Long term safety of levodopa/carbidopa infusion with ND0612: Results from a phase 2b, international, open-label study

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Background: ND0612 is in development as the first drug-device combination delivering liquid levodopa/carbidopa via continuous subcutaneous (SC) infusion to reduce motor fluctuations in patients with PD. The primary objective of this long-term study was to evaluate the safety and tolerability of a 24-hour regimen and a 16-hour 'waking day' regimen of ND0612.

Methods: This open-label safety study (NCT02726386) was conducted in PD patients (aged >30 years, Hoehn & Yahr Stage ≤3 during ON) taking ≥4 levodopa doses/day and ≥1 other PD medication and experiencing ≥2 hours of OFF time/day with predictable early-morning OFF periods. Patients were assigned to receive ND0612 for a regimen of either 16-hours/day or 24-hours/day. Safety and tolerability were assessed through treatment-emergent adverse event (TEAE) reporting.

Results: 214 patients were enrolled (24-hour regimen: n=90; 16-hour regimen: n=124) at 46 sites in 8 countries. Overall, 66.4% of patients were male and the mean ±SD age was 64.0 ±8.9 years. Over the course of the one-year treatment period, 86% of patients had ≥1 TEAE, 66% experienced treatment-related TEAE's and 5.6% experienced serious treatment-related TEAE's. Systemic safety is typical for PD patients treated with levodopa/carbidopa. The most frequent AEs were typical for a continuous subcutaneous mode of drug administration and included infusion-site nodules (30.8%), infusion-site hematoma (25.2%), and infusion-site pain (13.1%). Overall, 17.8% patients discontinued due to AEs.

Conclusions: ND0612 infusion was found to be safe with generally mild to moderate local AEs which were reversible and manageable and no unexpected TEAEs for systemic levodopa treatment. Long-term data will continue to be collected in patients enrolled in the study extension, some of whom are now in their fourth year of ND0612 treatment.

Objective

- ND0612 is a minimally-invasive, continuous, subcutaneous (SC) delivery system of levodopa/carbidopa that provides plasma levodopa levels with less variability than oral levodopa. Phase II clinical studies of ND0612 in PD patients with motor fluctuations have shown a significant, clinically meaningful reduction in OFF time with an increase in ON time with no or mild dyskinesia.[1,2]
- This phase 2b, international, open-label study assessed the long-term safety (systemic and local) and tolerability of continuous infusion with ND0612. Here we present 1 year data.
- Two regimens (both providing a total levodopa/carbidopa daily dose of 720/90mg) were tested:
  1. 24 hours 'round the clock' infusion.
  2. 16 hours 'waking day' infusion with a morning dose of oral levodopa.

Conclusions

- ND0612 infusion was generally safe and well-tolerated
  - Total exposure (including study extension) is >250 patient years
  - No unanticipated systemic TEAEs for levodopa/carbidopa in this PD population
  - Mild to moderate infusion site reactions were common, and were typical for a continuous subcutaneous mode of drug administration
- Long-term data will continue to be collected in patients enrolled in the study extension, some of whom are now in their 4th year of treatment
- A phase 3 double-blind, double-dummy pivotal efficacy trial (BouNDless) is currently being initiated to evaluate efficacy, safety and tolerability of ND0612 in a similar PD population

Results

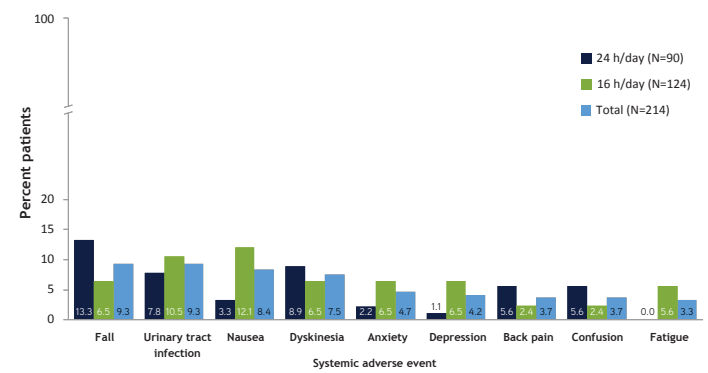
Baseline characteristics

Characteristic		(N=214)
Sex (male/female); n (%)		142 (66.4%)/72 (33.6%)
Age (years); mean ±SD		64.0 ± 8.9
Time from diagnosis (years); mean ± SD		9.0 ± 4.7
Duration of motor fluctuations (years); mean ±SD		5.3 ± 4.2
OFF time (hours per day); mean ±SD		5.5 ± 3.0
Levodopa dose (mg)	Mean ±SD	1040 ± 577 mg
	Median [range]	900 mg

