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Pharmacokinetics and efficacy of a novel formulation of carbidopa-levodopa (Accordion Pill®) in Parkinson's disease

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ABSTRACT

Introduction: Dopamine replacement via levodopa (LD) remains the most effective treatment for Parkinson's disease (PD), yet its use is often associated with motor complications within several years of continued use. The Accordion Pill® (AP-CD/LD) is a novel drug delivery system based on gastric retention of multilayer films containing immediate-release (IR) carbidopa (CD) and immediate- and controlled-release LD. The AP-CD/LD was designed to improve the consistency of LD in the bloodstream while offering patients with PD more consistent symptom management.

Methods: This phase 2, multicenter, open-label, two-way randomized crossover study included 4 cohorts of participants with PD, each receiving AP-CD/LD (50/250 mg, 50/375 mg or 50/500 mg) twice daily in one treatment period and an active comparator in the other treatment period. Pharmacokinetics (PK) and efficacy were evaluated for AP-CD/LD vs IR-CD/LD. Treatment-emergent adverse events (TEAEs) and patient- and investigator-reported measures were also evaluated.

Results: Compared with IR-CD/LD, treatment with either AP-CD/LD dose resulted in more stable LD plasma concentrations in both fluctuating and non-fluctuating PD patients, and significantly decreased C_{max} (57.1% and 66.8% decreases among fluctuating and non-fluctuating patients, respectively). Both AP doses significantly improved standard measures of motor symptoms: (daily OFF time, total ON time, and good ON time), as well as patient- and investigator-assessed measures, versus IR-CD/LD. The safety and tolerability profile of AP-CD/LD was consistent with the known properties of IR-CD/LD.

Conclusions: AP technology demonstrated effective controlled-release PK performance and reduced motor response fluctuations in advanced PD patients. A phase 3 randomized controlled trial is currently underway.

1. Introduction

Levodopa (LD) combined with an inhibitor of L-aromatic amino acid decarboxylase (eg, carbidopa [CD] or benserazide) is highly effective for the symptomatic relief of Parkinson's disease (PD), yet its clinical utility can be hampered by irregular drug uptake and rapid clearance [1,2]. Furthermore, motor fluctuations affect up to half of PD patients in as little as 2 years of continued LD therapy, with approximately one-third of patients experiencing LD-induced dyskinesias [3]. Though the reason these problems develop is inadequately understood, the phenomenology of both fluctuations and dyskinesias is strongly correlated to dose-by-dose LD plasma pharmacokinetics (PK) [2]. LD-induced dyskinesias can regularly occur with conventional oral LD doses as plasma levels exceed the threshold for improvement of bradykinesia and other Parkinsonian features. Improving the consistency of LD effect while avoiding peak-dose adverse effects (eg, dyskinesia) has been an unmet need of LD therapeutics for much of its half-century of use in the management of PD.

Currently available strategies to either block the breakdown of circulating LD (catechol-O-methyltransferase inhibitors) or slow catabolism of dopamine in the brain (monoamine oxidase-B inhibitors) have offered only modest gains. Other pharmaceutical approaches for more extended gastrointestinal release of CD and LD, including intestinal infusions [4,5], gastro-retentive extended-release formulations [6,7], and other extended drug-release technologies [8], have not been highly effective for various reasons. While delivering CD/LD by continuous jejunal or subcutaneous infusion has resulted in improved outcomes [9], such invasive approaches might not appeal to PD patients experiencing variability in medication effectiveness. Therefore, a more effective orally administered product remains a goal for pharmaceutical

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development. In addition to the AP technology reported here, other orally administered extended-release capsule formulations designed to improved CD/LD delivery have shown promising results against both IR and ER formulations [10,11].

In this report, we present PK, efficacy and safety results from 4 cohorts of patients with PD participating in a phase 2 proof-of-concept study of a novel CD/LD formulation within a proprietary drug delivery platform—the Accordion Pill® (AP)—designed to achieve more constant drug action though a gastric retention strategy. The AP consists of immediate-release (IR) CD and both IR and controlled-release LD impregnated into polymer films stacked and folded within a capsule designed to remain within the proximal upper intestine, the predominant site of LD absorption [12] (Supplemental Fig. 1).

The objectives of the study described here were to evaluate the pharmacokinetics, efficacy, and adverse event profile of the AP-CD/LD versus IR-CD/LD, with the intent to guide the design of the phase 3 AP-CD/LD studies now underway.

2. Methods

2.1. Ethics and study conduct

Under the sponsorship of Intec Pharma (Jerusalem, Israel), the study was conducted at multiple sites in Israel in accordance with the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice, and Israeli Laws and Regulations. The protocol and consent forms for study participation were reviewed and approved by an independent ethics committee at each clinical site. Before enrollment, each participant gave written informed consent after receiving a verbal and written explanation of the nature and purpose of the study. A data safety monitoring board (DSMB) was responsible for reviewing reported adverse events and to approve the initiation of subsequent treatment cohorts. The DSMB included two gastroenterologists, as well as consultants and the primary investigator of each site.

