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Editor's comment: Levodopa-carbidopa intestinal gel (LCIG) is a gel suspension of levodopa/carbidopa administered by continuous delivery via portable pump via PEG to a patients who typically have advanced PD. Although an expensive option, the effectiveness of this mode of treatment is confirmed by Antonini et al.'s long term study, which demonstrated a number of positive findings at 12 months, including almost 5 hours less off time, a 20% improvement in motor UPDRS, and worthwhile reductions in non-motor symptoms. 5% of patients had an adverse drug reaction leading to LCIG discontinuation, and the commonest side effects included loss of weight and abdominal pain (5.6 and 3.1% respectively). A particular concern is that of polyneuropathy (noted in 3%), and until the origin of this has been clarified, vitamin B12 supplementation is recommended.

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Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes

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ABSTRACT

Introduction: Intermittent oral delivery of levodopa is a major contributing factor for motor complications in Parkinson's disease (PD). Continuous infusion of levodopa-carbidopa intestinal gel (LCIG) into the jejunum using a portable pump via percutaneous endoscopic gastrostomy (PEG) improves motor complications and quality of life (QoL).
Objectives: To record long-term effectiveness of advanced PD patients undergoing LCIG infusion in routine care, by Unified Parkinson's Disease Rating Scale (UPDRS), Non-Motor Symptoms Scale (NMSS), PDQ-8 and EQ-5D questionnaires.
Methods: Overall, 375 patients from 75 movement disorder centers in 18 countries were enrolled in this prospective non-interventional study. The 12-month interim outcomes of the first 172 included patients are presented here.
Results: There were reductions of mean daily "Off" time from baseline (BL) (7.1 ± 3.5 h) and "On" time with dyskinesias (5.2 ± 4.5 h) at month 12 (M12) of −4.7 ± 3.4 and −1.7 ± 5.0 h respectively ($p < 0.0001$; $p = 0.0228$). UPDRS II and III "On" scores decreased from BL to M12 ($p = 0.0107$ and $p = 0.0128$). Total NMSS and PDQ-8 scores improved at M12 ($p = 0.0014$ and $p = 0.0100$). Mean LCIG dose administered through PEG at first visit (day after implantation) was 1304 ± 618 mg/day and remained stable through M12. Continuous LCIG infusion tolerability and adverse drug reactions were consistent with the known safety profile of previous studies.
Conclusions: This observational, routine-care study supports long-term safety and efficacy of LCIG infusion in advanced PD including motor, non-motor and QoL improvements.

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1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder with a high worldwide prevalence [1]. Levodopa, a dopamine precursor, is the most effective symptomatic therapy for the cardinal motor features of PD [2] but complications such as motor and non-motor response fluctuations and abnormal involuntary movements (dyskinesias) progressively develop in the majority of patients, becoming a major source of disability, substantially interfering with daily activities and social interactions, and impacting quality of life (QoL) [3–5]. Pharmacological strategies to treat motor fluctuations include fragmentation of levodopa doses, combination with catechol O-methyl transferase (COMT) and monoamine oxidase B (MAO-B) inhibitors or dopamine agonists (DA); amantadine has also shown some efficacy on levodopa-induced dyskinesias [6]. Patients failing these approaches may be considered for deep brain surgery (DBS), but continuous drug delivery via infusion therapies is a first line option for those with contraindications or unwillingness to undergo brain surgery.

Levodopa-carbidopa intestinal gel (LCIG) is a stable gel suspension of levodopa/carbidopa (4:1 ratio; 20/5 mg/mL) suitable for continuous delivery in advanced PD patients via portable pump into the duodenum through a percutaneous endoscopic gastrostomy (PEG) with a duodenal extension tube. Treatment with LCIG infusion has been shown to reduce motor fluctuations and dyskinesia in randomized controlled trials [7–9] and several open-label series [10–21].

To date, there are only a few studies conducted in large patient populations over extended follow-up periods. The aim of the current study is to collect clinical outcomes in a large multicenter and multinational cohort of patients with advanced PD receiving LCIG in routine clinical care and to evaluate effects on motor and non-motor symptoms and their impact on QoL over 24 months. Here we present 12-month interim results.

