

## Initiation and dose optimization for levodopa-carbidopa intestinal gel: Insights from phase 3 clinical trials



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### ABSTRACT

**Background:** Levodopa-carbidopa intestinal gel (LCIG) provides continuous infusion and reduces “off” time in advanced Parkinson's disease (PD) patients with motor fluctuations despite optimized pharmacotherapy.

**Methods:** Clinical experience with 2 LCIG dosing paradigms from phase 3 studies was examined. In an open-label, 54-week study, LCIG was initiated as daytime monotherapy via nasojejunal (NJ) tube then switched to percutaneous endoscopic gastrojejunostomy (PEG-J) tube; adjunctive therapy was permitted 28 days postPEG-J. In a 12-week, double-blind, placebo-controlled, double-dummy trial, patients continued stable doses of existing anti-PD medications, but LCIG replaced daytime oral levodopa-carbidopa and was initiated directly via PEG-J.

**Results:** In the open-label study, 92% of 354 patients received monotherapy at post-PEG-J week 4; mean titration duration was 7.6 days; dosing remained stable post-titration (mean total daily dose [TDD] was 1572 mg at last visit). In the double-blind trial, 84% received polypharmacy; mean titration took 7.1 days for the LCIG arm (TDD post-titration: 1181 mg;  $n = 37$ ). At post-PEG-J week 4, mean “off” time with LCIG was reduced by 3.9 h (open-label/monotherapy study) and 3.7 h (double-blind/polypharmacy trial). NJ treatment (open-label study only) required an additional procedure with related adverse events (AEs) and withdrawals. The most common AEs during PEG-J weeks 1–4 in the open-label/monotherapy and double-blind/polypharmacy trials, respectively, were complication of device insertion (35%, 57%) and abdominal pain (26%, 51%). Discontinuations due to nonprocedure/nondevice AEs were low (2.2%, 2.7%).

**Conclusion:** These results support the option of initiating LCIG with or without NJ and as either monotherapy or polypharmacy.

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### 1. Introduction

Although levodopa has been established as the gold standard

therapy for Parkinson's disease (PD) [1–5], disabling motor complications emerge with ongoing oral levodopa treatment [2–7]. Levodopa-associated motor complications are thought to develop at least in part due to pulsatile dopaminergic stimulation arising from oral levodopa's short half-life and oral route of administration [8–10]. In advanced PD patients, continuous drug delivery with levodopa-carbidopa intestinal gel (LCIG) significantly decreased

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“off” time versus standard oral levodopa-carbidopa immediate release (LC-IR) tablets in randomized [11–13] and open-label studies [14–19].

In countries where LCIG is currently approved, it is typically initiated as monotherapy for advanced PD via a temporary nasojejunal (NJ) tube. However, prior LCIG studies have generally been small, often retrospective, and provided limited information regarding initiation and titration methodology [13,20,21]. We, therefore, retrospectively examined clinical experiences with LCIG initiation and titration, along with efficacy and safety data, from the recent phase 3 studies supporting United States registration, in advanced PD.

One study was an international, open-label, long-term safety, 54-week study of LCIG first as monotherapy via NJ tube followed by percutaneous endoscopic gastrojejunostomy (PEG-J) tube in 354 patients [14,15]. The other registration study was a 12-week, randomized, double-blind, double-dummy, pivotal trial, with direct-to-PEG-J titration along with stable adjunctive therapy, in 71 patients [11]. These studies provided an opportunity to evaluate LCIG initiation (1) as monotherapy or as adjunctive therapy (polypharmacy), and (2) via NJ prior to PEG-J or directly via PEG-J.

