A Randomized, Phase 2a, Double-Blind, Placebo-Controlled Clinical Trial With NE3107 Adjunctive to Carbidopa/Levodopa in Patients With Parkinson's Disease

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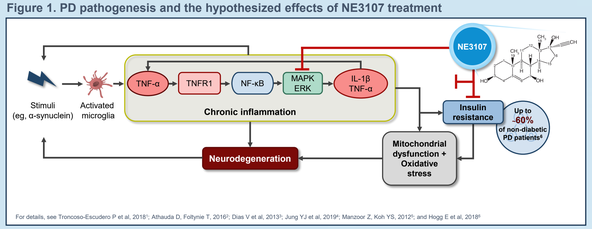
BACKGROUND

Figure 1. PD pathogenesis and the hypothesized effects of NE3107 treatment



For details, see Troncoso-Escudero P et al, 2018[1]; Athauda D, Foltynie T, 2016[2]; Dias V et al, 2013[3]; Jung YJ et al, 2019[4]; Manzoor Z, Koh YS, 2012[5]; and Hogg E et al, 2018[6]

- Chronic neuroinflammation, insulin resistance, and oxidative stress have neurodegenerative consequences and contribute to the progression of Parkinson's disease (PD; **Figure 1**)[1-6]
- NE3107 is an oral, blood-brain barrier–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[7]
  - In the context of PD, NE3107 may downregulate microglia to reduce purine- and glutamate-stimulated inhibition of dopamine receptors, potentially improving motor function[8]
  - 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[7,9-11]
  - In a marmoset model of Parkinson's disease, NE3107 appeared to improve mobility, augment levodopa activity, mitigate LID, and increase survival of TH+ neurons in the SNpc (for details see abstract #1353 in category Parkinson's Disease: Pharmacology and Therapy)
- Given that dopamine-replenishing drugs such as levodopa are unable to modify disease progression and are associated with debilitating side effects, there is a medical need for non-dopaminergic, safe, and effective alternate therapies that can slow or prevent the progression of PD[12-14]
- 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

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 of levodopa
- Here we report the exploratory efficacy of NE3107, specifically improvement of motor function, in C/L-treated patients with PD

METHODS

Study Design

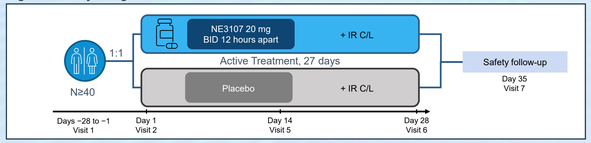
- In this phase 2a, double-blind, placebo-controlled, randomized clinical trial, at least 40 patients with PD were randomized 1:1 to receive either 20 mg oral NE3107 twice daily (BID; approximately 12 hours apart) or matching placebo in conjunction with C/L over 27 days (day 2 to day 28; **Figure 2**)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

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

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

Pharmacokinetics – changes in levodopa parameters between visits 2 and 5

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

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
  - Patients <70 years old randomized to NE3107 + C/L had a lower mean Part III score at baseline than that of the total patient population in the NE3107 + C/L group

