Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson’s Disease: Final 12-Month, Open-Label Results

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ABSTRACT: Motor complications in Parkinson’s disease (PD) are associated with long-term oral levodopa treatment and linked to pulsatile dopaminergic stimulation. L-dopa-carbidopa intestinal gel (LCIG) is delivered continuously by percutaneous endoscopic gastrojejunostomy tube (PEG-J), which reduces L-dopa-plasma-level...

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fluctuations and can translate to reduced motor complications. We present final results of the largest international, prospective, 54-week, open-label LCIG study. PD patients with severe motor fluctuations (>3 h/day “off” time) despite optimized therapy received LCIG monotherapy. Additional PD medications were allowed >28 days post-LCIG initiation. Safety was the primary endpoint measured through adverse events (AEs), device complications, and number of completers. Secondary endpoints included diary-assessed off time, “on” time with/without troublesome dyskinesia, UPDRS, and health-related quality-of-life (HRQoL) outcomes. Of 354 enrolled patients, 324 (91.5%) received PEG-J and 272 (78.8%) completed the study. Most AEs were mild/moderate and transient; complication of device insertion (34.9%) was the most common. Twenty-seven (7.6%) patients withdrew because of AEs. Serious AEs occurred in 105 (32.4%), most commonly complication of device insertion (6.5%). Mean daily off time decreased by 4.4 h/65.6% (P < 0.001).

Oral levodopa (l-dopa) is one of the most effective therapies for Parkinson’s disease (PD).1-4 During early disease stage, motor symptoms are well controlled with 3 to 4 daily doses. As PD progresses, however, oral l-dopa’s effect may not be sustained between doses and symptoms may re-emerge.3-6 Adjunctive therapies may further reduce the duration of motor complications (i.e., decrease “off” time by approximately 1-2 hours per day); however, dyskinesia and other adverse events (AEs) increase.7-9 Oral l-dopa pharmacokinetic properties contribute to oscillations in plasma l-dopa levels,3-5 which may be compounded by variability of gastric emptying and l-dopa absorption.10,11

Establishing stable plasma l-dopa levels may provide more continuous dopaminergic stimulation, resulting in decreased motor fluctuations.4,6 l-dopa-carbidopa intestinal gel (LCIG) offers continuous drug delivery and may provide a closer approximation of physiological continuous dopaminergic stimulation through its amelioration of plasma-level fluctuations, including the depth and frequency of serum troughs.5 LCIG is delivered continuously by portable pump through a percutaneous endoscopic gastrojejunostomy (PEG-J) tube,1,6,12 bypassing the stomach to eliminate variability associated with gastric emptying,5,10 resulting in a significant decrease in off time duration.5,12-15

The efficacy of LCIG as an adjunctive therapy was evaluated in a double-blind, double-dummy, phase III study, which showed a 4.0-hour reduction from baseline in off time among patients randomized to LCIG and a 1.9-hour difference in off time reduction versus optimized oral l-dopa (P = 0.0015).15 Previous open-label studies also showed statistically significant reductions in off time and/or dyskinesia versus baseline.13,14,16-21 However, these studies were small by design, comprised of 5 to 91 patients. This large study was designed to provide needed longer-term safety and efficacy results with clinical applicability to an international patient population with advanced PD. Furthermore, the study investigated the initiation and maintenance of LCIG as monotherapy, replacing adjunctive PD therapy.

Patients and Methods

The safety and efficacy of LCIG were evaluated in patients with advanced PD experiencing motor fluctuations despite optimized medical therapy in an open-label, phase III, 12-month study (ClinicalTrials.gov: NCT00335153). The study methodology has been reported on22 and is summarized below. The study protocol was approved by the institutional review board/ethics committee at all 86 centers in 16 countries. All patients provided written informed consent.

Study Design

The study included a screening period (≤28 days), baseline assessments, a nasojejunal (NJ) titration period (2-14 days), a PEG-J titration period (2-14 days), and a 54-week treatment period (Fig. 1A). The starting infusion dose was based on each patient’s previous daily dose of oral l-dopa. Usage of other PD medications that required tapering off was compensated for at the investigator’s discretion. Patients were hospitalized for NJ tube placement and initiation of LCIG titration as well as PEG-J tube placement and further dose optimization by PEG-J, if required. At the end of titration, patients entered long-term PEG-J treatment and assessments began on day 28. LCIG was administered by a portable pump during waking
hours; a morning dose/bolus was followed by continuous infusion for approximately 16 hours with additional rescue doses during the day, if clinically indicated. The use of oral immediate-release l-dopa-carbidopa was permitted only when the pump was turned off at night. Use of other PD medications was permitted after 28 days post-LCIG initiation at the investigator’s discretion. Apomorphine and controlled-release l-dopa-carbidopa were not permitted.

