Optimizing Delivery of Carbidopa/Levodopa via the Accordion Pill™: Comparative Pharmacokinetics and Safety From 2 Randomized Studies in Healthy Volunteers

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BACKGROUND

- Carbidopa/levodopa (CD/LD) is the gold-standard treatment for Parkinson's disease (PD)
- Long-term LD treatment is associated with motor fluctuations, with progressively longer OFF periods over time
- Improving the stability of LD plasma levels should improve efficacy, reduce adverse events (AEs), and may even delay disease progression
- The Accordion Pill™-CD/LD (AP-CD/LD) is a novel drug delivery system based on gastric-retention of multilayer films containing immediate-release CD and both immediate and controlled-release LD

OBJECTIVE

- To evaluate the pharmacokinetics (PK) and safety of AP-CD/LD versus immediate-release (IR)-CD/LD (Sinemet®) and under different meal conditions in healthy adults

RESULTS

Demographics

- A total of 18 and 30 healthy volunteers were enrolled in IN 11 005 and IN 14 001, respectively (**Table 1**)
- One participant discontinued due to an AE of nausea and vomiting following AP-CD/LD 50mg/500mg; 5 other participants had the second dose of IR-CD/LD withheld due to ongoing AEs of nausea and/or vomiting, though they were not removed from the study

TABLE 1: Baseline Demographics (IN 11 005 and IN 14 001)

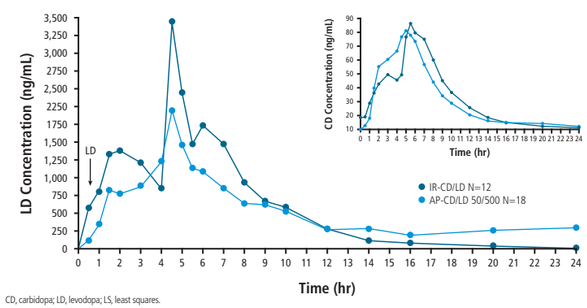
	Study IN 11 005 (N=18)	Study IN 14 001 (N=30)
Age, mean (SD), y	40.5 (6.1)	26.0 (7.1)
Male, n (%)	9 (50.0)	24 (80.0)
White, n (%)	18 (100)	30 (100)
Weight, mean (SD), kg	70.8 (13.0)	74.2 (8.3)
BMI, mean (SD), kg/m^2	25.4 (3.0)	25.2 (2.2)

BMI, body mass index; SD, standard deviation.

Levodopa Plasma Concentrations

- In study IN 11 005, AP-CD/LD produced more consistent mean LD plasma concentrations over time, with attenuated peak-trough differences compared with IR-CD/LD (**Figure 1**); mean plasma concentration of CD was similar between IR-CD/LD and AP-CD/LD (**Figure 1**, inset)

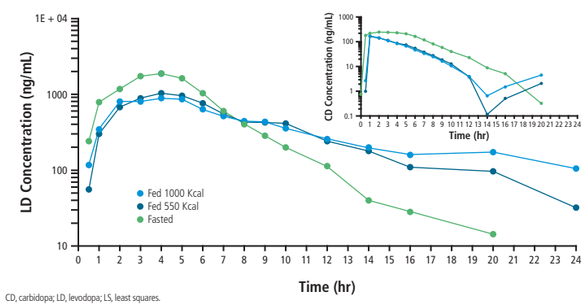
FIGURE 1: LS Mean Plasma Concentration Over Time (IN 11 005)



CD, carbidopa; LD, levodopa; LS, least squares.

- In study IN 14 001, LD plasma concentrations were similar following either a low/medium calorie or high-calorie meal; under fasting conditions, more variability was seen, including significantly shorter retention time versus either fed condition (P<0.05; **Figure 2**)
- Mean CD plasma concentrations were comparable between the low/medium and high-calorie meals, but significantly greater at nearly all collection times with fasting (P<0.05; **Figure 2**, inset)

FIGURE 2: LS Mean Plasma Concentration Over Time (IN 14 001)



CD, carbidopa; LD, levodopa; LS, least squares.

