Accordion Pill Carbidopa - Levodopa in patients with Advanced Parkinson's Disease- Phase II study

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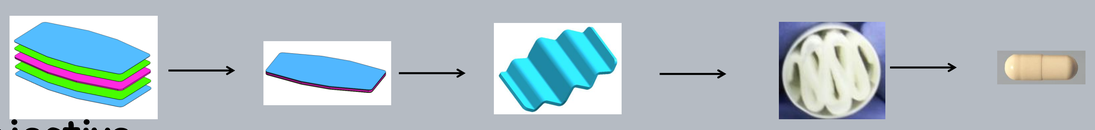
Background

Chronic LD therapy is associated with motor complications often related to the drug's peripheral pharmacokinetics. LD's absorption is confined to the upper part of the GI tract and is characterized by a short clearance half-life. Accordion pill carbidopa-levodopa (AP CD-LD) is a unique gastro-retentive formulation designed for achieving stable LD plasma levels to reduce both motor fluctuations and daily dosing requirements.

The AP is a multi-layer, planar structure that is composed of biodegradable films (IIG-listed excipients) folded in an accordion shape into a standard size capsule. Upon reaching the stomach, the AP unfolds and usually is retained in the stomach for up to 12 hours. Gastric retention is achieved under a regular calorie diet. The AP CD-LD combines immediate-release and controlled-release profiles of the CD and LD constituents.

The AP CD-LD structure:



Objective

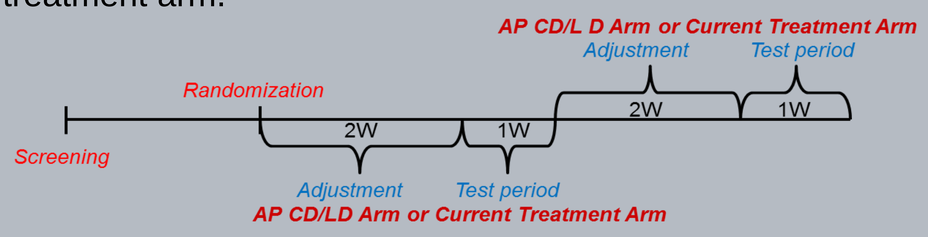
To evaluate the pharmacokinetic (PK) profile, efficacy and safety of the AP CD-LD formulation relative to patient's current treatment (including immediate-release and controlled-release CD-LD formulations) in advanced Parkinson's disease (PD) patients experiencing motor fluctuations.

Methods

This is a Phase II multi-center, open-label, two-way randomized crossover, multiple dose, active control clinical trial.

PK – Multiple dose Pharmacokinetics in 10 patients following 6 days treatment at home, AP CD-LD 50/375 given BID vs. QID of commercial IR18.75/187.5mg (daily equidose).

Efficacy and safety - A 42-day, pharmacodynamics study in 34 patients, taking AP CD-LD 50/375 (N=16) or 50/500 (N=18), vs. current CD-LD treatment. During days 1-20, self-administered at home with 2 weeks of drug adjustment: AP CD-LD was dosed at 0 and 8 hours later on each day, plus extra immediate-release CD-LD tablets, if needed. The reference products were the commercially-available CD-LD formulations, dosed according to each patient's optimized treatment. Patients diaries were collected at the last 3 days of each treatment arm.



Results

AP-CD/LD (mg)#	Study Type	N
50/375mg bid PK, PD	Multiple dose, multi center, open label, ***one week*** two-way crossover	ITT=12 **PP Efficacy=10** **PP PK= 8** DO= 1
50/375mg bid PD	Multiple dose, multi center, open label, ***three weeks*** two-way crossover	ITT= 17 **PP = 16** DO=1
50/500mg bid PD	Multiple dose, multi center, open label, ***three weeks*** two-way crossover	ITT = 22 **PP = 18** DO= 3

ITT – intent to treat, PP- per protocol, DO-drop out, # not including add-on dosing of IR-CD/LD, if needed

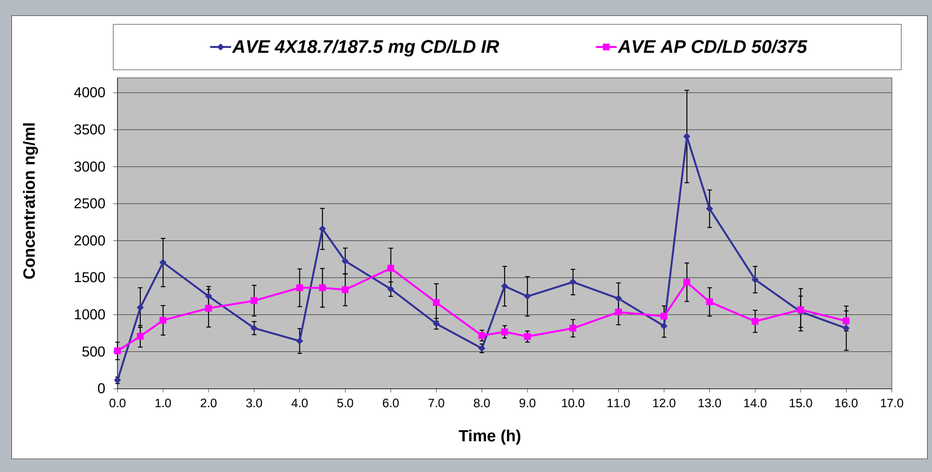
Study population

	Sex (males)	Age (range)	Duration of PD (range)	Hoehn & Yahr stage (range)	Average daily levodopa dose mg (range)
50/375mg PK	90%	68.8 (57-84)	10.6 (6-17)	2.6 (2-3)	815 (625-1000)
50/375mg PD	56.3%	66.8 (51-85)	9.3 (3-21)	2.4 (2-3)	779 (520-1200)
50/500mg	83.3%	66.3 (46-84)	12.4 (4-22)	2.5 (2-3)	781 (500-1000)

