

CLE-600: Treating nocturnal and early morning OFF symptomology in Parkinson's disease with the OLAR® platform

Berkovich, E., Fisher, R., Kagan, E., and Yahav, M., Clexio Biosciences LTD., Petach-Tikva, Israel

Background

Levodopa Parkinson's disease (PD) treatment is limited by its short duration of effect and fluctuations in plasma concentrations. Early wearing off during nighttime results in often troublesome nocturnal symptoms and early morning OFF (EMO), particularly in patients with the onset of motor fluctuations. Given its ideal pharmacokinetic profile for nighttime administration in PD patients, CLE-600 is being developed as a night pill for the treatment of PD nocturnal symptoms and EMO using a proprietary Oral Long Acting Release (OLAR®) drug delivery platform (see <https://www.clexio.com/forpeople/#pipeline>). CLE-600 is designed to gradually achieve stable and prolonged levels of Levodopa (LD) above night therapeutic levels for 8-10hr, to enable Parkinson patient's symptomatic control during the night and into the early morning. To test this hypothesis, Clexio has conducted a Ph1 study in healthy volunteers with CLE-600.

Study objectives

- To demonstrate safety, as reported by study subjects, and by clinical and laboratory assessments.
- To evaluate relationship of anatomical location assessed by X ray and the drug delivery system state on the PK profile.
- To evaluate the relative bioavailability of Levodopa/Carbidopa CLE-600 (Test) to the commercially available Sinemet® IR 100/25 mg Tabs (Reference).

Methods

18 healthy volunteers received Sinemet® 100/25 mg (LD/CD) tablet serving as the reference group for CLE-600. After a washout period of at least 48 hours, the subjects were administered CLE-600. Blood samples were collected at different time points between pre-dose and 24 hours post administration and assayed for plasma levodopa concentration. Subjects were also examined by fluoroscopy for the detection and location of the OLAR®.

Results

Following CLE-600 administration, radiographic examination revealed that the OLAR® was fully open in the stomach within 10 minutes of administration and still present in the stomach at least 8 hours later in all subjects (Figure 1). Following slow onset of release and absorption, resulting in a lag time of approximately 2hr, stable LD plasma levels were detected for more than 8hr. Analysis of the results showed that CLE-600 had a relative bioavailability of more than 70% compared to Sinemet®, together with a 75% relative reduction in Cmax and Tmax is prolonged from 0.7hr for Sinemet® to >4hr for CLE-600 (Figure 2).

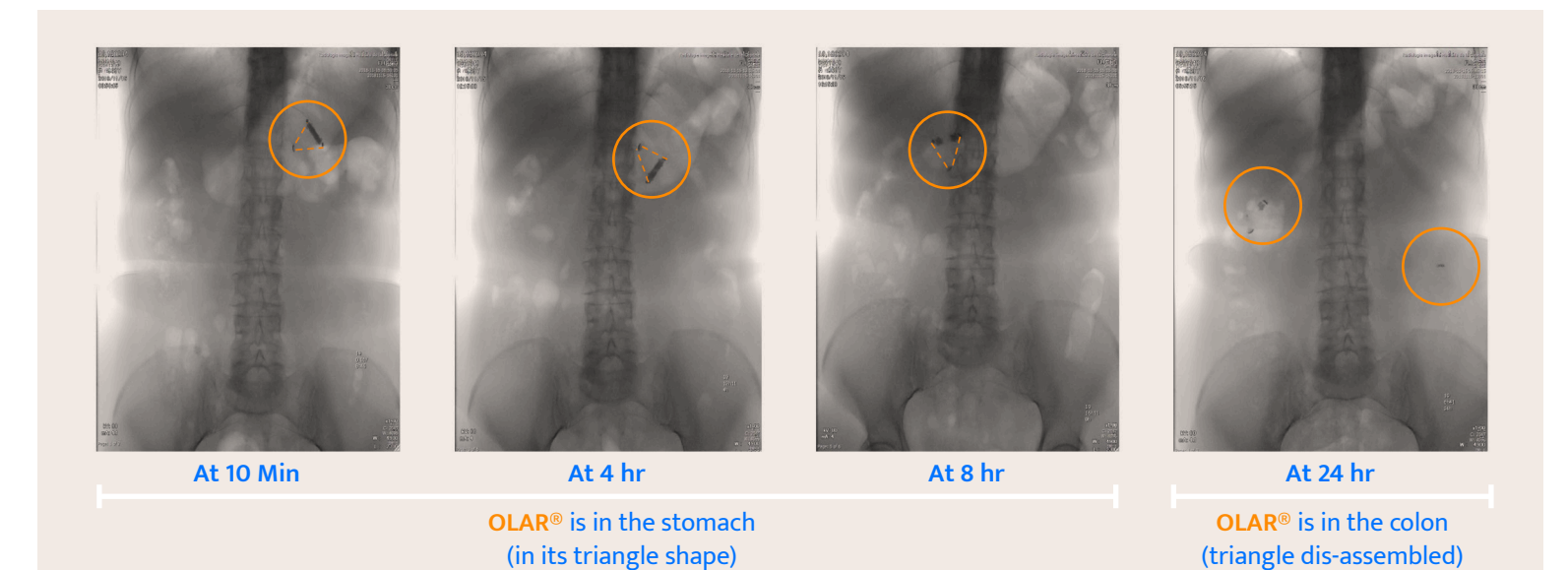


Figure 1 Gastric Retention by CLE-600: X-Ray example from the Phase 1 PK study demonstrates CLE-600 in an open, gastroretentive triangle shape 10 min after swallowing (left panel). The open gastroretentive triangle shape was still visible at 4 and 8hr after dosing (middle panels). At 24hr, CLE-600 disassembled parts are detected by x-ray in the colon (right panel).