PK of AP/CD-LD vs IR-CD/LD

- Apparent half-life ($t_{1/2}$) was increased from 1.8 h with IR-CD/LD to 5.2 h with AP-CD/LD, while C_{max} was decreased from 4,062 ng/mL to 1,951 ng/mL (**Table 2**)
- LD absorption was prolonged from ~2 h with IR-CD/LD to ~10 h with AP-CD/LD

TABLE 2: Pharmacokinetic Profile of AP-CD/LD vs IR-CD/LD (IN 11 005)

	Least-Squares Means			90% CI	
Parameter	AP-CD/LD	IR-CD/LD	Ratio	Lower	Upper
Levodopa Pharmacokinetics (N=12)					
$AUC_{0\text{-}t}$ (ng-hr/mL)	10,693	14,047	**0.761**	0.615	0.907
$AUC_{0\text{-}inf}$ (ng-hr/mL)	12,426	14,123	0.880	0.486	1.274
C_{max} (ng/mL)	1,951	4,062	**0.480**	0.153	0.808
T_{max} (hr)	4.67	4.83	0.966	-	-
K_e (1/hr)	0.2829	0.4041	0.700	-	-
$T_{½}$ (hr)	5.15	1.76	2.927	-	-
Carbidopa Pharmacokinetics (N=12)					
$AUC_{0\text{-}t}$ (ng-hr/mL)	491	530	0.926	0.789	1.064
$AUC_{0\text{-}inf}$ (ng-hr/mL)	505	554	0.912	0.698	1.126
C_{max} (ng/mL)	86.9	95.3	0.912	0.734	1.089
T_{max} (hr)	4.54	5.75	0.790	-	-
K_e (1/hr)	0.1591	0.1831	0.869	-	-
$T_{½}$ (hr)	5.36	4.98	1.077	-	-

Bold indicates significance at P<0.05, based on ANOVA.
ANOVA, analysis of variance; AUC, area under the plasma concentration versus time curve; $AUC_{0\text{-}inf}$, AUC from time 0 to infinity; $AUC_{0\text{-}t}$, AUC from time 0 to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; K_e, elimination rate constant; T_{max}, time to maximum plasma concentration; $T_{1/2}$, elimination half-life.

Food Effects on AP-CD/LD PK Profile

- The effects of food on the PK of AP-CD/LD are shown in **Table 3**; in particular, residence time and C_{max} are largely dependent on the presence of a recent meal

Safety

- In study 11 005, 38.9% of participants reported treatment-related AEs while receiving AP-CD/LD vs 83.3% receiving IR-CD/LD
  - The most common AE was nausea (27.8% and 61.1% with AP-CD/LD and IR-CD/LD, respectively)
- In study 14 001, the percentage of participants reporting one or more AEs was similar following either low/medium and high-calorie meals (46.7% and 30.0%), but higher for fasting (73.3%)
  - The most common AE was nausea, occurring in 16.7%, 26.7%, and 40% of healthy adults after high-calorie, low/medium calorie, and fasting conditions, respectively
- No serious AEs or deaths occurred in either study

TABLE 3: Food Effects on PK Profile of AP-CD/LD (IN 14 001)

	Fed 1000Kcal (N=30)	Fed 550Kcal (N=30)	Fasted (N=30)
Parameter	Mean (CV%)[1]	Mean (CV%)[1]	Mean (CV%)[1]
Levodopa			
$AUC_{0\text{-}t}$ (ng-hr/mL)	8,596 (24.4%)	8,330 (23.9%)	10,357 (28.6%)
$AUC_{0\text{-}inf}$ (ng-hr/mL)	8,434 (24.2%)	8,668 (25.8%)	10,497 (28.5%)
C_{max} (ng/mL)	1,288 (32.9%)	1,362 (32.4%)	2,544 (44.5%)
T_{max} (hr)	3.50 (1.00 - 24.02) [2]	4.00 (1.00 - 10.00) [2]	4.00 (1.00 - 7.00) [2]
T_{lag} (hr)	0.500 (0.00 - 1.00) [2]	0.500 (0.00 - 1.00) [2]	0.00 (0.00 - 0.500) [2]
K_e (1/hr)	0.3442 (54.9%)	0.3795 (54.2%)	0.4500 (24.3%)
$T_{½}$ (hr)	3.05 (76.4%)	2.99 (86.4%)	1.70 (50.6%)
MRT (hr)	8.29 (22.3%)	7.32 (22.9%)	4.94 (24.5%)
$MRT_{0\text{-}inf}$ (hr)	7.99 (28.7%)	7.56 (26.9%)	4.96 (24.7%)
Carbidopa			
$AUC_{0\text{-}t}$ (ng-hr/mL)	723 (40.7%)	736 (36.6%)	1,602 (40.3%)
$AUC_{0\text{-}inf}$ (ng-hr/mL)	765 (38.9%)	785 (33.9%)	1,649 (39.7%)
C_{max} (ng/mL)	180 (47.0%)	179 (40.2%)	267 (39.5%)
T_{max} (hr)	0.500 (0.500 - 4.00) [2]	0.500 (0.500 - 2.12) [2]	2.00 (0.500 - 5.00) [2]
T_{lag} (hr)	0.00 (0.00 - 0.52) [2]	0.00 (0.00 - 0.00) [2]	0.00 (0.00 - 0.00) [2]
K_e (1/hr)	0.3057 (21.8%)	0.3035 (26.3%)	0.3015 (20.9%)
$T_{½}$ (hr)	2.39 (26.0%)	2.52 (39.4%)	2.47 (37.0%)
MRT (hr)	3.34 (13.8%)	3.41 (10.1%)	4.44 (12.9%)
$MRT_{0\text{-}inf}$ (hr)	3.99 (15.1%)	4.18 (19.4%)	4.84 (13.4%)

