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Research Report

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

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Abstract.
Background: Levodopa-carbidopa intestinal gel (LCIG) is delivered continuously via intrajejunal percutaneous gastrostomy tube.
Objective: To examine long-term safety, efficacy and quality of life of LCIG in an open-label extension study.
Methods: Patients received 52 weeks of open-label LCIG treatment following a 12-week double-blind, double-dummy trial in which they were randomized to either LCIG or immediate-release oral levodopa-carbidopa. Patient cohort designation was by receipt of LCIG in the preceding trial randomization (continuing-LCIG vs. LCIG-naïve patients).
Results: Sixty-two of 66 subjects in the double-blind proceeded to the open-label extension. Most subjects (95%) reported ≥1 adverse event (AE); only 3 subjects (4.8%) discontinued due to AEs. AE incidence declined gradually over 52 weeks. Serious AEs were reported by 23%. LCIG-naïve patients ($N=29$) showed a decrease in "Off" time and an increase in "On" time without troublesome dyskinesia (change from baseline to final visit in mean [SD] hours = −2.34 [2.78] $P<0.001$ and 2.19 [3.70] $P=0.005$, respectively), while continuing-LCIG patients ($N=33$) showed sustained "Off" time duration and further improvement in "On" time without troublesome dyskinesia (−0.42 [2.67] $P=0.377$ and 1.00 [2.58] $P=0.036$, respectively). The majority of patients in both groups (LCIG-naïve, continuing-LCIG, respectively) were rated 'Much Improved' or 'Very Much Improved' at final visit on the Clinical Global Impression-Improvement scale (69.0%, 69.7%).
Conclusions: Continuing-LCIG patients continued to derive benefit from LCIG while the magnitude of improvement among LCIG-naïve patients was similar to that observed for patients on LCIG in the preceding double-blind study. The overall AE profile was consistent with previous phase 3 clinical trials involving the LCIG system.

Keywords: Parkinson's disease, levodopa-carbidopa intestinal gel, motor fluctuations, percutaneous endoscopic gastrostomy, clinical trial

INTRODUCTION

After nearly 50 years of use in the treatment of Parkinson's disease (PD), levodopa is still considered the "gold standard" that effectively controls motor

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deficits in the early stages of the disease [1–3]. As the disease progresses, treatment stability with oral levodopa erodes with the intrusion of levodopa-induced dyskinesias, end-of-dose wearing off, and "On"/"Off" fluctuations, that can be disabling for PD patients [4–6]. Approximately 40% of patients with PD experience motor fluctuations and/or dyskinesias after 4 to 6 years of levodopa therapy; a number that increases to 90% after 9 or more years [7]. Dyskinesias typically occur at peak dose, precluding further dose increases as a remedy. Although end-of-dose wearing off can be mitigated by more frequent dosing, other issues that magnify pulsatile delivery, including erratic gastric emptying, variable jejunal absorption, short drug half-life ($\leq$90 min), and patient compliance often limit dosing frequency [8]. Achieving continuous (tonic) striatal dopaminergic stimulation is thought to be key to reducing motor complications associated with long-term levodopa use. The levodopa-carbidopa intestinal gel (LCIG) system provides continuous levodopa infusion directly into the proximal small intestine via percutaneous endoscopic gastrojejunostomy (PEG-J), largely bypassing issues of gastric emptying and absorption, and producing more stable plasma concentrations of levodopa [9]. The tolerability profile of LCIG is generally comparable with that of oral therapies, with the exception of events related to the delivery system and its placement [10].

In the last few years, it has become recognized that peripheral neuropathy occurs with greater frequency in PD patients on levodopa compared with age-matched controls [11, 12]. There have also been several reports of cases of peripheral neuropathy in advanced PD patients undergoing LCIG therapy. Most were subacute or chronic-onset sensorimotor neuropathies, although rare cases clinically resembling Guillian Barré syndrome have been reported [13]. Mancini et al. [14] recently reported on 3 groups of consecutive PD patients: 50 on LCIG, 50 on oral levodopa and 50 on other dopaminergic therapy. Frequency of peripheral neuropathy of no evident cause was 28% in LCIG-treated, 20% in oral levodopa-treated, and 6% in other dopaminergic-treated PD patients. It has been hypothesized that high-dose levodopa promotes high levels of homocysteine and methylmalonic acid or reduces absorption of vitamins B6, B12, and folate essential for homocysteine metabolism, thus leading to peripheral neuropathy [10]. In this regard, cases of LCIG-associated peripheral neuropathy often have responded to vitamin supplementation without need for LCIG cessation, although LCIG cessation is sometimes necessary [10].

