Safety and efficacy of continuous subcutaneous foslevodopa-foscarbidopa in patients with advanced Parkinson's disease: a randomised, double-blind, active-controlled, phase 3 trial

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Summary

Background Levodopa is the most effective symptomatic therapy for Parkinson's disease, but patients with advanced Parkinson's disease develop motor fluctuations with chronic oral levodopa therapy. Foslevodopa-foscarbidopa is a soluble formulation of levodopa and carbidopa prodrugs that is delivered as a 24-h/day continuous subcutaneous infusion, and we aimed to assess the safety and efficacy of this formulation in patients with advanced Parkinson's disease.

Methods A 12-week randomised, double-blind, double-dummy, active-controlled study was done at 65 academic and community study centres in the USA and Australia. Patients with levodopa-responsive advanced Parkinson's disease inadequately controlled on current therapy, including at least 2·5 h of average daily off time, were randomly assigned (1:1) to continuous subcutaneous infusion of foslevodopa-foscarbidopa plus oral placebo or to oral immediate-release levodopa-carbidopa plus continuous subcutaneous infusion of placebo solution. Randomisation was stratified by site by means of a permutated-block schedule with a block size of two. The participants, treating investigators, study site personnel, and sponsor were masked to treatment group allocation. The primary and first key secondary endpoint in the hierarchical testing strategy were change from baseline to week 12 in on time without troublesome dyskinesia and off time, respectively; both endpoints were evaluated by an intention-to-treat analysis applying a mixed model for repeated measures analysis. Safety and tolerability were assessed throughout the study. The study is completed and is listed on ClinicalTrials.gov, NCT04380142.

Findings Between Oct 19, 2020, and Sept 29, 2021, of 270 participants screened and 174 enrolled, 141 were randomly assigned and received continuous subcutaneous infusion of foslevodopa-foscarbidopa plus oral placebo capsules (n=74) or oral encapsulated immediate-release levodopa-carbidopa plus continuous subcutaneous infusion of placebo solution (n=67). Compared with levodopa-carbidopa, foslevodopa-foscarbidopa showed a significantly greater increase in on time without troublesome dyskinesia (model-based mean [SE] 2·72 [0·52] *vs* 0·97 [0·50] h; difference 1·75 h, 95% CI 0·46 to 3·05; p=0·0083) and a significantly greater reduction in off time (–2·75 [0·50] *vs* –0·96 [0·49] h; difference –1·79 h, –3·03 to –0·54; p=0·0054). Hierarchical testing ended after the first secondary endpoint. Adverse events were reported in 63 (85%) of 74 patients in the foslevodopa-foscarbidopa group versus 42 (63%) of 67 in the levodopa-carbidopa group, and incidences of serious adverse events were similar between the groups (six [8%] of 74 *vs* four [6%] of 67, respectively). The most frequent adverse events in the foslevodopa-foscarbidopa group were infusion site adverse events (erythema 20 [27%]), pain 19 [26%]), cellulitis (14 [19%]), and oedema (nine [12%]), most of which were non-serious and mild–moderate in severity. The only system organ class that had more than one serious adverse event in the foslevodopa-foscarbidopa group was infections and infestations (catheter site cellulitis [one [1%]] and infusion site cellulitis [one [1%]). Adverse events led to premature discontinuation of study drug in 16 (22%) of 74 participants in the foslevodopa-foscarbidopa group versus one (1%) of 67 participants in the oral levodopa-carbidopa group.

Interpretation Foslevodopa-foscarbidopa improved motor fluctuations, with benefits in both on time without troublesome dyskinesia and off time. Foslevodopa-foscarbidopa has a favourable benefit-risk profile and represents a potential non-surgical alternative for patients with advanced Parkinson's disease.

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Introduction

Parkinson's disease is a progressive neurological disorder characterised by the degeneration of dopaminergic neurons in the substantia nigra and a decrease of dopamine in the brain.[1] The depletion of striatal dopamine leads to the cardinal clinical symptoms of

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Research in context

Evidence before this study

We searched PubMed (from database inception to July 29, 2022) using the search terms of "levodopa-carbidopa", "continuous levodopa infusion", "continuous dopaminergic stimulation", "device-aided levodopa therapy", and "continuous levodopa delivery" with no restriction on date or language. Previous studies of levodopa have shown that fluctuating plasma concentrations can be avoided with continuous delivery. Foslevodopa-foscarbidopa (also referred to as ABBV-951) is a new soluble formulation of levodopa and carbidopa prodrugs delivered as a 24-h/day continuous subcutaneous infusion via an infusion set connected to a portable pump. Systemic and local tolerability has been evaluated in animal models and in the clinical setting with generally favourable outcomes. A phase 1 study in healthy volunteers, in which foslevodopa-foscarbidopa was administered as a loading dose followed by a continuous infusion for up to 72 h, showed a low degree of fluctuation in levodopa concentration; mild infusion site pain was observed following the loading dose, which resolved when the flow rate was adjusted. Infusion site adverse events were reported in other phase 1 studies in patients with Parkinson's disease in which foslevodopa-foscarbidopa was administered at therapeutic doses for 24 h, 72 h, or for up to 28 days. Most adverse events were non-serious, mild, or moderate in severity, and resolved.

Added value of this study

Here we present the results of a phase 3 study of foslevodopa-foscarbidopa in patients with advanced Parkinson's disease whose motor fluctuations were inadequately controlled by their current therapy and exhibited at least 2·5 h of off time per day. This 12-week study is, we believe, the first completed phase 3 randomised, double-blind, double-dummy, active-controlled study to compare efficacy of continuous subcutaneous infusion of foslevodopa-foscarbidopa with oral immediate-release levodopa-carbidopa for the treatment of motor fluctuations in patients with advanced Parkinson's disease. Improved motor symptom control with foslevodopa-foscarbidopa was observed as early as the first post-baseline assessment and was sustained throughout the study. Given the 24 h administration and efficacy results, foslevodopa-foscarbidopa offers continuous symptom control throughout the day. Moreover, this study confirmed the ability of the foslevodopa-foscarbidopa drug–device combination product to deliver a wide range of individualised and therapeutically relevant doses of foslevodopa (approximately 600–4250 mg/day levodopa equivalents), which is needed to control motor symptoms in advanced Parkinson's disease, allowing for fine-tuning and optimisation. The systemic adverse events observed with foslevodopa-foscarbidopa were consistent with the well-established systemic safety profile of levodopa-containing medications. Furthermore, infusion site adverse events were similar to those observed with other subcutaneously delivered medications, supporting its favourable benefit–risk profile.

Implications of all the available evidence

Foslevodopa-foscarbidopa is a non-surgical, 24-h/day continuous pharmacological device-aided therapy with the potential to offer appropriate patients an effective alternative to available treatments for advanced Parkinson's disease, such as deep brain stimulation and levodopa-carbidopa intestinal gel. The safety of foslevodopa-foscarbidopa will continue to be followed-up through long-term, open-label extension studies and post-marketing pharmacovigilance.

