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ORIGINAL RESEARCH

Foslevodopa/Foscarbidopa in Younger Patients Earlier Within Advanced Parkinson's Disease: Post Hoc Analysis of a Randomized Trial

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ABSTRACT

Introduction: We evaluated continuous subcutaneously administered foslevodopa/foscarbidopa (LDp/CDp) in younger patients earlier within advanced Parkinson's disease (aPD).
Methods: This phase 3 trial included patients aged ≥ 30 years with levodopa-responsive PD, Mini-Mental State Examination score ≥ 24, and levodopa equivalent dose ≥ 400 mg/day. Patients were considered by the investigator as inadequately controlled on current oral/transdermal therapy and experienced ≥ 2.5 h/day "Off" time, with recognizable "On"/"Off" states. Patients were randomized (1:1) to LDp/CDp plus placebo capsules or orally administered immediate-release levodopa/carbidopa plus placebo infusion. This post hoc exploratory analysis focused

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on younger patients (≤ 65 years) earlier within aPD (Hoehn and Yahr stage ≤ 2 ["On" state], ≤ 5 years since motor fluctuations started). Outcomes included change from baseline (CFB) to week 12 in "Off" and "On" time, Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS) II, 39-item PD Questionnaire (PDQ-39), and PD Sleep Scale-2 (PDSS-2).

Results: Twenty-six patients met subgroup criteria (LDp/CDp, $n = 13$; orally administered levodopa/carbidopa, $n = 13$). Despite small sample sizes, at week 12, LDp/CDp was associated with significantly greater improvements in "Off" time (mean [SD] CFB −3.7 [3.1] vs −1.6 [2.9] h; $P = 0.0011$), "On" time without troublesome dyskinesia (+3.9 [3.3] vs +1.4 [3.8] h; $P = 0.0011$), and PDSS-2 (−6.4 [4.6] vs −1.8 [3.1]; $P = 0.0220$) vs orally administered levodopa/carbidopa. Mean (SD) CFB to week 12 (LDp/CDp vs orally administered levodopa/carbidopa) was +4.2 (2.8) vs +1.9 (4.6) h for "On" time without dyskinesia ($P = 0.0878$), −3.0 (6.4) vs −0.9 (3.5) for MDS-UPDRS II ($P = 0.3539$), and −9.9 (7.4) vs −1.9 (9.4) for PDQ-39 ($P = 0.0534$). For most assessments, treatment differences were numerically larger in the subgroup vs the overall population. Safety findings were consistent with the overall population.

Conclusions: LDp/CDp was associated with significantly greater improvements in motor function and sleep vs orally administered levodopa/carbidopa in younger patients earlier within aPD whose symptoms were inadequately controlled by oral/transdermal therapies. Larger real-world studies are needed to confirm findings.

Trial Registration: ClinicalTrials.gov identifier, NCT04380142.

Keywords: Advanced Parkinson's disease; Device-aided therapy; Early treatment; Foslevodopa/foscarbidopa; Oral levodopa; Parkinson's disease; Randomized controlled trial

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Key Summary Points

Why carry out this study?

Foslevodopa/foscarbidopa (LDp/CDp), a soluble formulation of levodopa/carbidopa (LD/CD) prodrugs delivered as a 24-h/day continuous subcutaneous infusion, is approved to treat motor fluctuations in adults with advanced Parkinson's disease (aPD) and has demonstrated superiority over oral immediate-release LD/CD in improving "On" and "Off" time in a phase 3 randomized trial.

There is a need to better understand the potential benefits of LDp/CDp therapy among younger patients who are earlier in the treatment journey for aPD.

This post hoc exploratory analysis of a phase 3 randomized trial evaluated the efficacy and safety of LDp/CDp vs oral immediate-release LD/CD in younger patients earlier within aPD.

What was learned from the study?

Younger patients earlier within aPD treated with LDp/CDp experienced significantly greater improvements in motor function and sleep quality compared with oral immediate-release LD/CD (though sample sizes were small); for most outcomes, findings were consistent with and numerically better than those observed in the overall study population.

Given the progressive nature of PD, clinicians should consider the potential therapeutic benefits associated with earlier initiation of LDp/CDp.

INTRODUCTION

The current standard pharmacological treatment for managing Parkinson's disease (PD) is based on orally administered levodopa (LD) and carbidopa (CD) [1]. However, the effectiveness of oral LD/CD to control motor symptoms diminishes over time as PD progresses [2]. Results from

previous studies show that continuous administration of dopaminergic treatments better controls motor symptoms in advanced PD (aPD) compared with intermittent oral administration [3, 4]. Foslevodopa/foscarbidopa (LDp/CDp) is a soluble formulation of LD/CD prodrugs delivered as a 24-h/day continuous subcutaneous infusion (CSCI) and is approved to treat motor fluctuations that are uncontrolled by oral treatments in adults with aPD [5]. The efficacy and safety of LDp/CDp have been demonstrated in two pivotal phase 3 clinical trials [4, 6]. In a phase 3 randomized controlled trial, LDp/CDp showed a positive benefit-risk profile and superior control of motor fluctuations compared with oral immediate-release LD/CD in patients with aPD [4].

