Patients Experiencing Motor Fluctuations With Parkinson's Disease: Participant Characteristics in the Accordance Phase 3 Efficacy and Safety Trial of Accordion Pill® Carbidopa/Levodopa

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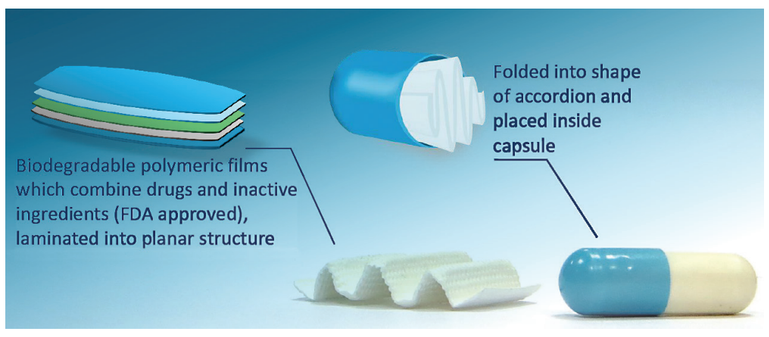
BACKGROUND

- Chronic levodopa (LD) treatment for Parkinson's disease (PD) is associated with the development of motor complications that are thought to occur as a result of intermittent or pulsatile stimulation of striatal dopamine receptors caused by fluctuating plasma LD levels[1]
- It has been postulated that more continuous delivery of LD will restore brain dopamine in a more physiologic manner[1]
- Both animal studies and a prospective double-blind study in patients with PD confirm that continuous delivery of LD is associated with improved tolerability and a reduced risk of motor complications[2]
- The Accordion Pill® (AP; **Figure 1**) is a novel drug formulation comprising multilayer films containing carbidopa (CD) as well as immediate-release (IR) and controlled-release LD, with an estimated apparent elimination half-life of ~7 hours[3]
- A Phase 2 study reported more stable LD plasma concentrations and lower C_{max} with AP-CD/LD than with IR-CD/LD in both fluctuating and non-fluctuating PD patients[4]
- Studies of another extended release preparation suggested that the optimal ratio of LD delivered by extended release vs IR, accounting for relative bioavailability, might be in the range of 2.1:1[5]
- Efficacy and safety of AP-CD/LD vs IR-CD/LD were evaluated in this Phase 3 study (Accordance [NCT02605434]) in adult patients with fluctuating PD and significant OFF time at study entry

FIGURE 1: Accordion Pill®



OBJECTIVE

- To provide baseline demographic and disease characteristics for participants in the Phase 3 Accordance study of the AP-CD/LD vs IR-CD/LD in patients with PD experiencing motor fluctuations, and changes in daily OFF time before and after treatment

METHODS

Study Design

- This was a multicenter, Phase 3, randomized, double-blind, double-dummy, active-controlled study of AP-CD/LD vs IR-CD/LD (Sinemet®)
- Male and female patients 30 years of age or older with a diagnosis of PD consistent with the United Kingdom Brain Bank Criteria were eligible to participate in the trial
- Key inclusion criteria were a daily LD intake of 400–1300 mg and ≥ 2.5 hours home diary OFF time daily at study entry
- The study included two unique 6-week, open-label, dose-titration phases: dose optimization of IR-CD/LD (active comparator, first 6 weeks), and conversion to AP-CD/LD (second 6 weeks)
- Participants were then randomized 1:1 to double-blind treatment with either IR-CD/LD or AP-CD/LD for 13 weeks, with a 2-week follow-up