Parkinson's disease: resting tremor, rigidity, bradykinesia, and postural instability.[2] No disease-modifying treatments are available for Parkinson's disease and levodopa, the amino-acid precursor of dopamine, remains the most effective symptomatic therapy.[3] Co-administration of a decarboxylase-inhibitor, such as carbidopa, has been shown to improve the bioavailability of levodopa in the CNS. Most patients with Parkinson's disease respond well to oral levodopa initially; however, its effectiveness diminishes over time. As Parkinson's disease progresses, patients begin to alternate periods of good motor control (on time) and periods of poor motor control and poor mobility (off time).[4] Higher doses of oral levodopa can reduce off time but tend to increase dyskinesia, which manifests as involuntary choreiform movements. Multiple classes of medications (dopamine agonists, catechol-*O*-methyltransferase [COMT] inhibitors, and monoamine oxidase B [MAO-B] inhibitors) were developed to reduce off time and can be used in combination with levodopa, but typically provide only modest benefit for motor fluctuations.[5]

There is scientific consensus that patients have advanced Parkinson's disease when optimised pharmacological therapies no longer effectively control motor symptoms, and motor complications are persistent and impair quality of life. At this stage, optimising dose or frequency of oral medications without inducing dyskinesia is difficult.[6,7] Device-aided therapies were developed in response to this challenge including surgical interventions (deep brain stimulation [DBS]), continuous delivery of medications such as continuous subcutaneous apomorphine infusion (CSAI), and continuous administration of enteral formulations of levodopa-carbidopa.[8] Additionally, ND0612, an investigational continuous subcutaneous infusion of levodopa-carbidopa, is being studied in a randomised clinical trial.[9] DBS improves off time and dyskinesia but requires a neurosurgical intervention that is associated with potentially serious complications and is not recommended for elderly patients who might have vascular disorders.[10] Reductions in off time were reported in CSAI studies, but the poor tolerability of high doses, reduced tolerability over time,

and formation of subcutaneous nodules are limitations.[10,11] Additionally, DBS and CSAI can rarely be used as a monotherapy for patients with advanced Parkinson's disease.[12] Another therapeutic option, levodopa-carbidopa intestinal gel, which is generally administered over 16 waking h/day, offers several clinical benefits but many eligible patients do not initiate it for fear of surgery or its complications, choosing instead to remain on oral therapy despite suboptimal symptom control.[13,14] Therefore, a significant unmet need exists for patients with advanced Parkinson's disease to have an individualised, continuous and non-surgical therapy that provides symptomatic relief via the predictable delivery of levodopa: the gold standard symptomatic therapy for Parkinson's disease.

Foslevodopa-foscarbidopa (also referred to as ABBV-951) is a new soluble formulation of levodopa and carbidopa prodrugs delivered as a 24-h/day continuous subcutaneous infusion (CSCI) via an infusion set connected to a portable pump for treatment of motor fluctuations in patients with advanced Parkinson's disease. On subcutaneous delivery, foslevodopa-foscarbidopa undergoes rapid enzymatic conversion via alkaline phosphatases to the pharmacologically active forms of levodopa-carbidopa.[15] Results from clinical studies showed that 24-h/day CSCI of foslevodopa-foscarbidopa provided stable levodopa exposure with a consistent overall pharmacokinetic profile and was generally safe and well tolerated.[15]

Here we report the primary results of the pivotal phase 3, randomised, active-controlled, multicentre study assessing the safety and efficacy of 24-h/day CSCI of foslevodopa-foscarbidopa compared with oral immediate-release levodopa-carbidopa for the treatment of motor fluctuations in patients with advanced Parkinson's disease.

Methods

Study design

The study was a phase 3, double-blind, double-dummy, active-controlled, multicentre study done across 65 academic and community sites in the USA and Australia. The study included a screening period (6–60 days), an oral levodopa-carbidopa stabilisation period (2–3 weeks), and a double-blind treatment period (12 weeks) for a total of 13 scheduled visits (appendix p 7).

The screening period included two eligibility confirmation visits in which participants or care partners received training on the infusion delivery system. Eligible participants were enrolled in the oral levodopa-carbidopa stabilisation period. All levodopa-containing medications and COMT inhibitors were converted to an equivalent amount of immediate-release levodopa-carbidopa and rounded to the closest multiple of 100 mg to deliver only full tablets of 100 mg levodopa and 25 mg carbidopa, allowing encapsulation during the randomised period to maintain masking. Non-levodopa-containing concomitant Parkinson's disease medications (eg, dopamine agonists, MAO-B inhibitors, and amantadine) were not included in the conversion algorithm and were allowed during the study but regimens had to remain unchanged until study completion (appendix p 11). Besides any allowed non-levodopa-containing Parkinson's disease medications, the therapeutic regimen of the stabilisation period consisted of only oral immediate-release levodopa-carbidopa, which the investigator could adjust as needed but always in increments of 100 mg levodopa and 25 mg carbidopa. The levodopa-carbidopa regimen could include night-time dosing to meet the requirements of each participant. No changes were to be made starting at least 7 days before randomisation (day 1) through to the end of the study. The double-blind treatment period included randomisation, a CSCI optimisation phase (4 weeks), and a maintenance phase (8 weeks) for a total of eight scheduled study visits. On the day of randomisation, participants presented in a practically defined off state (ie, they had taken no medications to treat Parkinson's disease symptoms for at least 12 h).

Treatment groups consisted of either 24-h/day CSCI of foslevodopa-foscarbidopa plus oral capsules of placebo for immediate-release levodopa–carbidopa or 24-h/day CSCI of placebo solution plus oral encapsulated immediate-release levodopa-carbidopa tablets (see randomisation and masking section). Changes to CSCI rate were permitted only during the CSCI optimisation phase and participants were evaluated at five subsequent visits, of which one was optional, and any intervening days as needed. Optimal clinical response was defined as maximising functional on time, minimising the number of off episodes during the day, and minimising on time with troublesome dyskinesia. After the 4-week CSCI optimisation phase, participants entered the maintenance phase (two visits) and required all study drug regimens and concomitant medications to remain stable. Dose adjustments of non-study-drug medications were made only if considered medically necessary by investigators. Safety assessments were done at each visit. Given that the safety data of foslevodopa-foscarbidopa is generally consistent with the well-established safety profile of levodopa-carbidopa, along with the relatively short double-blind treatment period, the study did not use an independent data safety monitoring board.

See Online for appendix

Participants

Eligible participants aged at least 30 years with a diagnosis of idiopathic and levodopa-responsive Parkinson's disease were required to be on a minimum of 400 mg/day levodopa equivalents (from levodopa-containing medications and COMT inhibitors), and have inadequately controlled motor fluctuations with an average off time of at least 2·5 h/day over 3 consecutive days. Full inclusion and exclusion criteria are given in the appendix (pp 2–3).

The study was approved by independent ethics committees or institutional review boards at each study site. The study was done and reported in accordance with the protocol (NCT04380142) and the International Council

on Harmonisation guidelines, and adhered to applicable regulations and the Declaration of Helsinki. Participants and their care partners (if participants had a care partner) provided written informed consent before screening.