2. Patients and methods

The study was conducted at movement disorder centers (MDCs) in 18 countries (Australia, Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Romania, Slovenia, Spain, Switzerland and United Kingdom). The first patient was enrolled in June 2010, and through June 2013, a total of 375 patients were included at 75 participating specialized MDCs. All patients who were enrolled since start of the study up through November 2012 (n = 172) were included in this 12-month interim analysis.

Male and female patients with advanced PD and motor complications eligible for LCIG treatment according to European Commission Summary Product Characteristics and to national reimbursement criteria were enrolled in this observational study. Treatment with LCIG, consisting of a water-based suspension containing micronized levodopa (20 mg/mL) and carbidopa (5 mg/mL) in methylcellulose (Duodopa®), was administered by continuous duodenal infusion over 16 h using a portable pump (CADD-Legacy); treatment was initiated in participating MDCs according to the standard clinical procedures in routine patient care. In 2010 when this study was launched, commercial LCIG treatment was required to be initiated with a temporary nasoduodenal tube for a recommended duration of approximately 7–14 days to verify drug efficacy and optimize dose and was then continued long-term by a PEG tube. Continuing use of other PD drugs as concomitant treatment to LCIG infusion was allowed in this study at the discretion of the treating physician.

The following efficacy and safety outcomes were assessed: Unified Parkinson's Disease Rating Scale (UPDRS) parts II, III, IV, and V. Complications of therapy (UPDRS IV: Items 32 and 39 were applied according to the Movement Disorder Society (MDS)-UPDRS to allow for calculation of actual hours of "Off" time and "On" time with dyskinesias, items 33 and 34 (dyskinesia severity and painful dyskinesias) were severity coded (0–4) and item 35 reflected the proportion of patients with early morning dystonia), activities of daily living (UPDRS II), motor performance (UPDRS III), both assessed at the "On" state. Non-motor symptoms were assessed using the Non-Motor Symptom Scale (NMSS), and patient reported QoL using disease-specific Parkinson's Disease Questionnaire short version with 8 items (PDQ-8) and generic EuroQoL – 5 Dimensions quality of life instrument (EQ-5D) questionnaires. To assess safety of LCIG infusion, all adverse drug reactions (ADR) were recorded during both temporal nasoduodenal tube and permanent PEG tube infusion. ADR were defined as adverse events reported by the investigator as "unlikely," "possibly," or "probably" related to the study drug system.

Data were recorded at baseline (BL) prior to initiation of LCIG, at day 1 (D1) of continuous LCIG infusion via PEG (defined as the first assessment after a run-in period with temporary nasoduodenal administration), and at follow-up visits 6 (M6) and 12 months (M12) thereafter.

UPDRS II, III, IV and V, and NMSS data were summarized with descriptive statistics. QoL data were analyzed according the validated standard procedures defined for the two questionnaires (PDQ-8 and EQ-5D). Paired t-tests and ANOVA on matched pairs over time were used for statistical testing of efficacy and QoL data comparing BL with D1, M6, and M12. ADRs were MedDRA-coded and summarized on a per-subject basis. Out of the 172 enrolled patients as of November 2012, efficacy data was analyzed for all patients with at least one follow-up visit (n = 148). All patients who received any infusion of LCIG (either via temporal nasoduodenal tube or with subsequent long-term PEG were included in the safety analysis population (n = 159)).

The protocol, patient information and informed consent were approved in all countries by national and/or local independent ethics committees and health authorities according to the applicable national regulatory requirements.

Table 1
Baseline patient demographics and disease characteristics.

