.

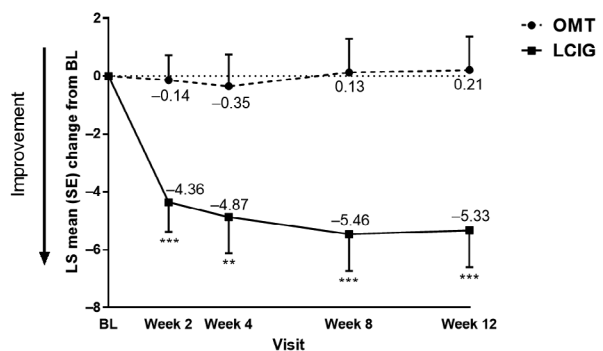
(C) Clinical Global Impressions of Change Index Scores



OMT (N)	32	30	30	29	29
LCIG (N)	27	26	26	26	25

MMRM difference of LCIG vs OMT: -2.11 ± 0.33 ; 95% CI, -2.78 to -1.44 ; $P < 0.0001$.

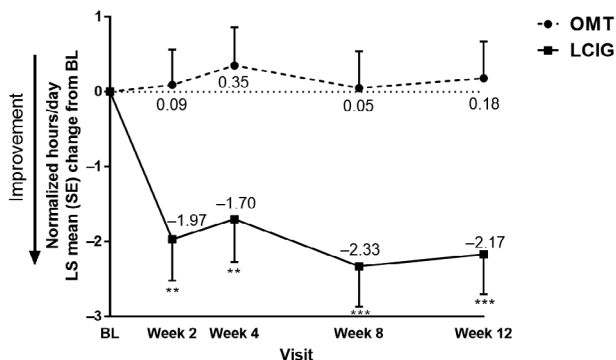
(D) UPDRS II Scores



OMT (N)	33	31	31	29	29
LCIG (N)	27	26	26	26	24

MMRM difference of LCIG vs OMT: -5.54 ± 1.52 ; 95% CI, -8.59 to -2.49 ; $P = 0.0006$.

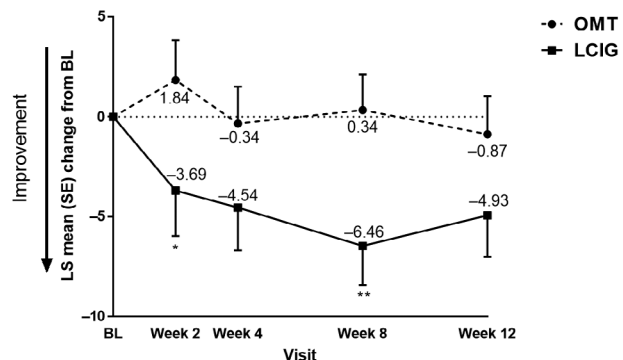
(E) Normalized "Off" Time



OMT (N)	32	29	28	28	28
LCIG (N)	27	25	24	25	25

MMRM difference of LCIG vs OMT: -2.35 ± 0.58 ; 95% CI, -3.51 to -1.19 ; $P = 0.0002$.

(F) UPDRS III Scores



OMT (N)	33	31	31	29	29
LCIG (N)	27	26	26	26	25

MMRM difference of LCIG vs OMT: -4.05 ± 2.24 ; 95% CI, -8.55 to 0.44 ; $P = 0.0762$.

FIG. 2. Key secondary outcomes. LS mean change from baseline of daily hours of (A) normalized "On" time without troublesome dyskinesia, (B) PDQ-8 summary index scores, (C) CGI-C scores, (D) UPDRS II, (E) normalized "Off" time, and (F) UPDRS III. Error bars represent SE. Asterisks indicate statistical significance compared with baseline in a $P < 0.05$ (*), $P < 0.01$ (**), and $P < 0.001$ (***). BL, baseline; CI, confidence interval; LCIG, levodopa-carbidopa intestinal gel; LS, least squares; MMRM, mixed-effect model repeated measures; OMT, optimized medical treatment; PDQ-8, Parkinson's Disease Questionnaire-8; SE, standard error; UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 2 Safety summary

Subjects with any	OMT (N = 33)n (%)	LCIG (N = 28)n (%)	Total (N = 61)n (%)
AE	9 (27.3)	18 (64.3)	27 (44.3)
Drug relationship	3 (9.1)	8 (28.6)	11 (18.0)
Severe AE	0	1 (3.6)	1 (1.6)
Serious AE	0	2 (7.1)	2 (3.3)
AE leading to discontinuation of study drug	0	2 (7.1)	2 (3.3)
Treatment-emergent GI events	0	9 (32.1)	9 (14.8)
TEAE other than GI event	9 (27.3)	15 (53.6)	24 (39.3)
Fatal AE	0	0	0
TEAEs occurring in at least 2 patients during 12-week treatment period			
Falling	2 (6.1)	5 (17.9)	7 (11.5)
<i>Procedural pain</i>	0	3 (10.7)	3 (4.9)
Depression	1 (3.0)	2 (7.1)	3 (4.9)
Parkinson's disease	2 (6.1)	1 (3.6)	3 (4.9)
<i>Abdominal pain</i>	0	2 (7.1)	2 (3.3)
Anxiety	0	2 (7.1)	2 (3.3)
Drug withdrawal syndrome	0	2 (7.1)	2 (3.3)
Hypertension	0	2 (7.1)	2 (3.3)
Urinary tract infection	0	2 (7.1)	2 (3.3)
Hematoma	1 (3.0)	1 (3.6)	2 (3.3)
Limb injury	1 (3.0)	1 (3.6)	2 (3.3)
Syncope	1 (3.0)	1 (3.6)	2 (3.3)
Vitamin B6 deficiency	1 (3.0)	1 (3.6)	2 (3.3)

Note: GI and GI procedure-related AEs are italicized.