## 2. Methods

These studies of LCIG (levodopa 20 mg/mL, carbidopa monohydrate 5 mg/mL) had similar eligibility criteria and safety and efficacy endpoints [11,14,15]. All patients had advanced, levodopa-responsive PD with severe motor fluctuations ( $\geq 3$  h of “off” time/day) despite optimized anti-PD pharmacotherapy. Patients were titrated for dose optimization, maximizing functional “on” time without troublesome dyskinesia (i.e. without dyskinesias that interfere with function or cause meaningful discomfort) while minimizing “off” episodes and troublesome dyskinesia. Initial titration periods were up to 2 weeks; completion was defined as 2 consecutive days with no dose adjustments. The key efficacy endpoint was change in “off” time from baseline assessed by patient diaries [22].

In both studies, after a 16-h daily infusion, the pump was turned off at night and oral LC-IR was permitted. For this report, “LCIG monotherapy” is defined as LCIG alone during the 16-h

infusion day with or without LC-IR at night. Other levodopa formulations and apomorphine were not permitted. Efficacy and safety analyses presented are per individual study protocol unless otherwise noted. No formal statistical comparisons between studies were performed.

### 2.1. Study designs

#### 2.1.1. Open-label study

Patients were to discontinue all adjunctive anti-PD medications (e.g. dopamine agonists, amantadine, catechol-O-methyl transferase inhibitors) prior to receiving LCIG (Fig. 1A) [14,15]. LCIG was initiated via a temporary NJ tube to confirm levodopa response and to optimize LCIG dosing before PEG-J placement. LCIG was titrated as monotherapy (with only LC-IR tablets permitted at night). At the investigator’s discretion, adjunctive anti-PD medications could be reinitiated after 28 days of treatment via PEG-J. Rescue medication, if needed, was extra LCIG doses (or LC-IR if LCIG was interrupted).

#### 2.1.2. Double-blind trial

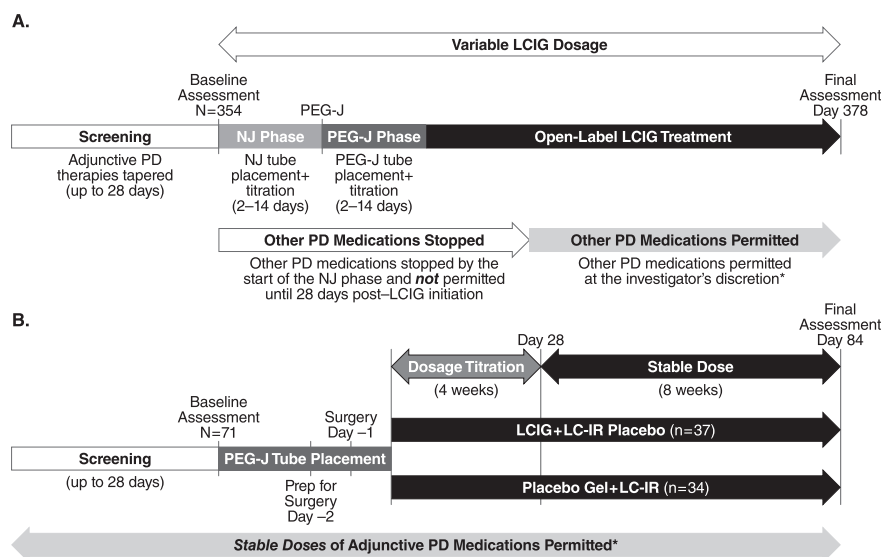
LCIG infusion, initiated via PEG-J, plus placebo capsules was compared with encapsulated LC-IR tablets plus placebo gel infusion (Fig. 1B) [11]. LCIG/LC-IR was titrated during the first 4 weeks, followed by an 8-week treatment period with a stable regimen. All concomitant anti-PD medications (except apomorphine/other levodopa formulations) were continued and kept stable throughout the 12-week study. Rescue medication, if needed, was open-label LC-IR tablets.

### 2.2. LCIG titration schemes

#### 2.2.1. Open-label study

The NJ and PEG-J titration phases each were to be completed 2–14 days. For the initial NJ phase, patients were hospitalized  $\leq 14$  days as needed for titration. The starting LCIG dose was calculated from the total daily dose (TDD) of LC-IR taken the day before NJ placement. The LCIG TDD consisted of individually adjusted morning, continuous maintenance, and extra doses.