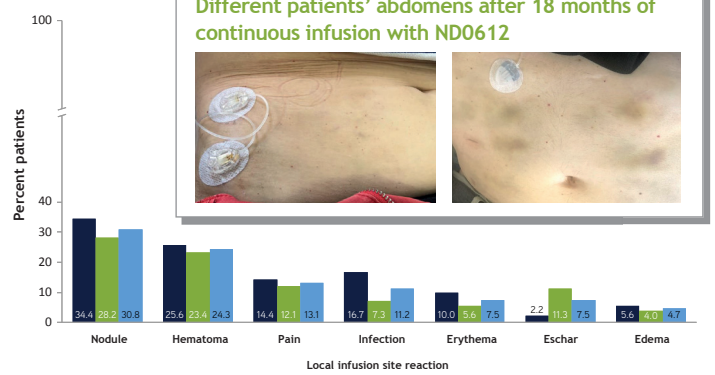
Levodopa/carbidopa infusion with ND0612 was overall well-tolerated over 1 year

	24h/Day (N=90)	16h/Day (N=124)	Total (N=214)
Any TEAEs; n (%)	9 (10.0%)	3 (0.04%)	12 (5.6%)
Local TEAEs; n (%)	58 (64.4%)	66 (53.2%)	124 (57.9%)
Drug-related TEAEs	65 (72.2%)	78 (62.9%)	143 (66.8%)
Serious TEAEs	17 (18.9%)	14 (11.3%)	31 (14.5%)
Drug-related SAEs	9 (10.0%)	3 (2.4%)	12 (5.6%)
TEAEs Leading to Death	0	1 (0.8%)	1 (0.5%)

Systemic safety over 1 year

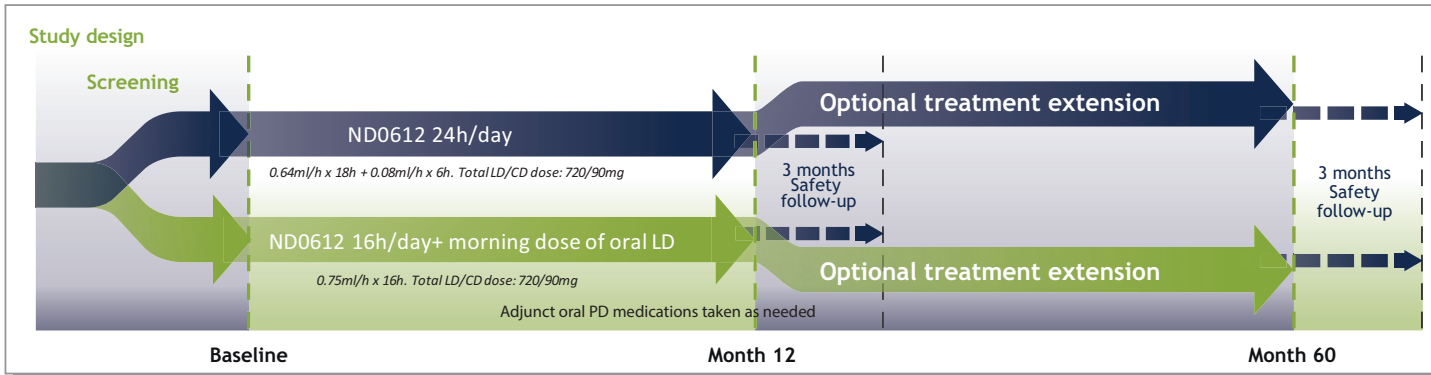


Mild to moderate infusion site reactions were typical for a continuous subcutaneous mode of drug administration[3] and were generally manageable and reversible



Different patients' abdomens after 18 months of continuous infusion with ND0612

Study design



References

1. Giladi et al. Mov Disord. 2017; 32 (suppl 2).
2. Olanow et al. Late-breaking poster at MDS, 2017.
3. Bhidayasiri et al. Parkinsonism Relat Disord 2016;33 Suppl 1:S42-S48.

Disclosures

S. Isaacson, W. Poewe and T. Simuni were investigators in the 012 BeyoND Study. Clintrex LLC (C. W. Olanow) provided consultancy. S. Oren, and R. Case are employed by NeuroDerm. No author has received financial remuneration for the preparation of this report. Assistance for this poster was provided by A. White and A. Patel (funded by NeuroDerm).