Real-world observational studies suggest that device-aided therapies for PD are typically considered late in the disease course, with many patients declining or requiring extended time to consider such treatments [7, 8]. Delayed initiation of device-aided therapies may miss a critical window during which patients still possess greater independence, cognitive ability, and capacity to adapt to such treatments. Although the invasive nature of surgical device-aided therapies (e.g., deep brain stimulation and LD/CD intestinal gel) traditionally relegates their use to later stages of disease [9], potentially bypassing this critical window, a nonsurgical device-aided therapy, such as LDp/CDp, presents a significantly lower barrier to initiation. This characteristic may position LDp/CDp as a favorable and accessible option for earlier consideration by clinicians, patients, and care partners. To determine whether earlier initiation of LDp/CDp could provide meaningful clinical benefits, we evaluated the efficacy and safety of LDp/CDp in a subgroup of younger patients earlier within aPD from a phase 3 randomized trial.

METHODS

Study Design and Patients

This study is a post hoc exploratory analysis of a phase 3, randomized, double-blind, active-controlled trial (NCT04380142) [4]. Eligible patients were aged ≥ 30 years, had a diagnosis of idiopathic and LD-responsive PD, had a Mini-Mental State Examination score ≥ 24, and were receiving an LD equivalent daily dose of ≥ 400 mg. Patients also had to be considered by the investigator as inadequately controlled on current oral/transdermal therapy and experience an average daily "Off" time of ≥ 2.5 h, with recognizable "On" and "Off" states. Patients were randomly assigned (1:1) to receive CSCI of LDp/CDp plus oral placebo capsules or oral encapsulated immediate-release LD/CD tablets plus CSCI of placebo solution. The double-blind treatment period included a 4-week optimization phase followed by an 8-week maintenance phase. During the optimization phase, investigators adjusted the LDp/CDp infusion rate to optimize clinical response, after which a stable treatment regimen was maintained. Adjustments to concomitant PD medications were not allowed during the 12-week treatment period unless medically necessary.

The study protocol, recruitment materials, and informed consent forms were approved by independent ethics committees or institutional review boards at each study site before enrollment. The study was conducted in accordance with the International Council for Harmonisation guidelines, the Declaration of Helsinki, and all applicable regional regulations. Patients and their care partners (if applicable) provided written informed consent before screening.

Assessments and Analysis

This analysis evaluated outcomes in a subgroup of younger patients (aged ≤ 65 years) earlier within aPD (Hoehn and Yahr stage score ≤ 2 ["On" state] and ≤ 5 years since start of any motor fluctuations [e.g., dyskinesia, wearing off, etc.]). These subgroup criteria were selected as a pragmatic starting point to identify patients who may be earlier in the aPD treatment pathway. The Hoehn and Yahr stage cutoff was selected because a score ≤ 2 excludes patients with postural instability, a key milestone of advancing disease that is associated with substantial additional morbidity [10].

Rather than overall disease duration, we used time since onset of motor fluctuations, as their emergence typically increases therapeutic needs and often prompts consideration of device-aided therapies [9]. The 5-year cutoff was selected because the mean duration of motor fluctuations was approximately 5 years in the overall population of the randomized trial [4]. Similarly, the age cutoff was selected as the mean age in the overall population was approximately 65 years, though age does not directly reflect disease stage. However, by selecting for patients below these means, we aimed to enrich the subgroup with patients who, in clinical practice, may have less of a delay in initiating device-aided therapies. Further details on eligibility criteria for the randomized study are described in the study design section and have been published previously [4].

Assessments included change from baseline to week 12 in "Off" time, "On" time without troublesome dyskinesia, and "On" time without dyskinesia. "Off" and "On" times were normalized to a 16-h waking day. Additional assessments included change from baseline to week 12 in Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) II score, 39-item Parkinson's Disease Questionnaire (PDQ-39) summary index, and Parkinson's Disease Sleep Scale-2 (PDSS-2) total score. Safety was evaluated by the proportion of patients experiencing treatment-emergent adverse events (TEAEs).

Standard descriptive analyses are presented. Continuous variables were summarized by mean and SD, and categorical variables were summarized using counts and percentages. Analysis of covariance was used to evaluate differences between groups with respect to change from baseline in efficacy outcomes. The treatment difference between LDp/CDp and oral LD/CD is presented for each efficacy outcome, and for contextualization, treatment differences are also presented for the overall population (defined as all randomized patients who received treatment in the trial). Statistical significance was defined as $P<0.05$. Safety was summarized by reporting the number and percentage of patients with TEAEs.

RESULTS

Patients

Of the 141 patients who were randomized and received blinded study drug, 26 were aged ≤ 65 years and considered earlier within aPD (LDp/CDp, $n=13$; oral LD/CD, $n=13$). In the LDp/CDp group, 11 of 13 patients completed the study (1 discontinued because of TEAE and 1 discontinued because of the inconvenience of wearing the pump and managing the tubing and infusion site selection). All 13 patients in the oral LD/CD group completed the study. Baseline demographics and clinical characteristics were comparable between the LDp/CDp and oral LD/CD treatment groups (Table 1). In the subgroup, the mean (SD) age was 56.7 (8.4) years in the LDp/CDp group and 53.2 (5.6) years in the oral LD/CD group, which was approximately 10 years younger than the mean age in the overall population. Most patients were male, White, and had a PD duration of < 10 years. A higher proportion of patients in the subgroup had PD duration of < 10 years compared with the overall population. At baseline, "Off" and "On" times, MDS-UPDRS II score, PDQ-39 summary index, and PDSS-2 total score were comparable to those of the overall population. Table 2 summarizes concomitant PD medications at baseline and week 12 among younger patients earlier within aPD. The most frequently co-administered medications with study drug were dopamine agonists, monoamine oxidase B inhibitors, and amantadine.