Recent reports describe the efficacy and safety results from two United States registration, phase 3 trials of LCIG in patients with advanced PD whose motor complications are not adequately controlled by standard oral therapy [15, 16]. In a 12-week, randomized, controlled, double-blind, double-dummy trial ($N = 71$), LCIG treatment produced 4.04 hours of improvement in mean daily "Off" time compared to baseline, 1.91 hours more than the improvement noted with immediate-release oral levodopa-carbidopa (LC-IR) treatment (95% CI: -3.05 to -0.76, $P = 0.0015$). This benefit of LCIG treatment translated to 4.11 hours of increase in mean daily "On" time without troublesome dyskinesia, 1.86 hours more than the improvement seen with LC-IR treatment (95% CI: 0.56 to 3.17, $P = 0.0059$) [15]. The change from baseline in both "Off" and "On" time without troublesome dyskinesia in this double-blind trial improved by comparable amounts in the large, 54-week trial of open-label LCIG treatment ($N = 354$) (-4.4 h, $P < 0.001$ and 4.8 h, $P < 0.001$, respectively) [16]. The most common adverse events (AEs) in these studies were associated with the PEG-J procedure or device and decreased substantially during the weeks after the procedure. Discontinuation due to AE was low in both studies (4.2% in the double-blind and 7.6% in the open-label).

This report presents the results of a 52-week, open-label extension of the double-blind study that examined long-term safety, efficacy, and quality of life in those advanced PD patients. As the PEG-J procedure was performed 12 weeks before the extension study start, we could uniquely examine levodopa safety during LCIG initiation independent of procedure-related events. Furthermore, the study design enabled us to separately examine AEs related to PEG-J maintenance from those acute events related to the procedure.

METHODS

Study design

In this phase 3, open-label, multicenter, continuation of treatment study, advanced PD patients with motor complications despite optimized standard therapy received 52-weeks of LCIG treatment (NCT00360568) after completing a 12-week, double-blind, double-dummy trial in which they were randomized to either LCIG or LC-IR (NCT00357994/NCT00660387) [15]. The primary objective of this study was to evaluate the long-term safety of LCIG. A secondary objective was to assess the

long-term maintenance of efficacy and quality of life. The study protocol was approved by each participating institution's respective internal review board or ethics committee, and each patient provided written informed consent prior to any procedure being performed.

The study design is summarized in Supplemental Fig. 1. Patients proceeded immediately from the double-blind trial into the open-label extension. Baseline evaluations were completed prior to starting open-label treatment. In order to maintain the blind, all patients were hospitalized for 2 to 7 days and retitrated to the optimum LCIG dose. After retitration, patients continued on open-label LCIG treatment for the remainder of 52 weeks. LCIG infusion was continuous over the waking day (approximately 16 hours) and was stopped at night when all patients were permitted to take LC-IR if medically indicated.

Patients

Eligible patients were those who elected to continue after completing the preceding double-blind study and demonstrated a good response to LC-IR or LCIG based on improvements on the Unified PD Rating Scale (UPDRS), the 39-item Parkinson's Disease Questionnaire (PDQ39), or the Clinical Global Impression-Improvement scale (CGI-I). No minimum "Off" time was required at the beginning of the extension trial, whereas $\geq$3 hours of "Off" time per day was an inclusion criterion for entry into the preceding study.

LCIG dosing & concomitant anti-PD medication

LCIG is supplied as a homogenous suspension of levodopa (20 mg/mL) and carbidopa monohydrate (5 mg/mL) in an aqueous gel (sodium carboxymethylcellulose), which is administered continuously through a portable infusion pump device (CADD-Legacy, Smiths Medical, Minneapolis, MN, USA). The starting dose of LCIG was based on the optimized oral levodopa-carbidopa dose that the subject received just prior to randomization in the double-blind study. Dosing could be adjusted by the investigator at any time during the study based on the subject's medical condition.

During the double-blind study, patients were required to maintain stable doses of concomitant anti-PD medications; apomorphine and sustained-release levodopa-carbidopa formulations were prohibited. In the open-label extension, patients could taper off concomitant anti-PD meds any time post-LCIG initiation.

Safety

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) [17], and tabulated by MedDRA Preferred Term (PT). Study investigators rated each event as mild, moderate or severe, and evaluated the potential relationship with study treatment (drug and device). Treatment-emergent AEs were defined as events with onset on or after the first day of open-label LCIG infusion and no more than 30 days after PEG-J removal. In order to evaluate AEs that may be related to LCIG initiation, AEs reported during weeks 1–4 were compared between treatment groups. Safety assessments also included monitoring complications of the infusion device.