Randomisation and masking

Investigators enrolled participants who were then randomly assigned by the interactive response technology system in a 1:1 ratio to receive CSCI of foslevodopa-foscarbidopa plus oral placebo capsules for immediate-release levodopa-carbidopa or CSCI of placebo solution for foslevodopa-foscarbidopa plus oral encapsulated immediate-release levodopa-carbidopa tablets. Randomisation was stratified by site by means of a permutated-block schedule with a block size of 2. Study sites had three distinct personnel with non-overlapping roles: a pharmacist or nurse provided the study drugs to patients, but along with investigators, site personnel, and participants, remained masked to treatment allocation throughout the study; investigators (or designees) did safety assessments, managed adverse events and the use of rescue medications; qualified examiners, who did all in-person efficacy assessments, did not have access to the results of other study assessments or medical records, and did not otherwise participate in the care or management of participants. Immediate-release levodopa–carbidopa tablets were over-encapsulated and identical in appearance to the placebo capsules. The foslevodopa-foscarbidopa and placebo solutions for infusion were packaged identically. Although the pump is designed to enable preprogramming of alternative infusion rates and extra doses for the patient to self-administer, the investigator or designee was required to disable the alternative infusion rates and extra dose functionalities to prevent unmasking. After the delivery of the loading dose on day 1, this pump functionality was disabled for the remainder of the study.

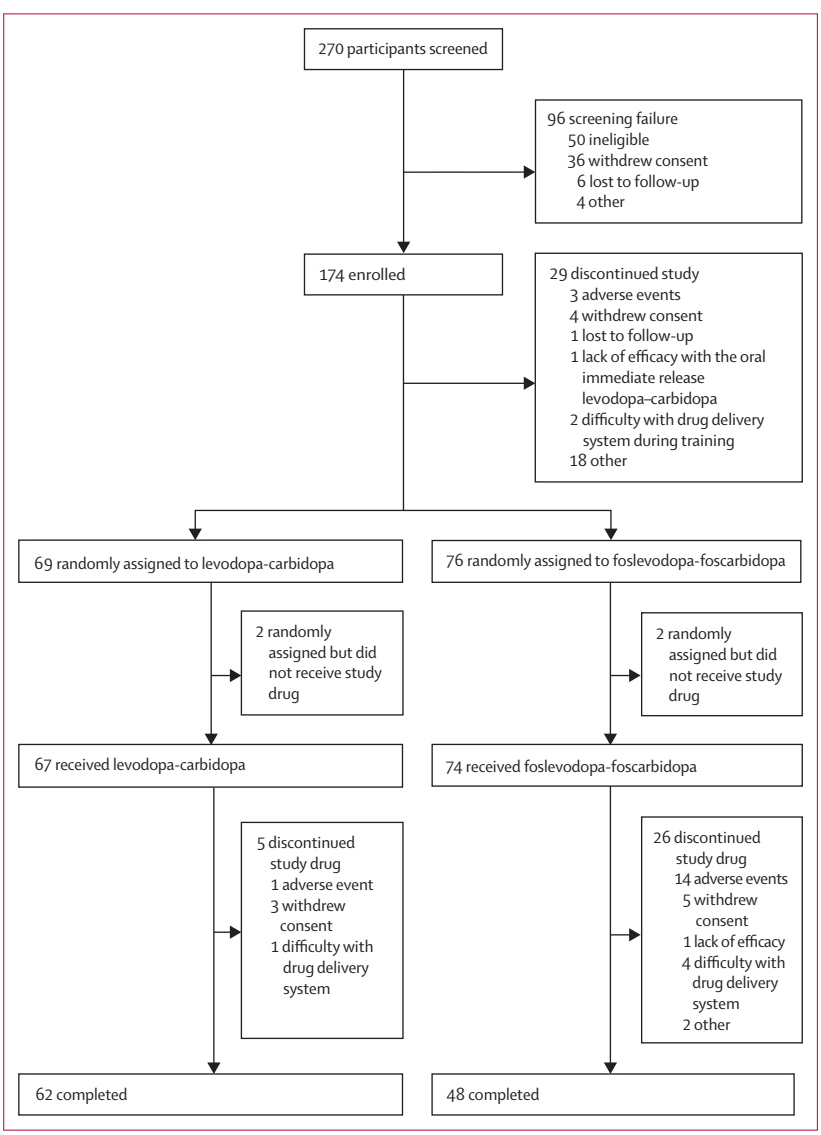

Figure 1: **Trial profile**
Full analysis set n=141. Safety analysis set n=141.

Procedures

On the day of randomisation, participants received a dual loading dose with both the oral study drug and study drug solution. The study drug solution was administered into the abdomen via an infusion set connected to an ambulatory pump. After the loading doses, each participant started CSCI of foslevodopa-foscarbidopa or placebo solution, and concurrently received masked oral study drug via the individualised regimen established during the oral levodopa-carbidopa stabilisation period. Each participant's starting continuous infusion rate was calculated on the basis of the stabilised oral immediate-release levodopa-carbidopa therapy at the end of the stabilisation period and an algorithm that was developed following a combination of pharmacokinetic and clinical considerations from phase 1 studies (appendix p 12). Infusion sites could be used for up to 3 days. All participants received open-label immediate-release levodopa-carbidopa tablets for use as rescue medication in the event of rapid deterioration of motor symptoms.

Outcomes

The primary efficacy endpoint was the change from baseline to week 12 of the double-blind treatment period in hours of average daily normalised on time without troublesome dyskinesia (sum of on time without dyskinesia and on time with non-troublesome dyskinesia) as assessed by the Parkinson's disease diary.[16,17] Key secondary endpoints in hierarchical order of analysis were change from baseline to week 12 in hours of average daily normalised off time as assessed by the Parkinson's disease diary, change from baseline to week 12 in Motor Aspects of Experiences of Daily Living as assessed by the Movement Disorder Society-Unified PD Rating Scale (MDS-UPDRS) part II score, and presence of morning

akinesia at week 12 (defined in this study as reporting off status in the Parkinson's disease diary as the predominant Parkinson's disease status during the first half-hour period on waking). Daily off and on times were normalised to a typical waking day (16 h) to account for different sleep patterns across participants. Other secondary endpoints in our hierarchical analysis were change from baseline to week 12 in hours of average daily normalised on time without dyskinesia as assessed by the Parkinson's disease diary, change from baseline in the Parkinson's disease Sleep Scale-2 (PDSS-2) total score, Parkinson's disease Questionaire-39 (PDQ-39) summary index, EQ-5D-5L summary index, and median bradykinesia and dyskinesia scores, along with IQRs of bradykinesia and dyskinesia scores as assessed by the Parkinson's KinetiGraph or Personal KinetiGraph (Global Kinetics, MN, USA) wearable device.

Safety and tolerability were assessed by the incidence of adverse events, changes in vital signs, clinical laboratory parameters, electrocardiograms, the Columbia-Suicide Severity Rating Scale (C-SSRS), and the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease—Rating Scale. Local skin tolerability was assessed by the Infusion Site Evaluation scale. Treatment-emergent adverse events were defined as events with onset after the first dose of study drug and until 30 days after the last dose of study drug.

