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ORIGINAL RESEARCH

Continuous Subcutaneous Foslevodopa/Foscarbidopa in Parkinson's Disease: Safety and Efficacy Results From a 12-Month, Single-Arm, Open-Label, Phase 3 Study

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ABSTRACT

Introduction: Foslevodopa/foscarbidopa, a soluble formulation of levodopa/carbidopa (LD/CD) prodrugs for the treatment of Parkinson's disease (PD), is administered as a 24-hour/day continuous subcutaneous infusion (CSCI) with a single infusion site. The efficacy and safety of foslevodopa/foscarbidopa versus oral immediate-release LD/CD was previously demonstrated in patients with PD in a 12-week, randomized, double-blind, phase 3 trial (NCT04380142). We report the results of a separate 52-week, open-label, phase 3 registrational trial (NCT03781167) that evaluated the safety/tolerability and efficacy of 24-hour/day foslevodopa/foscarbidopa CSCI in patients with advanced PD.

Methods: Male and female patients with levodopa-responsive PD and ≥ 2.5 hours of "Off" time/day received 24-hour/day foslevodopa/foscarbidopa CSCI at individually optimized therapeutic doses (approximately 700–4250 mg of LD per 24 hours) for 52 weeks. The primary endpoint was safety/tolerability.

Prior Presentation Data included in this manuscript have been previously presented at the following scientific congresses: American Academy of Neurology (AAN) Annual Meeting, Seattle, Washington, USA, April 2–7, 2022. 8th Congress of the European Academy of Neurology (EAN), Vienna, Austria, June 25–28, 2022. International Congress of Parkinson's Disease and Movement Disorders (MDS), Madrid, Spain, September 15–18, 2022. 9th Congress of the European Academy of Neurology (EAN), Budapest, Hungary, July 1–4, 2023. International Congress of Parkinson's Disease and Movement Disorders (MDS), Copenhagen, Denmark, August 27–31, 2023.

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Secondary endpoints included changes from baseline in normalized "Off" and "On" time, percentage of patients reporting morning akinesia, Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Parkinson's Disease Sleep Scale–2 (PDSS-2), 39-item Parkinson's Disease Questionnaire (PDQ-39), and EuroQol 5-dimension questionnaire (EQ-5D-5L).

Results: Of 244 enrolled patients, 107 discontinued, and 137 completed treatment. Infusion site events were the most common adverse events (AEs). AEs were mostly nonserious (25.8% of patients reported serious AEs) and mild/moderate in severity. At week 52, "On" time without troublesome dyskinesia and "Off" time were improved from baseline (mean [standard deviation (SD)] change in normalized "On" time without troublesome dyskinesia, 3.8 [3.3] hours; normalized "Off" time, −3.5 [3.1] hours). The percentage of patients experiencing morning akinesia dropped from 77.7% at baseline to 27.8% at week 52. Sleep quality (PDSS-2) and quality of life (PDQ-39 and EQ-5D-5L) also improved.

Conclusion: Foslevodopa/foscarbidopa has the potential to provide a safe and efficacious, individualized, 24-hour/day, nonsurgical alternative for patients with PD.

Trial Registration Number: ClinicalTrials.gov identifier NCT03781167.

Keywords: Advanced Parkinson's disease; Foslevodopa/foscarbidopa; Levodopa/carbidopa prodrugs; Motor fluctuations; Subcutaneous infusion

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Key Summary Points

Why carry out this study?

Foslevodopa/foscarbidopa is a soluble formulation of levodopa/carbidopa (LD/CD) prodrugs administered as a continuous (24-hour/day) subcutaneous infusion that has shown a favorable benefit/risk profile versus immediate-release LD/CD in a 12-week, randomized, double-blind, active-controlled, phase 3 study (NCT04380142).

This open-label registrational trial (NCT03781167) evaluated the safety/tolerability and efficacy of 52 weeks of treatment with foslevodopa/foscarbidopa in patients with advanced Parkinson's disease (PD) whose symptoms were not adequately controlled with oral medication.

What was learned from the study?

The continuous (24-hour/day) and individualized subcutaneous infusion of foslevodopa/foscarbidopa has the potential to become an efficacious, nonsurgical treatment alternative for patients with advanced PD.

The most common adverse events were infusion site events, the majority of which were mild/moderate in severity and nonserious.

There were improvements in motor fluctuations, morning akinesia, sleep, and quality of life that were observed from the first post-baseline visit and persisted through 52 weeks of treatment.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive degeneration of dopaminergic neurons [1, 2]. Oral administration of levodopa (LD) with carbidopa (CD) is the gold standard pharmacological treatment for PD, often effectively controlling motor symptoms in the early stages of the disease [2, 3]. However, as disease progresses, the buffering capacity of striatal dopaminergic neurons narrows and brain dopamine concentrations become increasingly dependent on plasma LD concentrations [2]. The short plasma half-life of LD and the unreliable absorption of oral LD tablets due to impaired gastric motility are responsible for the fluctuating LD plasma concentrations, which make it more challenging to adequately control PD symptoms [3–5]. As a result, patients develop disabling motor fluctuations, alternating between periods of good motor system control ("On" time) and periods of poor mobility, tremor, slowness, and stiffness ("Off" time); dyskinesias, defined as involuntary choreiform movements that typi-

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cally occur during the "On" time (peak-dose dyskinesia), can also develop and worsen over time [2]. To counteract motor complications, patients rely on increased doses and frequency of oral LD and/or additional concomitant medications such as dopamine agonists, anticholinergics, amantadine, selective monoamine oxidase (MAO) B inhibitors, and catechol-*O*-methyltransferase (COMT) inhibitors [5]. These complex drug regimens increase the risk of drug–drug interactions, prove burdensome to patients, and may promote medication nonadherence because of the number of tablets that must be taken [6–8].

Non-motor symptoms of PD, which include autonomic, neuropsychiatric, and sleep dysfunction, can precede or accompany motor complications [9–12] and can respond to dopaminergic therapy, but because most PD medication is administered during waking hours, a nocturnal treatment gap remains [5, 13]. In particular, sleep disturbances that may result from suboptimal nighttime treatment can negatively impact health-related quality of life (HRQoL), resulting in excessive daytime sleepiness and impaired daytime functioning for both patients and their care partners [14].