Efficacy and Safety Outcomes

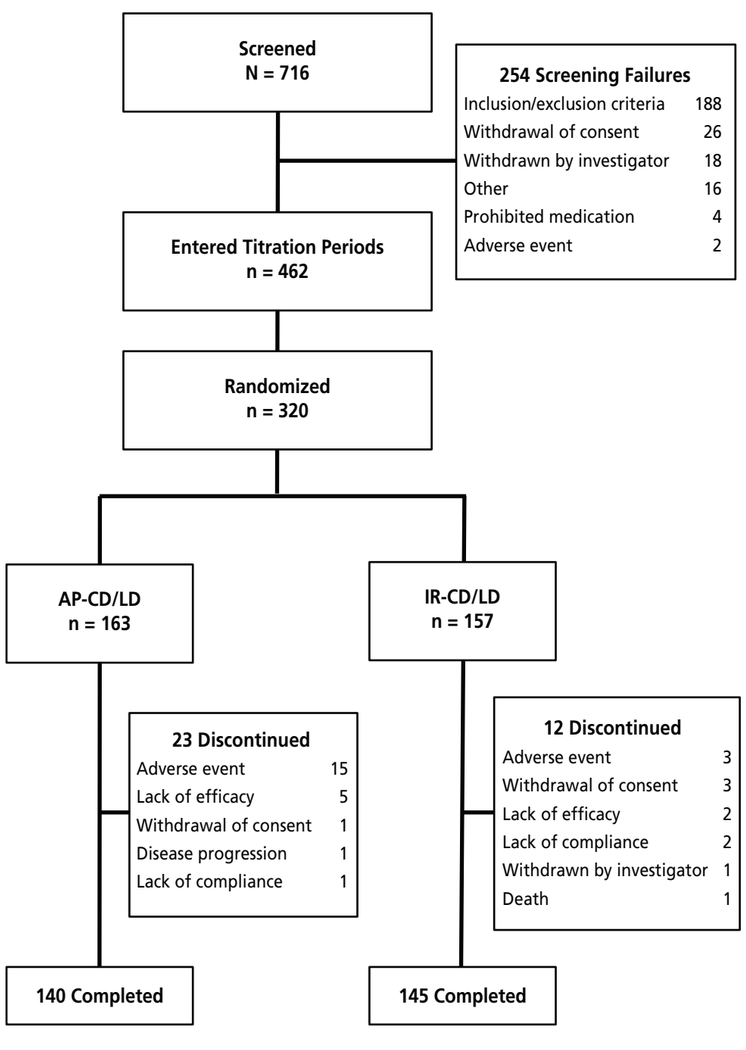
- The primary endpoint was change from Baseline (Visit 6) through study completion in the percentage of daily OFF time during waking hours
- Key secondary endpoints included:
  - Change from Baseline through study completion in ON time without troublesome dyskinesia during waking hours
  - Clinical Global Impression – Improvement (CGI-I) as recorded by physician and patient
  - Change from Baseline through study completion in Unified Parkinson's Disease Rating Scale (UPDRS) parts 2 and 3
- Safety was assessed via adverse events (AEs) and standard clinical and laboratory evaluations

RESULTS

Disposition

- A total of 716 patients were screened, 320 were randomized, and 285 participants completed the study (**Figure 2**)

FIGURE 2: Participant Disposition



Baseline Demographics and Disease Characteristics

- Demographic characteristics were well matched between treatment groups
- Most participants were white and male, with a mean age of 62.8 years for those receiving AP-CD/LD and 64.9 years for those receiving IR-CD/LD (**Table 1**)