Safety and tolerability provided the primary end-point whereas efficacy assessments provided the secondary endpoints.

**Patients**

Eligible patients were ≥30 years old, l-dopa responsive, met UK Parkinson’s Disease Society Brain Bank diagnostic criteria, and had severe motor fluctuations defined as ≥3 hours of daily off time at baseline (confirmed by the PD symptom diary), despite optimized treatment with available PD medications.

**Safety**

Safety measures included AEs, infusion device complications, and tolerability assessed by number of patients completing the study. Laboratory results, vital signs, and electrocardiogram (ECG) were monitored.

AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. Each event could be coded to one or more terms descriptive of the event. Planned hospitalization for baseline assessment and treatment initiation was not considered a serious AE (SAE) unless hospitalization was prolonged as a result of complications. All AEs reported are treatment-emergent AEs, which were defined as those that began or worsened from the time of NJ tube insertion until 30 days after PEG-J removal. AEs of special interest were monitored. These were AEs associated with neuropathy, the procedure and device (e.g., PEG-J placement), respiratory tract aspiration, weight loss, and cardiovascular fatalities.

**Efficacy**

Efficacy outcomes included assessed mean change from baseline to last visit in patient-diary off time, “on” time with troublesome dyskinesia, and on time without troublesome dyskinesia (on time without dyskinesia plus on time with nontroublesome dyskinesia, i.e., does not interfere with function or cause meaningful discomfort); the investigator-rated Clinical Global Impression-Improvement ( CGI-I) scale; the UPDRS parts II, III, total score (Parts I–III), and the dyskinesia items from Part IV (questions 32-34); the 39-item PD Questionnaire (PDQ-39)24; the EuroQol-5D (EQ-5D) Summary Index25; and the EuroQol visual analog scale (EQ-VAS).26 Efficacy assessments were collected during post-PEG-J weeks 4, 12, 24, and 54; PD diary and CGI-I were also collected at post-PEG-J week 36.

**Statistical Analyses**

Efficacy analyses included all patients who received LCIG during the post-PEG-J period and completed ≥1 postbaseline efficacy assessment. Safety analysis included all patients who had NJ placement and completed ≥1 postbaseline safety evaluation. The within-group
TABLE 1. Baseline characteristics (n = 354)

| Characteristic                           | Value                  |
|-----------------------------------------|------------------------|
| Age, years                              | Mean ± SD              |
| Sex, males, n (%)                       | 202 (57.1)             |
| Race, n (%)                             |                        |
| White                                   | 328 (92.7)             |
| Asian                                   | 22 (6.2)               |
| Black                                   | 4 (1.1)                |
| Weight, kg                              | Mean ± SD              |
| Median (range)                          | 70.8 ± 15.8            |
| PD duration in years, mean ± SD         | 12.5 ± 5.5             |
| 1-dopa dose at screening, mg/day, mean ± SD | 1,082.9 ± 582.1 |
| PD medications, n (%)                   |                        |
| Number of PD medication classes received |                        |
| One (all 1-dopa or derivative alone)    | 94 (26.6)              |
| Two                                     | 112 (31.6)             |
| Three                                   | 87 (24.6)              |
| More than three                         | 60 (16.9)              |
| Medication classes of those receiving ≥2 |
| l-dopa or derivatives                   | 259 (73.2)             |
| Dopamine agonists                       | 196 (55.4)             |
| COMT inhibitors                         | 100 (28.2)             |
| Amantadine                              | 106 (29.9)             |
| MAO-B inhibitors                        | 45 (12.7)              |
| Tertiary amines                         | 11 (3.1)               |
| Not recorded                            | 1 (0.3)                |
| Off time in hours/day, mean ± SD        | 6.75 ± 2.35            |
| On time without troublesome dyskinesia in hours/day, mean ± SD | 7.65 ± 2.45 |
| On time with troublesome dyskinesia in hours/day, mean ± SD | 1.61 ± 2.03 |
| CGI-S scale, mean ± SD                  | 4.85 ± 0.84            |
| UPDRS scores, mean ± SD                 |                        |
| Total (sum of Parts I, II and III)      | 48.4 ± 18.9            |
| Part II (activities of daily living)    | 17.4 ± 6.6             |
| Part III (motor symptoms)               | 28.8 ± 13.7            |
| Part IV (dyskinesia items nos. 32, 33 and 34 only) | 3.7 ± 2.4 |
| PDQ-39 Summary Index score, h SD        | 42.8 ± 15.1            |
| EQ-SD Summary Index score, SD mean ± SD  | 0.588 ± 0.195           |
| EQ-VAS score, mean ± SD                 | 50.2 ± 21.0            |

**Results**

**Patient Disposition and Baseline Measures**

Of 354 enrolled patients, 324 (91.5%) completed the NJ phase and 272 completed the study (76.8% of all patients enrolled, 84.0% of those who proceeded to PEG-J treatment; Fig. 1B).

