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ND0612 (levodopa/carbidopa for subcutaneous infusion) achieves stable levodopa plasma levels when administered in low and high doses in patients with PD

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Introduction

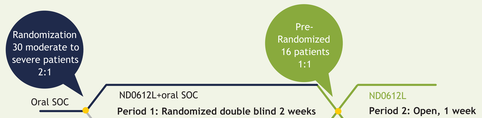
- Levodopa therapy remains the cornerstone of Parkinson's disease (PD) management, providing effective symptomatic relief to most PD patients. However, due to pharmacokinetic limitations and other disease-related factors, chronic treatment with oral levodopa is associated with the development of motor complications, which often limit its clinical utility.[1]
- Continuous levodopa infusion is considered the optimal delivery route when managing motor fluctuations in patients with advanced PD, but current infusion systems have to be surgically routed to the jejunum and are therefore associated with potentially serious safety complications.[2]
- ND0612 is a proprietary liquid formulation of levodopa/carbidopa (60/7.5 mg/mL), which has been developed for convenient subcutaneous (SC) administration to provide a continuous and stable source of levodopa in patients with moderate to severe PD.
- The objectives of these two Phase II studies were to characterize the levodopa pharmacokinetic profile derived from continuous SC administration of ND0612.

Methods

- Two Phase II studies were performed to assess the pharmacokinetic profile of levodopa obtained from ND0612.
- Two ND0612 dosing regimens were assessed: Low dose ND0612 (ND0612L) and High dose ND0612 (ND0612H).

Study 1: ND0612-003

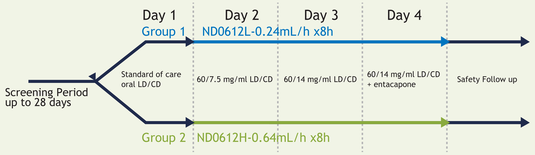
- Study ND0612-003 was a double-blind, placebo-controlled study, in which 30 PD patients with motor fluctuations (>2 hours OFF time) on optimized oral levodopa/carbidopa doses (≥3 doses/day) received low dose ND0612 or placebo, as adjunct to their current optimized oral treatment for 2-weeks, followed by a 1-week open label extension of ND0612 either with or without oral entacapone.
- All other stable (≥14 days) PD medications were permitted
- ND0612 infusions (levodopa/carbidopa: 60/14 mg/mL) were administered continuously with a day rate of 0.24mL/h and a night rate of 0.08 mL/h. The total daily dose of subcutaneous levodopa/carbidopa infusion was 270/63mg administered in 4.5 mL.
- The prespecified primary efficacy endpoint was the change in total OFF time from Baseline to Weeks 1 and 2 (post initiation). This was analyzed using a futility analysis with a margin of 1.6 hours reduction in OFF time.



During Period 1, all patients received their standard of care (SOC) 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 (patients were encouraged to discontinue oral levodopa/carbidopa).

Study 2: ND0612-004

- Study ND0612-004 was a Phase IIa study in which 16 PD patients on optimized oral levodopa/carbidopa doses and experiencing well-defined OFF periods (≥80% of days) were randomized to either ND0612L (total levodopa dose of 115mg over 8 hours) or ND0612H (total levodopa dose of 307 mg over 8 hours).
- The concentration of levodopa was 60 mg/mL in all treatment regimens throughout the study.



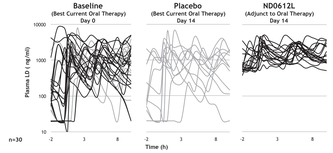
Day 1: all patients were treated with their standard oral levodopa.
Day 2: patients were treated with allocated regimen (ND0612L or ND0612H) administered with carbidopa at a concentration of 7.5mg/mL.
Day 3: patients received their allocated levodopa regimen with carbidopa at a concentration of 14mg/mL.
Day 4 was an optional evaluation of the impact of dual enzyme inhibition (DDC and COMT inhibition) with carbidopa and entacapone.

Results

ND0612-003: ND0612L

- All patients were compliant with the treatment protocol and, together with a caregiver and/or nurse, were able to fill the pump reservoir with the liquid drug, attach and operate the pump.
- Compared with the placebo group, patients treated with adjunct ND0612 over a period of 14 days (Period 1) exhibited a significant reduction in plasma levodopa concentration fluctuations (Fluctuation Index of 1.4 in the ND0612 group compared to 2.9 with placebo). The ND0612-treated group avoided the low trough levels observed in the placebo group, as reflected in a decreased peak-to-trough ratio of 4.8 in the ND0612 group versus 59.4 in the placebo group.
- When oral levodopa was discontinued (Period 2), the peaks and troughs in levodopa plasma levels were abolished, and mean levodopa levels were maintained at 550 ± 79 ng/mL. Co-administered entacapone further increased levodopa levels to 800 ± 144 ng/mL.
- The trial met its futility efficacy analysis endpoint; adjunct ND0612 reduced mean OFF by 2.42 hours in clinic and 2.13 hours in pilot home diaries, (vs. 0.41 hour and 1.39 hours with optimized oral therapy and placebo) (Figure 2).
- ND0612L was generally well tolerated and safe causing only transient local infusion site 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.

