Pharmacokinetics and safety of ND0612L (levodopa/carbidopa for subcutaneous infusion): Results from a phase II study in moderate to severe Parkinson's disease

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Introduction

Levodopa remains unchallenged as the most effective symptomatic therapy for people with Parkinson's disease (PD). Unfortunately however, long-term management with conventional oral levodopa is associated with the development of motor complications (motor fluctuations and dyskinesia) in the majority of patients.[1] In patients with advanced dopamine neurodegeneration, the 'fluctuating' response to levodopa mirrors the 'pulsatile' nature of levodopa pharmacokinetic delivery to the brain.[2, 3] In these patients, the efficacy of continuous levodopa infusions in reducing motor complications is well established.[4] However, poor levodopa solubility has previously prevented development as a subcutaneously deliverable liquid formulation, and as a result currently available delivery systems have to be surgically implanted to permit direct infusion into the jejunum.

ND0612L is a proprietary liquid formulation of levodopa/carbidopa (LD/CD 60/14 mg/ml), currently delivered by a belt pump system, which enables for the first time subcutaneous administration of LD/CD to achieve steady levodopa plasma levels. The aim of this study was to characterize the pharmacokinetic and clinical profile of ND0612L in PD patients with motor fluctuations.

Methods

Patients

- Key inclusion criteria:
  - Male or female patients with idiopathic PD, experiencing motor fluctuations averaging >2 waking hours OFF time per day, on optimized levodopa doses (≥3 doses per day), stable for ≥14 days prior to baseline.
  - Additional anti-PD medications were allowed if they had been taken in stable doses for ≥30 days prior to baseline.
- Key exclusion criteria:
  - Treatment with controlled release levodopa formulations, previous neurosurgical intervention for PD and/or presence of severe disabling dyskinesia.

Study design

- This was a Phase II randomized, placebo-controlled, double-blind, two-period study (Figure 1).
- During Period-1 all patients received their standard of care treatment (dose reductions permitted), and were randomized (2:1) to adjunct ND0612L or placebo.
- During Period-2, 16 patients were offered open-label ND0612L and were randomized (1:1) to receive ND0612L monotherapy or ND0612L plus oral entacapone (*i.e.* without their standard of care).

ND0612L (LD/CD 60/14 mg/mL)

- 0.08 ml/h during 8 hours (low night rate 18:00 through 2:00)
- 0.24 ml/h during the next 16 hours (high day rate, 2:00-18:00)
- Total daily volume: 4.5 cc
- Total LD daily dose: 270 mg
- Total CD daily dose: 63 mg

Figure 1: Study design

Assessments

- Blood samples for pharmacokinetic analysis of LD/CD/3-OMT were collected 2hr and 1hr prior to first morning oral levodopa dose, at 0hr, 0.5hr, 1hr, 1.5hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr, 9hr and 10hr post levodopa morning dose.
- Safety was assessed through the recording of adverse events (including dyskinesia and psychiatric adverse events), vital signs and standard laboratory measures.
- Additionally, exploratory efficacy end points were assessed including:
  - Daily duration of OFF and ON time with/without troublesome dyskinesia assessed via patient home diaries[5]
  - Quality of sleep, as assessed using the Parkinson's Disease Sleep Scale (PDSS)[6]
  - Quality of life, as assessed using the Parkinson's Disease Questionnaire (PDQ-39)[7]
  - Unified Parkinson's Disease Rating Scale (UPDRS) scores[8]
  - Investigators Global Impression of Change (CGI-C).[9]
- Among the exploratory efficacy end points, the pre-specified primary efficacy endpoint was the change in total OFF time from Baseline to Visit 3 (one week from dosing start) and 4.1 (two weeks from dosing start) according to home diaries during 3 days immediately prior to each of the visits. This was analyzed using a futility analysis with a predefined margin of 1.6 hours improvement in OFF time.

Results

- 30 moderate PD patients were randomized and completed the study.
- All patients were compliant with treatment protocol and were able to fill the pump reservoir with the liquid drug, attach and operate the pump daily; a caregiver and/or a nurse assisted some patients.
- Baseline characteristics for the 30 patients are given in Table 1.

Table 1: Baseline characteristics

	ND0612L N=19	Placebo N=11
Age (years)	63.8 ± 7.4	64.5 ± 6.9
PD duration (years)	8.6 ± 4.5	8.7 ± 3.8
Duration of LD therapy (years)	7.1 ± 4.2	7.5 ± 3.3
Duration of fluctuations (years)	5.7 ± 4.2	5.5 ± 2.9
Duration of dyskinesias (years)	2.9 ± 2.0	3.4 ± 1.8
Total daily LD dose (mg)	659.9 ± 428.2	743.2 ± 355.0
Daily home OFF time (hrs)	5.85 ± 2.83	5.67 ± 2.73
Daily in-clinic OFF time (hrs)	5.92 ±2.14	4.64 ± 2.89
Daily home ON time with troublesome dyskinesia (hrs)	0.92 ± 1.60	1.23 ± 2.37
Daily in-clinic ON time with troublesome dyskinesia (hrs)	0.67 ± 1.45	0.14 ± 0.45
Quality of sleep (PDSS sleep score)	56.8 ± 39.2	55.5 ± 34.2
Quality of life (PDQ-39 score)	38.6 ± 13.9	37.4 ± 12.1

