Effect of NE3107 on the Pharmacokinetics Profile of Carbidopa/Levodopa in Patients With Parkinson's Disease: A Phase 2, Double-Blind, Placebo-Controlled Study

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BACKGROUND

- Neuroinflammation, oxidative stress, and insulin resistance are thought to drive neurodegeneration in Parkinson's disease (PD)[1-4]
  - Chronic inflammation is maintained through inflammatory signaling cascades involving ERK and NF-κB and the release of pro-inflammatory cytokines, such as TNF-α and IL-1β[4]
- Levodopa improves motor control but lacks disease-modifying potential, and long-term exposure can trigger involuntary movements known as levodopa-induced dyskinesia (LID)[5,6]
- There is an urgent need for disease-modifying therapies that are compatible with levodopa and can mitigate LID[7]
- NE3107 is an oral, blood-brain–permeable molecule that binds ERK and has anti-inflammatory and insulin-sensitizing activities via inflammation-specific inhibition of ERK and NF-κB activation and decreased TNF-α signaling, without disrupting homeostasis[8]
- In a marmoset PD model, NE3107 was associated with improved mobility, enhanced levodopa activity, decreased neuronal death in the substantia nigra, and alleviation of LID[9]
- This phase 2, double-blind, placebo-controlled study assessed 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

OBJECTIVES

- The overall objective of this phase 2, double-blind, placebo-controlled, 28-day study was 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 carbidopa/levodopa (C/L)
- Here, we report the effects of NE3107 on the PK profile of concomitantly administered C/L

METHODS

Study Design

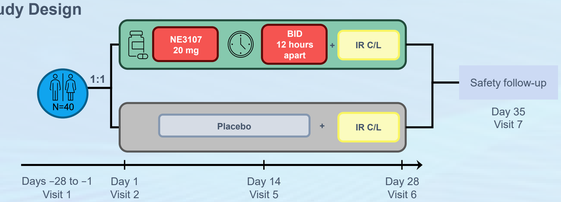
- This was a double-blind, placebo-controlled, phase 2 trial wherein C/L-treated patients with PD received either placebo or 20 mg oral NE3107 administered twice daily (approximately 12 hours apart) over 27 days (**Figure 1**)
- Endpoint assessments were carried out on day 1 (visit 2), day 14 (visit 5), day 28 (visit 6), and day 35 (visit 7) during the safety follow-up

Study Population

Key inclusion criteria

- Aged 30-80 years
- Diagnosis of PD with bradykinesia and a clear motor response to levodopa
- History of motor fluctuations with reliable early-morning OFF episodes
- Receiving a C/L dose of at least 300 mg daily

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
- Total OFF time over the 8-hour assessment period
- Total ON time with or without dyskinesia during the 8-hour study period

PK endpoints – changes in levodopa parameters between visits 2 and 5

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

RESULTS

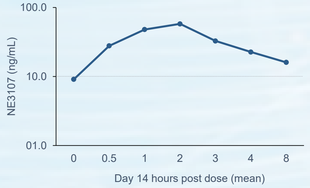
- Overall, the baseline characteristics for both treatment groups were well balanced, except that the NE3107 group had a lower total daily levodopa dose at baseline (**Table 1**)

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
Total daily levodopa, mean, mg	548	691
Years since diagnosis, mean	7.6	7.3
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 hr, mean, hr	1.95	1.93
OFF time within 4 hr, mean, hr	2.1	1.7

- An assessment of NE3107 plasma concentration on day 14 revealed that a 20-mg twice daily regimen yielded a mean trough of ~10 ng/mL (**Figure 2**)
- NE3107 has been shown to saturate its molecular target at a concentration <1 ng/mL,[10] thus our treatment regimen ensures target saturation throughout the treatment period

Figure 2. NE3107 plasma concentration on day 14



- A comparison of day 1 and day 14 PK parameters demonstrated that NE3107 administration did not affect the PK profile of levodopa (**Figure 3** and **Table 2**)
- In patients who received NE3107, 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, 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 and placebo, respectively

Figure 3. Plasma Levodopa PK Curves

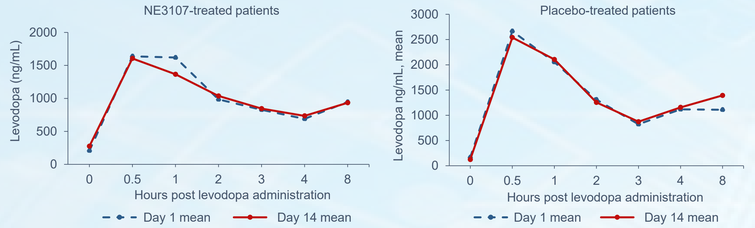


Table 2. Levodopa PK Profile

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

CONCLUSIONS

- In this phase 2, double-blind, placebo-controlled study of patients with PD, we performed drug-drug interaction assessments to ascertain the effects of NE3107 on the PK profile of levodopa
- NE3107 did not affect the PK profile of levodopa
- Our findings indicate the absence of adverse interactions of NE3107 with levodopa and suggest that no C/L dose adjustment is likely to be required for patients who receive NE3107 treatment
- These data support the clinical investigation of NE3107 in a larger, confirmatory, phase 3 trial in patients with PD

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DISCLOSURES

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

AUC, area under the curve; BID, twice per day; BMI, body mass index; C/L, carbidopa/levodopa; C_{max}, maximum serum concentration; C-SSRS, Columbia-Suicide Severity Rating Scale; ERK, extracellular signal-regulated kinases; IL, interleukin; IR, immediate release; MDS-UPDRS, Movement Disorder Society- Unified Parkinson's Disease Rating Scale; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PK, pharmacokinetics; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; T_{max}, time to reach C_{max}; TNF, tumor necrosis factor.

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