Rationale for a Potentially Pivotal Study of NE3107 in Parkinson's Disease

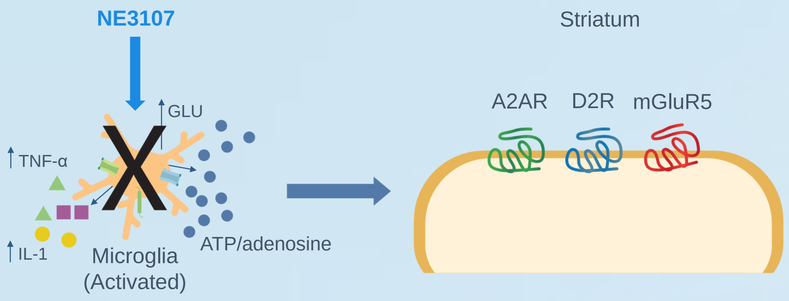
Nily Osman, Clarence Ahlem, Christopher Reading, Joseph Djan, Joseph Palumbo

BioVie Inc., Carson City, Nevada, USA.

BACKGROUND

- Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra of the brain, and patients can suffer from motor-related symptoms (such as tremors, bradykinesia, stiffness, and impaired balance) and non-motor symptoms (such as cognitive impairment and problems with mood, behavior, and sleep)[1,2]
- Levodopa, a dopamine precursor, can effectively improve motor function, but its prolonged use leads to levodopa-induced dyskinesia (LID) and diminished efficacy, leaving many patients unable to fully benefit in the longer term[1-3]
  - Levodopa lacks disease-modifying potential, and there is an urgent need for safe and effective therapies that can slow or prevent the progression of PD
- Chronic neuroinflammation, involving activated microglia and TNF-α release, and aberrant insulin signaling are thought to promote mitochondrial dysfunction, oxidative stress, and accumulation of α-synuclein, some of the key factors driving PD pathogenesis and progression[4-7]
- NE3107 is an oral, blood-brain barrier–permeable molecule that binds the inflammatory mediator ERK, to inhibit TNF-α signaling and inflammatory activation of ERK and NF-κB, without disrupting homeostasis[8]
- NE3107 potentially downregulates microglia to decrease purine- and glutamate-stimulated inhibition of D2R in heterotrimeric complexes[9] (**Figure 1**)
- Based on preclinical studies in which NE3107 demonstrated anti-inflammatory, insulin-sensitizing, pro-motoric, and neuroprotective effects, NE3107 is currently being evaluated for its ability to slow the progression of inflammation-driven neurodegenerative disorders, including AD and PD[2,8]

Figure 1. NE3107's hypothesized action on activated microglia



OBJECTIVES

- To assess the safety, tolerability, and efficacy of oral NE3107 in a randomized, placebo-controlled, potentially pivotal study in patients with PD over a duration of approximately 40 weeks
- As a rationale for a potentially pivotal, confirmatory study, here we report the outcomes of a phase 2 study of NE3107 in carbidopa/levodopa-treated patients with PD (NM201) and select assessments from a phase 2 study of NE3107 in patients with dementia

METHODS

- **PD trial NM201 (NCT05083260)** was an exploratory, phase 2, double-blind, placebo-controlled study assessing the safety, tolerability, and efficacy of NE3107, as well as the effects of NE3107 on levodopa PK
  - Over 40 patients with PD were randomized 1:1 to receive either 20 mg oral NE3107 + IR C/L or placebo + IR C/L over 27 days
  - Safety and tolerability endpoints included suicidality (measured by C-SSRS) and the incidence TEAEs and SAEs
  - Efficacy endpoints evaluated changes in MDS-UPDRS Part III score from baseline (practically-defined OFF) to postdose timepoints each day, changes from baseline in MDS-UPDRS Part I and II scores, motor state OFF time during study visits, time to onset of ON time, and changes in non-motor symptoms (measured using NMSS)
- **AD trial** (**NCT05227820**) was an exploratory, phase 2, open-label, single-arm study to assess the safety and efficacy of 20 mg oral NE3107 in 18 patients with MCI or mild dementia and 5 patients with moderate dementia over 3 months
  - Primary efficacy endpoints evaluated changes in functional connectivity, arterial perfusion, and glutathione levels using advanced MRI of the brain
  - Secondary efficacy endpoints assessed changes in cognitive, AD biomarkers, inflammatory biomarkers, depression severity, and dementia symptoms

RESULTS

NM201 Trial

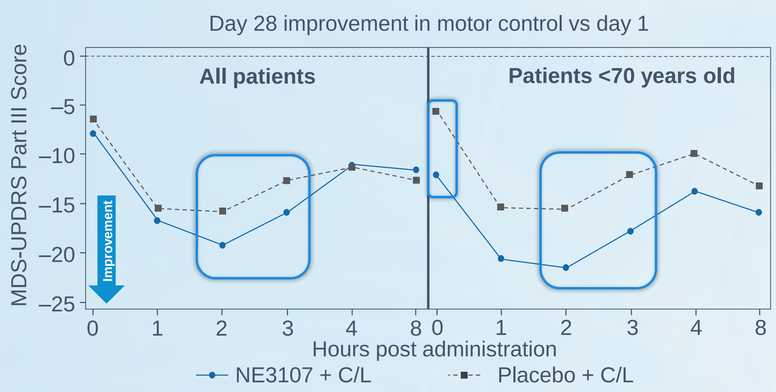
- In the NM201 trial, the baseline characteristics for both treatment groups were well balanced, except that the NE3107 group had a lower total daily levodopa dose and a higher Part III score at baseline (**Table 1**)
  - ~50% of the total patient population was <70 years old