2.2. Study design and procedures

This phase 2, multicenter, open-label, two-way randomized proof-of-concept study was designed to evaluate the pharmacokinetics, efficacy, and adverse event profile of the AP-CD/LD versus IR-CD/LD or participants' current CD/LD treatment. The study included 4 cohorts of patients with PD. In each cohort, participants were sequentially randomized to receive AP-CD/LD twice daily in one treatment period and an active comparator consisting of either IR-CD/LD or patients' current CD/LD treatment in the other treatment period (Fig. 1). For Cohort 1, the comparator was a marketed IR-CD/LD formulation (Dopicar®); for Cohorts 2, 3, and 4, patients' current CD/LD treatment when entering the study (which could include controlled-release formulations) was the comparator. All participants completed daily home diaries [13] to assess "on," "off," and "on with dyskinesia" at 30-min intervals. "On with dyskinesia" was further assessed to determine whether involuntary movements were "troublesome" or not.

For the 4 cohorts, the study plan differed in several ways. In Cohorts 1 and 2, dosing was carried out for the first 6 days at home (Fig. 1). On the night of the sixth day, participants were hospitalized in advance of PK studies the following morning (day 7). On Day 8, study medication was switched and administered at home from days 8 through day 13. On the night of the thirteenth day, participants were again hospitalized for PK evaluation the next day (day 14). Within a 7-day period afterwards, participants underwent a medical evaluation that included blood and urine testing. On PK testing day of the control treatment period, Cohort 1 participants were given supplementary CD capsules (12.5 mg QID) with their IR-CD/LD dose to increase the total CD intake since the amount of CD contained in the IR-CD/LD formulation is less than the 70–100 mg/day intake needed for optimal inhibition of peripheral L-neutral amino acid decarboxylase enzymatic activity [14]. Cohort 2 participants randomized to start the study with their current CD/LD treatment remained on their treatment for the first 6 days of the comparator week. On the seventh day of the comparator week, participants were given ¾ tablet of IR-CD/LD 25/250 mg QID to reach an equivalent daily LD dose of 750 mg and a daily CD dose of 75 mg (18.75/187.5 mg x 4 = 75/750 mg/day); the daily CD dose during comparator treatment was less than the daily CD dose during treatment with AP (100 mg). Food intake on PK study days is described in the supplemental methods.

For Cohorts 3 and 4, home dosing was conducted over two 21-day treatment periods (Fig. 1). Prior to reporting to the clinic on days 21 and 42, participants were instructed to take the AP-CD/LD after a meal; for those taking the comparator (ie, standard LD product), the dose could be taken with or without food. During the comparator study period, participants maintained their pre-study treatment regimen, which could be optimized by the investigator, if needed, during the first 2 weeks of treatment.

For the AP-CD/LD testing period, dosing was carried out twice-daily at 8-h intervals with the first dose taken in the morning. For all treatment cohorts, additional IR-CD/LD dosing was allowed, as needed, for symptom relief (Table 1). For Cohort 1, supplemental IR-CD/LD dosing was allowed after the 16-h scheduled dosing period, as needed. For Cohort 2, supplemental IR-CD/LD was allowed on Days 1–6 and 8–13 three times during the day (morning, noon, evening) as ½ tablet Dopicar (12.5/125 mg CD/LD) or ¼ tablet Dopicar (6.25/62.5 mg CD/LD). Supplemental IR-CD/LD was not allowed with the first AP-CD/LD dose for Cohorts 3 and 4, but could be taken as needed with the morning AP-CD/LD or at any other time of the day as ½ or ¼ tablet Dopicar (25/250 mg) during the 2nd and 3rd weeks.

2.3. Participants

Participants met conventional diagnostic criteria for LD-responsive PD (Hoehn & Yahr Stage 1–3 with a stable response to LD without "wearing-off"), as determined by experienced PD specialists at each study site. Participants must have been currently treated with LD 300–500 mg/day. At baseline, LD intake could be combined with either CD or benserazide. For Cohort 1, participants could not be experiencing wearing-off or other patterns of motor fluctuations. Participants in Cohorts 2, 3, and 4 needed to experience motor fluctuations leading to $\geq$2 h of daily OFF time. Additional participant information can be found in the supplemental methods.

2.4. Assessments

2.4.1. Pharmacokinetic assessments

The LD and CD PK profiles of patients treated with AP-CD/LD and IR-CD/LD were evaluated in Cohorts 1 and 2. On clinic days 7 and 14, blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 4.5, 5, 6, 7, 8, 8.5, 9, 10, 11, 12, 12.5, 13, 14, 15 and 16 h post-dose. Area under the concentration time curve (AUC) for the 16 h of awake time ($AUC_{0–16}$), initial concentration ($C_{hour\ 0}$), peak blood concentration (C_{max}), and time to reach C_{max} (T_{max}) values were derived. Additionally, 24-h AUC ($AUC_{0–24}$) and minimum concentration (C_{min}) were determined for Cohort 2. C_{max} and AUC were primary endpoints in Cohorts 1 and 2 (Table 1).

