Safety and Pharmacokinetics of Anti-Inflammatory NE3107 Treatment in Carbidopa/Levodopa-Treated Patients With Parkinson's Disease: A Phase 2a, Double-Blind, Placebo-Controlled Study

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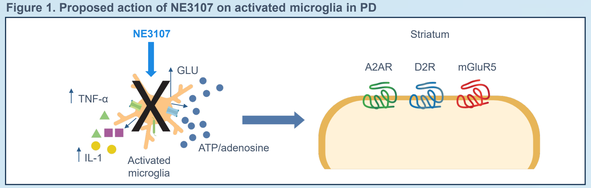
BACKGROUND

- Chronic neuroinflammation, oxidative stress, and impaired insulin signaling are thought to contribute to neurodegeneration and the subsequent progression of Parkinson's disease (PD)[1-2]
- Levodopa, a dopamine precursor, is a valuable treatment option, since it is effective in restoring motor function, but its prolonged use is associated with disabling side effects, such as levodopa-induced dyskinesia (LID), from hypersensitivity to dopamine[3-5]
  - Interestingly, important mediators of chronic neuroinflammation, such as ERK, NF-κB, and TNF-α, may be involved in the pathogenesis of LID[6-8]
  - Since levodopa lacks disease-modifying potential, there is a medical need for adjunctive therapies with a favorable safety and efficacy profile that can also slow or prevent disease progression
- NE3107 is an oral, blood-brain–permeable, anti-inflammatory, and insulin-sensitizing molecule that binds to the inflammatory mediator ERK and inhibits TNF-α signaling and inflammation-specific ERK and NF-κB activation without affecting the homeostatic functions of ERK[9]
  - NE3107 has been shown to have a favorable safety profile and demonstrated anti-inflammatory, insulin-sensitizing, pro-motoric, and neuroprotective effects in pre-clinical studies using rodents[9-12]
  - In a marmoset model of Parkinson's disease, NE3107 appeared to improve mobility, augment levodopa activity, mitigate LID, and increase survival of TH-positive neurons in the SNpc (for details see abstract #1353 in category Parkinson's Disease: Pharmacology and Therapy)
- In the context of PD, NE3107 may downregulate microglia to reduce purine- and glutamate-stimulated inhibition of dopamine receptors, potentially improving motor function[13] (**Figure 1**)
- Based on the encouraging pre-clinical results, we conducted a phase 2a clinical trial (NM201; NCT05083260) to assess the safety, tolerability, efficacy, and pharmacokinetics of NE3107 in levodopa-treated patients with PD

Figure 1. Proposed action of NE3107 on activated microglia in PD



OBJECTIVES

- The overall objectives of this clinical trial were to evaluate the safety, tolerability, and exploratory effects of anti-inflammatory NE3107 treatment adjunctive to concomitantly administered carbidopa/levodopa (C/L) in patients with PD and examine its effects on the pharmacokinetics (PK) of levodopa
- Here we report the safety of NE3107 from this trial and its effects on the PK profile of levodopa

METHODS

Study Design

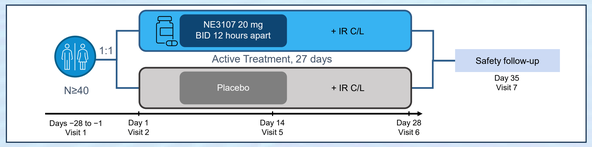
- In this phase 2a, double-blind, placebo-controlled, randomized clinical trial, at least 40 patients with PD were randomized 1:1 to receive either 20 mg oral NE3107 twice daily (BID; approximately 12 hours apart) or matching placebo in conjunction with C/L over 27 days (day 2 to day 28; **Figure 2**)
- Endpoints assessments were carried out on day 1 (visit 2), day 14 (visit 5), day 28 (visit 6), and day 35 (visit 7)

Study Population

Key inclusion criteria

- Aged 30-80 years
- Diagnosis of PD
- Marked response to levodopa
- History of motor fluctuations
- Early morning OFF episodes

