

Contents lists available at [ScienceDirect](http://ScienceDirect.com)

# Parkinsonism and Related Disorders

journal homepage: [www.elsevier.com/locate/parkreldis](http://www.elsevier.com/locate/parkreldis)

## Levodopa-carbidopa intestinal gel (LCIG) treatment in routine care of patients with advanced Parkinson's disease: An open-label prospective observational study of effectiveness, tolerability and healthcare costs



Sven E. Pålhagen<sup>a,\*</sup>, Olof Sydow<sup>a</sup>, Anders Johansson<sup>b</sup>, Dag Nyholm<sup>b</sup>, Bjorn Holmberg<sup>c</sup>, Hakan Widner<sup>d</sup>, Nil Dizdar<sup>e</sup>, Jan Linder<sup>f</sup>, Tove Hauge<sup>g</sup>, Rasmus Jansson<sup>h</sup>, Lars Bergmann<sup>i</sup>, Susanna Kjellander<sup>j</sup>, Thomas S. Marshall<sup>i</sup>

<sup>a</sup> Department of Neurology, Karolinska University Hospital, Stockholm, Sweden

<sup>b</sup> Department of Neuroscience, Neurology, Uppsala University, Sweden

<sup>c</sup> Department of Clinical Neuroscience, Sahlgrenska University Hospital, Gothenburg, Sweden

<sup>d</sup> Department of Neurology, Skane University Hospital, Lund, Sweden

<sup>e</sup> Department of Neurology and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

<sup>f</sup> Department of Neurology, Neurocentre Norrlands University Hospital, Umeå, Sweden

<sup>g</sup> Department of Neurology, Molde Hospital HNR, Molde, Norway

<sup>h</sup> Department of Geriatric Medicine and Rehabilitation, Sundsvall Hospital, Sundsvall, Sweden

<sup>i</sup> AbbVie Inc., USA

<sup>j</sup> AbbVie AB, Sweden

### ARTICLE INFO

#### Article history:

Received 19 February 2016

Received in revised form

11 May 2016

Accepted 2 June 2016

#### Keywords:

Parkinson's disease

Levodopa

Infusion

LCIG

Cost

### ABSTRACT

**Background:** Continuous infusion of levodopa-carbidopa intestinal gel (LCIG) can effectively manage motor and non-motor complications in advanced Parkinson's disease (PD). Healthcare costs, quality of life (QoL), effectiveness, and tolerability were assessed in routine care treatment with LCIG.

**Methods:** The seventy-seven patients enrolled in this prospective, open-label, 3-year study in routine medical care were LCIG-naïve (N = 37), or had previous LCIG treatment for <2 (N = 22), or ≥2 (N = 18) years. Healthcare costs were collected monthly. PD symptoms and QoL were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS), 39-item Parkinson's Disease Questionnaire (PDQ-39), and EuroQoL 5-Dimension Visual Analog Scale (EQ-5D VAS); LCIG dose, safety, and tolerability were monitored.

**Results:** Mean monthly costs per patient (€8226 ± 5952) were similar across cohorts, remained steady during 3-year follow-up, and increased with PD severity and QoL impairment. In LCIG-naïve patients, significant improvements compared to baseline were observed on the UPDRS total score and PDQ-39 summary index score through 18 months (n = 24; UPDRS, p = 0.033; PDQ-39, p = 0.049). Symptom control was maintained during 3-year follow-up in LCIG-experienced cohorts. Small changes in mean daily LCIG dose were observed. Adverse events were common and generally related to the device, procedure, levodopa, or laboratory evaluations.

**Conclusions:** Costs in LCIG-treated patients were stable over 3 years. LCIG treatment led to significant improvements in motor function and QoL over 18 months in LCIG-naïve patients and no worsening was observed in LCIG-experienced patients over 3 years despite natural PD progression over time. The long-term safety was consistent with the established LCIG profile.

© 2016 AbbVie Inc. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

After long-term treatment with oral levodopa, Parkinson's disease (PD) patients develop motor fluctuations and involuntary

\* Corresponding author. Department of Neurology, Karolinska University Hospital, Huddinge, SE-141 86, Stockholm, Sweden.

E-mail address: [sven.palshagen@karolinska.se](mailto:sven.palshagen@karolinska.se) (S.E. Pålshagen).

movements (dyskinesias) causing disabilities that interfere with daily activities and social interactions, and substantially impact quality of life (QoL) [1]. There is evidence that dyskinesia results from short-duration levodopa response and sensitization of post-synaptic receptors by pulsatile oral dopaminergic stimulation [2]. Clinical study results show that continuous dopaminergic delivery provides more stable levodopa plasma levels compared to oral treatment and control motor and non-motor symptoms in patients with advanced PD [3].

Levodopa-carbidopa intestinal gel (LCIG) is a stable suspension of levodopa and carbidopa, and suitable for continuous delivery via percutaneous endoscopic gastrostomy (PEG) tube with a duodenal extension. LCIG infusion reduced motor and non-motor complications in a randomized, placebo-controlled trial [4], open-label trials, and retrospective investigations extending over follow-up periods of one [5,6] to three years [7–9]. To date, there are few long-term prospective studies assessing healthcare costs associated with LCIG use; one report indicated that compared to standard oral medication, gains in quality-adjusted life years for LCIG were influenced by treatment duration and baseline disease characteristics [10]. A recent study of 10 patients prospectively followed for 12 months showed improvement in motor function and safety, but at an increased cost [11].

