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ORIGINAL RESEARCH

Real-World Safety and Effectiveness of 24-Hour Foslevodopa/Foscarbidopa in Parkinson's Disease: ROSSINI Study 6-Month Interim Results

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ABSTRACT

Introduction: Foslevodopa/foscarbidopa (LDp/CDp) is a nonsurgical 24-h continuous subcutaneous infusion for patients with advanced Parkinson's disease (aPD) and motor fluctuations uncontrolled on oral medications. We present the first multicountry real-world data from routine clinical practice.

Methods: ROSSINI (NCT06107426) is an ongoing 3-year multicountry, prospective, observational study of adults with aPD who are LDp/CDp-naïve (cohort A) or transitioning from LDp/CDp open-label extension studies (NCT04379050/NCT04750226, cohort B). For this interim analysis, the primary endpoint was change from baseline to 6 months in OFF time [Movement Disorder Society Unified Parkinson's Disease Rating Scale Part IV (MDS-UPDRS-IV) modified item 4.3]. Safety was assessed by monitoring adverse events (AEs). Interim results for 105 cohort A patients enrolled ≥ 6 months

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by March 24, 2025 are presented only; cohort B results were limited ($n=5$). Mixed-effects models for repeated measurements (continuous outcomes) were utilized, adjusted for country.
Results: Cohort A patients had a mean (SD) age of 68.5 (9.5) years, PD duration of 12.1 (5.3) years, and least squares mean (SE) OFF time of 5.2 (0.6) h at baseline. Patients on LDp/CDp showed statistically significant reductions (95% CI) in OFF time [(– 2.8 h (– 3.6, – 1.9), $P \leq .001$, $n=47/40$ at baseline/month 6], dyskinesia time [– 1.8 h (– 2.6, – 0.9), $P \leq 0.001$], MDS-UPDRS-III [– 5.0 (– 8.2, – 1.9), $P=0.002$], Parkinson's Disease Sleep Scale-2 [– 5.2 (– 8.0, – 2.4), $P \leq .001$], and 39-item Parkinson's Disease Questionnaire [PDQ-39, – 5.6 (– 9.2, – 2.0), $P=.002$] from baseline to month 6. Freezing of Gait Questionnaire, Gastrointestinal Dysfunction Scale in PD, and King's PD Pain Scale likewise showed statistically significant decreases ($P<.05$). Overall, 58 (55.2%) reported ≥ 1 AE, primarily nonserious and mild-to-moderate (12.4% serious, 17.1% severe), with hallucinations and infusion site events the most frequently reported events (5.7% each).
Conclusions: ROSSINI demonstrates reductions in motor fluctuations and nonmotor symptoms, and increased quality of life in patients with aPD after 6 months of LDp/CDp treatment. The safety profile was consistent with clinical trials.
Trial registration: ClinicalTrials.gov identifier, NCT06107426.

PLAIN LANGUAGE SUMMARY

Foslevodopa/foscarbidopa (LDp/CDp) treatment provides continuous medication through a pump that infuses medicine under the skin for people with advanced Parkinson's disease whose motor symptoms are not managed well by oral medications. This study reports global data gathered during routine medical practices. The ROSSINI study is a 3-year observational project involving patients with advanced Parkinson's disease and includes adults who are either new to LDp/CDp treatment (group A) or continuing their treatment from previous studies (group B). The main goal is to observe changes in the daily hours patients experience recurring motor symptoms (OFF time) over 36 months. Patient safety is monitored through reported side effects. This article shares interim findings for 105 group A patients enrolled for at least 6 months. Group A patients had an average age of 68.5 years, a Parkinson's disease duration of about 12 years, and approximately 5.2 daily hours of OFF time. The study shows that LDp/CDp significantly reduced daily OFF time after 6 months, with improvements in disease-specific sleep, pain and gut issues, and overall quality of life. About half of patients reported at least one mild-to-moderate side effect, with some severe or serious; hallucinations and skin reactions were the most common side effects. These preliminary results suggest that LDp/CDp effectively improves both motor and nonmotor

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symptoms, enhancing patients' quality of life, and is safe for use in routine care.

Keywords: Carbidopa; Foslevodopa; Foscarbidopa; Levodopa; Parkinson's disease; Real-world evidence; Treatment

Key Summary Points

Why carry out this study?

Clinical evidence from phase III trials suggests that foslevodopa/foscarbidopa (LDp/CDp) is efficacious at managing symptoms for patients with advanced PD (aPD), but robust real-world (RW) data are needed.

To capture the impact of LDp/CDp in the real world, the first-ever, 3-year, multicountry, prospective, observational, two-cohort, open-label ROSSINI (NCT06107426) study is being conducted to evaluate key motor and nonmotor PD-related outcomes, and safety among adults with aPD who are naïve to treatment (cohort A) or transitioning from LDp/CDp open-label extension studies (NCT04379050/NCT04750226, cohort B).

What was learned from the study

In this first interim analysis of 105 patients from cohort A enrolled for at least 6 months, treatment with LDp/CDp resulted in statistically significant, clinically meaningful, and sustained reductions in motor fluctuations, dyskinesia, motor symptoms, freezing of gait, PD-related sleep disturbances, PD-related pain, PD-related gastrointestinal dysfunction, and increased quality of life over 6 months of treatment. The most common adverse events (> 5%) were hallucinations and infusion site events.

These findings provide the first prospective RW data demonstrating that treatment with LDp/CDp confers sustained motor and nonmotor symptom control with a favorable safety profile among patients with aPD in routine clinical practice.

INTRODUCTION

Patients with advanced Parkinson's disease (aPD) and associated motor complications require a tailored therapeutic approach due to their unique needs and responses to levodopa (LD) [1]. Though effective in the early stages of PD, the duration of efficacy among oral levodopa-containing formulations wanes with advancing PD, necessitating modifications of oral treatments, and, once oral treatments no longer provide sufficient symptomatic control, the use of surgical device-aided therapies (DATs) or nonsurgical continuous subcutaneous infusions (CSCIs) [2]. These include the intrajejunal administration of levodopa/carbidopa intestinal gel/carbidopa-levodopa enteral suspension (LCIG/CLES) or LD/entacapone/CD (LECIG), continuous subcutaneous apomorphine infusion (CSAI), and deep brain stimulation (DBS), with each varying in efficacy and invasiveness [3]. While surgical DATs remain efficacious, they are highly invasive and potentially irreversible which has led to hesitation among patients when considering these treatment options [4]. Foslevodopa/foscarbidopa (LDp/CDp) is a nonsurgical alternative as a highly soluble formulation of LD/CD prodrugs that is delivered by CSCI over 24 h, providing stable LD exposure across a wide range of doses required to manage PD-related motor symptoms [5].