The initial morning dose was calculated as a proportion of the patient’s usual morning dose of oral levodopa (typically 60–80%,

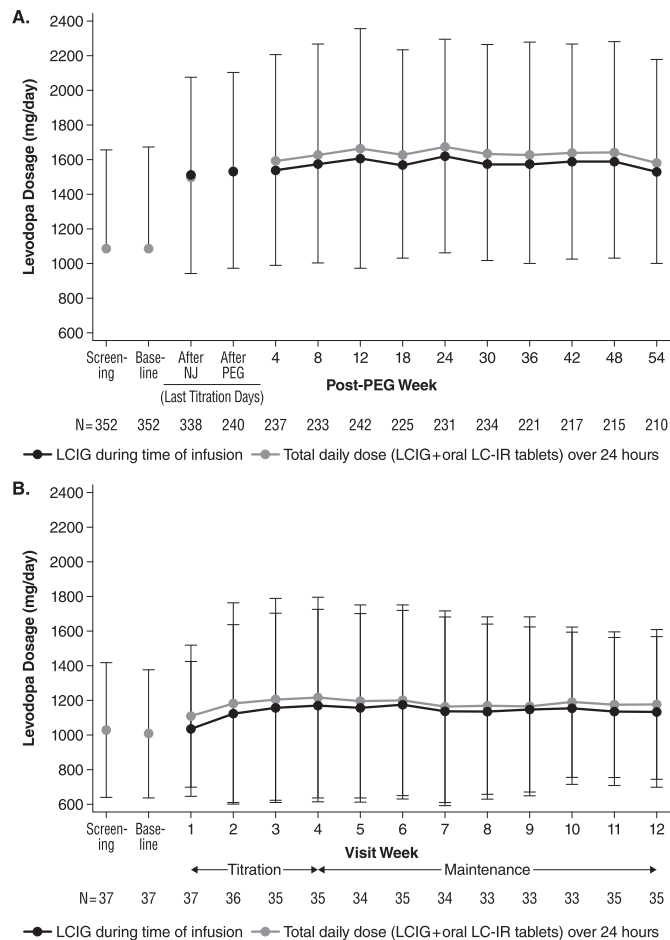


**Fig. 1.** Study designs: A. Open-label study. B. Double-blind study. \*Sustained-release levodopa-carbidopa, other levodopa formulations, and apomorphine excluded. Levodopa-carbidopa intestinal gel (LCIG); levodopa-carbidopa immediate release (LC-IR); nasojejunal (NJ); Parkinson’s disease (PD); percutaneous endoscopic gastrojejunostomy (PEG-J).

depending upon the usual dose). The initial continuous maintenance dose was 90% of the LC-IR TDD prior to LCIG treatment, minus the morning dose, and administered over 16 h. Dosage was adjusted per investigator discretion; patients were monitored hourly for symptoms and dose adjustments. Extra doses to control emergent symptoms were also individualized, with 20-mg incremental change permitted. During titration, extra doses could be self-administered every hour; post-titration only every 2 h. The final NJ dose was the initial PEG-J dose.

### 2.2.2. Double-blind trial

The initial dosage was based on the LC-IR dosing established during screening. To maintain the double-dummy blind, levodopa-carbidopa dose adjustments were made only daily in the morning, as previously described [11]. Both gel infusion and oral capsules were simultaneously adjusted in matched, fixed increments during the titration period, with no change permitted during the maintenance phase, and the pump was locked so patients could not modify the dose. After the initial 2-week, in-hospital titration period, additional adjustments were permitted during weekly



