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BouNDless: An active-controlled randomized, double-blind double-dummy study of continuous ND0612 infusion in patients with fluctuating Parkinson's disease

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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 the most effective pharmacological strategies to manage motor complications in advanced patients.[1] Current levodopa infusion systems have to be surgically routed to the duodenum and are associated with potentially serious complications[2] that can impact clinical utility.
- Subcutaneous infusion of levodopa has the potential to provide a better tolerated and more 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 demonstrated that ND0612 maintains steady, therapeutic levodopa plasma concentrations,[3, 4] and a small Phase II efficacy study (n=38) showed that infusion of ND0612 significantly reduced daily OFF time and morning akinesia while increasing 'good ON' time compared to baseline.[5]

Objective

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

Methods

- BouNDless is a multicenter, randomized, active-controlled, double-blind, double-dummy, parallel group clinical trial.

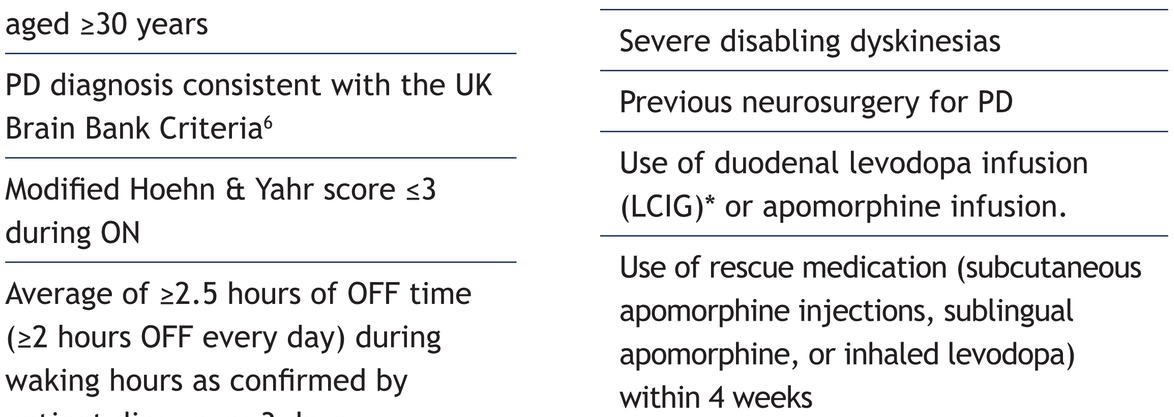
Inclusion/exclusion criteria

Key inclusion criteria
Male and female patients, aged ≥30 years
PD diagnosis consistent with the UK Brain Bank Criteria[6]
Modified Hoehn & Yahr score ≤3 during ON
Average of ≥2.5 hours of OFF time (≥2 hours OFF every day) during waking hours as confirmed by patient diary over 3 days
Taking ≥4 levodopa doses/day (≥3 doses/day of Rytary) at a total daily dose of ≥400mg

Key exclusion criteria
Atypical or secondary parkinsonism.
Severe disabling dyskinesias
Previous neurosurgery for PD
Use of duodenal levodopa infusion (LCIG)* or apomorphine infusion.
Use of rescue medication (subcutaneous apomorphine injections, sublingual apomorphine, or inhaled levodopa) within 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.*

Study Design



Study medication

- In the IR LD/CD Regimen Optimization 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 Optimization Period, all patients are converted to ND0612 and doses of oral IR LD/CD, if necessary, adjusted to minimize motor complications.
  - ND0612 is administered using a pump system (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 phase, 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 the study.
- All patients entering the optional open-label extension receive active ND0612 for a further 12 months. The switch of patients receiving placebo infusion to active ND0612 treatment is performed via interactive web response system (IWRS) kit allocation to avoid unblinding of the main part of the study.

Endpoints

- Efficacy is assessed as the change from Baseline to the end of the of the double-blind assessment period.
- Clinical assessments are assessed by a blinded rater.

Efficacy
Daily ON time without troublesome dyskinesia (sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia) per patient diary[7]
OFF time per patient diary
MDS-UPDRS Part II[8]* (Motor Aspects of Experiences of Daily Living)
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)

Safety and tolerability
AEs reporting
Local skin safety at infusion site
Rates of premature discontinuation
Study treatment compliance

**Clinical assessments are by blinded-rater.*

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 fluctuations.

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Disclosures

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