Table 1. Baseline Characteristics

Characteristic	NE3107 + IR C/L (n=22)	Placebo + IR C/L (n=23)
Age, mean, (y)	67.6	66
Gender, n (%) Female Male	 9 (41) 13 (59)	 8 (35) 15 (65)
Weight, mean (kg)	80.1	80.8
BMI, mean	28.2	27.9
Time since diagnosis, mean (y)	7.6	7.3
Total daily levodopa, mean (mg)	548	691
MDS-UPDRS Scores, mean Part I Part II Part III	 6.8 9.4 28.4	 7.5 8.2 25.8
ON time without dyskinesia within 4 h, mean (h)	1.95	1.93
OFF time within 4 h, mean (h)	2.1	1.7

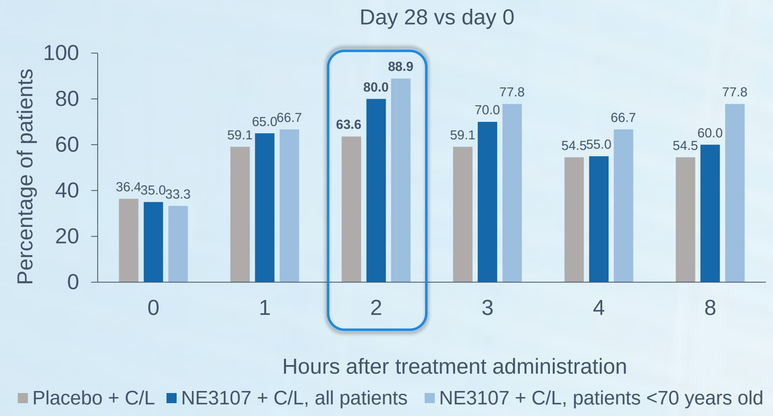
- Patients treated with NE3107 + C/L experienced greater improvements (3+ points) in their MDS-UPDRS Part III score than patients treated with placebo + C/L at the 2- and 3-hour marks (**Figure 2**)
  - Patients who received NE3107 + C/L had a lower Part III disease score at time 0 (before medication administration) compared to patients treated with placebo + C/L
- Patients <70 years old treated with NE3107 + C/L experienced improvements that were ~6 points better than those who received placebo + C/L (**Figure 2**)
  - NE3107-treated patients <70 years old had lower morning OFF state Part III scores prior to medication administration (t=0) compared to those treated with C/L alone
- 5 (26%) of the 19 patients treated with NE3107, compared to none of the 19 placebo-treated patients, who had a baseline of morning OFF experienced a morning ON state prior to receiving their morning medications on day 28
  - This difference was statistically significant (*P*=0.046)

Figure 2. 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 to 63.6% of patients treated with placebo + C/L (**Figure 3**)

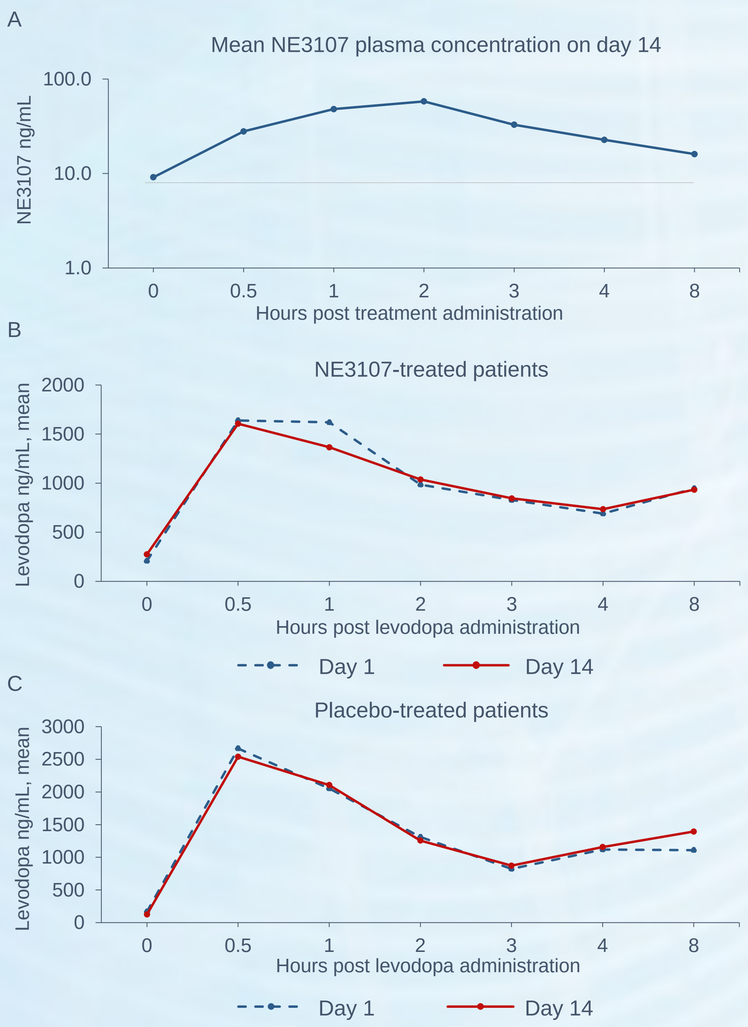
Figure 3. Percentage of patients experiencing >30% improvement in MDS-UPDRS Part III scores



