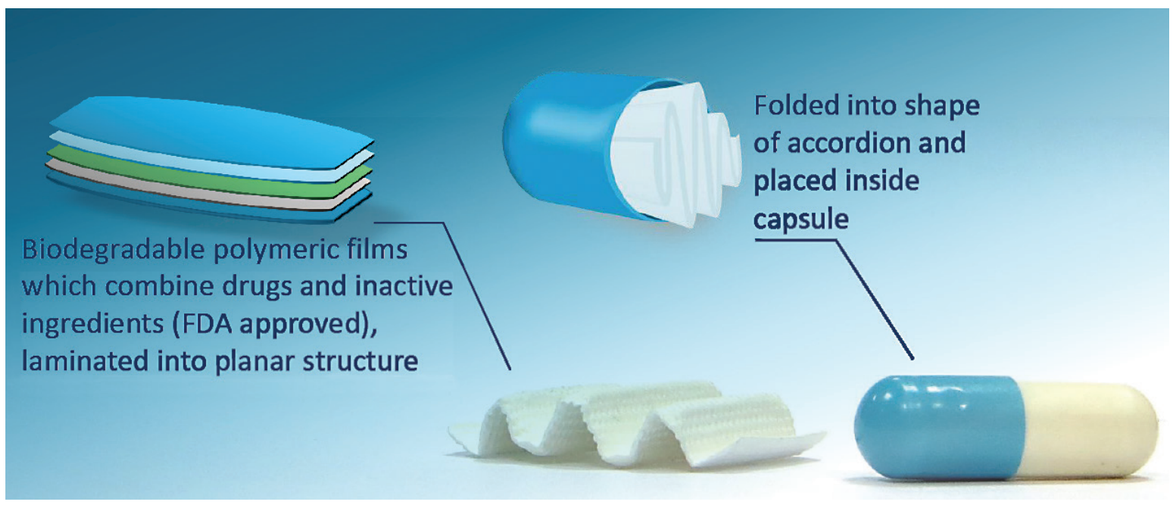
Pharmacokinetics of Accordion Pill® Carbidopa/Levodopa Following Multiple Doses in Patients With Parkinson's Disease

C. Warren Olanow,[1] Fabrizio Stocchi,[2] Mika Leinonen,[1] Nadav Navon,[3] Jeffrey A. Meckler,[4] R. Michael Gendreau[4]
[1]Clintrex LLC, Sarasota, FL, US; [2]IRCCS San Raffaele Pisana, Tosinvest Sanità, Rome, Italy; [3]Intec Pharma, LTD, Jerusalem, Israel; [4]Intec Pharma, Inc, New York, NY, US

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 and minimize wearing off episodes[1]
- Both animal studies and a prospective double-blind study in patients with PD confirm that continuous delivery of LD is associated with 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 recent Phase 2 study reported more stable LD plasma concentrations and lower C_{max} with AP-CD/LD BID than with IR-CD/LD QID in both fluctuating and non-fluctuating PD patients;[4] to determine optimal dosing, AP-CD/LD BID or TID vs IR-CD/LD are being evaluated in a recently completed Phase 3 study (Accordance [NCT02605434]) in adult patients with fluctuating PD

FIGURE 1: Accordion Pill®



OBJECTIVE

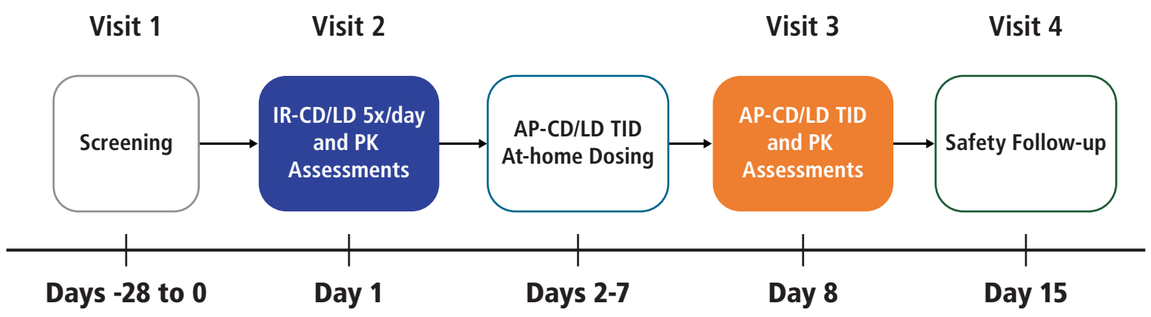
- To determine if AP-CD/LD TID provides a more consistent delivery of LD than IR-CD/LD, with the goal of reducing motor complications associated with CD/LD therapy in patients with PD