Efficacy and quality of life

Efficacy outcomes included the mean change from baseline to last visit in "Off" time; "On" time without troublesome dyskinesia; the UPDRS [18] scores total (sum of parts I, II, and III), parts I, II, III, IV, and part IV dyskinesia subscore (sum of questions 32, 33 and 34); and the CGI-I. Health-related quality-of-life measures included the PDQ-39 [19], EuroQual quality of life- 5 Dimensions (EQ-5D), and the Zarit Burden Interview (ZBI). The ZBI is a self-administered, 22-item questionnaire completed by caregivers that is designed to assess the caregiver/patient relationship and evaluate the caregiver's health condition, psychological well-being, finances, and social life. Each item on the ZBI is scored on a scale of 0 to 4, with 4 being the greatest burden.

For 3 consecutive days prior to scheduled study visits at baseline and weeks 4, 12, 24, 36, and 52, patients recorded motor symptom status at 30 minute intervals using a 24-h home diary [20]. Patients recorded status as "Off", "On" with troublesome dyskinesia, "On" with non-troublesome dyskinesia, "On" without dyskinesia, or asleep. The efficacy measure "On" time without troublesome dyskinesia is the sum of "On" time with non-troublesome dyskinesia and "On" time without dyskinesia. Diary variables were normalized to a 16-h waking day and averaged over the 3 consecutive days.

Patients completed the UPDRS in the "on" state ($\sim$2–4 h post-morning dose), PDQ-39, EQ-5D, and ZBI during study visits at baseline and weeks 12, 24, and 52. At baseline, clinicians rated the severity of patients' symptoms on the CGI-Severity scale (CGI-S) (scores range from 1 [normal] to 7 [among

the most extremely ill]). At visits 4, 12, 24, 36, and 52, clinicians rated improvement from baseline on the CGI-I (scores range from 1 [very much improved] to 7 [very much worse] with 4 equals no change).

Statistical analyses

All patients who received LCIG during the extension study were included in summaries of baseline characteristics and safety. All patients who also had baseline and at least 1 post-baseline efficacy or quality-of-life assessment were included in the efficacy/quality-of-life analyses. The final measures in the preceding double-blind study served as the baseline measures for the extension. Within group change from baseline to each visit and to endpoint was assessed with a one-sample *t*-test. For safety data, the incidence of AEs and infusion-device complications was summarized.

RESULTS

Patient disposition and baseline measures

Of 66 patients completing the double-blind study, 62 entered into the open-label LCIG extension study (Fig. 1). The 4 patients who did not participate in the extension were based in Germany and instead decided to receive LCIG as the commercial product Duodopa®. Twenty-two sites in the United States, New Zealand, and Germany enrolled patients. Extension study participants previously treated with LC-IR in the double-blind study will be referred to as "LCIG naïve" ($n = 29$); those who previously received LCIG in the double-blind will be referred to as "continuing LCIG" ($n = 33$).

Seventy-one percent ($n = 44$) of patients were male, 92% ($n = 57$) were white, and at baseline the mean (SD) age was 64.1 (7.9) years, PD duration was