Statistical analysis

A sample size of 52 participants per group was calculated to provide 90% power to detect a target difference of 1·86 h between the two treatment groups on the primary endpoint with a two-sided significance level of 0·05, assuming a common standard deviation of 2·9 h (nQuery Version 8.4.0.0). This sample size had approximately 90% power for the key secondary endpoints. Approximately 130 participants were planned to be randomly assigned assuming that approximately 20% would prematurely discontinue during the double-blind treatment period. Efficacy analyses were done on the full analysis set, which included all randomly assigned participants who received any dose of study drug during the double-blind treatment period, and who had baseline and at least one post-baseline observation for at least one assessment. Demographic and safety analyses were done on the safety analysis set, which consisted of all participants who received any dose of study drug during the double-blind treatment period. The primary endpoint was analysed by means of mixed model repeated measures (MMRMs), including data on change from baseline to each post-baseline visit in mean daily normalised on time without troublesome dyskinesia obtained from Parkinson's disease diaries. The model included fixed categorical effects of treatment, country, and scheduled assessment visits, and interaction between time and treatment as well as between treatment and baseline. Missing data in patients who discontinued during the double-blind treatment period were handled in the MMRM model on the basis of the missing at random assumption, and model parameters were estimated by means of the restricted maximum likelihood method. Secondary endpoints were included in multiplicity adjustment of the type I error to control the familywise error rate at a 2-sided significance level of 0·05. The first morning status on waking (off or not off) on the last valid Parkinson's disease diary day at each post-baseline visit was analysed by means of a generalised linear mixed model with a logit link function to compare the probability of morning akinesia between treatment groups. Prespecified sensitivity analyses were done to account for missing data (appendix pp 8–9). For safety data, the incidence of adverse events and serious adverse events were summarised. All analyses were done by means of SAS Version 9.4.

The study is listed on ClinicalTrials.gov, NCT04380142.

	Oral levodopa–carbidopa group (n=67)	Foslevodopa–foscarbidopa group (n=74)	Total (n=141)
Sex			
Male	49 (73%)	50 (68%)	99 (70%)
Female	18 (27%)	24 (32%)	42 (30%)
Age, years	66·6 (9·8)	66·3 (9·2)	66·4 (9·5)
<65 years	24 (36%)	27 (36%)	51 (36%)
≥65 years	43 (64%)	47 (64%)	90 (64%)
Race			
White	61 (91%)	70 (95%)	131 (93%)
Black or African American	2 (3%)	2 (3%)	4 (3%)
Asian	3 (4%)	0	3 (2%)
American Indian or Alaska Native	0	1 (1%)	1 (1%)
Native Hawaiian or other Pacific Islander	1 (1%)	1 (1%)	2 (1%)
Country			
Australia	9 (13%)	12 (16%)	21 (15%)
USA	58 (87%)	62 (84%)	120 (85%)
Body mass index, kg/m²	26·34 (23·33–31·19)	26·31 (22·73–29·88)	26·34 (23·01–30·29)
MMSE score	28·83 (1·27)	28·72 (1·60)	28·77 (1·45)
Duration since Parkinson's disease diagnosis, years	8·79 (5·49)	8·38 (4·22)	8·58 (4·85)
<10 years	44 (66%)	51 (69%)	95 (67%)
≥10 years	23 (34%)	23 (31%)	46 (33%)
Hoehn and Yahr stage (MDS-UPDRS)			
0	1 (1%)	0	1 (1%)
1	4 (6%)	9 (12%)	13 (9%)
2	45 (67%)	43 (58%)	88 (62%)
3	14 (21%)	20 (27%)	34 (24%)
4	2 (3%)	2 (3%)	4 (3%)
5	1 (1%)	0	1 (1%)
Levodopa,* mg/day	1000 (600–1500)	1050 (800–1500)	1000 (800–1500)
Concomitant dopamine agonist use			
Yes	25 (37%)	34 (46%)	59 (42%)
No	42 (63%)	40 (54%)	82 (58%)

(Table 1 continues on next page)

	Oral levodopa–carbidopa group (n=67)	Foslevodopa–foscarbidopa group (n=74)	Total (n=141)
(Continued from previous page)			
Parkinson's disease diary outcomes, †normalised hours			
Off time	5·91 (1·88)	6·34 (2·27)‡	6·13 (2·10)§
On time without troublesome dyskinesia	9·49 (2·62)	9·20 (2·42)‡	9·34 (2·51)§
On time without dyskinesia	7·47 (3·73)	7·23 (3·14)‡	7·35 (3·42)§
On time with non-troublesome dyskinesia	2·02 (2·75)	1·97 (2·47)‡	1·99 (2·60)§
On time with troublesome dyskinesia	0·60 (1·46)	0·46 (0·86)‡	0·53 (1·18)§
Presence of morning akinesia	51/67 (76%)	56/71 (79%)	107/138 (78%)
MDS-UPDRS part II score	13·27 (6·37)	15·31 (6·93)	14·34 (6·73)
PDSS-2 total score	18·88 (9·25)¶	21·19 (8·80)‖	20·09 (9·06)**
PDQ-39 summary index	26·15 (14·46)¶	30·68 (16·05)‡	28·53 (15·43)**
EQ-5D-5L summary index	0·748 (0·12)††	0·752 (0·14)‖	0·750 (0·13)‡‡
Median PKG bradykinesia score	26·63 (7·68)§§	25·97 (7·65)¶	26·28 (7·64)¶¶
IQR of PKG bradykinesia score	17·80 (4·26)§§	17·13 (4·18)¶	17·44 (4·21) ¶¶
Median PKG dyskinesia score	3·70 (5·45)§§	4·46 (10·14)¶	4·10 (8·24) ¶¶
IQR of PKG dyskinesia score	11·31 (16·61)§§	12·31 (20·37)¶	11·83 (18·62)¶¶

Data are n (%), mean (SD), or median (IQR), unless stated otherwise. Total column included for ease of describing overall study population. On time without troublesome dyskinesia is the sum of on time without dyskinesia and on time with non-troublesome dyskinesia. Morning akinesia is defined as reporting off status as the first morning symptom on waking. MMSE=Mini-Mental State Examination. MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale. PDSS-2=Parkinson's Disease Sleep Scale-2. PDQ-39=39-item Parkinson's Disease Questionnaire. PKG=Parkinson's KinetiGraph or Personal KinetiGraph (Global Kinetics, MN, USA). *Immediate-release levodopa after conversion from levodopa-containing medications and catechol-*O*-methyltransferase inhibitors and subsequent adjustments. †Assessed using a 24-h diary and normalised to a 16-h waking day. ‡n=73. §n=140. ¶n=66. ‖n=72. **n=139. ††n=65. ‡‡n=137. §§n=59. ¶¶n=125.

Table 1: **Baseline characteristics (full analysis set)**

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

The study was done between Oct 19, 2020, and Sept 29, 2021. A total of 270 participants were screened with 174 enrolled in the open-label oral levodopa-carbidopa stabilisation period (figure 1). Of those, 145 participants were randomly assigned to double-blind treatment at 57 study centres, and 141 received blinded study drug. A total of 110 participants completed the trial (foslevodopa-foscarbidopa group, n=48, levodopa-carbidopa group n=62, figure 1). Primary reasons for drug discontinuation in both groups were adverse events, withdrawn consent, and difficulty with the drug delivery system (figure 1).

Participant demographics and baseline characteristics were similar between treatment groups (table 1). The majority of participants were male (99 [70%] of 141) and White (131 [93%] of 141), and the mean age was 66·4 (SD 9·47) years. The mean (SD) duration of Parkinson's disease since diagnosis was 8·58 (4·85) years. The mean (SD) of off times in the oral levodopa-carbidopa and foslevodopa-foscarbidopa groups were 5·9 (1·88) and 6·34 (2·27) h, respectively. The majority of participants in both treatment groups (99 [70·2%] of 141) were taking additional concomitant Parkinson's disease medications other than immediate-release levodopa-carbidopa at baseline before randomisation; 23 (34%) of 67 in the oral levodopa–carbidopa group and 19 (26%) of 74 in the foslevodopa-foscarbidopa group did not receive any concomitant Parkinson's disease medication.

