Efficacy of ND0612 for nocturnal problems and early morning OFF: A blinded rater study of 2 dosing regimens

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Introduction

- Nocturnal symptoms and early morning OFF (EMO) periods are significant contributors to poor quality of life in patients with Parkinson’s disease (PD) experiencing motor fluctuations.1,2 Patients suffer a variety of problems including difficulty turning in bed, restless legs and sleep fragmentation, as well as early morning akinesia, dystonia, and tremor.2

- ND0612 is a drug-device combination that continuously delivers liquid levodopa/carbidopa (60/7.5 mg/ml) by subcutaneous infusion through a non-surgical mini-pump system to reduce motor complications in PD. Phase 1 & 2 trials have demonstrated that ND0612 maintained steady, therapeutic levodopa plasma concentrations that were associated with reduced OFF time.3

- We have previously reported the primary efficacy results from this Phase-2 study (NCT02577523) which showed that continuous delivery of ND0612 reduced total daily OFF time.4 In this analysis of secondary outcomes, we focus on the benefits of treatment on nocturnal symptoms and EMO periods.

Methods

- This was a 28-day randomized, parallel-group, open label, blinded-rater study.
- Outcomes of interest include Change from baseline to endpoint in:
  - Percent of subjects with full ON at 8 & 9 AM (Key secondary endpoint)
  - Overnight sleep quality, as assessed using PDSS-2
  - Subjective patient assessment of sleep quality (5 point scale)
  - Early morning (8 AM) UPDRS motor score (post-hoc analysis)

Study design

Male and female (10 – 80 years) patients with a diagnosis of PD and a Hoehn & Yahr stage ≤2 (during ON) were eligible for the study. Patients had to be taking ≤4 levodopa doses per day (≥3 doses/day of VX-085), have ≥2.5 hours of OFF time per day including predictable and well defined EMO periods, and be a ‘good’ early morning response to levodopa. A total of 38 subjects were randomized (1:1, n=19 in both groups) to 2 dosing regimens of ND0612: R1 (24 hour infusion with ND0612, total LD/CD dose of 720/90 mg) or R2 (24-hour ‘waking day’ infusion with ND0612, total LD/CD dose of 538/68 mg + a morning one LD/CD 350/15 mg). Supplemental oral LD/CD was used as needed.

Results

The proportion of subjects with full ON increased at 8AM and 9AM with 24 hour dosing (R1)

- Baseline
- Day 28

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<thead>
<tr>
<th>Time</th>
<th>Percent of Subjects with Full ON at 8 &amp; 9 AM</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>11%</td>
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<tr>
<td>Day 28</td>
<td>50%</td>
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Change from baseline data are mean [95% CI]. Waking day infusion (R2) had no significant effect on nocturnal sleep quality.

Early morning (8 AM) UPDRS motor scores significantly improved in both groups

- Baseline
- Day 28

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean (SD) UPDRS Motor Score at 8 AM</th>
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<tr>
<td>Baseline</td>
<td>37.4 (34.3)</td>
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<tr>
<td>Day 28</td>
<td>20.3 (26.7)</td>
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Males were analyzed, 24 hour, ‘round-the-clock’ levodopa infusion with ND0612 significantly increased morning ON-time with a relevant improvement in motor status.

Sleep quality also improved, indicating that patients tolerated the pump overnight.

In this study, R2 (waking day dosing) was not optimized for nighttime and early morning use because it provided a relatively low daily levodopa dose and daily treatment initiation was delayed until a nurse started the pump. A longer daytime regimen of 16 hours (LD/CD 720/90 mg) starting immediately upon waking is under evaluation.

ND0612 may provide a novel non-surgical option for continuous 24-hour levodopa delivery in patients with PD experiencing motor fluctuations, in particular nocturnal symptoms and early morning OFF.

Conclusions

References


Disclosures

Alberto Espay and Aaron Ellenbogen were investigators in the 200x study and they or their institutions have received payment for participation. Chiries LLC (K. Kieburtz and C. W. Olanow) provided consultancy for this study. S. Oren and R. Case are employed by NeuroDerm. No author has received financial remuneration for the preparation of this report. Assistance for the poster was provided by A. White and A. Patel (funded by NeuroDerm).