2.4.2. Efficacy assessments

Efficacy was assessed in Cohorts 2, 3, and 4 using standard measures for clinical trials in PD. Change in Total Daily OFF time was a primary endpoint in Cohorts 3 and 4. Details of the a priori primary and secondary endpoints evaluated are provided in Table 1. In addition to the primary and secondary objectives, a comparison of total daily LD dosage and number of daily LD doses between treatment groups were assessed.

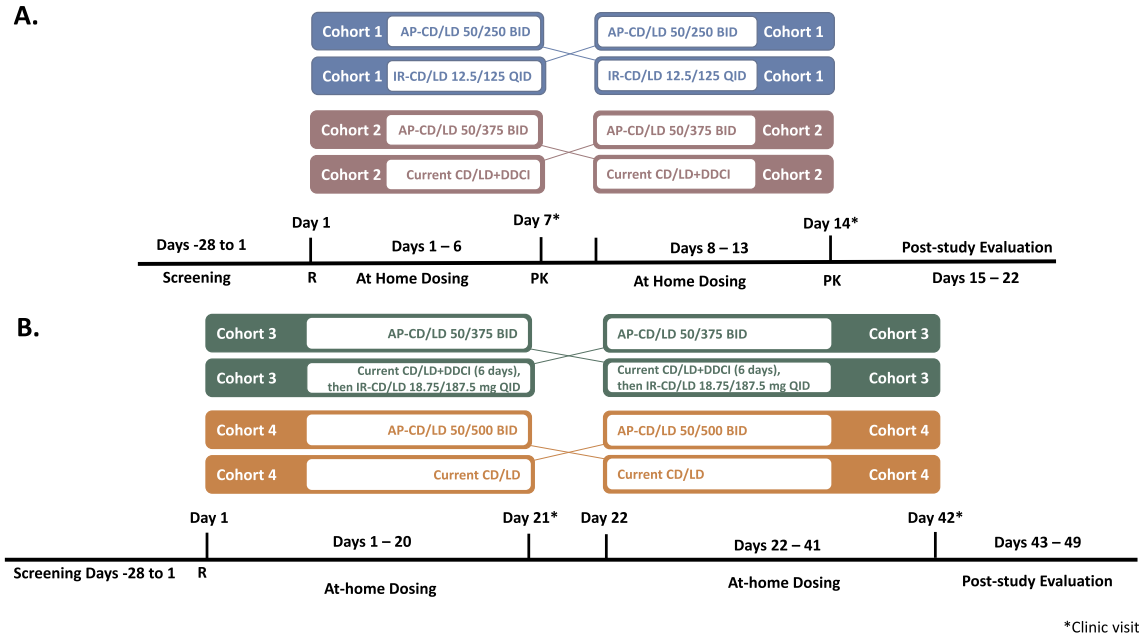

Fig. 1. Crossover Study Design and Cohort Dosing. *Clinic visit. AP-CD/LD, Accordion Pill carbidopa/levodopa; BID, twice daily; DDCI, dopamine decarboxylase inhibitor; IR, immediate release; QID, four times a day.

2.4.3. Clinical Global Impression (CGI)

The Clinical Global Impression (CGI) is a 7-point scale to evaluate the change from baseline, with 1 indicating "very much improved" and 7 being "very much worse." The CGI was completed in the clinic separately by patients and investigators on days 21 and 42.

2.4.4. Safety assessments

Safety was evaluated in all cohorts via adverse event (AE) monitoring, physical examinations, and laboratory measurements. AE profile was a primary endpoint in all cohorts.

2.5. Statistical analyses

2.5.1. PK analysis (Cohorts 1 and 2)

$AUC_{0\text{-}16}$ was calculated by the linear trapezoidal method. T_{max} was estimated as the sampling time at which C_{max} first occurred relative to dosing. Statistical analyses were performed using the General Linear Models (GLM) procedure of SAS® version 9.1.3 (Cary, NC). The statistical model contained main effects of sequence, participant nested within sequence, treatment, and period. Confidence Intervals (90%) for AP-to-IR area and C_{max} ratios were calculated by the *t* test approach (2, 1-sided) at $\alpha = 0.10$ overall, $\alpha = 0.05$ each side, both before and after log (ln) transformation of the values.

2.5.2. Efficacy analyses (Cohorts 2, 3, 4)

The effect of the carryover between treatments was assessed using non-parametric Wilcoxon Rank Sum test. If there was no evidence of differential carryover effects, a classic crossover analysis was performed to compare the change in the quantitative parameters between the two treatment cohorts using the non-parametric Signed-Rank test.

For quantitative parameters, a mixed-effect model for repeated measures was applied to analyze treatment differences. The model included terms for study arm, treatment, and visit as fixed effects and participant nested within study arm as a random effect. All tests were two-tailed; a *P* value ≤ 5% was considered statistically significant.

