# Stable levodopa plasma levels with ND0612 (levodopa/carbidopa for subcutaneous infusion) in patients with Parkinson's Disease with motor fluctuations

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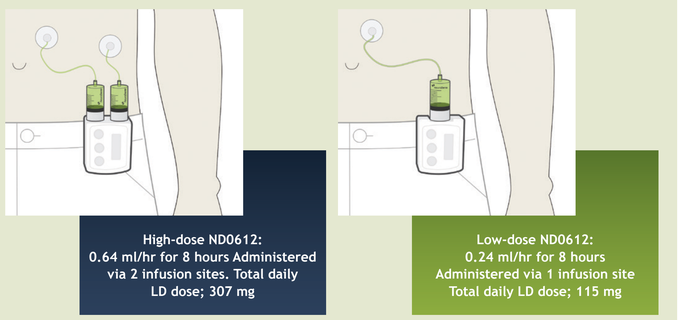
## Introduction

Continuous levodopa/carbidopa administration is considered to be the optimal delivery route for treating patients with Parkinson's Disease (PD) who have motor fluctuations. Poor levodopa solubility has prevented the development of a subcutaneously-deliverable formulation. Current infusion systems require gastrointestinal surgery to deliver continuous levodopa directly into the duodenum and are associated with potentially serious complications.

ND0612 is a proprietary liquid formulation of levodopa/carbidopa (LD/CD) 60/7.5 mg/mL that enables for the first time subcutaneous administration of LD/CD to achieve stable levodopa plasma levels. ND0612 is administered continuously for 24 hours with an infusion pump via one or two infusion sites (Figure 1) and provides a daily dose between 270-720 mg LD and 34 -90 mg CD.



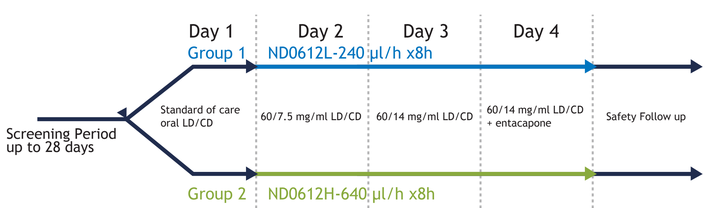

## Study Objectives

The aims of this Phase II dose-finding study were to assess the safety, tolerability and pharmacokinetics (PK) of six dose regimens of ND0612. In particular, the study assessed whether continuous delivery of ND0612 at low doses (0.24 mL/hr) or high doses (0.64 mL/hr) with 2 LD/CD formulations containing either high or low concentrations of carbidopa, can provide reduced variability in plasma LD concentration in comparison with intermittent dosing of standard of care oral LD/CD formulations.

## Methods

Sixteen patients with PD treated with oral levodopa/carbidopa and experiencing motor fluctuations were randomized to one of two treatment groups: Group 1-ND0612L; low dose ND0612 (0.24mL/hr), or Group 2-ND0612H; high dose ND0612 (0.64 mL/hr). All patients were treated with standard oral LD/CD on day 1, followed by ND0612 subcutaneous infusion for 3 days administered with formulations containing low or high carbidopa concentrations (7.5 mg/mL and 14 mg/mL respectively) on days 2 and 3, and with adjunct entacapone on day 4 (Figure 2). The Pharmacokinetics (PK) of LD in the various ND0612 regimens were compared with the PK of standard of care oral LD.

### Figure 2: Study design




## Results

### *Patient disposition and clinical characteristics*

16 patients with PD were randomized to treatment with low-dose ND0612 (N=9) or high-dose ND0612 (N=7). All randomized patients completed the study. Table 1 presents the baseline demographic and clinical characteristics for both groups.

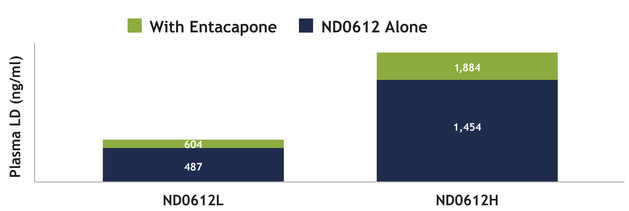
### Table 1. Baseline demographic and clinical characteristics

| Variable | Group 1 ND0612L (n=9) | Group 2 ND0612H (n=7) |
|---|---|---|
| Age (years) | 62.3 ± 8.2 | 64.1 ± 6.1 |
| % Male | 66.7% | 85.7% |
| BMI (kg/m$^2$) | 30.0 ± 5.2 | 28.4 ± 5.3 |
| Hoehn and Yahr stage; n (%) | | |
| Stage 2 | 4 (44.4%) | 2 (28.6) |
| Stage 2.5 | 3 (33.3%) | 2 (28.6) |
| Stage 3 | 2 (22.2%) | 2 (28.6) |
| Stage 4 | - | 1 (14.3) |
| PD duration (years) | 8.0 ± 2.0 | 10.9 ± 5.3 |
| Duration of motor fluctuations (years) | 5.2 ± 3.5 | 6.4 ± 4.5 |
| Duration of dyskinesia (years) | 3.0 ± 3.1 | 5.1 ± 4.2 |
| UPDRS Total | 36.7 ± 19.9 | 42.7 ± 23.1 |

