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A post hoc comparison of levodopa-carbidopa intestinal gel daytime monotherapy vs polytherapy safety and efficacy in patients with advanced Parkinson's disease: Results from 6 phase 3/3b open-label studies

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ABSTRACT

Introduction: As Parkinson's disease (PD) progresses, the number/frequency of PD medications tend to increase, which is correlated with decreased patient compliance and suboptimal control of PD symptoms. We investigated efficacy and safety of levodopa-carbidopa intestinal gel (LCIG) daytime monotherapy (with or without nighttime oral levodopa-carbidopa) compared with polytherapy (LCIG with ≥1 adjunctive PD therapy) in advanced PD patients.
Methods: This post hoc descriptive study compared LCIG stable daytime monotherapy with LCIG stable polytherapy in all six phase 3/3b open-label studies from both US and international sites; because of study design variability, pooling data for comparison was not appropriate. Efficacy assessments included PD diary data (mean change from baseline in "Off" time and "On" time with or without troublesome dyskinesia), mean Unified PD Rating Scale scores (Parts II and III), and 39-item Parkinson's Disease Questionnaire (PDQ-39) summary index. Adverse events were also assessed.
Results: Overall, LCIG daytime monotherapy and polytherapy demonstrated similar efficacy/safety profiles in advanced PD patients, regardless of treatment duration or population. LCIG monotherapy vs. polytherapy groups experienced similar mean decreases in "Off" time (4.6 vs. 4.1 h/day) and similar increases in "On" time without troublesome dyskinesia (4.6 vs. 4.1 h/day). In most studies, PDQ-39 summary index scores were reduced from baseline by ≥5 points, regardless of patient population or study duration. Adverse events not related to the procedure/device were similar in both groups.
Conclusion: Our data suggest that, for appropriate patients, LCIG monotherapy can provide a more simplified treatment option with similar efficacy and safety.

1. Introduction

Levodopa therapy remains the gold standard for managing motor symptoms of earlier stages of Parkinson's disease (PD) [1–4]. However, long-term use (4 to 10 years or longer) of intermittent oral levodopa is associated with disabling motor fluctuations between "On" time (when medication is providing benefit regarding mobility, slowness, and stiffness) and "Off" time (when medication has worn off and is no longer providing benefit regarding mobility, slowness, and stiffness), and levodopa-induced dyskinesia [5–7]. Adjusting levodopa dose and administration frequency to optimize treatment of levodopa-related motor symptoms can be challenging because of the short half-life of levodopa and the pulsatile stimulation of the dopaminergic system that occurs with oral administration [1]. In addition, treating motor complications in PD often requires using levodopa in combination with multiple adjunctive therapies, including monoamine oxidase B inhibitors, dopamine agonists, and catechol-*O*-methyltransferase inhibitors [8]. Most adjunctive therapies initially reduce motor fluctuations, providing modest benefit, but can be associated with increased dyskinesia and risk of other adverse effects [9]. As PD progresses, the number and frequency of PD medications tend to increase, which correlates with reduced patient compliance and suboptimal control of PD symptoms [10,11].

Continuous dopamine receptor stimulation from stabilized levodopa plasma levels can provide relief from Parkinsonian symptoms and reduce

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motor complications [12–15]. Levodopa-carbidopa intestinal gel (LCIG, designated in the United States as carbidopa-levodopa enteral suspension and in Japan as ABT-SLV187, referred to as LCIG from here on for the purposes of this report) is continuously delivered via percutaneous endoscopic gastrojejunostomy tube (PEG-J) and portable infusion pump. LCIG provides physiologically continuous dopaminergic stimulation. Results from multiple phase 3/3b studies demonstrate markedly reduced motor complications, including improvements from baseline in "Off" time by ≥3 h, improved non-motor symptoms, and improved quality of life in patients with advanced PD being treated with LCIG [8,16–19]. The clinically meaningful benefits of LCIG were maintained in a long-term, open-label, extended-access trial with a mean follow-up of 4.1 years, the longest prospective, multinational study of LCIG safety and efficacy to date [17]. Patient populations in four of the six aforementioned studies were predominantly white. However, similar efficacy and safety results have also been reported in Asian patients with PD [20,21].

The use of LCIG as a daytime monotherapy (with or without nighttime oral levodopa) has the potential to reduce pill burden. Using data from six studies (five phase 3 studies including extension studies and one phase 3b study), we investigated the efficacy and safety of stable LCIG daytime monotherapy (with or without nighttime oral levodopa-carbidopa) compared with stable polytherapy (LCIG with ≥1 adjunctive anti-PD therapy) in patients with advanced PD.

2. Methods

2.1. Study design

This post hoc descriptive comparison study was performed on data collected from five phase 3 and one phase 3b studies that assessed the long-term safety and tolerability of LCIG (Fig. 1). The studies include (1) a 52-week open-label extension study (NCT00360568), herein referred to as OLE [16], in patients who previously completed a 12-week double-blind, double-dummy study (NCT00660387/NCT0357994) [8], in which patients continued to receive LCIG or switched from oral levodopa-carbidopa immediate-release (LC-IR) to LCIG [16]; (2) a 54-week open-label study of LCIG (NCT00335153), herein referred to as OLS [18]; (3) an ongoing open-label phase 3 extended-access study (NCT00660673), herein referred to as OLA, in patients who completed participation in OLE or OLS (OLS patients in Canada completed ≥6 months of LCIG treatment); (4) a 60-week, single-arm, open-label, 2-part, phase 3b study (NCT01736176), herein referred to as P3b; (5) a 12-week, open-label, single-arm study of LCIG in Asian patients (NCT01960842), herein referred to as AOLS; and (6) an ongoing, open-label extension study (NCT02082249), herein referred to as AOLE, in patients who participated in AOLS. AOLE comprised two periods: part 1 (52 weeks of LCIG treatment) and part 2 (after the initial 52 weeks; data not discussed herein).