2.5.3. Comparison of LD doses by treatment (Cohorts 2, 3, 4)

Total LD dosage (mg/day) was calculated by the last 3 at-home days (days 4, 5, 6) of each treatment according to the home diaries. The number of LD doses per day was defined as the number of doses taken during the last 3 at-home days (days 4, 5, 6) of each treatment period according to the home diaries.

3. Results

3.1. Participants

A total of 63 participants were enrolled in the study: 12, 12, 17 and 22 in Cohorts 1, 2, 3 and 4, respectively (Supplemental Fig. 2). Participants were primarily white men diagnosed with PD for ≥5 years and a mean Hoehn & Yahr score of ~2.5 (Table 2). The mean (SD) LD dosage at baseline was 696.3 (115.2), 627.8 (109.4), and 680.7 (122.4) mg/day in Cohorts 2, 3 and 4, respectively (Table 2).

3.2. Pharmacokinetic evaluation

3.2.1. Levodopa

In participants with early non-fluctuating PD receiving AP-CD/LD 50/250 BID (Cohort 1), the relative bioavailability of LD over 16 h was high (94.1%; CI, 86.8–101.4%) and comparable with IR-CD/LD, indicating good absorption. LD plasma concentrations were more stable with AP-CD/LD BID than IR-CD/LD 12.5/125 mg QID (Fig. 2A). Compared with IR, C_{max} decreased 66.8% (CI, 47.2–86.4%) with AP treatment ($P = 0.012$). Gastric retention of LD was confirmed by a significantly longer T_{max} with AP-CD/LD 50/250 (3.38 h) than IR-CD/LD (0.81 h, $P < 0.001$; Supplemental Table 1).

In participants with advanced fluctuating PD receiving AP-CD/LD 50/375 BID (Cohort 2), the relative bioavailability of LD over 16 h (79.9%; CI, 67.1–92.6%) was slightly lower with AP-CD/LD than IR-CD/LD 18.75/187.5 mg QID ($P = 0.022$), though LD plasma concentration was more stable with AP than IR (Fig. 2B). Compared with IR, C_{max} decreased up to 57.1% (CI, 37.5–76.8%; $P = 0.006$) and C_{min} increased by 383% (CI, 183.2–582.9%; $P = 0.033$) with the AP-CD/LD (Supplemental Table 1). Time to reach peak LD concentration (T_{max} at first peak) was significantly longer with AP (5.13 h) versus IR (0.71 h; $P < 0.001$). Absolute peak-to-trough fluctuation with AP was half that of IR (49.6%; CI, 0.30, 0.69; $P = 0.002$), indicating a significantly more stable LD plasma profile with AP vs IR.

Table 1
Study Design Summary, Treatment Groups, and Participant Inclusion Criteria and Characteristics

Phase 2, open-label, multicenter, 2-way, crossover study

Study Sites	Cohort 1	Cohort 2	Cohort 3	Cohort 4
	2	3	5	6
Participants				
Enrolled, N[a]	12	12	17	22
Age Range, y	18 to 80, inclusive	18 to 80, inclusive	> 30 years	> 30 years
Hoehn &Yahr stages	I to III	I to III	I to III	I to III
Motor Symptoms	Non-fluctuating[b]	Fluctuating[e]	Fluctuating[e]	Fluctuating[e]
Current LD Treatment	LD 300 – 500 mg/day, stable for ≥ 1 month	LD 600 – 900 mg/day, stable for ≥ 1 month	LD 500-900 mg/day + DDCI,[f] stable for ≥ 1 month	LD 500-900 mg/day + DDCI,[f] stable for ≥ 1 month
Minimum Body Weight	≥50 kg	≥50 kg	None specified	None specified
Dosing and Concomitant Medications				
Treatment Duration	14 days (cross-over on day 8)	14 days (cross-over on day 8)	42 days (cross-over on day 22)	42 days (cross-over on day 22)
AP-CD/LD dosage	100/500 mg (50/250 mg BID)[c]	100/750 mg/day (50/375 mg BID)	100/750 mg/day (50/375 mg BID)	100/1000 mg/day (50/500 mg BID)
Comparator IR-CD/LD dosage	50/500 mg (12.5/125 mg QID) for 6 days, then additional IR-CD/LD on PK days 7 and 14[d]	Current treatment for 6 days, then additional IR-CD/LD 18.75/187.5 mg QID on PK days 7 and 14	Current Treatment	Current Treatment
Concomitant Dopamine Agonists	Allowed if stable for ≥1 month	Allowed if stable for ≥1 month	Allowed if stable for ≥1 month	Allowed if stable for ≥1 month
Supplemental IR-CD/LD Dosing	• Allowed after the 16-hour scheduled dosing period, as need • No additional IR-CD/LD was taken on any of the study days	• Allowed on Days 1-6 and 8-13 three times during the day (morning, noon, evening) as ½ tablet Dopicar (12.5/125mg CD/LD) or ¼ tablet Dopicar (6.25/62.5mg CD/LD)	• Not allowed with the first AP-CD/LD dose • Allowed in 2nd and 3rd week with the morning AP-CD/LD or in any other time of the day as 1/2 or 1/4 tablet of Dopicar® (25/250mg), if needed	• Not allowed with the first AP-CD/LD dose • Allowed in 2nd and 3rd week with the morning AP-CD/LD or in any other time of the day as 1/2 or 1/4 tablet of Dopicar® (25/250mg), if needed
Objectives and Endpoints				
Primary Objectives	Pharmacokinetics and Safety	Pharmacokinetics and Safety	Efficacy and Safety	Efficacy and Safety
Primary Endpoints	C_{max}, AUC, AE profile	C_{max}, AUC, AE profile	Change in Total Daily OFF time, AE profile	Change in Total Daily OFF time, AE profile
Secondary Objectives	• Participant and investigator global evaluation and satisfaction with AP-CD/LD vs IR-CD/LD • To evaluate dyskinesias (AIMS)	• To assess participant and investigator global evaluation and satisfaction with AP-CD/LD vs IR-CD/LD • Pharmacodynamics	• To assess participant and investigator global evaluation and satisfaction with AP-CD/LD vs IR-CD/LD • At-home diary evaluation	• To assess participant and investigator global evaluation and satisfaction with AP-CD/LD vs IR-CD/LD • At-home diary evaluation
Secondary Endpoints	CGI; GSS; AIMS	ON/OFF chart on PK days for 16 h UPDRS on PK days, every h for 16 h At-home diary evaluation	ON/OFF time; CGI; GSS; UPDRS; AIMS; SCOPA	ON/OFF time; CGI; GSS; UPDRS; AIMS; SCOPA