The objective of this study was to assess healthcare costs over 3 years, including drug, direct medical, direct non-medical, and indirect costs; to evaluate the impact of LCIG treatment duration and disease severity on healthcare costs; and to monitor long-term LCIG effectiveness and safety in routine medical care. Twelve-month interim results in the LCIG-naïve cohort were previously published [12].

## 2. Methods

### 2.1. Study design

This prospective, open-label, long-term study (EudraCT #2005-002654-21) was conducted in routine care with 3-year follow-up at 10 sites between March 2006 and April 2011. The study was approved by the Regional Committee for Medical and Health Research Ethics at the University Hospital in Trondheim, Norway. In Sweden, the ethical review board considered this investigation as patient follow-up, and approval was not required. Patient signed informed consent was obtained before any study-related procedures.

### 2.2. Patients

Patients on LCIG for  $\geq 12$  weeks prior to the study or naïve to LCIG were eligible. For LCIG-naïve patients, investigators had to consider a change from conventional PD treatment. Criteria for treatment according to the Summary of Products Characteristics (SmPC) for Duodopa<sup>®</sup> had to be fulfilled. Patients suffering from diseases that, in the opinion of the investigator, might interfere with the study objectives or those who the investigator determined to be unable to comply with study requirements were excluded. Patients were allocated to one of the three cohorts: LCIG-naïve, LCIG treatment  $< 2$  years (LCIG $< 2$ Y) or  $\geq 2$  years (LCIG $\geq 2$ Y).

### 2.3. Study assessments

LCIG-naïve patients were assessed while on conventional PD treatment before the initial LCIG infusion: month (M)  $-3$  represents baseline before the initial LCIG infusion and M0 indicates the start of LCIG treatment. Baseline assessments for LCIG $< 2$ Y and LCIG $\geq 2$ Y cohorts were at study inclusion (M0). Follow-up visits

were conducted every 3 months up to M12 and every 6 months thereafter through M36.

Direct medical, direct non-medical, indirect, and drug-related costs were collected monthly through phone interviews by study nurses (Supplementary Table 1). The consumption of healthcare resources was costed out with national product- or service-specific unit costs (Supplementary Table 2). Costs obtained in Swedish Kronor (2010 index) were converted to Euro using the median exchange rate of 2010.

Health-related QoL was measured utilizing the 39-item Parkinson's Disease Questionnaire (PDQ-39) and EuroQoL 5-Dimensions Visual Analog Scale (EQ-5D VAS). PD symptoms were measured by the Unified Parkinson's Disease Rating Scale (UPDRS), the PD stage and best "on" time were assessed with the Hoehn and Yahr (HY) scale, and activities of daily living were measured by the Schwab and England Activity of Daily Living (ADL) Scale. Cognition and mood/depression were monitored using the Mini-Mental State Examination (MMSE) and Montgomery-Åsberg Depression Rating Scale (MADRS). Mean daily LCIG doses (morning dose, continuous maintenance dose, and extra bolus) were recorded by volume of gel (mL) and converted to mg levodopa.

To monitor safety of LCIG treatment, vital signs, clinical laboratory assessments, ECG, and treatment-emergent adverse events (AEs) were recorded. AE classification was determined by the investigator. AEs were defined as those occurring on the first day of LCIG treatment (LCIG-naïve cohort) or inclusion to study (LCIG-experienced cohorts) through 7 days after the last LCIG infusion or end of study participation.

### 2.4. Statistical analyses

To evaluate healthcare costs, it was estimated that 75 patients should be recruited. One protocol-defined interim analysis was performed presenting 12-month outcomes of the LCIG-naïve cohort [12]. No adjustment for multiplicity was applied. Clinical data were analyzed using descriptive statistics. A Wilcoxon signed-rank test was used for statistics of efficacy and QoL data analyzing change from baseline (M-3 for LCIG-naïve cohort; M0 for LCIG-experienced cohorts).

## 3. Results

### 3.1. Patients

Seventy-seven patients enrolled in the study. All patients except one were treated with LCIG and allocated to LCIG-naïve (N = 36), LCIG $< 2$ Y (N = 22), or LCIG $\geq 2$ Y (N = 18). In the LCIG-naïve cohort, 15 patients (41.7%) terminated the study prematurely: due to AEs (n = 7), lack of efficacy (n = 5), withdrawal of consent (n = 2), and protocol violation (n = 1). Six patients (27.3%) in the LCIG $< 2$ Y and 6 patients (33.3%) in the LCIG $\geq 2$ Y cohort prematurely terminated the study due to AEs (n = 5, n = 2), protocol violation (n = 1, n = 2), or withdrawal of consent (n = 0, n = 2) (Supplementary Fig. 1).

Disease characteristics reported at M0 ( $\geq 3$  months after LCIG initiation for LCIG-naïve patients) are presented in Table 1. The mean (SD) duration of prior LCIG infusion at M0 in the LCIG $< 2$ Y and LCIG $\geq 2$ Y was 1.2 (0.7) and 3.5 (1.3) years, respectively. Age, PD symptom scale scores, and QoL measures were lower on average in the LCIG-naïve cohort and higher in the LCIG $\geq 2$ Y cohort, while similar cognitive and mental scores were seen across cohorts (Table 1).