Efficacy and safety data from recent phase III clinical trials demonstrate that LDp/CDp improves motor complications with benefits in both ON time without troublesome dyskinesia and OFF time while demonstrating a favorable benefit/risk profile in patients with aPD when compared with oral immediate-release LD/CD [6] and during open-label extension trials [7–9]. These data illustrate its potential as a nonsurgical treatment alternative that is safe and well-tolerated with flexible dosing for patients with aPD. Nevertheless, robust real-world (RW) evidence surrounding the effectiveness of LDp/CDp among patients with aPD is lacking due to its only recent availability. As such, it is important to evaluate efficacy outcomes used in clinical trials to measure improvements in

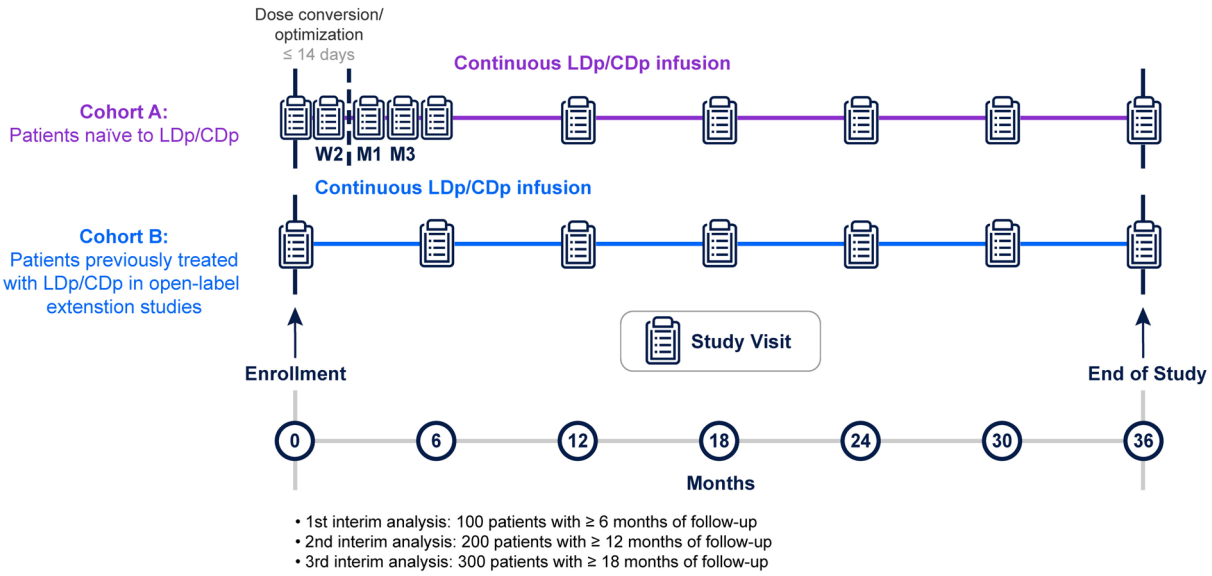

Fig. 1 Study design schematic. *LDp/CDp* foslevodopa/foscarbidopa, *M* month, *W* week

motor fluctuations and PD-related nonmotor symptoms in RW settings.

The purpose of this study is to therefore evaluate the long-term effectiveness, safety, and tolerability of LDp/CDp in patients with aPD during routine clinical practice. The primary objective of this study is to evaluate the long-term effectiveness of LDp/CDp on motor complications. Secondary objectives explore nonmotor symptom- and quality of life (QoL)-changes following treatment, as well as the frequency of safety events. Here, we report for the first time RW 6-month interim data.

METHODS

Study Design

The Real-World Outcomes with Continuous Subcutaneous Levodopa (ROSSINI, NCT06107426) study is an ongoing 3-year multicountry, prospective, two-cohort, open-label investigation of adults with aPD. Across 66 global sites in Australia, Austria, Canada, Denmark, Germany, Israel, Romania, Spain, Sweden, and the United States (US), adults naïve to LDp/CDp (cohort A, $n \approx 400$) or transitioning from LDp/CDp open-label extension (OLE) studies (NCT04379050/NCT04750226, cohort B, up to $n \approx 150$) are being enrolled. The standard deviation (SD) for a change from baseline in hours of OFF time is estimated to 3.5 h based on previous studies with LCIG treatment [10, 11] and with LDp/CDp [9]. Assuming an SD of 3.5 h and a 50% dropout rate at 3 years of follow-up, a target sample size of approximately 400 LDp/CDp-naïve patients for cohort A would yield an estimated precision of 0.49 h for the primary endpoint. Depending on the cohort, patients will attend 7–10 visits over the course of the study (Fig. 1).

In this work, we report on the first interim analysis of 105 patients from cohort A who were enrolled for at least 6 months by March 24, 2025.

Ethical Approval

This study is approved by all global institutions and conducted in accordance with Advarra (central institutional review board; reference number: 00023875); Ethics (Helsinki) Committee at the Sheba Medical Center (0660—23-SMC); Ethics Committee for Investigation with Medicinal Products at Puerta de Hierro Majadahonda

University Hospital (178/23); Ethics Committee of the Medical University of Graz (36—261 ex 23/24); Ethics Committee of the State Medical Association of Baden-Württemberg, Stuttgart (B-F-2023—115); Institutional Review Board (00005790); Ottawa Health Science Network Research Ethics Board (20240555—01H) Royal Melbourne Hospital Human Research Ethics Committee (HREC/103037/MH-2023); Scientific Ethics Committee (none available); and Swedish Ethical Review Board (2023—06693—01) guidelines. Documentation of ethics approval from each country, and their respective institutions, can be found in Supplementary Material 2. Patients consented to fully comply with study-related procedures and prior to their initiation, each patient or legal authorized representative voluntarily signed an Authorization for Use/Disclosure of Data informed consent form according to national regulations after the study was explained and patients' questions were answered.

Patients

Eligible patients included adults 18 years or older with a diagnosis of levodopa-responsive aPD. The decision to initiate treatment with LDp/CDp (cohort A) or continue to treat with LDp/CDp (cohort B) was made by the patients' clinician (movement disorder specialist or general neurologist) prior to any solicitation of study entry. Eligibility for LDp/CDp therapy was in accordance with the approved local label in the participating country and local reimbursement regulations, if applicable.

Patients were excluded if diagnosed with any condition included in the contraindications section of the approved local LDp/CDp label in the participating country or had a Mini-Mental State Examination (MMSE) score of less than 24; however, patients with an MMSE score of 19–23 could be included if they were able to handle the therapy and follow study procedures with the help of a permanent caregiver per the investigator's judgement. Patients were excluded if they were also participating in a concurrent interventional clinical trial (not including noninterventional studies, postmarketing observational studies, or registry participation) from enrollment and throughout the study.

Outcomes

Efficacy

For the entire study, the primary endpoint is change from baseline to month 36 in absolute hours of OFF time as assessed by the Movement Disorder Society Unified Parkinson's Disease Rating Scale Part IV (MDS-UPDRS-IV) modified item 4.3. The primary endpoint of this interim analysis was change in absolute hours of OFF time from baseline to month 6.

Additional endpoints were changes from baseline to month 6 in absolute hours of dyskinesia time (MDS-UPDRS-IV modified item 4.1), motor aspects of experiences of daily living (m-EDL, MDS-UPDRS-II score), motor symptoms (MDS-UPDRS-III score), freezing of gait (Freezing of Gait Questionnaire [FOGQ] score), PD-related pain [King's PD Pain Scale (KPPS) score], PD-related sleep disturbances [Parkinson's Disease Sleep Scale-2 (PDSS-2) score], PD-related gastrointestinal dysfunction [Gastrointestinal Dysfunction Scale in PD (GIDS-PD) score], disease-specific QoL [39-item Parkinson's Disease Questionnaire (PDQ-39) score], generic caregiver burden [Modified Caregiver Strain Index (MCSI) score] as reported by respective caregivers, generic daytime sleepiness [Epworth Sleepiness Scale ([ESS) score], and generic depression [Beck Depression Inventory (BDI) score].