EFFICACY

Figures 1 and 2 present the change from baseline to week 12 in efficacy outcomes for the subgroup of younger patients earlier within aPD. At week 12, treatment with LDp/CDp was associated with significantly greater improvements from baseline in "Off" time vs oral LD/CD (mean [SD] change from baseline, −3.7 [3.1] vs −1.6 [2.9] h; least squares mean [LSM] [SE] difference, −2.4 [1.0] h; $P=0.0234$; Fig. 1a). Treatment with

Table 1 Baseline demographics and clinical characteristics

Characteristic	Younger patients earlier within aPD		Overall population	
	LDp/CDp (*n* = 13)	Oral LD/CD (*n* = 13)	LDp/CDp (*n* = 74)	Oral LD/CD (*n* = 67)
Age, years, mean (SD)	56.7 (8.4)	53.2 (5.6)	66.3 (9.2)	66.6 (9.8)
Sex, *n* (%)				
Male	11 (84.6)	10 (76.9)	50 (67.6)	49 (73.1)
Female	2 (15.4)	3 (23.1)	24 (32.4)	18 (26.9)
Race, *n* (%)				
White	12 (92.3)	10 (76.9)	70 (94.6)	61 (91.0)
Other	1 (7.7)	3 (23.1)	4 (5.4)	6 (9.0)
Geographic region, *n* (%)				
USA	11 (84.6)	10 (76.9)	62 (83.8)	58 (86.6)
Australia	2 (15.4)	3 (23.1)	12 (16.2)	9 (13.4)
Duration of PD since diagnosis, *n* (%)				
< 10 years	11 (84.6)	13 (100)	51 (68.9)	44 (65.7)
≥ 10 years	2 (15.4)	0	23 (31.1)	23 (34.3)
"Off" time, hours, mean (SD)	6.3 (1.9)	6.6 (2.1)	6.3 (2.3)[a]	5.9 (1.9)
"On" time without troublesome dyskinesia, hours, mean (SD)	10.8 (2.7)	9.3 (2.7)	9.2 (2.4)[a]	9.5 (2.6)
"On" time without dyskinesia, hours, mean (SD)	9.4 (2.5)	7.8 (3.8)	7.2 (3.1)[a]	7.5 (3.7)
MDS-UPDRS II score, mean (SD)	12.7 (8.0)	11.6 (4.7)	15.3 (6.9)	13.3 (6.4)
PDQ-39 summary index, mean (SD)	26.8 (14.9)	25.2 (9.6)[b]	30.7 (16.1)[a]	26.2 (14.5)
PDSS-2 total score, mean (SD)	22.3 (9.4)[b]	18.3 (6.1)[b]	21.2 (8.8)[c]	18.9 (9.3)[d]

aPD advanced Parkinson's disease, *LD/CD* levodopa/carbidopa, *LDp/CDp* foslevodopa/foscarbidopa, *MDS-UPDRS* Movement Disorder Society Unified Parkinson's Disease Rating Scale, *PD* Parkinson's disease, *PDQ-39* 39-item Parkinson's Disease Questionnaire, *PDSS-2* Parkinson's Disease Sleep Scale-2

[a]*n* = 73, [b]*n* = 12, [c]*n* = 72, [d]*n* = 66

LDp/CDp was also associated with significantly greater improvements from baseline to week 12 in "On" time without troublesome dyskinesia vs oral LD/CD (mean [SD] change from baseline, +3.9 [3.3] vs +1.4 [3.8] h; LSM [SE] difference, 3.4 [1.3] h; $P = 0.0204$; Fig. 1b). For "On" time without dyskinesia, the mean (SD) change from baseline to week 12 (LDp/CDp vs oral LD/CD) was +4.2 (2.8) vs +1.9 (4.6) h; the between-group difference did not reach significance (LSM [SE] difference, 2.7 [1.5] h; $P = 0.0878$; Fig. 1c). The LSM (SE) treatment difference between LDp/CDp and oral LD/CD was numerically greater in the subgroup vs the overall population for change in "Off" time (−2.4 [1.0] vs −1.8 [0.6] h), "On" time without troublesome dyskinesia (3.4 [1.3] vs 1.8 [0.7] h), and "On" time without dyskinesia (2.7 [1.5] vs 1.8 [0.7] h).

Table 2 Concomitant PD medications in younger patients earlier within aPD

Baseline, *n* (%)	**LDp/CDp (*n* = 13)**	**Oral LD/CD (*n* = 13)**
None reported	2 (15.4)	4 (30.8)
Any reported	11 (84.6)	9 (69.2)
Dopamine agonist	8 (61.5)	5 (38.5)
Pramipexole	3 (23.1)	5 (38.5)
Ropinirole	3 (23.1)	0
Rotigotine	3 (23.1)	0
Monoamine oxidase B inhibitor	6 (46.2)	5 (38.5)
Rasagiline	4 (30.8)	2 (15.4)
Safinamide	1 (7.7)	3 (23.1)
Selegiline	1 (7.7)	0
Amantadine	2 (15.4)	4 (30.8)
Trihexyphenidyl	1 (7.7)	1 (7.7)
Istradefylline	1 (7.7)	0
Week 12, *n* (%)	**LDp/CDp (*n* = 6)**	**Oral LD/CD (*n* = 10)**
None reported	2 (33.3)	3 (30.0)
Any reported	4 (66.7)	7 (70.0)
Dopamine agonist	2 (33.3)	3 (30.0)
Pramipexole	1 (16.7)	3 (30.0)
Rotigotine	1 (16.7)	0
Monoamine oxidase B inhibitor	1 (16.7)	4 (40.0)
Rasagiline	0	2 (20.0)
Safinamide	1 (16.7)	2 (20.0)
Amantadine	1 (16.7)	4 (40.0)
Istradefylline	1 (16.7)	0

aPD advanced Parkinson's disease, *LD/CD* levodopa/carbidopa, *LDp/CDp* foslevodopa/foscarbidopa, *PD* Parkinson's disease