METHODS

Study Design

- This was an open label, cross-over, pharmacokinetic (PK) study comparing AP-CD/LD 50/500 mg TID and IR-CD/LD 37.5/150 mg 5x daily in patients with PD (**Figure 2**)
- PK samples were collected pre-dose (0 min) and at 30-minute intervals post-dose over 16 hours and again at 24 hours post-dose

FIGURE 2: Study Design



AP-CD/LD 50/500 mg TID; IR-CD/LD 37.5/150 mg 5x daily.
AP, Accordion Pill; CD, carbidopa; IR, immediate-release; LD, levodopa; PK, pharmacokinetic; TID, 3x daily.
On day 1, participants arrived at the clinic in the practically-defined OFF state and received 1.5 tablets of standard oral IR-CD/LD 25/100 mg 5x daily; participants were discharged and instructed to take AP-CD/LD 50/500 mg TID (5-h intervals) for 7 days; on day 8, participants returned to the clinic in the practically defined OFF state and received AP-CD/LD 50/500 mg TID.

Pharmacokinetic and Safety Outcomes

- The primary endpoint was the variability in plasma LD concentration between 4 and 16 hours assessed by the LD fluctuation index ($FI_{4\text{-}16h}$), defined as $(C_{max}\text{-}C_{min})/C_{average}$, after standard IR-CD/LD on day 1 and AP-CD/LD on day 8
- The key secondary endpoint was the coefficient of variation (CV): standard deviation of plasma LD concentrations divided by the average concentration
- Multiple sensitivity analyses were performed
- Safety assessments included adverse events (AEs), vital signs, clinical laboratory values, and physical and neurological examination

Statistical Analyses

- Populations
  - PK population: all participants who received ≥1 dose of study drug and had ≥1 post-baseline PK evaluation
  - Safety analysis population: all participants who received ≥1 dose of study drug
- FIs and CVs were compared between day 1 (IR-CD/LD) and day 8 (AP-CD/LD) using paired *t* tests
- Safety and tolerability were summarized with descriptive statistics

RESULTS

Disposition, Demographics, and Clinical Characteristics

- All 12 enrolled patients completed the study and were included in the safety and PK analysis populations
- Most patients were male (58.3%) and all were white, with an average of 3.2 years of motor complications and a mean daily LD dose at baseline of 627 mg (**Table 1**)

TABLE 1: Baseline Demographics and Characteristics

Characteristic	Safety and PK Population (N = 12)
Age, y, mean (SD)	68.9 (9.6)
Gender, n (%)	
Female	5 (41.7)
Male	7 (58.3)
White, not Hispanic or Latino, n (%)	12 (100.0)
Weight (kg), mean (SD)	72.2 (10.6)
Height (cm), mean (SD)	167.0 (8.2)
BMI (kg/m^2), mean (SD)	25.8 (2.2)
Years since diagnosis of PD, mean (SD)	9.3 (4.1)
Years since start of motor complications, mean (SD)	3.2 (3.3)
Daily LD dose (mg), mean (SD)	627 (82)
Concomitant medications, n (%)	
Carbidopa	9 (75.0)
Benserazide	3 (25.0)
COMT inhibitors	10 (83.3)

BMI, body mass index; COMT, catechol-*O*-methyltransferase; LD, levodopa; PD, Parkinson's disease; PK, pharmacokinetic; SD, standard deviation

AP-CD/LD Pharmacokinetics

- Primary Endpoint: Treatment with AP-CD/LD TID resulted in significantly less variability in steady-state LD plasma levels vs standard IR-CD/LD therapy, with a mean (95% confidence interval) $FI_{4\text{-}16h}$ difference of -0.63 (-1.03, -0.24; *P*=0.005) (**Table 2**)
- Key Secondary Endpoint: Results were consistent with the primary endpoint, with a mean (95% confidence interval) IR-CD/LD vs AP-CD/LD $CV_{4\text{-}16h}$ difference of -11.2 (-22.2, -0.2; *P*=0.047) (**Table 2**)

