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Safety, efficacy and tolerability of continuous SC LD/CD (ND0612H) infusion in PD patients with motor fluctuations

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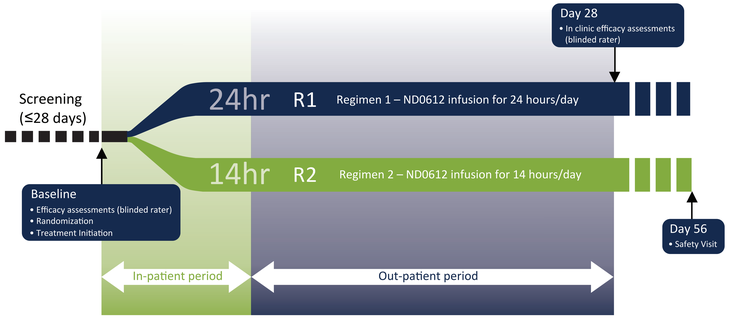
Introduction

- ND0612 is a proprietary liquid formulation of levodopa/carbidopa (60 mg/mL levodopa and 7.5 mg/mL of carbidopa) delivered by continuous subcutaneous infusion designed to provide continuous stable levodopa delivery to reduce motor complications in patients with moderate and advanced PD, while avoiding the surgical risks of intra-intestinal levodopa infusion.
- It is currently unknown whether providing 'round the clock' levodopa delivery provides additional benefits to patients versus a 'waking day' regimen.
- We performed a 28-day randomized, parallel-group, open label, blinded-rater study aimed at evaluating the safety, efficacy and tolerability of two dosing regimens of ND0612. Regimen 1 (R1) provided 24 hours ND0612 delivery and Regimen 2 (R2) provided 14 hours ND0612 delivery.
- Poster 1377 provides details of the methods and baseline characteristics for this study.

Methods



Subjects with fluctuating PD were randomized (1:1) to 2 dosing regimens of ND0612: R1 (24 hours infusion with ND0612, total LD/CD dose of 720/90 mg) or R2 (14 hours 'waking-day' infusion with ND0612, total LD/CD dose of 538/68mg + morning oral LD/CD 150/15 mg). Supplemental oral LD/CD was used as needed.

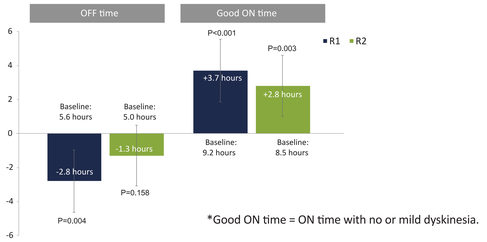
The primary endpoint was change from baseline to Day 28 in daily OFF time, as assessed in clinic by a blinded rater over 8 hours and normalized to 16 hours day.

The key secondary efficacy endpoint was the effect of ND0612 on morning akinesia.

Results

- 33 of 38 randomized subjects (87%) completed the study. Two subjects discontinued due to adverse events, two patients discontinued due to lack of efficacy and one patient withdrew consent.
- The primary endpoint (reduction in OFF time) and key secondary endpoints were met in R1 (Figures 2 and 3).
- Reduction in OFF time was associated with a significant increase in Good ON time (both regimens), and no increase in troublesome dyskinesia.
- The average oral levodopa dosing frequency reduced from 6.9 times/day at baseline to 2.3 times/day at Day 28. Likewise, mean oral levodopa doses decreased from 1100 mg at baseline to 330 mg at Day 28.

Figure 2: R1 significantly reduced OFF time and increased good* ON time



*Good ON time = ON time with no or mild dyskinesia.

Figure 3: R1 significantly reduced morning akinesia (increased achievement of ON time at 8 AM and 9 AM)

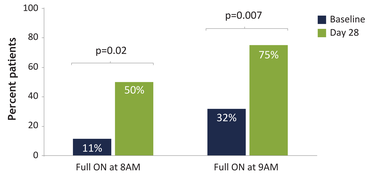
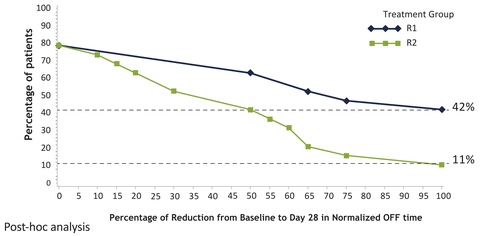
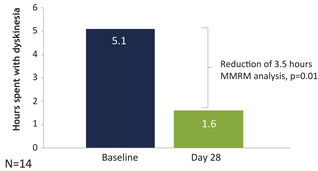


Figure 4: 42% of patients treated with R1 achieved complete resolution of OFF time (zero hours)



Post-hoc analysis

Figure 5. ND0612H reduced time with troublesome dyskinesia*



*Post-hoc subgroup analysis (pooled R1 and R2) of patients who had ≥1 hour of moderate to severe dyskinesia at baseline. Troublesome dyskinesia is defined as the sum of moderate and severe dyskinesia

Figure 6: Improvements in motor function (reduction in UPDRS Part III scores) in R1

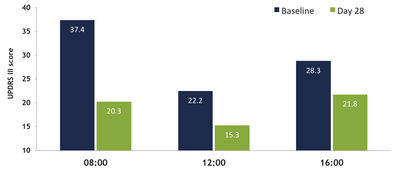


Table 1: Incidence of Adverse events with ND0612

Adverse event	Regimen 1 N=19	Regimen 2 N=19	Overall N=38
Any AE; n (%)	15 (79%)	14 (74%)	29 (76%)
Serious AE; n (%)	2 (11%)	2 (11%)	4 (11%)
Discontinued due to an AE	1 (5%)	1 (5%)	2 (5%)
Frequent AEs; n (%)			
Infusion site nodules	11 (58%)	7 (37%)	18 (47%)
Infusion site bruising	4 (21%)	3 (16%)	7 (18%)
Infusion site erythema	5 (26%)	2 (11%)	7 (18%)
Infusion site hemorrhage	2 (11%)	3 (16%)	5 (13)%

- Both regimens were well tolerated.
- 4 subjects reported 6 Serious Adverse Events: one subject had a subcutaneous abscess and orthostatic hypotension and another had worsening of PD symptoms (these 2 patients discontinued), one subject fell and fractured his nose, and one case of suspected panniculitis that was eventually ruled out.
- ND0612H infusion pump systems were reliable with only few minor, correctable malfunctions reported. No inconvenience related to the wearing of the device was reported for either day or night administration.

Conclusions

- 24 hour infusion of ND0612H (R1) significantly reduced daily OFF time and morning akinesia and increased good ON time.
- 42% of R1 patients experienced a complete resolution of OFF-time.
- Although the 14-hour day only infusion regimen, R2, was not designed to provide optimal ND0612H dosing, significant improvements in good ON time were observed.
- No safety concerns were identified. Infusion site adverse events were common, yet generally well tolerated.
- These findings suggest that ND0612 SC infusion can provide significant benefits for patients with advanced PD, while avoiding the surgical risks of currently available therapies.

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1377: Study methodology and baseline results