CONSTANT THERAPEUTIC LEVODOPA PLASMA CONCENTRATIONS MAINTAINED BY CONTINUOUS SUBCUTANEOUS ADMINISTRATION OF ND−0612, A NOVEL FORMULATION OF LEVODOPA/CARBIDOPA

(17th International Congress of Parkinson's Disease and Movement Disorders, June 2013, Sydney, Australia - Abstract number: 452)

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Background

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 preparations and enzyme inhibitors have had only limited success at improving these problems. Furthermore, though invasive strategies to maintain constant plasma LD concentration (such as continuous 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 with a novel LD/carbidopa(CD) product, ND0612, a stable liquid formulation of the two drugs. Our previous studies found that pharmacokinetic profiles of LD could be greatly improved with continuous subcutaneous (SC) administration of CD, by smoothing the plasma LD concentration peaks linked to the oral CD dosing. Our investigations further observed that, continuous parenteral administration of LD (which avoids erratic absorption in the gut and 1st-pass hepatic metabolism), improved LD bioavailability.

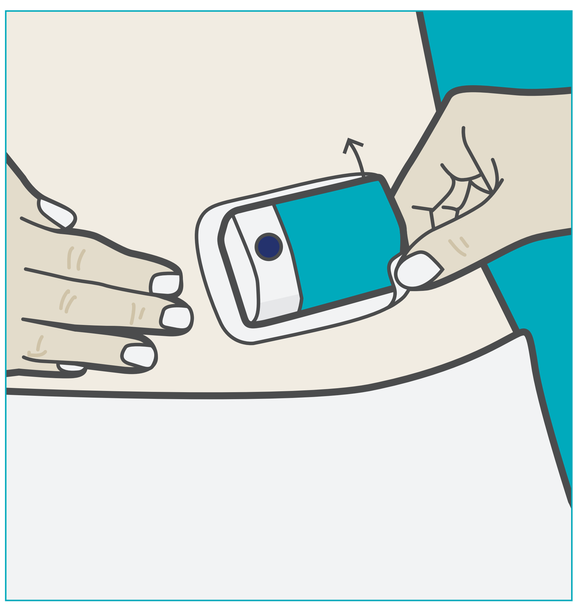
Objectives

In healthy subjects, using continuous SC administration of escalating doses with a soluble formulation of LD and CD (ND0612), we sought to determine:

- Maximally tolerated doses, by determining the safety and tolerability of ND0612 compared to saline infusion
- Steady-state plasma concentration of LD and CD with ND0612

Different dosages, rates of infusion and needle length were tested as well as concomitant administration of entacapone.

Materials and Methods



Fifty-four healthy male Caucasians volunteers, aged 18 - 40 years, were tested in a Phase I, dose-escalating, randomized double-blind placebo-controlled study of ND0612.
ND0612, a proprietary liquid formulation of LD/CD was administered continuously via a SC infusion pump over 24 hrs.

There were 9 treatment arms (6 subjects per arm):
ND0612 (LD/CD) 6%/1.5% at rates of:

- 80 µl/hr
- 120 µl/hr
- 160 µl/hr
- 200 µl/hr
- 200 µl/hr (short needle -6mm instead of 10 mm used in the whole study)
- 240 µl/hr
- 80 µl/h for 8 hrs and 240 µl/h for 16 hrs
- 240 µl/hr + oral entacapone 200 mg administered every 2 hrs

and ND0612 5%/1.25% (LD/CD) rate 240 µl/hr

The dose of ND0612 was escalated based on the review and approval of the Data Monitoring Committee, who reviewed local and systemic safety.
LD/CD doses ranged between 120/30 and 360/90 mg LD/CD per 24 hrs.

Systemic and local skin safety were assessed at the following time points: 1, 24, 48, and 72hr after start of infusion and, if necessary, longer follow up was performed.