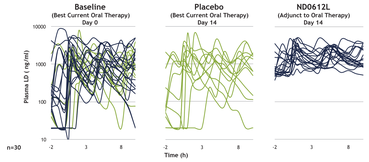
All are mean ± SD data

Pharmacokinetic analyses

Period 1

- Compared with the placebo group, PD patients treated with adjunct ND0612L over a period of 14 days exhibited a clinically significant reduction in plasma levodopa concentration fluctuations (Figure 2).
- Patients treated with adjunct ND0612L had their plasma levodopa concentrations consistently maintained above a mean (± SD) of 800 ± 570ng/ml, and completely avoided the low trough levels (range of 60ng/ml) observed in the placebo group. These observations translated into a decreased peak-to-trough ratio, and a decreased fluctuation index in the group receiving ND0612L compared with placebo.

Figure 2: ND0612L transforms levodopa pharmacokinetics



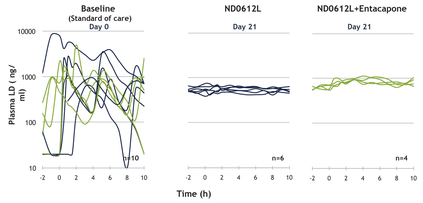
Fluctuation index = mean peak concentration - mean trough concentration/average concentration

Peak to trough	53.7	59.4	4.8
Fluctuation index	2.4	2.9	1.4

Period 2

- All 16 patients chose to continue to Period-2 in which plasma levodopa levels were maintained at a mean (± SD) of 550 ± 79ng/ml with ND0612L monotherapy and 800 ± 144ng/ml with ND0612L plus oral entacapone (Figure 3).
- In these patients, the oral levodopa intake was reduced by a median of 80%, with 3 of 16 patients completely discontinuing oral levodopa therapy.

Figure 3: ND0612L as monotherapy*



**Data are shown for the 10 patients who did not require additional oral LD for their PD control on the day of pharmacokinetic analysis*

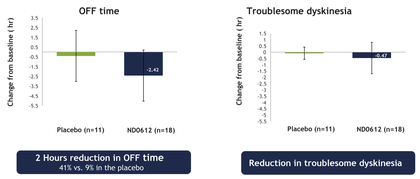
Safety analyses

- ND0612L was generally well tolerated and safe causing only minimal and transient local cutaneous reactions and no particular systemic AEs.
- No local or systemic AE caused a treatment discontinuation or withdrawal from the study; all 16 per protocol patients chose to continue to additional second open period of the study.
- In particular, there were no AEs of dyskinesia or psychiatric symptoms reported during the study.

Exploratory efficacy analyses - Period 1

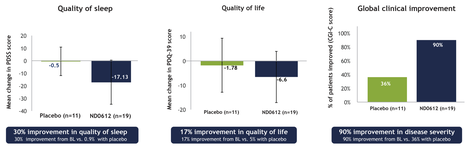
- Exploratory efficacy analysis showed that ND0612L treatment reduced OFF time by a mean (± SD) of 2.42 ± 2.62 hours (in clinic) and 2.13 ± 2.24 hours (home diaries) from baseline. By contrast, mean OFF time reduction with placebo was 0.41 ± 2.62 hours (in clinic) and 1.39 ± 2.33 hours (home diaries). Thus, ND0612L met the primary efficacy endpoint for the futility analysis (i.e. OFF time reduction greater than the prespecified threshold of 1.6 hours).
- This reduction in OFF time was not accompanied by an increase in troublesome dyskinesia; indeed a small decrease in dyskinesia in the ND0612L treated group was observed. (Figure 4).

Figure 4: Reductions in (a) OFF time and (b) ON time spent with troublesome dyskinesia with ND0612L



- ND0612L also improved (Figure 5):
  - Sleep quality: 17.1 ± 17.58 improvement in PDSS scores from baseline vs. 0.5 ± 11.35 with placebo.
  - Quality of life: 6.6 ± 10.52 improvement in PDQ-39 scores from baseline vs 1.78 ± 11.10 with placebo.
  - Global impression: 90% of the patients had improved CGI-C scores vs. 36% in placebo.

Figure 5: ND0612L improves (a) quality of sleep, (b) quality of life and (c) global clinical disease severity



Conclusions

These data suggest that subcutaneous continuous delivery of LD/CD with ND0612L provides relatively stable LD levels with reduced fluctuations compared with oral levodopa and is generally well tolerated. These results reinforce the idea that steady levodopa concentrations translate into clinical benefits.

The clinically significant impact on reduction in OFF time and the positive outcomes from the other exploratory efficacy endpoints, suggest that ND0612L should improve patients' quality of life by offering significant efficacy against motor complications in this often difficult to treat population.

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Disclosures

Nir Giladi, Yoseph Caraco, Tanya Gurevitch and Ruth Djaldetti report personal compensation for speaking and/or consultative services from Neuroderm.

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