### 3.2. Healthcare costs

The mean total monthly costs per patient were similar in all

**Table 1**  
Demographics and disease characteristics at month 0.<sup>a</sup>

Mean (SD)	LCIG-naïve N = 27	LCIG <2 years N = 22	LCIG ≥2 years N = 18
<b>Demographics</b>			
Age, years	64.6 (6.4)	65.4 (5.2)	66.6 (8.7)
Age at Parkinson's disease diagnosis, years	53.9 (5.1)	51.3 (6.2)	49.1 (10.9)
Age at initiation of levodopa treatment, years	54.1 (5.1)	51.2 (6.2)	49.1 (10.7)
Duration of LCIG treatment at Month 0, years	0.4 (0.1)	1.2 (0.7)	3.5 (1.3)
<b>Unified Parkinson's disease rating scale</b>			
Total Score	43.1 (16.7)	46.2 (17.3)	47.8 (16.4)
Part I: Mentation, Behavior and mood	2.4 (1.8)	2.0 (1.8)	2.7 (1.8)
Part II: Activities of daily living	12.3 (5.1)	13.7 (6.3)	15.4 (5.9)
Part III: Motor examination	22.0 (9.7)	23.4 (11.1)	22.4 (9.8)
Part IV: Complications of therapy	6.5 (2.7)	7.1 (3.4)	7.2 (3.0)
<b>Hoehn and Yahr</b>			
Best "on" stage during last month	2.0 (0.9)	2.5 (0.7)	2.5 (0.7)
Worst stage during last month	3.6 (1.1)	3.7 (0.9)	4.0 (0.6)
<b>EuroQol-5 dimensions</b>			
Societal preferences (Descriptive Score)	0.67 (0.27)	0.68 (0.27)	0.62 (0.24)
Individual preferences (Visual Analog Scale)	0.68 (0.18)	0.65 (0.18)	0.58 (0.23)
<b>39-item Parkinson's disease questionnaire summary index</b>			
	27.1 (11.8)	30.3 (10.7)	36.6 (15.4)
<b>Schwab and England activities of daily living scale</b>			
	80.4 (13.2)	75.5 (14.4)	74.4 (11.5)
<b>Mini-mental status examination</b>			
	27.8 (2.4)	28.0 (2.2)	28.2 (1.4)
<b>Montgomery-Åsberg depression rating scale</b>			
	9.0 (5.3)	7.8 (5.2)	8.8 (5.8)

LCIG, levodopa-carbidopa intestinal gel.

<sup>a</sup> Month 0 was the first follow up ≥ 3 months after LCIG initiation for LCIG-naïve cohort and the study enrollment for LCIG<2Y and LCIG≥2Y cohorts.

three cohorts (Fig. 1a), and the monthly costs per patient remained similar to M0 throughout the 3-year follow-up. The increase between M-3 and M0 on drug costs was due to the initiation of LCIG treatment in the LCIG-naïve cohort (Fig. 1b). The monthly costs per patient increased in relation to severity of PD symptoms and QoL impairment (Fig. 1c, d).

### 3.3. Effectiveness

In the LCIG-naïve cohort, the mean UPDRS total score decreased from baseline to first follow-up and was maintained through M18 ( $p = 0.033$ ) (Fig. 2a). The mean (SD) UPDRS Part IV score decreased from 9.4 (2.6) at baseline to 6.5 (2.7) at M0 ( $p < 0.001$ ) and 6.4 (3.0) at M36 ( $p < 0.001$ ). The mean UPDRS Part II score decreased from 15.5 (5.7) at baseline to 12.3 (5.1) at M0 ( $p < 0.005$ ) and 12.9 (7.7) at M24 ( $p = 0.024$ ). The mean UPDRS Part III score decreased from 24.4 (11.0) at baseline to 22.0 (9.7) at M0 ( $p < 0.005$ ). There were no significant changes in the mean UPDRS Part I score at any time point compared with baseline. The mean PDQ-39 total score decreased from M0 ( $p < 0.001$ ) through M9 and at M18 ( $p = 0.049$ ) (Fig. 2b), and the mean EQ-5D VAS improved from M0 ( $p < 0.001$ ) through M36 ( $p = 0.043$ ) (Fig. 2c).

In LCIG-experienced cohorts, EQ-5D VAS scores numerically improved over the course of the study (Fig. 2c), while the PDQ-39 Summary Index initially decreased (improvement) in the first months and then numerically increased (deteriorated) until the last visit (Fig. 2b). The mean HY, ADL, MMSE, and MADRS scores remained unchanged in all cohorts throughout the 3-year follow-up.

### 3.4. Drug exposure and safety

The mean daily levodopa dose was generally stable from M0 through M36, with only a small numerical increase in daily levodopa dose observed in LCIG-naïve patients over 3 year follow-up (Table 2). In the LCIG-naïve cohort, 80.6% of patients experienced AEs, and all patients in the LCIG<2Y and LCIG≥2Y cohorts reported at least one AE (Table 2). Many AEs were related to the device and associated procedures: device removals/changes, tube dislocations or occlusions, stoma site infections, excessive granulation tissue, or

infections. The other clusters of AEs consisted of events related to PD or levodopa such as gastrointestinal disorders or psychiatric disorders, and were reported by comparable proportions of patients in all cohorts. Two events of polyneuropathy were reported. The AEs most commonly leading to study termination were delusion ( $n = 2$  patients), dementia ( $n = 2$ ), device related infection ( $n = 2$ ), and medical device complication ( $n = 2$ ); the specific AEs leading to discontinuation for 2 patients were not reported.

