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Levodopa-carbidopa intestinal gel in advanced Parkinson's: Final results of the GLORIA registry

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ABSTRACT

Introduction: This registry evaluated the 24-month safety and efficacy of levodopa-carbidopa intestinal gel (LCIG) treatment in advanced Parkinson's disease (PD) patients under routine clinical care.
Methods: Motor fluctuations, dyskinesia, non-motor symptoms, quality of life, and safety were evaluated. Observations were fully prospective for treatment-naïve patients (60% of patients) and partially retrospective for patients with ≤12 months of pre-treatment with LCIG (40% of patients). Hours of "On" and "Off" time were assessed with a modified version of the Unified Parkinson's Disease Rating Scale part IV items 32 and 39.
Results: Overall, 375 patients were enrolled by 75 movement disorder centers in 18 countries and 258 patients completed the registry. At 24 months LCIG treatment led to significant reductions from baseline in "Off" time (hours/day) (mean ± SD = −4.1 ± 3.5, $P < 0.001$), "On" time with dyskinesia (hours/day) (−1.1 ± 4.8, $P = 0.006$), Non-Motor Symptom Scale total (−16.7 ± 43.2, $P < 0.001$) and individual domains scores, and Parkinson's Disease Questionnaire-8 item total score (−7.1 ± 21.0, $P < 0.001$). Adverse events deemed to have a possible/probable causal relationship to treatment drug/device were reported in 194 (54%) patients; the most frequently reported were decreased weight (6.7%), device related infections (5.9%), device dislocations (4.8%), device issues (4.8%), and polyneuropathy (4.5%).
Conclusions: LCIG treatment led to sustained improvements in motor fluctuations, non-motor symptoms particularly sleep/fatigue, mood/cognition and gastrointestinal domains, as well as quality of life in advanced PD patients over 24 months. Safety events were consistent with the established safety profile of LCIG.

1. Introduction

Levodopa is the most efficacious drug for the treatment of Parkinson's disease (PD), but the long-term use of standard oral administration is associated with the development of disabling

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motor complications in most patients. Fluctuations in motor response are related to fluctuating peripheral levodopa plasma levels and are often associated with a variety of non-motor symptoms [1–4]. These motor and non-motor complications are aggravated by erratic gastric emptying, and substantially impact daily activities, social interactions, and patient quality of life (QoL) [5,6].

Levodopa-carbidopa intestinal gel (LCIG, also carbidopa-levodopa enteral suspension in the United States, CLES) is continuously delivered to the upper intestine ensuring more stable levodopa plasma levels than standard oral levodopa therapy [7,8]. This reduces motor response fluctuations and has also been shown to improve non-motor complaints commonly associated with chronic oral levodopa treatment [9–14].

To date only a few studies have assessed the long-term safety and efficacy of LCIG treatment in routine clinical care and a majority of these studies included a limited number of patients or lacked systematic collection of efficacy data and adverse events [11,15–19]. The objective of the GLORIA registry (global long-term registry on efficacy and safety of LCIG in patients with advanced Parkinson's disease in routine care) was to prospectively evaluate the long-term effectiveness of LCIG on motor and non-motor symptoms (NMS), QoL, and safety in a large cohort of advanced PD patients.

2. Methods

2.1. Study design

In this 24-month (M), multi-national, non-interventional, observational registry, advanced PD patients with persistent motor complications received LCIG treatment at 75 movement disorder centers across 18 countries (Australia, Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Romania, Slovenia, Spain, Switzerland, and United Kingdom). The study protocol was approved by national and/or local independent ethics committees and health authorities at each participating institution and country. All patients provided written informed consent before enrollment in the registry.

LCIG treatment was initiated via a temporary nasojejunal (NJ) tube to verify drug efficacy and optimize dose before being administered through PEG-J (according to local label and reimbursement criteria). Concomitant medications were permitted at the discretion of the treating physician.