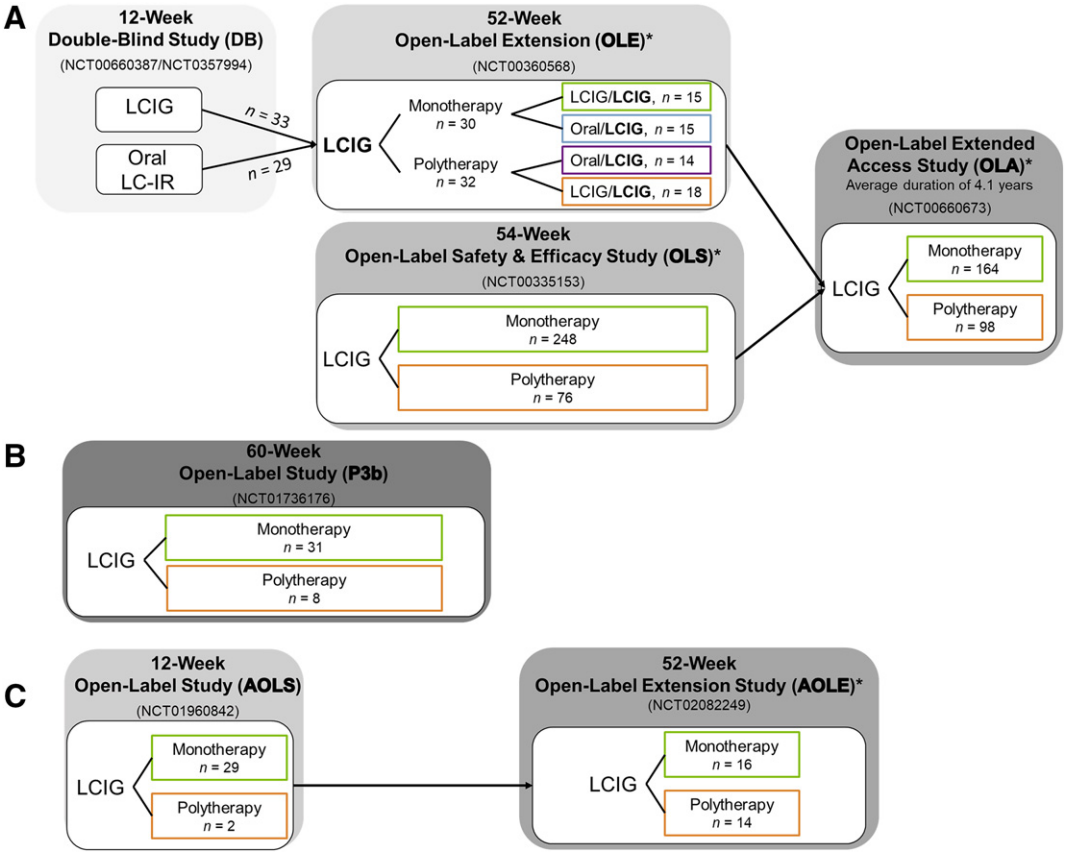

Fig. 1. Schematic of patient groups in five phase 3 trials and one phase 3b trial. (A) Patients who began LCIG or oral levodopa-carbidopa treatment in a 12-week study and then continued/began LCIG treatment in a 52-week open-label extension study; results from a 54-week open-label study for patients treated with LCIG; and results from an extended-access-to-treatment study. In the extended-access study, the change from initial LCIG treatment (in either the 12-week double-blind study or the 54-week open-label study) to the extended-access endpoint (average LCIG treatment of 4.1 years) or the change from the extended-access study baseline to endpoint (average LCIG treatment of 3 years) was assessed. (B) Results from a 60-week open-label study in patients treated with LCIG. (C) Results from a 12-week open-label study in patients treated with LCIG and its open-label extension study. AOLE, ongoing, open-label extension study in patients who participated in AOLS; AOLS, 12-week, open-label, single-arm study of LCIG in Asian patients; LCIG, levodopa-carbidopa intestinal gel; levodopa-carbidopa immediate-release, immediate-release levodopa-carbidopa; OLA, ongoing open-label phase 3 extended-access study in patients who completed participation in OLE or OLS; OLE, 52-week open-label extension study in patients who previously completed a 12-week double-blind, double-dummy study in which patients continued to receive LCIG or switched from oral LC-IR to LCIG; OLS, 54-week open-label study of LCIG; Pb3, 60-week, single-arm, open-label, 2-part, phase 3b study; SD, standard deviation. *study allowed some form of concomitant anti-Parkinson's disease medication.

These studies were conducted in accord with the Good Clinical Practice guidelines as defined by the International Council on Harmonisation, the Declaration of Helsinki, and all applicable federal and local regulations, including the European Union Clinical Trials Directive. Study protocols and informed consent documents were approved by independent ethics committees and/or institutional review boards.

2.2. Patients

Eligible patients were adults aged 30 years or older who had levodopa-responsive advanced PD who met United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria and whose daily "Off" time was uncontrolled by available PD medical therapy. Patients enrolled in OLS, P3b, and AOLS were required to have ≥3 h of "Off" time per day. In the initial studies (prior to enrolling in the OLE, OLA, or AOLE extension studies), patients were required to have ≥3 h of "Off" time. Patients were excluded if they had clinically significant issues (medical, laboratory, psychiatric, or surgical) at baseline that the investigator determined could interfere with participation in the study or if patients had significant cognitive impairment or dementia defined as Mini-Mental State Examination total score < 24 at screening visit 1.

2.3. Treatment

2.3.1. LCIG dosing

LCIG is supplied as a homogenous suspension of 20 mg/mL levodopa and 5 mg/mL carbidopa in an aqueous sodium carboxymethylcellulose gel. All patients received LCIG daytime therapy for approximately 16 h/day. OLS, P3b, and AOLS starting LCIG dose was based on each patient's oral levodopa dose before start of LCIG. OLE baseline LCIG dose was based on each patient's optimized oral levodopa dose prior to the 12-week double-blind study and re-titrated as needed before initiation of OLE. Initial LCIG dose in OLA was based on each patient's dose at the end of OLE or OLS. AOLS patients continued into AOLE part 1 at their current LCIG dose. The total daily infusion dose included the individually adjusted morning dose, continuous dose, and extra doses.

2.3.2. Adjunctive therapies

Use of oral levodopa-carbidopa immediate- or controlled-release formulations was permitted when the pump was turned off at night or for rescue therapy. Adjunctive PD therapies (e.g. dopamine agonists, catechol-O-methyltransferase inhibitors, or monoamine oxidase B inhibitors) could be tapered off after LCIG initiation in OLE; were only allowed after week 4 in OLS; were withheld in OLA unless deemed medically appropriate by the investigator; were required to be discontinued prior to LCIG initiation in P3b; and were required to be tapered and/or discontinued in AOLS, which continued into AOLE. However, in AOLE, physicians were allowed to add back concomitant PD medications if these were deemed medically necessary.

2.4. Assessments

2.4.1. Efficacy assessments

In all studies, efficacy was assessed using the Parkinson's Disease Diary (PD Diary), UPDRS, and PDQ-39. Efficacy outcomes included mean (SD) change from baseline (before study treatment) to last visit in "Off" time; "On" time without troublesome dyskinesia; "On" time with troublesome dyskinesia; mean UPDRS scores for part II (activities of daily living), part III (motor examination), and part IV (complications of therapy including dyskinesia); and PDQ-39 summary index score (quality of life). In OLA, both mean (SD) change from baseline before initial LCIG treatment and mean (SD) change from OLA baseline were determined. UPDRS was completed during the "On" state (~2 to 4 h after morning LCIG dose).

2.4.2. Safety assessments

Incidence of treatment-emergent adverse events (AEs), severity, and potential relationship with treatment were recorded from the first day of LCIG infusion to 30 days after PEG-J removal for patients who did not continue in an extension study or commercial LCIG, or until the first treatment dose in the extension study. The Medical Dictionary for Regulatory Activities (MedDRA) preferred term was used to code AEs.

2.5. Statistical analysis

Efficacy analysis included all patients who received LCIG and had a baseline and ≥1 post-baseline efficacy or quality-of-life assessment. Safety analysis included all patients who received LCIG in OLE; all patients who had nasojejunal (NJ) tube placement in OLS; all patients who had ≥1 LCIG dose in OLA; all patients who had PEG-J placement in P3b; all patients who had NJ placement in AOLS; and all patients who received ≥1 LCIG infusion in AOLE. In this post hoc analysis, patients were stratified into 2 groups: those who were on stable LCIG daytime monotherapy (with or without nighttime oral levodopa-carbidopa) and those who were on stable polytherapy (LCIG with ≥1 or more adjunctive anti-PD therapy). Descriptive statistics are presented for all data; because of the post hoc, non-randomized nature of the 2 groups, more advanced statistical comparisons were not performed. Because of the variability in study design (including eligibility criteria, duration of therapy, and use of adjunctive therapy), pooling the data for comparison was not appropriate.

