Accordion Pill Can Ease Motor Fluctuations in People with Advanced Disease, Phase 2 Data Show

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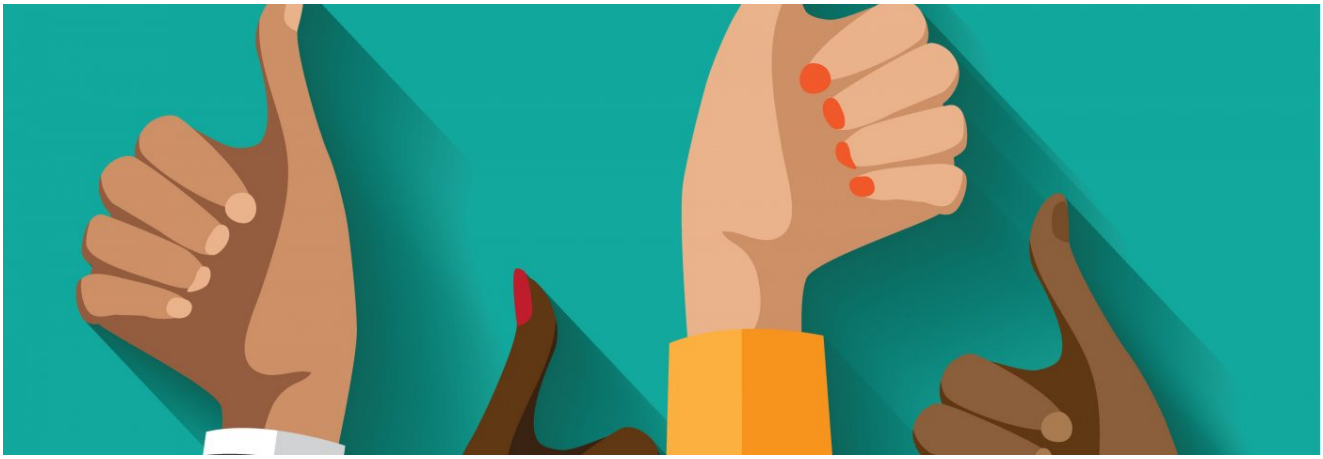

Oral treatment with Accordion Pill-Carbidopa/Levodopa (AP-CD/LD) lessened the variability of levodopa plasma levels and eased motor fluctuations in people with advanced Parkinson's, according to results of a Phase 2 trial.

The study, "Pharmacokinetics and efficacy of a novel formulation of carbidopa-levodopa (Accordion Pill®) in Parkinson's disease" appeared in the journal *Parkinsonism & Related Disorders.* These findings were also presented at the recent 2019 IAPRD World Congress, in Montreal.

Progressive depletion of dopamine levels in the brain results in the hallmark motor symptoms of Parkinson's. Levodopa is the standard treatment and normally given with carbidopa to ensure delivery to the brain and conversion to dopamine.

People with advanced disease often develop motor fluctuations, characterized by a return of symptoms between levodopa doses due to the drug's short-term effects. This is associated with levodopa's limited absorption in the upper part of the gastrointestinal tract.

Intec Pharma's AP-CD/LD aims to address this problem. The pill has a specific gastric retention and release system with carbidopa and levodopa, which enables release in both immediate and controlled-release modes. Controlled release enables a slow discharge into the stomach over eight to 12 hours, and potentially more steady absorption.

The multicenter, open-label Phase 2 study tested multiple doses of AP-CD/LD – 50/250 mg, 50/375 mg and 50/500 mg — twice per day in more than 60 patients. The treatment's pharmacokinetics (PK) — its absorption, distribution, and metabolism in the body, and its

excretion — and effectiveness were compared to Sinemet, an approved immediate-release (IR) combination (marketed by Merck) which contains 37.5 mg of carbidopa and 150 mg of levodopa.

Results of groups 1 to 4 — out of the six taking part in the trial — showed that all AP-CD/LD doses led to more stable plasma levels of levodopa than Sinemet, and significantly lessened levodopa's maximum concentration by 57.1% and 66.8% in patients with and without motor fluctuations.

The 50/375 and 50/500 doses significantly reduced motor fluctuations compared to the patients' current treatment. These doses lowered the mean daily off time — when patients experience tremors and dyskinesia, or involuntary movements — by up to 45% compared to Sinemet.

In turn, the total duration of on time (without dyskinesia) and good on time — without dyskinesia or with non-troublesome dyskinesia — were greater with these AP-CD/LD doses than with Sinemet, as were the proportions of total or good on time during waking hours. Overall, both the duration of off periods and/or on time with troublesome dyskinesia were significantly reduced with both AP-CD/LD doses.

The findings further showed that both these AP/CD-LD doses significantly improved patient and investigator ratings on the Global Clinical Impression scale of Parkinson's severity.

Treatment-emergent adverse events associated with AP-CD/LD use were in line with the known safety profile of CD/LD formulations. No new safety issues were found throughout the trial.

"AP technology demonstrated effective controlled-release PK performance and reduced motor response fluctuations in advanced [Parkinson's] patients," the scientists wrote.

"Importantly, the substantially improved ON time for the AP versus IR [Sinemet] was attained without an emergence of troublesome dyskinesia," they added.

Intec Pharma is conducting a Phase 3 study in the U.S., Europe and Israel called ACCORDANCE (NCT02605434) that will compare the safety and efficacy of AP-CD/LD and Sinemet in 462 adults with advanced Parkinson's. Two different AP-CD/LD doses are being tested — 50 mg of carbidopa with 400 or 500 mg of levodopa, two or three times a day.

As these doses generally match those used in the Phase 2 study, the investigators expect "similar stable LD and CD plasma levels within the therapeutic range necessary for [Parkinson's} symptom control." Topline results are reported as likely to be released this summer.