Eighty-two patients (23.2%) prematurely discontinued, of whom 27 (7.6%) discontinued as the result of an AE. Other reasons for withdrawal were administrative reasons (4.0%; e.g., protocol-specified discontinuations for timely study closure), major protocol violations (2.5%), lack of efficacy (2.0%), and withdrawal of consent (7.1%; reasons for withdrawal of consent were not collected).

At baseline, patients had a mean ± standard deviation (SD) age of 64.1 ± 9.1 years, PD duration of 12.5 ± 5.5 years, and off time of 6.75 ± 2.35 hours per day (Table 1). Ninety-four patients (26.6%) were on l-dopa (or l-dopa derivative) monotherapy, whereas 259 (73.2%) were receiving ≥2 PD medications (including l-dopa for all patients) in any combination (primarily dopamine agonists [55.4% of all patients], amantadine [29.9%], and catechol-O-methyltransferase (COMT) inhibitors [28.2%]), all of which were discontinued before LCIG treatment.

**Total Daily l-dopa Dose**

All patients were converted to l-dopa-carbidopa monotherapy based on the l-dopa component of their previous PD therapy. On the last titration day (NJ or PEG-J, whichever was a patient’s final titration period), the mean total daily l-dopa dose was 1,547.4 mg, which included a mean of 1,537.0 mg from LCIG; only 4.4% (15 of 338) of patients received oral immediate-release l-dopa-carbidopa at nighttime, with an average dose of 235 mg. Initial titration during the NJ period was completed in a mean of 4.5 ± 2.2 days. The mean LCIG dose remained relatively constant throughout the study, ranging from 1,551.0 to 1,630.5 mg, depending on time point, and was 1,572.4 mg at last visit (Supporting Fig. 1). In the post-PEG-J phase, 76.5% (n = 248) of patients received only l-dopa-carbidopa, as LCIG with or without oral l-dopa-carbidopa, including 27.8% (n = 90) who received LCIG monotherapy. Among patients receiving adjunctive medications, 12.7% (n = 41) received dopamine agonists, 9.6% (n = 31) amantadine, 3.7% (n = 12) COMT inhibitors, and 1.5% (n = 5) monoamine oxidase (MAO)-B inhibitors.
TABLE 2. AEs and SAEs in the percutaneous endoscopic gastrojejunostomy treatment period (n = 324)

| MedDRA Preferred Term* | No. of Patients (%) |
|------------------------|---------------------|
| Any AE                 | 298 (92.0)          |
| AEs reported in ≥10%   |                     |
| Complication of device insertionb | 113 (34.9) |
| Abdominal pain         | 101 (31.2)          |
| Procedural pain        | 67 (20.7)           |
| Nausea                 | 54 (16.7)           |
| Excessive granulation tissue | 52 (16.0) |
| Postoperative wound infection | 50 (15.4) |
| Fall                   | 49 (15.1)           |
| Constipation           | 47 (14.5)           |
| Constipation           | 44 (13.6)           |
| Incision site erythema | 42 (13.0)           |
| Urinary tract infection| 37 (11.4)           |
| Any SAE                | 105 (32.4)          |
| SAEs reported in ≥1%   |                     |
| Complication of device insertionb | 21 (6.5) |
| Abdominal pain         | 10 (3.1)            |
| Peritonitis            | 9 (2.8)             |
| Polynuropathy          | 9 (2.8)             |
| PD†                    | 8 (2.5)             |
| Pneumoperitoneum       | 8 (2.5)             |
| Hip fracture           | 6 (1.9)             |
| Pneumonia              | 6 (1.9)             |
| Device dislocation     | 5 (1.5)             |
| Depression             | 4 (1.2)             |

*A single event could be coded to >1 preferred term.

*bEvents with this term were most often additionally coded to abdominal pain, abdominal discomfort, abdominal distension, flatulence, and pneumoperitoneum.