3. Results

3.1. Patient baseline demographics

Demographics and baseline characteristics are summarized by therapy status in Table 1. In OLE, 30 patients were on stable LCIG daytime monotherapy (15 patients who received LCIG in the double-blind study [LCIG/LCIG] and 15 patients who received oral levodopa in the double-blind study [Oral/LCIG]) and 32 patients were on stable LCIG polytherapy (18 patients in the LCIG/LCIG group and 14 patients in the Oral/LCIG group). In OLS, of the 324 patients who had PEG-J placement, 248 (76%) were on stable LCIG daytime monotherapy (90/248 [36%] received LCIG only with no nighttime oral levodopa), and 76 (24%) were on stable LCIG polytherapy. A total of 262 patients from OLE and OLS continued LCIG treatment in OLA (164 [63%] on stable LCIG daytime monotherapy and 98 [37%] on stable LCIG polytherapy). Thirty-one of 39 patients in P3b and 29 of 31 patients in AOLS were on stable LCIG daytime monotherapy. In AOLE, 16 patients (53%) continued stable LCIG daytime monotherapy and 14 patients (47%) were on stable LCIG polytherapy. Patient distribution by age, sex, and PD duration were similar between monotherapy and polytherapy groups in OLE, OLS, OLA, P3b, and AOLE. Across all studies, the majority of patients were male, with the exception of AOLS; the average age was between 59 and 78 years; and the average PD duration was between 9.5 and 16 years.

A variety of concomitant anti-PD medications were used across studies. The most commonly used concomitant medications overall in each study were dopamine agonist in OLE; amantadine, pramipexole, ropinirole, and entacapone in OLS; amantadine, pramipexole, ropinirole, entacapone, and rasagiline in OLA; entacapone in P3b; entacapone, amantadine, ropinirole, zonisamide, rotigotine, and benserazide/levodopa in AOLS; and rotigotine, amantadine, pramipexole, ropinirole, trihexyphenidyl, cabergoline, istradefylline, and selegiline in AOLE.

3.2. Total daily levodopa dose

With LCIG treatment, the average total daily levodopa dose increased to a similar degree in all studies and groups (Table 2). Across the studies, the average increase in daily levodopa dose ranged from −105.8 mg to 680.1 mg. The largest increase in average daily levodopa dose occurred in the 60-week P3b study. Details regarding doses of non–

Table 1
Baseline demographics by therapy status (safety population).

Parameter	Mean (SD)[a]													
	OLE				OLS		OLA		P3b		AOLS		AOLE	
	LCIG/LCIG Mono (n = 15)	Oral/LCIG Mono (n = 15)	LCIG/LCIG Poly (n = 18)	Oral/LCIG Poly (n = 14)	LCIG Mono (n = 248)	LCIG Poly (n = 76)	LCIG Mono (n = 164)	LCIG Poly (n = 98)	LCIG Mono (n = 31)	LCIG Poly (n = 8)	LCIG Mono (n = 29)	LCIG Poly (n = 2)	LCIG Mono (n = 16)	LCIG Poly (n = 14)
Age, years	64.2 (9.1)	66.3 (5.7)	62.5 (9.3)	62.6 (7.3)	64.8 (8.9)	62.6 (9.1)	64.5 (8.5)	63.5 (9.5)	64.7 (10.0)	62.6 (11.5)	60.5 (9.8)	78 (7.1)	61.6 (7.8)	59.1 (11.5)
PD duration, years	10.7 (4.9)	12.7 (6.3)	9.5 (4.9)	10.0 (4.8)	12.1 (5.2)	13.3 (6.4)	11.3 (5.2)	11.6 (5.6)	12.3 (5.2)	8.5 (5.2)	12.1 (5.1)	16 (2.3)	10.6 (4.0)	13.9 (5.5)
Sex, n (%)														
Male	10 (66.7)	10 (66.7)	13 (72.2)	11 (78.6)	139 (56.0)	46 (60.5)	101 (61.6)	61 (62.2)	18 (58.1)	5 (62.5)	12 (41.4)	0	7 (43.8)	6 (42.9)
Female	5 (33.3)	5 (33.3)	5 (27.8)	3 (21.4)	109 (44.0)	30 (39.5)	63 (38.4)	37 (37.8)	13 (41.9)	3 (37.5)	17 (58.6)	2 (100)	9 (56.3)	8 (57.1)

AOLE ongoing, open-label extension study in patients who participated in AOLS, *AOLS* 12-week, open-label, single-arm study of LCIG in Asian patients, *LCIG* levodopa-carbidopa intestinal gel, *Mono* monotherapy, *OLA* ongoing open-label phase 3 extended-access study in patients who completed participation in OLE or OLS, *OLE* 52-week open-label extension study in patients who previously completed a 12-week double-blind, double-dummy study in which patients continued to receive LCIG or switched from oral levodopa-carbidopa immediate-release to LCIG, *OLS* 54-week open-label study of LCIG, *Pb3* 60-week, single-arm, open-label, 2-part, phase 3b study, *PD* Parkinson's disease, *Poly* polytherapy, *SD* standard deviation.

[a] Data are presented as mean (SD), unless otherwise noted.

Table 2
Parkinson's disease medication profile by study.

OLE (52 weeks)	Mean (SD) daily levodopa dose, mg		
	Baseline[a] (n = 62)	Post titration[b] (n = 62)	Change
Patient group[c]			
LCIG/LCIG monotherapy (n = 15)	950.0 (316.8)	1331.7 (346.9)	381.7
Oral/LCIG monotherapy (n = 15)	1293.3 (571.3)	1706.5 (656.7)	413.2
LCIG/LCIG polytherapy (n = 18)	1091.7 (427.1)	1329.1 (530.9)	237.4
Oral/LCIG polytherapy (n = 14)	1035.7 (317.7)	1594.8 (689.5)	559.1
OLS (54 weeks)	Baseline[d] (n = 322)	Post titration (n = 324)	Change
Total levodopa dose, mg			
LCIG monotherapy (n = 248)	1084.8 (578.3)	1523.8 (530.6)	439
LCIG polytherapy (n = 76)	1114.7 (594.7)	1510.4 (589.8)	395.7
OLA (average treatment 4.1 years)	Initial titration[e] (n = 71)	Endpoint (n = 71)	Change
Total levodopa dose, mg			
LCIG monotherapy (n = 40)	1578.6 (647.1)	1763.4 (617.6)	184.8
LCIG polytherapy (n = 31)	1599.4 (666.7)	1808.2 (937.1)	208.8
P3b (60 weeks)	Screening[f] (n = 39)	Final[g] (n = 37)	Change
Total levodopa dose, mg			
LCIG monotherapy (n = 31)	1028.8 (647.9)	1708.9 (705.9)	680.1
LCIG polytherapy (n = 8)	1184.4 (860.3)	1789.2 (729.2)	604.8
AOLS (12 weeks)	Last titration day[h] (n = 30)	Last visit (n = 30)	Change
Total levodopa dose, mg			
LCIG monotherapy (n = 28)	1139.9 (597.15)	1217.9 (493.3)	78
LCIG polytherapy (n = 2)	789.4 (267.88)	1363.3 (387.5)	573.9
AOLE (52 weeks)	Initial study dose[i] (n = 30)	Last visit (n = 30)	Change
Total levodopa dose, mg			
LCIG monotherapy (n = 16)	1287.4 (713.3)	1181.6 (569.9)	−105.8
LCIG polytherapy (n = 14)	984.3 (363.3)	1023.0 (342.2)	38.7

AOLE ongoing, open-label extension study in patients who participated in AOLS, *AOLS* 12-week, open-label, single-arm study of LCIG in Asian patients, *LCIG* levodopa-carbidopa intestinal gel, *NJ* nasojejunal, *OLA* ongoing open-label phase 3 extended-access study in patients who completed participation in OLE or OLS, *OLE* 52-week open-label extension study in patients who previously completed a 12-week double-blind, double-dummy study in which patients continued to receive LCIG or switched from oral levodopa-carbidopa immediate-release to LCIG, *OLS* 54-week open-label study of LCIG; *Pb3* 60-week, single-arm, open-label, 2-part, phase 3b study, *SD* standard deviation.