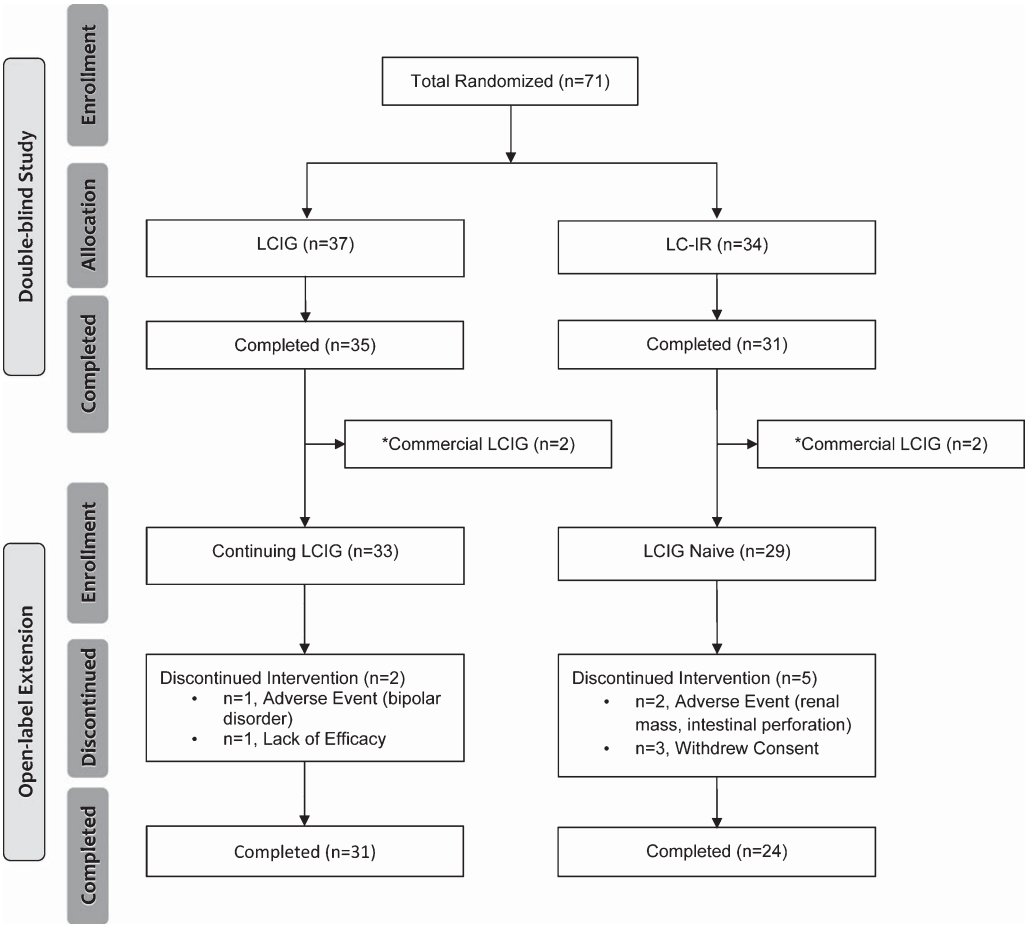

Fig. 1. Patient Disposition. LCIG, levodopa-carbidopa intestinal gel; LC-IR, immediate release levodopa-carbidopa. *Patients living in a country where LCIG is approved for commercial use.

Table 1
Baseline demographics and patient characteristics

Parameter	Continuing LCIG $N = 33$	LCIG Naïve $N = 29$	All Patients $N = 62$
Age, y	63.6 (9.0)	64.8 (6.6)	64.1 (7.9)
Age category, *n* (%)			
< 65 y	19 (57.6)	13 (44.8)	32 (51.6)
≥ 65 y	14 (42.4)	16 (55.2)	30 (48.4)
Male, *n* (%)	23 (69.7)	21 (72.4)	44 (71.0)
Race, *n* (%)			
American Indian or Alaska Native	1 (3.0)	0	1 (1.6)
Asian	1 (3.0)	3 (10.3)	4 (6.5)
Black	0	0	0
White	31 (93.9)	26 (89.7)	57 (91.9)
Hispanic or Latino, *n* (%)	2 (6.1)	1 (3.4)	3 (4.8)
MMSE total score	28.8 (1.5)	28.9 (1.5)	28.8 (1.5)
Duration of Parkinson's disease, y	10.07 (4.84)	11.39 (5.70)	10.69 (5.26)
"Off" time, h per day	3.11 (2.56)	5.08 (2.03)	4.03 (2.52)
"On" time without troublesome dyskinesia, h per day[a]	11.83 (2.68)	9.86 (2.61)	10.91 (2.80)
"On" time with troublesome dyskinesia, h per day[b]	1.06 (2.04)	1.06 (1.73)	1.06 (1.89)
UPDRS total score (parts I, II, III)	26.4 (18.9)	30.3 (16.1)	28.2 (17.6)
CGI-S	3.0 (1.3)	3.7 (1.3)	3.3 (1.3)
PDQ-39 summary index	22.0 (17.1)	32.1 (17.2)	26.7 (17.7)

UPDRS, Unified Parkinson's Disease Rating Scale; CGI-S, Clinical Global Impression-Severity; PDQ, Parkinson's Disease Questionnaire. Data are means (standard deviation) unless otherwise indicated. [a]"On" time without troublesome dyskinesia equals "On" time without dyskinesia plus "On" time with nontroublesome dyskinesia.

10.7 (5.3) years, and Mini-Mental State Examination (MMSE) [21] score was 28.8 (1.5). There were no clinically meaningful differences in demographics between patient groups (Table 1). Baseline efficacy measures reflected improvement from treatment in the preceding study. At baseline, the continuing-LCIG group had both decreased "Off" time (3.1 [2.6] vs. 5.1 [2.0] h) and increased "On" time without troublesome dyskinesia (11.8 [2.7] vs. 9.9 [2.6] h) compared to the LCIG-naïve group. Overall, the UPDRS scores were lower in the continuing-LCIG group than in the LCIG-naïve group, respectively: UPDRS total score = 26.4 (18.9) vs. 30.3 (16.1), UPDRS part IV dyskinesia items = 2.2 (1.9) vs. 2.3 (2.1) and UPDRS part IV score = 5.8 (2.7) vs. 6.8 (3.1). The PDQ-39 summary index was also lower at baseline in the continuing-LCIG group than the LCIG-naïve group (22.0 [17.1] vs. 32.1 [17.2]).

