Sustained Long-Term Safety and Tolerability of Foslevodopa/ Foscarbidopa in Parkinson's Disease: 96-Week Primary Treatment Period Results from an Ongoing Open-Label Extension Study

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OBJECTIVE

Evaluate the long-term safety, tolerability, and efficacy of foslevodopa/ foscarbidopa (LDp/CDp) in people with advanced Parkinson's disease (PD) treated through week 96 of an open-label extension study (OLES)

CONCLUSIONS

Results from this OLES combined with the previous 52-week study show a maintained a favorable risk/benefit profile of LDp/CDp through at least 148 weeks of treatment

Initial LDp/CDp-related improvements in "Off" time, "On" time without troublesome dyskinesia, and morning akinesia persisted with continued treatment

These findings support the use of LDp/CDp as an effective long-term strategy to manage motor symptoms in patients with advanced PD

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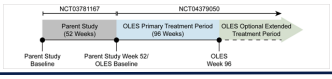
References: [1] Aldred J et al. Neurol Ther. 2023;12(6):1937-1958.

INTRODUCTION

- As PD advances, intermittent dosing of dopaminergic treatments such as levodopa/carbidopa (LD/CD) becomes less effective at managing symptoms
- Foslevodopa/foscarbidopa (LDp/CDp) 24-hour/day continuous subcutaneous infusion is indicated to treat motor fluctuations in people with advanced PD whose symptoms are inadequately controlled by oral treatment regimens
- A previous 52-week, single-arm, open-label study showed LDp/CDp treatment was associated with significant improvements in motor fluctuations and quality of life (QoL)[1]
- To understand long-term safety and efficacy beyond 52 weeks, an open-label extension study (OLES) was conducted with patients who completed the parent study

METHODS – Study Design

- The OLES consists of a 96-week primary treatment period and optional extended treatment period that is open-ended and ongoing
  - Patients with 96 week visits are considered study completers, extended treatment follow-up was optional
- OLES eligibility: patients who completed the parent study and remained on LDp/CDp
  - Eligibility for parent study: adults (≥30 years) with LD-responsive idiopathic PD not adequately controlled with current therapy (≥2.5 h/day "Off" time), and normal cognitive function (MMSE [Mini mental state examination]scores ≥24; scores of 19–23 were acceptable if the investigator deemed patients could understand the study and operate the LDp/CDp system)



METHODS

- LDp/CDp infusion rates were individually optimized (between 600–4250 mg LD equivalents/24h)
  - Dose at OLES initiation was the last prescribed dose of the parent study and could be adjusted at any time at investigator's discretion
  - Investigators could preprogram extra doses and additional "high" and "low" infusion rates that patients could self- administer to accommodate changes in demand over the day
- Primary objective was safety, assessed by frequency of adverse events (AE)
- Secondary objectives included: change in average daily "Off" time and "On" times (normalized to a 16h waking day; assessed by PD Diary), morning akinesia ("Off" state upon awakening), and PD-related QoL assessed by the 39-item Parkinson's disease questionnaire (PDQ-39)
- Visits occurred every 12 weeks; PD diary data was reported every 12 weeks, and PDQ-39 every 24 weeks

Statistical Analysis

- This was a planned interim analysis for when all patients reached the 96-week primary treatment visit (cutoff May 15, 2024)
- Safety data was summarized for all patients who received at least 1 dose of LDp/CDp during the OLES from the 96-week primary treatment and elapsed optional extension period
- Efficacy data were summarized using descriptive statistics. Only valid PD diary days (records with no more than 2 hours of missing data (≤ 4 missing entries) OR at least 12 awake hour entries for the entire 24-hour diary) and PDQ-39 summary index assessments (≤15% missing answers) were included
- p-values (not controlled for multiplicity) were obtained from two-sided paired-sample t-tests and compared change from parent study baseline

RESULTS

Demographics and Baseline Characteristics

Characteristic	N=129
Age, years, mean (SD)	63.1 (9.2)
Sex, n (%)	
Female	47 (36.4)
Male	82 (63.6)
Race, n (%)	
Asian	1 (0.8)
American Indian or Alaska Native	16 (12.4)
White	112 (86.6)
Disease duration, years, mean (SD)	10.2 (4.9)
MMSE total score[a]	28.3 (2.1)
PD diary, normalized h/day, mean (SD)[b]	
"Off" time	6.1 (2.2)
"On" time without dyskinesia	6.6 (3.4)
"On" time with non-troublesome dyskinesia	2.5 (2.6)
"On" time with troublesome dyskinesia	0.8 (1.5)
PDQ-39 Summary Index[c]	23.0 (14.8)

MMSE, Mini Mental-State Examination; PD, Parkinson's disease; PDQ-39, 39-item Parkinson's Disease Questionnaire. [a]n=119, [b]n=109, [c]n=121

- 129 patients enrolled in the OLES; n=39 (30.2%) completed the study, n=57 (44.2%) remain in the optional open-ended extension period, and n=33 (25.6%) prematurely discontinued

Adverse Events During the OLES

	Total, n (%), N=129
Any AE	119 (92.2)
Any AE considered associated with LDp/CDp	96 (74.4)
Any serious AE	48 (37.2)
Any severe AE	42 (32.6)
Any AE leading to discontinuation of LDp/CDp	17 (13.2)
Any AE leading to death	7 (5.4)
Most common AEs (≥15% of patients)	
Fall	42 (32.6)
Infusion site erythema	29 (22.5)
Infusion site cellulitis	24 (18.6)
Hallucination	22 (17.1)

AE, adverse event; LDp/CDp, foslevodopa/foscarbidopa. AEs were evaluated in from OLES baseline until the data cutoff in the safety analysis set, defined as any patients who received any LDp/CDp in this period. All AEs are treatment-emergent and do not imply relationship to study drug unless indicated.