2.2. Patients

Enrolled participants were male and female advanced PD patients with persistent severe motor complications that were eligible for LCIG treatment according to European Commission Summary Product Characteristics and national reimbursement criteria. Clinical observations were recorded prospectively for up to 24M for LCIG-naïve patients. For patients who had received LCIG for ≤12M before enrollment in the registry, clinical observations were collected retrospectively up to the day of registry enrollment followed by prospective documentation for a total observation period of 24M. Efficacy and safety outcomes were comparable between the retrospective and prospective cohorts (Supplemental Table 1).

2.3. Efficacy

Efficacy outcomes included the mean change from baseline to study visit in the Unified Parkinson's Disease Rating Scale (UPDRS) parts II, III, and IV; “Off” time and the dyskinesia items from UPDRS part IV. UPDRS IV items 39 and 32 were modified by using the rating instructions for the corresponding parts 4.3 and 4.1 of the MDS-UPDRS to allow for calculation of actual hours of “Off” time and “On” time with dyskinesias. UPDRS was conducted in the “On” state. NMS were assessed using the NMS Scale (NMSS) and patient reported QoL measures included the disease-specific 8-item Parkinson's Disease Questionnaire (PDQ-8) and the generic EuroQoL- 5 Dimensions (EQ-5D) descriptive score and visual analog scale (VAS). Efficacy assessments were collected at baseline before LCIG treatment initiation with temporary NJ (concomitant PD medications were administered at the discretion of threating physician), at discharge from hospital following PEG-J placement (D1), 6M, 12M, 18M, and 24M.

Primary efficacy analyses included all patients who had a baseline efficacy evaluation, received ≥1 dose of LCIG and ≥1 post-baseline safety and efficacy evaluation (N = 329). Safety analyses included all patients who received ≥1 dose of LCIG and had ≥1 post-baseline safety evaluation (N = 356). Last visit was defined as a patient's last reported study visit. ANOVA over time and paired t-tests were performed for the comparison of all efficacy outcomes to baseline. The targeted enrollment for adequate sample size was 400 patients. Missing data was accounted for using survey methodology.

2.4. Safety

Adverse drug reactions (ADRs), which included all adverse events with a reasonable possibility of being causally related to the treatment drug or device as determined by the investigator, were recorded for the duration of the registry and for 28 days following a patient's last reported study visit. ADRs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) [20] and categorized by the study investigator as mild, moderate or severe and as having an unlikely, possible or probable relationship to LCIG treatment. Serious ADRs and product complaints were monitored and recorded. Gastrointestinal (GI)-related ADRs reported by the investigator were categorized post hoc by the authors as either procedure-related, device-related, or “other” type of GI reaction not directly related to the procedure or device (e.g. decreased weight, nausea). Daily levodopa equivalent dose (LED) was calculated for the reported administration of LCIG and concomitant oral PD treatment for each study visit, according to published conversion factors [21].

3. Results

Of the 375 patients enrolled, 258 (69%) completed the registry (Supplemental Fig. 1). The mean ± SD exposure to PEG-J was 640.7 ± 198.3 days. Patient demographics, PD characteristics, and baseline assessments of motor symptoms, NMS, and QoL are summarized in Table 1. Over the course of the study, the percentage of patients receiving LCIG as a monotherapy ranged between 36 and 40% (36%, n = 98/273 at M18; 40%, n = 126/316 at M6) (Supplemental Table 2). The most common concomitant medications across all study visits were oral levodopa and dopamine agonists. Among patients that received LCIG as a monotherapy, the mean daily LED ranged from 1509 ± 719 mg at D1 (n = 126) to a maximum of 1795 ± 878 mg at M18 (n = 98). The mean daily LED for patients with LCIG combination therapy ranged from 1960 ± 873 mg at D1 (n = 225) to a maximum of 2013 ± 880 mg at M6 (n = 189) (Supplemental Table 2).

3.1. Efficacy

At last visit, LCIG-treated patients showed significant reductions in “Off” time compared to baseline (modified UPDRS IV item 39, mean change from baseline ± SD = −3.9 ± 3.5 h/day, 95% CI = [-4.4, −3.5], $P < 0.001$, n = 207) (Fig. 1A). Significant and sustained

Table 1
Baseline demographics and disease characteristics.