**Fig. 2.** Mean levodopa dosages over time in patients receiving LCIG: A. Open-label study. B. Double-blind study. Note: The mean  $\pm$  SD total daily dose contribution from LCIG is levodopa administered as a morning dose and a continuous maintenance dose (plus, for the open-label study only, the extra LCIG doses that were permitted). LC-IR was used at night when the pump was turned off and replacement in the event infusion was disrupted. Panel A adapted from Fernandez HH, Standaert DG, Hauser RA, Lang AE, Fung VSC, Klostermann F, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson disease: final 12-month, open-label results. *Mov. Disord.* 30 (2015) 500–509. Levodopa-carbidopa intestinal gel (LCIG); levodopa-carbidopa immediate release (LC-IR); nasojejunal (NJ); percutaneous endoscopic gastrostomy (PEG).

visits until week 4. Extra doses were not permitted, although oral LC-IR as rescue medication was allowed.

## 3. Results

### 3.1. Titration, levodopa dosage, and adjunctive therapy

#### 3.1.1. Open-label study

Of 354 enrolled patients, 80% were receiving adjunctive medications at screening along with a mean  $\pm$  SD levodopa TDD of  $1083 \pm 582$  mg/day (Fig. 2A). For the 324 patients who proceeded to the PEG-J phase, the mean  $\pm$  SD time to LCIG dose optimization was  $4.5 \pm 2.1$  days in the NJ period,  $3.1 \pm 2.7$  days for fine-tuning after PEG-J placement, for a total of  $7.6 \pm 3.4$  days. The mean levodopa TDD of LCIG during the last NJ titration day was  $1507 \pm 570$  mg, similar to the  $1532 \pm 561$  mg at the end of PEG-J titration, and increased from screening for nearly all patients. Throughout the study, the mean extra dose was  $43 \pm 20$  mg of levodopa. Patients self-administered a mean  $\pm$  SD  $2.9 \pm 1.5$  and  $1.6 \pm 1.2$  extra doses/day during the NJ and PEG-J titration periods, respectively. On patients' last titration day, which occurred before post-PEG-J week 4, mean total extra LCIG (levodopa) dose was  $120 \pm 120$  mg ( $6 \pm 6$  mL of LCIG;  $n = 252$ ).

The mean TDD remained stable throughout the post-PEG-J period (weeks 4–54), and was  $1572 \pm 566$  mg at last visit, with similar proportions of patients receiving dosing increases or decreases  $>50$  mg and by similar magnitudes. The mean  $\pm$  SD morning levodopa dose of LCIG was  $177 \pm 68$  mg ( $8.9 \pm 3.4$  mL of LCIG). About 86% of patients required a morning dose  $<250$  mg (Table 1). The mean  $\pm$  SD continuous LCIG dosage was  $82 \pm 33$  mg/h. About 85% of patients required a continuous dosage from 40 to 120 mg/h (Table 1). Patients self-administered a mean of approximately 1 extra dose/day (mean  $43 \pm 20$  mg per dose) before visits at post-PEG-J weeks 4 to 54. Starting at week 12 visit,  $>40\%$  of patients did not require extra doses the day prior to scheduled visits.

LCIG was used as daytime monotherapy for the first 4 weeks by 297/324 patients (92%; 8% required early reintroduction of anti-PD medications, as determined by investigators and individually approved by the medical monitor), 86% (236/276) of patients received monotherapy at the end of the study (weeks 49–54), and 76% received monotherapy throughout treatment. The most

**Table 1**  
LCIG doses<sup>a</sup> in the open-label study ( $n = 317$ ).

Morning dose <sup>b</sup>	n (%)
$<50$ mg	2 (<1)
$\geq 50$ – $<100$ mg	31 (10)
$\geq 100$ – $<150$ mg	79 (25)
$\geq 150$ – $<200$ mg	80 (25)
$\geq 200$ – $<250$ mg	81 (26)
$\geq 250$ – $<300$ mg	23 (7)
$\geq 300$ – $<350$ mg	16 (5)
$\geq 350$ mg	5 (2)
Continuous dose	n (%)
$<40$ mg/h	17 (5)
$\geq 40$ – $<80$ mg/h	149 (47)
$\geq 80$ – $<120$ mg/h	119 (38)
$\geq 120$ – $<160$ mg/h	24 (8)
$\geq 160$ – $<200$ mg/h	5 (2)
$\geq 200$ – $<240$ mg/h	3 (1)

LCIG, levodopa-carbidopa intestinal gel.