At baseline CGI-S scores indicated that patients in the continuing-LCIG group ($n = 32$, median score = 'Mildly Ill", range = 'Normal' to 'Markedly Ill') were less ill compared to the LCIG-naïve group ($n = 28$, median score = 'Moderately Ill', range = 'Normal' to 'Severely Ill').

Concomitant anti-PD medication

Thirty-eight of the 62 enrolled patients were on levodopa monotherapy (daytime LCIG monotherapy with or without nighttime LC-IR) at the start of the open-label extension titration (continuing-LCIG = 19 out of 33, LCIG-naïve = 19 out of 29). The most common concomitant anti-PD medication at study start was a dopamine agonist (overall = 15 [24%], continuing-LCIG = 9 [27%], LCIG-naïve = 6 [21%]). At the end of the study, weeks 40–52, 36 of 55 patients were on levodopa monotherapy (continuing-LCIG = 17 out of 31, LCIG-naïve = 19 out of 24).

Safety

No deaths were reported in the study. Incidence of treatment-emergent AEs and SAEs is reported in Table 2. Forty-eight patients (77%) reported at least 1 AE assessed as possibly or probably related to treatment. Most AEs were mild to moderate in severity. Only 3 subjects (4.8%) discontinued due to an AE (see Fig. 1). AE incidence gradually decreased over the 1 year, from 52% to 24%, when examined in 30-day increments ($N = 55$–62).

The most common SAEs overall were complication of device insertion (3 patients [5%]), abdominal pain, asthenia, and pneumonia (2 each [3%]). In the continuing-LCIG treatment group, SAEs experienced by a single patient each included gastrointestinal hemorrhage, intestinal obstruction, gastrointestinal injury, lumbar spinal stenosis, urethral stenosis, urinary retention, hypoxia, and pneumonia aspiration. Serious adverse events that occurred in 1 patient each in the LCIG-naïve treatment group were angina pectoris, fecaloma, intestinal ischemia, intestinal

Table 2
Adverse event summary

Adverse Event (AE) *n* (% of cohort)	Continuing LCIG *N* = 33	LCIG Naïve *N* = 29	All Patients *N* = 62
Subjects with at least 1 AE	31 (94%)	28 (97%)	59 (95%)
Subjects with at least 1 serious AE	5 (15%)	9 (31%)	14 (23%)
Deaths	0	0	0
AEs reported in ≥10% of all patients			
Incision site erythema	7 (21%)	11 (38%)	18 (29%)
Fall	7 (21%)	6 (21%)	13 (21%)
Decreased vitamin B6	8 (24%)	5 (17%)	13 (21%)
Postoperative wound infection	5 (15%)	6 (21%)	11 (18%)
Constipation	4 (12%)	5 (17%)	9 (15%)
Insomnia	2 (6%)	7 (24%)	9 (15%)
Nausea	4 (12%)	5 (17%)	9 (15%)
Urinary tract infection	5 (15%)	4 (14%)	9 (15%)
Parkinson's disease[a]	4 (12%)	4 (14%)	8 (13%)
Post procedural discharge	3 (9%)	5 (17%)	8 (13%)
Procedural pain	4 (12%)	4 (14%)	8 (13%)
Seborrheic keratosis	5 (15%)	3 (10%)	8 (13%)
Arthralgia	5 (15%)	2 (7%)	7 (11%)
Blood homocysteine increased	5 (15%)	2 (7%)	7 (11%)
Dyskinesia	4 (12%)	3 (10%)	7 (11%)
Freezing phenomenon	4 (12%)	3 (10%)	7 (11%)
Serious AEs reported in ≥2 patients across groups[b]			
Complication of device insertion[c]	1 (3%)	2 (7%)	3 (5%)
Abdominal pain	1 (3%)	1 (3%)	2 (3%)
Asthenia	1 (3%)	1 (3%)	2 (3%)
Pneumonia	0	2 (7%)	2 (3%)

Adverse events reported are treatment-emergent. A single event could be coded to ≥1 preferred term. [a]Refers to a reemergence of Parkinson's symptoms most often due to a problem with drug delivery. [b]SAEs reported in 1 patient: continuing-LCIG = gastrointestinal hemorrhage, intestinal obstruction, gastrointestinal injury, lumbar spinal stenosis, urethral stenosis, urinary retention, hypoxia, pneumonia aspiration; LCIG-naïve = angina pectoris, fecaloma, intestinal ischemia, intestinal perforation, peritonitis, cholecystitis, gastroenteritis, sepsis, procedural pain, colonoscopy, muscle rigidity, syncope, delusion, hallucination, auditory hallucination, paranoia, renal mass, benign prostatic hyperplasia, hypertension. [c]Events with this term were most often additionally coded to abdominal pain.