The mean (SD) change from baseline to week 12 in MDS-UPDRS II score was −3.0 (6.4) in the LDp/CDp group and −0.9 (3.5) in the oral LD/CD group; the LSM (SE) difference was −1.6 (1.7) and did not reach significance ($P = 0.3539$; Fig. 2a). For PDQ-39 summary index, the mean (SD) change from baseline to week 12 was significant for LDp/CDp (−9.9 [7.4]; $P = 0.0023$) but not for oral LD/CD (−1.9 [9.4]; $P = 0.5056$); however, the between-group treatment difference did not reach significance (LSM [SE] difference, −6.2 [3.0]; $P = 0.0534$; Fig. 2b). At week 12, treatment with LDp/CDp was associated with significantly greater improvements

from baseline in PDSS-2 total score vs oral LD/CD (mean [SD] change from baseline, −6.4 [4.6] vs −1.8 [3.1]; LSM [SE] difference, −4.5 [1.8]; $P=0.0220$; Fig. 2c). The LSM (SE) treatment difference between LDp/CDp and oral LD/CD in the subgroup was similar to that observed in the overall population for change in MDS-UPDRS II score (−1.6 [1.7] vs −1.6 [1.1]), numerically higher for change in PDQ-39 summary index (−6.2 [3.0] vs −4.1 [2.0]), and numerically lower for change in PDSS-2 total score (−4.5 [1.8] vs −5.4 [1.3]).

Safety

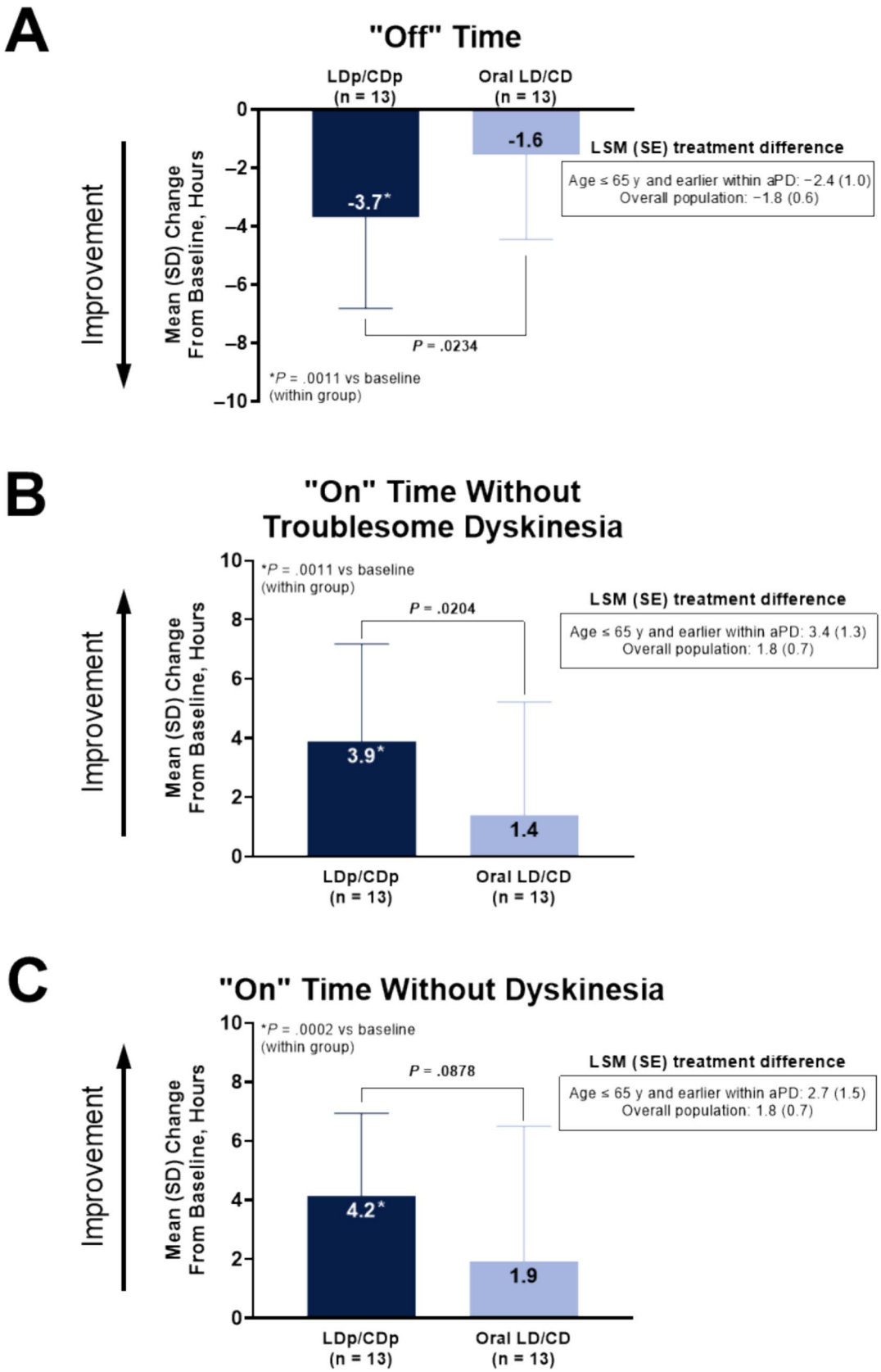
Among younger patients earlier within aPD, TEAEs were reported in 92.3% ($n=12$) of patients treated with LDp/CDp and 76.9% ($n=10$) of those treated with oral LD/CD (Table 3). Most patients experienced TEAEs that were mild or moderate in severity. Treatment-related TEAEs were more common with LDp/CDp (76.9% [$n=10$]) than with oral LD/CD (30.8% [$n=4$]). Only one patient experienced a TEAE that led to treatment discontinuation (infusion site pain), which occurred in the LDp/CDp group. The most commonly reported TEAE (occurring in ≥15% of patients) included infusion site TEAEs (infusion site pain, erythema, papule, and nodule). Infusion site TEAEs and infusion-related TEAEs occurred more frequently with LDp/CDp than with oral LD/CD. Hallucination/psychosis occurred in 15.4% ($n=2$) of patients in the LDp/CDp group and was not reported in the oral LD/CD group. Falls were more common in the oral LD/CD group (30.8% [$n=4$]) than in the LDp/CDp group (15.4% [$n=2$]). There were no events of polyneuropathy and weight loss. Serious TEAEs occurred in 23.1% ($n=3$ [infusion site cellulitis, psychotic disorders, and catheter site cellulitis]) of patients in the LDp/CDp group and 7.7% ($n=1$ [nephrolithiasis]) of patients in the oral LD/CD group. Consistent with safety findings in the subgroup, most patients in the overall population experienced TEAEs that were mild or moderate in severity, nonserious, and did not require treatment discontinuation; the most common TEAEs were also similar between the two populations.