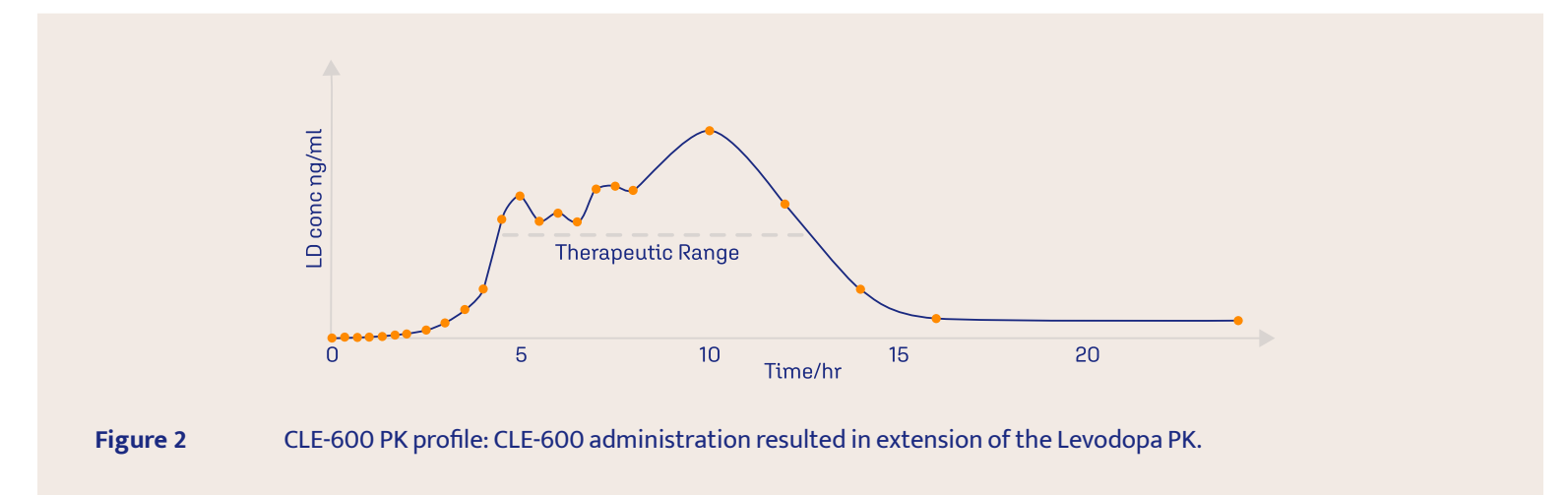


Figure 2 CLE-600 PK profile: CLE-600 administration resulted in extension of the Levodopa PK.

Oral Long Acting Release (OLAR®) technology

OLAR® is a novel platform designed for continuous drug delivery to the GI tract.

- Orally administered, non-invasive.
- Targeting more efficient drug absorption and lower drug plasma fluctuations. Continuous drug release for 8 – 24 hours, under fast and fed conditions.
- Versatile platform, suitable for multiple APIs and enabling high drug loading.

OLAR® innovative pillars

- Size:** swallowable, but not passing pylorus
- Strength:** withstands gastric forces
- Timer disassembly:** based on inner tablet dissolution

Made only of pharmaceutical excipients

The OLAR® mechanism



Folded configuration – Enables swallowing

A platform designed to be swallowed in a folded configuration, in a capsule.

Unfolded configuration – Controls gastric retention

After swallowing, platform unfolds to a triangle, with a size bigger than average pylorus. It is then retained in the stomach while releasing inner formulation (multiple tablets).

Disassembled configuration – Allowing gastric exit

After formulation dissolution/ erosion, the platform disassembles to parts smaller than the pyloric size, thus emptied from the stomach and soften/degrade in intestine.

Safety

Overall, the administration of single-dose CLE-600 was safe and well tolerated in healthy subjects. There were no notable safety concerns related to the number and subject incidence of the TEAEs as well as clinical laboratory test results, vital signs, and ECG assessments in this study.

Conclusion

The ability to treat PD night symptomology and early morning OFF, is a high unmet need in Parkinson's disease and among the main reasons for low Quality of Life (QoL) reported by PD patients. CLE-600 is being developed as the first oral solution dedicated for PD nocturnal problems and morning akinesia. Following an extended lag time, a prolonged LD PK profile correlating with gastric retention of CLE-600 was demonstrated while no significant AEs were reported. In PD patients, CLE-600 is intended to provide sufficient circulating plasma levodopa to address nocturnal symptomology and to avoid early morning OFF, whilst not interfering with the patient's regular daytime levodopa therapy. CLE-600 results warrant further development and testing in Parkinson's patients experiencing nocturnal symptoms and early morning OFF.