perforation, peritonitis, cholecystitis, gastroenteritis, sepsis, procedural pain, colonoscopy, muscle rigidity, syncope, delusion, hallucination, auditory hallucination, paranoia, renal mass, benign prostatic hyperplasia, and hypertension. All reports of complication of device insertion (associated with tube replacement) and abdominal pain were assessed as probably related to study treatment. Asthenia was rated as possibly related and unrelated. Both cases of pneumonia were investigator-rated as unrelated to study treatment.

Overall, the most frequently reported AEs were incision site erythema (18 patients [29%]), fall and decreased vitamin B6 (13 each [21%]), and post-operative wound infection (11 [18%]). All incidents of incision site erythema, falls, and decreased vitamin B6 were mild or moderate in severity. A baseline vitamin B6 value was reported for only 4 patients, 3 of whom had a low value. Post-operative wound infection was mild or moderate in all 11 patients, 10 of whom were treated with antibiotics. There was no relationship between the timing of postoperative wound infections and PEG or J-tube replacements.

During the first 4 weeks, AEs potentially associated with levodopa such as dyskinesia, hallucinations, and orthostatic hypotension did not occur with a clinically meaningful increased incidence in the LCIG-naïve group compared to the continuing-LCIG group (difference of 1 patient for each). Over the entire study, polyneuropathy as an AE was reported in 6 (9.7%) patients (3 continuing, 3 naïve); in none was this serious or led to study discontinuation.

Separately-reported complications related to the infusion-device, including pump (55%), intestinal (J) tube (50%), PEG (36%), stoma site (44%), and other (16%, most of which were device connection issues), were reported for 81% (50) of patients. Thirty-three (53%) patients' device complication was associated with an AE. Overall, device complication incidence was fairly stable when examined in 13-week increments (range = 48–58%, *N* = 55–62).

Efficacy

At final visit, continuing-LCIG patients maintained their improved "Off" time obtained during the

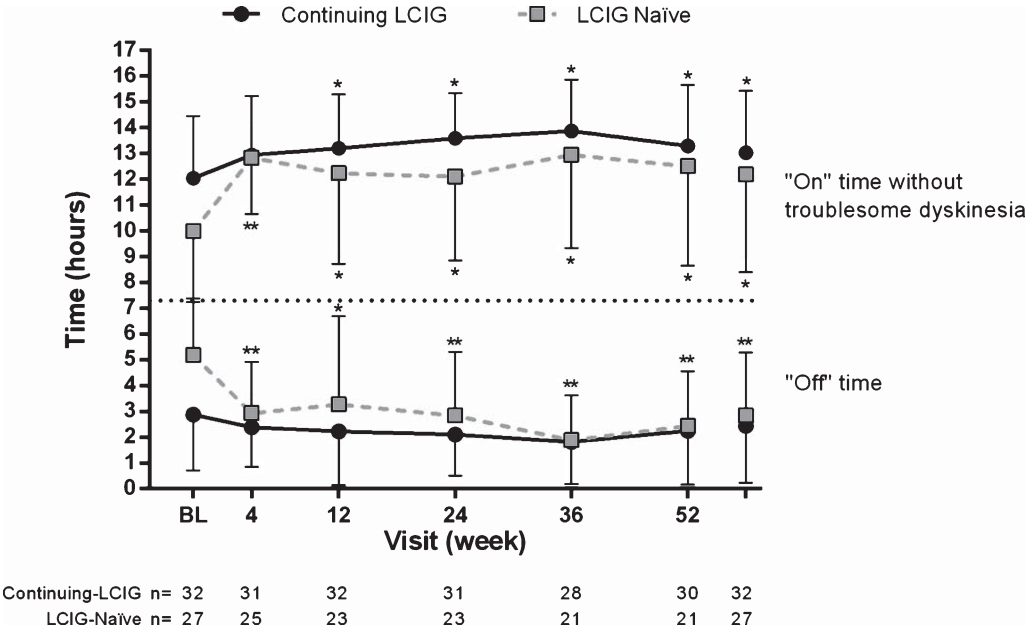

Fig. 2. Average Daily "Off" Time and "On" Time Without Troublesome Dyskinesia by Visit. PD Symptom Diary results, normalized to a 16-hour day, mean (standard deviation); BL = Baseline, EP = Endpoint. Baseline presented is for subjects with at least 1 post-baseline observation. $^{**}P < 0.001$; $^{*}P < 0.05$; P value reflects change from baseline.

double-blind study (Fig. 2, Table 3). LCIG-naïve patients showed significant improvement in "Off" time starting at Week 4 (mean change from baseline, −2.27 hours; $P < 0.001$) and continuing to final visit (−2.34 hours; $P < 0.001$). Both LCIG-naïve and continuing-LCIG patients showed significant improvement in "On" time without troublesome dyskinesia (2.19 and 1.00 hours, respectively; $P < 0.05$ for each) (Fig. 2, Table 3).

