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

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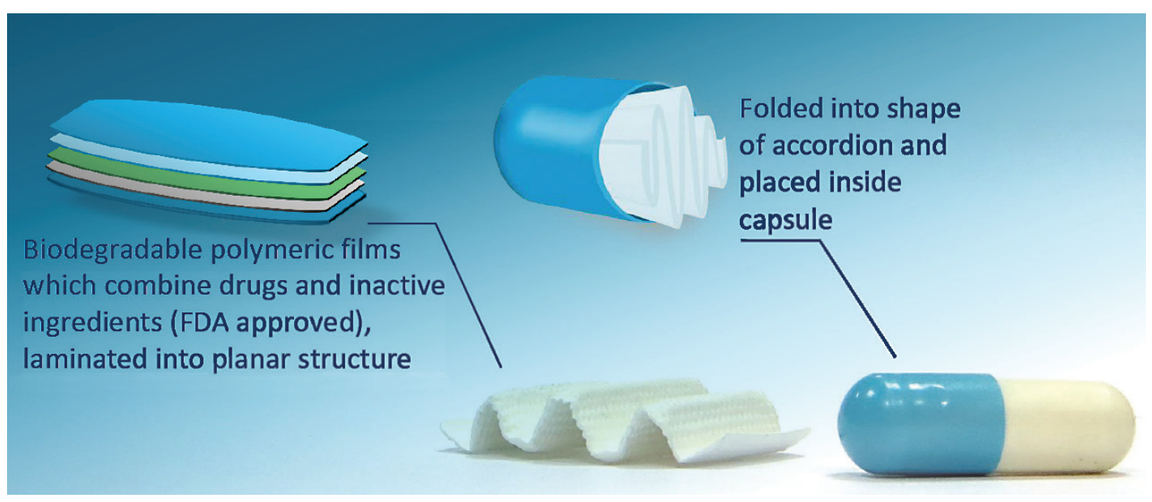
BACKGROUND

- 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 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]

OBJECTIVE

- To determine if AP-CD/LD 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

FIGURE 1: Accordion Pill®



METHODS

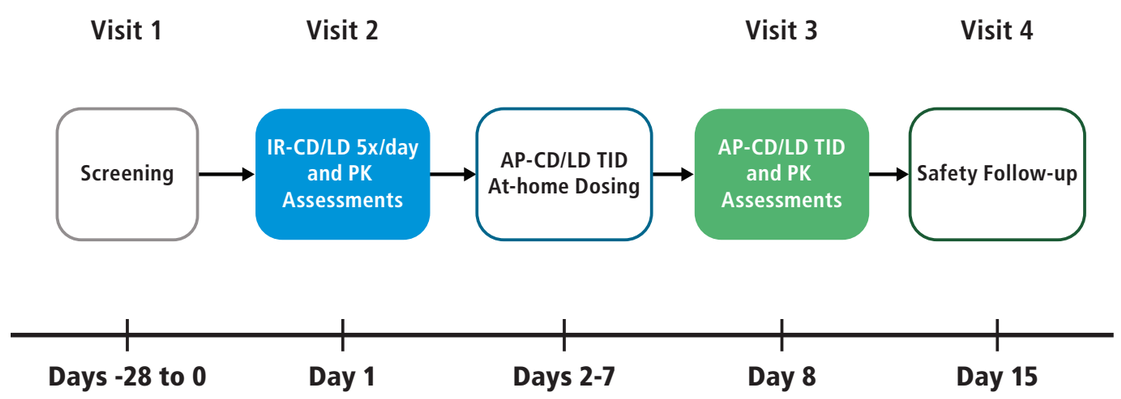
Study Design

- This was an open label cross-over pharmacokinetic (PK) study comparing AP-CD/LD 50/500 mg 3x daily (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

Efficacy and Safety Outcomes

- The primary endpoint was the variability in plasma LD concentration between 4 and 16 hours assessed by the LD fluctuation index ($FI_{4\text{-}16}$) ($[C_{max}\text{-}C_{min}]/C_{average}$) 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

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.