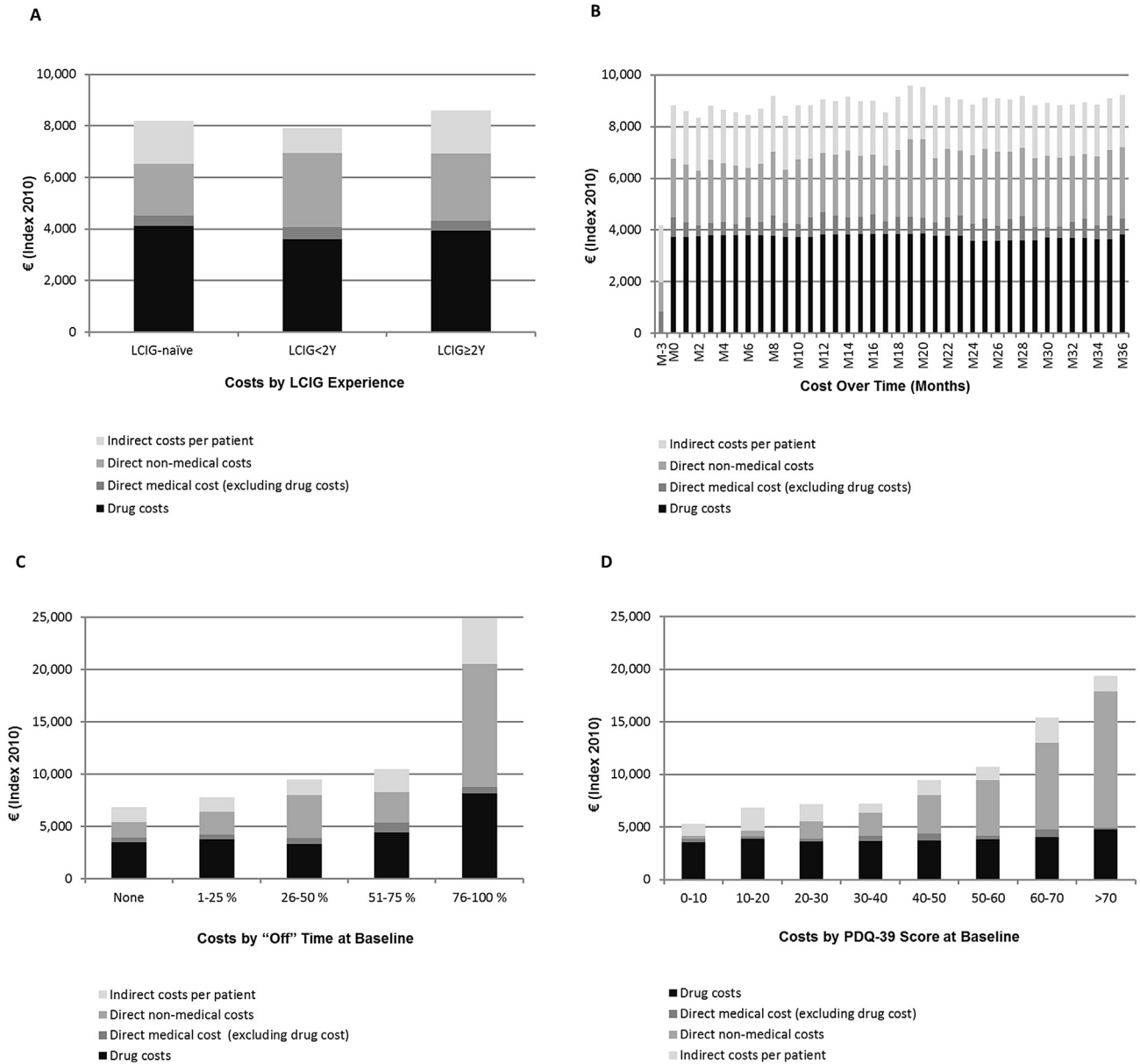
Mean laboratory parameters were generally similar in all cohorts and typically remained stable during 3-year follow-up. For LCIG-naïve, LCIG<2Y and LCIG≥2Y respectively, mean (SD) vitamin B12 levels increased from M0, 499.1 (529.7), 401.5 (214.4), and 472.4 (277.5) pmol/L by 200.7 (752.2), 226.1 (367.4), and 250.0 (592.2) pmol/L. Mean (SD) folic acid levels increased from M0, 120.2 (218.8), 102.3 (150.2), and 86.3 (131.8) nmol/L by 161.2 (435.9), 141.0 (435.9), and 42.1 (181.8) nmol/L. Mean homocysteine levels decreased slightly from M0, 22.7 (10.4), 19.6 (6.2), and 21.4 (9.7) μmol/L by -2.9 (13.34), -0.2 (6.1) and -1.5 (8.3) μmol/L at the final visit.

Four deaths were reported in this study: two in the LCIG-naïve and two in the LCIG<2Y cohorts. The relationship to study drug was classified by the local study investigator to be unrelated ( $n = 2$ ), unlikely related ( $n = 1$ ; drug toxicity related to medications for depression, anxiety, and pain: codeine, paracetamol, mirtazapine, and zopiclone) and possibly related ( $n = 1$ ; cardiac arrest).

## 4. Discussion

This study represents the largest prospective, long-term study evaluating healthcare costs and clinical effectiveness including patient-reported QoL in advanced PD patients treated with LCIG for various durations (naïve, <2 and ≥ 2 years). The long study duration allowed evaluation of outcomes throughout 3 years of follow-up, extending up to a maximum of 6.5 years LCIG exposure in some patients. LCIG-naïve patients included in this study represent a cohort of advanced PD patients similar to routine care populations described in other open-label [6,9] and randomized, controlled [4] trials.