DISCUSSION

This post hoc exploratory analysis of a phase 3 randomized trial aimed to determine whether the initiation of LDp/CDp in patients at a younger age and earlier within their aPD course is clinically beneficial. Study findings indicate that younger patients earlier within aPD treated with nonsurgical CSCI of LDp/CDp experienced significantly greater improvements in motor function and sleep quality compared with those who received oral immediate-release LD/CD. Improvements observed with LDp/CDp may reflect the benefit of continuous dopaminergic stimulation, which may minimize oscillations in dopamine levels and reduce motor fluctuations typically associated with intermittent oral dosing and resulting pulsatile stimulation [11].

LDp/CDp was associated with significant improvements from baseline to week 12 in "Off" time, "On" time without troublesome dyskinesia, "On" time without dyskinesia, PDQ-39 summary index, and PDSS-2 total score. In contrast, there were no statistically significant improvements over 12 weeks in the oral LD/CD group. Improvements in "Off" time, "On" time without troublesome dyskinesia, and sleep were significantly higher with LDp/CDp than with oral LD/CD. Quality of life and sleep improvements with LDp/CDp exceeded minimal clinically important difference (MCID) thresholds [12, 13], while the mean change in MDS-UPDRS II was slightly below the threshold (−3.0 vs MCID of −3.05) [14]. Considering the significant improvements in "Off" and "On" time, clinically meaningful improvements in MDS-UPDRS II might also have been expected but may not have been observed as a result of the small sample size. Similarly, the treatment difference between LDp/CDp and oral LD/CD for quality of life approached statistical significance ($P=0.0534$), suggesting a trend toward greater improvement with LDp/CDp that may not have reached significance as a result of the small sample size.

Importantly, treatment differences for most assessed outcomes were numerically greater in the subgroup than those observed in the overall population [4], suggesting a potential disease stage-dependent benefit from earlier initiation of