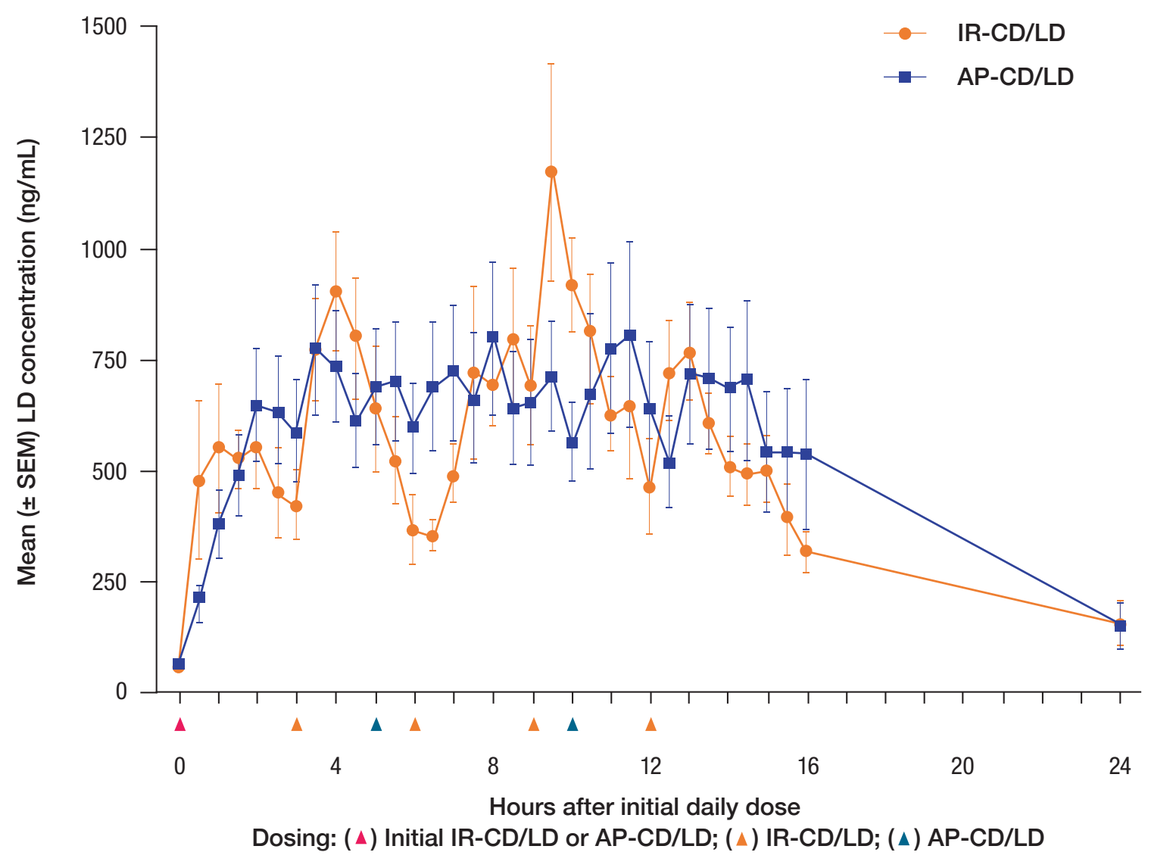
TABLE 2: Primary and Key Secondary Pharmacokinetic Endpoints (PK Population)

PK Parameter	Day 1 IR-CD/LD, Mean (SD) (N = 12)	Day 8 AP-CD/LD, Mean (SD) (N = 12)	Day 1 vs Day 8 Difference (95% CI) (N = 12)	*P* value
$FI_{4\text{-}16h}$	2.22 (0.63)	1.59 (0.57)	-0.63 (-1.03, -0.24)	0.0048
$CV_{4\text{-}16h}$ (%)	55.0 (12.0)	43.8 (17.7)	-11.2 (-22.2, -0.2)	0.0467

AP, Accordion Pill; CD, carbidopa; CI, confidence interval; CV, coefficient of variation; FI, fluctuation index; IR, immediate-release; LD, levodopa; PK, pharmacokinetic; SD, standard deviation.