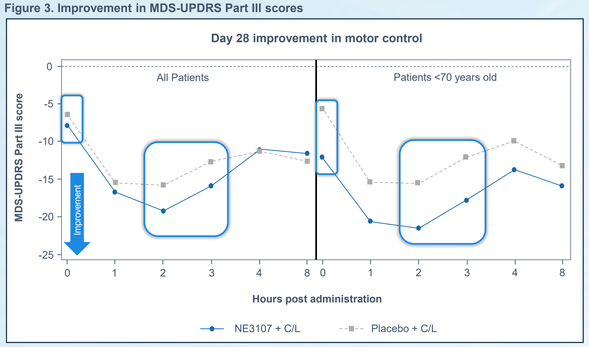
Table 1. Baseline characteristics

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

Change in MDS-UPDRS Part III scores

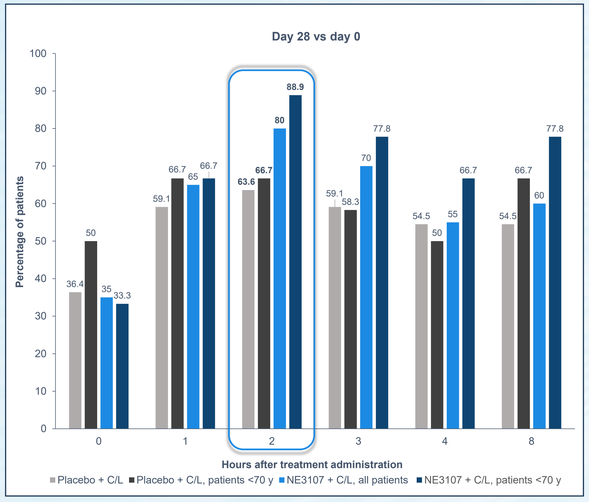
- On day 28, patients treated with NE3107 + C/L demonstrated a lower (3+ points) MDS-UPDRS Part III (motor) score than patients treated with placebo + C/L at the 2- and 3-hour marks, indicating improved motor control (**Figure 3**)
  - Patients who received NE3107 + C/L had a lower Part III disease score at time 0 (before medication administration) compared to patients treated with placebo + C/L
- On day 28, patients <70 years old treated with NE3107 + C/L experienced improvements that were ~6 points better than those who received placebo + C/L at the 2- and 3-hour marks (**Figure 3**)
  - NE3107 +C/L-treated patients <70 years old had lower morning OFF state MDS-UPDRS Part III scores prior to medication administration (t=0) compared to those treated with placebo + C/L

Figure 3. Improvement in MDS-UPDRS Part III scores



- 80% of NE3107 + C/L-treated patients and 88.9% of NE3107 + C/L-treated patients <70 years of age demonstrated >30% improvement in their MDS-UPDRS Part III scores 2 hours post administration from baseline, compared with 63.6% and 66.7% of all patients and patients <70 years of age, respectively, treated with placebo + C/L (**Figure 4**)

Figure 4. Percentage of patients experiencing >30% improvement in MDS-UPDRS Part III scores



Morning ON state

- All patients who completed the study (n=19 for NE3107 + C/L; n=19 for placebo + C/L) were in the practically-defined OFF state in the morning (time 0) at baseline
- On day 28, 5 (26%) of all 19 patients treated with NE3107 + C/L, compared to none of the 19 patients treated with placebo + C/L, experienced a morning ON state prior to receiving their morning medications (**Table 2**)
  - This difference was statistically significant (P=0.046)

Table 2. Number of patients achieving morning ON state

	NE3107 + C/L	Placebo + C/L	*P*-value
n	19	19	
Day 28 "ON" at t=0, n (%)	5 (26%)	0	0.046

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 clinical efficacy objectives
- Additionally, NE3107 had a favorable safety profile and did not alter plasma levodopa concentration (for details see poster #1 in category Clinical Trials and Therapy in Movement Disorders (non-PD) (non-Dystonia))
- NE3107 + C/L combination treatment was associated with clinically meaningful[15] and superior improvements (3+ points) on the motor examination part (Part III) of the MDS-UPDRS
  - Patients <70 years of age appeared to demonstrate greater motor control with NE3107, suggesting that younger patients, presumably with milder disease (less PD progression), may benefit more from an anti-inflammatory, NE3107 intervention
- At the end of the study, only patients who received NE3107 + C/L, and not placebo + C/L, were assessed as being in the morning ON state prior to receiving their morning medication, an improvement in motor function that is clinically meaningful for patients with PD
- These data are in line with the presumed roles of neuroinflammation and insulin resistance in the pathophysiology of PD and the potential effect of NE3107 on glutamate- and purine-stimulated inhibition of dopamine receptors
  - One study showed that exposure to anti-TNFα therapy conferred significant protection against developing PD among patients with inflammatory bowel disease[16]
  - In a recent phase 2 trial of patients with dementia, NE3107 treatment was associated with decreased TNF-α[17]
- Our findings demonstrate the potential intrinsic and levodopa-enhancing, pro-motoric activity of NE3107 that is consistent with data from pre-clinical trials and support further clinical investigation of nondopaminergic therapies in late-phase clinical trials

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AIMS, Abnormal Involuntary Movement Scale; AUC, area under the curve; BID, twice per day; C_{max}, maximum serum concentration; C-SSRS, Columbia-Suicide Severity Rating Scale; ERK, extracellular signal-regulated kinase; IL, interleukin; IR, immediate release; LID, levodopa-induced dyskinesia; MAPK, mitogen-activated protein kinases; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; SAE, serious adverse event; 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; TNFR1, TNF-α receptor 1.