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

AP-CD/LD Pharmacokinetics

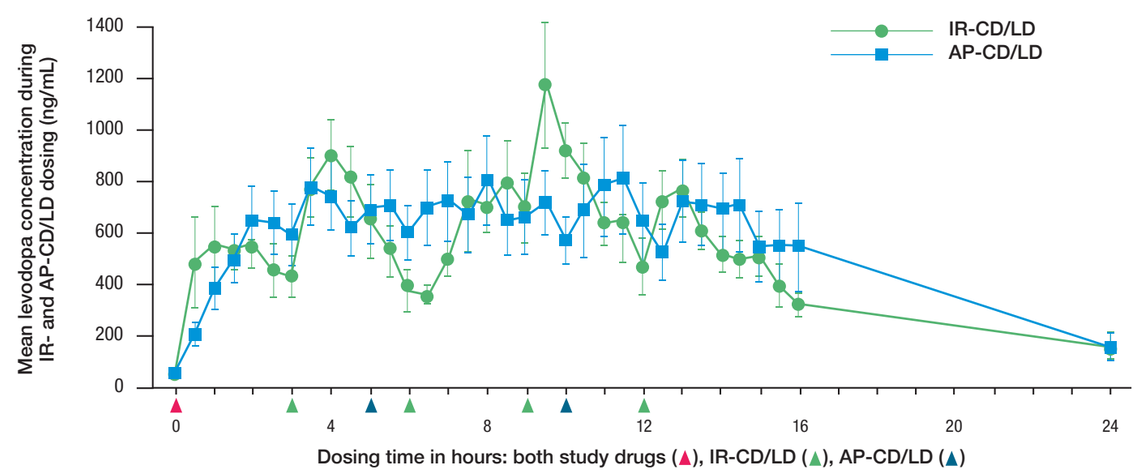
- Primary Endpoint: Treatment with AP-CD/LD TID resulted in significantly less variability in steady-state LD plasma levels vs standard IR-CD/LD therapy, with a mean (95% confidence interval) $FI_{4\text{-}16h}$ difference of -0.63 (-1.03, -0.24; *P*=0.005) (**Table 1**)
- Key Secondary Endpoint: Results 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 1**)
  - 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**)
- Similar results were observed for all sensitivity analyses of the primary endpoint, including fluctuation index at 2-h intervals (**Figure 4**)

TABLE 1: 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

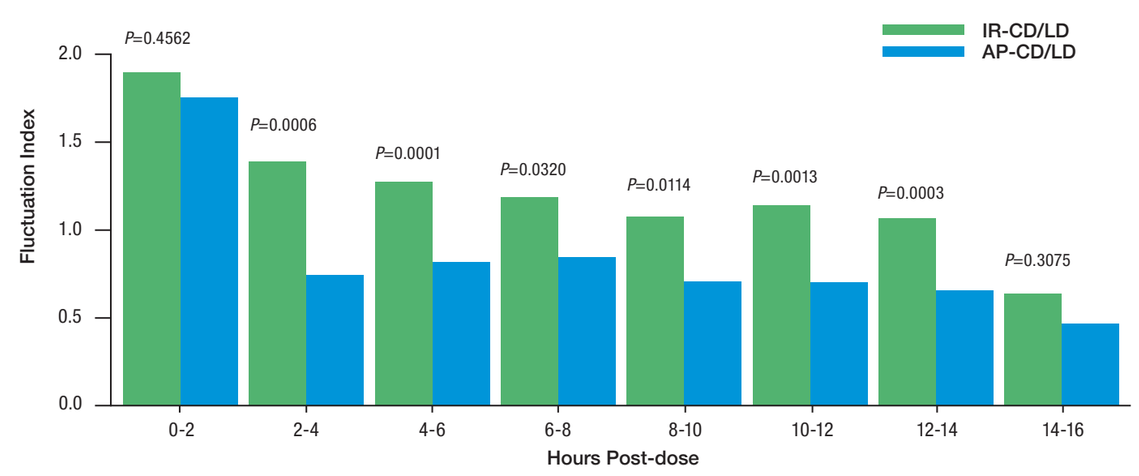
AP, Accordion Pill; CD, carbidopa; CI, confidence interval; CV, coefficient of variation; FI, fluctuation index; IR, immediate-release; LD, levodopa; PK, pharmacokinetic; SD, standard deviation.

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



AP, Accordion Pill; CD, carbidopa; IR, immediate-release; LD, levodopa; PK, pharmacokinetic.

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.

TABLE 2: Secondary Pharmacokinetic Endpoints (PK Population)

PK Parameter	Day 1 IR-CD/LD (N = 12)	Day 8 AP-CD/LD (N = 12)
$C_{max,\ 0\text{-}24h}$ (ng/mL), geometric mean (SD)	1589.5 (773.0)	1176.9 (638.8)
$C_{min,\ 4\text{-}16h}$ (ng/mL), geometric mean (SD)	183.5 (122.3)	227.5 (181.8)
$C_{max} - C_{min\ 4\text{-}16h}$ (ng/mL)	1444	967
$C_{max\ mean} - C_{min\ mean\ 4\text{-}16h}$ (ng/mL)[a]	1174-319 = 855	808-521 = 287

[a] Maximum and minimum average concentrations at 4-16 h (arithmetic means).
AP, Accordion Pill; CD, carbidopa; C_{max}, maximum LD concentration; C_{min}, minimum LD concentration; IR, immediate-release; LD, levodopa; PK, pharmacokinetic; SD, standard deviation.

Safety and Tolerability

- There were no serious adverse events (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 levodopa 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 as compared to standard IR-CD/LD treatment

REFERENCES

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Presented at the XXIV World Congress on Parkinson's Disease and Related Disorders 16-19 June, 2019 | Montréal, Canada

Funded by Intec Pharma, LTD

Medical writing and editing assistance provided by Prescott Medical Communications Group, Chicago, IL, US