- The plasma LD concentration-time curve illustrates that AP-CD/LD treatment resulted in less variability in LD plasma concentration, attenuating the low trough and high peak levels observed with IR-CD/LD over 24 hours (**Figure 3**)

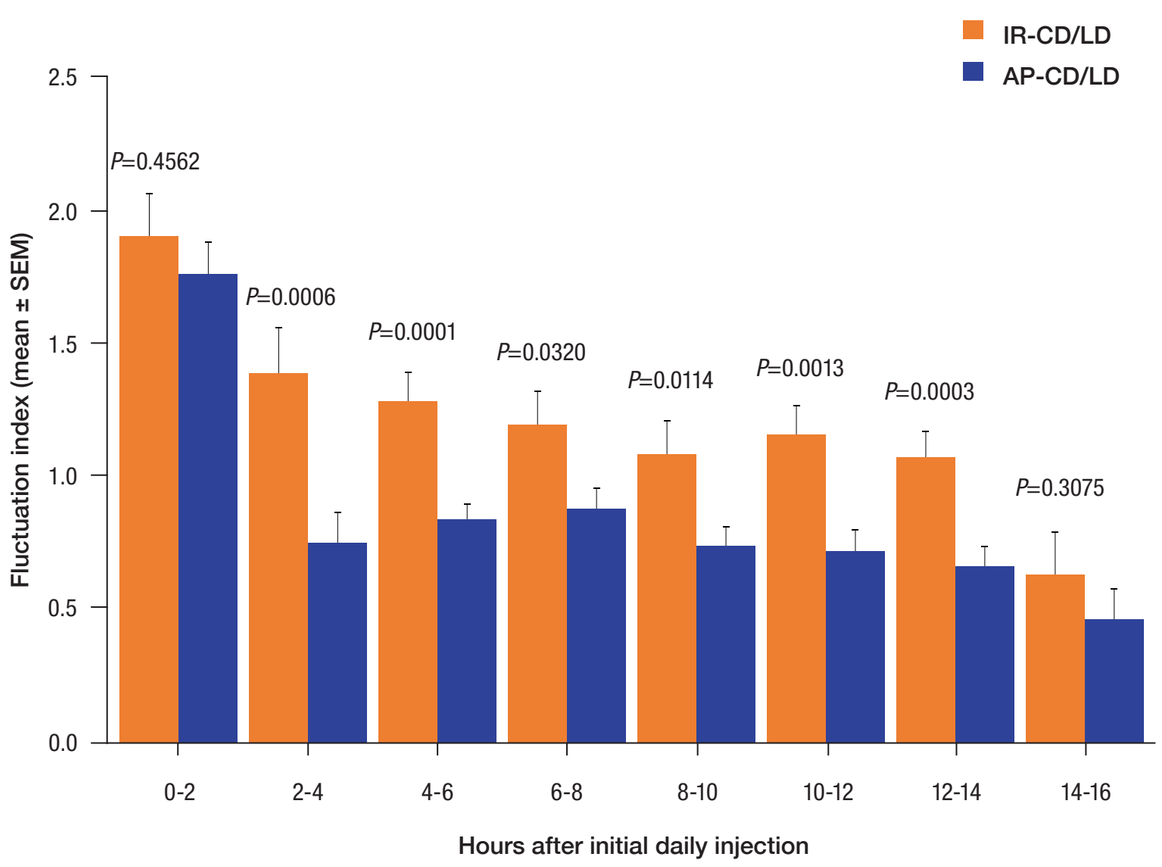
FIGURE 3: Plasma LD Concentration-Time Curve (PK Population)



AP, Accordion Pill; CD, carbidopa; IR, immediate-release; LD, levodopa; PK, pharmacokinetic; SEM, standard error of the mean.

- Similar results were observed for all sensitivity analyses of the primary endpoint, including fluctuation index at 2-h intervals (**Figure 4**)

FIGURE 4: Fluctuation Index at 2-hour Intervals (PK Population)



P values = IR-CD/LD (day 1) vs AP-CD/LD (day 8)
AP, Accordion Pill; CD, carbidopa; IR, immediate-release; LD, levodopa; PK, pharmacokinetic; SEM, standard error of the mean.

Safety and Tolerability

- There were no serious or severe AEs, discontinuations due to an AE, or deaths
- There were no significant findings on laboratory tests, vital signs, or physical/neurological examinations

CONCLUSIONS

- AP-CD/LD 50/500 mg TID provided stable plasma LD levels compared with standard IR-CD/LD 37.5/150 mg dosed 5x daily
- AP-CD/LD was well tolerated, with no new safety signals
- These results suggest that treatment with AP-CD/LD may reduce motor complications in patients with advanced PD versus standard IR-CD/LD treatment

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