<sup>a</sup> 1 mL of LCIG contains 20 mg of levodopa.

<sup>b</sup> Morning dose does not include the additional 3 mL of LCIG needed to compensate for the volume needed for tube priming (i.e. equivalent to 60 mg of levodopa administered during the tube flush that occurs after turning off the pump).

common adjunctive medications during the study were dopamine agonists (13%) and amantadine (10%).

### 3.1.2. Double-blind trial

The titration scheme was constrained/limited by protocol blinding, and LCIG replaced only the levodopa portion of patients' prior/routine therapies (only 16% of patients received monotherapy prior to randomization). Despite these limitations, which additionally restricted how rapidly titration could proceed, dose optimization was achieved in a mean  $7.1 \pm 2.5$  days for the LCIG arm ( $n = 37$ ). The mean levodopa TDD was higher versus baseline (Fig. 2B) – increased for practically all patients – with TDD of  $1005 \pm 374$  mg in the LCIG arm at baseline,  $1181 \pm 480$  mg after titration, and a mean  $\pm$  SD rescue dose of  $140 \pm 81$  mg (LC-IR tablets).

### 3.2. Efficacy in each study

At 4 weeks post PEG-J (the first assessment post-titration in both studies), patients in the open-label monotherapy study had a mean change from baseline (improvement) of  $-3.9 \pm 3.1$  h of “off” time, which was similar to the mean change of  $-3.7 \pm 2.5$  h for the LCIG arm in the double-blind adjunctive-therapy trial. “On” time without troublesome dyskinesia increased (improved) by  $4.3 \pm 3.8$  h in the open-label study and, in the double-blind study, by  $3.6 \pm 3.4$  h in the LCIG arm.

At 12 weeks (the double-blind trial's primary endpoint), mean change in “off” time was similar between the open-label study ( $-3.9 \pm 3.2$  h;  $P < 0.001$ ) and LCIG arm of the double-blind trial ( $-3.3 \pm 3.1$  h; Supplemental Fig. 1). The 12-week increase in “on”

time without troublesome dyskinesia also paralleled the change in “off” time in the open-label study ( $4.5 \pm 3.6$  h;  $P < 0.001$ ) and the double-blind trial ( $3.3 \pm 3.3$  h for LCIG).

Discontinuations due to lack of efficacy were rare, occurring in 2 patients in the open-label study (at days 77 and 91) and none of the 37 LCIG patients in the double-blind trial.

### 3.3. Tolerability

#### 3.3.1. NJ (Open-label study only)

Of 354 patients entering the NJ phase of the open-label study, 30 discontinued during the NJ phase due to withdrawal of consent (12 patients, reasons not collected), protocol violation (7 patients), adverse event (AE; 5 patients), lack of efficacy (5 patients; occurring on days 5–8), or administrative reason (1 patient). Of 5 patients discontinuing due to an AE, 2 reported AEs that investigators deemed possibly related to treatment (dysphagia, vomiting, and complication of device insertion during NJ placement in 1 patient and hallucination in the other).

During the NJ phase, 166 patients (47%) experienced AEs; 91 patients (26%) experienced AEs possibly/probably related to treatment. Overall, the most common AEs during the NJ phase were insomnia (7.9%), complication of device insertion (7.3%), and oropharyngeal pain (6.5%; Table 2). For these 3 AEs, all cases were of mild-to-moderate severity except for 1 case of insomnia, which was categorized as severe and resolved the following day. Serious AEs were infrequent (1.7%: hepatic steatosis and syncope for 1 patient; anemia, pneumonia, urinary tract infection, weight decreased, and basal cell carcinoma for 1 patient each).

**Table 2**

Most common adverse events (reported by >5% of patients in any study arm) through the first 4 weeks after PEG-J placement.