Characteristic	Value
Age, years, mean ± SD	66.4 ± 8.8
Sex, n (%)	
Male	220 (58.7)
Female	155 (41.3)
LCIG History, n (%)	
LCIG-naïve	225 (60)
LCIG ≤ 12M before enrollment	150 (40)
Baseline LED, mg/day, mean ± SD	1319 ± 617
PD duration, years, mean ± SD	12.7 ± 6.3
Hoehn & Yahr, mean ± SD	
During "On"	2.8 ± 0.8
During "Off"	4.0 ± 0.9
UPDRS Part IV, hours/day, mean ± SD	
Modified item 39: "Off" time	6.0 ± 3.2
Modified item 32: Time with dyskinesia	4.3 ± 3.8
UPDRS Part II (activities of daily living), mean ± SD	16.5 ± 9.8
UPDRS Part III (motor examination), mean ± SD	24.6 ± 12.0
NMSS, total score, mean ± SD	69.2 ± 42.1
PDQ-8 Total Score (quality of life), mean ± SD	46.8 ± 18.6
EQ-5D score, mean ± SD	0.4 ± 0.32
EQ-VAS score, mean ± SD	48.0 ± 21.3
PD medications reported at baseline, n (%)	
Levodopa	367 (97.9)
Dopamine agonists	253 (67.5)
COMT inhibitors	212 (56.5)
MAO-B inhibitors	133 (35.5)
Amantadine	102 (27.2)
Other oral	50 (13.3)

LCIG = levodopa-carbidopa intestinal gel, LED = levodopa equivalent dose, PD = Parkinson's disease, UPDRS = Unified Parkinson's Disease Rating Scale, NMSS = Non-motor symptom scale,PDQ-8 = Parkinson's Disease Questionnaire 8-item, EQ-5D = Euro Quality of Life 5 Dimensions, EQ-VAS = Euro Quality of Life Visual Analog Scale, COMT = catechol-*O*-methyltransferase, MAO-B = monoamine oxidase.

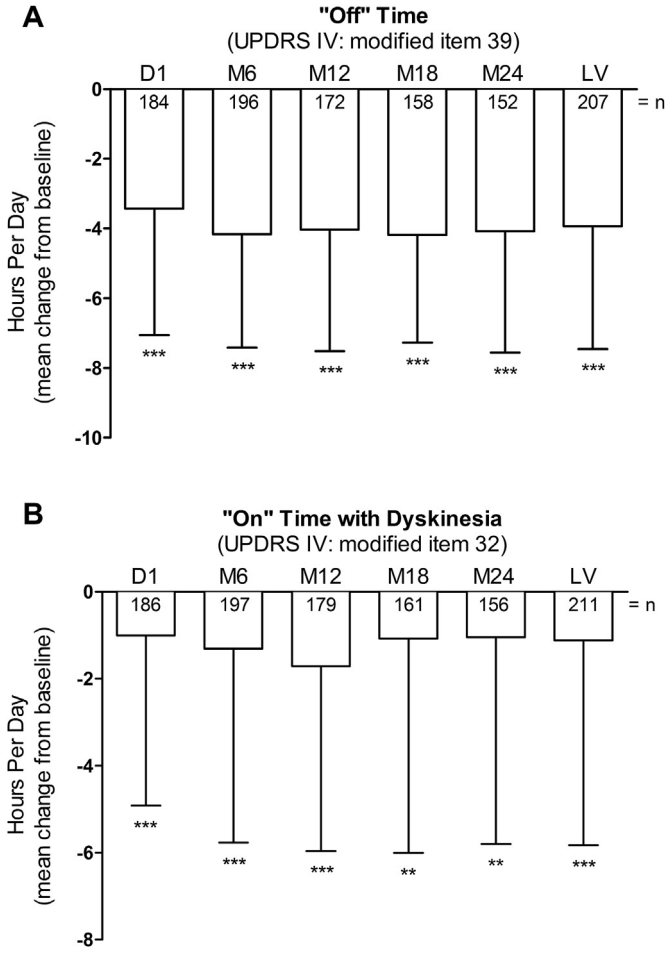

Fig. 1. Motor symptom efficacy. Mean change from baseline of daily hours of A. "Off" time (modified UPDRS Part IV Items 39) and B. "On" time with dyskinesia (modified UPDRS Part IV Item 32). Error bars indicate SD. Asterisks indicate statistical significance compared to baseline in a paired *t*-test at the $P < 0.01$ (**) and $P < 0.001$ (***) levels. UPDRS = Unified Parkinson's Disease Rating Scale; BL = baseline; D1 = discharge from hospital post-PEG-J placement; M = month; LV = patient's last reported study visit.

