Safety and efficacy of continuous subcutaneous levodopa–carbidopa infusion (ND0612) for Parkinson's disease with motor fluctuations (BouNDless): a phase 3, randomised, double-blind, double-dummy, multicentre trial

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Correction:

Errata

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Summary

Background

Conventional oral levodopa therapy for the treatment of Parkinson's disease can be associated with variations in plasma concentrations. Levodopa infusion strategies might provide more consistent drug delivery and fewer motor fluctuations. We aimed to assess the safety and efficacy of a continuous 24 h/day subcutaneous infusion of ND0612 (a levodopa–carbidopa solution) compared with oral immediate-release levodopa–carbidopa for the treatment of motor fluctuations in people with Parkinson's disease.

Methods

We conducted a phase 3, randomised, double-blind, double-dummy, active-controlled, multicentre trial at 117 academic and community neurology sites in 16 countries, including in Europe, Israel, and the USA. Eligible participants were men and women aged 30 years or older with a diagnosis of Parkinson's disease (Hoehn and Yahr stage ≤3 in the on state) who experienced at least 2·5 h/day of off time. Participants underwent an open-label run-in phase (<12 weeks), during which time optimal regimens were established for both oral immediate-release levodopa–carbidopa and for 24 h/day subcutaneous ND0612 infusion (levodopa–carbidopa 60·0/7·5 mg/mL), with supplemental oral levodopa–carbidopa if needed. Participants were then randomly assigned (1:1) to 12 weeks of double-blind treatment with their optimised regimen of either subcutaneous ND0612 or oral levodopa–carbidopa, with matching oral or subcutaneous placebo given as required to maintain blinding. Randomisation was done via an interactive web response system, stratified by region, using a permuted block schedule. Participants, study partners, treating investigators, study site personnel, and the sponsor were masked to treatment group allocation. The primary efficacy endpoint was the change from baseline (ie, time of randomisation, when all patients were receiving an optimised open-label ND0612 regimen) to end of the double-blind phase in total daily on time without troublesome dyskinesia, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, NCT04006210, and is complete.

Findings

Between Sept 30, 2019, and April 8, 2022, 381 participants were enrolled, of whom 259 (68%) were randomly assigned, 128 (49%) to subcutaneous ND0612 and 131 (51%) to oral levodopa–carbidopa. 243 (94%) participants completed the study. Treatment with subcutaneous ND0612 provided an additional 1·72 h (95% CI 1·08 to 2·36) of on time without troublesome dyskinesia compared with oral levodopa–carbidopa (change from baseline of −0·48 h [−0·94 to −0·02] with subcutaneous ND0612 *vs* −2·20 h [−2·65 to −1·74] with oral levodopa–carbidopa; p<0·0001). Significant treatment differences favouring subcutaneous ND0612 were also found in the first four of nine prespecified hierarchical outcomes of daily off time (−1·40 h [95% CI −1·99 to −0·80]), Movement Disorders Society-Unified Parkinson's Disease Rating Scale part II scores (−3·05 [−4·28 to −1·81]), Patients Global Impression of Change (odds ratio [OR] 5·31 [2·67 to 10·58]), and Clinical Global Impression of Improvement (OR 7·23 [3·57 to 14·64]). Hierarchical testing ended after the fourth secondary endpoint. Adverse events were reported by 287 (89%) of 322 participants during open-label ND0612 optimisation, and by 103 (80%) of 128 in the ND0612 group and 97 (74%) of 131 in the oral levodopa–carbidopa group during the double-blind phase. The most common adverse events were infusion-site reactions (266 [83%] participants during open-label ND0612, and 73 [57%] in the ND0612 group *vs* 56 [43%] in the oral levodopa–carbidopa group during the double-blind phase), most of which were mild. Serious adverse events in four participants in the ND0612 group were related to study treatment (infusion-site cellulitis [n=2], infusion-site abscess and infusion-site ulcer [n=1]; and paraesthesia and peripheral sensorimotor neuropathy [n=1]). One participant in the ND0612 group died during the double-blind phase, but the death was not related to study treatment (fall leading to traumatic brain injury).

Interpretation

Results of this phase 3 study showed that subcutaneous ND0612 used in combination with oral immediate-release levodopa–carbidopa increased on time without troublesome dyskinesia and reduced off time, with a favourable benefit–risk profile. ND0612 might offer a safe and efficacious subcutaneous levodopa infusion approach to managing motor fluctuations in people with Parkinson's disease. The ongoing open-label extension phase will provide further information on the long-term efficacy and safety of treatment.

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