(*continued on next page*)

Table 1 (*continued*)

Phase 2, open-label, multicenter, 2-way, crossover study				
Study Sites	Cohort 1	Cohort 2	Cohort 3	Cohort 4
	2	3	5	6
Evaluations Derived From At-Home Diaries		• Total ON time (ON state without dyskinesia) • Good ON time (ON state or ON with non-troublesome dyskinesias) • ON time w/ troublesome dyskinesia • OFF time + Bad time (OFF state or ON w/ troublesome dyskinesia) • Proportion of Good ON time during waking hours • Duration of ON per dose (average total ON time divided by number of daily doses) • Number of LD doses/day • Frequency of LD doses/day • Total LD dose/day • Proportion of daily ON time • Time to ON	• Total ON time (ON state without dyskinesia) • Good ON time (ON state or ON with non-troublesome dyskinesias) • ON time w/ troublesome dyskinesia • OFF time + Bad time (OFF state or ON w/troublesome dyskinesia) • Proportion of Good ON time during waking hours • Duration of ON per dose (average total ON time divided by number of daily doses) • Number of LD doses/day • Frequency of LD doses/day • Total LD dose/day • Proportion of daily ON time • Time to ON	• Total ON time (ON state without dyskinesia) • Good ON time (ON state or ON with non-troublesome dyskinesias) • ON time w/ troublesome dyskinesia • OFF time + Bad time (OFF state or ON w/troublesome dyskinesia) • Proportion of Good ON time during waking hours • Duration of ON per dose (average total ON time divided by number of daily doses) • Number of LD doses/day • Frequency of LD doses/day • Total LD dose/day • Proportion of daily ON time • Time to ON

AE, adverse event; AIMs, Abnormal Involuntary Movement Scale; AP-CD/LD, Accordion Pill Carbidopa/Levodopa; BID, twice daily; CD, carbidopa; CGI, Clinical Global Impression; DDCI, dopa decarboxylase inhibitor; GSS, Global Satisfaction Scale; IR, immediate release; ITT, intention-to-treat; LD, levodopa; PD, Parkinson's disease; PK, pharmacokinetic; QID, four times daily; SCOPA, Scales for Outcome in Parkinson's Disease–Sleep; UPDRS, Unified Parkinson's Disease Rating Scale

[a] ITT population.

[b] Stable response to levodopa, with no "wearing off."

[c] AP-CD/LD in this study group did not contain the IR component of LD.

[d] On PK study days 7 and 14, additional 12.5 mg CD was administered QID to reach the recommended dose of 70-100 mg/day CD for full decarboxylase saturation.

[e] Self-reported end-of-dose wearing off, defined by ≥2 daily episodes of a decline in function from peak benefit, with at least 2–3 OFF hours/day (not including early morning akinesia or nocturnal akinesia).

[f] 4 or more divided doses per day, individual doses not exceeding 150 mg.

Table 2
Baseline demographics and clinical characteristics.