Demographics	
Gender	
Female	96 (55.8%)
Male	76 (44.2%)
Age (years)	66.5 ± 9.3
<65 years	60 (35.0%)
≥65 years	112 (65.0%)
Medical history	
Time since PD diagnosis (years)	12.6 ± 6.6
Hoehn and Yahr	2.8 ± 0.8
Dementia	20 (11.7%)
Impulse control disorder	26 (15.2%)
PD symptoms and QoL measures at baseline	
"Off" time (UPDRS item 39) hours/day	7.1 ± 3.5
Time with dyskinesia (UPDRS item 32) hours/day	5.2 ± 4.5
UPDRS II (activities of daily living) at "On" state	16.5 ± 10.7
UPDRS III (motor examination) at "On" state	26.5 ± 12.3
Non-Motor Symptoms Scale (NMSS total score)	75.3 ± 42.2
Quality of life (PDQ-8 total score)	48.6 ± 19.0
Previous PD medication as reported at baseline	
Levodopa	n (97.1%)
Total daily dose (mg)	884 ± 444
Dopamine agonist	n (64.5%)
COMT inhibitors	n (55.8%)
MAO-B inhibitors	n (33.1%)
Amantadine	n (22.7%)
Other oral medications	n (16.9%)

Data presented in mean ± standard deviation (SD) or number (%).
Parkinson's disease (PD), Unified Parkinson's Disease Rating Scale (UPDRS), Non-Motor Symptoms Scale (NMSS), Parkinson's Disease Questionnaire – 8 item (PDQ-8), Catechol O-methyl transferase (COMT), Monoamine oxidase-B (MAO-B).

3. Results

Demographics, medical history, and PD characteristics of the 172 enrolled patients are summarized in Table 1. The mean age was 66.5 ± 9.3 years, and mean duration of PD was 12.6 ± 6.6 years. Baseline assessments of motor and non-motor symptoms and patient-reported QoL are presented in Table 1.

The mean ± standard deviation (SD) dose of orally-administered levodopa at BL was 884 ± 444 mg/day and a majority of patients was on one or more additional antiparkinsonian drugs, mainly COMT inhibitors and DAs (Table 1). At the start of LCIG, approximately half of the patients were using oral levodopa, and approximately 40% were using other anti-PD medications; these proportions decreased to approximately 25% for both oral levodopa and other anti-PD medications at M12. Primary reasons to start LCIG treatment were disabling "Off" periods and dyskinesias, present in 94.8% and 62.8% of patients, respectively. The median duration of infusion per day was 16 h at D1. The mean ± SD total daily LCIG dose was 1304 ± 62 mg/day at D1 and remained

relatively stable through M6 (1350 ± 624 mg/day) and M12 (1412 ± 650 mg/day). An additional morning dose was administered in 93.1% of patients, and extra boli were administered in all patients, with a mean ± SD of 1.7 ± 1.3 boli/day (41.2 ± 20.9 mg/bolus). At M12 the proportion of patients with a morning dose or extra boluses declined to 73.0% and 77.4%, respectively, while the frequency and doses of the administered boli remained similar (2.0 ± 1.4 boli/day; 42.6 ± 22.5 mg/boli).

Out of the 172 patients, 24 (14.4%) discontinued LCIG prematurely: 8 (4.7%) during the run-in period (LCIG infusion via nasoduodenal tube), 14 (8.1%) by M6, and a further 2 (1.2%) by M12. Reasons for premature discontinuation included adverse events (ADRs, concomitant diseases, or death; n = 15, 8.7%), withdrawal of consent (n = 5, 2.9%), and lack of efficacy (n = 4, 2.3%). A total of 33 patients (19.2%) did not return after inclusion to one of the follow-up visits: 5 (2.9%) at D1, 13 (7.6%) at M6 and 15 (8.7%) at M12, and were considered as "lost to follow-up." Thus, of the 172 patients enrolled, 57 were no longer included in the study, including 24 who discontinued prematurely and 33 lost to follow-up.