Interestingly, the average monthly costs per patient were generally similar across cohorts suggesting stabilization of PD

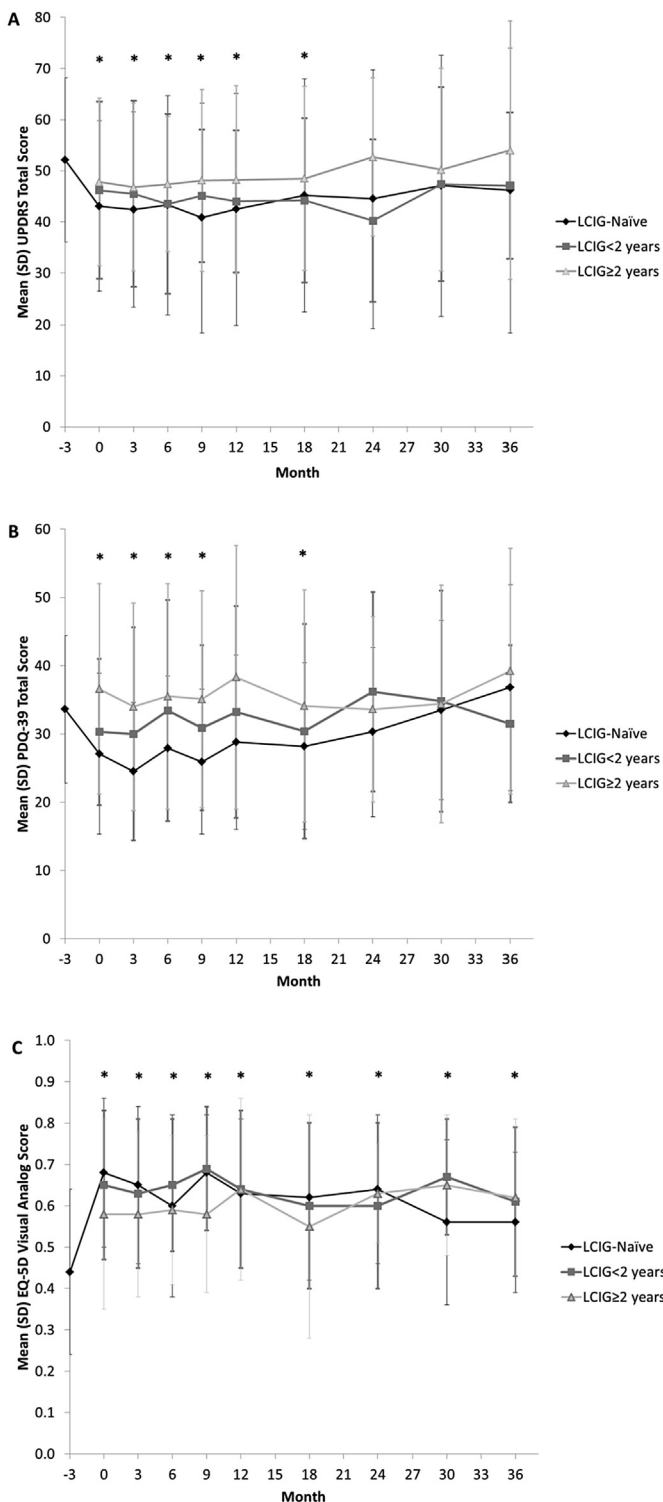


**Fig. 1.** Mean monthly healthcare costs per patient. **a** by LCIG experience; **b** over time (all cohorts combined); **c**) by "off" time at baseline; and, **d**) by PDQ-39 score intervals at baseline. Costs were collected in Swedish Kronor (Index 2010) for each patient on a monthly basis and converted to Euro using the median exchange rate from 2010: n = 37 (LCIG-naïve), n = 22 (LCIG<2 years), n = 18 (LCIG≥2 years).

symptoms and maintenance of QoL, for long-term benefit of LCIG treatment. This might be unexpected since baseline disease characteristics showed a gradual higher age, advanced disease stage, increased severity of symptoms, and impaired QoL across cohorts, likely reflecting the different disease states at start of the 3-year follow-up, and suggesting sustained LCIG benefits across a range of patient characteristics. The only difference over time was an increase in drug-related costs in the LCIG-naïve cohort between baseline (M-3) and first follow-up visit (M0), due to initiation of LCIG treatment; costs in the LCIG-naïve cohort then remained unchanged over the subsequent 3 years. Notably, costs were higher for patients with more severe PD symptoms according to "off" time, or with more affected QoL, so healthcare costs may be better managed in patients with less severe advanced PD. Similarly, a comparison between patients treated with LCIG and matched patients on conventional treatment showed evidence for cost-effectiveness of

LCIG in advanced PD patients [10].

Efficacy results in the LCIG-naïve cohort with LCIG initiation showed marked improvements relative to baseline. In the two LCIG-experienced cohorts, all efficacy assessments were stable, reflecting preservation of PD status, motor performance, and QoL over 3 years. Comparable improvements in UPDRS scores were reported in other, shorter studies, which have also demonstrated that the largest improvements in PD motor symptoms and QoL are typically observed in the immediate months following initiation of LCIG treatment [3,4,13,14,21]. To our knowledge, no other study reported significant improvements of motor complications that were maintained over a 3-year follow-up with QoL benefits, and this is the first report of LCIG efficacy up to 6.5 years. Similar benefits in QoL (PDQ-39 and EQ-5D) were shown recently in open-label, routine-care studies [6,15] and a randomized, controlled trial [4].