Phase 2, open-label, multicenter, 2-way, crossover study				
	Cohort 1 n = 12	Cohort 2 n = 12	Cohort 3 n = 17	Cohort 4 n = 22
Demographics				
Age				
mean ± SD, y	67.8 ± 7.3	67.5 ± 8.8	66.8 ± 11.4	67.7 ± 9.6
range, y	54.3–76.5	56.0–83.0	49.0–84.0	46.4–83.5
Sex, n (%)				
males	12 (100)	9 (75)	10 (58.8)	18 (81.8)
females	0	3 (25)	7 (41.2)	4 (18.2)
Race, n (%)				
Caucasian	12 (100)	9 (75.0)	16 (94.1)	20 (90.9)
Asian	0	2 (16.7)	1 (5.9)	0
other	0	1 (8.3)	0	2 (9.1)
Baseline Clinical Characteristics, mean ± SD				
PD duration, y	5.2 ± 3.1	12.0 ± 3.9	9.0 ± 4.8	13.5 ± 5.8
LD treatment duration, y	2.8 ± 2	8.9 ± 3.9	5.3 ± 2.8	9.5 ± 6.7
LD dose mg	Not recorded	696.3 ± 115.2	627.8 ± 109.4	680.7 ± 122.4
H & Y Stage, n (%)				
1.5	1 (8.3)			
2	10 (83.3)	3 (25.0)	7 (41.2)	6 (27.3)
2.5	0	6 (50.0)	5 (29.4)	8 (36.4)
3	1 (8.3)	3 (25.0)	5 (29.4)	8 (36.4)
OFF hours per day				
2–3	N/A	2 (28.6)	5 (31.3)	2 (11.1)
4–5	N/A	3 (42.9)	8 (50.0)	4 (22.2)
> 5	N/A	2 (28.6)	3 (18.8)	12 (66.7)

H & Y, Hoehn & Yahr; SD, standard deviation.

3.2.2. Carbidopa

In participants with early non-fluctuating PD (Cohort 1), the bioavailability of CD over 16 h with AP-CD/LD was significantly higher than IR-CD/LD (121.7%; CI, 109.7–133.6%; $P = 0.010$), indicating better absorption of CD with the AP. C_{max} significantly increased with AP-CD/LD (126.8%, CI, 111.8–141.7%) versus IR-CD/LD ($P = 0.010$; Supplemental Table 1). Prolonged absorption of CD was confirmed as T_{max} significantly increased from 2.0 h with IR to 5.0 h with AP ($P < 0.001$).

In participants with advanced fluctuating PD (Cohort 2), the relative bioavailability of CD with AP-CD/LD 50/375 BID was significantly higher than that of IR-CD/LD 18.75/187.5 mg QID (159.2%; CI, 127.2–191.3%; $P = 0.014$), though it is important to note that the daily dose of CD was 25 mg less with comparator versus AP (Supplemental Table 1). C_{max} of carbidopa with AP exceeded that of IR ($P = 0.045$), and there were no between-cohort differences in C_{min}. T_{max} was significantly longer with AP (4.0 h) versus IR (2.0 h; $P = 0.010$).

3.3. Efficacy Evaluation

3.3.1. Efficacy in participants with motor fluctuations (Cohorts 2, 3, 4)

Overall, treatment with either AP-CD/LD 50/375 BID or AP-CD/LD 50/500 BID significantly improved motor fluctuations compared with participants' current treatment. AP-CD/LD 50/375 and 50/500 significantly reduced mean daily OFF time by 44% in Cohort 3 (from 4.3 h with current IR treatment to 2.4 h with AP-CD/LD; $P < 0.001$) and by 45% in Cohort 4 (from 5.1 h with current IR treatment to 2.8 h with AP-CD/LD; $P < 0.001$). In Cohort 2, use of AP-CD/LD 50/375 vs IR-CD/LD resulted in a trend for diminished daily OFF time observed, though the treatment difference was not significant ($P = 0.054$).

In Cohorts 3 and 4, total ON time (ON state without dyskinesia), good ON time (ON state or ON with non-troublesome dyskinesia), the proportion of total ON time during waking hours, and the proportion of good ON time during waking hours significantly increased with both AP-CD/LD 50/375 (Cohort 3) and 50/500 (Group 4), while both bad time (OFF state or ON with troublesome dyskinesia) and ON time with