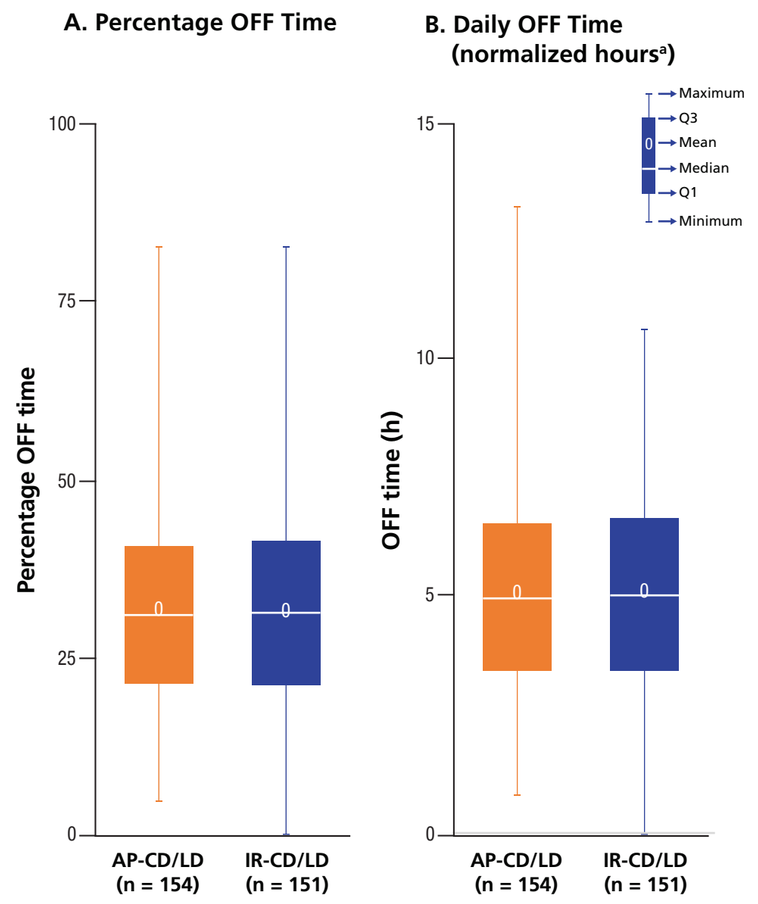
TABLE 1: Baseline Demographics

Characteristic	AP-CD/LD (n = 163)	IR-CD/LD (n = 157)
Age, y, mean (SD)	62.8 (9.1)	64.9 (8.8)
Weight (kg), mean (SD)	78.9 (17.3)	78.1 (15.2)
Height (m), mean (SD)[a]	1.7 (0.1)	1.7 (0.1)
BMI (kg/m²), mean (SD)[a]	27.2 (5.3)	27.4 (4.9)
Sex, n (%)		
Female	49 (30.1)	57 (36.3)
Male	114 (69.9)	100 (63.7)
Race, n (%)		
White	158 (96.9)	152 (96.8)
Black or African-American	1 (0.6)	1 (0.6)
Asian	2 (1.2)	3 (1.9)
American Indian or Alaska Native	1 (0.6)	0
Mixed/Other	1 (0.6)	1 (0.6)
Ethnicity, n (%)		
Hispanic or Latino	8 (4.9)	9 (5.7)
Not Hispanic or Latino	155 (95.1)	148 (94.3)
Geographic Region, n (%)		
United States of America	51 (31.3)	48 (30.6)
Western Europe/Israel	56 (34.4)	54 (34.4)
Eastern Europe	56 (34.4)	55 (35.0)
Age at PD diagnosis, mean (SD), y	54.0 (9.3)	56.5 (9.0)
PD duration, mean (SD), y	9.0 (4.7)	8.4 (3.8)

[a]AP-CD/LD group, n = 161
AP, Accordion Pill; BMI, body mass index; CD, carbidopa; IR, immediate-release; LD, levodopa; PD, Parkinson's disease; SD, standard deviation

- Baseline percentage OFF time and daily OFF time were similar between treatment groups (**Figure 3**)

FIGURE 3: Baseline OFF Time: A) Percentage OFF Time and B) Daily OFF Time in Normalized Hours (mITT Population)



[a]Data presented in hours, normalized to a 16-hour day.
AP, Accordion Pill; CD, carbidopa; IR, immediate-release; LD, levodopa; mITT, modified intention-to-treat; Q1, first quartile; Q3, third quartile

Dosing

- Overall, participants taking AP-CD/LD were optimized to and tolerated higher daily doses of LD than those taking IR-CD/LD (**Table 2**)

TABLE 2: Optimized Daily LD Dosage at Start of Double-blind Maintenance Period (mITT Population)