**Fig. 2. Clinical efficacy over time by LCIG experience.** **a** Unified Parkinson's Disease Rating Scale (UPDRS) total score; **b** Parkinson's Disease Questionnaire (PDQ-39) total score; and, **c** EuroQol 5-Dimensions visual analog scale (EQ-5D VAS). Asterisks (\*) represent significant changes ( $p \leq 0.05$ ) based on a Wilcoxon signed-rank test compared to baseline for LCIG-naïve patients. M-3:  $n = 36$  (LCIG-naïve baseline); for LCIG-naïve, LCIG < 2 years and LCIG  $\geq 2$  years cohorts, M0:  $n = 27, 22,$  and  $18$ ; M12:  $n = 25, 20,$  and  $17$ ; M24:  $n = 23, 18,$  and  $15$ ; M36:  $n = 21, 16,$  and  $12$ .

The induction benefits at treatment initiation and the maintenance benefits observed during ongoing LCIG treatment were achieved in all three cohorts without significant changes of average daily LCIG dose over 3 years. Other studies conducted in routine care also reported stable LCIG doses over time suggesting that tolerance does not develop with long-term LCIG treatment [8,9].

Nearly all patients experienced at least one AE, mostly commonly an event related to the device or associated procedures. The higher rate of premature terminations observed in LCIG-naïve patients relative to the LCIG-experienced patients may represent a higher potential for AEs during LCIG initiation. Reported incidences of device complications were similar in an open-label study [14] and higher in a randomized, controlled trial [4]. Rates of AEs classified as "psychiatric disorders" and "gastrointestinal disorders" are consistent with the overall profile in advanced PD patients [14–16] and have also been described for oral levodopa-carbidopa [13]. The pattern and frequency of AEs were consistent with the known safety profile based on previous clinical studies [6–9].

Long-term levodopa exposure has been associated with decreased vitamin B12 and increased homocysteine levels [17]. Counterintuitively, in this study, mean values of vitamin B12 and folic acid increased and mean homocysteine levels decreased. Despite this population trend, some AEs of vitamin B12 deficiency or hyper-homocysteinaemia were reported; however, these were not paralleled by clinical abnormalities. Two cases of polyneuropathy were reported, which were mild and considered unrelated by the study investigator. Polyneuropathy has been discussed as a possible complication of LCIG infusion and is listed as potential adverse drug reaction in the SmPC of LCIG, however, the etiology remains unclear [18–20]. Prophylactic vitamin B12 supplementation during LCIG treatment has been proposed [17,20]. Many patients used concomitant supplements in this study, which may have induced the observed laboratory trends and confounded the influence of LCIG. Limitations of data assessments in this study conducted in routine care (different laboratories and reference ranges in participating hospitals, variations in the initiation of vitamin supplementation) prevent a detailed investigation of the vitamin-related findings.

Although this study bears some design-related limitations such as the open-label nature and lack of a control arm, the standardized format of healthcare cost collection and utilization of validated QoL assessments during routine medical care support the robustness of data. Therefore, we consider that outcomes represent "real world" clinical practice. In addition, findings are consistent with results in other open-label studies and a randomized, controlled trial [4–9].

In conclusion, this prospective, long-term study in routine medical care demonstrated significantly improved PD symptoms and QoL through 18M and stable motor function over 3 year follow-up in LCIG-naïve advanced PD patients, despite natural progression of PD over time. Additionally, the data demonstrate stable healthcare costs over 3 years and a significant influence of disease severity and QoL on healthcare costs. The consistency in healthcare costs across cohorts reflects the significant effectiveness after LCIG initiation in naïve patients and sustained stabilization of disease symptoms and QoL throughout LCIG treatment. Combined, the improvement and maintenance in patients treated with LCIG, and the evidence of a correlation between healthcare costs and disease severity are suggestive that LCIG treatment may contribute to stabilizing long-term costs. The economic and clinical outcomes combined with the relative safety and tolerability of LCIG indicates that LCIG treatment has an appropriate benefit-risk profile to consider for long-term treatment of PD.