- Overall, 92.2% of patients experienced ≥1 AE in the OLES
- AEs were the primary reason for discontinuation in n=13 (10.1%) patients
- The LDp/CDp safety profile was generally similar to that reported in the parent study[1] but showed notable shifts
  - Falls were more frequent in the OLES than in the parent study (32.6% vs 16.8%[1])
  - The OLES had lower rates for infusion-site erythema (22.5% vs 52.0%[1]) and cellulitis (18.6% vs 23.0%[1])
  - Hallucinations were similar in frequency in both studies. In the OLES, majority were mild (n/N=8/22) or moderate (n/N=12/22)

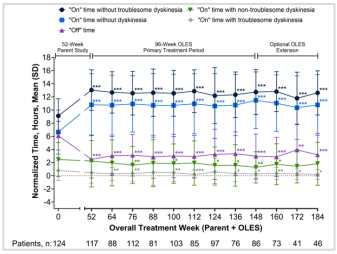
LDp/CDp Dosing During the OLES

	N=129
LDp/CDp base infusion rate, LD mg/h, mean (SD)	
Initial prescription	79.5 (31.2)
Final prescription	85.9 (34.1)
"High" Rate, % of base rate, mean (SD)	
Initial prescription	107.5 (5.6)
Final prescription	106.6 (5.1)
"Low" Rate, % of base rate, mean (SD)	
Initial prescription	87.5 (11.2)
Final prescription	86.5 (12.6)
Time using flow rate, % of time, mean (SD)	
Base	55.8 (29.9)
High	25.0 (24.9)
Low	19.2 (23.8)
Total LD Daily Dose, mg/day, mean (SD)[a]	
Initial prescription	1908.3 (747.2)
Final prescription	2060.7 (818.2)

LD, Levodopa; LDp/CDp, foslevodopa/foscarbidopa
[a]Calculated as 'base' (mL/hr)*24 hours/day*170.75 mg LD/mL

- Mean (SD) duration of LDp/CDp exposure from parent study baseline was 1278 (357) days, out of which 909 (359) days was during the OLES

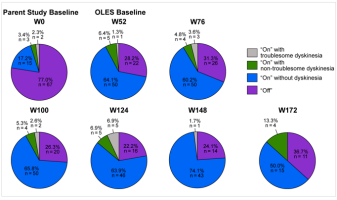
Improvements in "Off" and "On" Time Were Sustained from the Parent Study



OLES, Open-label extension study. Treatment weeks are defined relative to treatment initiation in the parent study. Week 52 corresponds to the OLES baseline, and week 148 corresponds to the end of the primary treatment period. Patient n at each time point corresponds to the number of patients in the OLES with valid PD diary recording days. p-values indicate comparisons to parent study baseline values for patients in the OLES. *p < 0.05, **p < 0.01, ***p ≤ 0.001.

- Improvements in "Off" time and "On" time without dyskinesia were sustained throughout the OLES, up to 184 weeks of total treatment
- At week 96 of the OLES (treatment week 148) the mean (SD) change from the parent study baseline in "Off" time was -3.1 (3.9) h/day, and "On" time without troublesome dyskinesia was 3.3 (4.0) h/day

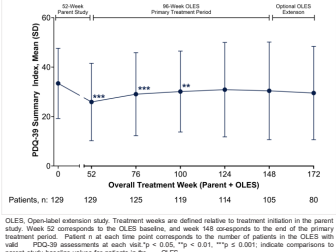
Distribution of First Morning Motor State Upon Awakening



OLES, Open-label extension study; W,weeks.Treatment weeks are defined relative to treatment initiation in the parent study. Week 52 corresponds to the OLES baseline, and week 148 corresponds to the end of the primary treatment period. First motor symptom data were only included for a patient if there were ≤2 missing entries between 0:00 am and 12:00 pm.

- The treatment-related improvements in morning akinesia observed during the parent study were maintained in the OLES; at each point, fewer patients awoke in the "Off"state compared with baseline of the parent study

Improvements in PDQ-39 Summary Index Were Maintained through 100 Total Weeks of Treatment



OLES, Open-label extension study. Treatment weeks are defined relative to treatment initiation in the parent study. Week 52 corresponds to the OLES baseline, and week 148 corresponds to the end of the primary treatment period. Patient n at each time point corresponds to the number of patients in the OLES with valid PDQ-39 assessments at each visit.*p < 0.05, **p < 0.01, ***p ≤ 0.001; indicate comparisons to parent study baseline values for patients in the OLES.

- Decreases (improvements) in PDQ-39 summary index were maintained through 100 total weeks of treatment with LDp/CDp; significant differences were no longer detected after treatment week 100

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