The mean ± SD daily hours spent in the "Off" state (UPDRS IV item 39) significantly decreased at D1, M6, and M12 with a maximum reduction of 4.7 ± 3.4 h at M12 ($p < 0.0001$, Fig. 1A). Mean ± SD daily hours of "On" time with dyskinesias (UPDRS IV item 32) significantly decreased at M6 and M12 by 1.7 ± 5.5 and 1.7 ± 5.0 h ($p = 0.0155$ and $p = 0.0228$, respectively). The mean UPDRS item 33 (dyskinesia severity) was reduced from 1.7 ± 1.2 at BL to 0.9 ± 1.2 ($p < 0.0001$) at M12, and UPDRS item 34 (painful dyskinesias) from 0.8 ± 1.1 at BL to 0.6 ± 1.2 ($p = 0.0004$) at M12. The proportion of patients experiencing early morning dystonia (UPDRS item 35) was 50.5% at BL and decreased at M12 to 24.0% ($p = 0.0035$). UPDRS II activities of daily living "On" scores (mean ± SD) were reduced at M12 by 3.1 ± 8.7 points ($p = 0.0107$), respectively, and UPDRS III motor examination "On" scores (mean ± SD) were reduced at M12 by 3.3 ± 11.0 points ($p = 0.0128$) (Fig. 1B).

NMSS total scores (mean ± SD) significantly decreased at M6 and M12 ($p = 0.0001$ and $p = 0.0014$) with a maximum reduction of −22.2 ± 50.6 points at M12 (Fig. 2A). In addition, significant improvements of non-motor symptoms were observed up to M12 in 3 out of the 9 NMSS domains: domain 2 (sleep/fatigue: −7.5 ± 13.1, $p = 0.0001$), domain 6 (gastrointestinal tract: −2.6 ± 7.1, $p = 0.0096$) and domain 7 (urinary: −2.8 ± 8.7, $p = 0.0199$) while significant improvements in domain 3 (mood/cognition: −4.1 ± 16.7, $p = 0.0426$) was evident only at M6.

PDQ-8 scores (mean ± SD) significantly improved at each follow-up with a maximum reduction of −8.6 ± 22.6 at M12 ($p = 0.0100$) (Fig. 2B). In 3 out of the 8 PDQ-8 items significant QoL improvements were observed at M12: item 1 (difficulty getting around in public places: −0.5 ± 1.3, $p = 0.0074$), item 3 (felt depressed: −0.4 ± 1.4, $p = 0.0372$), and item 8 (embarrassed by having PD: −0.5 ± 1.6, $p = 0.0312$) while significant improvements in item 7 (painful muscle cramps and pains: −0.5 ± 1.3, $p = 0.0031$) were evident only at M6.

The EQ-5D descriptive score and visual analog scale (VAS) significantly improved up to M6 by +0.12 ± 0.35 and up to M12 by +0.17 ± 0.25 ($p = 0.0076$ and $p = 0.0001$ respectively; Fig. 2C).