**Table 2**  
Summary of adverse events and levodopa exposure.

		LCIG-Naïve N = 36	LCIG <2 Years N = 22	LCIG ≥2 Years N = 18
Mean (SD) total daily levodopa dose	M0	1654 (548)	1366 (488)	1514 (886)
	M12	1784 (724)	1376 (496)	1650 (884)
	M24	1898 (794)	1410 (530)	1448 (502)
	M36	1848 (734)	1494 (512)	1572 (596)
Any adverse event		29 (80.6%)	22 (100.0%)	18 (100.0%)
<b>Adverse events occurring in &gt;10% of any cohort</b>				
<b>System organ class</b>				
<b>Preferred term</b>				
Blood and lymphatic system disorders	Anaemia	7 (19.4%)	5 (22.7%)	3 (16.7%)
Gastrointestinal disorders	Constipation	8 (22.2%)	3 (13.6%)	5 (27.8%)
	Oesophagitis	–	1 (4.5%)	3 (16.7%)
Infections and infestations	Bronchitis	–	–	2 (11.1%)
	Device related infection	7 (19.4%)	6 (27.3%)	5 (27.8%)
	Pneumonia	4 (11.1%)	2 (9.1%)	2 (11.1%)
	Urinary tract infection	3 (8.3%)	4 (18.2%)	4 (22.2%)
Injury, poisoning and procedural complications	Device dislocation	10 (27.8%)	9 (40.9%)	6 (33.3%)
	Device occlusion	5 (13.9%)	1 (4.5%)	2 (11.1%)
	Fall	2 (5.6%)	5 (22.7%)	4 (22.2%)
	Medical device complication	1 (2.8%)	–	2 (11.1%)
Investigations	Blood homocysteine increased	2 (5.6%)	4 (18.2%)	6 (33.3%)
Metabolism and nutrition disorders	Dehydration	1 (2.8%)	–	2 (11.1%)
	Hyperhomocysteinaemia	4 (11.1%)	1 (4.5%)	–
	Vitamin b12 deficiency	1 (2.8%)	3 (13.6%)	1 (5.6%)
Musculoskeletal and connective tissue disorders	Back pain	5 (13.9%)	4 (18.2%)	3 (16.7%)
Nervous system disorders	Dizziness	–	–	2 (11.1%)
	Dyskinesia	2 (5.6%)	1 (4.5%)	2 (11.1%)
Psychiatric disorders	Depression	7 (19.4%)	4 (18.2%)	2 (11.1%)
	Hallucination	11 (30.6%)	3 (13.6%)	3 (16.7%)
	Insomnia	6 (16.7%)	3 (13.6%)	1 (5.6%)
Renal and urinary disorders	Micturition urgency	–	6 (27.3%)	2 (11.1%)
	Urinary incontinence	1 (2.8%)	3 (13.6%)	–
Skin and subcutaneous tissue disorders	Excessive granulation tissue	6 (16.7%)	7 (31.8%)	2 (11.1%)
Surgical and medical procedures	Medical device change	15 (41.7%)	14 (63.6%)	4 (22.2%)
	Medical device removal	1 (2.8%)	3 (13.6%)	–

LCIG, levodopa-carbidopa intestinal gel; M, month.

## Funding

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.

## Conflicts of interest statement

Dr. Pålhagen was national coordinator/primary investigator of this study and received compensations from NeuroNova AB, Novartis AB, AbbVie (formerly Abbott) AB and Orion Pharma AB as well as research support from the Swedish Parkinson's Disease Foundation. Dr. Sydow reports grants and non-financial support from AbbVie. Dr. Johansson reports his employer received compensation from Solvay Pharmaceuticals for the extra time and resources required during the conduct of the study; his employer received grants and lecture fees from AbbVie and grants from Medtronic. Dr. Nyholm reports grants from AbbVie, Swedish Research Council, Swedish PD Foundation, Ipsen AB, AstraZeneca as well as personal fees from AbbVie, Nordiclifu Care, from H. Lundbeck AB, Sensidose AB, Liber AB, Movement Disorder Society, Jemardator AB and Netdoktor.se. Drs. Holmberg, Widner, Hauge and Jansson have nothing to disclose. Dr. Dizdar reports her financial institution received financial support to conduct the study from AbbVie (formerly Abbott); she received lecture fees from AbbVie. Dr. Linder reports consulting/lecture fees from AbbVie, lecture fees from Ipsen and compensation for education from H. Lundbeck and Nordiclifu Care. Drs. Bergmann, Marshall and Ms. Kjellander are employees of AbbVie with stock and/or stock options.

## Acknowledgements

Medical writing support was provided by Urs E. Gasser of Clin-Research Ltd, and Jane M. Rodgers and Amy M. Spiegel of AbbVie Inc. Statistical analyses were performed by Statisticon AB, Uppsala, Sweden and the health economic study report was written by The Swedish Institute of Health Economics, Lund, Sweden, funded by AbbVie.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.parkreldis.2016.06.002>.

## References

- [1] S. Chapuis, L. Ouchchane, O. Metz, L. Gerbaud, F. Durif, Impact of the motor complications of Parkinson's disease on the quality of life, *Mov. Disord.* 20 (2005) 224–230.
- [2] G. Fabbrini, J.M. Brotchie, F. Grandas, M. Nomoto, C.G. Goetz, Levodopa-induced dyskinesias, *Mov. Disord.* 22 (2007) 1379–1389 quiz 1523.
- [3] D. Nyholm, H. Askmark, C. Gomes-Trolin, T. Knutson, H. Lennernas, C. Nystrom, S.M. Aquilonius, Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets, *Clin. Neuropharmacol.* 26 (2003) 156–163.
- [4] C.W. Olanow, K. Kieburtz, P. Odin, A.J. Espay, D.G. Standaert, H.H. Fernandez, A. Vanaganas, A.A. Othman, K.L. Widnell, W.Z. Robieson, Y. Pritchett, K. Chatamra, J. Benesh, R.A. Lenz, A. Antonini, L.H.S. Group, 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.* 13 (2014) 141–149.
- [5] H.H. Fernandez, D.G. Standaert, R.A. Hauser, A.E. Lang, V.S. Fung, F. Klostermann, M.F. Lew, P. Odin, M. Steiger, E.Z. Yakupov, S. Chouinard, O. Suchowersky, J. Dubow, C.M. Hall, K. Chatamra, W.Z. Robieson, J.A. Benesh, A.J. Espay, Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results, *Mov. Disord.* 30 (2015) 500–509.