reductions in "On" time with dyskinesia (modified UPDRS IV item 32) were also observed at last visit (−1.1 ± 4.7, 95% CI = [-1.8, −0.5], $P < 0.001$, n = 211) (Fig. 1B). Additional improvements observed at last visit included UPDRS IV item 33 (dyskinesia severity, −0.9 ± 1.3, 95% CI = [-1.1, −0.7], $P < 0.001$, n = 188), UPDRS IV item 34 (dyskinesia-related pain, −0.6 ± 1.2, 95% CI = [-0.8, −0.4], $P < 0.001$, n = 187), and UPDRS IV item 35 (early morning dystonia, −0.2 ± 0.6, 95% CI = [-0.2, −0.1], $P < 0.001$, n = 250). UPDRS II and III scores (assessed when "On", Supplemental Table 3) showed significant reductions compared to baseline through 18M (−2.0 ± 9.1, 95% CI = [-3.4, −0.5], $P = 0.007$) and 24M (−1.9 ± 11.8, 95% CI = [-3.6, −0.2], $P = 0.026$), respectively.

The NMSS total score was significantly reduced from baseline at all study visits with a mean change of −14.4 ± 44.8 at last visit (95% CI = [-20.3, −8.5], $P < 0.001$, n = 227) (Fig. 2A). At last visit, 5/9 NMSS domain scores were significantly reduced compared to baseline: cardiovascular (last visit: mean change from baseline = −0.6 ± 4.1, 95% CI = [-1.1, −0.0], $P = 0.044$), sleep/fatigue (−4.5 ± 10.6, 95% CI = [-5.9, −3.1], $P < 0.001$), mood/cognition (−2.8 ± 14.7, 95% CI = [-4.7, −0.9], $P = 0.004$), gastrointestinal tract (−2.2 ± 7.3, 95% CI = [-3.1, −1.2], $P < 0.001$), and miscellaneous (−1.5 ± 9.9, 95% CI = [-2.8, −0.2], $P = 0.022$) (Fig. 2B and Supplemental Table 3).

Quality of life, as measured by the PDQ-8, was significantly improved in LCIG-treated patients at every study visit (last visit: −5.3 ± 20.7, 95% CI = [-8.2, −2.5], $P < 0.001$, n = 205) (Fig. 2C). Significant improvements were maintained through last visit in three PDQ-8 items: item 1 (difficulty getting around in public places, −0.4 ± 1.4, 95% CI = [-0.6, −0.2], $P < 0.001$), item 7 (had painful muscle cramps and pain, −0.3 ± 1.4, 95% CI = [-0.5, −0.1], $P = 0.002$), and item 8 (felt embarrassed by having PD, −0.5 ± 1.4, 95% CI = [-0.7, −0.3], $P < 0.001$) (Supplemental Table 4). Significant improvements were observed in the EQ-5D descriptive and VAS scores compared to baseline (18M: EQ-5D, 0.06 ± 0.34, 95% CI = [0.0, 0.1], $P = 0.025$; last visit: VAS, 11.9 ± 28.3, 95% CI = [7.9, 15.9], $P < 0.001$) (Supplemental Table 4).

3.2. Safety

Overall, 194 (54.5%, N = 356) patients experienced one or more ADRs (Table 2). The most frequently reported ADRs during the PEG-J treatment period were decreased weight (6.7%, n = 24), device-related infections (5.9%, n = 21), device dislocations (4.8%, n = 17), device issues (4.8%, n = 17), and polyneuropathy (4.5%, n = 16) (Table 2). Thirty-nine percent of patients (n = 139/356) reported ≥ 1 GI-related ADR during the PEG-J treatment period, of which procedure-related ADRs were reported in 35 patients (9.8%), device-related in 93 (26%), and other GI ADRs in 63 (18%). These ADRs were generally transient, with the highest prevalence of GI-related ADRs (13.5%) and serious GI-related ADRs (4.5%) occurring during the first 2 weeks of LCIG treatment post-PEG-J placement (Supplemental Fig. 2).