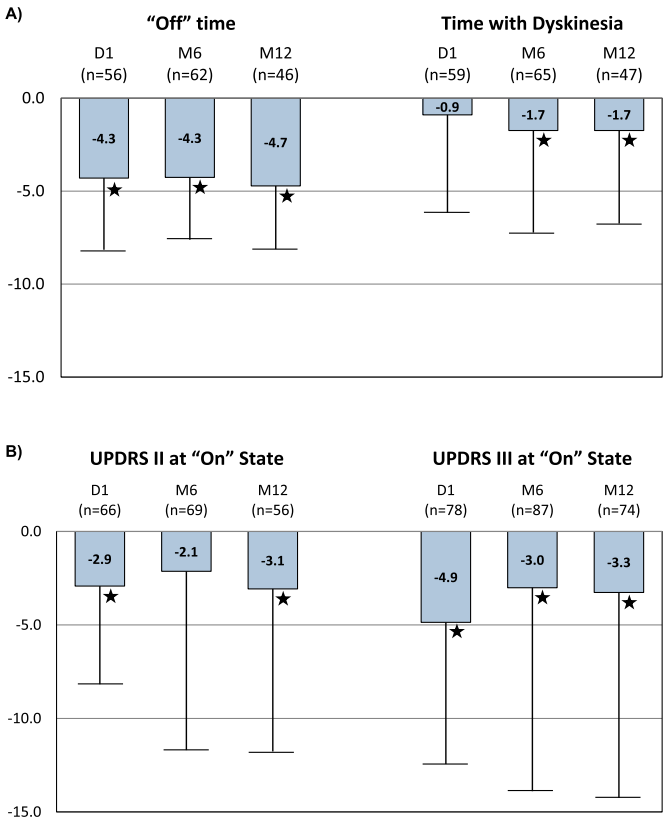

Fig. 1. Mean change from baseline at D1, M6, and M12 of LCIG treatment via PEG tube in A) hours of "Off" time and "On" time with dyskinesias as measured by UPDRS Part IV; B) UPDRS II and UPDRS III scores. Bars are standard deviation. Asterisks represent statistical significance ($p \leq 0.05$) compared to baseline from paired t-test. Unified Parkinson's Disease Rating Scale (UPDRS).

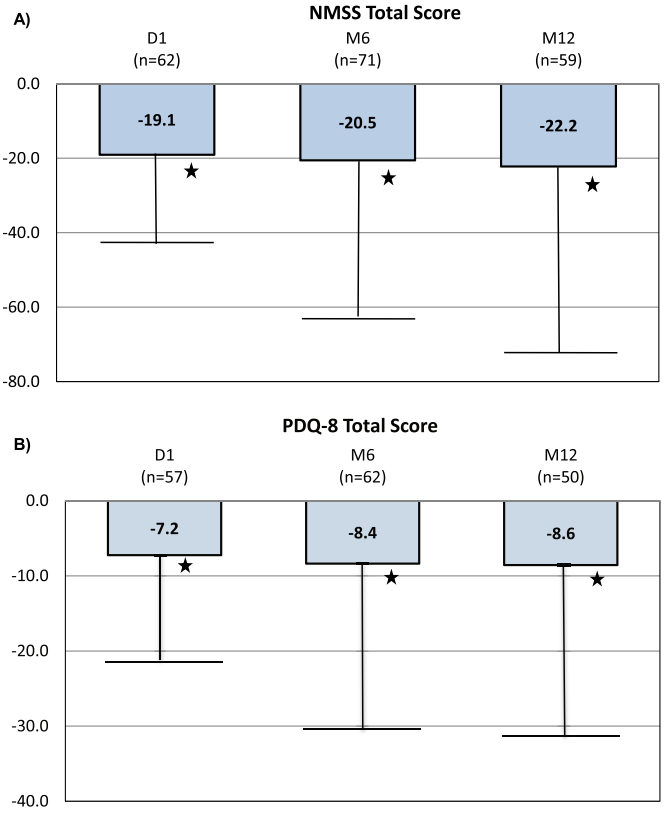

Fig. 2. Non-motor symptoms and quality of life Fig. 2: Mean change from baseline to D1, M6, and M12 of LCIG treatment with PEG tube in A) NMSS total score, B) PDQ-8 total score and C) EQ-5D descriptive score and EQ-5D VAS. Bars are standard deviation. Asterisks represent statistical significance ($p \leq 0.05$) compared to baseline from paired t-test. Non-Motor Symptoms Scale (NMSS), Parkinson's Disease Questionnaire – 8 item (PDQ-8), EuroQuol- 5 dimensions (EQ-5D), Visual Analog Scale (VAS).

During the initial 12-month treatment follow-up of the patients, 75 (47.2%) of the 159 patients in the safety analysis population experienced at least one ADR, and 37 (23.3%) patients experienced serious ADRs (Table 2A). All ADRs with an incidence ≥1.5% are shown in Table 2B. The most common serious ADRs (reported in more than one patient) were: device dislocation (n = 4), post-operative wound infection (n = 2), "On" and "Off" phenomenon (n = 2) and hallucination (n = 2). Eight (5.0%) patients reported an ADR leading to discontinuation of LCIG (Table 2C). Changes of the LCIG infusion rate (temporary interruption, increase or reduction of dose) due to ADRs were recorded in 26 (16.3%) patients. During the period between start of data collection (June 2010) and data base snapshot for this interim analysis, 8 patients died; in the investigators' judgment, none of the deaths were considered to be related to LCIG.