Each participant's initial foslevodopa-foscarbidopa optimisation was considered complete when no changes to the infusion rate were made for at least 15 days. Of 55 participants in the foslevodopa-foscarbidopa group whose entire treatment duration was at least 15 days, the mean number of visits for initial optimisation was 2·4 (SD 1·5). Of these 55 participants, 22 (40%) completed optimisation in one visit and 11 (20%) completed optimisation in two visits.

The study met the primary efficacy outcome with foslevodopa-foscarbidopa providing a significant improvement (increase) in on time without troublesome dyskinesia at week 12 compared with oral levodopa–carbidopa (model-based mean [SE] change from baseline 2·72 [0·52] vs 0·97 [0·50] h; difference 1·75 h, 95% CI (0·46 to 3·05); p=0·0083; table 2).

Similarly, treatment with foslevodopa-foscarbidopa CSCI showed a significant improvement (decrease) in off time at week 12 compared with oral levodopa-carbidopa (model-based mean [SE] change from baseline –2·75 [0·50] *vs* –0·96 [0·49] h; difference –1·79 h, 95% CI (–3·03 to –0·54); p=0·0054; table 2). The improvements in on and off times were observed as early as the first post-baseline assessment and continued to the end of the double-blind treatment period at week 12 (figure 2). The sensitivity analyses also showed that CSCI of foslevodopa-foscarbidopa resulted in significant improvements in on time without troublesome dyskinesia and off time compared with oral immediate-release levodopa-carbidopa (appendix pp 8–9). Hierarchical testing for significance was terminated at the next comparison, as the next prespecified endpoint, change in MDS-UPDRS part II score, did not reach significance (oral levodopa-carbidopa –1·06 [0·79] *vs* foslevodopa-foscarbidopa –2·65 [0·82]; table 2). A smaller proportion of participants in the foslevodopa-foscarbidopa group reported being off at the time of waking compared with the oral levodopa-carbidopa group (eight [17%] of 47] *vs* 38 [63%] of 60]), despite the oral levodopa–carbidopa group including night-time oral dosing if needed (appendix p 10).

On time without dyskinesia showed a 25% (3·96 [3·77] h) increase from baseline in the foslevodopa-foscarbidopa group compared with a 7% (1·15 [3·63] h) increase in the oral levodopa–carbidopa group as a percentage of the waking day (figure 3). Results of other secondary efficacy measures are reported in table 2.

Adverse events were reported in 63 (85%) of 74 foslevodopa-foscarbidopa participants and 42 (63%) of

67 levodopa-carbidopa participants (table 3). Incidences of serious adverse events were similar between the groups (foslevodopa-foscarbidopa, six [8%] of 74; levodopa–carbidopa, four [6%] of 67; table 3). The incidence of infusion site adverse events was higher in the foslevodopa-foscarbidopa group, with erythema (20 [27%] of 74), pain (19 [26%] of 74), cellulitis (14 [19%] of 74), and oedema (nine [12%] of 74) at the infusion site being the most frequently reported. Most adverse events were non-serious and mild or moderate in severity. Two participants reported serious infusion site infection adverse events (infusion site cellulitis and catheter site cellulitis) in the foslevodopa-foscarbidopa group that required treatment with antibiotics (appendix p 13). None of the infusion site adverse events resulted in systemic complications. Falls were reported in six (8%) of 74 participants in the foslevodopa-foscarbidopa group and 12 (18%) of 67 in the oral levodopa-carbidopa group (table 3). Hallucinations or psychosis events were reported in 11 (15%) of 74 participants in the foslevodopa-foscarbidopa group and two (3%) of 67 participants in the levodopa-carbidopa group (table 3). In the majority of participants in each treatment group (two of two in the oral levodopa–carbidopa group and nine of 11 in the foslevodopa-foscarbidopa group), hallucination or psychosis events were non-serious and mild or moderate in severity, and no action was taken with the study drug. The incidence of adverse events leading to study drug discontinuation was higher in the foslevodopa-foscarbidopa group with infusion site adverse events (cellulitis four [5%] of 74), pain (three [4%] of 74), bruising (two [3%] of 74), haemorrhage (two [3%] of 74), and oedema (two [3%] of 74) being most common. Of the 16 adverse events leading to study drug discontinuation in the foslevodopa-foscarbidopa group, 12 occurred during the optimisation phase (within the first 4 weeks of initiation of study drug). No deaths were reported in the foslevodopa-foscarbidopa group; one participant had a serious adverse event leading to death in the oral levodopa-carbidopa group, which was considered by the investigator as not related to study drug (table 3). No clinically meaningful changes from baseline were observed for laboratory results, vital signs, or electrocardiogram for either treatment group. There was no evidence of increased suicidality on the basis of the review of C-SSRS data.

	Oral levodopa-carbidopa group (n=67)	Foslevodopa-foscarbidopa group (n=74)	Treatment difference (SE; 95% CI)	p value
Primary efficacy measure				
On time without troublesome dyskinesia, h/day	0·97 (0·50)	2·72 (0·52)*	1·75 (0·65; 0·46 to 3·05)	0·0083
Key secondary efficacy measures				
Off time, h/day	−0·96 (0·49)	−2·75 (0·50)*	−1·79 (0·63; −3·03 to −0·54)	0·0054
MDS-UPDRS part II score	−1·06 (0·79)	−2·65 (0·82)	−1·58 (1·05; 3·65 to 0·48)	0·13
Morning akinesia, n/N (%)	38/60 (63%)	8/47 (17%)	0·12 (0·49; 0·04 to 0·31)	..
Other secondary efficacy measures				
On time without dyskinesia, h/day	1·32 (0·53)	3·13 (0·54)*	1·81 (0·68; 0·46 to 3·16)	..
PDSS-2 total score	−2·52 (1·12)†	−7·92 (1·18)‡	−5·40 (1·32; −8·03 to −2·78)	..
PDQ-39 summary index	−2·28 (1·75)†	−6·38 (1·83)§	−4·10 (2·04; −8·14 to 0·05)	..
EQ-5D-5L summary index	0·002 (0·021)†	0·051 (0·022)‡	0·049 (0·025; −0·001 to 0·100)	..
Median PKG bradykinesia score	−0·34 (0·52)†	1·38 (0·56)¶	1·72 (0·72; 0·30 to 3·15)	..
IQR of PKG bradykinesia score	0·13 (0·49)†	0·31 (0·54)¶	0·18 (0·69; −1·20 to 1·55)	..
Median PKG dyskinesia score	1·02 (1·38)†	−1·71 (1·41)¶	−2·73 (1·96; −6·61 to 1·15)	..
IQR of PKG dyskinesia score	2·72 (2·59)†	−2·77 (2·64)¶	−5·49 (3·65; −12·71 to 1·73)	..