Serious ADRs occurred in 109 (30.6%) patients and 55 (15.4%) patients had a severe ADR (Table 2). Device dislocation was the most frequently reported serious ADR during the PEG-J treatment

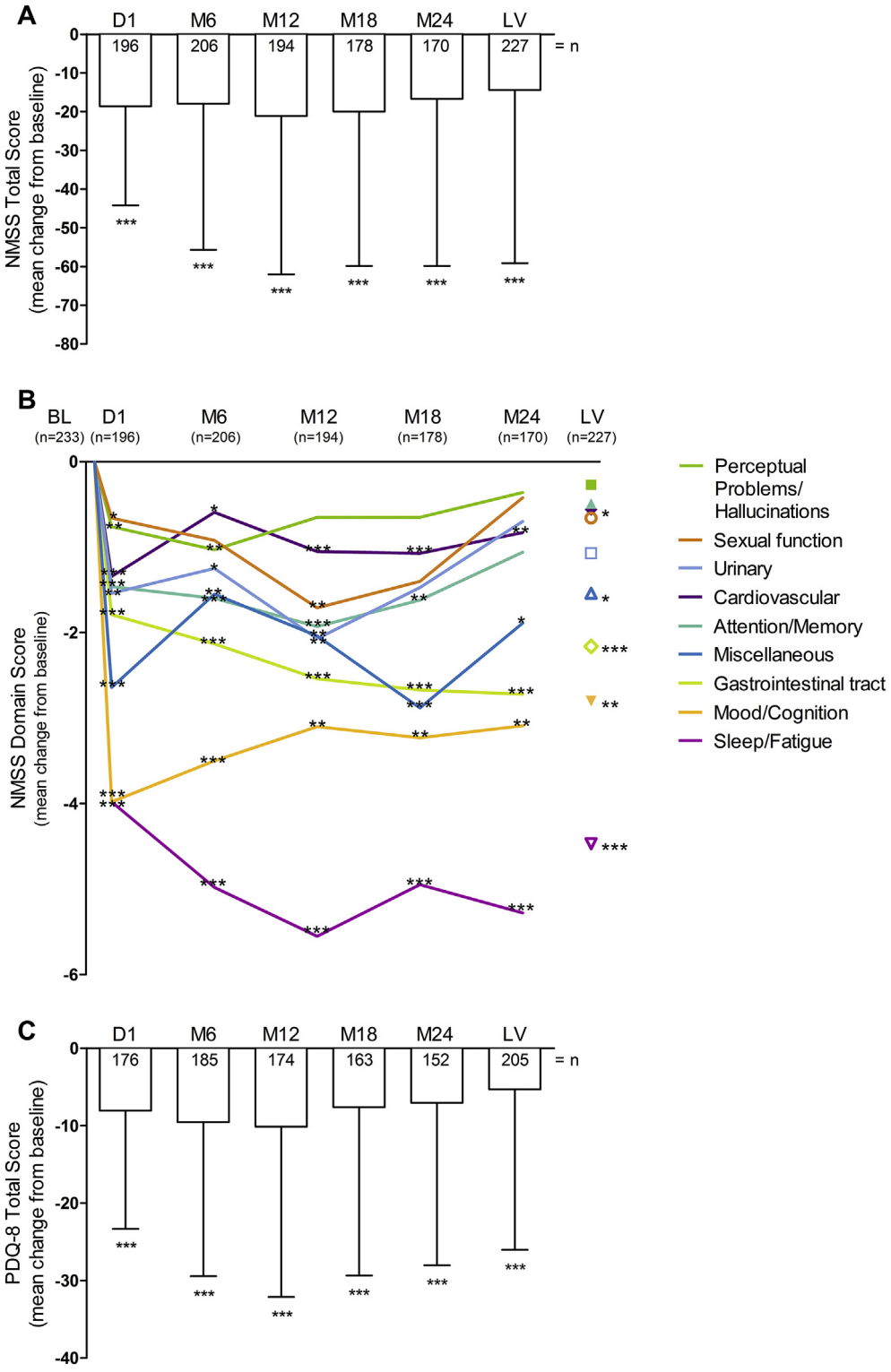

Fig. 2. Non-motor symptom efficacy. Mean change from baseline in A. NMSS total score, B. NMSS domain scores over 2-year follow-up, and C. PDQ-8 total score. Error bars indicate SD. NMSS = Non-Motor Symptom Scale, PDQ-8 = Parkinson's Disease Questionnaire 8-item, BL = baseline; D1 = discharge from hospital post-PEG-J placement; M = month; LV = patient's last reported study visit. $P < 0.05$ (*), $P < 0.01$ (**), and $P < 0.001$ (***).

period (2.2%, n = 8). Twenty-five (7.0%) patients experienced at least one ADR that led to discontinuation of LCIG treatment and device dislocation was the only ADR leading to discontinuation reported by more than 1 patient (n = 2, 0.6%).

Twenty-nine deaths (8%, N = 356) occurred during the registry period: 23 were deemed unrelated to treatment, 5 possibly related, and 1 probably related (Table 2). Of the possibly related deaths, 2 were the result of pneumonia followed by septic shock and/or organ failure on treatment days 463 and 452, 1 occurred on treatment day 511 and was the result of pneumonia followed by a stroke, 1

Table 2
Safety summary.[a]

Safety	n (% of N = 356)
Patients with at least one ADR	194 (55)
Patients with at least one GI-related ADR	139 (39)
Patients with at least one serious ADR	109 (31)
Patients with at least one severe ADR	55 (15)
Deaths	29 (8.1)
Unrelated to treatment	23 (6.5)
Possibly related to treatment	5 (1.4)
Probably related to treatment	1 (0.3)
ADRs occurring in ≥3% of patients	
Weight decreased	*24 (6.7)*
Device related infection	*21 (5.9)*
Device dislocation	*17 (4.8)*
Device issue	*17 (4.8)*
Polyneuropathy	16 (4.5)
Device lead issue	*14 (3.9)*
Medical device complication	*13 (3.7)*
Abdominal pain	*13 (3.7)*