[a] Oral levodopa prior to 12-week double-blind study.

[b] Levodopa dose was captured after titration was complete. The final levodopa dose at the end of the study was not captured.

[c] In the initial 12-week double-blind study, patients either received LCIG (defined as LCIG/LCIG) or oral levodopa-carbidopa (Oral/LCIG); both groups received LCIG in the open-label extension study. The number of patients in each group reflects the monotherapy/polytherapy status during the extension study.

[d] Oral levodopa prior to NJ placement. Two patients' baseline Parkinson's disease medications were not recorded because of a data-capturing issue.

[e] Indicates dose following titration in first study treated with LCIG. Dosing data were collected in 71 of 262 patients.

[f] Oral levodopa taken on the day before the first LCIG treatment.

[g] Only patient dosing diaries with ≥12.8 h of pump operation after LCIG dose optimization were included in the analysis. LCIG monotherapy n = 30, LCIG polytherapy n = 7.

[h] Oral levodopa taken on the day before LCIG initiation.

[i] AOLS patients continued into AOLE Part 1 at their current LCIG dose.

levodopa-based PD therapies were not consistently available among the various studies to allow comparison analysis of levodopa-equivalent daily dosing between groups.

3.3. Efficacy

On average, regardless of study duration or patient population, both LCIG monotherapy and polytherapy groups experienced a decrease in "Off" time of ≥4 h per day and an increase in "On" time without troublesome dyskinesia of ≥4 h per day (Fig. 2). The average reduction in "Off" time for LCIG daytime monotherapy across all studies was 4.6 h per day, compared with polytherapy, which was 4.1 h per day. The average increase in "On" time without troublesome dyskinesia for LCIG daytime monotherapy vs. polytherapy was 4.6 and 4.1 h per day, respectively. The average decrease in "On" time with troublesome dyskinesia for LCIG daytime monotherapy was 0.3 h per day, compared with polytherapy, which was 0.2 h per day.

Changes from baseline in Unified PD Rating Scale (UPDRS) part II (self-evaluation of activities of daily living) and part III (clinician-scored motor evaluation) scores were similar for patients on LCIG daytime monotherapy compared with polytherapy (Table 3). In OLE, OLS, P3b, and AOLS, UPDRS parts II and III scores decreased from baseline in both LCIG monotherapy and polytherapy treatment groups. However, from before initial LCIG in OLE/OLS to the last visit in OLA (average duration of 4.1 years), mean ± standard deviation (SD) change in UPDRS part II was 1.8 ± 7.7 and 4.7 ± 7.6 points for LCIG monotherapy and polytherapy, respectively; part III scores increased similarly in both groups. Similarly, in AOLE, mean change from baseline in UPDRS Part II and III scores was minimal in the LCIG monotherapy group and scores worsened in the polytherapy group, respectively.

Overall, the average improvements from baseline in quality of life were similar in LCIG daytime monotherapy and polytherapy groups in all studies, with the exception of OLA (Table 3). The 39-item Parkinson's Disease Questionnaire (PDQ-39) summary index scores were reduced by ≥5 points, regardless of patient population or study duration from baseline to last visit in OLE, OLS, P3b, AOLS, and AOLE. The only study that did not exhibit improvements in quality of life was OLA, with average treatment duration of 4.1 years. However, from initial LCIG in OLE/OLS to the last visit in OLA, mean (SD) change in the PDQ-39 summary index score was −3.2 (17.9) points in the LCIG monotherapy group compared with 5.4 (13.6) points in the polytherapy group. Therefore, in the LCIG monotherapy group, PDQ-39 scores remained improved but returned to near baseline levels (prior to initial LCIG therapy).

3.4. Safety

Because the procedure/device is the same for both treatment regimens, this report focused on AEs that were not related to the procedure/device. Procedure-/device-related AEs have been reported previously across studies [22]. In all studies, AEs not related to the procedure or device were similar for patients on LCIG daytime monotherapy and polytherapy (Table 4). The most common non-procedure/device-related AEs across all studies were falls, nausea, and decreased vitamin B_6 levels. Most AEs were mild to moderate in severity in both monotherapy and polytherapy groups in all studies. The exception to this pattern was in OLA, in which approximately 50% of patients in both treatment groups reported severe AEs (LCIG monotherapy: 80 patients, 49%; polytherapy: 49 patients, 50%). Similarly, in all studies, most AEs were not serious, except in OLA, where just over half of patients in both groups reported serious AEs (51.2% and 57.1% in the LCIG monotherapy and polytherapy groups, respectively). Over an average treatment period of 4.1 years, the percentage of patients in OLA who reported a severe or serious AE was numerically lower in the LCIG monotherapy group compared with the polytherapy group. In OLA, serious AEs occurring in ≥3% of LCIG monotherapy or polytherapy patients, respectively, were anemia (0.6% vs. 4.1%), abdominal pain (1.2% vs. 3.1%), complication of device insertion (3.0% vs. 9.2%), death (1.8% vs. 3.1%), pneumonia (4.9% vs. 9.2%), post-operative wound infection (3.7% vs. 2.0%), fall (3.7% vs. 6.1%), weight decreased (1.2% vs. 6.1%), PD (1.8% vs. 4.1%), mental status changes (0 vs. 3.1%), pleural effusion (0.6% vs. 3.1%), and pneumonia aspiration (1.8% vs. 5.1%). In most studies, there were few or no fatal AEs. Though, in the long-term OLA, there were numerically more fatal AEs in the LCIG monotherapy group compared with the polytherapy group, ≥99% of fatal AEs were deemed unrelated to investigational therapy. A detailed description of deaths in OLA were previously reported [17].

4. Discussion

This post hoc analysis of data from five phase 3 and one phase 3b study evaluated the long-term efficacy and safety of stable LCIG daytime monotherapy (with and without nighttime oral levodopa-carbidopa) compared with stable polytherapy (LCIG with ≥1 adjunctive anti-PD therapy) in patients with advanced PD. Overall, LCIG daytime monotherapy and LCIG polytherapy demonstrated similar efficacy and safety profiles in patients with advanced PD, regardless of treatment duration or population. As PD progresses, the number of anti-PD medications and frequency of dosing tend to increase [11]. Complicated treatment regimens with multiple medications can lead to non-adherence and poor symptom management [10,23–25]. The data presented here suggest that LCIG daytime monotherapy can provide a more simplified treatment option with efficacy similar to that of polytherapy in appropriate patients.

Various clinical studies have evaluated the use of LCIG in patients with advanced PD, reporting LCIG daytime monotherapy (with or without nighttime oral carbidopa/levodopa) use in 61% to 100% of patients [16,20,26–34]. However, the safety and efficacy of daytime LCIG monotherapy compared with polytherapy were evaluated in only some of the studies [20,27,29,34]. Overall, results from these studies demonstrated that LCIG daytime monotherapy is efficacious (i.e. significantly improves PD symptoms, activities of daily living, and quality of life) and is well-tolerated with a safety profile consistent with polytherapy.