The inability to adequately control PD symptoms with oral treatment can be mitigated by delivering therapy in a continuous, rather than intermittent, fashion. Continuous therapy, including deep brain stimulation (DBS), LD/CD intestinal gel (LCIG), or continuous subcutaneous apomorphine infusion (CSAI), often necessitates the use of medical devices. While these device-aided therapies are efficacious, patients are not always amenable to considering them, either because of their invasiveness (fear of surgery and/or associated complications, cosmetic concerns) or because of possible side effects. The relegated availability to specialized centers in some areas and the regional application of international guidelines on the use of advanced therapies in PD further impact the consideration of these therapies among patients and physicians [15–18]. For example, DBS may not be recommended for elderly patients or patients with dementia or psychotic disorders [5, 18]. Similarly, the progressive loss of efficacy and the panniculitis-related reduction in apomorphine absorption may limit the use of CSAI in some patients [16, 19]. LD remains the standard of care for the treatment of PD because of its efficacy and favorable safety profile; however, the benefits of its continuous delivery (e.g., LCIG) are diminished by the surgical procedure needed to initiate treatment. These challenges represent an unmet medical need for patients with advanced PD (aPD) and underscore the need for a nonsurgical therapeutic option that can provide predictable and stable LD plasma concentrations and continuous symptomatic relief 24 hours/day.

Foslevodopa/foscarbidopa (previously known and referred to as ABBV-951) is a soluble formulation of LD and CD prodrugs developed for the treatment of motor fluctuations in patients with aPD that is administered as a 24-hour/day continuous subcutaneous infusion (CSCI) by a single infusion set connected to a portable pump [20, 21]. Upon delivery, foslevodopa/foscarbidopa undergoes rapid enzymatic conversion to the pharmacologically active forms of LD/CD. Results from a phase 1 study demonstrated that CSCI of foslevodopa/foscarbidopa quickly reached and maintained consistent and predictable steady-state plasma levels of LD across the broad range of LD doses needed to individually control symptoms in the heterogeneous aPD population [20]. In a 12-week, phase 3, double-blind, double-dummy study of foslevodopa/foscarbidopa versus oral immediate-release LD/CD, treatment with foslevodopa/foscarbidopa resulted in significantly greater improvements in motor fluctuations compared with immediate-release LD/CD and showed a favorable benefit/risk profile [22].

Here we report the final results of a separate 52-week, phase 3, open-label registrational study assessing the safety, tolerability, and efficacy of 24-hour/day CSCI of foslevodopa/foscarbidopa in patients with aPD.

METHODS

Study Design and Approvals

This 52-week, phase 3, open-label, single-arm, multicenter study (NCT03781167) was designed to assess the safety, tolerability, and efficacy of foslevodopa/foscarbidopa administered as a 24-hour/day CSCI in patients with PD whose motor symptoms were inadequately controlled by their current treatment. The study was conducted at 60 sites across 13 countries (Australia, Belgium, Canada, Denmark, Germany, Italy, Japan, Netherlands, Russia, Spain, Sweden, United Kingdom, and United States); patient enrollment occurred between June 6, 2019, and August 25, 2021.

The study consisted of a screening period (two study visits conducted within a 10- to 42-day timeframe) and a two-part treatment period (4-week optimization period, followed by a 48-week maintenance period) (Fig. S1 in the supplementary material). Foslevodopa/foscarbidopa dosing was initiated on study day 1, and follow-up visits were planned for day 2 and weeks 1, 2, 3, 4, 6, 13, 26, 39, and 52.

Patients

Eligible patients included adults aged 30 years or older diagnosed with LD-responsive idiopathic PD. Before initiation of foslevodopa/foscarbidopa, patients must have had symptoms that, in the investigator's opinion, were not adequately controlled by their current therapy, and must have experienced an average of $\geq$ 2.5 hours of "Off" time per day, as assessed by the electronic PD diary over two consecutive days prior to day 1 (study enrollment) [23–25]. Patients who had received DBS therapy were eligible for this study provided they were considered to be in stable condition, remained LD-responsive, and met all other eligibility criteria. Patients were required to be receiving stable PD medications for at least 30 days before foslevodopa/foscarbidopa initiation, and those medications must have included at least one formulation of LD. Patients also had to have had recognizable "Off" and "On" states established through investigator observation and confirmed by PD diary entries recorded during a concordance test performed within the screening period ($\geq$ 75% concordance had to be established). Low vitamin B_{12} (< 200 pg/mL) or low-normal B_{12} (< 300 pg/mL) with elevated methylmalonic acid (MMA; > 0.41 μmol/L) at screening visit 1 had to be corrected via vitamin supplementation for patients to be eligible for enrollment; subjects with normal vitamin B_{12} or low-normal vitamin B_{12} without elevated MMA plasma level at re-test during the screening period were eligible for enrollment. Patients must not have had a history of significant skin conditions (e.g., psoriasis, atopic dermatitis) or evidence of recent sunburn, acne, scar tissue, tattoo, or discoloration that, in the opinion of the investigator, could interfere with the clinical assessment of the infusion site.

Treatment

The delivery system used in this study (Canè Crono PAR Series 3 pump, Canè S.p.A., Rivoli, Italy) is a commercially available pump qualified for the delivery of subcutaneous infusions. Among the available commercial devices, this pump was considered to most closely meet the technical specifications envisioned for the delivery of this medication, while a proprietary pump specifically developed for use with foslevodopa/foscarbidopa was under development. The Canè pump was able to provide hourly continuous infusion rates of foslevodopa/foscarbidopa ranging from 0.17 to 1.04 mL/hour (approximately 700 to 4250 mg of LD per 24 hours), with an incremental precision of 0.01 mL/h (approximately 1.7 mg of LD per hour). In routine clinical use, patients will have the option of a lower hourly infusion rate (0.15 mL/hour, equivalent to a minimum of approximately 600 mg of LD per day). Foslevodopa/foscarbidopa solution is delivered though a single infusion cannula (one infusion site). It was recommended to be inserted in the periumbilical area of the abdomen, $\geq$ 5 cm from the navel and $\geq$ 2.5 cm from previous infusion sites, with infusion site rotation required at least every 3 days. In this study, the

pump could be carried using a provided fabric carrying case with an associated elastic belt or collar strap.

Healthcare providers (HCPs) programmed the starting hourly infusion rate into the pump to deliver a total daily dose of foslevodopa calculated from each individual patient's baseline daily intake of oral LD. All LD-containing medications and COMT inhibitors taken during waking time (considered to be 16 hours/day on average) were transformed to LD-equivalents leveraging published guidance [26, 27] (Tables S1 and S2 in the supplementary material) and then converted to foslevodopa and adjusted to a 24-hour treatment period using an algorithm based on LD molecular weight and pharmacokinetic data from phase 1 foslevodopa/foscarbidopa studies. Concomitant PD medications that did not contain LD or COMT inhibitors were permitted in the study and were not included in the calculation of LD equivalents used in the conversion algorithm (Table S3 in the supplementary material).