†Patients requiring hospitalization or extended hospitalization resulting from PD.

inhibitors (Supporting Table 1). At last visit, 27.8% (n = 88) of patients received immediate-release L-dopa-carbidopa (mean total dosage: 174.6 mg/night).

**Safety**

AEs were reported in 166 (46.9%) patients during the NJ period; the most common AEs were insomnia (7.9%), complication of device insertion (7.3%), and oropharyngeal pain (6.5%). During the post-PEG-J period, 298 (92.0%) patients experienced AEs (Table 2). The most common were complication of device insertion (34.9%), abdominal pain (31.2%), and procedural pain (20.7%). For the majority of subjects, AEs were mild (18.5%) or moderate (43.8%) and transient, with the highest incidence occurring during week 1 post-PEG-J (Supporting Fig. 2), with 65.1% of patients experiencing an AE at week 1 post-PEG-J, compared with 24.4%, 15.4%, and 17.1% by weeks 2, 3, and 4, respectively. SAEs were reported in 105 (32.4%) patients; the most common included complication of device insertion (6.5%), abdominal pain (3.1%), and peritonitis and polyneuropathy (each 2.8%; Table 2). There were no clinically meaningful changes in laboratory values, vital signs, or ECG.

Among AEs of special interest, procedure/device-related AEs were reported for 68.5% of patients, primarily complication of device insertion (33.6%), abdominal pain (26.5%), procedural pain (20.4%), excessive granulation tissue (15.4%), postoperative wound infection (15.1%), incision-site erythema (12.7%), procedural-site reaction (9.3%), postprocedural discharge (7.7%), incision-site pain (6.2%), and pneumoperitoneum (5.9%). There were no treatment-emergent cardiovascular fatalities. Aspiration-related AEs (14.8% of patients) were primarily dyspepsia (4.0%), pneumonia (3.1%), gastroesophageal reflux disease (2.2%), pyrexia (2.2%), dysphagia (1.9%), and atelectasis (1.5%). Fourteen aspiration events occurred within 7 days of initial PEG placement and 3 within 7 days of tube replacement/repositioning that required endoscopy. AEs related to polyneuropathy (6.8% of patients) were coded to the following MedDRA preferred terms: polyneuropathy (3.1% [which led to discontinuation for 1 patient]); peripheral sensory neuropathy (0.9%); Guillain-Barré syndrome-like neuropathy (coded as Guillain-Barré Syndrome; see Discussion; 0.6%); mononeuropathy (0.6%); neuropathy peripheral (0.6%); and peripheral sensorimotor neuropathy (0.6%). Weight-loss-related AEs occurred in 15.4% of patients.

Twenty-seven (7.6%) patients had an AE leading to withdrawal, 5 during the NJ period, and 22 patients post-PEG-J. Withdrawals during the NJ period were the result of dysphagia, vomiting, and complication of device insertion in 1 patient as well as pneumonia, QT prolongation, anxiety, and hallucination (1 patient each). In the post-PEG-J period, the most common reasons were complication of device insertion (n = 6), abdominal pain (n = 3), dyskinesia (n = 2), death of unknown etiology (n = 2), and completed suicide (n = 2; both patients had a history of depression). There were 8 subjects who had procedure/device-related AEs resulting in discontinuation.

A total of 8 deaths (2.3%) were reported; none were considered treatment related. Seven of these deaths occurred during the LCIG treatment period or within 30 days after PEG-J removal and included deaths attributed to suicide (n = 2), unknown etiology (n = 2), multiple complications (n = 1), cerebrovascular accident (n = 1), and cachexia (n = 1). One patient with a history of deep vein thrombosis (DVT) died 93 days post-PEG-J removal (i.e., not treatment emergent) as a result of DVT.

Device complications (i.e., related to device function, but not necessarily associated with an AE) were reported for 87.0% of patients: intestinal tube complication (50.9%); pump or stoma complication (35.8% each); and PEG-J or other complication (35.2% each).

**Efficacy**

Off time was significantly decreased from baseline to last visit by 4.4 ± 2.9 hours per day, or 65.6% (P < 0.001; Fig. 2 and Supporting Table 2). This improvement was sustained throughout all post-PEG-J
visits (weeks 4-54; \( P < 0.001 \)). Similarly, on time without troublesome dyskinesia increased by 4.8 ± 3.4 hours per day, or 62.9% \( (P < 0.001) \), and on time with troublesome dyskinesia decreased by 0.4 ± 2.8 hours per day, or 22.5% \( (P = 0.023) \). These improvements were sustained at all visits \( (P < 0.05) \).