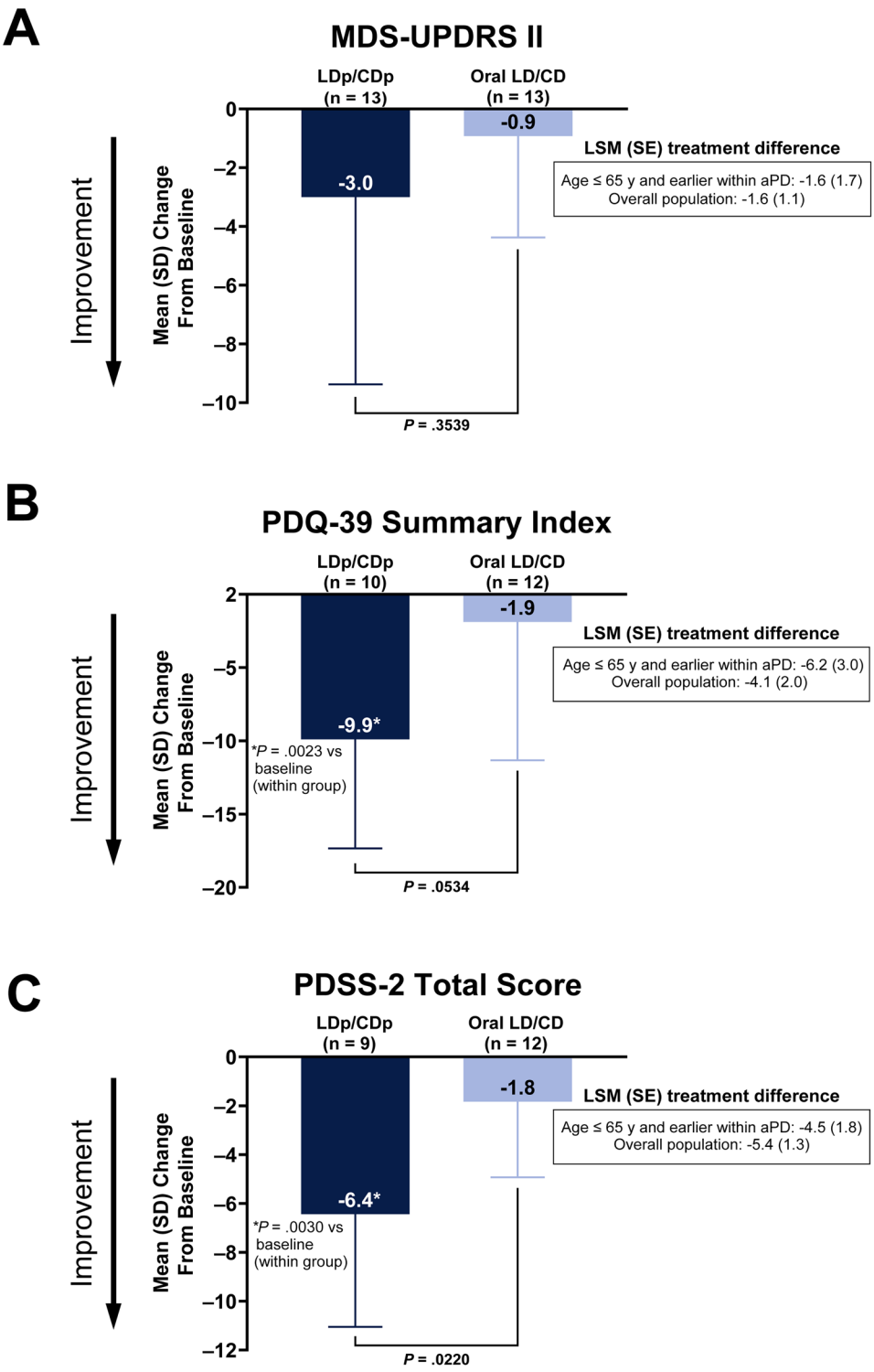

A
"Off" Time
LDp/CDp (n = 13)
Oral LD/CD (n = 13)
0
−2
−4
−6
−8
−10
-3.7*
-1.6
LSM (SE) treatment difference
Age ≤ 65 y and earlier within aPD: −2.4 (1.0)
Overall population: −1.8 (0.6)
P = .0234
*P = .0011 vs baseline (within group)
Improvement
Mean (SD) Change From Baseline, Hours
B
"On" Time Without Troublesome Dyskinesia
10
8
6
4
2
0
*P = .0011 vs baseline (within group)
P = .0204
LSM (SE) treatment difference
Age ≤ 65 y and earlier within aPD: 3.4 (1.3)
Overall population: 1.8 (0.7)
3.9*
1.4
LDp/CDp (n = 13)
Oral LD/CD (n = 13)
Improvement
Mean (SD) Change From Baseline, Hours
C
"On" Time Without Dyskinesia
10
8
6
4
2
0
*P = .0002 vs baseline (within group)
P = .0878
LSM (SE) treatment difference
Age ≤ 65 y and earlier within aPD: 2.7 (1.5)
Overall population: 1.8 (0.7)
4.2*
1.9
LDp/CDp (n = 13)
Oral LD/CD (n = 13)
Improvement
Mean (SD) Change From Baseline, Hours

◂**Fig. 1** Change from baseline to week 12 in "Off" time (**a**) and "On" time (**b**, **c**) in younger patients earlier within aPD. *aPD* advanced Parkinson's disease, *LD/CD* levodopa/carbidopa, *LDp/CDp* foslevodopa/foscarbidopa, *LSM* least squares mean, *y* year

LDp/CDp therapy. This finding may be driven by the subgroup being younger than the overall study population and potentially exhibiting greater functional independence and higher preserved dopaminergic function, which may allow for a more pronounced symptomatic benefit. Typically, device-aided therapies increase good "On" time [6, 15], and younger, less advanced patients are more likely to be symptom free during these periods [16], which may further explain the observed findings.

Findings from a 52-week open-label trial of LDp/CDp, which included a similar population (patients with aPD who were inadequately controlled on current PD therapy and experiencing an average daily "Off" time of ≥ 2.5 h, with recognizable "On" and "Off" states), showed similar findings; younger patients (aged < 65 years) and patients with Hoehn and Yahr stage score ≤ 2 had a higher likelihood of achieving clinically meaningful improvements in outcomes compared with older patients (≥ 65 years) and those with Hoehn and Yahr stage score > 2 [17]. Earlier initiation of other device-aided therapies has also been shown to improve patient outcomes. In a prospective observational study, patients with an earlier phase of aPD (aged < 71 years and aPD duration < 3 years) treated with continuous subcutaneous infusion of apomorphine experienced marked improvements in motor fluctuations [18]. Additionally, in a randomized controlled trial of patients with PD and early motor complications (aged 18–60 years; disease duration ≥ 4 years; Hoehn and Yahr stage score ≤ 2 ["On" state]; motor symptom improvement ≥ 50% with dopaminergic medication based on the UPDRS III; presence of fluctuations or dyskinesia for ≤ 3 years; and either a UPDRS II score > 6 in the worst condition despite medical treatment or a Social and Occupational Functioning Assessment Scale score of 51 to 80), patients who received neurostimulation with medical therapy had greater improvements in motor complications and quality of life compared with those who received medical therapy alone [19]. In a post hoc analysis of the GLORIA registry, younger patients and those with shorter disease duration treated with LD/CD intestinal gel showed similar quality of life benefits and greater improvements in activities of daily living when compared with older patients and patients with longer PD duration [20]. Taken together, these findings provide further evidence that there may be a therapeutic advantage in initiating LDp/CDp earlier in the disease course.