During the optimization period, concurrently with adjustments of the foslevodopa/foscarbidopa infusion rate, HCPs could increase, decrease, or even suspend concomitant PD medications to achieve the therapeutic approach that, in the HCP's opinion, best controlled the patient's symptoms. After the optimization period, patients were required to maintain a stable regimen of concomitant PD medications, unless modifications were considered medically necessary by the investigator. All allowed concomitant therapy and prohibited medications are listed in Table S3 in the supplementary material. Oral LD (100 mg of LD/DOPA decarboxylase inhibitor [DDCI]) or LD inhalation powder (84 mg) were permitted as rescue therapies in cases of rapid deterioration of symptom control (e.g., pump malfunction). The foslevodopa/foscarbidopa infusion could be interrupted at any time during the day for up to 1 hour (e.g., for hygiene, intimacy, swimming) with no expected clinical consequences and without the need to change infusion sets or rotate infusion sites.

In this study, patients started foslevodopa/foscarbidopa infusion from a practically defined "Off" state (i.e., no PD medications for at least 12 hour before foslevodopa/foscarbidopa initiation). To achieve quick symptom control from an "Off" state, initiation of CSCI was preceded by a loading dose corresponding to each patient's typical first/morning dose of LD/DDCI. In this study, the loading dose was administered orally. The HCP could further modify daily doses of foslevodopa/foscarbidopa during the optimization period by adjusting the hourly infusion rate until the optimal clinical response (defined as maximizing functional "On" time during the day by minimizing "Off" episodes and "On" time with troublesome dyskinesia) for the individual patient was attained. If needed, the hourly infusion rate of foslevodopa/foscarbidopa could be adjusted by the HCP at any point during the study, based on clinical response.

To facilitate dose optimization and provide patients and their HCPs flexibility, investigators could preprogram two alternative infusion rates within the allowed range, generally one higher and one lower than the base rate. If these functionalities were enabled by the HCP, patients could choose to use the higher alternative infusion rate as needed (e.g., during intense/extended physical activity or periods of time with increased dopaminergic demand). Alternatively, patients could switch to the lower alternative infusion rate before going to sleep. Patients could also self-administer a bolus of solution as an extra dose (between 0.11 and 0.3 mL; equivalent to approximately 20–50 mg LD), at a maximum frequency (lockout time of 1–24 hours programmable in 15-minute increments) determined by the investigator. The maximum frequency and volumes of the extra dose could only be programmed/modified by the HCP.

Patients and/or care partners who could manage the delivery system as needed received in-office training on the correct use of the delivery system, infusion site selection, and infusion set application and handling before initiation of therapy. Patients and/or care partners were also instructed on appropriate infusion site rotation (rotating the infusion site at least every 3 days, using a new infusion set with each new insertion) and to pay special attention to the use of aseptic technique (including hand

washing) and good skin care practices (including cleaning of the infusion site with soap and water followed by an alcohol wipe).

Additional strategies aiming to improve both the patient experience and study retention were implemented following study initiation, as reflected in an amendment to the study protocol. These strategies included providing the option of a more user-friendly infusion set and additional education related to aseptic care and device management for patients and HCPs.

Patients who completed the 52-week treatment period could enroll in a long-term extension study of foslevodopa/foscarbidopa safety/tolerability and efficacy (NCT04379050). A 30-day safety follow-up was planned for patients who prematurely discontinued or for those who completed the 52-week treatment but opted not to enroll in the extension study.

Assessments

Safety

Safety evaluations included the proportion of patients reporting AEs, changes in laboratory parameters, vital sign measurements, and electrocardiogram values from baseline. Local (skin) tolerability was additionally assessed by the Infusion Site Evaluation Scale (adapted from FDA guidance [28]).

Efficacy

Efficacy endpoints included change from baseline to the end of the study for average daily "Off" and "On" time as assessed by the PD diary (an electronic version of the PD diary was completed by patients using a hand-held device for two consecutive days immediately prior to each study visit) and normalized to a 16-hour waking day, the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I–IV (with Part III measured in the patient's best "On" state), the Parkinson's Disease Sleep Scale–2 (PDSS-2), the 39-item Parkinson's Disease Questionnaire (PDQ-39) summary index, the EuroQol 5-dimension questionnaire (EQ-5D-5L), and the proportion of patients with morning akinesia (defined as reporting "Off" status in the PD diary as the predominant PD status during the first half-hour period upon awakening).

Statistical Analysis

The sample size of approximately 240 patients would provide a 70%, 91%, and 99% probability of observing an AE with an annual incidence of 0.005, 0.01, and 0.02, respectively. The safety analysis set included all patients who received at least one infusion of foslevodopa/foscarbidopa at any given time during the study. Efficacy was assessed in the full analysis set, which included all patients who received at least one infusion of foslevodopa/foscarbidopa and who had baseline and treatment observations for at least one measure of efficacy. Safety events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0, and were summarized using descriptive statistics. Efficacy endpoints were summarized using descriptive statistics, and a paired-sample t test was performed to measure the change from baseline. If no valid PD diary data were available for a visit, "Off" and "On" times were considered missing for that visit. No multiplicity adjustments were made for efficacy endpoints, so p values presented throughout this manuscript are nominal. Statistical analyses were performed using SAS® version 9.2 or later (SAS Institute Inc., Cary, NC, USA). Three interim analyses were conducted for the study prior to the final analysis.

Compliance with Ethics Guidelines

The study received institutional review board approval at all participating institutions (supplemental appendix) and was conducted in accordance with the International Council for Harmonisation, the Declaration of Helsinki of 1964 and its later amendments, and all applicable regulations and guidelines. Patients were required to provide written informed consent before undergoing any study-related procedures. This study was registered at ClinicalTrials.gov (NCT03781167). Where relevant, permissions were obtained to use the scales employed in this study (Mini-Mental State

Examination [MMSE], EQ-5D-5L, MDS-UPDRS, PDQ-39, PDSS-2, PD diary).

RESULTS

Patients

Between June 6, 2019, and August 25, 2021, 244 patients were enrolled in the study, of whom 107 prematurely discontinued treatment with foslevodopa/foscarbidopa, and 137 completed the 52-week study drug treatment (Fig. 1). Of the 137 patients who completed 52 weeks of study treatment, 94.2% (n = 129) enrolled in the subsequent long-term extension study, which remains ongoing. Primary reasons for discontinuation (patients could have multiple reasons for discontinuation) included AEs (n = 56, 23.0%), withdrawn consent (n = 30, 12.3%), and lack of efficacy (n = 11, 4.5%). The discontinuation rate was higher during the first 10 weeks after initiation of foslevodopa/foscarbidopa (66 of 107 patients) and was generally stable thereafter. Given the higher frequency of premature discontinuations during the optimization period of the study, when patients were still adjusting to the drug delivery system, a number of strategies were implemented to improve both patient experience and retention in the study. Some of these strategies, which included the introduction of an alternative, more user-friendly infusion set option and additional patient- and HCP-specific education related to aseptic care and management of devices for infusion therapies, were reflected in a study protocol amendment that was implemented during the study.