On the CGI-I scale at end of treatment, 22.4% of patients were “very much improved,” 55.5% “much improved,” and 13.7% “minimally improved.” There was no change for 3.1% of patients, whereas 2.8% were “minimally worse,” 1.0% “much worse,” and none were “very much worse.”

On the efficacy measures commonly associated with function and health-related quality of life (HRQoL), significant improvement \( (P < 0.001) \) was noted by week 4 of long-term treatment and was maintained through the end of the study (Fig. 3). From baseline to last visit, the mean change was \(-4.4 ± 6.5\) points for the UPDRS Part II (activities of daily living), \(+0.064 ± 0.203\) points for the EQ-5D Summary Index, and \(+14.0 ± 24.8\) points for the EQ-VAS. From screening to last visit, the mean \(±\)SD change in the PDQ-39 Summary Index was \(-6.9 ± 14.1\) points. Seven of the eight PDQ-39 domains (except social support) showed statistically significant mean improvements (Supporting Table 3).

**Discussion**

This prospective study provides long-term safety and efficacy data for over 12 months in the largest cohort to date of patients with advanced PD treated with LCIG. Here, LCIG was initiated as monotherapy, replacing both oral \( l \)-dopa and other adjunctive PD medications in patients with PD who experienced severe motor complications despite optimized pharmacological therapy. Continuous infusion of LCIG throughout the day led to significant improvements in off time of \(-4.4\) hours per day (65.6%), as assessed by patient-completed diary, which were sustained throughout the 54-week trial. This outcome is of a magnitude expected to be clinically meaningful to patients, well beyond the 1-hour change in off time deemed clinically important in the literature.\(^{28}\) Of note, the reduction in off time corresponded to a significant increase in on time without troublesome dyskinesia. Even with optimized LCIG, there was some residual off time (approximately 2.5 hours in this cohort), but both the physician- and patient-perceived improvements were robust, with significant and enduring improvements in motor function as assessed by the UPDRS and CGI-I, as well as HRQoL as assessed by the PDQ-39 and EuroQoL. In fact, HRQoL improvements began as early as week 4 and were maintained through the duration of the 54-week study period. Furthermore, total daily dosing, after initial titration/optimization, was stable throughout the study, suggesting that patients do not develop tolerance to LCIG. Moreover, although adjunctive therapies were permitted after 28 days, there was low use of these therapies and 76.5% of patients remained on \( l \)-dopa-carbidopa monotherapy. This is valuable given that it simplifies patient treatment regimens and could decrease AEs resulting from multiple dopaminergic medications.

The most common AEs in this study were associated with device insertion, were generally transient, and decreased substantially after the first week post-PEG-J tube placement. Device complications were most common in the first week after PEG-J placement. In the NJ phase, insomnia may have been related to causes including hospitalization itself and was deemed not related to the system in the majority of cases. SAEs occurred in 105 (32.4%) patients; the most common included complication of device insertion (6.5%), abdominal pain (3.1%), and peritonitis and polynuropathy (each 2.8%). There were 2 SAEs of suicide, both in subjects under the age of 65 with a medical history of depression; neither reported suicidal ideation, but patients with PD as a group are at increased risk of suicide (by 5.3-fold in one study),\(^{29}\) and clinically relevant depression has been reported in 35% of patients with PD.\(^{30}\) In a study employing multivariable regression, the only factor associated with suicidal ideation or behavior in advanced PD was severity of depression,\(^{31}\) so physicians should be vigilant about the emotional state of all patients with advanced PD. Considering the patient population in our study (mean 64.1 years old, mean PD duration of 12.5 years; baseline CGI-S of “markedly ill” or worse for approximately two thirds), the procedure was generally well tolerated with few discontinuations resulting from AEs (7.6%). Of the 272 subjects who completed this study, 203 (74.6%) enrolled in the extension study, 66 (24.3%) transitioned to commercial LCIG, and 3 (1.1%) discontinued treatment.
To further examine procedure-related AEs, an adjudication committee consisting of independent expert gastroenterologists reviewed treatment-emergent AEs and SAEs categorized as “procedure and device-associated events” in the ongoing LCIG phase III program, including this study. The committee found that the rate of gastrointestinal AEs was generally consistent with ranges reported in the literature for the PEG-J procedure. Patients with PD are at increased risk of neuropathy. The cause of this is uncertain, but it has been suggested that it may be related to the metabolic effects of long-term L-dopa therapy. The rate in our study is consistent with reports in the literature for patients receiving L-dopa. The open-label design of this trial and lack of a control group are study limitations, in that the potential contributions of placebo effect cannot be assessed. However, the present trial is the largest sample of LCIG-treated patients studied worldwide thus far, which is a key strength. Moreover, these results demonstrate the maintenance of LCIG effects over 12 months, which is consistent with the recently reported.

