ND0612, A NOVEL FORMULATION OF LEVODOPA/CARBIDOPA FOR CONTINUOUS, SUBCUTANEOUS ADMINISTRATION, ACHIEVES STEADY-STATE LEVODOPA PLASMA CONCENTRATIONS IN PARKINSON'S DISEASE PATIENTS

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Background

Figure 1 Dose-Dependent Constant LD Plasma Concentrations Following Continuous SC Administration of ND0612

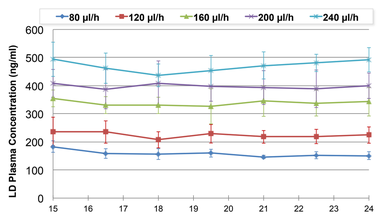
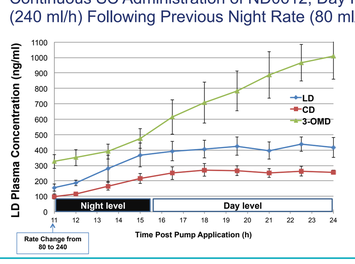


Figure 2 Continuous SC Administration of ND0612, Day Rate (240 ml/h) Following Previous Night Rate (80 ml/h)



Improving the consistency of plasma levodopa (LD) concentration with oral dosing has been a longstanding pharmacological challenge. "Off" states and dyskinesias, can be linked to variability in plasma LD concentration. Sustained-release LD preparations and enzymes inhibitors have had only limited success at improving these problems. Furthermore, though invasive strategies to maintain constant plasma LD concentration (intravenous or intra-duodenal infusion) can improve consistency of anti-Parkinsonian effect with reduction in dyskinesias and "off" periods, these strategies are impractical for most patients. More convenient methods for continuous LD delivery still constitute a major unmet need for managing PD.

NeuroDerm investigated the effect of continuous subcutaneous delivery of ND0612, a novel liquid formulation of LD/carbidopa(CD), on the safety, tolerability and LD pharmacokinetics (PK) in PD patients.

In a recently completed study in healthy volunteers (Poster 452), steady state, dose-dependent, LD plasma concentrations were maintained (Figure 1). Accordingly, the administration of ND0612 at a low night rate and a higher day rate resulted in, respectively, lower and higher plasma concentrations of LD (Figure 2). Based on those results, the dosage of ND0612 for the present study was selected.

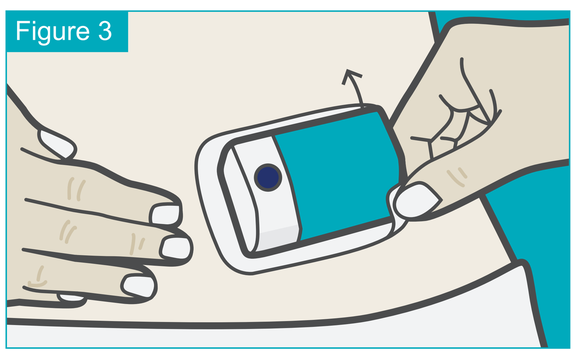
Objectives

This study was performed in PD subjects, using continuous SC administration of a soluble formulation of LD and CD (ND0612). We aimed:

- To determine the safety and tolerability of subcutaneous ND0612 versus saline, administered for 24 hours in PD patients.
- To determine the steady state plasma concentration of LD, CD and 3-OMD following oral LD/CD (Stalevo® 100) with and without continuous SC delivery of ND0612.

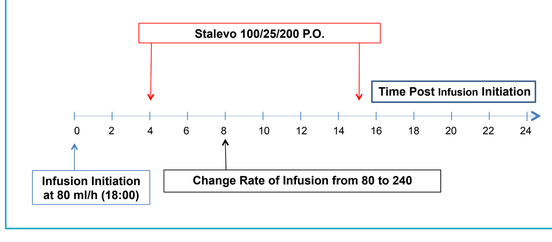
Materials and Methods

Figure 3



- Study design: Randomized, double-blind crossover trial
- Subjects: 8 PD patients with motor fluctuations
- Subcutaneous delivery pump (Figure 3)
- Treatment arms: ND0612 (LD/CD 6%/1.5%) or placebo, administered over 24 hrs together with two Stalevo® 100 doses, at bed-time (22:00) and again in the morning (09:00) (see Figure 4)
- Dose: During the day, ND0612 was administered at 240 µl/hr over 16 hrs and at night, 80 µl/hr over 8 hrs, for a total of 4.5ml/24hr (total LD/CD intake: 270/67 mg)

Figure 4 Study Design Chart



Assessments

- Plasma LD, CD and 3-OMD concentrations were quantified at multiple time points: 7,8 ,9 ,10 ,11 ,12 ,13 ,14 and 15 hours after the pump application
- Systemic and local safety and tolerability were assessed at 25h, 36h, 60h, 84h, 1 week, 2 weeks, 3 weeks, 4 weeks, 6 weeks and, if necessary, 8 weeks or more after treatment.