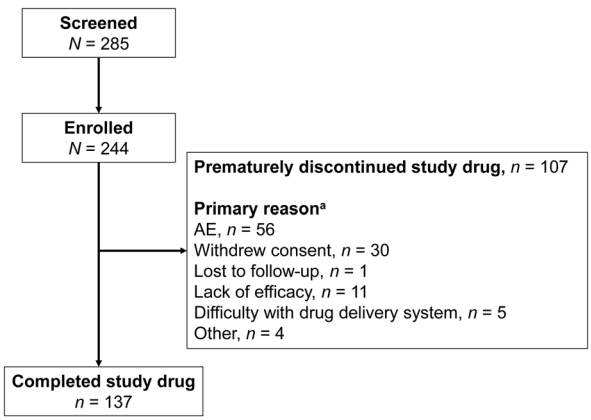

Fig. 1 Patient disposition (all enrolled patients). [a]Patients could have more than one reason for discontinuation. *AE* adverse event

The majority of the 244 enrolled patients were male (59.8%) and White (84.8%) with a mean (standard deviation [SD]) age of 63.9 (9.2) years and PD duration of 10.7 (5.2) years since diagnosis. Patients' mean (SD) baseline normalized "Off" time was 5.9 (2.2) hours, and their MDS-UPDRS total score was 50.4 (18.9) (Table 1). Initial optimization (no change to the base infusion rate for at least 15 days) was achieved within a mean (SD) of 3.5 (2.5) outpatient visits, and 31.2% (n = 64) of patients achieved optimization in just one visit (Table 2).

The baseline LD intake (in equivalents) was 1064.9 (584.8) mg/day. The mean (SD) study drug exposure for the 244 patients included in this analysis (including all enrolled patients who received at least one dose of study drug) was 242.9 (152.3) days, and 141 of 244 patients (57.8%) maintained a treatment duration $\geq$ 274 days (Table S4 in the supplementary material). The mean (SD) LD equivalent dose from foslevodopa/foscarbidopa was 1621.9 (657.3) mg at week 1, and 1859.8 (717.3) mg at week 52 (Table S5 in the supplementary material). Alternative infusion rates were common, with 87.7% (n = 214) and 87.3% (n = 213) of patients prescribed additional high and low infusion rates, respectively, at their last study prescription. As previously noted, some non-LD-containing concomitant PD medications were allowed in this study. At baseline, 13.5% (n = 33) of patients were taking only LD, 32.8% (n = 80) were taking one class of concomitant medication, and 53.3% (n = 130) were taking two or more additional classes of PD medications (includes all PD medications in addition to oral LD, which all patients were required to take before the study). The proportion of patients using no concomitant PD medication increased from 21.7% (n/N = 53/244) in week 1 to 28.0% (n/N = 60/214) by week 4, and remained at 26.7% (n/N = 55/206) during the maintenance period, while the proportion of

Table 1 Baseline demographics and clinical characteristics (safety analysis set)

Characteristic	Total $N = 244$
Age, years	63.9 (9.2)
< 65, *n* (%)	119 (48.8)
≥ 65, *n* (%)	125 (51.2)
Sex, *n* (%)	
Female	98 (40.2)
Male	146 (59.8)
Race, *n* (%)	
White	207 (84.8)
Black or African American	1 (0.4)
Asian	34 (13.9)
American Indian or Alaska Native	1 (0.4)
Multiple	1 (0.4)
BMI, kg/m^2	25.0 (4.8)[a]
MMSE total score	28.7 (1.7)[b]
PD duration since diagnosis, years	10.7 (5.2)
< 10, *n* (%)	131 (53.7)
≥ 10, *n* (%)	113 (46.3)
Duration of motor fluctuations, years	6.6 (4.7)[c]
Total daily levodopa equivalent dose[d], mg	1064.9 (584.8)[a]
Concomitant medication in addition to oral LD, *n* (%)	
1 class	80 (32.8)
≥ 2 classes	130 (53.3)
Daily "Off" time[e], h	5.9 (2.2)[f]
Daily "On" time without dyskinesia[e], h	6.5 (3.4)[f]
Daily "On" time with non-troublesome dyskinesia[e], h	2.6 (2.6)[f]
Daily "On" time with troublesome dyskinesia[e], h	1.0 (1.7)[f]
Daily "On" time without troublesome dyskinesia[e], h	9.1 (2.5)[f]
MDS-UPDRS total score[g,h]	50.4 (18.9)
Part I	11.1 (6.4)
Part II	15.8 (7.4)
Part III	23.5 (11.5)
Part IV	9.5 (3.2)
Hoehn and Yahr	2.2 (0.7)
PDSS-2 total score	20.4 (9.6)[c]
PDQ-39 summary index	34.5 (15.0)[c]
EQ-5D-5L summary index[i]	0.644 (0.1745)[j]
EQ-5D-5L VAS	57.0 (22.2)[j]

BMI body mass index, *EQ-5D-5L* EuroQol 5-dimension questionnaire, *h* hours, *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, *PDSS-2* Parkinson's Disease Sleep Scale–2, *VAS* visual analog scale

Data are mean (standard deviation) unless otherwise specified

[a] $n = 241$

[b] $n = 242$

[c] $n = 243$

[d] Includes levodopa-containing medication and catechol-*O*-methyltransferase inhibitors only

[e] Normalized to a 16-hour waking day

[f] $n = 236$

[g] Measured in the "On" state

[h] Total of parts I–III

[i] Based on the USA index value, which ranges from a worst score of −0.109 to a best score of 1

[j] $n = 229$

patients using two or more classes of concomitant medications (including all permitted medications listed in Table S3 in the supplementary material) decreased from 42.6% ($n/N = 104/244$) in week 1 to 35.0% ($n/N = 72/206$) during

Table 2 Initial optimization (safety analysis set)

Visits to optimization	Total $N = 205$
Number of visits to foslevodopa/foscarbidopa optimization, mean (SD)	3.5 (2.5)
1	64 (31.2)
2	18 (8.8)
3–6	99 (48.3)
> 6	24 (11.7)

SD standard deviation
Data are *n* (%) unless otherwise specified
Optimization was considered complete when there was no change to the base infusion rate for at least 15 days

the maintenance period (Table S6 in the supplementary material).

Safety

A total of 230 of 244 patients (94.3%) experienced at least one AE (all AEs, even those that would be expected for any infusion therapy, such as infusion site redness, were collected during this study). The majority of AEs were nonserious, mild or moderate in severity, and resolved. Sixty-three patients experienced at least one severe AE. Serious AEs (SAEs) were reported in 25.8% of patients. (Table 3).