Adverse event	NJ period		PEG-J weeks 1–4	
	Open-label ( $n = 354$ )		Open-label ( $n = 324$ )	Double-blind LCIG arm ( $n = 37$ )
	$n$ (%) of patients		$n$ (%) of patients	
Any adverse event	166 (46.9)		254 (78.4)	32 (86.5)
Any serious adverse event	6 (1.7)		44 (13.6)	5 (13.5)
Complication of device insertion <sup>a</sup>	26 (7.3)		112 (34.6)	21 (56.8)
Abdominal pain	7 (2.0)		84 (25.9)	19 (51.4)
Insomnia	28 (7.9)		36 (11.1)	4 (10.8)
Procedural pain	0		59 (18.2)	9 (24.3)
Constipation	13 (3.7)		36 (11.1)	8 (21.6)
Nausea	14 (4.0)		34 (10.5)	9 (24.3)
Oropharyngeal pain	23 (6.5)		24 (7.4)	3 (8.1)
Anxiety	11 (3.1)		20 (6.2)	2 (5.4)
Headache	13 (3.7)		17 (5.2)	1 (2.7)
Vomiting	8 (2.3)		18 (5.6)	2 (5.4)
Incision site erythema	1 (0.3)		23 (7.1)	3 (8.1)
Post-operative wound infection	Not applicable		23 (7.1)	3 (8.1)
Orthostatic hypotension	7 (2.0)		12 (3.7)	4 (10.8)
Pneumoperitoneum	Not applicable		19 (5.9)	4 (10.8)
Dyskinesia	2 (0.6)		14 (4.3)	2 (5.4)
Procedural site reaction	0		16 (4.9)	2 (5.4)
Dizziness	6 (1.7)		8 (2.5)	3 (8.1)
Dyspepsia	4 (1.1)		10 (3.1)	2 (5.4)
Abdominal distension	1 (0.3)		12 (3.7)	2 (5.4)
Flatulence	0		9 (2.8)	6 (16.2)
Diarrhea	2 (0.6)		8 (2.5)	2 (5.4)
Post-procedural discharge	0		9 (2.8)	3 (8.1)
Confusional state	2 (0.6)		4 (1.2)	3 (8.1)
Hiatus hernia	3 (0.8)		3 (0.9)	3 (8.1)
Pyrexia	1 (0.3)		6 (1.9)	2 (5.4)
Atelectasis	1 (0.3)		4 (1.2)	3 (8.1)
Post-operative ileus	1 (0.3)		2 (0.6)	2 (5.4)

NJ, nasojejunal; PEG-J, percutaneous endoscopic gastrojejunostomy. Adverse events reported are treatment-emergent. A single event could be coded to  $\geq 1$  preferred term.

<sup>a</sup> Events with this term were most often additionally coded to abdominal pain.



AEs that could be representative of aspiration/aspiration pneumonia (3.4% of patients) are of particular relevance to the NJ period. Dysphagia and dyspnea were experienced by 3 patients each, gastroesophageal reflux disease and pneumonia were experienced by 2 each, and pyrexia and atelectasis were experienced by 1 each.

### 3.3.2. PEG-J (Open-label and double-blind studies)

The most common AEs during PEG-J weeks 1–4, as assessed for the open-label study ( $n = 324$ ) and in the LCIG arm of the direct-to-PEG-J double-blind trial ( $n = 37$ ), respectively, were complication of device insertion (35% and 57%) and abdominal pain (26% and 51%) (Table 2). In both studies, the most common AEs were associated with the procedure or device and decreased substantially after week 1. The types and incidence of AEs not associated with the procedure or device were similar between the trials; discontinuations for those AEs were similar between those receiving LCIG in the open-label and double-blind studies (2.2% and 2.7%, respectively).