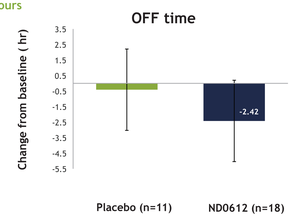
Figure 1: ND0612L transforms levodopa pharmacokinetics



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

Figure 2: ND0612L significantly reduces OFF time by 2 hours



Baseline OFF time (in clinic) was 4.64 ± 2.89 hours in the placebo group and 5.92 ± 2.14 hours in the ND0612L group.

ND0612-004: ND0612

- Fluctuations in levodopa plasma levels were again markedly reduced (both doses <0.0001) in comparison to baseline oral levodopa/carbidopa. Figure 3 shows pharmacokinetic data from representative patients in each group.
- Both ND0612L and ND0612H reached stable, therapeutic levodopa plasma concentrations, and no relevant differences in levodopa bioavailability were observed with the two carbidopa concentrations (further details on the impact of carbidopa levels can be found in Poster 1393 at this Congress).
- Levodopa plasma concentrations were dose proportional with ND0612H achieving around 3-fold higher plasma levels than ND0612L, which is in accordance with the approximately 3-fold increase in daily levodopa dose infused in the ND0612H versus ND0612L treatment groups.
- Co-administration of entacapone increased LD plasma levels to a mean of 604ng/mL and 1844ng/mL in the low and high dose arms respectively (Figure 4).
- Treatment with ND0612 was well tolerated. During safety follow-up, 8 patients reported a total of 10 adverse events, only one of which was considered treatment-related (raised GGT and SGOT enzymes). On infusion site assessment, patients experienced transient, mild and non-troublesome local reactions, all of which completely resolved spontaneously.

Figure 3. Pharmacokinetics of levodopa following continuous SC administration of ND0612L & ND0612H (0-8 hours) (a) Individual patient from ND0612L group (b) Individual patient from ND0612H group

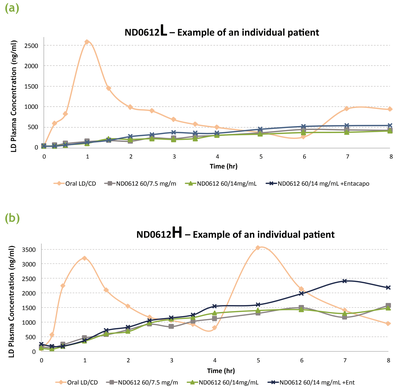
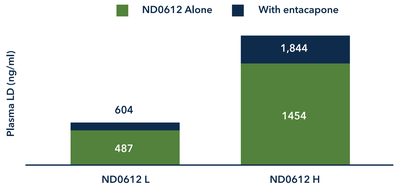


Figure 4 Levodopa plasma levels following administration of ND0612 alone and with adjunct oral entacapone



Conclusions

- Continuous SC infusion of ND6012 at low and high doses provides stable levodopa levels, and significantly reduces levodopa plasma level fluctuations in comparison to standard oral levodopa/carbidopa therapy.
- Inclusion of entacapone in the ND0612 regimen further increased plasma levodopa levels.
- Adding ND0612L to standard of care provides clinically significant improvement in motor complications.
- The high and stable plasma levels provided by ND0612H indicate that it may offer a viable alternative to more invasive surgical procedures for advanced PD.
  - **Poster 1337** provides the results of a pharmacokinetic comparison of ND0612 versus the levodopa/carbidopa intestinal gel
  - **Poster LBA41** provides the first results of a Phase II study, which evaluated the efficacy of two regimens of ND0612H (24 hours & 14 hours infusion) in reducing OFF time.
- Treatment with ND0612 was well tolerated with an expected systemic safety profile, and transient local infusion site reactions.
- Treatment with ND0612 (low and high doses) offers a simple and effective method of delivering stable and continuous levodopa levels to PD patients with moderate to severe PD, and may influence the current treatment paradigm in these patients.

References

1. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurol 2006;5(8):677-687.
2. Nyholm D. Duodopa® treatment for advanced Parkinson's disease: a review of efficacy and safety. Parkinsonism Relat Disord. 2012 Sep;18(8):916-29.

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