FIG. 3. Mean ± SD changes from baseline on other efficacy measures including function and health-related quality of life. *Baseline value from screening. ***P < 0.001 versus baseline, one-sample t test.
12-week, double-blind, double-dummy, phase III study comparing LCIG with optimized oral immediate-release l-dopa-carbidopa (both treatments concomitant with unchanged adjunctive therapies). The double-blind study showed that the difference in off time decrease was significant at -1.91 hours (P = 0.0015; least squares [LS] mean of -4.04 hours for LCIG [n = 35] vs. -2.14 hours for oral l-dopa-carbidopa [n = 31] over an “optimized” baseline). Also in line with our study, the median CGI-I endpoint score was “much improved” for LCIG versus “minimally improved” for oral therapy, the mean UPDRS Part II score changed by -1.8 points (LS mean) in the LCIG arm (3.0-point improvement over oral therapy; P = 0.0086), and the PDQ-39 Summary Index score changed by -10.9 points (LS mean) with LCIG (7-point improvement over oral therapy; P = 0.0155).

Safety results in the double-blind study were consistent with our study. The most common AEs were related to the procedure, device, oral l-dopa, or underlying disease, most commonly abdominal pain (42%), procedural pain (32%), and nausea (25%). AEs were generally mild to moderate and declined within the first 2 weeks following the PEG-J procedure. Gastrointestinal AEs were typical for a PEG-J procedure.

Continuous drug delivery is integral to the therapeutic profile of LCIG. In countries where it is approved, LCIG is indicated for the treatment of advanced l-dopa-responsive PD with severe motor fluctuations and dyskinesia when available combinations of oral PD medications have not given satisfactory results. In this setting, the restricted mean duration of LCIG treatment in Sweden was approximately 7.8 years; 60% of patients were ongoing, and the most common reason for discontinuation was death (unrelated to LCIG). Furthermore, when LCIG is initiated, the large majority of patients do not require adjunctive agents and can be maintained on l-dopa-carbidopa monotherapy, facilitating dose adjustment for efficacy or managing AEs and simplifying patients’ therapeutic regimens. Overall, our safety and efficacy results are further reinforced by results from these and other LCIG studies that have been systematically compiled and published.

Apomorphine infusion and DBS are also associated with significant reductions in off time and with HRQoL improvements. LCIG will provide another treatment option for patients with motor complications despite optimized therapy, offering an additional treatment option suiting patient-specific needs and contraindications.

In summary, in this long-term, open-label study, LCIG demonstrated sustained, significant, and clinically meaningful improvements not only in motor complications, but also in HRQoL in advanced PD.

LCIG was associated with robust improvements in off and on time, at a consistent mean daily dose throughout the study period, and without worsening dyskinesia throughout 54 weeks. As assessed by the low rate of study withdrawal resulting from AEs (7.6%), LCIG was generally well tolerated. Nonetheless, 92% of the patients reported >1 AE, most commonly associated with PEG-J tube placement during the first week post-PEG-J placement. LCIG provides an effective therapeutic option for advanced PD patients with severe motor complications despite optimized oral pharmacologic therapy.