The most common AEs were infusion site AEs (by MedDRA preferred terms: erythema [52.0%], nodule [28.7%], cellulitis [23.0%], edema [19.3%], pain [15.6%], reaction [12.3%], and abscess [11.1%]), followed by hallucination (17.2%), and fall (16.8%). Infusion site cellulitis ($n = 10$, 4.1%) and infusion site abscess ($n = 8$, 3.3%) were the most common SAEs (Table 3). The median time to onset for infusion site-related infections was 43.5 days, and most events resolved, with a median duration of 15.5 days. The median time to onset for infusion site reactions was 8.0 days, and most events resolved, with a median duration of 12.0 days.

Table 3 Overview of treatment-emergent adverse events (safety analysis set)

Adverse events, *n* (%)	Total $N = 244$
AEs	230 (94.3)
AEs considered associated with study drug	224 (91.8)
Severe AEs[a]	63 (25.8)
SAEs[a]	63 (25.8)
AEs leading to discontinuation of study drug	64 (26.2)
Deaths[b,c]	3 (1.2)
AEs occurring in > 10% of patients	
Infusion site erythema	127 (52.0)
Infusion site nodule	70 (28.7)
Infusion site cellulitis	56 (23.0)
Infusion site edema	47 (19.3)
Hallucination	42 (17.2)
Fall	41 (16.8)
Infusion site pain	38 (15.6)
Infusion site reaction	30 (12.3)
Anxiety	29 (11.9)
Infusion site abscess	27 (11.1)
Dizziness	25 (10.2)
SAEs occurring in > 2 patients	
Infusion site cellulitis	10 (4.1)
Infusion site abscess	8 (3.3)
Hallucination	7 (2.9)
Parkinson's disease	6 (2.5)
Psychotic disorder	6 (2.5)
Urinary tract infection	4 (1.6)
Sepsis	3 (1.2)

Table 3 continued

Adverse events, *n* (%) Total*N* = 244	
Pneumonia	3 (1.2)

AE adverse event, *SAE* serious adverse event

[a]While the values for severe AEs and SAEs were the same, the patients reporting these events were not the same for each event

[b]There were a total of five deaths in the safety population; two were non-treatment-emergent (did not occur during study treatment or within 30 days of the last foslevodopa/foscarbidopa infusion); all were determined by investigators to be unrelated to the study drug

[c]Treatment-emergent deaths include subdural hematoma (most likely related to traumatic injury from an accidental fall) and cerebral mass effect, cardiorespiratory arrest, and cerebrovascular accident

Preferred terms classified using the Medical Dictionary for Regulatory Activities, version 24.0

Fewer than one-third (n = 72, 29.5%) of patients were observed to have an Infusion Site Evaluation Scale grade $\geq$ 5 or letter grade $\geq$ D (defined a priori as notable skin reactions) at any point in the study (Table S7 in the supplementary material). Data for AEs identified as AEs of special interest (AESIs) are provided in Table S8 in the supplementary material. No fatal infusion site AEs were reported. Safety results were consistent across all interim analyses, which are reported in Table S9 in the supplementary material.

There were no clinically relevant findings in the mean changes from baseline for any laboratory parameters, vital signs, or electrocardiogram values. There were three treatment-emergent (occurring during study treatment or within 30 days of the last foslevodopa/foscarbidopa infusion) deaths during the study, including subdural hematoma (most likely related to traumatic injury from an accidental fall) and cerebral mass effect, cardiorespiratory arrest, and cerebrovascular accident. None of the treatment-emergent deaths were considered related to the study drug.

A total of 64 patients (26.2%) had AEs contributing to discontinuation of the study drug, nearly half of which (n = 26, 40.6%) occurred during the optimization period. The most common AEs leading to study drug discontinuation were hallucination (n = 10, 4.1%), infusion site erythema (n = 9, 3.7%), infusion site cellulitis (n = 9, 3.7%), infusion site nodule (n = 5, 2.0%), and dyskinesia (n = 5, 2.0%).

Efficacy

Treatment with foslevodopa/foscarbidopa resulted in a decrease in hours of "Off" time and increase in hours of "On" time without troublesome dyskinesia as early as at the first post-baseline assessment (week 1), and these improvements were sustained for the entire duration of the study (Fig. 2). At week 52, the mean (SD) change from baseline in normalized "Off" time was −3.5 (3.1) hours ($p \leq 0.001$), which represents a 59% average reduction in "Off" time from baseline. Normalized "On" time without troublesome dyskinesia (the sum of "On" time without dyskinesia and "On" time with non-troublesome dyskinesia) increased from baseline to week 52 by 3.8 (3.3) hours (41% increase from baseline, $p \leq 0.001$), driven entirely by increases in "On" time without dyskinesia, which, on average, increased by 58% compared to baseline (3.9 [4.2] hours; $p \leq 0.001$). Hours of "On" time with non-troublesome dyskinesia decreased, resulting in a greater change from baseline in "On" time without dyskinesia than "On" time without troublesome dyskinesia.

For this study, morning akinesia was defined as reporting "Off" status in the PD diary as the predominant PD status during the first half-hour period upon awakening. At week 52, approximately 50% fewer patients reported morning akinesia compared to baseline. At baseline, 77.7% (n/N = 129/166) of patients experienced morning akinesia, which decreased to 19.2% (n/N = 20/104) at week 26, and 27.8% (n/N = 25/90) at week 52. The reduction of early morning "Off" time was accompanied by a marked increase in the proportion of patients reporting "On" time without dyskinesia on awakening (62.2%; n/N = 56/90 at week 52) (Fig. 3).

Treatment with foslevodopa/foscarbidopa also resulted in improvement in the PDSS-2 total score and its domain scores at all time