- [6] A. Antonini, A. Yegin, C. Preda, L. Bergmann, W. Poewe, G. s. investigators, coordinators, 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, *Park. Relat. Disord.* 21 (2015) 231–235.
- [7] A. Antonini, P. Odin, L. Opiano, V. Tomantschger, C. Pacchetti, B. Pickut, U.E. Gasser, D. Calandrella, F. Mancini, M. Zibetti, B. Minafra, I. Bertaina, P. De Deyn, C. Cras, E. Wolf, S. Spielberger, W. Poewe, Effect and safety of duodenal levodopa infusion in advanced Parkinson's disease: a retrospective multi-center outcome assessment in patient routine care, *J. Neural Transm. (Vienna)* 120 (2013) 1553–1558.
- [8] D. Nyholm, K. Klangemo, A. Johansson, Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson's disease, *Eur. J. Neurol.* 19 (2012) 1079–1085.
- [9] M. Zibetti, A. Merola, V. Ricchi, A. Marchisio, C.A. Artusi, L. Rizzi, E. Montanaro, D. Reggio, C. De Angelis, M. Rizzone, L. Lopiano, Long-term duodenal levodopa infusion in Parkinson's disease: a 3-year motor and cognitive follow-up study, *J. Neurol.* 260 (2013) 105–114.
- [10] J. Lowin, A. Bergman, K.R. Chaudhuri, L.J. Findley, C. Roeder, M. Schifflers, E. Wood, S. Morris, A cost-effectiveness analysis of levodopa/carbidopa intestinal gel compared to standard care in late stage Parkinson's disease in the UK, *J. Med. Econ.* 14 (2011) 584–593.
- [11] C. Lundqvist, A.G. Beiske, O. Reiertsen, I.S. Kristiansen, Real life cost and quality of life associated with continuous intraduodenal levodopa infusion compared with oral treatment in Parkinson patients, *J. Neurol.* 261 (2014) 2438–2445.
- [12] S.E. Pålhagen, N. Dizdar, T. Hauge, B. Holmberg, R. Jansson, J. Linder, D. Nyholm, O. Sydow, M. Wainwright, H. Widner, A. Johansson, Interim analysis of long-term intraduodenal levodopa infusion in advanced Parkinson disease, *Acta Neurol. Scand.* 126 (2012) e29–33.
- [13] P. Reddy, P. Martinez-Martin, A. Rizos, A. Martin, G.C. Faye, I. Forgacs, P. Odin, A. Antonini, K.R. Chaudhuri, Intrajejunal levodopa versus conventional therapy in Parkinson disease: motor and nonmotor effects, *Clin. Neuropharmacol.* 35 (2012) 205–207.
- [14] K. Eggert, C. Schrader, M. Hahn, M. Stamelou, A. Russmann, R. Dengler, W. Oertel, P. Odin, Continuous jejunal levodopa infusion in patients with advanced parkinson disease: practical aspects and outcome of motor and non-motor complications, *Clin. Neuropharmacol.* 31 (2008) 151–166.
- [15] A. Antonini, F. Mancini, M. Canesi, R. Zangaglia, I.U. Isaías, L. Manfredi, C. Pacchetti, M. Zibetti, F. Natuzzi, L. Lopiano, G. Nappi, G. Pezzoli, Duodenal levodopa infusion improves quality of life in advanced Parkinson's disease, *Neurodegener. Dis.* 5 (2008) 244–246.
- [16] A. Annic, D. Devos, D. Seguy, K. Dujardin, A. Destee, L. Defebvre, Continuous dopaminergic stimulation by Duodopa in advanced Parkinson's disease: efficacy and safety, *Rev. Neurol. Paris.* 165 (2009) 718–727.
- [17] P.P. Urban, I. Wellach, S. Faiss, P. Layer, T. Rosenkranz, K. Knop, J. Weis, Subacute axonal neuropathy in Parkinson's disease with cobalamin and vitamin B6 deficiency under duodopa therapy, *Mov. Disord.* 25 (2010) 1748–1752.
- [18] A. Merola, M. Zibetti, M.G. Rizzone, M. Troiano, C.A. Artusi, S. Angrisano, D. Cocito, L. Lopiano, Prospective assessment of peripheral neuropathy in duodopa-treated parkinsonian patients, *Acta Neurol. Scand.* 129 (2014) e1–5.
- [19] C. Jugel, F. Ehlen, B. Taskin, F. Marzinzik, T. Muller, F. Klostermann, Neuropathy in Parkinson's disease patients with intestinal levodopa infusion versus oral drugs, *PLoS One* 8 (2013) e66639.
- [20] F. Mancini, C. Comi, G.D. Oggioni, C. Pacchetti, D. Calandrella, M. Coletti Moja, G. Riboldazzi, S. Tunesi, M. Dal Fante, L. Manfredi, M. Lacerenza, R. Cantello, A. Antonini, Prevalence and features of peripheral neuropathy in Parkinson's disease patients under different therapeutic regimens, *Park. Relat. Disord.* 20 (2014) 27–31.
- [21] J.T. Slevin, H.H. Fernandez, C. Zadikoff, C. Hall, S. Eaton, J. Dubow, K. Chatamra, J. Benesh, Long-term safety and maintenance of efficacy of levodopa-carbidopa intestinal gel: an open-label extension of the double-blind pivotal study in advanced Parkinson's disease patients, *J. Park. Dis.* 5 (2015) 165–174.