Initially only the MDS-UDPRS-IV modified items 4.1 and 4.3 scores but not the absolute hours were captured. For patients with absolute hours of OFF and dyskinesia time collected on paper, these data were retrospectively entered into the database, but for 51 patients (~ 50%), only item 4.1 and 4.3 scores were available for this first interim analysis. With more patients in the upcoming larger interim and final analyses (around 400 patients), the impact will be much smaller.

The proportion of patients treated with LDp/CDp monotherapy at month 6 as well as additional practical aspects of LDp/CDp treatment

including cannula size, infusion site, and therapy duration were evaluated.

Safety

Safety evaluations included the proportion of patients reporting adverse events (AEs) and serious AEs (SAEs).

Statistical Analysis

Primary, secondary, and exploratory endpoints were assessed among patients in the full analysis set (FAS), defined as all patients receiving any LDp/CDp infusion in the study who had both a baseline and postbaseline observation for at least one efficacy endpoint. Baseline assessments were defined as the last assessment on or prior to the date of first study treatment. Safety outcomes were assessed among patients in the safety analysis set which included all subjects receiving any LDp/CDp infusion. There was no imputation of missing data.

Demographics, baseline characteristics, reported reasons for treatment discontinuation, and frequency of AEs were descriptively summarized. Mixed-effects models for repeated measurements were used for continuous outcome variables, both adjusted for country with the statistical significance set at $P<0.05$. As a small proportion of patients did not complete baseline assessments of patient-reported outcomes or had it completed after receiving the first study treatment, these patients did not have a valid baseline assessment and did not contribute to change from baseline analyses, with de facto sample sizes for these outcomes reduced.

RESULTS

Patients

At the first interim analysis, 105 cohort A patients were enrolled (safety analysis set, $n=105$; FAS, $n=98$). Of patients in the safety analysis set, half were recruited from Germany (49.5%) followed by Denmark (15.2%), Sweden (13.3%), Israel (10.5%), and Spain (5.7%) with the remaining patients (≤ 3%) residing in Austria, Canada, or Romania (Supplementary Material 1, Fig. S1). At the data cut-off date (April 24, 2025), 34/105 (32.4%) patients had discontinued the study treatment. Among these, 29/105 (27.6%) discontinued treatment by Month 6. Primary reasons for treatment discontinuation included withdrawal from treatment by the patient themselves (15/105, 14.3%), AEs (10/105, 9.5%), and lack of efficacy/not meeting patient expectations (4/105, 3.8%); 1% of patients discontinued due to progressive disease or no longer clinically benefiting ($n=1$ each). Only hallucination was reported as a discontinuation reason for more than one patient ($n=2$). One patient continued treatment after discontinuing the study. Like recent open-label phase III registrational trial data [9], the discontinuation rate was highest during the first month of the study but decreased and remained stable thereafter (Supplementary Material 1, Fig. S2). Due to approval timelines, patients recruited from Australia and the US have not yet reached 6 months of follow-up. Consequently, the following results predominantly represent patients from Europe.

Over half of patients in the safety analysis set were male (56.2% [59/105)] with a mean (SD) age of 68.5 (9.5) years and a PD duration of 12.1 (5.3) years since diagnosis at baseline (Table 1). Patients' least square (LS) mean [standard error (SE)] OFF time was 5.2 (0.6) hours with LS mean (SE) MDS-UPDRS-II and PDQ-39 summary index scores of 15.4 (1.8) and 34.4 (2.8) at baseline (Table 1). Only 5/105 (4.8%) patients had previously used surgical DATs (DBS: $n=4$; LCIG: $n=1$) and 1/105 (0.95%) patient had used a nonsurgical CSCI (CSCI with apomorphine).

The recommended starting infusion rate was calculated by converting the total LD dosage (from all LD-containing medications and catechol-O-methyltransferase inhibitors) during a 16-h waking day to the equivalent dosage of immediate-release LD and then converted to the corresponding total dose of LDp/CDp. The LD equivalent daily dose (LEDD) for all prior PD medications was 1068.2 mg/day. The LD equivalent dose (LED) base infusion rate increased by 13.7% from 58.0 mg/h at baseline to 66.0 mg/h at month 1 which remained mostly stable

Table 1 Baseline characteristics for the first interim analysis population (full analysis set)

Characteristic	*n*	Cohort A (*N* = 105)
Age, years, mean (SD)	105	68.5 (9.5)
< 65 years, %	32	30.5
≥ 65 years, %	73	69.5
Sex, male, %	59	56.2
PD duration, years, mean (SD)	104	12.1 (5.3)
< 10 years, %	41	39.4
≥ 10 years, %	63	60.6
Time since onset of motor fluctuations, years, mean (SD)	98	6.4 (5.3)
Previous use of device-aided treatment, %	6	5.7
MMSE score, mean (SD)	103	27.5 (3.4)
OFF time (modified MDS-UPDRS-IV, item 4.3), h, LS mean (SE)	47	5.2 (0.6)
OFF time score (modified MDS-UPDRS-IV, item 4.3), LS mean (SE)	96	1.7 (0.1)
Dyskinesia time (modified MDS-UPDRS-IV, item 4.1), h, LS mean (SE)	47	3.3 (0.4)
Dyskinesia time score (modified MDS-UPDRS-IV, item 4.1), LS mean (SE)	96	1.4 (0.1)
MDS-UPDRS-II total score, LS mean (SE)	69	15.4 (1.8)
PDQ-39 summary index score, LS mean (SE)	72	34.4 (2.8)

LDp/CDp foslevodopa/foscarbidopa, *LS* least squares, *MDS-UPDRS* Movement Disorder Society-Unified Parkinson's Disease Rating Scale, *MMSE* Mini-Mental State Examination, *PD* Parkinson's disease, *PDQ-39* 39-item Parkinson's Disease Questionnaire

thereafter [68.8 mg/h by month 6 (18.5%)] with patients receiving a mean daily LED of 1466 mg (at initiation) to 1491 mg from LDp/CDp (at month 6; Fig. 2). All patients had alternative low and high infusion rates programmed at treatment initiation except one, with infusion rates moderately increasing over the 6-month follow-up period; alternative high infusion rates were approximately 9–12% higher than the base rate and alternative low infusion rates were approximately 26–29% lower than the base rate during the 6 months of follow-up (Fig. 2). Fifty-six percent of patients (46/82) did not adjust the base rate between initiation and week 2, and 61.4% (51/83) did not adjust in the period of week 2 to month 1, respectively. Before study treatment, data on prior PD medications were available for 87/105 patients with 70.5% receiving levodopa and derivatives, 54.3% dopamine agonists, 44.8% type-B monoamine oxidase (MAOB) inhibitors, 29.5% catechol-O-methyltransferase (COMT) inhibitors, 13.3% amantadine, and 1.0% anticholinergic drugs. During the entire 6 months of follow-up, 15.2% (16/105) of patients in the safety analysis set were continuously treated with LDp/CDp as a monotherapy (without any concomitant PD medication). Similar to prior treatment with LDp/CDp, the remaining 84.8% (89/105) of patients received additional PD medications which primarily included levodopa and derivatives [72.4% (+ 1.9%)], dopamine agonists [52.4% (– 1.9%)], MAOB inhibitors [40.0% (– 4.8%)], COMT inhibitors [27.6% (– 1.9%)], amantadine [13.3% (0%)], and anticholinergic drugs [1.0% (0%)] taken at any time over the 6 months of follow-up.