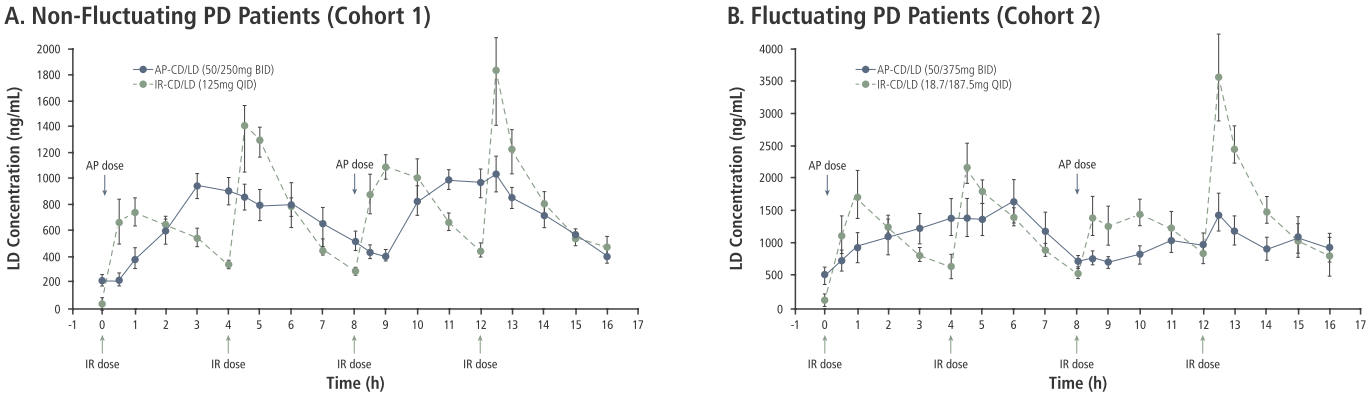

Fig. 2. Mean Levodopa Plasma Concentrations. A. Cohort 1 Non-fluctuating PD. B. Cohort 2 Fluctuating PD. AP-CD/LD, Accordion Pill carbidopa/levodopa; BID, twice daily; IR, immediate release; PD, Parkinson's disease; QID, four times a day.

Table 3
Pharmacodynamic parameters and AP-CD/LD effects on LD dosing (per protocol population).

	Cohort 3 n = 16		Cohort 4 n = 18	
Mean ± SD	Treatment Difference AP-CD/LD 50/375 BID vs Current Treatment	*P* value[a]	Treatment Difference AP-CD/LD 50/500 BID vs Current Treatment	*P* value[a]
Daily OFF Time[b,c], h	−1.85 ± 2.28	< 0.001	−2.32 ± 3.65	< 0.001
Total ON Time[d], h	1.98 ± 2.39	< 0.001	2.58 ± 4.94	< 0.001
Good ON Time[e], h	2.08 ± 2.16	< 0.001	2.69 ± 4.37	< 0.001
ON w/troublesome dyskinesia, h	−0.55 ± 0.58	0.860	−0.57 ± 1.33	0.002
Bad time[f], h	−1.91 ± 2.24	< 0.001	−2.90 ± 4.14	< 0.001
Time to ON, min	−23.39 ± 87.79[i]	0.306	−11.57 ± 78.05	0.554
Proportion Total ON/waking hrs, %	12.08 ± 15.67	< 0.001	16.27 ± 30.16	< 0.001
Proportion Good ON/waking hrs, %	12.34 ± 13.01	< 0.001	16.83 ± 24.93	< 0.001
Total LD dose/day, mg	96.22 ± 203.60	< 0.001	396.53 ± 168.04	< 0.001
#LD doses/day[g], n	−2.82 ± 2.29	< 0.001	−1.35 ± 1.97	< 0.001
Frequency LD doses/day[h], n	−2.57 ± 1.98	< 0.001	−1.11 ± 1.84	< 0.001
Duration Good ON/dose, h	2.64 ± 2.00	< 0.001	1.48 ± 1.72	0.004

AP-CD/LD, Accordion Pill Carbidopa/Levodopa; BID, twice daily; CD, carbidopa; IR, immediate release; LD, levodopa; MMRM, mixed-effect model for repeated measures; SD, standard deviation.

[a] MMRM.

[b] Measured using Hauser ON-OFF daily diaries between treatments: participants were instructed to complete the diary during the last 3 at-home days of treatment for each half-hour time, indicating their status during that half-hour time period; the diary included 5 categories (OFF, ON, ON with non-troublesome dyskinesia, ON with troublesome dyskinesia, Asleep). All times were calculated as the average daily time of 16 h, starting from first daily morning dosing time, over the last 3 days of at-home dosing.

[c] Daily OFF time was the primary endpoint in Groups 3 and 4, and a secondary endpoint in Group 2.

[d] ON state without dyskinesia.

[e] ON state or ON with non-troublesome dyskinesia.

[f] OFF state or ON with troublesome dyskinesia.

[g] Number of doses taken during the last 3 at-home days (days 18, 19, 20) of each treatment per home diaries.

[h] Number of doses taken during the last 3 at-home days; doses taken at the same time were counted as one dose.

[i] n = 15.

troublesome dyskinesias significantly decreased with both AP doses (Table 3).

3.3.2. AP-CD/LD effects on dosing

In Cohort 3, the mean total LD dose was significantly greater with AP-CD/LD (878.26 ± 137.97 mg) versus current treatment (782.03 ± 162.17 mg; $P < 0.001$). Similarly, the total LD dose in Cohort 4 was significantly greater with AP-CD/LD (1165.50 ± 102.68 mg) compared with current treatment (768.98 ± 189.01 mg; $P < 0.001$). While treatment with the AP significantly increased total LD intake dose per day, the number and frequency of LD doses taken per day significantly decreased and the duration (hours) of good ON time per dose significantly increased (Table 3).

3.3.3. Clinical Global Impression

Treatment with either AP-CD/LD 50/375 (Cohort 3) or AP-CD/LD 50/500 (Cohort 4) significantly improved both patient and investigator ratings on the CGI versus current treatment ($P < 0.01$ all).