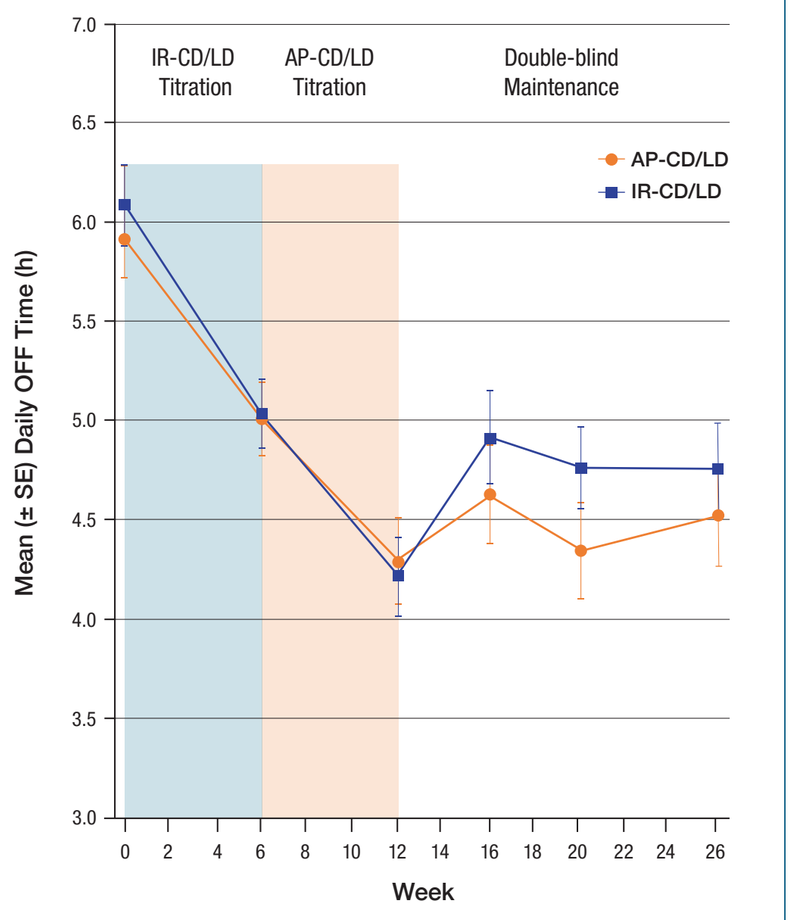
AP-CD/LD (n = 304)		IR-CD/LD (n = 305)	
LD daily dose (mg), mean (SD)	1,345.7 (207.3)	LD daily dose (mg), mean (SD)	897.0 (242.7)
LD daily dose category	n (%)	LD daily dose category	n (%)
800 mg (400 mg BID)	11 (3.6)	400-800 mg	137 (44.9)
1000 mg (500 mg BID)	31 (10.2)	900-1100 mg	108 (35.4)
1200 mg (400 mg TID)	79 (26.0)	1200 mg +	60 (19.7)
1500 mg (500 mg TID)	183 (60.2)		

AP, Accordion Pill; BID, twice daily; CD, carbidopa; IR, immediate-release; LD, levodopa; mITT, modified intention-to-treat; SD, standard deviation; TID, 3x daily

Daily OFF Time

- AP-CD/LD treatment during the double-blind maintenance period resulted in lower mean daily OFF time as compared with IR-CD/LD, however the difference between treatment groups did not reach statistical significance at any timepoint (**Figure 4**)