Results

Figure 5 LD PK Following Continuous Two-rate SC ND0612 with Oral Stalevo on the PK of LD

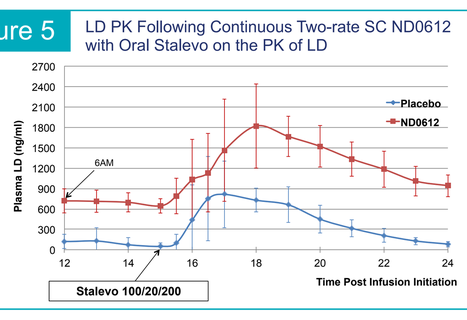


Figure 6

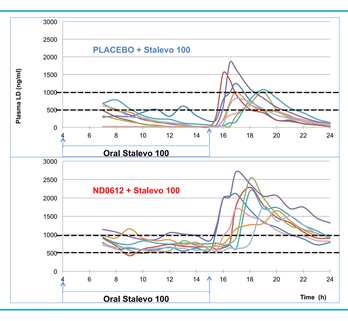
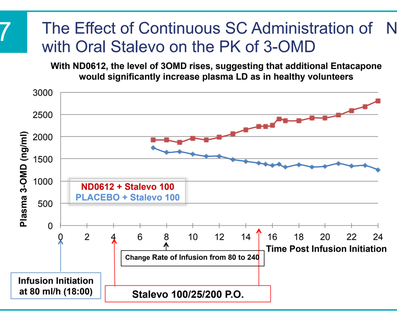


Figure 7 The Effect of Continuous SC Administration of ND0612 with Oral Stalevo on the PK of 3-OMD



Tables 1&2

Treatment	Peak to Trough Ratio $T_{0\text{-}9h}$
Stalevo 100	22
ND0612	1.1
ND0612 + Stalevo 100	2.3
Stalevo 100 *vs.* ND0612 + Stalevo 100	X10
Stalevo 100 *vs.* ND0612	X20

Treatment	Time above (as % of t=17h measured)	
	900 ng/ml	1200 ng/ml
Stalevo 100	0h	0h (0%)
ND0612 + Stalevo 100	>8h (47%)	5.5h (34%)
ND0612 + Stalevo 100 vs. Stalevo 100	+ at least 8h	+5.5h

Data management is still ongoing and preliminary results are presented here.
Pharmacokinetic data have been analyzed.

Preliminary demographics and disposition

- Age: 60-75 years old
- Gender: 4 males and 4 females
- BMI: 25-40
- All subjects completed the study and its follow-up.

PD characteristics

- Mean PD disease duration: 7.4 yrs
- Mean total daily dose of levodopa: 403.6 mg

Preliminary safety assessment

Overall, the subcutaneous administration of ND0612 was associated with a favorable safety profile, similar to the healthy volunteers. Additional detailed data reporting adverse events, vital signs, and laboratory measurements are still under analysis.

Local skin safety

ND0612 showed good tolerability and safety. In some subjects, small, transient papules/nodules could be felt following deep palpation of infusion sites (findings also previously noted in healthy volunteers receiving ND0612).

Pharmacokinetics

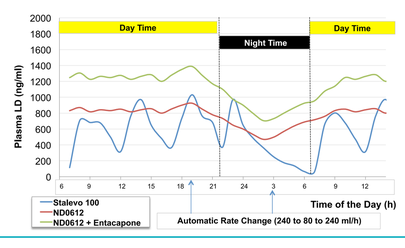
ND0612, delivered subcutaneously, achieved steady-state plasma LD concentrations ranging from 700-900 ng/ml (typical therapeutic concentrations of LD) (see Figure 5 & 6).
The LD plasma concentration in patients in this study was 50-100% higher than encountered in our previous study of young healthy volunteers.

The plasma concentration of 3-OMD was not elevated following oral Stalevo® administration alone, whereas it was considerably increased following oral Stalevo® with concomittant continuous SC administration of ND0612 (Figure 7). This suggests that with ND0612, peripheral catechol-O-methyl transferase (COMT) was the main metabolic pathway acting on LD. The amount of entacapone provided in Stalevo® was apparently insufficient to inhibit the extensive COMT activity. Therefore, we conclude that additional inhibition of COMT would further contribute to increasing plasma LD concentration.

ND0612 significantly reduced (10- to 20-fold) the fluctuations of LD plasma concentration and markedly increased the time LD plasma concentrations were above 900-1200 ng/ml (considered to be therapeutic). (Tables 1 & 2)

Conclusions

Figure 8 Predicted LD Plasma Concentrations of Two-rate ND0612 With & W/O Oral Entacapone as Compared to Stalevo 100/25/200



We describe a novel and practical way for achieving more constant LD plasma concentration in the therapeutic range for PD subjects.
Continuous SC delivery of ND0612 is safe and well tolerated.
In PD patients, subcutaneous ND0612 delivery achieved steady-state plasma LD concentrations ranging from 700-900 ng/ml (which is a typical therapeutic range).
Fluctuations in LD plasma concentration were significantly reduced.
With ND0612, LD concentration can be adjusted by controlling the infusion rate (programmed during day and night) and by adding oral LD/CD or a COMT inhibitor (see Figure 8).
These promising findings suggest that continuous SC administration of ND0612 is a strategy for ameliorating motor fluctuations in PD.

ND0612 has been successfully studied in completed Phase I and Phase IIa clinical studies, and further investigations are planned, including a randomized, double-blind, placebo-controlled Phase II study in PD patients (to evaluate the safety and efficacy of repeated dosing with ND0612).