Abbreviations: OMT, optimized medical treatment; LCIG, levodopa-carbidopa intestinal gel; AE, adverse event; GI, gastrointestinal; TEAE, treatment-emergent AE.

Dyskinesia reductions in the LCIG versus OMT groups using UDysRS total scores and Part I (ON-dyskinesia) are supported by the significant increase in “On” time without troublesome dyskinesia. This is similar to other clinical trials with LCIG at 12 weeks.¹⁶⁻¹⁸ The significant reductions in mAIMS total score at week 12 in this study also support the reductions observed in the UDysRS Part III, which was developed using aspects of the AIMS scale.²³ The observations presented here from both PD diaries and the mAIMS further support the improvements on dyskinesia with LCIG in patients with advanced PD. Patients treated with LCIG experienced fewer dyskinesias despite taking higher daily doses of levodopa (1211.5 ± 374.89 mg to 1215.0 ± 403.40 mg) versus the OMT group (876.7 ± 365.04 mg to 912.4 ± 371.17 mg). This suggests that continuous levodopa infusion per se reduces severity and duration of dyskinesias as compared with pulsatile levodopa delivery. Patients from both treatment groups who were receiving treatment with amantadine were required to maintain a stable treatment regimen through the study to minimize the

influence of concomitant amantadine treatment on changes in dyskinesias.

In this study, LCIG treatment significantly improved normalized hours/day of “Off” time at all timepoints versus OMT. The reduction in normalized “Off” time was less than that observed in previous LCIG clinical trials^{16,17}; however, those trials required ≥ 3 hours of “Off” time for inclusion and patients enrolled in those studies had higher mean hours of “Off” time at baseline. It is noteworthy that improvements in “Off” time were not sacrificed by the dyskinetic efficacy, even though patients had significant baseline dyskinesia burden, suggesting that LCIG therapy allows plasma levodopa levels to remain in the therapeutic window for longer during the day.

There was a significant improvement in QoL assessed by PDQ-8 summary index scores in patients treated with LCIG versus OMT. Other LCIG studies have demonstrated significant improvements in QoL using the PDQ-8¹⁹ and the expanded PDQ-39.¹⁶⁻¹⁸ This was not

surprising, as dyskinesias have been shown to impact patient QoL⁶; however, a direct correlation between improvement in dyskinesias and QoL was not assessed in this study. Additionally, in this study, treatment with LCIG versus OMT significantly reduced total KPPS scores and specific aspects of pain, including musculoskeletal pain, fluctuation-related pain, and nocturnal pain.

These results indicate that LCIG reduces dyskinesia and can be a useful therapeutic strategy, particularly in patients experiencing both dyskinesia and “Off” periods. We conducted a targeted assessment of LCIG effects on dyskinesia using the UDysRS as a primary measure with other scales as supporting measures and found robust improvement versus OMT that was sustained throughout 12 weeks. LCIG appears to be a good therapeutic option in patients who have troublesome dyskinesia and “Off” phases despite use of OMT. The LCIG dose was relatively stable over the treatment period, as seen in prior studies.²¹

The main limitation is the open-label nature of the study. We cannot exclude a component of placebo effect in the LCIG outcomes observed, but LCIG has previously been shown to be effective for “Off” time, and the magnitude of the changes in dyskinesia, “Off” time, and QoL measures are large, are in line with previous studies, and are unlikely due to placebo alone. However, the objective dyskinesia was rated blindly by the same rater to eliminate interrater effect. Additionally, while the study was powered to detect significant differences in UDysRS total score, it was not powered to detect differences in UDysRS subscale scores.

Safety observations are consistent with the established safety profile from clinical trials and observational studies.^{16-18,21} In this study, 64.3% of patients in the LCIG group reported an AE versus 27.3% in the OMT group. One patient (LCIG group) had a severe AE (pneumoperitoneum) and 2 patients (7.1%) (both LCIG group) experienced SAEs.

The primary and all key ranked secondary efficacy endpoints including “On” time without troublesome dyskinesia, QoL, impressions of change, “Off” time, and activities of daily living met statistical significance, except for the UPDRS Part III score after multiplicity adjustment. LCIG treatment was generally well tolerated. AEs were similar with the established safety profile. ■

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Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials they sponsor. This includes access to anonymized, individual, and trial-level data (analysis datasets), as well as other information (eg, protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.