Due to the progressive nature of PD, it is important to take into consideration the length of individual trials when making comparisons across studies. The study by Puente et al. [29], an assessment of LCIG monotherapy in patients with advanced PD, is of similar length to the 60-week P3b we report on herein. Patients in both studies experienced similar improvements in activities of daily living, motor examination, and complications of therapy, including dyskinesia. However, compared with the current study, Puente et al. reported greater mean quality-of-life benefits associated with increases in daily "On" time and improvements in overall motor symptom control with LCIG monotherapy. A study by Caceres-Redondo et al. [26], investigating the impact of LCIG monotherapy treatment on motor and cognitive outcomes in patients with advanced PD, is of similar duration to the OLA, with an average treatment time of 4.1 years. Not surprisingly, both studies reported similar moderate increases in UPDRS part II scores, presumably due to slow motor worsening captured with longer duration observation. However, Caceres-Redondo et al. reported improvement in quality of life, unlike the moderate increases in PDQ-39 symptom index scores reported in OLA.

Patients in each study reported herein, regardless of monotherapy status, experienced similar increases in total daily levodopa dose over the course of the study. These results are similar to those of other studies that documented increased levodopa dosing with continuous administration of LCIG [2,17,26,31,35]. Continuous administration of LCIG may allow for higher doses of levodopa while avoiding the pulsatile stimulation that results in dyskinesia and reduced tolerability. Though AEs were reported by the majority of patients, irrespective of treatment group, most were mild or moderate in severity and related to procedure/device complications. In OLA, in general, a smaller proportion of patients in the LCIG daytime monotherapy group reported serious AEs compared with the polytherapy group, and the majority of serious AEs reported were procedure- or device-related. Overall, non-procedure- or device-related AEs reported in the studies described herein were associated with the

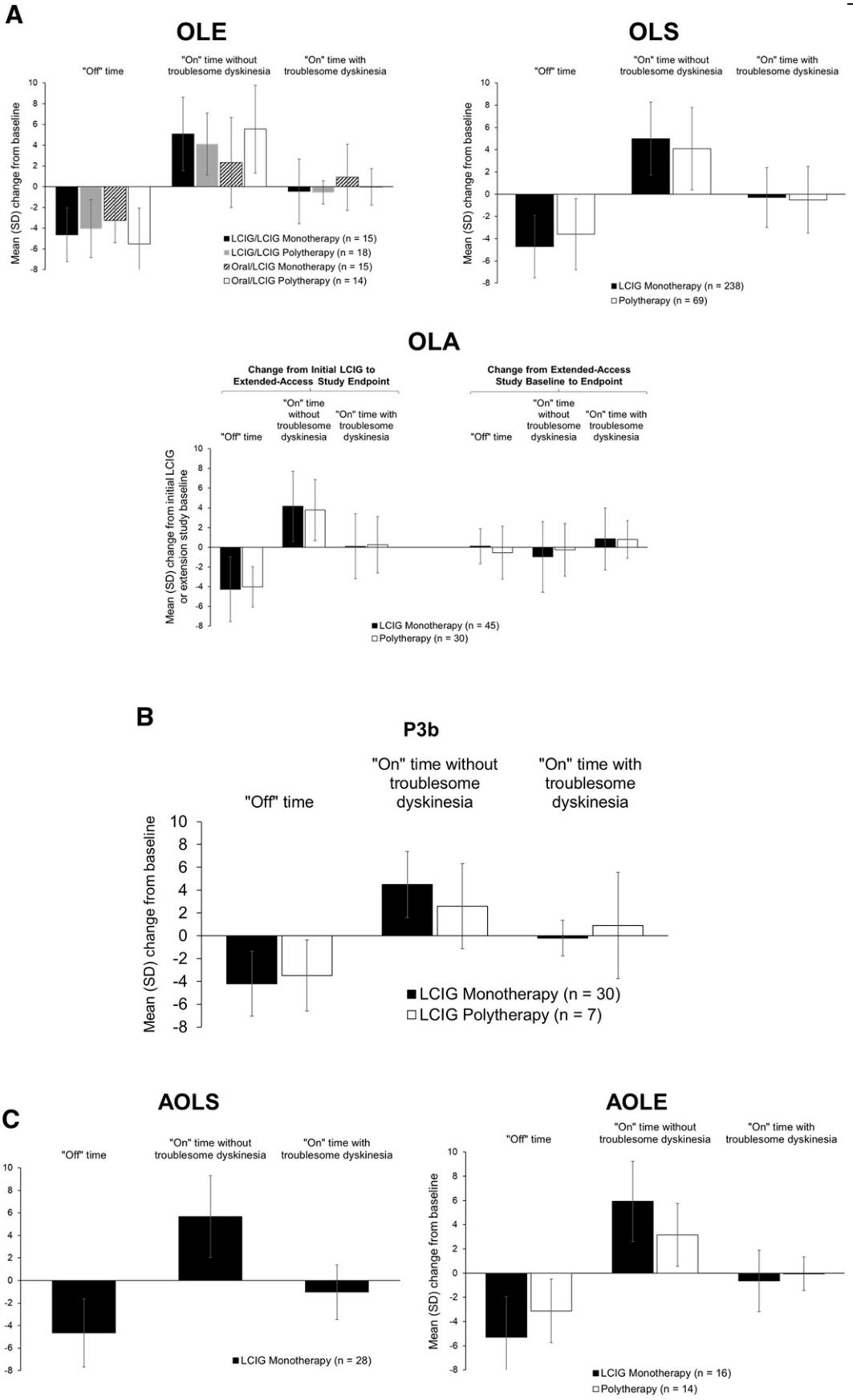

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Table 3
Mean (SD) change from baseline in UPDRS assessments and PDQ-39 Summary Index scores.

OLE (52 weeks)[a]	UPDRS scores			PDQ-39
	Part II	Part III	Part IV	Summary index score
LCIG/LCIG monotherapy (n = 14)	−1.79 (3.93)	0.91 (7.04)	−3.43 (2.56)	−12.77 (12.76)
Oral/LCIG monotherapy (n = 12)	0.33 (6.23)	−5.13 (10.51)	−0.92 (3.32)	−8.07 (12.65)
LCIG/LCIG polytherapy (n = 17)	−2.24 (5.61)	−1.88 (4.30)	−3.59 (2.09)	−5.89 (16.61)
Oral/LCIG polytherapy (n = 12)	−1.68 (7.27)	−3.66 (12.95)	−3.25 (3.31)	−13.81 (14.14)
OLS (54 weeks)[b]				
LCIG monotherapy[j]	−4.7 (6.43)	−8.2 (13.21)	−3.6 (3.49)	−7.01 (14.33)
LCIG polytherapy (n = 66)	−3.6 (6.52)	−4.5 (12.85)	−3.3 (3.43)	−6.25 (13.19)
OLA (average treatment 4.1 years)[c]				
Change from initial LCIG to study endpoint				
LCIG monotherapy (n = 45)	1.78 (7.72)	4.71 (14.32)	−2.84 (3.52)	7.53 (12.64)[g]
LCIG polytherapy (n = 34)	4.74 (7.59)	4.45 (15.36)	−1.50 (3.85)	10 (14.12)[h]
Change from study baseline to endpoint				
LCIG monotherapy (n = 47)	5.47 (5.58)	9.82 (9.37)	0.53 (2.78)	−3.23 (17.88)[i]
LCIG polytherapy (n = 35)	7.00 (5.27)	8.52 (12.17)	1.09 (2.98)	5.4 (13.56)
P3b (60 weeks)[d]				
LCIG monotherapy (n = 29)	−4.4 (5.37)	−3.9 (10.38)	−3.4 (3.45)	−7.5 (15.24)
LCIG polytherapy (n = 7)	−4.4 (5.35)	−5.1 (4.81)	−1.4 (2.64)	−7.3 (15.52)
AOLS (12 weeks)[e]				
LCIG monotherapy (n = 28)	−2.0 (5.88)	−2.8 (7.57)	−3.5 (3.20)	−12.9 (11.04)
LCIG polytherapy (n = 2)	1.5 (4.95)	7.0 (19.80)	1.0 (2.38)	0.8 (13.79)
AOLE (52 weeks)[f]				
LCIG monotherapy (n = 16)	−0.5 (6.91)	−0.8 (11.50)	−4.2 (3.41)	−10.1 (14.05)
LCIG polytherapy (n = 14)	2.6 (3.96)	3.9 (9.76)	−1.3 (3.02)	−6.6 (7.98)