Results

Pharmacokinetics results

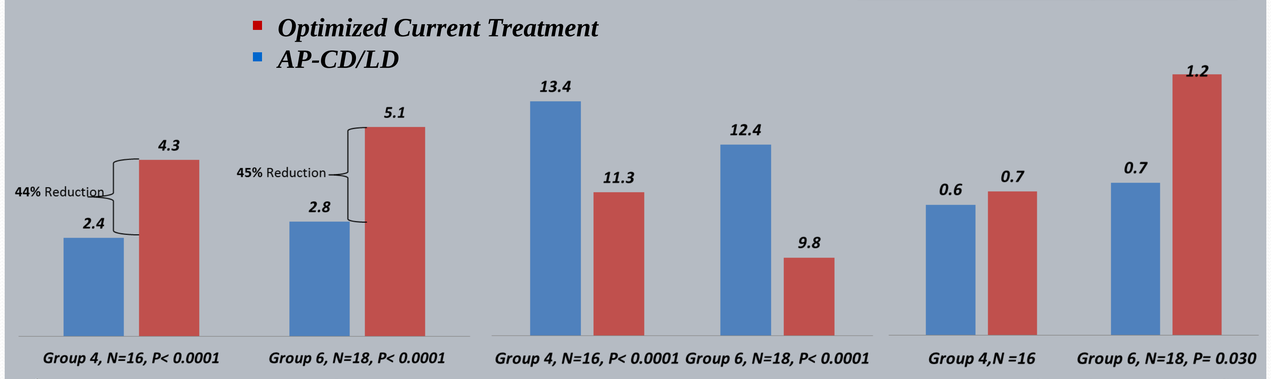
Mean Levodopa Plasma Concentrations



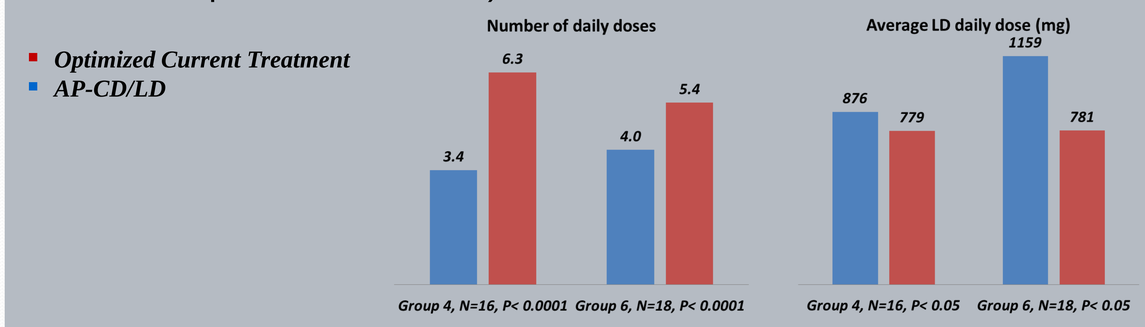
- ✓ AP CD-LD demonstrates a controlled-release PK profile, with significantly more stable LD levels. LD's absorption phase was increased by more than 6-fold.
- ✓ B.i.d. administration of AP CD-LD provided daily coverage of therapeutic LD plasma levels.
- ✓ Peak-to-trough fluctuations (mean C_{max} – mean C_{min}) with the AP CD-LD formulation were half of those with the reference product (p=0.0023).
- ✓ The LD morning plasma levels (pre-first dose) were significantly higher (p=0.0191) than those achieved with the immediate-release CD-LD (522ng/ml vs. 68ng/ml)
- ✓ LD's high bioavailability was preserved. Mean $AUC_{0\text{-}24hr}$, achieved with the AP CD-LD, was 95% of the mean $AUC_{0\text{-}24hr}$ achieved by immediate-release CD-LD.

Pharmacodynamics results

Mean Total OFF Time ***Total Good ON Time*** ***Total ON Time With Troublesome Dyskinesia***



- ✓ The decrease in OFF time was greater with increasing dose (-1.9 hours for 50/375 mg compared to -2.3 hours for 50/500 mg).
- ✓ Good ON time (ON time without dyskinesias" plus "ON time with non-troublesome dyskinesias) (+2.1 hours vs. +2.6 hours, respectively) also demonstrated an increased benefit with increasing dose. Thus, with increasing AP pill LD content, more ON time was achieved.
- ✓ Patients treated with AP-CD/LD 50/500 mg had significantly less ON time with dyskinesias than patients taking conventional treatment with LD + DDCI (0.7 hours compared to 1.2 hours)



- ✓ Despite a higher total daily levodopa dose in the AP-CD/LD groups compared to current treatment, the total ON time with troublesome dyskinesias was decreased.
- ✓ The average number of LD doses was significantly reduced.

Safety

- ✓ No related serious adverse events were reported.
- ✓ The most commonly observed adverse events were GI (nausea and vomiting) and nonspecific symptoms such as fatigue and somnolence. The severity of AE was mild and did not differ in consistent or major ways from the current treatment formulations.

Conclusions

The results indicate that AP CD-LD is well tolerated and provides clinically meaningful benefits in the treatment of PD with motor fluctuations.