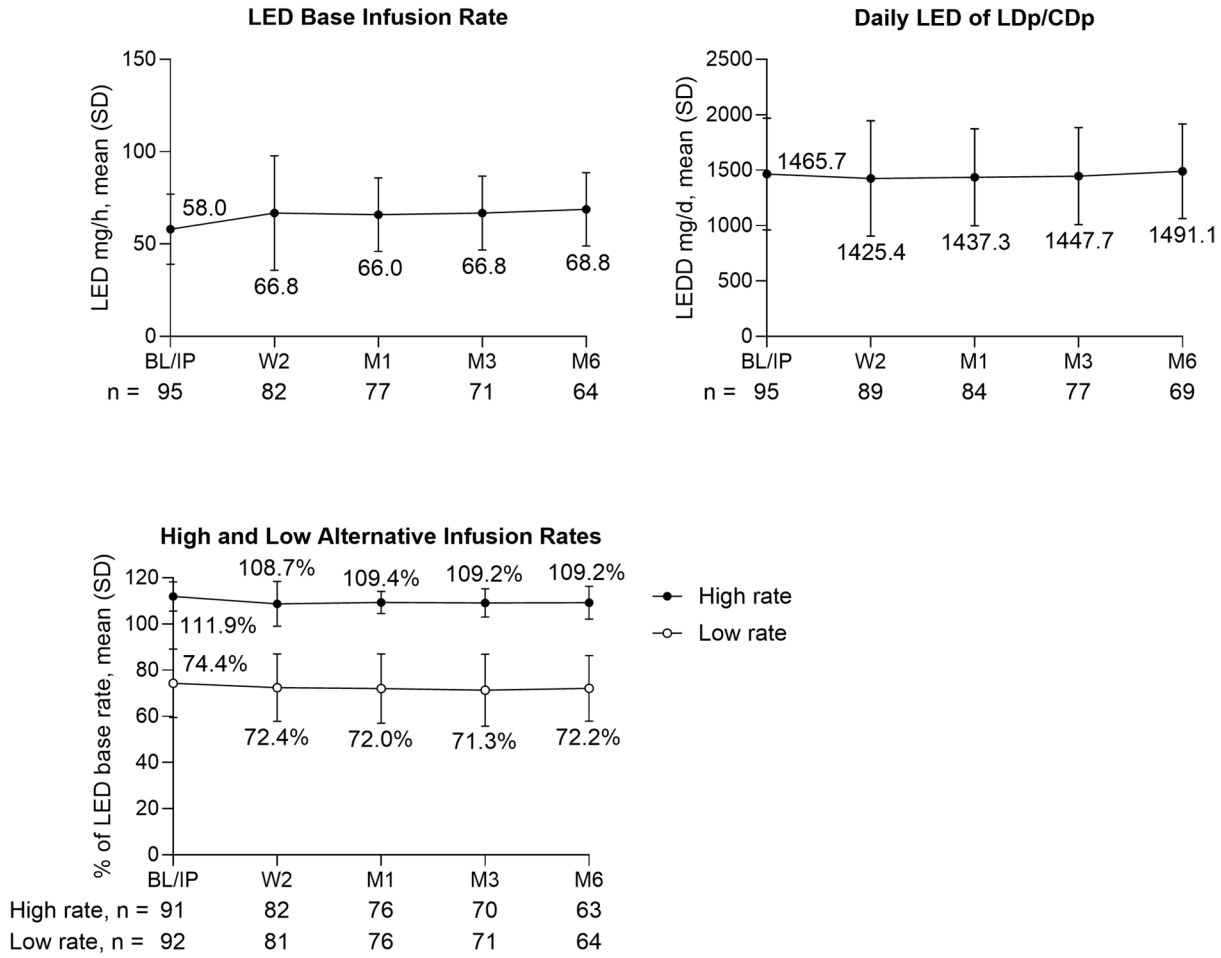

Fig. 2 Base levodopa equivalent dose infusion rate, total daily dose level, and mean dose infusion rates of alternative high and low flow rates (full analysis set). *BL* baseline, *IP* initial prescription, *LDp/CDp* foslevodopa/foscarbidopa, *LED* levodopa equivalent dose, *LEDD* levodopa equivalent daily dose, *M* month, *SD* standard deviation, *W* week

Efficacy

Among patients in the FAS with available OFF and dyskinesia time hours at baseline ($n=47$) and month 6 ($n=40$, 7 patients only had baseline data), treatment with LDp/CDp demonstrated statistically significant, clinically meaningful [change from baseline to month 6 meets or exceeds the outcome-specific minimal clinically important difference (MCID)], and sustained reductions (SE; 95% CI) of motor complications at month 6: OFF time was reduced by – 2.8 (– 52.9%; 0.4; – 3.6, – 1.9; $P\leq0.001$) h (primary endpoint) and dyskinesia time by – 1.8 h (– 53.2%; 0.4; – 2.6, – 0.9; $P\leq0.001$, Fig. 3). In addition, while MDS-UPDRS-II scores nominally decreased but did not reach statistical significance [– 1.0 (0.9; – 2.8, 0.8; $P=0.279$)], significant and clinically relevant reductions in MDS-UPDRS-III scores [– 5.0 (1.6; – 8.2, – 1.9; $P=0.002$)] were observed by month 6, with FOGQ scores decreasing similarly throughout the duration of the study and by – 2.1 (0.8; – 3.8, – 0.4; $P=0.014$) score points by month 6 (Fig. 3); at month 3, a reduction of – 3.0 score points reached the MCID for FOGQ scores. KPPS scores decreased significantly in a sustained manner by – 9.1 score points (1.7; – 12.5, -5.7; $P\leq0.001$) as well as PDSS-2 and GIDS-PD scores by – 5.2 (1.4; – 8.0, – 2.4; $P\leq0.001$) and – 4.4 score points (1.6; – 7.6, – 1.1; $P=0.008$), respectively (Fig. 4);

change in chronic pain, fluctuation-related pain, nocturnal pain, and discoloration subdomains (KPPS), change in motor symptoms at night, PD symptoms at night, and disturbed sleep subdomains (PDSS-2), and change in bowel irritability and upper GI symptoms subdomains (GIDS-PD) reached statistical significance by month 6 (Supplementary Material 1, Table S1). PDQ-39 scores significantly decreased by – 5.6 (1.8; – 9.2, – 2.0; $P=0.002$) score points by month 6 and in a sustained manner over the course of the study (Fig. 5) with changes in mobility, emotional well-being, and bodily discomfort subdomains reaching statistical significance by month 6 from baseline (Supplementary Material 1, Table S1). Overall, MCSI scores decreased nominally [– 1.2 (1.3; – 3.7, 1.4; $P=0.361$)] for respective caregivers (Supplementary Material 1, Figure S3), if available, for the total population. No clinically meaningful changes were observed for ESS and BDI scores over 6 months of treatment with LDp/CDp (Table 2).

Safety

Of 105 total patients in the safety analysis set, 58 (55.2%) patients reported AEs. Among the AEs reported by > 5% of patients, hallucination and infusion site infection were the most common (6/105 patients, 5.7% each; Table 3). Most patients reported mild-to-moderate AEs with 18/105 patients (17.1%) reporting severe and 13/105 patients (12.4%) reporting serious AEs, including abdominal wall abscess and hallucination in 2 patients each (1.9%). Two deaths were reported, both classified as being non-related to study treatment (exacerbated porphyria with aspiration pneumonia/lymphoma). Lastly, mean body weight remained largely unchanged throughout 6 months of treatment [– 0.5 kg (– 0.7%) by month 6, Supplementary Material 1, Table S2].