3.4. Adverse events

Treatment-emergent AEs (TEAEs) observed with AP-CD/LD were generally consistent with the known safety profile of CD/LD formulations. No new safety issues were observed throughout the study. A total of 2 AEs were reported by patients in Cohort 1 (during AP-CD/LD 50/250 treatment) and consisted of single cases of mild insomnia and mild vomiting (Supplemental Table 2). Four TEAEs were considered related to AP-CD/LD 50/375 mg in Cohort 2: abdominal discomfort, nausea, chest pain, and abdominal pain, each occurring once. All TEAEs resolved without sequelae.

In Cohort 3, a total of 10 AEs were reported (9 among 8 participants in the AP-CD/LD 50/375 treatment arm and 1 by a participant in the current treatment arm). None of the AEs occurred more than once in any participant. Only 2 AEs were deemed possibly related to study drug (nausea and abdominal pain, 1 each). A single SAE of myocardial infarction was determined to be unrelated to AP-CD/LD; it resolved and did not result in participant withdrawal.

In Cohort 4, a total of 13 TEAEs were reported by 11 patients (9 by 8 patients in the AP-CD/LD treatment arm, and 4 by 4 patients in the current treatment arm). All TEAEs were mild or moderate and completely resolved; only 1 TEAE (nausea) was considered probably related AP-CD/LD treatment. An SAE (small intestine obstruction) was reported with the participant's initial treatment prior to AP-CD/LD 50/500 mg dosing, resulting in the participant's withdrawal from the study.

4. Discussion

This is the first report regarding the safety and usefulness of a new technology—the Accordion Pill, AP-CD/LD—for the treatment of patients with advanced PD. The outcomes from clinical testing highlight the potential of the AP-CD/LD formulation for improving PD therapeutics.

The goal of an improved oral CD/LD product for managing PD motor fluctuations can be largely defined by plasma LD pharmacokinetics—that is, achieving a target concentration of ~1 μg/mL with relatively small variability. The AP-CD/LD 50/375, dosed BID over 8-h intervals, achieved LD plasma concentrations within or close to the therapeutic range for adequate symptomatic control [3]. Overall, the PK profile of AP-CD/LD 50/375 is similar to the PK of intestinal CD/LD infusion and better than PK parameters reported for other orally administered LD products developed for extended dopaminergic effect [15,16].

In addition to more consistent LD plasma concentrations with AP-CD/LD regardless of whether patients were experiencing motor fluctuations, this new delivery platform resulted in increased ON time and

decreased OFF time compared with the IR form. Given the high correlation of clinical effect with LD pharmacokinetics, the efficacy of the AP-CD/LD 50/500 dose in Cohort 4 was not unexpected. Importantly, the substantially improved ON time for the AP versus IR was attained without an emergence of troublesome dyskinesia. Furthermore, daily OFF time in Cohorts 3 and 4 was significantly reduced with AP vs IR. Though Cohort 2 daily OFF time missed statistical significance for improvement, this measure was a secondary outcome in Cohort 2 as the treatment period was only 6 days (versus 21) and did not include a prior conversion and dose optimization period as was required for Cohorts 3 and 4.

Results from this study suggest that AP-CD/LD can reduce pill burden and improve overnight LD effect. Reducing daily LD dosing burden may improve medication adherence since IR-LD intake schedules can be difficult for compliance [17]. In this study, the 8-h spacing between AP administrations suggests that some patients could manage a twice-daily treatment regimen. Additionally, the mean morning predose LD plasma concentration in Cohort 4 was approximately 0.5 μg/mL, suggesting that a larger evening dose (or one closer to bedtime) might provide a persisting therapeutic effect throughout the night and continuing until morning. Additionally, LD plasma concentrations were not altered from the therapeutic range when patients consumed conventional meals (Cohorts 1 and 2 received a mid-range caloric meal 30 min prior to dosing on PK assessment days), further underscoring the practical application of the AP for everyday management of PD.

Compared with other clinical trials of extended-release LD formulations, our investigations of the three AP formulations were relatively brief, and the AP formulations were not compared with other extended-release CD/LD products. Comparisons to the other formulations also need to take into account this study's unblinded ratings of Parkinsonism, the small treatment cohort sizes, as well as the homogeneity of the participant population, which was primarily white males. We recognize that for participants in Cohort 2, the total dosage of CD was greater during treatment with AP-CD/LD 50/375 than treatment with comparator CD/LD, though whether this difference would have had any impact on the results is uncertain.

The valuable information gathered in this pilot study has informed and guided the further development of the AP for PD in an ongoing phase 3 multicenter, randomized, placebo-controlled study (NCT02605434). In the phase 3 study, both BID and TID regimens of AP-50/400 and AP-50/500 mg doses are being tested. As these doses are the same or similar to those used in the pilot study reported here, similar stable LD and CD plasma levels within the therapeutic range necessary for PD symptom control are expected from the phase 3 study.

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Appendix A. Supplementary data

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