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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