The safety profile of LDp/CDp in this subgroup analysis was generally consistent with the overall study population and similar to that of other medications administered via subcutaneous infusion [21, 22]. LDp/CDp was generally well tolerated, and most TEAEs were reported to be mild or moderate in severity and nonserious, with only one patient experiencing a TEAE leading to treatment discontinuation. The observed TEAEs of special interest were consistent with those expected based on the patient population, therapeutic class, and administration route. Infusion site and infusion-related events were the most frequently observed TEAEs in this analysis. Their occurrence raises important considerations for treatment acceptability and long-term adherence, particularly for younger patients. For these individuals, such TEAEs could diminish the acceptability of a therapy that may provide better motor control, an issue of heightened importance given their longer anticipated course of disease management. However, a post hoc analysis of multiple phase 3 trials of LDp/CDp showed that most infusion site events were nonserious and mild or moderate in severity, and the majority of presumed infections were managed with empirical oral antibiotics without leading to treatment discontinuation [23]. Careful patient selection, setting treatment expectations, and educating patients and caregivers on device handling, aseptic technique, and proper skin care are essential to help prevent or mitigate TEAEs, decrease discontinuations, and support long-term adherence. Further clinical guidance and considerations for the initiation and maintenance of LDp/CDp treatment and management of associated TEAEs have been previously reported in detail [24].


A
MDS-UPDRS II
LDp/CDp (n = 13)
Oral LD/CD (n = 13)
-3.0
-0.9
LSM (SE) treatment difference
Age ≤ 65 y and earlier within aPD: -1.6 (1.7)
Overall population: -1.6 (1.1)
Improvement
Mean (SD) Change From Baseline
0
−2
−4
−6
−8
−10
P = .3539
B
PDQ-39 Summary Index
LDp/CDp (n = 10)
Oral LD/CD (n = 12)
-9.9*
-1.9
LSM (SE) treatment difference
Age ≤ 65 y and earlier within aPD: -6.2 (3.0)
Overall population: -4.1 (2.0)
*P = .0023 vs baseline (within group)
Improvement
Mean (SD) Change From Baseline
2
−5
−10
−15
−20
P = .0534
C
PDSS-2 Total Score
LDp/CDp (n = 9)
Oral LD/CD (n = 12)
-6.4*
-1.8
LSM (SE) treatment difference
Age ≤ 65 y and earlier within aPD: -4.5 (1.8)
Overall population: -5.4 (1.3)
*P = .0030 vs baseline (within group)
Improvement
Mean (SD) Change From Baseline
0
−2
−4
−6
−8
−10
−12
P = .0220

◂**Fig. 2** Change from baseline to week 12 in MDS-UPDRS II score (**a**), PDQ-39 summary index (**b**), and PDSS-2 total score (**c**) in younger patients earlier within aPD. *aPD* advanced Parkinson's disease, *LD/CD* levodopa/carbidopa, *LDp/CDp* foslevodopa/foscarbidopa, *LSM* least squares mean, *MDS-UPDRS* Movement Disorder Society Unified Parkinson's Disease Rating Scale, *PDQ-39* 39-item Parkinson's Disease Questionnaire, *PDSS-2* Parkinson's Disease Sleep Scale-2, *y* year

Several limitations of this analysis should be acknowledged. First, there is no universally accepted definition of aPD, and there is even less consensus for what constitutes being "earlier within aPD." However, we used Hoehn and Yahr stage score ≤ 2 and ≤ 5 years since onset of motor fluctuations as a pragmatic starting point to define patients earlier in the treatment pathway (full eligibility criteria for the phase 3 trial are mentioned in the Methods). The Hoehn and Yahr stage scale provides a way to gauge disease progression; however, it is not solely determinant of aPD and is often used in combination with other assessments for a comprehensive evaluation. Although other studies have used disease duration to define patients earlier within aPD [18, 20], we believe that time since start of motor fluctuations may be a more valid criterion than disease duration, as patients can have widely different durations of their "honeymoon period" (i.e., duration of initial stable responses to treatment before start of disabling motor fluctuations) [16]. Nonetheless, a previous analysis of LDp/CDp studies has suggested that shorter PD duration is associated with improved outcomes [25].

The small sample size and the post hoc exploratory nature of this analysis limit the interpretation of our findings. Younger patients may be expected to better tolerate treatment; however, the limited number of patients in this subgroup precluded meaningful comparisons of safety outcomes with the overall population. Further, comparisons with a subgroup of older patients or those with more advanced disease may have been more informative but were not feasible as a result of sample size constraints and were outside the scope of this exploratory analysis. In addition, the duration of motor fluctuations was reported by patients and may be subject to recall bias. Another limitation of this analysis is that sleep was the only non-motor symptom assessed in the randomized trial; a detailed evaluation of other non-motor symptoms (e.g., pain and gastrointestinal dysfunction) in this subgroup population would be clinically relevant. Lastly, the impact of LDp/CDp on dyskinesia in this subgroup remains unclear. This is an important area for future investigation, particularly given that dyskinesia tends to be more prominent in patients with young-onset PD [26]. Several ongoing and planned real-world prospective studies [27–31] will evaluate LDp/CDp in routine clinical practice, help validate findings from this analysis, and address important research questions that could not be answered by the present study.