Figure 2. Study design



Assessments

Safety and tolerability – assessed during safety follow-up on day 35 (visit 7)

- Incidence and temporal profile of TEAEs (including those leading to withdrawal of study drug)
- Incidence of SAEs
- Suicidality, measured by the C-SSRS
- Changes in physical examination, vital signs, and laboratory data

PK – changes in levodopa parameters between day 1 (visit 2) and day 14 (visit 5)

- AUC
- C_{max}
- T_{max}
- Estimation of elimination half-life when feasible

Clinical efficacy – changes between visit 1 and visits 2, 5, and 6 and between visit 2 and visits 5 and 6

- MDS-UPDRS assessments
  - Change in Part III score from baseline (practically-defined OFF) to postdose timepoints each day
  - Average Part III score when ON
  - Part I score
  - Part II score
- Motor state OFF time during study visits
- Motor state ON time with or without troublesome dyskinesia during study visits
- Time to onset of ON time
- Non-Motor Symptom Assessment Scale for Parkinson's Disease (NMSS)
- Dyskinesia severity and troublesome/non-troublesome status during study visits
- Tremor activity

RESULTS

- Overall, the baseline characteristics for both treatment groups were well balanced, except that the NE3107 group had a lower total daily levodopa dose and a higher MDS-UPDRS Part III (motor) score at baseline (**Table 1**)
  - There were no statistically significant differences between the two treatment arms
  - Approximately 50% of the total patient population was <70 years old

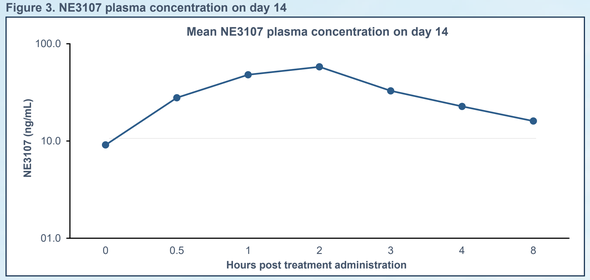
Table 1. Baseline characteristics

Characteristic	NE3107 + C/L (n=22)	Placebo + C/L (n=23)	NE3107 + C/L, patients <70 y (n=12)	Placebo + C/L, patients <70 y (n=11)
Age, mean (y)	67.6	66	61.3	57.7
Gender, n (%) Female Male	 9 (41) 13 (59)	 8 (35) 15 (65)	 3 (25) 9 (75)	 4 (36) 7 (64)
Weight, mean (kg)	80.1	80.8	87.0	86.8
BMI, mean	28.2	27.9	29.4	29.6
Time since diagnosis, mean (y)	7.6	7.3	7.7	9.0
Total daily levodopa, mean (mg)	548	691	563	646
MDS-UPDRS scores, mean Part I Part II Part III	 6.8 9.4 28.4	 7.5 8.2 25.8	 6.3 6.0 24.1	 6.9 8.1 23.1
ON time without dyskinesia within 4 h, mean (h)	1.95	1.93	1.88	1.23
OFF time within 4 h, mean (h)	2.1	1.7	2.3	2.0

NE3107 plasma concentration

- An assessment of NE3107 plasma concentration on day 14 (visit 5) revealed that a 20-mg BID regimen yielded a mean trough of ~10 ng/mL (**Figure 3**)
  - NE3107 has been shown to saturate its molecular target at a concentration <1 ng/mL,[14] thus our treatment regimen ensures target saturation throughout the treatment period

Figure 3. NE3107 plasma concentration on day 14



Effect of NE3107 treatment on levodopa PK

- A comparison of day 1 and day 14 PK parameters demonstrated that NE3107 administration did not affect the PK profile of levodopa (**Figure 4** and **Table 2**)
  - In patients who received NE3107 + C/L, levodopa AUC was 4243.08 (±1913.81) ng·h/mL and 4127.41 (±1568.47) ng·h/mL on day 1 and day 14, respectively
  - In patients who received placebo + C/L, levodopa AUC was 3175.55 (±2526.68) ng·h/mL and 3093.19 (±1919.73) ng·h/mL on day 1 and day 14, respectively
  - PK analysis on day 14 showed that levodopa reached a maximum serum concentration (C_{max}) of 2089.15 (±973.08) ng/mL and 3093.19 (±1919.73) ng/mL in patients treated with NE3107 + C/L and placebo + C/L, respectively