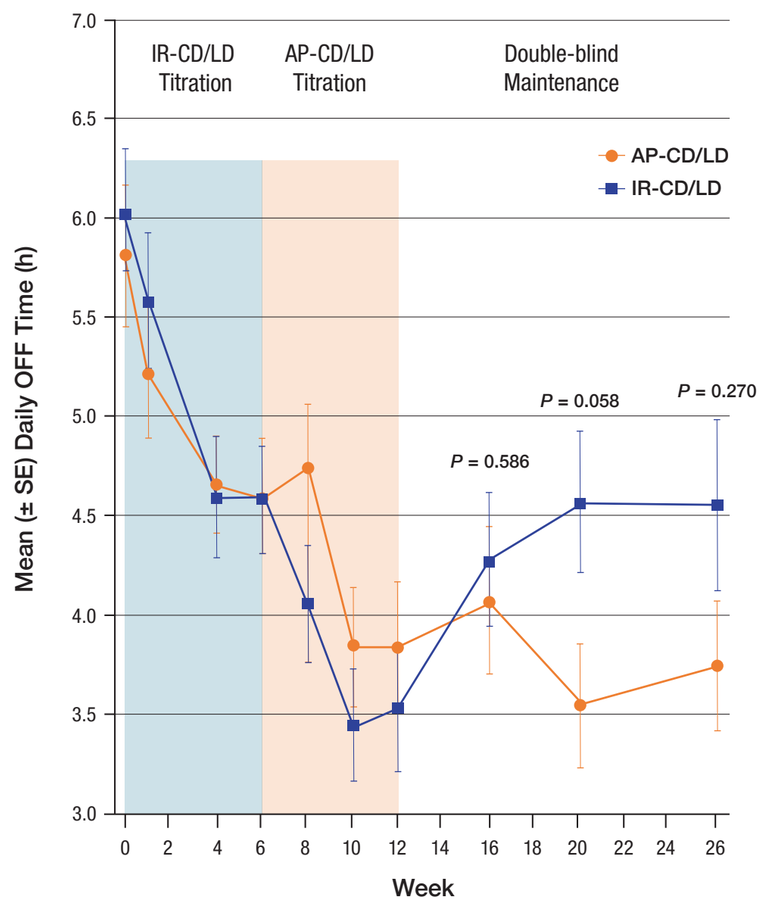
FIGURE 4: Daily OFF Time



AP, Accordion Pill; CD, carbidopa; IR, immediate-release; LD, levodopa; SE, standard error

- Despite the AP platform providing more total LD on average than standard IR treatment, examination of the top-line results of the Phase 3 Accordance study led to the conclusion that in many cases, this more continuous delivery method did not deliver enough LD to achieve optimal efficacy
  - The maximum dose of LD available from the AP platform in this study was a 50/500 mg capsule dosed TID, for a total of 1500 mg LD daily
- Given the possibility that the overall double-blind results may have been confounded by including data from participants who titrated to the maximum available dose of AP-CD/LD (50/500 mg TID) and who may not have achieved optimal efficacy, an *ad hoc* analysis was performed limited to those participants who had been titrated to AP doses less than the maximum allowable (approximately 39% of the intention-to-treat population)
- The results of this analysis (**Figure 5**) demonstrate a greater difference in mean daily OFF time between AP-CD/LD and IR-CD/LD in participants who were not dose limited during the AP titration process, as compared to the full population (**Figure 4**). This suggests that for many participants, AP doses higher than those available in this study may have been necessary to achieve optimal efficacy

FIGURE 5: Primary Analysis: Less Than 500 mg TID Population



P values = AP-CD/LD vs IR-CD/LD.
AP, Accordion Pill; CD, carbidopa; IR, immediate-release; LD, levodopa; SE, standard error

CONCLUSIONS

- This Phase 3 double-blind study of AP-CD/LD vs IR-CD/LD randomized 320 fluctuating PD patients, with 285 completing the study
- Participants in the AP-CD/LD and IR-CD/LD treatment groups were well matched for demographic and disease characteristics
- Study results recently became available, and while AP-CD/LD provided treatment for Parkinson's disease symptoms comparable to the Sinemet active comparator, it did not demonstrate a statistically significant reduction in OFF time over that obtained with IR-CD/LD under the conditions established in the protocol; even so, a favorable safety profile was observed, demonstrating for the first time the long-term safety of the Accordion Pill
- Future studies will need to evaluate the utility of higher doses of LD delivered by the AP platform

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