Safety and PK in NM201

- No drug-related adverse events were observed
- An analysis of NE3107 plasma concentration on day 14 revealed that a 20 mg twice daily regimen yielded a mean trough of ~10 ng/mL, significantly higher than the concentration required to saturate its molecular target (<1 ng/mL)[10] (**Figure 4A**)
- NE3107 did not affect the PK profile of levodopa (**Figures 4B** and **4C**)

Figure 4. PK analysis



AD Phase 2 Trial

- NE3107 was associated with improvements in neurophysiological, neuropsychological, and biomarker status in the AD phase 2 trial
  - Plasma TNF-α levels decreased from baseline in 61% (n=11) of all 18 patients analyzed and 64% (n=9) of 14 patients with MMSE ≥20 (MCI or mild dementia), suggesting lower inflammation
  - Brain glutathione levels were increased from baseline in 59% (n=13) of all 22 patients analyzed and 67% (n=12) of 18 patients with MMSE ≥20, indicating decreased oxidative stress[11]
  - Patients with MMSE ≥20 had statistically significant improvements in their ADAS-Cog11 (*P*=0.0173) and ADCOMS (*P*=0.0094), suggesting improved cognitive functioning
  - Improvements from baseline in ADAS-Cog11 significantly correlated with changes in brain glutathione (r=–0.45; *P*<0.05) and TNF-α (r=0.59; *P*<0.05) levels in the total patient population and patients with MCI or mild dementia, respectively
  - Patients with depression at baseline (68%; 15/22) had a significantly decreased mean PHQ-9 (depression) score (*P*=0.0147) after NE3107 treatment, including improvements in the sleep disturbance domain
  - NE3107 treatment was associated with several patient- and study partner-reported benefits, including improved mood and memory

CONCLUSIONS

- The NM201 exploratory, phase 2, placebo-controlled, double-blind, randomized study assessed the safety, efficacy, and PK of NE3107 in combination with C/L in patients with PD, and met both of its objectives
  - NE3107 + C/L combination treatment was associated with clinically meaningful[12] and superior improvements (3+ points) on the motor examination part (Part III) of the MDS-UPDRS
  - Patients <70 years of age experienced greater motor control with NE3107, suggesting that younger patients, presumably with 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
  - The observed pro-motoric effects of NE3107 were likely not the result of increased plasma levodopa concentrations
- Our findings demonstrate the potential intrinsic and levodopa-enhancing, pro-motoric activity of NE3107 that is consistent with data from animal models and support further clinical investigation of NE3107 in late-phase trials
- In our phase 2 study in patients with dementia, NE3107 treatment was associated with improved brain functional connectivity, cognition, mood, and sleep, as well as decreased inflammation, oxidative stress, and depression symptoms
- To date, no safety signal has been observed in any clinical study of NE3107
- Our data form the basis of a future, potentially pivotal confirmatory study to demonstrate the safety and efficacy of NE3107 in PD
  - Patients with a diagnosis of PD, history of motor fluctuations with significant morning bradykinesia, and a demonstrated response to levodopa may be eligible to participate
  - Patients will be randomized 1:1 to receive 20 mg oral NE3107 twice daily or placebo over approximately 40 weeks

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DISCLOSURES

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A2AR, adenosine receptor; AD, Alzheimer's disease; ADAS-Cog11, 11-subunit Cognitive Subscale of the Alzheimer's Disease Assessment Scale; ADCOMS, Alzheimer's Disease Composite Score; ATP, adenosine triphosphate; BMI, body mass index; C-SSRS, Columbia-Suicide Severity Rating Scale; D2R, dopamine receptor; ERK, extracellular signal-regulated kinases; GLU, glutamate; IL-1, interleukin-1; IR C/L, immediate release carbidopa/levodopa; MCI, mild cognitive impairment; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; mGlu5R, metabotropic glutamate receptor subtype 5; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMSS, Non-Motor Symptom Assessment Scale for Parkinson's Disease; PHQ-9, 9-item submodule of the Patient Health Questionnaire; PK, pharmacokinetics; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TNF-α, tumor necrosis factor alpha.

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