Figure 4. Plasma levodopa PK curves

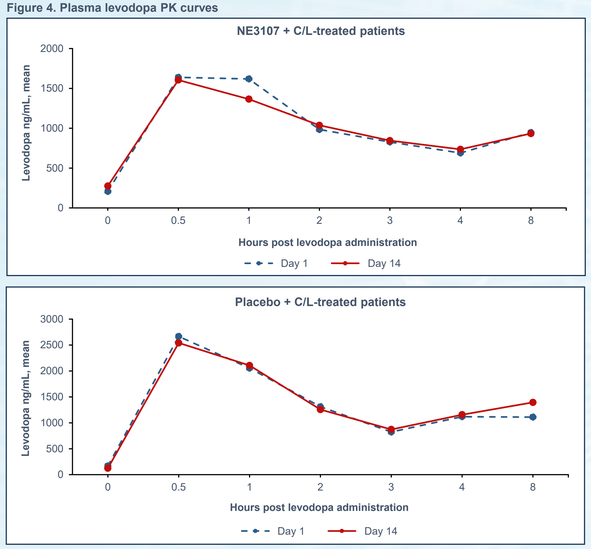


Table 2. Levodopa PK profile

Parameter	NE3107 + C/L n=20		Placebo + C/L n=20	
	Day 1 mean (SD)	Day 14 mean (SD)	Day 1 mean (SD)	Day 14 mean (SD)
AUC, ng·h/mL	4243.08 (1913.81)	4127.41 (1568.47)	5580.50 (3387.98)	5587.94 (3198.04)
C_{max}, ng/mL	2112.75 (1103.19)	2089.15 (973.08)	3175.55 (2526.68)	3093.19 (1919.73)
T_{max}, h	1.00 (0.65)	1.28 (1.2)	0.93 (0.65)	1.18 (1.17)

Safety assessment

- Four patients withdrew prior to study completion for reasons unrelated to drug tolerability
- There were no serious adverse reactions during this study

CONCLUSIONS

- The NM201 exploratory, phase 2a, randomized, double-blind, placebo-controlled study assessed the safety, efficacy, and pharmacokinetics of NE3107 in combination with C/L in patients with PD and met its objectives
  - NE3107 + C/L combination treatment was associated with clinically meaningful[15] and superior improvements on the motor examination part (Part III) of the MDS-UPDRS, especially in patients <70 years of age, and enabled patients to be in the morning ON state prior to their morning medication (for details see poster #2 in category Clinical Trials and Therapy in Movement Disorders (non-PD) (non-Dystonia))
  - NE3107 had a favorable safety profile, consistent with previous observations
  - Most importantly, the observed pro-motoric effects of NE3107 were likely not the result of increased plasma levodopa concentrations
- The findings of the NM201 study, together with the results of the marmoset study, suggest that through its anti-inflammatory and insulin-sensitizing properties, NE3107 may possess intrinsic pro-motoric and potentially levodopa-enhancing activities, while having a favorable safety profile, and support further investigation of the safety and clinical benefit of nondopaminergic therapies in late-phase clinical trials

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A2AR, adenosine receptor; ATP, adenosine triphosphate; AUC, area under the curve; C_{max}, maximum serum concentration; C-SSRS, Columbia-Suicide Severity Rating Scale; D2R, dopamine receptor; ERK, extracellular signal-regulated kinase; GLU, glutamate; IL, interleukin; IR, immediate release; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; *mGluR5*, metabolic glutamate receptor substrate 5; NF-κB, nuclear factor kappa B; SAE, serious adverse event; SD, standard deviation; SNpc, substantia nigra pars compacta; TEAE, treatment-emergent adverse event; TH, tyrosine hydroxylase; T_{max}, time to reach C_{max}; TNF-α, tumor necrosis factor-α.