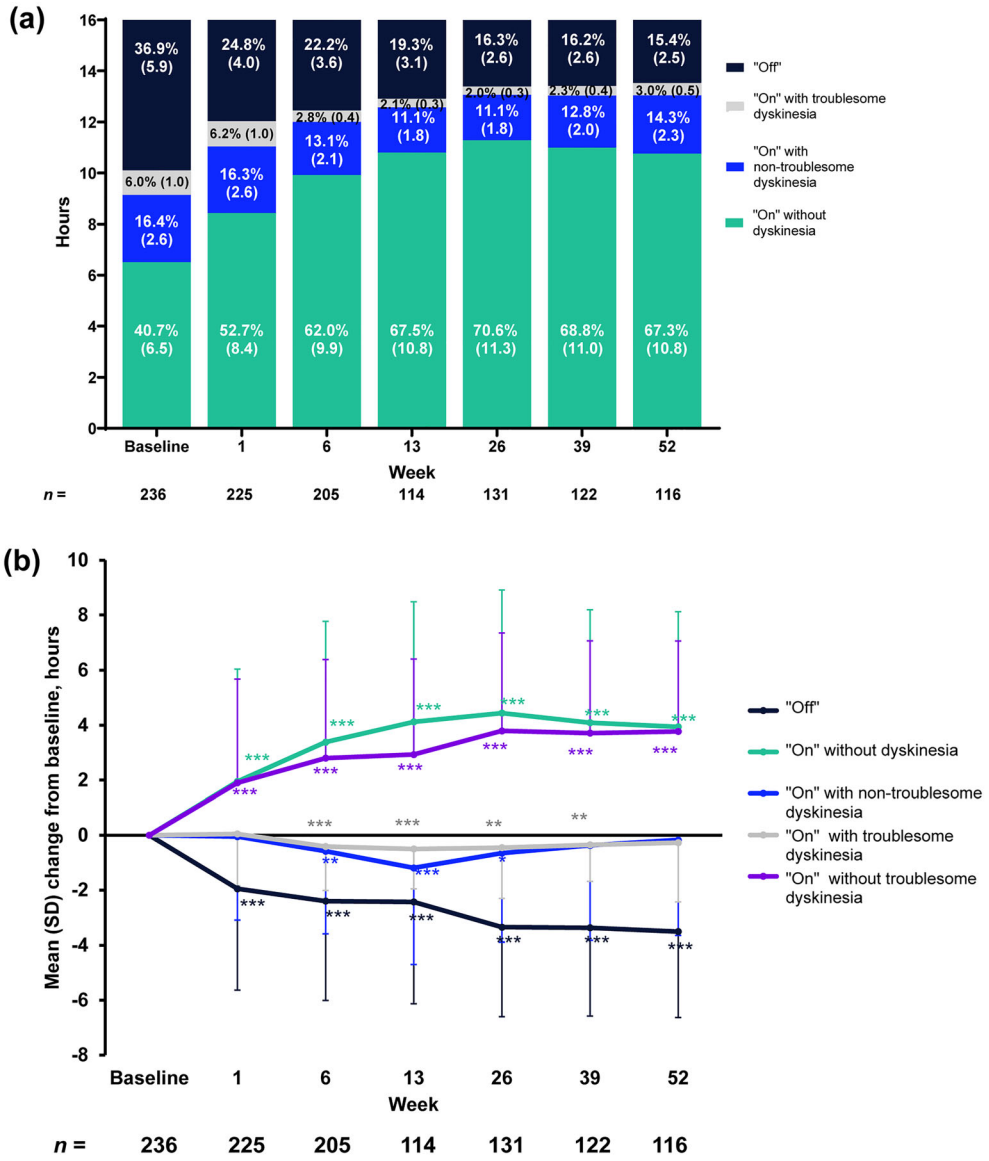

Fig. 2 "Off" and "On" time (full analysis set). *SD* standard deviation. **a** Mean hours of "Off" and "On" time distributed over a 16-hour day. **b** Change from baseline in "Off" and "On" time. "Off" and "On" times are normalized to a 16-hour waking day. "On" time without troublesome dyskinesia is the sum of "On" time without dyskinesia and "On" time with non-troublesome dyskinesia. *n* values were determined from valid diaries. If a patient completed a weekly visit but did not have a diary, they were not included in the analysis. $^{***}p \leq 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$, calculated using a two-sided paired-sample *t* test

points measured. There were also improvements in the PDQ-39 Summary Index and dimensions of mobility, activities of daily living, stigma, and bodily discomfort, and improvements in the EQ-5D-5L summary index and visual analog scale scores at all study time points ($p \leq 0.001$ for all; Fig. 4 and Table S10 in the supplementary material).

Finally, patients experienced improvements in MDS-UPDRS Part II (motor aspects of experiences of daily living) and Part IV (motor complications) at week 52 ($p \leq 0.001$ for both). No significant improvements were observed for

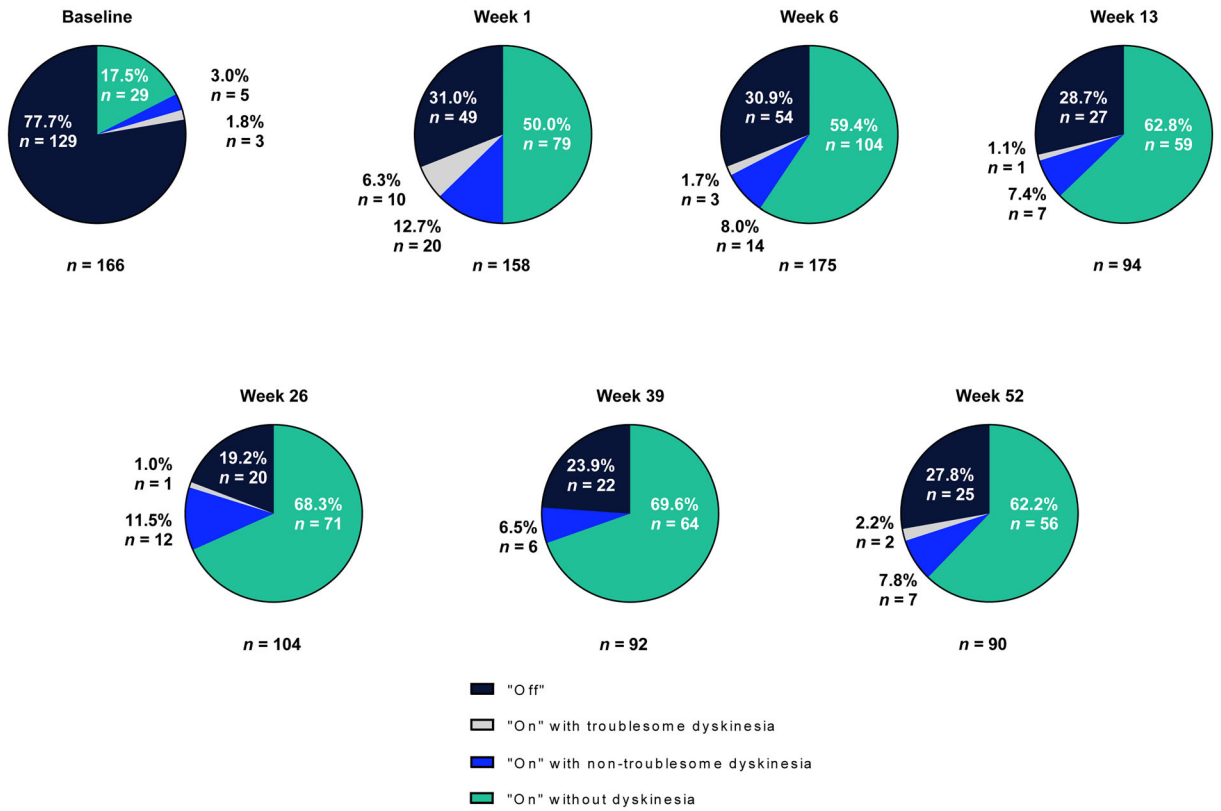

Fig. 3 Distribution of first morning state on awakening: percentage of patients (full analysis set). Symptoms assessed by 24-hour Parkinson's disease diary. *n* values were determined from valid diaries. If a patient completed a weekly visit but did not have a diary, they were not included in the analysis

MDS-UPDRS Part III (motor examination) at week 52 (Fig. S2 in the supplementary material).