Practical considerations

Most patients [53/72 (73.6%)] used the infusion set with the 9 mm cannula at month 6 with the majority (58/67 [86.6%)] having used only the abdomen as an infusion site; the remaining 13.4% of patients used thighs, arms, and lower back infusion sites. On month 6, 94.2% (65/69) of patients received LDp/CDp treatment for a 24-h duration whereas the remaining 4 patients had a median (range) therapy duration of 16 h (16, 22 h). On month 6, 87.9% (58/66) of patients received one vial per day.

DISCUSSION

The interim results of this RW study demonstrate that treatment with LDp/CDp appears to be safe and effective in routine clinical practice, as evidenced by significant and clinically meaningful reductions in motor and nonmotor symptoms. Such reductions in OFF time, dyskinesia time, and MDS-UPDRS-III scores (ON state) were sustained over 6 months together with scores for PD-related sleep disturbances (PDSS-2), PD-related pain (KPPS), and PD-related gastrointestinal dysfunction (GIDS-PD). The established MCID for FOGQ scores [12] was met at month 3, the significant decrease remains potentially relevant. It is possible that the reduction in FOGQ scores was related to decreases in OFF time, dyskinesia time, or improved MDS-UPDRS-III scores. Additionally, the changes in OFF time observed in this study were equal to those previously reported in a pivotal phase III trial (– 2.8 h vs – 2.8 h) [6] suggesting that CSCI over 24 h with LDp/CDp has a similar effectiveness in improving burdensome motor fluctuations in a RW setting. Further, these reductions in OFF time were observed despite patients having a nominally shorter duration of OFF time at baseline (5.2 h vs. 5.9 h) [6] and were similar to 6-month reductions observed with LCIG treatment in a real-world setting (3.6 h) [13]. Importantly, 27.6% of cohort A patients discontinued LDp/CDp treatment by month 6, a rate similar to or lower than discontinuation rates observed after 6 months of apomorphine CSCI (27.0–36.8%) [14, 15] and to those observed in the two key phase III LDp/CDp trials (35.1% after 3 months and to 43.8% after 12 months) [6, 9]. Overall, discontinuation rates were well within or below the range of DATs in advanced PD [6, 9, 16], but

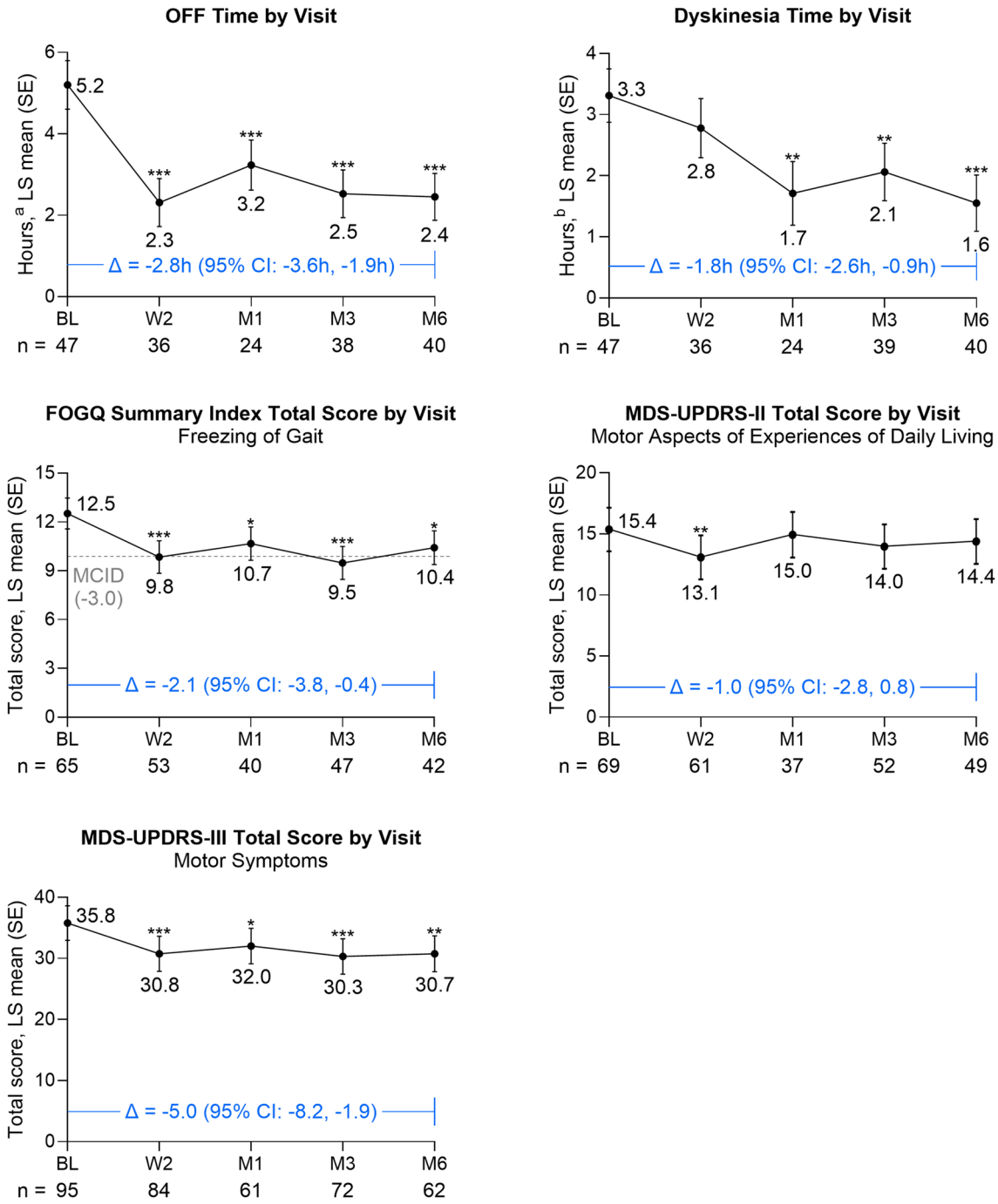

Fig. 3 LS means by visit for motor fluctuations as measured by total OFF time hours, total dyskinesia time hours, FOGQ scores, MDS-UPDRS-II scores, and MDS-UPDRS-III scores (full analysis set). $^{*}P < .05$, $^{**}P \leq .01$, $^{***}P \leq .001$ for LS mean difference from baseline to timepoint. *Dashed lines* indicate thresholds for meeting defined MCID from baseline. [Δ]Values represent LS mean change from baseline to M6, estimated from a mixed model for repeated measures adjusted for country. *BL* baseline, *h* hours, *FOGQ* Freezing of Gait Questionnaire, *LS* least squares, *M* month, *MDS-UPDRS-II, -III, or -IV* Movement Disorder Society Unified Parkinson's Disease Rating Scale Part II, III, or IV, *MCID* minimal clinically important difference, *SE* standard error, *W* week. [a]As assessed by MDS-UPDRS-IV, modified item 4.3. [b]As assessed by MDS-UPDRS-IV, modified item 4.1. MCID references: FOGQ (−− 3.0) [12]

need to be interpreted with caution across different study designs. Trial discontinuations can also introduce bias in evidence-based medicine [17]. In addition, factors such as baseline severity of motor fluctuations, initial dose titration strategies, concomitant nonmotor symptoms, and patient behavior may require greater attention as potential predictors of adherence [18, 19].