Continuing-LCIG patients showed improvement in the UPDRS part IV score and part IV dyskinesia subscore at final visit (Table 3). In LCIG-naïve patients, statistically significant improvement in the UPDRS part IV score was observed at last visit (−1.4; $P = 0.022$), but not for the part IV dyskinesia subscore (−0.1; $P = 0.824$). No statistically significant change at final visit was observed in the other UPDRS scores for either patient group (Table 3).

The majority of patients in both groups were assessed by the investigator on the CGI-I as having improved at last visit: continuing-LCIG = 'Very Much Improved' (39.4%), 'Much Improved' (30.3%), and 'Minimally Improved' (15.2%) vs. 'No Change' (12.1%) and 'Minimally Worse' (3.0%); LCIG-naïve = 'Very Much Improved' (41.4%), 'Much Improved' (27.6%), and 'Minimally Improved' (13.8%) vs. 'Minimally Worse' (10.3%) and 'Much Worse' (6.9%). Mean CGI-I scores at the final assessment were statistically significant for both the continuing-LCIG and LCIG-naïve treatment groups (2.1 and 2.3, respectively; $P < 0.001$ for each) (Table 3).

The continuing-LCIG group showed sustained improvement in the PDQ-39 summary index, EQ-5D summary index, EQ-5D VAS score, and ZBI score (Table 3). LCIG-naïve patients did not show significant improvement from baseline to final visit on the quality-of-life measures, although significant improvement was occasionally observed at earlier time points [data on file].

DISCUSSION

This study evaluated the long-term safety and maintenance of efficacy and quality of life of 52 weeks of open-label LCIG treatment in advanced PD patients who completed a 12-week, double-blind trial of either LCIG or LC-IR treatment. The safety profile was consistent with that of the LCIG system observed in the preceding double-blind study [15], and the separate, long-term open-label study [16], with the exception of a lack of acute events likely to be associated with the PEG-J procedure. Most subjects experienced at least 1 AE (95% in the extension vs. 97% in the double-blind), and most events were mild or moderate in severity. SAEs were reported by 23% in the extension versus 17% in the double-blind, despite the much longer

Table 3
Efficacy and quality-of-life measures

	N	Mean Change from Baseline	95% CI	*P* value
"Off" time, h per day				
Continuing LCIG	32	−0.42 (2.67)	(−1.39, 0.54)	0.377
LCIG Naive	27	−2.34 (2.78)	(−3.44, −1.24)	<0.001
"On" time without troublesome dyskinesia, h per day[a]				
Continuing LCIG	32	1.00 (2.58)	(0.07, 1.93)	0.036
LCIG Naive	27	2.19 (3.70)	(0.72, 3.65)	0.005
UPDRS part I				
Continuing LCIG	33	0.3 (1.9)	(−0.4, 1.0)	0.361
LCIG Naive	26	0.7 (1.7)	(0.0, 1.3)	0.06
UPDRS part II				
Continuing LCIG	33	0.5 (3.4)	(−0.7, 1.7)	0.447
LCIG Naive	26	−1.0 (7.0)	(−3.9, 1.8)	0.453
UPDRS part III				
Continuing LCIG	33	1.5 (7.0)	(−1.0, 4.0)	0.226
LCIG Naive	25	−0.5 (10.4)	(−4.8, 3.8)	0.82
UPDRS total score (parts I, II, III)				
Continuing LCIG	33	2.3 (9.0)	(−0.9, 5.5)	0.16
LCIG Naive	25	−1.0 (15.0)	(−7.2, 5.2)	0.748
UPDRS part IV dyskinesia subscore (sum of questions 32, 33, 34)				
Continuing LCIG	33	−0.8 (1.7)	(−1.4, −0.3)	0.006
LCIG Naive	26	−0.1 (1.7)	(−0.8, 0.6)	0.824
UPDRS part IV				
Continuing LCIG	33	−1.6 (2.5)	(−2.5, −0.8)	<0.001
LCIG Naive	26	−1.4 (3.0)	(−2.6, −0.2)	0.022
CGI-I at final assessment[b]				
Continuing LCIG	33	2.1 (1.2)	(1.7, 2.5)	<0.001
LCIG Naive	29	2.3 (1.6)	(1.7, 2.9)	<0.001
PDQ-39 summary index				
Continuing LCIG	32	1.5 (12.7)	(−3.1, 6.1)	0.505
LCIG Naive	26	−3.5 (13.4)	(−8.9, 1.9)	0.191
EQ-5D summary index				
Continuing LCIG	33	−0.009 (0.173)	(−0.071, 0.052)	0.755
LCIG Naive	26	−0.006 (0.220)	(−0.094, 0.083)	0.898
EQ-5D visual analog scale				
Continuing LCIG	33	−0.9 (15.1)	(−6.2, 4.5)	0.74
LCIG Naive	26	4.5 (15.5)	(−1.8, 10.8)	0.152
Zarit Burden Interview				
Continuing LCIG	24	1.1 (9.7)	(−3.0, 5.2)	0.576
LCIG Naive	20	−1.8 (9.0)	(−6.0, 2.5)	0.397