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References

1. Hauser RA. Levodopa: past, present, and future. Eur Neurol 2009; 62:1-8.
2. Hornykiewicz O. A brief history of levodopa. J Neurol 2010; 257(Suppl 2):S249-S252.
3. Lundqvist C. Continuous levodopa for advanced Parkinson’s disease. Neuropsychiatr Dis Treat 2007;3:335-348.
4. Antonini A, Chaudhuri KR, Martinez-Martín P, Odin P. Oral and infusion levodopa-based strategies for managing motor complications in patients with Parkinson’s disease. CNS Drugs 2010;24:119-129.
5. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson’s disease: scientific rationale and clinical implications. Lancet Neurol 2006;5:677-687.
6. Chaudhuri KR, Rizos A, Sethi KD. Motor and nonmotor complications in Parkinson’s disease: an argument for continuous drug delivery? J Neurol Transm 2013;120:1305-1320.
7. Mouradian MM, Heuser IJ, Baronti F, Fabbrini G, Juncos JL, Chase TN. Pathogenesis of dyskinesias in Parkinson’s disease. Ann Neurol 1989;25:523-526.
8. Chase TN. The significance of continuous dopaminergic stimulation in the treatment of Parkinson’s disease. Drugs 1998;55:1-9.
9. Stowe R, Ives N, Clarke CE, et al. Meta-analysis of the comparative efficacy and safety of adjuvant treatment to levodopa in later Parkinson’s disease. Mov Disord 2011;26:587-598.
10. Antonini A, Odin P. Pros and cons of apomorphine and L-dopa continuous infusion in advanced Parkinson’s disease. Parkinsonism Relat Disord 2009;15(Suppl 4):S97-S100.
11. Deleu D, Northway MG, Hanssens Y. Clinical pharmacokinetic and pharmacodynamic properties of drugs used in the treatment of Parkinson’s disease. Clin Pharmacokinet 2002;41:261-309.
12. Nyholm D, Askmark H, Gomes-Trolin C, et al. Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. Clin Neuropharmacol 2003;26:156-163.
13. Abbruzzese G, Barone P, Bonuccelli U, Lopiano L, Antonini A. Continuous intestinal infusion of levodopa/carbidopa in advanced Parkinson’s disease: efficacy, safety and patient selection. Funt Neurold 2012;27:147-154.
14. Nyholm D, Nilsson Remahl AI, Dzidar N, et al. Duodenal levodopa infusion monotherapy vs oral polyparmacy in advanced Parkinson’s disease. Neurology 2003;64:216-223.
15. Olanow CW, Kieburtz K, Odin P, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson’s disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014;13:141-149.
16. Eggert K, Schrader C, Hahn M, et al. Continuous jejunal levodopa infusion in patients with advanced Parkinson’s disease. Practical aspects and outcome of motor and non-motor complications. Clin Neuropharmacol 2008;31:151-166.
17. Antonini A, Isaacs IJ, Canesi M, et al. Duodenal levodopa infusion for advanced Parkinson’s disease: 12-month treatment outcome. Mov Disord 2007;22:1145-1149.
18. Antonini A, Mancini F, Canesi M, et al. Duodenal levodopa infusion improves quality of life in advanced Parkinson’s disease. Neurodegener Dis 2008;5:244-246.
19. Puente V, De Fabregues O, Oliveras C, et al. 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 2010;16:218-221.
20. Honig H, Antonini A, Martinez-Martin P, et al. Intrajejunal levodopa infusion in Parkinson’s disease: a pilot multicenter study of effects on nonmotor symptoms and quality of life. Mov Disord 2009;24:1468-1474.
21. Devos D; French DUODOPA Study Group. Patient profile, indications, efficacy and safety of duodenal levodopa infusion in advanced Parkinson’s disease. Mov Disord 2009;24:993-1000.
22. Fernandez HH, Vanagunas A, Odin P, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson’s disease open-label study: interim results. Parkinsonism Relat Disord 2013;19:339-345.
23. Fahn S, Elton RL; UPDRS Program Members. Unified Parkinson’s Disease Rating Scale. In: Fahn S, Marsen CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson’s Disease. Florham Park, NJ, USA: Macmillan; 1987:153-163.
24. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The PDQ-8: development and validation of a short-form Parkinson’s Disease Questionnaire. Psychol Health 1997;12:805-814.
25. Kostic VS, Perkmezovic T, Tomic A, et al. Suicide and suicidal ideation in Parkinson’s disease. Mov Disord 2011;26:813-818.
26. Reijnders JS, Ehrt U, Weber WE, et al. A systematic review of prevalence studies of depression in Parkinson’s disease. Mov Disord 2008;23:75-81.
27. Blomberg J, Lagergren J, Martin L, Mattsson F, Lagergren P. Complications after percutaneous endoscopic gastrostomy in a prospective study. Scand J Gastroenterol 2012;47:737-742.