Plasma LD, CD and 3-OMD concentrations were determined at multiple time points.
Pharmacokinetics sampling times included: 15, 16.5, 18, 19.5, 21, 22.5 and 24h after the application.

Results

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

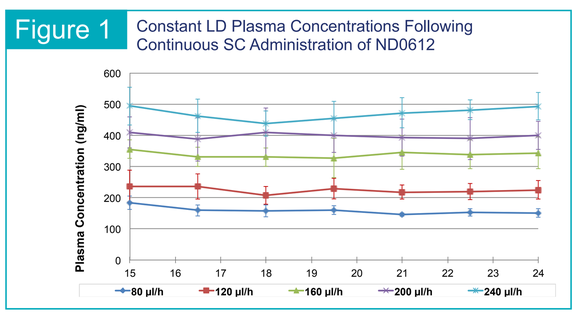


Figure 2 Constant CD Plasma Concentrations Following Continuous SC Administration of ND0612

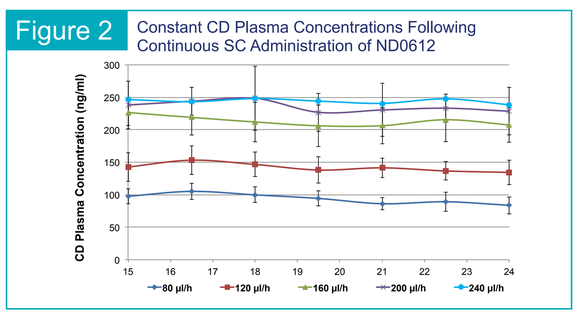


Figure 3 Linear correlation between ND0612 dose and LD, CD and 3-OMD plasma concentrations

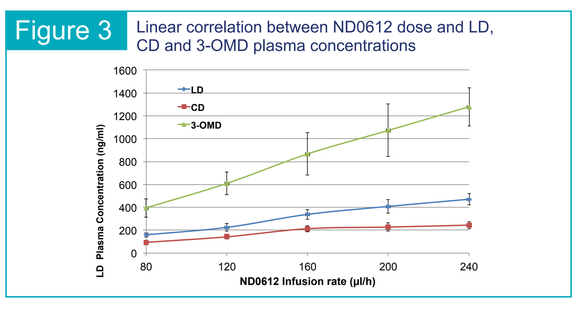


Figure 4 Continuous SC Administration of ND0612, Day Rate (240 ml/h) Following Previous Night Rate (80 ml/h)

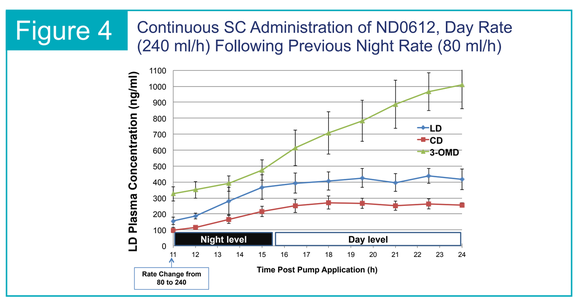


Figure 5 Continuous SC Administration of ND0612 with Oral Entacapone

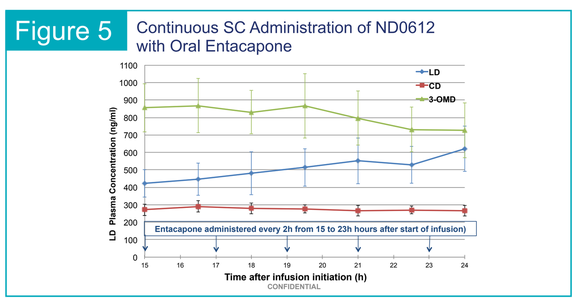


Figure 6 Repeat Dosing: Predicted ND0612 with Stalevo 50 vs. Actual Sinemet 100 and Stalevo100