AOLE ongoing, open-label extension study in patients who participated in AOLS, *AOLS* 12-week, open-label, single-arm study of LCIG in Asian patients, *LCIG* levodopa-carbidopa intestinal gel, *OLA* ongoing open-label phase 3 extended-access study in patients who completed participation in OLE or OLS, *OLE* 52-week open-label extension study in patients who previously completed a 12-week double-blind, double-dummy study in which patients continued to receive LCIG or switched from oral immediate-release levodopa-carbidopa to LCIG, *OLS* 54-week open-label study of LCIG, *Pb3* 60-week, single-arm, open-label, 2-part, phase 3b study, *PDQ-39* 39-item Parkinson's Disease Questionnaire, *SD* standard deviation, *UPDRS* Unified Parkinson's Disease Rating Scale.

[a] Patients who began LCIG or oral levodopa-carbidopa treatment in a 12-week study and then continued/began LCIG treatment in a 52-week open-label extension study.

[b] Results from a 54-week open-label study in patients treated with LCIG.

[c] Results from an extended-access-to-treatment study. In the extended-access study, the change from initial LCIG treatment (in either the 12-week double-blind study or the 54-week open-label study) to the extended-access endpoint (average LCIG treatment of 4 years) or the change from the extended-access study baseline to endpoint (average LCIG treatment of 3 years) was assessed.

[d] Results from a 60-week open-label study in patients treated with LCIG.

[e] Results from a 12-week open-label study in patients treated with LCIG.

[f] Results from an open-label extension study. LCIG = levodopa-carbidopa intestinal gel.

[g] n = 46.

[h] n = 35.

[i] n = 30.

[j] n = 222 (Part II), n = 220 (Part III), n = 221 (Part IV).

gastrointestinal tract (e.g. nausea and constipation) or long-term levodopa exposure (e.g. changes in homocysteine, B_6, and dyskinesia) and underlying PD in an elderly patient population (e.g. fall and dyskinesia), consistent with the LCIG safety profile established in the literature [20,26,29,32–34].

This post hoc analysis is limited by the fact that each trial assessed had slightly different study designs (e.g. outpatient vs. inpatient titration, use of adjunctive therapy, patient selection, duration of therapy). In addition, the efficacy and safety of LCIG daytime monotherapy compared with polytherapy was not prospectively assessed in these studies, nor were they planned as an a priori head-to-head comparison. As such, we did not perform advanced statistical comparisons, nor was pooling the data an option. Further, individual patient disease characteristics may have limited the ability of a patient to be treated with LCIG monotherapy, thus limiting the conclusions that can be drawn from the comparison between LCIG monotherapy and polytherapy. Nevertheless, the studies reported herein demonstrate that LCIG monotherapy may provide a more simplified long-term treatment option with potentially similar efficacy to polytherapy for appropriate patients in the advanced PD setting. Future prospective studies assessing the safety and efficacy of LCIG monotherapy vs. polytherapy are warranted.

Authors' roles

All authors agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the publication.

← **Fig. 2.** Mean (SD) change from baseline in "Off" and "On" times as assessed by a Parkinson's disease diary. (A) Patients who began LCIG or oral levodopa-carbidopa treatment in a 12-week study and then continued/began LCIG treatment in a 52-week open-label extension study; results from a 54-week open-label study in patients treated with LCIG; and results from an extended-access-to-treatment study. In the extended-access study, the change from initial LCIG treatment (in either the 12-week double-blind study or the 54-week open-label study) to the extended-access endpoint (average LCIG treatment of 4 years) or the change from the extended-access study baseline to endpoint (average LCIG treatment of 3 years) was assessed. (B) Results from a 60-week open-label study in patients treated with LCIG. (C) Results from a 12-week open-label study in patients treated with LCIG and its open-label extension study. AOLE, ongoing, open-label extension study in patients who participated in AOLS; AOLS, 12-week, open-label, single-arm study of LCIG in Asian patients; LCIG, levodopa-carbidopa intestinal gel; OLA, ongoing open-label phase 3 extended-access study in patients who completed participation in OLE or OLS; OLE, 52-week open-label extension study in patients who previously completed a 12-week double-blind, double-dummy study in which patients continued to receive LCIG or switched from oral levodopa-carbidopa immediate-release to LCIG; OLS, 54-week open-label study of LCIG; Pb3, 60-week, single-arm, open-label, 2-part, phase 3b study; SD, standard deviation.

Table 4
Adverse events.

	Patients, n (%)	
OLE (52 weeks)		
Preferred term[a]	LCIG/LCIG or oral/LCIG daytime monotherapy (N = 30)	LCIG/LCIG or oral/LCIG polytherapy (N = 32)
Any AE	27 (90.0)	32 (100)
Serious AEs	6 (20.0)	8 (25.0)
AEs leading to discontinuation	2 (6.7)	1 (3.1)
Fatal AEs	0	0
Non-procedure/device-related AEs (>15% of patients in any group)		
Fall	7 (23.3)	6 (18.8)
Vitamin B_6 decreased	6 (20.0)	7 (21.9)
Nausea	5 (16.7)	4 (12.5)
Freezing phenomenon	5 (16.7)	2 (6.3)
Constipation	3 (10.0)	6 (18.8)
Urinary tract infection	3 (10.0)	6 (18.8)
Parkinson's disease[b]	2 (6.7)	6 (18.8)
Blood homocysteine increased	2 (6.7)	5 (15.6)
Insomnia	1 (3.3)	8 (25.0)
Arthralgia	1 (3.3)	6 (18.8)
Orthostatic hypotension	1 (3.3)	5 (15.6)
Seborrhoeic keratosis	1 (3.3)	7 (21.9)
Back pain	1 (3.3)	5 (15.6)
Depression	0	5 (15.6)

	Patients, n (%)	
OLS (54 weeks)		
Preferred term[a]	Daytime monotherapy (N = 248)	Polytherapy (N = 76)
Any AE	225 (90.7)	73 (96.1)
Serious AEs	80 (32.3)	25 (32.9)
AEs leading to discontinuation	19 (7.7)	3 (3.9)
Fatal AEs	7 (2.8)[c]	0
Non-procedure/device-related AEs (>15% of patients in any group)		
Nausea	39 (15.7)	15 (19.7)
Fall	39 (15.7)	10 (13.2)
Insomnia	34 (13.7)	10 (13.2)
Constipation	32 (12.9)	15 (19.7)
Dyskinesia	16 (6.5)	15 (19.7)