Efficacy results for week 52 were consistent across all interim analyses (Table S9 in the supplementary material).

DISCUSSION

The results of this study demonstrate that treatment with 24-hour/day CSCI of foslevodopa/foscarbidopa for up to 52 weeks was generally safe and well tolerated and resulted in a sustained increase in "On" time without troublesome dyskinesia and reduction in "Off" time. This study builds upon the findings of a 12-week, phase 3, double-blind, double-dummy study of foslevodopa/foscarbidopa versus oral immediate-release LD/CD, which reported superior improvements for motor fluctuations in patients with aPD treated with foslevodopa/foscarbidopa compared with patients treated with immediate-release LD/CD [22].

While infusion site AEs were common, they were mostly nonserious, mild or moderate in severity, and generally consistent with those reported by other continuous subcutaneous therapies [29, 30]. Studies of CSCI of insulin, apomorphine, and LD/CD indicate that infusion site/skin events among continuous subcutaneous therapy users (both adults and children) are common [29–36] and occur throughout the duration of use [29]. Skin infections are also frequently reported with CSCI therapies, with most studies noting occurrences of infusion site infections in 17–41% of patients receiving subcutaneous insulin for diabetes [31–33]. Furthermore, results from an epidemiological investigation

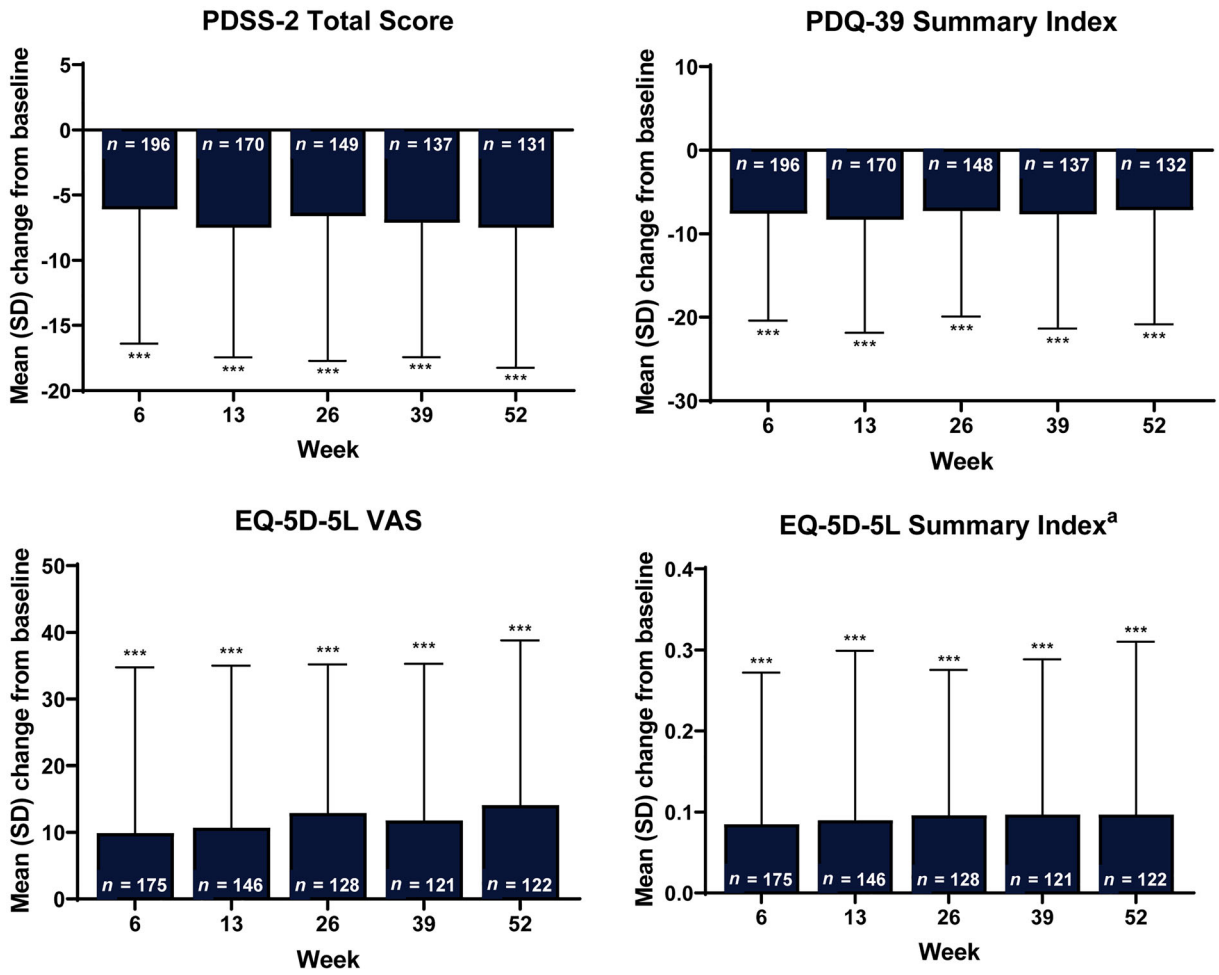

Fig. 4 Change from baseline in sleep, QoL, and HRQoL (full analysis set). *EQ-5D-5L* EuroQol 5-dimension questionnaire, *HRQoL* health-related quality of life, *PDQ-39* 39-item Parkinson's Disease Questionnaire, *PDSS-2* Parkinson's Disease Sleep Scale–2, *QoL* quality of life, *VAS* visual analog scale. $^{***}p \leq 0.001$, calculated using a two-sided paired-sample *t* test. [a]Based on the USA index value, which ranges from a worst score of −0.109 to a best score of 1

showed that minor skin infections occurred at least once per year among 13–15% of patients who were treated with long-term subcutaneous administration of insulin and CSAI for chronic conditions [29].

Published literature offers insight on managing infusion site skin events with subcutaneous administration including the need for AE identification and monitoring, patient/caregiver education on appropriate infusion site selection and cannula placement, regular (and possibly more frequent) rotation of infusion sites and replacement of infusion sets, use of aseptic technique and good skin care practices, and close collaboration between patients and HCPs (including physicians and nurses) to ensure optimal outcomes [37, 38]. The strategies implemented to improve the patient experience in the current study reflected these insights, and the results were generally favorable, reinforcing the importance of patient/caregiver training and education prior to initiation of foslevodopa/foscarbidopa.