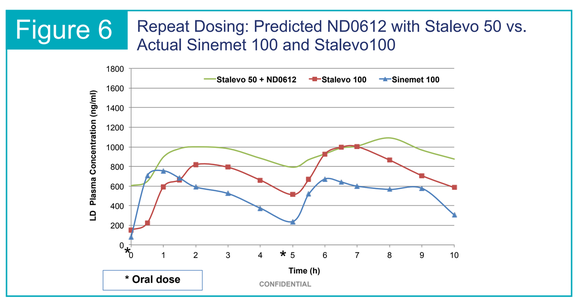


Table 1 ND0612 Decreases LD Peak to Trough Ratios

	Peak to Trough (12h) – Cmax/Cmin	
	NeuroDerm Study	IPX study
Sinemet 100	40.5	82.2
IPX066		12.0
Stalevo 100	32.9	
Stalevo 50	29.8*	
Sinemet 100 +ND0612	2.9*	
Stalevo 100 + ND0612	3.1*	
Stalevo 50 + ND0612	2.1*	

x7 x14 x19

* Predicted

Demographics and disposition of study participants

- Age: 20-39 years
- BMI: 18-28
- Number of follow up days: 15-137
- All subjects completed the study and its follow up.

Systemic safety

There were no significant systemic adverse events related to SC administration of ND0612. No clinically relevant effects were encountered in laboratory measurements or vital signs.
The most frequent adverse event was application site pain, characterized by pain elicited only upon touching, palpation and examination. Pain was not reported spontaneously, except for one event.
Other adverse events were headache and nasopharyngitis. The majority of AEs were recorded as mild and no serious AE were reported during the study.

Local safety

Good local tolerance was observed, as demonstrated by mean Draize scores <1, lack of pruritus and skin staining, and only one reported adverse event of pain. In some subjects, small and tender nodules (~0.5cm in diameter) were detected upon deep palpation; these disappeared within several days or weeks. There was no clear dose-responseness to the development of these nodules.

Pharmacokinetics

Constant LD and CD concentrations were maintained during the 9 hours of PK sampling (Figure 1 & 2). LD, CD and 3-OMD plasma concentrations increased linearly as a function of dose (infusion rate) of ND0612 (Figure 3).

Administration of ND0612 at a low night rate (80µl/h) and a high day rate (240 µl/h) resulted in respective lower and higher plasma concentration of LD (Figure 4). The time to reach steady state concentrations after changing the rate of administration was approximately 4 hours. An increase in the rate of administration several hours prior to waking would possibly prevent morning akinesia.

Administration of ND0612 together with repeated dosing of oral entacapone 200 mg showed an increase in LD plasma concentration of ~50%, with corresponding decrease in 3-OMD plasma concentration (Figure 5).

The results showed that continuous SC administration of ND0612 showed constant LD concentration and therefore prevented LD plasma fluctuations.
Based on pharmacokinetic simulations, continuous administration of SC ND0612 administered with small doses of oral LD should be able to markedly decrease LD plasma fluctuations. From these calculations, peak-to-trough ratio would be 20 times lower than the best available oral LD/CD treatments (Figure 6 and Table 1).

Conclusions

- Continuous SC delivery of ND0612 is safe and tolerable
- Dose dependent, constant, LD plasma concentrations are attained with ND0612
- ND0612 decreases LD plasma fluctuations and its peak-to-trough ratio
- ND0612 can be administered at differing day and night infusion rates
- ND0612 could be administered together with other oral PD medications such as small doses of LD or entacapone

Based on literature review it is expected that LD plasma concentrations would be at least 35% higher in elderly PD patients than in healthy young subjects.
It is suggested that ND0612 may provide a good treatment option, as monotherapy or adjunct therapy, for the treatment of motor fluctuations of PD.
A pharmacokinetic study in PD patients has been conducted and preliminary results are reported in another poster presentation at this congress (LBA-26).
A randomized, double-blind, placebo-controlled Phase II study in PD patients is planned to evaluate the safety and efficacy of repeated dosing of ND0612.