Of the numerous nonmotor symptoms associated with PD, sleep disturbances are experienced by up to 88% of patients [20]. Relative to healthy individuals, patients with PD experience diminished sleep quality. In part, this may be due to persistent motor fluctuations and associated tremor, dystonia, akinesia, and restlessness [21], as well as nocturia arising from nocturnal polyuria with overactive bladder symptoms [22]. Recent findings corroborate the efficacy of LDp/CDp in improving nocturia [23] and an additional post hoc analysis demonstrates that treatment with LDp/CDp results in clinically meaningful within-group reductions in PDSS-2 total scores, as well as statistically significant between-group reductions when compared with oral LD/CD [23]. A comparison of nighttime dosing warrants caution given that the pivotal phase III results disallowed or partially allowed the reduction of nighttime LDp/CDp flow rates [6, 9]; however, the LD doses observed in our study delivered at alternative lower infusion rates, (presumably during nighttime), suggest that a meaningful treatment benefit is achievable at night with lower LDp/CDp doses relative to phase III trials. In our study, a reduction in PDSS-2 total scores was observed, consistent with results from the open-label phase III trial [9], potentially reinforcing the benefits of LDp/CDp for PD-related sleep disturbances and suggesting the need for 24-h treatment delivery.

In addition to PD-related sleep disturbances, pain is a frequently reported nonmotor symptom irrespective of disease severity, but given its complex etiology, often goes underdiagnosed and may be treated unsystematically [24]. For patients with PD, PD-related pain can arise from both OFF periods and moderate-to-severe dyskinesia, severely impacting QoL [25]. As assessed by the PD-specific pain scale or KPPS [26], infusion therapies have shown a strong ability to attenuate pain in patients with aPD as illustrated in the DYSCOVER LCIG study [27]. Of note, treatment with LCIG significantly decreased KPPS total scores primarily via improvements in musculoskeletal pain, fluctuation-related pain, and nocturnal pain subdomains [27]. More broadly, a subsequent post hoc analysis of the DYSCOVER study further highlights that a higher dyskinesia burden is positively correlated with worse pain (higher KPPS scores) and poorer QoL (higher PDQ-8 scores) [28] suggesting that treating dyskinesia is likely to result in concomitant improvements in pain and QoL. In support of these findings, we observed statistically significant, clinically meaningful, and sustained reductions in KPPS total scores, largely driven by improvements in the subdomains of chronic pain, fluctuation-related pain, nocturnal pain, and discoloration. In this regard, therapeutic strategies that optimize dopaminergic absorption, timing, and dosages of levodopa-containing formulations may attenuate pain for individuals with aPD [29] and improve QoL. Specifically, continuous levodopa delivery may have a role in improving PD-related pain as recent clinical data suggest that even strong opiate-based analgesics or larger doses of oral levodopa are insufficient in managing PD-related pain [30]. While not systematically assessed in this observational study, the evaluation of serum vitamin B levels could provide additional insight on PD-related pain given the association between LD-mediated neuropathy and vitamin B status [31, 32].

Gastrointestinal dysfunction (GID) is another burdensome nonmotor symptom of PD that can significantly lessen QoL for patients, particularly due to the impact of swallowing difficulties and constipation [33]. With the recent advent of the GIDS-PD instrument [34], the presence and severity of GID in patients with PD can be increasingly assessed. In our study, GIDS-PD scores were significantly decreased by the 6-month visit with significant improvements in bowel irritability and upper GI subdomains suggesting that treatment with LDp/CDp may alleviate GID over time.

Correspondingly, we found decreases in PDQ-39 total scores. More specifically, treatment with

