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 unchanged as the most effective symptomatic treatment 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 neuron degeneration, the “fluctuating response to levodopa mirrors the ‘pulsatile’ nature of levodopa pharmacokinetics delivery to the brain.”2, 3 As a result, currently available delivery systems have been surgically implanted to deliver levodopa subcutaneously.

ND0612L is a proprietary liquid formulation of levodopa/carbidopa (LD/CD 80:14 mg/ml), currently delivered by a belt pump system, which enables for the first time continuous administration of levodopa (LD) 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/carbidopa therapy for at least 3 months.

- 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 (In this period we permitted a slow decrease in the dose of oral levodopa over a period of 14 days to ensure that plasma levodopa levels were maintained at a mean (±SD) of 500 ± 200 ng/ml). All patients were randomized (1:1) to receive ND0612L monotherapy or ND0612L plus oral entacapone (i.e. without their standard of care).

- All patients were compliant with treatment protocol and were randomized (1:1) to receive ND0612L monotherapy or ND0612L plus oral entacapone (Figure 3).

- Period 1: Randomized double blind 2 weeks
  - Placebo + oral SOC

- All 16 patients chose to continue to Period-2 in which plasma levodopa levels were maintained at a mean (±SD) of 500 ± 200 ng/ml with ND0612L plus oral entacapone (Figure 3).

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). These data suggest that subcutaneous continuous delivery of LD/CD with ND0612L provides relative stability over 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.

- Safety analyses
  - In patients treated with adjunct ND0612L, generally well tolerated and safe causing only minimal and transient local cutaneous reactions and no particular systems AE.
  - No local or systemic AE caused a treatment discontinuation or withdrawal from the study; all 16 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.

Conclusions

These data suggest that subcutaneous continuous delivery of LD/CD with ND0612L provides relative stability over 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, support that ND0612L should improve patients’ quality of life by offering significant efficacy against motor complications in this often difficult to treat population.

References


Disclosures

Nir Glidé, Joseph Caraco, Tanya Gurevitch and Ruth Djaldetti report personal compensation for speaking and/or consulting services from Neuroderm. Yael Cohen, Oran Yacobi-Zeevi and Sheli Oren are employed by Neuroderm.