Data are mean (SD) change from baseline to final visit. *P* value is from a 1-sample *t*-test of mean change from baseline. UPDRS, Unified Parkinson's Disease Rating Scale; CGI-I, Clinical Global Impression-Improvement; PDQ, Parkinson's Disease Questionnaire; EQ-5D, EuroQual quality of life-5 Dimensions. [a]"On" time without troublesome dyskinesia equals "On" time without dyskinesia plus "On" time with nontroublesome dyskinesia. [b]For CGI-I, *P* value is from 1-sample *t*-test comparing the mean CGI-I to 4 = no change. The CGI-I ratings are as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

treatment period. Both studies had low discontinuation due to AE (3 patients each), supportive of the tolerability of the LCIG system and notable given the one-year duration of the extension study.

There were no clinically meaningful differences in AEs between the continuing-LCIG and LCIG-naïve patients. AEs potentially associated with levodopa did not occur with increased incidence in the LCIG-naïve group during LCIG initiation. Rates of neuropathy were consistent with background rates in PD patients on levodopa [11, 22, 23]; there were no cases of Guillain-Barré syndrome. The observed decreases in vitamin B6 were mild to moderate in severity and similar to previously reported values for both LCIG-treated and oral levodopa-treated PD patients [10, 14]. Reporting of AEs commonly associated with the procedure/device, such as incision site erythema, post-operative wound infection, and post-procedural discharge are reflective of longer-term events related to PEG-J maintenance. AE incidence gradually decreased over the 52 weeks. Incidence of infusion-device complications was consistent with the preceding study (81% in the extension vs. 89% in the double-blind) and stable over time.

Subjects in both the continuing-LCIG and LCIG-naïve groups derived benefit from open-label LCIG treatment. After showing clinically meaningful improvement across efficacy measures in the double-blind study, continuing-LCIG patients showed sustained improvement on long-term, open-label LCIG treatment as measured by PD Diary and the CGI-I scale. Following initiation of open-label LCIG treatment, LCIG-naïve patients further improved across the same efficacy measures to levels similar to those of the continuing-LCIG patients. Notably, the number of patients with a 50% reduction in "Off" time at one year was comparable to that observed in the 54-week open-label study [16] [data on file].

These patients were not naïve to treatment, both groups having already exhibited change from baseline in efficacy and quality-of-life measures while on LC-IR or LCIG treatment during the preceding double-blind study. This could explain why significant improvement was not observed at the final visit across all the efficacy and quality-of-life measures. As the UPDRS was administered in the best "on" state, it is less surprising that part III motor scores did not significantly improve. There were no significant changes in most UPDRS or QOL endpoints. In other phase 3 studies, UPDRS and PDQ-39 scores significantly improved with LCIG treatment [15, 16]. The data suggest that continuing-LCIG patients may have approached maximum improvement on several measures during the double-blind study. Additionally, the lack of significant further improvement may relate to the natural progression of the disease in these patients. Finally, study design limitations including a small sample size and open-label treatment with a lack of a control group may have limited the ability to assess efficacy and quality-of-life improvements.

The study demonstrated continued safety and tolerability as well as improvement in on time without troublesome dyskinesia in patients with advanced PD. Patients on long-term, open-label LCIG treatment sustain the efficacy and quality-of-life improvement achieved during the first 12 weeks of treatment. The safety profile of the LCIG system is stable over the longer-term and is acceptable to patients as evidenced by a low rate of discontinuation. LCIG has the potential to address a significant unmet need in this patient population with limited therapeutic options.

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Ms. Hall is an employee of AbbVie and holds stock and/or stock options.

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SUPPLEMENTARY MATERIAL

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