The systemic safety profile of foslevodopa/foscarbidopa was generally consistent with the well-established safety profile of other

LD-containing medications, including oral LD/CD [39]. The most commonly reported systemic AEs with foslevodopa/foscarbidopa were hallucinations and falls, the majority of which were nonserious, and mild/moderate in severity; their presentation was generally not different in terms of nature, severity, specificity, and outcome from that reported with oral LD-containing medications and LD-containing infusion therapies such as LCIG. Hallucination is a known manifestation seen in patients with aPD, present in up to 40% of individuals with PD, and is an established class effect for LD-containing medications [40–42], although hallucinations are more common with dopamine agonists than with LD [5]. The potential contribution from continuous 24-hour/day delivery of LD-containing medications on the worsening of hallucinations is debated, as there is literature to suggest a relationship between both worsening and improvement of hallucination with 24-hour continuous dosing [13, 43–45]. However, recent literature summarizing practical recommendations from clinics using 24-hour LCIG therapy generally recommends reducing nighttime infusion rates for the initial optimization of 24-hour therapy to avoid the risk of worsening hallucinations, psychosis, and nightmares [13]. In the current study of foslevodopa/foscarbidopa, the allowed infusion rate reduction per protocol was initially limited to within 20% of the base infusion rate, unless additional reduction was deemed medically necessary, a limitation that was removed in the long-term extension study and will likely not exist in real-world clinical practice. The ability to further individualize nighttime dosing of foslevodopa/foscarbidopa in real-world clinical practice should improve physicians' ability to meet the specific needs of each patient.

Motor symptom improvements were observed as early as the first post-baseline assessment (week 1) after initiation of 24-hour/day CSCI of foslevodopa/foscarbidopa and persisted throughout the 52-week treatment period. Reduced "Off" time was complemented by an increase in "good On" time ("On" time without troublesome dyskinesia, defined as the sum of "On" time with no dyskinesia and "On" time with non-troublesome dyskinesia). The increase in "good On" time was driven by increases in the most desirable state of "On" time without dyskinesia rather than "On" time with non-troublesome dyskinesia. The reduction of "Off" time is particularly exemplified by the meaningful reduction in morning akinesia, with almost 50% more patients awakening in the "On" state without any dyskinesia at week 52 compared with baseline (changed from 17.5% at baseline to 62.2% at week 52). Treatment with foslevodopa/foscarbidopa also resulted in improved motor experiences of daily living.

Reduction in early morning akinesia, improved sleep outcomes, and overall improvement in HRQoL measures are among the added benefits of continuous (24-hour/day) delivery of foslevodopa/foscarbidopa. In this study, treatment with foslevodopa/foscarbidopa resulted in improved sleep, quality of life (QoL), and HRQoL. These data support mounting evidence in the literature that sustained dopaminergic stimulation may be helpful for reducing early morning "Off" symptoms [46, 47]. Improving sleep and early morning symptoms is of particular importance because sleep is one of the strongest factors associated with HRQoL [48]. Sleep disturbances are associated with an increased risk of falls and worsening of cognition in patients with PD [49], while improvements in patients' sleep are associated with reduced caregiver burden [50]. Likewise, early morning "Off" periods occur in more than half of patients with PD, are associated with other motor and non-motor symptoms, and have a significant negative impact on patients' QoL [46, 51].

Among the limitations to consider when interpreting results from this investigation are the open-label nature of the study and the lack of randomization and of a comparator. Because all patients received the same intervention, our ability to reach definitive conclusions regarding the relative efficacy of foslevodopa/foscarbidopa is limited. Additionally, only patients who completed each study visit were included in the efficacy analysis, and no adjustments were made to account for premature discontinuation. However, the results of this study are in line with those from the double-blind study,

supporting the significant improvements in motor fluctuations with foslevodopa/foscarbidopa compared with oral immediate-release LD/CD [22].

CONCLUSION

In summary, individualized 24-hour/day CSCI of foslevodopa/foscarbidopa demonstrated a favorable benefit/risk profile in patients with aPD. The systemic safety profile was generally consistent with other LD-containing medications, and local tolerability was comparable to that reported by other continuous infusions that use the subcutaneous route of delivery. The majority of the AEs, including infusion site AEs, were nonserious, mild or moderate in severity, and resolved with or without treatment. It is clear from the literature that infusion site AEs are common with subcutaneous therapies and that there is no singular or universal solution for prevention. It is important that HCPs (including physicians and nurses), patients, and care partners be educated about how to recognize and respond to infusion site side effects if they occur. The prevention and management of infusion site AEs should be among the top priorities to consider when initiating foslevodopa/foscarbidopa to promote adherence to therapy and a positive experience for patients and their care partners. Strategies to improve patient outcomes will be explored in future publications that focus on clinical practice recommendations for use of foslevodopa/foscarbidopa.

Foslevodopa/foscarbidopa administered by 24-hour/day CSCI also demonstrated improvement in motor fluctuations, sleep, and QoL throughout the 52-week treatment period. Although these results are from a single-arm, open-label study, they support the benefit of a continuous, 24-hour/day infusion of LD and are consistent with the results from the double-blind study. Overall, by providing individualized, continuous, 24-hour/day, subcutaneous delivery of LD and CD prodrugs, foslevodopa/foscarbidopa has the potential to provide an efficacious and safe nonsurgical alternative therapy to other currently available treatments for controlling fluctuations and improving QoL in patients with aPD.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized individual and trial-level data (analysis datasets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. 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 and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. These data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select "Home".

Declarations

Conflict of interest. Jason Aldred is a study investigator for AbbVie, AC Immune, Annovis, Aptinyx, AstraZeneca, Atara, Athira, Biogen, BioVie, Boston Scientific, Celgene, Cerevance, Cerevel, Denali, EIP, Eli Lilly, Impax, Inhibikase, IRL Therapeutics, Merz, Neuraly, Neurocrine, Neuoderm, Novartis, PD Gene/PSG, Praxis, Revance, Roche/Genentech, Sage, Sanofi/Genzyme, Scion NeuroStim, Takeda, Theravance, Triplet/HSG, and UCB. He has received honorarium from AbbVie, Allergan, Boston Scientific Teva, US World Meds,

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Ethical Approval. The study received institutional review board approval at all participating institutions (supplemental appendix) and was conducted in accordance with the International Council for Harmonisation, the Declaration of Helsinki of 1964 and its later amendments, and all applicable regulations and guidelines. Patients were required to provide written informed consent before undergoing any study-related procedures. This study was registered at ClinicalTrials.gov (NCT03781167). Where relevant, permissions were obtained to use the scales employed in this study (MMSE, EQ-5D-5L, MDS-UPDRS, PDQ-39, PDSS-2, PD diary).

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