Across the entire 54-week post-PEG-J period of the open-label study ( $n = 324$ ), the most common AEs typically occurred early in the study (during the first week). Overall, serious AEs were reported in 105 (32%) patients, most often complication of device insertion (6.5%), abdominal pain (3.1%), and peritonitis (2.8%) [14]. AEs leading to withdrawal occurred in 22 patients post PEG-J, and the most common were complication of device insertion (6 patients), abdominal pain (3 patients), dyskinesia (2 patients), death of unknown etiology (2 patients), and completed suicide (2 patients; both with a history of depression). There were 8 deaths, with none considered related to the treatment system; 7 were due to AEs that occurred during the PEG-J phase (e.g. suicide in 2 patients; cerebrovascular accident, cachexia, and multiple complications in 1 patient each) [14].

During the full 12-week, double-blind study, the most common AEs generally reflected those occurring in the first week. Overall, serious AEs were generally similar between arms and were reported in 5 (14%) patients in the LCIG arm, with the most common being confusional state ( $n = 2$ ) [11]. Two (5.4%) of the 37 LCIG patients discontinued: psychosis and a protocol violation (difficulty swallowing the oral capsules) for 1 (2.7%) patient each. There were no deaths [11].

## 4. Discussion

The LCIG phase 3 program demonstrated that it is possible to initiate and titrate LCIG as daytime monotherapy in advanced PD (open-label trial) as well as adjunctive therapy with other anti-PD medications (double-blind trial). Further, introduction of LCIG directly via PEG-J, as permitted by current prescribing guidelines, has been shown to be practical and effective while avoiding another procedure and NJ-specific AEs – as well as potential discontinuations – in patients who might otherwise benefit from LCIG therapy.

The goal of titration in these studies was to optimize motor function while minimizing motor fluctuations and disabling dyskinesias. The dose-adjustment methodology in the open-label study utilized flexible titration during the first 2 weeks of treatment. In contrast, the double-blind trial employed a strict/dictated titration methodology to maintain the treatment blind, which restricted how rapidly titration could proceed. However, despite these study differences, time to optimization of LCIG in the double-blind study was comparable to that in the open-label study (means of 7.1 and 7.6 days, respectively).

As expected, mean titrated LCIG dose post PEG-J was higher in the open-label monotherapy study (1532 mg) than that of the double-blind adjunctive trial (1181 mg); however, AEs during the first 4 weeks post PEG-J were generally similar between studies. In

both studies, the mean post-titration TDD for LCIG (1572 mg and 1181 mg at last visit, respectively) was higher than that of oral levodopa at screening (1083 mg and 1097 mg).

In the large open-label study, long-term data over more than a year showed that mean TDD remained steady, patients achieved and sustained a significant improvement in “off” time, and use of extra doses was minimal (a mean of ~1/day in weeks 4–54). Morning and continuous doses typically fell into typical ranges: 86% of patients required a morning dose of <250 mg and 85% required a continuous dosage of 40–120 mg/h. The on-treatment mean TDD (1572 mg at last visit) was generally higher than the mean levodopa TDD at screening (1083 mg), which reflected the discontinuation of adjunctive medications. This increase is also likely to be related to reduced plasma fluctuation with LCIG treatment, which permitted more precise targeting of plasma levels that allowed somewhat higher doses while reducing fluctuations that exceed patients' narrow therapeutic windows.

A key finding in the open-label study was that although 80% of patients had used adjunctive therapies at screening and adjunctive therapy was permitted after the initial 4-week period, three quarters of this advanced PD population received LCIG monotherapy throughout the study. This study provided an example of how complex anti-PD regimens might be converted to much simpler but potentially more effective LCIG monotherapy. Compared with polypharmacy, LCIG monotherapy facilitates ease of dose adjustments, when required, to address AEs or PD symptoms [13] and avoids AEs associated with adjunctive medications that patients may no longer need, such as dopamine agonists. In addition, monotherapy simplifies complicated treatment regimens, which may improve adherence issues including overall compliance and mistimed dosing, particularly in older patients [21,23–25]. In cases where adjunctive treatments are needed (e.g. amantadine or dopamine agonists), reintroduction can be achieved safely without impacting efficacy. Although AEs associated with long-term use of levodopa-carbidopa were not fully evaluated in this study, long-term AE data are being examined. Monotherapy may lead to higher levodopa doses and increase the risk of known levodopa-associated AEs, such as somnolence, compulsive behaviors, depression, nausea, and neuropathy.