[1] Values are presented as arithmetic means.
[2] Median (Range).
$AUC_{0\text{-}inf}$, area under the plasma concentration versus time curve; $AUC_{0\text{-}inf}$, AUC from time 0 to infinity; $AUC_{0\text{-}t}$, AUC from time 0 to the last measurable concentration; CV%,coefficient of variation; C_{max}, maximum plasma concentration; K_e, elimination rate constant; MRT, mean residence time; $MRT_{0\text{-}inf}$, MRT from 0 to infinity; PK, pharmacokinetic; T_{lag}, absorption time lag; T_{max}, time to maximum plasma concentration; $T_{1/2}$, elimination half-life.

CONCLUSIONS

- In two phase 1 trials conducted in healthy adults, single-dose AP-CD/LD provided more consistent LD plasma levels and less peak-trough fluctuation than IR-CD/LD
- AP-CD/LD should be taken with meals
- The safety of AP-CD/LD was similar to the known safety of CD/LD
- AP-CD/LD for advanced PD with motor fluctuations is currently being investigated in a pivotal phase 3 study being conducted in 10 countries

METHODS

Study Design

- IN 11 005 was a randomized, two-way crossover study in which healthy adults received a single dose of AP-CD/LD 50mg/500mg and two consecutive doses of IR-CD/LD 25mg/250mg (0 h and 4 h) following an overnight fast, with a 7-day washout between treatments
- IN 14 001 was a randomized, three-way crossover food-effect PK study in which healthy adults received a single dose of AP-CD/LD 50mg/500mg following high-calorie, low/medium calorie, or fasting conditions

Participants

- Eligible participants were healthy male and female volunteers aged 30 to 65 y (IN 11 005) or 18 to 45 y (IN 14 001), with a body mass index (BMI) of 18 to 29, inclusive
- Volunteers were not eligible if they had an active gastrointestinal (GI) disorder or unusual feeling of diarrhea, constipation, nausea, vomiting, bleeding, pain or GI discomfort, or frequent dyspepsia; had taken anticholinergic or other drugs known to affect GI motility (IN 11 005) or taken any medications, vitamins, herbal or dietary supplements (IN 14 001) within 14 days; donated blood or plasma within 3 months; adhered to an abnormal diet within 4 weeks; or anticipated difficulty fasting or consuming the standard meals provided, including any food allergy
- Concomitant medications known to possibly interfere with CD or LD or those that possibly potentiate CD/LD side effects, as well as medications that possibly interfere with biliary excretion, glucuronidation, or intestinal beta glucuronidase, must have been discontinued at least 14 days prior to the first dose of study drug through 10 days following the final dose of study drug

Serial Blood Samples

- Serial blood samples for PK assessments were obtained at baseline (0 h, pre-dosing) and at 0.5, 1.0, 1.5 (IN 11 005 only), 2, 3, 4, 4.5 (IN 11 005), 5, 5.5 (IN 11 005), 6, 7, 8, 9, 10, 12, 14, 16, 20, and 24 hours post-dosing

PK Parameters

- Primary PK variables were maximum plasma concentration (C_{max}), area under the plasma concentration versus time curve (AUC) from time 0 to the last measurable concentration ($AUC_{0\text{-}t}$), and AUC from time 0 to infinity ($AUC_{0\text{-}inf}$)
- Secondary PK variables were elimination half-life ($t_{1/2}$), elimination rate constant (K_e), and absorption lag time (t_{lag}); additional parameters included mean residence time (MRT) for study IN 14 001

Safety Analyses

- Safety was assessed via adverse event (AE) monitoring and standard clinical laboratory tests

Statistical Analyses

- PK populations included all participants with sufficient plasma drug concentration to measure the concentration-time profile in at least two periods; safety populations included all volunteers who received at least one dose of study drug
- PK measurements were performed using non-compartmental methods in Phoenix WinNonlin version 6.3 or higher (Pharsight Corp., Mountain View, CA)
- PK parameters were evaluated using an analysis of variance (ANOVA) with main effects of sequence, subjects nested within sequence, period, and treatment; geometric least-squares (LS) means, ratios of geometric LS means, and 90% confidence intervals (CIs) were calculated
- Statistical analyses were conducted using SAS version 9.1.3 (SAS Institute, Cary, NC)

DISCLOSURES

NN, ZW, RMG, and JAM are employees of Intec Pharma.

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