BouNDless: An active-controlled randomized, double-blind double-dummy trial of continuous levodopa/carbidopa delivery (ND0612) in patients with Parkinson's disease experiencing motor fluctuations

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Background

- The management of motor fluctuations remains a priority for patients with Parkinson's disease (PD). Infusion therapies have become progressively established as an effective pharmacological strategy to manage uncontrolled motor fluctuations.[1] Current levodopa/carbidopa infusion systems have to be surgically routed to the duodenum and are associated with serious complications[2] that can impact clinical utility.
- Subcutaneous infusion of levodopa carbidopa may provide a well-tolerated and convenient route of continuous levodopa delivery. However, poor levodopa solubility has, until now, precluded this approach.
- ND0612 is an investigational drug-device combination that has been designed to continuously deliver liquid levodopa/carbidopa (60/7.5 mg/mL) by subcutaneous infusion.
- Two previous pharmacokinetic studies in PD patients with motor fluctuations have shown that ND0612 maintains steady, therapeutic levodopa plasma concentrations.[3, 4] A small Phase II efficacy study (n=38) showed infusion of ND0612 significantly reduced daily OFF time and morning akinesia while increasing ON time without moderate or severe dyskinesia compared to baseline.[5]

Objective

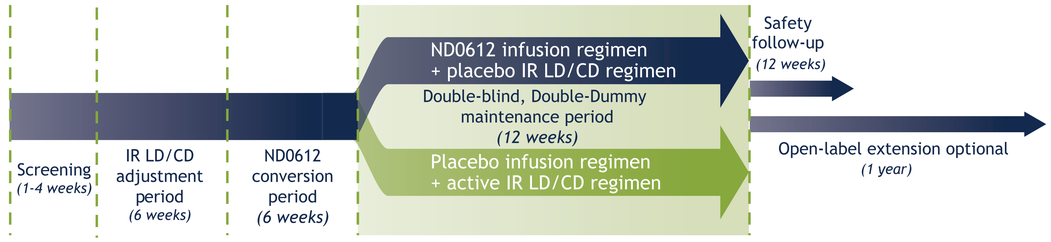
The aim of this phase III study (NCT04006210) is to determine the efficacy, safety, and tolerability of continuous subcutaneous ND0612 infusion in comparison to oral immediate-release levodopa/carbidopa (IR LD/CD) in patients with PD patients experiencing motor fluctuations.

Conclusions

- BouNDless is the first phase III randomized, active-controlled trial designed to assess the efficacy and safety of treatment with continuous subcutaneous ND0612 in comparison to oral immediate-release LD/CD in patients with PD experiencing motor complications.
- Another ongoing study (NCT02726386) is examining the long-term safety of ND0612 in a similar population of PD patients with motor fluctuations, with some patients in their 4th year of treatment.

Methods

Study design: A multicenter, randomized, active-controlled, double-blind, double-dummy, parallel group clinical trial



Inclusion/exclusion criteria

Key inclusion criteria	Key exclusion criteria
Male and female patients, aged ≥30 years	Atypical or secondary parkinsonism.
PD diagnosis consistent with the UK Brain Bank Criteria[6]	Severe disabling dyskinesias
Modified Hoehn & Yahr score ≤3 during ON	Previous neurosurgery for PD
Average of ≥2.5 hours of OFF time (≥2 hours OFF each day during waking hours as confirmed by patient diary over 3 days)	Use of duodenal levodopa infusion (LCIG)*
Taking ≥4 levodopa doses/day (≥3 doses/day of Rytary) at a total daily dose of ≥400mg	Use of rescue medication (subcutaneous apomorphine injections, sublingual apomorphine, or inhaled levodopa) within prior 4 weeks
	Previous participation in ND0612 studies
	History of significant skin conditions or disorders

** Patients who have discontinued LCIG treatment at least 6 months before enrollment and have undergone stoma closure surgery at least 6 months before enrollment, may be included in this study.*

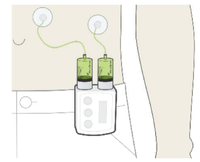
Endpoints

Efficacy	Safety and tolerability
PRIMARY: Daily ON time without troublesome dyskinesia (sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia)[7]	AEs reporting
OFF time	Infusion site reaction
MDS-UPDRS Part II[8]* (Motor Aspects of Experiences of Daily Living)	Rates of premature discontinuation due to AEs
Patient Global Impression of Change (PGIC)	
Clinical Global Impression of Improvement (CGI-I)*	
MDS-UPDRS Part III (motor score) during OFF*	
PD Quality of Life questionnaire (PDQ-39)	
Parkinson's disease sleep scale (PDSS)	
Proportion of responders (OFF time)	

**Clinical assessments are by blinded-rater.*

Study medication

- In the IR LD/CD regimen adjustment period, patients' current oral levodopa formulations (including COMT inhibitors) are converted to supplied IR LD/CD followed by dose adjustment to minimize motor complications.
- In the ND0612 regimen conversion period, all patients are converted to ND0612 and supplemental oral IR LD/CD, if necessary.
  - ND0612 is administered (2 infusion sites) over 24 hours to a total LD/CD dose of 720/90 mg/day.



  - Immediate release LD/CD and its placebo counterparts are overencapsulated for an identical appearance.
- During the double-blind maintenance period (DBMP), patients receive either the ND0612 and placebo IR LD/CD regimen, or the placebo infusion and active IR LD/CD regimen. ND0612 and placebo infusion are supplied in identical vials and packaging, and are similar in color and appearance, thereby enabling double-blind conditions.
- Changes to other antiparkinsonian medications are not permitted during all periods of the study.
- At the end of the double blind maintenance period, all patients entering the optional open-label extension receive active ND0612 for a further 12 months. The treatment allocation is randomized and blinded.

References

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Disclosures

O. Rascol is an investigator in the BouNDless study.

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