### *Pharmacokinetics*

- Fluctuations in levodopa plasma levels were markedly reduced for all ND0612 regimens in comparison to standard of care oral levodopa/carbidopa. Fluctuation rate was assessed by Modified Fluctuation Index: mixed measures repeated model [MMRM] analysis of model's root mean square estimate [MSE]. All Modified Fluctuation Index p values were significantly reduced ($p < 0.0001$) Vs. baseline oral levodopa (Table 2).
- Both high dose and low dose ND0612 regimens maintained stable, therapeutic levodopa plasma concentrations.
- The concentration of carbidopa in the ND0612 formulation did not affect the maximum levodopa plasma concentrations in neither the high or low dose regimens.
- Mean Cmax (±SD) levodopa plasma concentrations were proportional in accordance with LD dose i.e. a 3 fold higher plasma LD level was measured for high-dose ND0612 compared to low-dose ND0612 (Table 2, Figure 3);
- In the low-dose group levodopa mean Cmax(±SD) was: 618 (±495.8) and 487 (± 103.6) ng/ml for low and high concentrations of carbidopa respectively. In the high-dose group levodopa mean Cmax was 1355 (± 269.8) and 1454 (± 269.7) ng/ml for low and high concentration of carbidopa respectively.
- The addition of entacapone increased the mean Cmax levodopa levels achieved; 604 (± 105.8) ng/ml for low dose ND0612; and 1844 (± 381.9) ng/ml for the high dose ND0612 (Table 2, Figure 3).

### Figure 3. Levodopa levels (Cmax) with ND0612L and ND0612H levels alone and with oral entacapone




### Table 2. Mean (±SD) Levodopa pharmacokinetic parameters

| Study Group | Treatment | PK Parameter | | |
|---|---|---|---|---|
| | | **Modified Fluctuation Index** *[p value vs Baseline Day2]* | **$C_{max}$ [ng/mL]** | **AUC (0-8h) [ng.h/mL]** |
| **Low-Dose ND0612 N = 9** | Baseline Oral LD/CD | 535 (±30.9) | 1820 (±498.5) | 5743 (±2169.6) |
| | ND0612 Low carbidopa concentration | 103 (±43.8) *[p<0.0001]* | 618 (±495.8) | 2,487 (±873.8) |
| | ND0612 High carbidopa concentration | 65 (±43.8) *[p<0.0001]* | 487 (±103.6) | 2,434 (±441.7) |
| | ND0612 High carbidopa concentration + Entacapone | 73 (±46.2) *[p<0.0001]* | 604 (±105.8) | 2,923 (±517.8) |
| **High-Dose ND0612 N = 7** | Baseline Oral LD/CD | 535 (±30.9) | 2262 (±726.0) | 8414 (±3566.2) |
| | ND0612 Low carbidopa concentration | 97 (±49.6) *[p<0.0001]* | 1,355 (±269.8) | 6,466 (±1,404.4) |
| | ND0612 High carbidopa concentration | 130 (±49.6) *[p<0.0001]* | 1,454 (±269.7) | 7,549 (±1,620.5) |
| | ND0612 High carbidopa concentration + Entacapone | 111 (±49.0) *[p<0.0001]* | 1,844 (±381.9) | 8,853 (±1,557.7) |

*Baseline Modifed fluctuation Index (Model's root mean square estmate [MSE]) of fluctuation calculated for all 16 patents in both groups.*

### *Safety*

Treatment with ND0612 was well tolerated; No SAEs or early discontinuations were reported. Mild, transient local reactions at the infusion site were common. The majority of patients (15/16) had at least one positive score on the Draize (erythema + edema) test. The highest mean Draize score was observed at Day 4. On a scale of 0-8, the mean scores were 1.13 and 1.14 for the Low-dose and High-dose groups respectively, indicating a mild reaction. All patients developed at least 1 injection site nodule during the 6-month period of safety follow-up. The development of nodules was a delayed reaction, with peak severity at Week 3. Nodules were considered not troublesome, and all had completely resolved by month 4-6.

## Conclusions

- Both low and high dose ND0612 regimens reached stable, therapeutic levodopa plasma concentrations. The marked fluctuations in levodopa plasma concentration seen with standard of care oral LD therapy were significantly reduced with ND0612.
- Similarly high levodopa plasma concentrations were achieved irrespective of whether ND0612 was given with low or high concentrations of carbidopa. Concomitant COMT inhibition with entacapone (on top of carbidopa) was found to further increase plasma concentrations and AUC without negatively affecting the Modified Fluctuation Index.
- Treatment with ND0612 was well tolerated; mild, transient local reactions at the infusion site were noted.
- The high and stable plasma levels provided by ND0612 indicate that it may offer a viable alternative to more invasive surgical procedures for patients with advanced PD who experience motor fluctuations.

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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.Yael Cohen, Oron Yacobi-Zeevi and Sheila Oren are employed by Neuroderm