Hallucination	12 (3.4)
Serious ADRs occurring in ≥1% of patients[b]	
Device dislocation	*8 (2.2)*
Device issue	*7 (2.0)*
Parkinson's disease	7 (2.0)
Parkinsonism	7 (2.0)
Medical device complication	*6 (1.7)*
Device malfunction	*5 (1.4)*
Device occlusion	*5 (1.4)*
Abdominal pain	*4 (1.1)*
Hallucination	*4 (1.1)*
Pneumonia	4 (1.1)
Polyneuropathy	4 (1.1)

Gastrointestinal and gastrointestinal procedure-related ADRs are italicized.
ADR = adverse drug reaction (adverse events with a possible/probable relationship to the treatment drug or device), GI = gastrointestinal, LCIG = levodopa-carbidopa intestinal gel, PEG-J = percutaneous endoscopic gastrojejunostomy.
[a] Data indicates incidence of ADRs.
[b] During 24 months of LCIG infusion via PEG-J.

occurred on treatment day 425 and was the result of a fatal seizure, and 1 occurred on treatment day 645 and was the result of unknown causes following a small bowel obstruction that occurred 3 weeks before patient death. The patient death deemed probably related to treatment occurred after 646 days of treatment and was the result of a small bowel perforation and peritonitis.

4. Discussion

This primary analysis of the GLORIA registry represents the largest cohort of advanced PD patients treated with LCIG and provides evidence for the long-term effectiveness in reducing motor fluctuations and dyskinesia during routine clinical care. In addition, there were improvements in QoL and a variety of non-motor symptoms, and the safety profile was overall satisfactory.

LCIG led to sizable reductions in the amount of time patients spent in the “Off” state. On average, patients maintained at least a 50% reduction in “Off” time at every study visit. This reduction in “Off” time observed was well above the 1-h change that is deemed clinically relevant [22] and was consistent with other published open-label studies and randomized controlled trials on LCIG [9–11].