	Patients, n (%)	
OLA (average treatment 4.1 years)		
Preferred term[a]	Daytime monotherapy (N = 164)	Polytherapy (N = 98)
Any AE	148 (90.2)	98 (100)
Serious AEs	84 (51.2)	56 (57.1)
AEs leading to discontinuation	37 (22.6)	25 (25.5)
Fatal AEs	27 (16.5)[d]	11 (11.2)[e]
Non-procedure/device-related AEs (>15% of patients in any group)		
Vitamin B_6 decreased	37 (22.6)	21 (21.4)
Fall	33 (20.1)	22 (22.4)
Blood homocysteine increased	28 (17.1)	20 (20.4)
Urinary tract infection	25 (15.2)	25 (25.5)
Weight decreased	15 (9.1)	21 (21.4)
Depression	15 (9.1)	15 (15.3)
Insomnia	13 (7.9)	16 (16.3)
Parkinson's disease[b]	12 (7.3)	21 (21.4)
Nausea	12 (7.3)	20 (20.4)
Dyskinesia	11 (6.7)	16 (16.3)

	Patients, n (%)	
P3b (60 weeks)		
Preferred term	Daytime monotherapy (N = 31)	Polytherapy (N = 8)
Any AE	30 (96.8)	7 (87.5)
Serious AEs	3 (37.5)	5 (16.1)
AEs leading to discontinuation	1 (12.5)	4 (12.9)
Fatal AEs	1 (3.2)[f]	0
Non-procedure/device-related AEs (>15% of patients in any group)		
Anxiety	7 (22.6)	1 (12.5)
Fall	7 (22.6)	0
Weight decreased	5 (16.1)	2 (25.0)
Urinary tract infection	4 (12.9)	2 (25.0)

Table 4 (*continued*)

	Patients, n (%)	
AOLS (12 weeks)		
Preferred term	Daytime monotherapy (N = 29)	Polytherapy (N = 2)
Any AE	29 (100)	2 (100)
Serious AEs	2 (6.9)	2 (100)
AEs leading to discontinuation	0	1 (50.0)
Fatal AEs	0	1 (50.0)[f]
Non-procedure/device-related AEs (>15% of patients in any group)		
Constipation	7 (24.1)	0
Diarrhea	5 (17.2)	1 (50)
Fall	5 (17.2)	1 (50)
Nasopharyngitis	6 (20.7)	0
Blood homocysteine increased	5 (17.2)	0
Dyskinesia	5 (17.2)	0

	Patients, n (%)	
AOLE (52 weeks)		
Preferred term[a]	Daytime monotherapy (N = 16)	Polytherapy (N = 14)
Any AE	16 (100)	14 (100)
Serious AEs	3 (18.8)	3 (21.4)
AEs leading to discontinuation	0	1 (7.1)
Fatal AEs	0	0
Non-procedure/device-related AEs (>15% of patients in any group)		
Nasopharyngitis	6 (37.5)	5 (35.7)
Blood homocysteine increased	5 (31.3)	0 (0)
Constipation	5 (31.3)	4 (28.6)
Diarrhea	4 (25.0)	3 (21.4)
Contusion	0 (0)	3 (21.4)
Epistaxis	3 (18.8)	0 (0)
Fall	3 (18.8)	2 (14.3)
Vomiting	3 (18.8)	1 (7.1)

AE adverse event, *AOLE* ongoing, open-label extension study in patients who participated in AOLS, *AOLS* 12-week, open-label, single-arm study of LCIG in Asian patients, *LCIG* levodopa-carbidopa intestinal gel, *OLA* ongoing open-label phase 3 extended-access study in patients who completed participation in OLE or OLS, *OLE* 52-week open-label extension study in patients who previously completed a 12-week double-blind, double-dummy study in which patients continued to receive LCIG or switched from oral levodopa-carbidopa immediate-release to LCIG, *OLS* 54-week open-label study of LCIG, *Pb3* 60-week, single-arm, open-label, 2-part, phase 3b study, *SD* standard deviation.

[a] A single event could be coded to >1 preferred term.
[b] Refers to a reemergence of Parkinson's disease symptoms.
[c] All fatal AEs were deemed unrelated to study treatment.
[d] One (0.6%) fatal AE of intestinal dilation was deemed related to study treatment.
[e] One (1.0%) fatal AE of cardiac arrest was deemed related to study treatment.
[f] Fatal AE had no reasonable possibility of being related to study treatment.

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Cindy Zadikoff participated in the original research conception and design, data acquisition, data interpretation, review and critique of the manuscript throughout the editorial process, and approval of the final manuscript draft submitted for publication.

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Data availability

AbbVie, Inc., is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g. 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 researcher who engages 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.

References

[1] C. Lundqvist, Continuous levodopa for advanced Parkinson's disease, Neuropsychiatr. Dis. Treat. 3 (3) (2007) 335–348.
[2] A. Antonini, K.R. Chaudhuri, P. Martinez-Martin, P. Odin, Oral and infusion levodopa-based strategies for managing motor complications in patients with Parkinson's disease, CNS drugs. 24 (2) (2010) 119–129.
[3] R.A. Hauser, Levodopa: past, present, and future, Eur. Neurol. 62 (1) (2009) 1–8.
[4] O. Hornykiewicz, A brief history of levodopa, J. Neurol. 257 (Suppl. 2) (2010) S249–S252.
[5] J.E. Ahlskog, M.D. Muenter, Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature, Movement disorders: official journal of the Movement Disorder Society. 16 (3) (2001) 448–458.
[6] J.A. Obeso, C.W. Olanow, J.G. Nutt, Levodopa motor complications in Parkinson's disease, Trends Neurosci. 23 (10 Suppl) (2000) S2–S7.
[7] S. Chapuis, L. Ouchchane, O. Metz, L. Gerbaud, F. Durif, Impact of the motor complications of Parkinson's disease on the quality of life, Movement disorders: official journal of the Movement Disorder Society. 20 (2) (2005) 224–230.
[8] C.W. Olanow, K. Kieburtz, P. Odin, A.J. Espay, D.G. Standaert, H.H. Fernandez, A. Vanagunas, A.A. Othman, K.L. Widnell, W.Z. Robieson, Y. Pritchett, K. Chatamra, J. Benesh, R.A. Lenz, A. Antonini, L.H.S. Group, Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study, The Lancet. Neurology. 13 (2) (2014) 141–149.
[9] R. Stowe, N. Ives, C.E. Clarke, K. Handley, A. Furmston, K. Deane, J.J. van Hilten, K. Wheatley, R. Gray, Meta-analysis of the comparative efficacy and safety of adjuvant treatment to levodopa in later Parkinson's disease, Movement disorders: official journal of the Movement Disorder Society. 26 (4) (2011) 587–598.
[10] J.E. Fleisher, M.B. Stern, Medication nonadherence in Parkinson's disease, Current neurology and neuroscience reports. 13 (10) (2013) 382.
[11] K.L. Davis, H.M. Edin, J.K. Allen, Prevalence and cost of medication nonadherence in Parkinson's disease: evidence from administrative claims data, Movement disorders: official journal of the Movement Disorder Society. 25 (4) (2010) 474–480.
[12] F. Stocchi, L. Vacca, S. Ruggieri, C.W. Olanow, Intermittent vs continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study, Arch. Neurol. 62 (6) (2005) 905–910.
[13] D. Nyholm, S.M. Aquilonius, Levodopa infusion therapy in Parkinson disease: state of the art in 2004, Clin. Neuropharmacol. 27 (5) (2004) 245–256.
[14] D. Nyholm, H. Askmark, C. Gomes-Trolin, T. Knutson, H. Lennernas, C. Nystrom, S.M. Aquilonius, Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets, Clin. Neuropharmacol. 26 (3) (2003) 156–163.
[15] C.W. Olanow, J.A. Obeso, F. Stocchi, Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications, The Lancet. Neurology. 5 (8) (2006) 677–687.
[16] J.T. Slevin, H.H. Fernandez, C. Zadikoff, C. Hall, S. Eaton, J. Dubow, K. Chatamra, J. Benesh, Long-term safety and maintenance of efficacy of levodopa-carbidopa intestinal gel: an open-label extension of the double-blind pivotal study in advanced Parkinson's disease patients, J. Park. Dis. 5 (1) (2015) 165–174.
[17] H.H. Fernandez, J.T. Boyd, V.S.C. Fung, M.F. Lew, R.L. Rodriguez, J.T. Slevin, D.G. Standaert, C. Zadikoff, A.D. Vanagunas, K. Chatamra, S. Eaton, M.F. Facheris, C. Hall, W.Z. Robieson, J. Benesh, A.J. Espay, Long-term safety and efficacy of levodopa-carbidopa intestinal gel in advanced Parkinson's disease, Movement disorders official journal of the Movement Disorder Society. 33 (6) (2018) 928–936.
[18] H.H. Fernandez, D.G. Standaert, R.A. Hauser, A.E. Lang, V.S. Fung, F. Klostermann, M.F. Lew, P. Odin, M. Steiger, E.Z. Yakupov, S. Chouinard, O. Suchowersky, J. Dubow, C.M. Hall, K. Chatamra, W.Z. Robieson, J.A. Benesh, A.J. Espay,

Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results, Movement disorders: official journal of the Movement Disorder Society. 30 (4) (2015) 500–509.
[19] D.G. Standaert, J.T. Boyd, P. Odin, W.Z. Robieson, J. Zamudio, K. Chatamra, Systematic evaluation of levodopa-carbidopa intestinal gel patient-responder characteristics, NPJ Parkinson's disease. 4 (2018) 4.
[20] M. Murata, M. Mihara, K. Hasegawa, B. Jeon, C.H. Tsai, N. Nishikawa, T. Oeda, M. Yokoyama, W.Z. Robieson, D. Ryman, S. Eaton, K. Chatamra, J. Benesh, Efficacy and safety of levodopa-carbidopa intestinal gel from a study in Japanese, Taiwanese, and Korean advanced Parkinson's disease patients, NPJ Parkinson's disease. 2 (2016) 16020.
[21] M. Murata, M. Mihara, K. Hasegawa, B. Jeon, C.H. Tsai, N. Nishikawa, T. Oeda, M. Yokoyama, W.Z. Robieson, K. Chatamra, M.F. Facheris, J. Benesh, Safety and efficacy of levodopa-carbidopa intestinal gel: results from an open-label extension study in Japanese, Korean and Taiwanese patients with advanced Parkinson's disease, Ther. Adv. Neurol. Disord. 11 (2018)(1756286418759315).
[22] A.E. Lang, R.L. Rodriguez, J.T. Boyd, S. Chouinard, C. Zadikoff, A.J. Espay, J.T. Slevin, H.H. Fernandez, M.F. Lew, D.A. Stein, P. Odin, V.S. Fung, F. Klostermann, A. Fasano, P.V. Draganov, N. Schmulewitz, W.Z. Robieson, S. Eaton, K. Chatamra, J.A. Benesh, J. Dubow, Integrated safety of levodopa-carbidopa intestinal gel from prospective clinical trials, Movement disorders: official journal of the Movement Disorder Society. 31 (4) (2016) 538–546.
[23] D.J. Daley, P.K. Myint, R.J. Gray, K.H. Deane, Systematic review on factors associated with medication non-adherence in Parkinson's disease, Parkinsonism Relat. Disord. 18 (10) (2012) 1053–1061.
[24] K.A. Grosset, I. Bone, D.G. Grosset, Suboptimal medication adherence in Parkinson's disease, Movement disorders: official journal of the Movement Disorder Society. 20 (11) (2005) 1502–1507.
[25] N. Malek, D.G. Grosset, Medication adherence in patients with Parkinson's disease, CNS drugs. 29 (1) (2015) 47–53.
[26] M.T. Caceres-Redondo, F. Carrillo, M.J. Lama, I. Huertas-Fernandez, L. Vargas-Gonzalez, M. Carballo, P. Mir, Long-term levodopa/carbidopa intestinal gel in advanced Parkinson's disease, J. Neurol. 261 (3) (2014) 561–569.
[27] J.T. Boyd, C. Zadikoff, J.A. Benesh, J. Zamudio, W.Z. Robieson, P. Kukreja, Safety and efficacy of levodopa-carbidopa monotherapy in patients with advanced Parkinson's disease, Oral presentation at: XXIII World Congress of Neurology, Kyoto, Japan, September 16-21 (2017).
[28] D. Nyholm, K. Klangemo, A. Johansson, Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson's disease, Eur. J. Neurol. 19 (8) (2012) 1079–1085.
[29] V. Puente, O. De Fabregues, C. Oliveras, G. Ribera, C. Pont-Sunyer, R. Vivanco, G. Cucurella, E. Giralt, T. Delgado, C. Garcia, A. Seoane, R. Campo, Eighteen month study of continuous intraduodenal levodopa infusion in patients with advanced Parkinson's disease: impact on control of fluctuations and quality of life, Parkinsonism Relat. Disord. 16 (3) (2010) 218–221.
[30] M. Sensi, F. Preda, L. Trevisani, E. Contini, D. Gragnaniello, J.G. Capone, E. Sette, N. Golfre-Andreasi, V. Tugnoli, M.R. Tola, R. Quatrale, Emerging issues on selection criteria of levodopa carbidopa infusion therapy: considerations on outcome of 28 consecutive patients, J. Neural Transm. 121 (6) (2014) 633–642.
[31] M. Zibetti, A. Merola, C.A. Artusi, L. Rizzi, S. Angrisano, D. Reggio, C. De Angelis, M. Rizzone, L. Lopiano, Levodopa/carbidopa intestinal gel infusion in advanced Parkinson's disease: a 7-year experience, Eur. J. Neurol. 21 (2) (2014) 312–318.
[32] S. Bohlega, H. Abou Al-Shaar, T. Alkhairallah, F. Al-Ajlan, N. Hasan, K. Alkahtani, Levodopa-Carbidopa intestinal gel infusion therapy in advanced Parkinson's disease: single middle eastern center experience, Eur. Neurol. 74 (5–6) (2015) 227–236.
[33] M. Karlsborg, L. Korbo, L. Regeur, A. Glad, Duodopa pump treatment in patients with advanced Parkinson's disease, Dan. Med. Bull. 57 (6) (2010) A4155.
[34] D. Nyholm, A.I. Nilsson Remahl, N. Dizdar, R. Constantinescu, B. Holmberg, R. Jansson, S.M. Aquilonius, H. Askmark, Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease, Neurology. 64 (2) (2005) 216–223.
[35] J. Timpka, T. Fox, K. Fox, H. Honig, P. Odin, P. Martinez-Martin, A. Antonini, K.R. Chaudhuri, Improvement of dyskinesias with L-dopa infusion in advanced Parkinson's disease, Acta Neurol. Scand. 133 (6) (2016) 451–458.