28. Ikin M, DeLegge MH, Fang JC, McClave SA, Kundu S, d’Othee BJ, et al. Multidisciplinary practical guidelines for gastrointestinal access for enteral nutrition and decompression from the Society of Interventional Radiology and American Gastroenterological Association (AGA) Institute, with endorsement by Canadian Interventional Radiological Association (CIRA) and Cardiovascular and Interventional Radiological Society of Europe (CIRSE). Gastroenterol 2011;141:742-765.
29. Epstein M, Johnson D, Hawes R, et al. Gastrointestinal safety of the levodopa-carbidopa intestinal gel delivery system in treating advanced Parkinson’s patients [abstract]. Mov Disord 2013;28(Suppl 1):402.
30. Rajabally YA, Martey J. Neuropathy in Parkinson disease: prevalence and determinants. Neurology 2011;77:1947-1950.
31. Toth C, Brown MS, Furtado S, Suchoworsky O, Zachodne D. Neuropathy as a potential complication of levodopa use in Parkinson’s disease. Mov Disord 2008;23:1850-1859.
32. EPAG, Blomberg J, Lagergren J, Martin L, Mattsson F, Lagergren P. Complications after percutaneous endoscopic gastrostomy in a prospective study. Scand J Gastroenterol 2012;47:737-742.
33. Cornblath DR, Ares Pensado B, et al. Efficacy of long-term continuous subcutaneous apomorphine infusion in advanced Parkinson’s disease with motor fluctuations: a multicenter study. Mov Disord 2008;23:1130-1136.
34. Ilkin M, DeLegge MH, Fang JC, McClave SA, Kundu S, d’Othee BJ, et al. Multidisciplinary practical guidelines for gastrointestinal access for enteral nutrition and decompression from the Society of Interventional Radiology and American Gastroenterological Association (AGA) Institute, with endorsement by Canadian Interventional Radiological Association (CIRA) and Cardiovascular and Interventional Radiological Society of Europe (CIRSE). Gastroenterol 2011;141:742-765.
35. Epstein M, Johnson D, Hawes R, et al. Gastrointestinal safety of the levodopa-carbidopa intestinal gel delivery system in treating advanced Parkinson’s patients [abstract]. Mov Disord 2013;28(Suppl 1):402.
36. Rajabally YA, Martey J. Neuropathy in Parkinson disease: prevalence and determinants. Neurology 2011;77:1947-1950.
37. Freeman R, Cornblath D, Anand P, et al. Incidence of peripheral neuropathy in advanced Parkinson’s subjects treated with levodopa-carbidopa intestinal gel [abstract]. Mov Disord 2013;28(Suppl 1):403.
38. Muller T, van Laar T, Cornblath DR, et al. Peripheral neuropathy in Parkinson’s disease: levodopa exposure and implications for duodenal delivery. Parkinsonism Relat Disord 2013;19:501-507.
39. Duodopa intestinal gel. Summary of product characteristics. Maid-enhead, UK: AbbVie Limited; 2013.
40. Nyholm D, Klengerno K, Johansson A. Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson’s disease. Eur J Neurol 2012;19:1079-1085.
41. Nyholm D, Duodopa® treatment for advanced Parkinson’s disease: a randomized trial of deep-brain stimulation for Parkinson’s disease. N Engl J Med 2006;355:896-908.
42. Williams A, Gill S, Varma T, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson’s disease (PD SURG trial): a randomised, open-label trial. Lancet Neurol 2010;9:581-591.
43. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA 2009;301:63-73.
44. Martinez-Martin P, Reddy P, Antonini A, et al. Chronic subcutaneous infusion therapy with apomorphine in advanced Parkinson’s disease compared to conventional therapy: a real life study of non motor effect. J Parkinsons Dis 2011;1:197-203.
45. Nyholm D, Constantinescu R, Holmberg B, Dizdar N, Askarm H. Comparison of apomorphine and levodopa infusions in four patients with Parkinson’s disease with symptom fluctuations. Acta Neurol Scand 2009;119:345-348.
46. De Gaspari D, Sari C, Landi A, et al. Clinical and neuropsychological follow up at 12 months in patients with complicated Parkinson’s disease treated with subcutaneous apomorphine infusion or deep brain stimulation of the subthalamic nucleus. J Neurol Neurosurg Psychiatry 2006;77:450-453.
47. García Ruiz PJ, Sesar Ignacio A, Ares Pensado B, et al. Complications after percutaneous endoscopic gastrostomy in a prospective study. Scand J Gastroenterol 2012;47:737-742.
48. Epstein M, Johnson D, Hawes R, et al. Gastrointestinal safety of the levodopa-carbidopa intestinal gel delivery system in treating advanced Parkinson’s patients [abstract]. Mov Disord 2013;28(Suppl 1):402.
49. Rajabally YA, Martey J. Neuropathy in Parkinson disease: prevalence and determinants. Neurology 2011;77:1947-1950.
50. Merola A, Zibetti M, Angrisano S, Rizzi L, Lanotte M, Lopiano L. Duodopa intestinal gel. Summary of product characteristics. Maidenhead, UK: AbbVie Limited; 2013.

Supporting Data

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