Data reported as least squares mean change from baseline (SE), unless otherwise stated. Treatment difference is the difference between least squares mean changes (SE). Morning akinesia reported as least squares mean of odds ratio (SE) at week 12. Secondary efficacy endpoints were tested in a hierarchical order. On time without troublesome dyskinesia is the sum of on time without dyskinesia and on time with non-troublesome dyskinesia. Morning akinesia is defined as reporting off status as the first morning symptom on waking. On and off times and morning akinesia were assessed using a 24-h Parkinson's disease diary and normalised to a 16-h waking day. EQ-5D-5L summary index is based on the weighted scoring algorithm for the USA. MDS-UPDRS=Movement Disorder Society—Unified Parkinson's Disease Rating Scale. PDSS-2=Parkinson's Disease Sleep Scale-2. PDQ-39=39-item Parkinson's Disease Questionnaire. PKG=Parkinson's KinetiGraph or Personal KinetiGraph (Global Kinetics, MN, USA). *n=73. †n=59. ‡n=44. §n=45. ¶n=66.

Table 2: **Summary of primary and secondary efficacy findings (full analysis set)**

Discussion

In a prospective, double-blind, double-dummy study, we showed that 24-h/day CSCI of foslevodopa-foscarbidopa provided significant and clinically meaningful[18] improvements in hours of on time without troublesome dyskinesia and in off time in patients with advanced Parkinson's disease compared with oral immediate-release levodopa-carbidopa. The observed treatment difference in favour of foslevodopa-foscarbidopa was in line with the target effect considered during the study design. Moreover, we found evidence to suggest that the improvement in on time without troublesome dyskinesiain the foslevodopa-foscarbidopa group might have been driven by improvement in the most desirable state of on time without any dyskinesia

Although the results of our analyses cannot be referred to as significant after missing the second of the secondary endpoints (MDS-UPDRS part II) in a hierarchical approach, the magnitude of the results provides some support for the benefit of 24-h/day CSCI with foslevodopa-foscarbidopa. For MDS-UPDRS part II, the reason for the lack of significance is unclear but a numerical improvement favouring foslevodopa-foscarbidopa was observed, the unadjusted magnitude of which is considered clinically meaningful for this patient population.[19] Additionally, the proportion of patients reporting morning akinesia in the oral levodopa-carbidopa group was almost nine times higher than in the foslevodopa-foscarbidopa group at the end of the double-blind period. Similarly, numerical improvements were seen in measures of Parkinson's disease-related sleep disturbances favouring

	Oral levodopa-carbidopa group (n=67)	Foslevodopa-foscarbidopa group (n=74)
Adverse events	42 (63%)	63 (85%)
Deaths	1 (1%)	0
Serious adverse events	4 (6%)	6 (8%)
Severe adverse events	1 (1%)	7 (9%)
Any adverse event leading to death	1 (1%)*	0
Any adverse event leading to premature study drug discontinuation†	1 (1%)	16 (22%)
Any adverse event considered related to study drug	15 (22%)	52 (70%)
Adverse events of special interest		
Infusion site events	8 (12%)	53 (72%)
Hallucinations or psychosis	2 (3%)	11 (15%)
Falls and associated injuries	17 (25%)	13 (18%)
Somnolence	1 (1%)	1 (1%)
Polyneuropathy	2 (3%)	2 (3%)
Weight loss	1 (1%)	1 (1%)
Most frequent adverse events‡		
Infusion site erythema	1 (1%)	20 (27%)
Infusion site pain	1 (1%)	19 (26%)
Infusion site cellulitis	0	14 (19%)
Infusion site oedema	0	9 (12%)
Dyskinesia	4 (6%)	8 (11%)
Fall	12 (18%)	6 (8%)
Infusion site bruising	2 (3%)	6 (8%)
Infusion site haemorrhage	0	6 (8%)
Infusion site nodule	0	6 (8%)
On and off phenomena	0	6 (8%)
Hallucination	1 (1%)	5 (7%)
Balance disorder	0	4 (5%)
Constipation	0	4 (5%)
Hallucination, visual	0	4 (5%)
Infusion site induration	0	4 (5%)
Infusion site infection	0	4 (5%)
Infusion site pruritus	0	4 (5%)
Peripheral swelling	0	4 (5%)

Data are n (%). Preferred terms classified according to the Medical Dictionary for Regulatory Activities version 24·0. *Considered by the investigator to have no reasonable possibility of being related to study drug. †Adverse events were one of the reasons for discontinuation, irrespective of whether it was the primary reason. ‡Occurring in ≥5% of patients. Further details are included in the appendix (pp 13–14) for serious and severe adverse events.

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

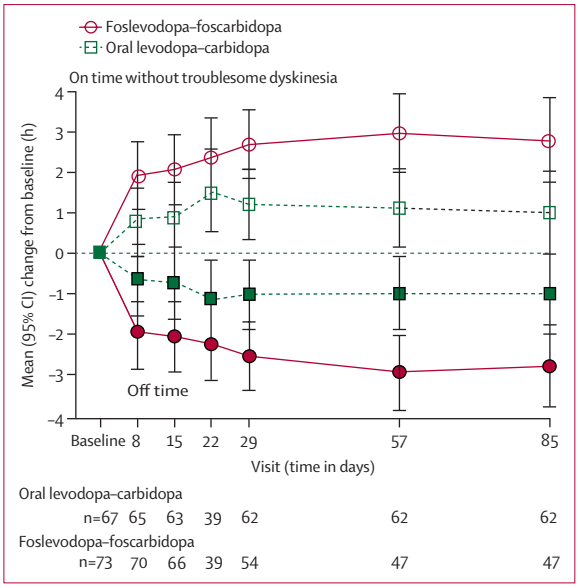

Figure 2: **Least squares mean (95% CI) of change from baseline in average daily on time without troublesome dyskinesia and off time (full analysis set)**
Assessed using a 24-h Parkinson's disease diary and normalised to a 16-h waking day. On time without troublesome dyskinesia is the sum of on time without dyskinesia and on time with non-troublesome dyskinesia. Error bars represent the 95% CI of the least squares mean change from baseline. Day 22 was an optional visit at the investigator's discretion and based on the participant's Parkinson's disease symptoms.

foslevodopa-foscarbidopa. Given the strong association of motor and non-motor symptoms, especially sleep, with patients' quality of life, the aforementioned improvements with foslevodopa-foscarbidopa could have led to the potential improvement in quality of life as measured by the PDQ-39.[20,21] Most Parkinson's disease therapies are administered during waking hours, which creates a treatment gap for patients who continue to have nocturnal symptoms and wake up in a functional off state. With existing therapies, some patients must decide between leaving nocturnal symptoms untreated or interrupting their night-time sleep to take medications. Therefore, although changes in morning akinesia, sleep, and quality of life were not significant after controlling for multiple analyses, the numerical improvements suggest the possibility of important potential benefits of 24-h/day CSCI of foslevodopa-foscarbidopa and warrant further investigation.