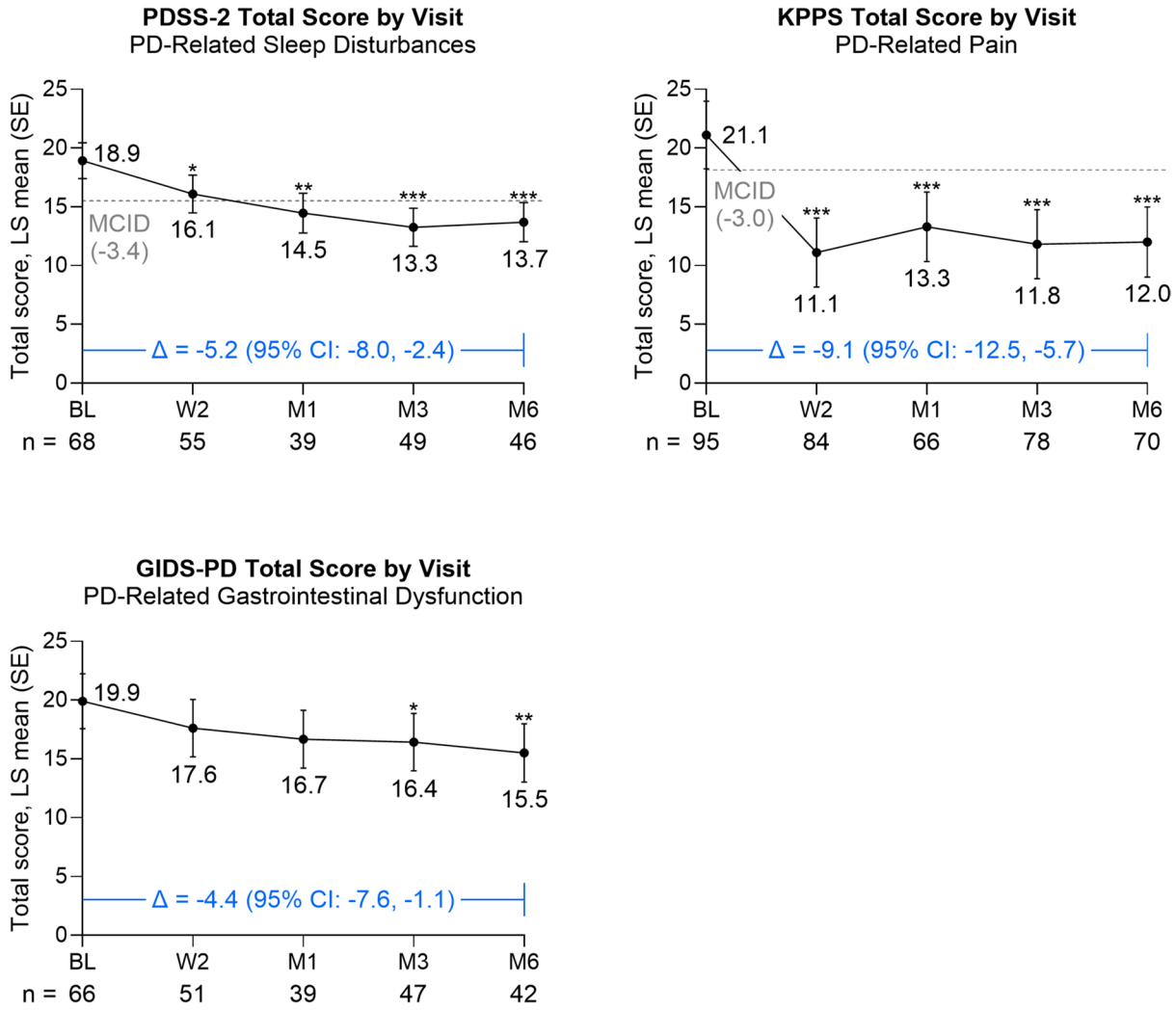

Fig. 4 LS means by visit for nonmotor symptoms as measured by PDSS-2, KPPS, and GIDS-PD scores (full analysis set). $^{*}P < .05$, $^{**}P \leq .01$, $^{***}P \leq .001$ for LS mean difference from baseline to timepoint. *Dashed lines* indicate thresholds for meeting defined MCID from baseline. $^{\Delta}$Values represent LS mean change from baseline to M6, estimated from a mixed model for repeated measures adjusted for country. *BL* baseline, *GIDS-PD* Gastrointestinal Dysfunction Scale in Parkinson's Disease, *KPPS* King's Parkinson's Disease Pain Scale, *LS* least squares, *M* month, *MCID* minimal clinically important difference, *PDSS-2* Parkinson's Disease Sleep Scale-2, *SE* standard error, *W* week. MCID references: PDSS-2 (– 3.44) [38]; KPPS (– 3.0) [39]

LDp/CDp significantly improved mobility, emotional well-being, and bodily discomfort subdomains. While preliminary, the stable reduction in PDQ-39 scores observed here is akin to what is observed with long-term use of LDp/CDp in a clinical trial setting [9].

For caregivers of patients with aPD, caregiving burden typically worsens with advancing disease [35]. In contrast, caregiver burden did not worsen in our study potentially related to the observed effectiveness of LDp/CDp treatment. In addition, more than half (57%) of patients placed the cannula themselves at month 6 and operated the infusion device themselves which could have limited the necessity for assistance by their caregiver. Nevertheless, caregivers are often heavily involved in taking care of their care partner's therapeutic device requiring

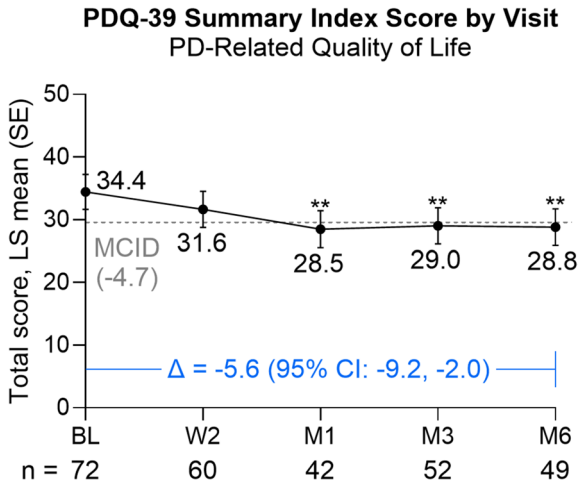

Fig. 5 LS means by visit for quality of life as measured by PDQ-39 scores (full analysis set). *$P < .05$, **$P \leq .01$ for LS mean difference from baseline to timepoint. $^{\Delta}$Values represent LS mean change from baseline to M6, estimated from a mixed model for repeated measures adjusted for country. *BL* baseline, *LS* least squares, *M* month, *MCID* minimal clinically important difference, *PDQ-39* 39-item Parkinson's Disease Questionnaire, *SE* standard error. MCID reference: PDQ-39 (– 4.72) [40]

additional education to ensure proper management [36]. Similarly to caregiver burden, no clinically meaningful changes (and no worsenings) were observed for the remaining nondisease-specific instruments utilized including the ESS (daytime sleepiness) and BDI (depression). A contributing factor may be that these scales may have lower sensitivity due to their lack of disease specificity.

LDp/CDp dosing, including the alternative high and low rates as a percentage of the base rate, generally remained stable after initial optimization to therapy. At month 6, the alternative low rate was 72% of the base rate which may have helped mitigate the risk of hallucinations and preserve the efficacy on motor symptoms including morning akinesia as previously demonstrated [9].

Compared with pivotal phase III trials [6, 9], we observed a lower incidence of AEs and discontinuations. Infusion site events were common but led to discontinuations in less than 10% of patients. Clinical practice suggests that education on proper drug administration and device management are key to limiting infusion site events [36]. Further, such events can be generally minimized with diligent hygiene, daily rotation of infusions sites, massage, and potentially ultrasound [37]. In addition, hallucinations led to discontinuations in only 2 patients. The fact that this RW study provided more opportunities for flexible dosing and adjustment, especially of nighttime infusion rates, may have contributed to a lower rate of hallucinations than in clinical trials; however, comparisons of results from this study with pivotal trials should be interpreted cautiously due to differences in observational design, patient

Table 2 Summary of additional efficacy outcomes with LDp/CDp in cohort A

Outcome, LS mean (SE)	Baseline	Week 2	Month 1	Month 3	Month 6	CFB to Month 6
Generic daytime sleepiness	10.1 (0.9)	9.8 (0.9)	9.6 (0.9)	9.4 (0.9)	9.1 (0.9)	– 0.9 (0.6; 95% CI: – 2.2, 0.3)
ESS summary index score	67	52	40	49	45	
n						
P value from baseline	–	.609	.518	.271	.148	
Generic depression	10.5 (1.5)	9.1 (1.6)	8.7 (1.6)	8.9 (1.6)	9.9 (1.6)	– 0.5 (0.9; 95% CI: – 2.4,
BDI total score	69	61	37	56	49	1.3)
n						
P value from baseline	–	0.112	0.086	0.077	0.569	

BDI Beck Depression Inventory, *CFB* change from baseline, *ESS* Epworth Sleepiness Scale, *LS* least squares

Table 3 Overview of adverse events

n (%)	*N* = 105
Any AE	58 (55.2)
AE with reasonable possibility of being related to study treatment	43 (41.0)
AE with reasonable possibility of being related to study device	21 (20.0)
AE that is considered associated with product complaint	12 (11.4)
Severe AE	18 (17.1)
Serious AE	13 (12.4)
AEs leading to treatment discontinuation[a]	9 (8.6)
Hallucination	2 (1.9)
Abdominal wall abscess	1 (1.0)
Anxiety	1 (1.0)
Depression	1 (1.0)
Drug ineffective	1 (1.0)
Glaucoma	1 (1.0)
Infusion site urticaria	1 (1.0)
Nausea	1 (1.0)
Psychotic disorder	1 (1.0)
Skin infection	1 (1.0)
Swelling	1 (1.0)
Deaths[b]	2 (1.9)
AEs occurring in ≥ 3% of patients	
Hallucination	6 (5.7)
Infusion site infection	6 (5.7)
Abscess	4 (3.8)
Anxiety	4 (3.8)
Skin infection	4 (3.8)
Skin reaction	4 (3.8)
Serious AEs occurring in ≥ 2% patients	
Abdominal wall abscess	2 (1.9)
Hallucination	2 (1.9)

AE adverse event

[a]Patients may have had more than one AE that led to treatment discontinuation[b]One death was due to suspected porphyria, exacerbated by metamizole, aspiration pneumonia; the other death was due to lymphoma and pleural effusion

selection, and flexible dosing especially at nighttime in this RW study. Subsequent interim analyses with larger patient numbers and longer follow-up will provide more insight.

