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 nighttime pill for treatment of PD nocturnal symptoms and EMO using a proprietary Oral Long Acting Release (OLAR®) drug delivery platform (see [https://www.clexio.com/products/3/1] pipeline). CLE-600 is designed to gradually achieve stable and prolonged levels of Levodopa (LD) above night therapeutic levels for 8-10 hr, 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 2 hr, stable LD plasma levels were detected for more than 8 hr. 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 0.7 hr for Sinemet® to >4 hr for CLE-600 (Figure 2).

Conclusion
The ability to treat PD nighttime 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.

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

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 hr and 8 hr 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.