The double-blind trial is suggestive that an NJ period is not necessarily required to initiate LCIG. Rather, treatment can begin directly with the PEG-J procedure. This is of great importance because it highlights that patients' motor outcomes may be comparable whether they receive direct PEG-J or temporary NJ placement. NJ requires an additional procedure, and sedation and hospitalization are associated with elevated risks for PD patients [26]. Nonetheless, initiating LCIG via a temporary NJ tube might be helpful in select patients to ensure that they can handle the treatment system with a favorable response prior to permanent PEG-J.

Twelve of the 30 patients who discontinued the open-label study during the NJ period withdrew consent and 5 discontinued due to an AE. As levodopa-responsive PD was a key inclusion criterion, withdrawal due to lack of efficacy was uncommon in the NJ ( $n = 5$ , 1.4%) and PEG-J periods ( $n = 2$ , 0.6%) of the open-label study and did not occur in the LCIG arm of the double-blind trial. The pivotal placebo-controlled trial suggests that careful evaluation of a patient's response to oral levodopa is indicative of response to LCIG. Thus, evaluation of direct-to-PEG-J titration versus an initial NJ phase for individual patients should carefully consider factors including the potential advantages and disadvantages of NJ-tube placement, including tolerance for the NJ procedure and benefit-risk to the patient.

This review has several limitations, primarily that no direct comparative analyses of these 2 unique trials can be performed. LCIG was assessed as flexibly dosed monotherapy via NJ and PEG-J

in an open-label study and as adjunctive anti-PD therapy at stable doses via only PEG-J in a double-blind study. The number of patients and long duration of the open-label study, when compared with previously published literature, lend credibility to the dosing results. The smaller sample size and shorter duration of the placebo-controlled trial limits interpretation; however, its double-blind, double-dummy design is a key strength. Ideally, the use of direct-to-PEG-J titration versus temporary NJ placement should be evaluated prospectively in a single study; similarly, LCIG monotherapy should be evaluated against LCIG treatment with adjunctive anti-PD medication in both the short and long term.

Clinical trial data illustrate that dose optimization with LCIG can be achieved within several days for most patients. Similar reductions in “off” time have been shown whether LCIG was initiated as monotherapy or with ongoing adjunctive anti-PD medications. The rates of discontinuation attributed to AEs that were not procedure/device associated was also similar when LCIG was used as monotherapy or polypharmacy. In practice, monotherapy may facilitate dose adjustments and simplify compliance.

Further, these studies demonstrate that it is feasible to initiate LCIG directly via PEG-J without an initial NJ period, although the results may not be generalizable across the advanced PD population due to variability in individual patient characteristics, such as disease severity and fragility. As the NJ titration period was associated with additional complications (e.g. AEs of insomnia and oropharyngeal pain) and requires another procedure for placement under anesthesia, these data support the safety and efficacy of considering a direct-to-PEG-J initiation. While a subgroup of patients who have failed other therapies or remain difficult to treat may need the NJ tube, NJ placement may be best viewed as an optional procedure after a careful discussion of its potential risks and benefits in select patients.

#### Full financial disclosures of all authors

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#### Author roles

- (1) Conception and design of the study: M.F.L., K.C., J.S.D., J.A.B., V.S.C.F.; acquisition of data: M.F.L., J.T.S., R.K., J.C.M.C., V.S.C.F.; analysis of data: W.Z.R.; interpretation of data: All authors
- (2) Drafting the article or revising it critically for important intellectual content: All authors
- (3) Final approval of the version to be submitted: All authors

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.parkreldis.2015.04.022>.

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