Safety, Tolerability, and Efficacy of NE3107 From a Phase 2, Double-Blind, Placebo-Controlled Study in Levodopa/Carbidopa-Treated Patients With Parkinson's Disease

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BACKGROUND

- Disrupting the feed-forward loop formed by neuroinflammation, insulin resistance, and oxidative stress may be an effective strategy to limit PD progression[1-6]
- NE3107 is an oral, blood-brain–permeable molecule that binds ERK and has anti-inflammatory and insulin-sensitizing activities via inhibition of inflammation-stimulated ERK and NF-κB activation and TNF-α signaling, without disrupting homeostasis[7]
- NE3107 has an excellent safety profile and was shown to improve insulin sensitivity and glucose metabolism and reduce CRP and HbA1c in obese and inflamed patients with impaired glucose tolerance or T2D[7]
- In a marmoset PD model, NE3107 was associated with improved mobility, enhanced levodopa activity, and decreased neuronal death in the substantia nigra; it also alleviated levodopa-induced dyskinesia, a side effect of long-term exposure to levodopa[8]
- We conducted a phase 2, double-blind, placebo-controlled study to assess the safety, tolerability, and exploratory efficacy of NE3107 in levodopa-treated PD participants and the effects of NE3107 on the PK profile of carbidopa/levodopa (C/L)

OBJECTIVES

- The objectives of this phase 2, double-blind, placebo-controlled, 28-day trial were to assess the safety, tolerability, and exploratory efficacy of NE3107 in levodopa-treated PD participants and examine the effects of NE3107 on the PK profile of concomitantly administered C/L
- Here we report the safety, tolerability, and exploratory efficacy of NE3107 in levodopa-treated patients with PD

METHODS

Study Design

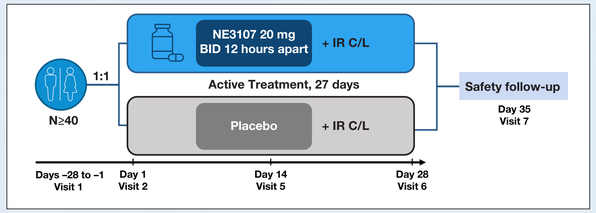
- This was a double-blind, placebo-controlled, phase 2 trial wherein 40 C/L-treated patients with PD were randomized 1:1 and received either 20 mg oral NE3107 twice daily (approximately 12 hours apart) or matching placebo for 27 days (days 2-28)
- Endpoint assessments were carried out on day 1 (visit 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 1. Study Design



Assessments

Safety and tolerability endpoints

- 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

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

- MDS-UPDRS assessments
  - Change in MDS-UPDRS Part III Score from baseline (practically defined OFF) to postdose timepoints each day
  - Average MDS-UPDRS Part III Score when ON
  - MDS-UPDRS Part I Score
  - MDS-UPDRS Part II Score
- Motor state OFF time during study visits
- Motor state ON time with or without 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

RESULTS

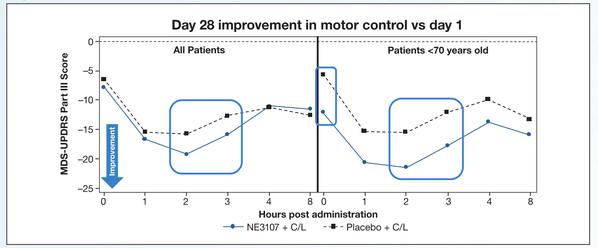
- Overall, the baseline characteristics for both treatment groups were well balanced, except that the NE3107 group had a lower total daily levodopa dose and a higher Part III Score at baseline **(Table 1)**
- ~50% of the total patient population was <70 years old

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	9 (41)	8 (35)
Male	13 (59)	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	6.8	7.5
Part II	9.4	8.2
Part III	28.4	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 and C/L experienced greater improvements (3+ points) in their MDS-UPDRS Part III Score than patients treated with placebo and C/L at the 2- and 3-hour marks **(Figure 2)**
- Patients <70 years old treated with NE3107 and C/L experienced improvements that were ~6 points better than those who received placebo and 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

Figure 2. Improvement in MDS-UPDRS Part III Scores



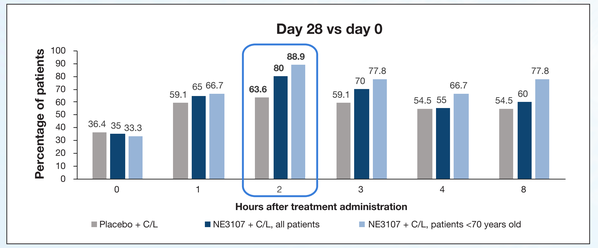
- 26% (5/19) of patients treated with NE3107, compared to none (0/19) of the placebo-treated patients, who had a baseline of morning OFF experienced a morning ON state prior to receiving their morning medications on day 28 **(Table 2)**
  - This difference was statistically significant (*P*=0.046)

Table 2. Percentage 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**

- 80% of NE3107 and C/L-treated patients and 88.9% of NE3107 and C/L-treated patients <70 years of age demonstrated >30% Part III score improvements 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

- No drug-related adverse events were observed
- NE3107 did not affect the PK profile of levodopa

CONCLUSIONS

- Our phase 2, placebo-controlled, double-blind study assessing the safety, efficacy, and PK of NE3107 in patients with PD met both of its objectives
- NE3107-levodopa combination treatment was associated with clinically meaningful[9] 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, and not levodopa alone, were assessed as being in the morning ON state before 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 not the result of increased plasma levodopa concentrations
- The 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

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Disclosures

CA, CR, JD, and JP are employees of BioVie Inc.

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BID, twice per day; BMI, body mass index; CRP, C-reactive protein; C-SSRS, Columbia-Suicide Severity Rating Scale; ERK, extracellular signal-regulated kinase; HbA1c, hemoglobin A1C; IR C/L, immediate release carbidopa/levodopa; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; NF-κB, nuclear factor kappa B; PD, Parkinson's disease; PK, pharmacokinetics; SAE, serious adverse event; T2D, type 2 diabetes; TEAE, treatment-emergent adverse event; TNF-α, tumor necrosis factor alpha.