As Parkinson's disease progresses, the need for individual optimisation of therapy to address patient needs increases, and the therapeutic management of symptoms becomes increasingly complex. Conversion from oral immediate-release levodopa-carbidopa to initiation of foslevodopa-foscarbidopa was done in a single outpatient visit and initial optimisation was achieved quickly, in a mean of 2·4 visits. In real world clinical practice, physicians will have the flexibility to adjust the dose of foslevodopa-foscarbidopa as frequently or over as long a period as needed. To that end, our study also showed the capability of the foslevodopa-foscarbidopa drug–device combination product to provide the wide range of therapeutically relevant doses of levodopa that are normally needed to control symptoms and motor fluctuations in the advanced Parkinson's disease patient population, from approximately 600 mg to 4250 mg of levodopa equivalents over a 24-h period. Importantly, foslevodopa-foscarbidopa infusion rates could be adjusted in small increments, equivalent to approximately 1·7 mg of levodopa per h,

enabling individual fine-tuning and optimisation of therapy. Furthermore, one-quarter of participants in the foslevodopa-foscarbidopa group had their motor symptoms controlled exclusively by foslevodopa-foscarbidopa in the absence of scheduled concomitant Parkinson's disease medications. Since the study design required concomitant Parkinson's disease medications to remain stable, further investigation is needed to fully assess the potential of foslevodopa-foscarbidopa to reduce or eliminate the simultaneous use of concomitant Parkinson's disease medications.

The safety profile observed in this phase 3 trial was consistent with other studies of foslevodopa-foscarbidopa, and there were no new significant safety concerns. Foslevodopa-foscarbidopa was generally safe and well-tolerated with the majority of adverse events, including infusion site adverse events, reported as non-serious and mild or moderate in severity. The incidence of serious adverse events was generally similar between the treatment groups. Adverse events of special interest were as expected given the patient population, drug class, and route of administration. Overall, the systemic safety profile of foslevodopa-foscarbidopa was consistent with the established safety profile of other levodopa-containing therapies.

Although the incidence of infusion site adverse events was higher in the foslevodopa-foscarbidopa group compared with the oral levodopa–carbidopa group (which infused saline solution as placebo), this incidence was similar to those observed with other subcutaneously delivered medications.[22,23] Adverse events, in particular, infusion site adverse events, were the most common reason for premature discontinuation of the study drug in the foslevodopa-foscarbidopa infusion group, most of which occurred within the first few weeks following treatment initiation. These early discontinuations probably coincided with a period of familiarisation and adjustment with the drug delivery system, which reinforces the importance of health-care professional and patient training on the proper use of the foslevodopa-foscarbidopa drug–device combination product. Infusion site adverse events will continue to be monitored with the aim of identifying potential preventative and mitigation strategies to decrease their incidence, decrease the potential for early discontinuations, and improve overall patient experience.

Falls are a significant cause of disability and reduced quality of life in patients with Parkinson's disease and are recognised as being difficult to manage.[24] The causes of falls in Parkinson's disease are probably multifactorial and extend beyond motor impairment and dyskinesia, but it has been hypothesised that addressing motor impairment and dyskinesia with dopaminergic medications might improve or reduce the occurrence of falls.[25] In our study, participants receiving foslevodopa-foscarbidopa had a lower incidence of falls compared with those receiving oral levodopa-carbidopa. We

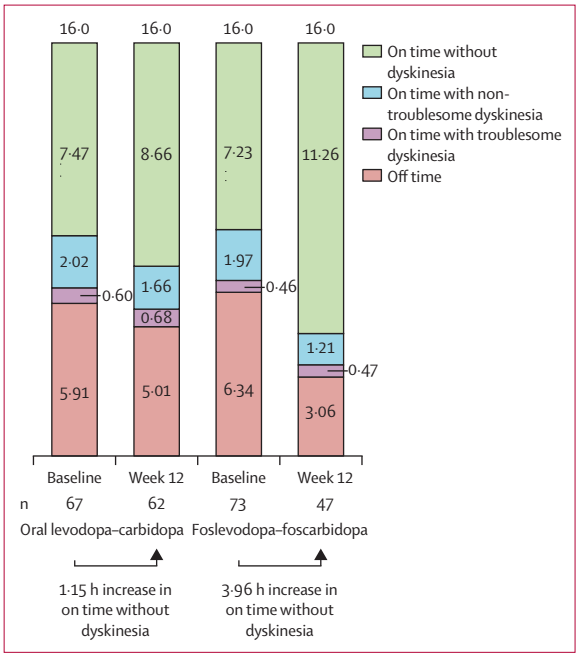

Figure 3: **Raw or unadjusted mean on and off hours in a 16-h waking day at baseline *vs* week 12 (full analysis set)**
Data are reported as raw or unadjusted mean to communicate how 100% of the waking hours are accounted for. Assessed using a 24-h Parkinson's disease diary and normalised to a 16-h waking day. On time with non-troublesome dyskinesia and on time with troublesome dyskinesia were not secondary endpoints in the hierarchical analysis, but were prespecified as other efficacy endpoints.

hypothesise that 24-h/day CSCI of foslevodopa-foscarbidopa could potentially reduce the risk of falls in patients with advanced Parkinson's disease, for example by reducing off periods, sudden motor fluctuations, freezing, or early morning akinesia. Previous studies also implicated non-motor features, such as sleep disturbances, in an increased risk of falls, and further exploration of this hypothesis is warranted.[25]

Hallucinations and psychosis are present in up to 40% of individuals with Parkinson's disease, and these symptoms have been associated with increased age, longer disease duration, and treatment with dopaminergic therapy.[26,27] In our study, 11 participants in the foslevodopa-foscarbidopa group reported hallucinations or psychosis events, but two had a medical history of hallucination and six were using a concomitant dopamine agonist; only one participant in the foslevodopa-foscarbidopa group discontinued study drug treatments owing to hallucinations or psychosis. Although the reason for the higher rate of hallucinations or psychosis events in the foslevodopa-foscarbidopa group is not entirely clear, one consideration is that 24-h/day dopaminergic therapy might increase the risk of hallucinations or psychosis events, as suggested by the adverse event rates in our study and supported by findings from a study of 24-h/day apomorphine therapy.[28] In our study, most hallucination or psychosis events were non-serious, mild or moderate in severity, and consistent with what is

expected in patients with advanced Parkinson's disease taking levodopa-carbidopa medications. Of note, concomitant Parkinson's disease medications were required to remain unchanged for the study duration: as such, participants had no opportunity to taper concomitant medications while optimising or maintaining foslevodopa-foscarbidopa, a limitation that will not exist in real world practice.

Key strengths of the study include the double-blind, double-dummy design, with comparison with an active control in a prospective trial. Limitations include the 12-week duration, and open-label studies are ongoing to assess the longer-term safety and benefits of foslevodopa-foscarbidopa CSCI (NCT04750226, NCT03781167, NCT05094050). A second limitation is that the Parkinson's disease diary entries could be subject to recall bias, therefore participants were encouraged to record their symptoms in real-time every 30 min to minimise bias. Additionally, unlike clinical practice, during the stabilisation period the oral immediate-release levodopa-carbidopa regimen could only be adjusted in 100 mg levodopa and 25 mg carbidopa increments because of the need to maintain capsule masking during the double-blind period.

In summary, 24-h/day CSCI of foslevodopa-foscarbidopa showed superior improvement of motor fluctuations compared with oral immediate-release levodopa-carbidopa in patients with advanced Parkinson's disease. The systemic safety profile of foslevodopa-foscarbidopa was generally consistent with the well established safety profile of levodopa-containing medications. Most infusion site adverse events were mild or moderate and similar to those observed with other subcutaneously delivered medications, suggesting a favourable benefit-risk profile. As a 24-h/day CSCI, foslevodopa-foscarbidopa delivers a wide range of therapeutically relevant doses that can control motor symptoms and reduce motor fluctuations in patients with advanced Parkinson's disease, and offers a potentially safe and effective, individualised, and non-surgical alternative to available treatments.