Limitations

The primary limitations of this study are the observational nature and the lack of a control

group. Study procedures and eligibility criteria limit participation in a way that may reduce the representativity of results regarding more frail patients where LDp/CDp is considered. In addition, some outcomes are self-reported and are thus subject to recall bias. Patient assessments were not dictated by a strict protocol but rather in a RW setting based on routine clinical practice, clinicians' judgement, and patient availability, which could result in the underreporting of safety events when such assessments require defined time intervals. The recovery of missing data for absolute hours of OFF and dyskinesia time was not possible in some patients which could affect the magnitude of change in these outcomes. Further and while validated, the absolute hours of these outcomes were assessed by patient recall over 7 days which could result in recall bias. In addition, up to 18% of patients completed certain patient-reported outcomes for the baseline visit after receiving the first study treatment. As a result, these patients did not have a valid baseline assessment for change-from-baseline analyses. The de facto sample size for these outcomes was thus reduced. Coupled with higher discontinuation rates, the observed effects in all outcomes may consequently be influenced by attrition bias and could overestimate treatment benefits if those who discontinued experienced less favorable outcomes.

CONCLUSIONS

Interim results from the ROSSINI study provide the first prospective RW data for LDp/CDp, showing reductions in motor complications and nonmotor symptoms, and increased QoL with 6 months of treatment. A consistent safety profile was confirmed in routine clinical practice, with the majority of AEs being non-serious, mild to moderate, and manageable coupled with lower AE incidences and discontinuation rates than in clinical trials overall. To assess the long-term effectiveness of LDp/CDp, a second interim analysis will be conducted on 200 patients with at least 12 months of follow-up.

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Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, synopses, or statistical analysis plans [SAPs)], as long as the trials are not part of an ongoing or planned regulatory submission. These clinical trial data can be requested by any qualified researchers

who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, SAP, and execution of a Data Use Agreement (DUA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select "Home".

Declarations

Conflicts of Interest. Financial arrangements of the authors with companies whose products may be related to the present report are listed as declared by the authors: Wolfgang H. Jost serves as an advisor and speaker for AbbVie, Bial, Desitin, Stada, UCB, and Zambon. Filip Bergquist has received advisory and lecture fees from AbbVie and research support in kind from Global Kinetics Corporation. Andrew Evans has received honoraria AbbVie, Abbott, STADA, Pfizer, Ipsen, Encapsulate, Seqirus, Bluerock for presentations, grant support from the Michael J. Fox Foundation, the National Health and Medical Research Council, and has been a scientific advisory board member for AbbVie and STADA. Sharon Hassin-Baer is a study investigator and an advisor for AbbVie; has received funding/grant support from AbbVie; speaker honoraria from AbbVie, Medison, and Allergan; has received consultancy fees from Neuroderm, Takeda, and Teva; and has received advisory fees from Teva and AbbVie. Robert A. Hauser has received speaking fees from Abbvie, Amneal Pharmaceuticals, Kyowa Kirin, Neurocrine Biosciences, and Supernus; has received consulting fees from Abbvie, ABLi Therapeutics, Amneal, Biogen, Cerevance, Cerevel, Clario, Forsee Pharmaceuticals, HanAll Biopharma, Inhibikase, Intrance (PSG), Kiefe RX, Kyowa Kirin, Mitsubishi Tanabe, Nano PharmaSolutions, Neurocrine, Neuroderm, NDP Pharmaceuticals, Photopharmics, Regenxbio, Revance, Serina Therapeutics, Stoparkinson, Sumitomo, Supernus, Theravance, Truebinding, UCB, and Zambon; serves on a scientific advisory board for Stoparkinson, Inhibikase, and PhotoPharmics; has stock options in Enterin, Inhibikase, and Axial Therapeutics; has received intellectual property interests from a PD Diary through his University; acknowledges a Center of Excellence grant from the Parkinson Foundation; and Robert A. Hauser's University has received research support from Abbvie, Inc., Amneal Pharmaceuticals, Annovis Bio Inc, Biogen MA, Inc., Cavion, Inc., Cerevance Beta, Inc., Cerevel Therapeutics, Enterin, F. Hoffman La Roche Ltd, Genentech, Inc., Global Kinetics Corporation, Inhibikase Therapeutics, Michael J Fox Foundation, Motric Bio, Inc., NeuroDerm Ltd, Sage Therapeutics, Scion NeuroStim, Sun Pharma Advanced Research Company, Ltd., Teva Branded Pharmaceuticals, Truebinding, Inc., UCB, and UCB Biopharma SRL. Tove Henriksen has served as a speaker for AbbVie, Britannia, Convatec, Ipsen, Lundbeck, Neuoderm, and Nordic Infucare; is a primary investigator for the M15—741 and M15—737 studies and a study sponsored by Britannia; and is a board member of a data monitoring committee for a Lundbeck-sponsored study. Irene A. Malaty has participated in research funded by AbbVie, Aevum, Dystonia Coalition, Emalex, Neuroderm, Parkinson Foundation, Praxis, Revance, and Sage but has no owner interest in any pharmaceutical company; has received consulting fees from AbbVie and Aevum; has received travel compensation or honoraria from Medscape, Parkinson Study Group, and Parkinson Foundation; and has received royalties from Robert Rose Publishers. Tiago A. Mestre has received research support from the Canadian Institutes of Health Research, the Ontario Research Fund, Michael J Fox Foundation, Parkinson Canada, University of Ottawa/Parkinson Research Consortium, Weston Brain Foundation; has received personal compensation as a consultant for AbbVie, CHDI, Sunovion, Valeo Pharma, Roche, Biogen, nQ Medical; and has received personal compensation as honoraria and for speakers bureau for AbbVie, Valeo Pharma. Pablo Mir has received financial support from the Spanish Ministry of Science and Innovation, the Instituto de Salud Carlos III-Fondo Europeo de Desarrollo Regional, Consejería de Economía, Innovación, Ciencia y Empleo de la Junta de Andalucía, the Consejería de Salud y Bienestar Social de la Junta de Andalucía the Consejería de Transformación

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Ethical Approval. This study is approved by all global institutions and conducted in accordance with Advarra (central institutional review board; reference number: 00023875); Ethics (Helsinki) Committee at the Sheba Medical Center (0660—23-SMC); Ethics Committee for Investigation with Medicinal Products at Puerta de Hierro Majadahonda University Hospital (178/23); Ethics Committee of the Medical University of Graz (36—261 ex 23/24); Ethics Committee of the State Medical Association of Baden-Württemberg, Stuttgart (B-F-2023—115); Institutional Review Board (00005790); Ottawa Health Science Network Research Ethics Board (20240555—01H) Royal Melbourne Hospital Human Research Ethics Committee (HREC/103037/MH-2023); Scientific Ethics Committee (none available); and Swedish Ethical Review Board (2023—06693—01) guidelines. Documentation of ethics approval from each country, and their respective institutions, can be found in Supplementary Material 2. Patients consented to fully comply with study-related procedures and prior to their initiation, each patient or legal authorized representative voluntarily signed an Authorization for Use/Disclosure of Data informed consent form according to national regulations after the study was explained and patients' questions were answered.

Investigators. Wolfgang H. Jost, Filip Bergquist, Andrew Evans, Sharon Hassin-Baer, Robert A. Hauser, Tove Henriksen, Irene A. Malaty, Tiago A. Mestre, Pablo Mir, Ramon Rodriguez, Petra Schwingenschuh, Mihaela Simu, and Jason Aldred were study investigators.

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