“Off” time improvements occurred alongside reductions in the proportion of “On” time spent with dyskinesia. The average “On” time with dyskinesia was reduced by 25% at 24M. Importantly, this was observed despite increased total levodopa equivalent dose following the switch from oral levodopa to LCIG and increases in LED over the 24M follow-up period. This is consistent with literature suggesting that switching to continuous levodopa delivery improves not only motor fluctuations but also reduces pre-existing dyskinesia [2,6,9,23,24]. Increases in the daily levodopa dose are common in clinical practice when switching from oral PD medications to LCIG and similar magnitudes of LED increase have been previously reported [17]. The continuous nature of levodopa delivery with LCIG often allows for an increase in LED for optimal motor symptom control while limiting many of the undesirable side effects associated with high oral levodopa dose. Given that GLORIA was a registry and not a controlled, clinical trial, there were no specific requirements for dose optimization prior to LCIG initiation. Procedures in this registry reflected the 'real-world' routine clinical setting, where treating physicians determined that all oral treatment options had been exhausted and LCIG was now indicated.

Improvements in UPDRS II and III scores were also observed across the registry, however they were only significant through M18 (UPDRS II) while change at M24 in the UPDRS III score falls below the minimal clinically important difference threshold. These data are similar to those reported in previous studies examining LCIG treatment, including Palhagen et al. [17], and may reflect worsening/progression of the disease. It is important to note that QoL remained improved over all time points in a stable manner which is consistent with other studies on LCIG [9,10,27].

Consistent with the interim analysis of this registry [12] and the EuroInf study [25], LCIG led to a significant reduction in NMS burden at 24M. NMS domains that showed persistent improvement over the entire follow-up period included the cardiovascular, sleep/fatigue, mood/cognition, gastrointestinal tract, and “miscellaneous” domains. Notably, disturbances in sleep/fatigue, which have a strong impact on QoL, showed the greatest magnitude of improvement at 24M, arguing for improved sleep quality as motor fluctuations improved [26].

Given the characteristics of this registry (which included some retrospective data) the safety analyses cannot be directly compared to previous studies, however the most frequently reported ADRs were consistent with the established safety profile of LCIG [9–11,28]. Device and procedure-related events were the most frequently reported ADRs and were generally transient, occurring at highest prevalence within the first 2 weeks post-PEG-J placement. These data emphasize the need for close monitoring in the immediate post-PEG-J placement period. Additionally, the GI-related ADRs were consistent with the known long-term complications of the PEG-J procedure [29]. Given the demographics of the registry population, LCIG procedure and treatment was generally well tolerated, with a low rate of discontinuation due to ADR (7.0%) that was consistent with previously published reports [10]. Of the 29 deaths that occurred during the registry, 5 were deemed possibly related to treatment and 1 was probably related to treatment. The determination of possibly related deaths was based upon the investigator's judgment that there was reasonable support for an association between the treatment and an event (e.g. pneumonia); however, a causal relationship between treatment and death was undetermined. The 1 probably related death, resulting from of a fatal small bowel perforation, occurred after 646 days of treatment and underscores the invasiveness and inherent risks of chronic PEG-J use in an elderly population. Timely investigations of a patient's abdominal complaints and the involvement of GI specialists and interdisciplinary care and management teams may reduce the inherent risks of chronic PEG-J use in the elderly.

This registry provides important clinical data related to the use of LCIG to treat advanced PD patients, however there are some limitations associated with the registry design. These limitations include the registry's open-label design and the lack of a control group, which does not allow for comparative efficacy and safety assessments. This limitation is particularly relevant in evaluating

the significance of LCIG on NMS as a recent double-blind randomized study examining the effects of rotigotine and placebo on NMS severity in PD patients with severe non-motor disability demonstrated similar improvements (>30%) in both the treatment and placebo study groups [30]. Additional limitations include the statistical method employed for the efficacy analyses, which did not carry the last observation forward, and the partially retrospective nature of data collection for 40% of the enrolled patients, which resulted in some missing data during the documentation period.