Contributors

MJS, JA, KB, NF, VSCF, AJ, TEK, KK, IL, DO, WZR, MAS, DGS, ST, EOV, HZ, MFF, and RAH participated in data acquisition. JA, KB, NF, AJ, WZR, DGS, HZ, and MFF participated in study design. MJS, MFF, and NF assessed and verified the data. WZR and HZ participated in statistical analysis. All authors participated in data interpretation, critically reviewed this manuscript, and provided final approval for publication. All authors had full access to all data in the study and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

MJS received honoraria or consultation fees from Allergan, Abbott, AbbVie, Acorda, Medtronic, Merz Therapeutics, Neurocrine Pharmaceuticals, Sunovion, and Teva. JA is a study investigator and has received honoraria from AbbVie, Allergan, Teva, US World Meds, Medtronic, and Abbot; he is an investigator in studies sponsored by AbbVie, Biogen, Acadia, Northwestern University, Neuroderm, Massachusetts General Hospital, and AstraZeneca. He is also a scientific advisor for AbbVie. VSCF receives a salary from NSW Health; has received unrestricted research grants from the Michael J Fox Foundation, AbbVie and Merz; has been on Advisory Boards for AbbVie, Allergan, Ipsen, Merz, Praxis, Seqirus, Stada, Teva, and UCB; he receives royalties from Health Press. TEK has received funding from Stada, AbbVie, UCB Pharma, Seqiris, and Teva. KK has served as a consultant for AbbVie and has participated in AbbVie speakers' bureaus. IL is a member of the faculty of the University of California San Diego and is supported by an endowment and university funds; she also receives funds as Chief Editor of *Frontiers in Neurology* and as member of the Rossy PSP Toronto Center; she is an investigator in studies funded by Roche, AbbVie, Biogen, Centogene, EIP-Pharma, Biohaven Pharmaceuticals, Novartis, and United Biopharma SR–UCB; she receives funds and participates in studies from the National Institutes of Health, the Michael J Fox Foundation, the Parkinson Foundation, the Lewy Body Association, and CurePSP; she is a member of the Scientific Advisory Board for Amydis but does not receive funds. DO has received speaking honoraria from AbbVie. MAS has received consulting fees from Medtronic, and clinical trial funding from AbbVie, US WorldMeds, Sanofi, Abbott, Takeda, and Insightec. DGS is a member of the faculty of the University of Alabama at Birmingham; is supported by endowment and university funds; and is an investigator in studies funded by AbbVie, the American Parkinson Disease Association, the Michael J Fox Foundation for Parkinson Research, Alabama Department of Commerce, the Department of Defense, and NIH grants P50NS108675, R25NS079188, and T32NS095775; he has a clinical practice and is compensated for these activities through the University of Alabama Health Services Foundation; in addition, he has served as a consultant for or received honoraria from AbbVie, the Parkinson Study Group, Curium Pharma, Roche, Appello, the International Parkinson Disease and Movement Disorder Society, Theravance, McGraw Hill, Sanofi-Aventis, and Alnylam Pharmaceutics. EOV has received consulting fees from AbbVie, Acorda, Allergan, and Medtronic. RAH has served on a scientific advisory board for Inhibikase Therapeutics, Impel NeuroPharma, CereSpir, and Vivifi Biotech; he has received financial compensation for work as a consultant from AbbVie, Acadia Pharmaceuticals, Acorda Therapeutics, Adamas Pharmaceuticals, Affiris, Amneal Pharmaceuticals, ApoPharma, Aptinyx, AstraZeneca, Axovant Gene Therapies, Biomarin International, Biotie Therapies, Britannia Pharmaceuticals., Cadent Therapeutics, Cerevance, Cerevel Therapeutics, Curium, Cynapsus Therapeutics, Denali Therapeutics, Eli Lilly, Enterin, F Hoffmann-La Roche, GE Healthcare, Global Kinetics Business Consultants, Global Life Sciences Solutions, Impax Laboratories, Impel NeuroPharma, Inhibikase Therapeutics, Intec, Intrance Medical Systems, International Stem Cell Corporation (ISCO), Jazz Pharmaceuticals, Kashiv BioSciences, KeifeRx, Kyowa Kirin, Lundbeck, Merz Pharma, the Michael J Fox Foundation, Mitsubishi Tanabe Pharma America, the National Parkinson Foundation, Neuro Challenge Foundation for Parkinson's, Neurocrine Biosciences, NeuroDerm, Neuropore Therapies, Novus Biologicals, Orion, Parkinson Study Group, Perception OpCo (Cerevel Therapeutics), Pfizer, Pharma Two B, PharmaTher, Prexton Therapeutics, Regenera Pharma, Research Catalyst, Revance Therapeutics, Sanofi-Aventis, Sarepta Therapeutics, Scion NeuroStim, Seelos Therapeutics, Sio Gene Therapies, Sunovion Pharmaceuticals, Supernus Pharmaceuticals, Takeda Pharmaceuticals, Teva Pharmaceutical Industries, Tolmar Pharmaceuticals, UCB Biosciences, US WorldMeds, and Vivifi Biotech. He serves on speakers' bureaus for AbbVie, Acorda Therapeutics, Adamas Pharmaceuticals, Amneal Pharmaceuticals, Kyowa Kirin, Lundbeck, Neurocrine Biosciences, Sunovion Pharmaceuticals, Teva Pharmaceuticals, and US WorldMeds. He has received research support from AbbVie, Adamas Pharmaceuticals, AstraZeneca, Atlantic Research–Chelsea Therapeutics, Axovant Sciences, Biogen, Biotie Therapies, Cavion, Centogene, Cerevance, Cerevel Therapeutics, Civitas Therapeutics, Cynapsus Therapeutics, Dart NeuroScience, Enterin, F Hoffman-La Roche, Global Kinetics Corporation, Impax Laboratories, Intec Pharma, Integrative Research Laboratories Sweden, Jazz Pharmaceuticals, Kyowa Kirin, Lundbeck, the Michael J Fox Foundation, National Institutes of Health, National Institute of Neurological Disorders and Stroke, Neuraly, NeuroDerm, Northwestern University, the Parkinson Study Group, Pfizer, Pharma Two B, Prexton Therapeutics, Revance Therapeutics, Sanofi US Services, Sun Pharma

Advanced Research, Sunovion Pharmaceuticals, and UCB Biopharma; he holds stock in Axial Biotherapeutics and Inhibikase Therapeutics, and has received license fee payments from USF for Parkinson's Disease Diary. KB is a former employee of AbbVie, is currently employed by Harmony Biosciences, and might hold AbbVie stock or options. MFF, NF, AJ, WZR, ST, and HZ are employees of AbbVie and might hold stock or options.

Data sharing

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual, and trial-level data (analysis datasets), as well as other information (eg, 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, statistical analysis plan, and execution of a data sharing agreement. Data requests can be submitted at any time after regulatory approval of foslevodopa-foscarbidopa in the USA and Europe and after acceptance of this Article for publication. The data will be accessible for 12 months after regulatory approval of foslevodopa-foscarbidopa, with possible extensions considered. For more information, visit the website.

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