4. Discussion

This investigation represents the largest cohort of advanced PD patients treated with LCIG in routine clinical care, involving 75 movement disorder centers in 18 countries. The population included in this study represents a cohort of advanced PD patients with pronounced motor fluctuations similar to cohorts described in other studies [14,15,20] This interim analysis showed marked improvements on motor complications as well as several non-motor symptoms and QoL, with a safety profile consistent with the published LCIG data [7,8,13,15,16–18].

Specifically, there were robust reductions in total daily "Off" time as recorded via the UPDRS IV item 39. While the original UPDRS requires the patient to judge the percentage of daily "Off" time in 25% increments, use of the descriptors for the corresponding item of the MDS-UPDRS provided more detailed questioning about hours of sleep and wake time reported as daily "Off" hours [22]. The average reduction of 4.7 h is similar to the 4.0 h "Off"-time reduction recorded by patient diary in the LCIG arm of the recent double-blind, double-dummy trial [8].

Patients in the cohort described here also reported significant reductions in daily "On"-time with dyskinesias and dyskinesia severity both at M6 and M12, which is consistent with previous open-label reports [16–20]. Interestingly, the reduction of the severity of dyskinesia was more marked compared to the decrease in the duration of dyskinesias.

The methodology of this observational study did not allow differential assessment of non-troublesome and troublesome dyskinesias, but baseline dyskinesia severity was mild to moderate in this cohort. On average, dyskinesia reduction occurred despite mean increases in daily levodopa exposure after switching from oral levodopa treatment to LCIG, consistent with the concept that there is a therapeutic window in advanced PD and that continuous delivery seems to be a key factor in the management of motor fluctuations [8]. The mean LCIG dose appeared to increase from BL to D1, which was associated with a decrease in concomitant anti-PD use, suggesting that LCIG was increased to compensate for tapering of other medications upon initiation of LCIG. Subsequently, the mean LCIG dose administered through PEG at D1 remained stable over 12 months. Stable LCIG doses were also reported in other studies conducted in medical routine care [14,20] suggesting no tolerance development in long-term treatment.

We also observed an improvement of both UPDRS parts II and III of approximately 20% by M12. Other clinical studies with LCIG also reported significant decreases of the UPDRS II and III scores [13,16], and it is unclear whether UPDRS III improvements primarily reflect continuous delivery and increased effective levodopa dose, or improved mobility as a consequence of reduced dyskinesia severity and "Off" time. Both factors may have contributed to these improvements.

There was a significant improvement in total NMSS score (27% and 29% reduction) at M6 and M12, respectively, which is consistent with the concept that specific non-motor features can be ameliorated by optimizing dopaminergic delivery [23]. Indeed, Storch and colleagues have recently shown that a majority of PD patients with motor fluctuations report greater prevalence of a variety of non-motor symptoms when in the "Off" as compared to the "On" state and also had greater non-motor symptom severity in the "Off" versus "On" state [24]. Improvement in the NMSS does not allow us to establish precisely whether this is linked to "Off" time reduction, but the observation that this was driven by items such as sleep/fatigue and urinary problems supports sensitivity of these domains to dopaminergic therapy [12]. Moreover, presence of sleep/fatigue and urinary problems were also reported in a recent survey as reason for therapy change by both patients and neurologists in a large percentage of advanced PD. [25].

Finally, the beneficial effects observed on the key motor and non-motor outcomes of this interim analysis were also reflected by a marked improvement in quality of life (18% reduction of the PDQ-8 score) [19–21].

Table 2
Safety and tolerability of LCIG infusion.