In conclusion, LCIG treatment in advanced PD patients in routine care led to significant and sustained reductions in motor fluctuations and NMS burden and improvements in QoL, despite natural PD progression over the 2-year follow-up. The safety results were consistent with the previously established safety profile of LCIG.

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Author contributions and disclosures

Dr. Antonini was as a study investigator and has received compensation for consultancy and speaker related activities from Acadia, Sunovion, UCB, Boston Scientific, Angelini, Medtronic, GE, Boehringer Ingelheim, AbbVie, Zambon. He also received research support from Mundipharma. Dr. Antonini's contributions include study concept and design, acquisition and interpretation of the data, and review and critique of the manuscript.

Dr. Poewe was a study investigator and has received compensation from AbbVie, Astra Zeneca, Teva, Novartis, GSK, Boehringer-Ingelheim, UCB, Orion Pharma, Zambon and Merz Pharmaceuticals (consultancy and lecture fees in relation to clinical drug development programmes for PD) outside the submitted work. He has received royalties from Thieme, Wiley Blackwell and Oxford University Press. Dr. Poewe's contributions include study concept and design, acquisition and interpretation of the data, and review and critique of the manuscript.

Dr. Chaudhuri was a study investigator and has received honorarium from UCB, AbbVie, Britannia, Mundipharma, Boehringer Ingelheim, and GSK Pharmaceuticals for lecturing at symposia. He has acted as a consultant for UCB, AbbVie, Britannia, Neuronova and Mundipharma. He has received research funding from Parkinson's UK, NIHR, PDNMG, as well as educational grants from UCB, Britannia, AbbVie, GSK Pharmaceuticals, Boehringer Ingelheim, and Neuronova. Dr. Chaudhuri receives royalties from Oxford University Press and holds intellectual property rights for the Kings Parkinson's Pain Scale and Parkinson's Disease Sleep Scale 2. Dr. Chaudhuri's contributions include acquisition and interpretation of the data, and review and critique of the manuscript.

Dr. Jech was a study investigator and received honoraria from AbbVie, Medtronic, Ipsen, Allergan, Cardion for consultancies and lectures. Dr. Jech's contributions include acquisition and interpretation of the data, and review and critique of the manuscript.

Dr. Pickut was a study investigator and has received compensation from AbbVie, GSK, St. Jude Medical, and Teva for advisory boards, consultancy and speaker-related activities, and research support from Novartis. Dr. Pickut's contributions include acquisition of the data, and review and critique of the manuscript.

Dr. Pirtosek was a study investigator and has received compensation from AbbVie for speaker related activities. Dr. Pirtosek's contributions include acquisition and interpretation of the data, and review and critique of the manuscript.

Dr. Szasz was a study investigator and received compensation from AbbVie, Novartis, UCB, Boehringer-Ingelheim, GSK, Ever, Lundbeck, Teva, Pfizer for speaker activities. Dr. Szasz's contributions include acquisition and interpretation of the data, and review and critique of the manuscript.

Dr. Valldeoriola was a study investigator and received honoraria from AbbVie, Medtronic, Boston Scientific, UCB Pharma and Italfármaco for professional advice and lectures. Dr. Valldeoriola's contributions include acquisition and interpretation of the data, and review and critique of the manuscript.

Dr. Winkler was a study investigator and has participated in advisory boards for AbbVie, UCB, and BIAL, and has received lecture fees from AbbVie, LicherMT, and BIAL. Dr. Winkler's contributions include acquisition and interpretation of the data, and review and critique of the manuscript.

Dr. Bergmann is an employee of AbbVie and holds AbbVie stock and/or stock options. Dr. Bergmann's contributions include acquisition and interpretation of the data, and review and critique of the manuscript.

Dr. Yegin is a former employee of AbbVie. Dr. Yegin's contributions include acquisition and interpretation of the data, and review and critique of the manuscript.

Dr. Onuk is an employee of AbbVie and holds AbbVie stock and/or stock options. Dr. Onuk's contributions include acquisition and interpretation of the data, and review and critique of the manuscript.

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Co-investigator appendix

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Appendix A. Supplementary data

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