CONCLUSION

Results from this post hoc exploratory analysis indicated that younger patients earlier within aPD treated with LDp/CDp experienced significantly greater improvements in motor symptoms and sleep compared with those who received oral immediate-release LD/CD. Improvements in motor symptoms and quality of life were potentially more pronounced in this subgroup analysis than those observed in the overall study population. LDp/CDp was generally well tolerated and had a favorable benefit-risk profile. These findings provide preliminary evidence supporting the use of LDp/CDp in younger patients earlier within the aPD treatment journey as a potential first-line device-aided therapy for those experiencing uncontrolled motor fluctuations despite optimized oral therapy. Given the progressive nature of PD, clinicians should consider the potential therapeutic benefits associated with earlier initiation of LDp/CDp.

Table 3 Overview of TEAEs

TEAE, *n* (%)	Younger patients earlier within aPD		Overall population	
	LDp/CDp (*n* = 13)	Oral LD/CD (*n* = 13)	LDp/CDp (*n* = 74)	Oral LD/CD (*n* = 67)
Any TEAE	12 (92.3)	10 (76.9)	63 (85.1)	42 (62.7)
Mild	10 (76.9)	9 (69.2)	52 (70.3)	37 (55.2)
Moderate	9 (69.2)	3 (23.1)	42 (56.8)	12 (17.9)
Severe	2 (15.4)	0	7 (9.5)	1 (1.5)
Serious TEAE	3 (23.1)	1 (7.7)	6 (8.1)	4 (6.0)
TEAE considered associated with study drug[a]	10 (76.9)	4 (30.8)	52 (70.3)	15 (22.4)
TEAE leading to treatment discontinuation	1 (7.7)	0	16 (21.6)	1 (1.5)
TEAE leading to death	0	0	0	1 (1.5)
TEAEs occurring in ≥ 15% of patients receiving LDp/CDp				
Infusion site pain	5 (38.5)	0	19 (25.7)	1 (1.5)
Infusion site erythema	4 (30.8)	1 (7.7)	20 (27.0)	1 (1.5)
Infusion site papule	3 (23.1)	0	3 (4.1)	0
Infusion site nodule	2 (15.4)	0	6 (8.1)	0
Infusion site cellulitis	1 (7.7)	1 (7.7)	14 (18.9)	0
TEAEs of special interest				
Infusion-related reaction	8 (61.5)	2 (15.4)	46 (62.2)	5 (7.5)
Infusion-related infection	4 (30.8)	1 (7.7)	21 (28.4)	2 (3.0)
Hallucinations/psychosis	2 (15.4)	0	11 (14.9)	2 (3.0)
Falls and associated injuries	2 (15.4)	4 (30.8)	13 (17.6)	17 (25.4)
Dyskinesia	1 (7.7)	1 (7.7)	8 (10.8)	4 (6.0)
Somnolence	0	1 (7.7)	1 (1.4)	1 (1.5)
Polyneuropathy	0	0	2 (2.7)	2 (3.0)
Weight loss	0	0	1 (1.4)	1 (1.5)
"On" and "Off" phenomenon	0	0	6 (8.1)	0

aPD advanced Parkinson's disease, *LD/CD* levodopa/carbidopa, *LDp/CDp* foslevodopa/foscarbidopa, *TEAE* treatment-emergent adverse event

[a]As assessed by the investigator

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Data Availability. AbbVie is committed to responsible data sharing regarding the studies we sponsor. This includes access to anonymized individual data, as well as other information (e.g., protocols and analysis plans). These 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 approval in the USA and Europe, and after acceptance of this manuscript for publication. The 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. Angelo Antonini has received compensation for consultancy and speaker-related activities from AbbVie, Bayer, Bial, Britannia, Ever Pharma, Ferrer Teva, Roche, Stada, Theravance Biopharma, and Zambon and receives research support from Horizon2020 Grant 101016902, Ministry of University and Research (MUR), Ministry of Health, European Union—NextGenerationEU—NRRP M6C2—Investment: 2.1 "Enhancement and strengthening of biomedical research within the NSH." Bruno Bergmans has received investigator-initiated grants from AbbVie. He has a clinical practice at AZ St-Jan Brugge in Brugge, Belgium, and is an academic consultant at Ghent University Hospital in Ghent, Belgium. He is the principal investigator for multiple clinical trials in Brugge, Belgium. He has received investigator-initiated grants from Merz Pharma GmbH; has served as a speaker for EG, Merz GmbH, Teva, and Zambon; and has served as an advisory board member for AbbVie, Abbott, Boston Scientific, EG, Ipsen, Merz GmbH, Orion Pharma, Teva, and UCB. His institution has received grants from AbbVie, Abbott, Boston Scientific, EG (for the organization of a deep-brain stimulation symposium sponsored by the International Parkinson and Movement Disorders Society), Elekta, GSK, Ipsen, Medtronic, Merck, Merz GmbH, Orion Pharma, Schwabe, and Teva. Drew S Kern has served as an advisor for the Colorado Clinical and Translational Sciences Institute (CCTSI) Data Safety Monitoring Board; has received honoraria for advisement/consulting from AbbVie, Abbott, Alpha Omega Engineering, Boston Scientific, and Medtronic; and has received grants from Boston Scientific and Medtronic. Florin Gandor has served as an advisory board member for AbbVie and has received honoraria from AbbVie, Bial Pharma, Merz, and Stada. Noriko Nishikawa has received speaker honoraria from AbbVie GK, Eisai, Ono, and Takeda and has served as an advisor for AbbVie. David G Standaert is a member of the faculty of the University

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Ethical Approval. The study protocol, recruitment materials, and informed consent forms were approved by independent ethics committees or institutional review boards at each study site before enrollment. The study was conducted in accordance with the International Council for Harmonisation guidelines, the Declaration of Helsinki, and all applicable regional regulations. Patients and their care partners (if applicable) provided written informed consent before screening.

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