A) Summary of Adverse Drug Reactions (ADRs)

	Number (%) of patients
Patients with at least one ADR	75 (47.2%)
Patients with at least one ADR possibly or probably related to treatment	66 (41.5%)
Patients with at least one serious ADR	37 (23.3%)
Patients with at least one severe ADR	15 (9.4%)
Patients with at least one ADR leading to LCIG discontinuation	8 (5.0%)
Patients with at least one ADR leading to LCIG interruption	14 (8.8%)
Patients with at least one ADR leading to LCIG decrease	8 (5.0%)
Patients with at least one ADR leading to LCIG increase	4 (2.5%)

B) ADRs reported in patients at an incidence ≥1.5%

Preferred term	Number (%) of patients
Weight decreased	9 (5.6%)
Device dislocation	6 (3.8%)
Abdominal pain	5 (3.1%)
Polyneuropathy	5 (3.1%)
Granuloma	4 (2.5%)
Injection site infections	4 (2.5%)
Postoperative wound infection	4 (2.5%)
Device complication	3 (1.9%)
Gastrointestinal stoma complication	3 (1.9%)
Hallucination	3 (1.9%)

C) ADRs leading to study discontinuation[a]

System/organ class	Preferred term	Number (%) of patients
Cardiac disorders	Cardiac failure	1 (<1%)
	Myocardial infarction	1 (<1%)
General disorders and administration site conditions	Device dislocation	1 (<1%)
	Device infusion issue	1 (<1%)
Gastrointestinal disorders	Nausea	1 (<1%)
	Duodenal ulcer	1 (<1%)
	Gastro-esophageal reflux disease	1 (<1%)
Infections and infestations	Postoperative wound infection	1 (<1%)
Psychiatric disorders	Psychotic disorder	1 (<1%)
Other	Not specified[b]	1 (<1%)

A) Overall summary of adverse drug reactions (ADRs) reported during LCIG infusion with temporary nasoduodenal tube and long-term PEG tube, B) ADRs reported with an incidence of ≥1.5% and C) ADRs leading to study discontinuation.

[a] N = 159 patients in safety analysis, 8 total discontinued due to an ADR. Each patient discontinuation could be attributed to ≥1 ADRs.

[b] Records of treating physician indicated "other" without further specification.

In addition to long-term efficacy, the study confirmed the established safety profile of LCIG over a longer time period. The level of premature discontinuations reported in this study was lower than [16] or comparable with other studies [11]. Discontinuation of treatment with LCIG due to ADRs was observed in 5.0% of patients and related mainly to gastrointestinal or device complications or postoperative wound infection. Complications of LCIG treatment such as postoperative wound infection, site injection infection and granuloma were the most common events. Cases of polyneuropathy were reported in this and also in other studies [11,20] Neuropathy has been considered as a possible complication of LCIG infusion however, the etiology remains unclear [26–30]. It has been suggested that vitamin B12 deficiency might be implicated and that vitamin B12 should be supplemented during LCIG treatment [29]. Physicians should be aware of this possibility and monitor their patients accordingly [29,30].

Since this investigation is being conducted as an observational study collecting data recorded during routine medical care, we consider these outcomes to be close to 'real world' clinical practice. In general, our outcomes are consistent with results generated in controlled short-term clinical studies. The results reported here have been derived from a 12-month interim analysis while recordings of clinical outcomes will continue through 24 months in this large cohort of 375 patients with advanced PD to assess benefits of LCIG infusion over a 2-year period. A limitation of the study is the potential positive selection bias inherent of this type of study design over time, which may reflect real life practice.

In conclusion, the consistent significant and clinically-relevant improvements over 12 months in motor fluctuations, non-motor symptoms and QoL at stable LCIG doses and confirmation of the established safety profile add to the existing evidence of LCIG treatment in advanced PD patients and suggest consideration of LCIG as a long-term treatment strategy in patients with advanced PD.

Disclosures

Angelo Antonini and Werner Poewe have received honoraria for consulting services and symposia from AbbVie. Ashley Yegin, Cornelia Preda and Lars Bergmann are employees of AbbVie, and hold AbbVie stock and/or stock options. This work was funded by AbbVie Inc. AbbVie participated in the study design, research, data collection, analysis and interpretation of data, writing, reviewing, and approving the publication.

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