Effects of NE3107 on Depression and Multi-modal Outcomes in a Phase 2, Open-label Study in Patients With Cognitive Decline Due to Degenerative Dementias

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BACKGROUND

- Chronic neuroinflammation is thought to have pathogenic roles in neurodegenerative disorders,[1] such as Alzheimer's disease (AD) and Parkinson's disease (PD); insulin resistance and diabetes[2,3]; and mood disorders, such as depression[3]
  - TNF-α, a master regulator of pro-inflammatory responses, is intimately involved in the pathogenesis of neurocognitive disorders and insulin resistance,[1,2] and it may also contribute to emotional dysregulation, particularly depressive disorder[4]
  - Increases in biomarkers of systemic inflammation were found to be associated with an increased risk of depression[5]
  - Patients with major depression were shown to have elevated levels of pro-inflammatory markers, particularly TNF-α[4]
- AD, impaired glucose metabolism, and depression are frequently seen to occur simultaneously[6-8]
- Therefore, reduction of chronic neuroinflammation with the help of anti-inflammatory agents may improve depression symptoms,[4] AD pathology,[8] and cognition[9]
- NE3107 is an oral, small-molecule, blood-brain barrier–permeable compound with potential anti-inflammatory and insulin-sensitizing functions resulting from binding to ERK and selective inhibition of ERK-, NF-κB–, and TNF-α–stimulated inflammatory signaling[10]
- In an exploratory, open-label, phase 2 study with 23 patients with mild to moderate dementia, NE3107 was associated with the following improvements:
  - Increased perfusion and functional connectivity in several regions of the brain (primary endpoint)
  - Reduced inflammation (lower TNF-α), CSF AD biomarkers (P-tau and P-tau:Aβ42 ratio), and oxidative stress (increased brain glutathione)
  - Better neurocognitive functioning (including improved ADAS-Cog11, QDRS, and ADCOMS)
  - Significant improvements in the clinician-, patient-, and caretaker-rated Global Rating of Change (GRC)
- Given the significant role of TNF-α in neuroinflammation, AD, and depression, we evaluated the potential scope of the anti-inflammatory effects of NE3107, including any anti-depressive effects, as well as the overall treatment experience for patients in this phase 2 trial

OBJECTIVES

- This exploratory, phase 2, open-label, 3-month study explored the potential effects of anti-inflammatory NE3107 treatment on neurophysiological health, neurocognitive function, biomarker status, oxidative stress, depression symptoms, and functional improvement (GRC), as well as the overall treatment experience, in patients with dementia
- Here, we report the post-treatment changes in depression and dementia symptoms, patient experience, and the outcomes of multi-modal correlation analyses to demonstrate correlations between the anti-inflammatory effects of NE3107 and any associated meaningful clinical outcomes

METHODS

Study Design

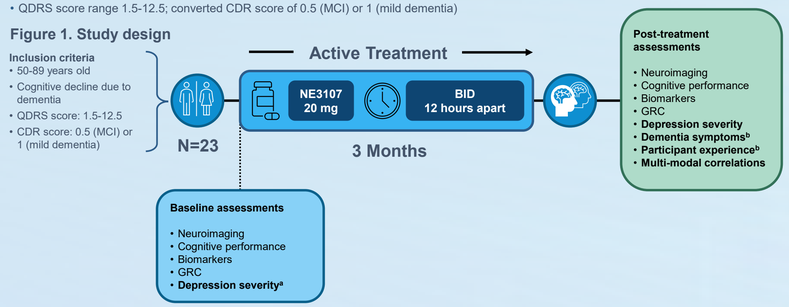
- This was a single-arm, open-label, phase 2 trial evaluating the efficacy and safety of 20-mg oral NE3107 administered twice daily (approximately 12 hours apart) to patients with clinical dementia over a duration of 3 months (**Figure 1**)

Study Population

Key inclusion criteria

- Aged 50-89 years
- Diagnosis of cognitive decline due to degenerative dementia
- QDRS score range 1.5-12.5; converted CDR score of 0.5 (MCI) or 1 (mild dementia)

Figure 1. Study design



[a]Depression severity was assessed using the PHQ-9, a submodule of the full PHQ used to screen for depression and assess its severity.[11]
[b]Participants' (patients and study partners) experience with dementia before and after treatment with NE3107, meaningful changes after treatment, and treatment experience were evaluated in a 60-minute, semi-structured interview.

Assessments

Primary – change from baseline to treatment completion

- Multi-modal brain MRIs performed at baseline and treatment completion assessed structural and functional cerebral alterations associated with AD

Secondary – change from baseline to treatment completion

- Serological inflammatory marker: TNF-α
- AD CSF biomarkers: Aβ42, P-tau, and P-tau:Aβ42 ratio
- Cognitive performance assessments, including ADAS-Cog11, MoCA, and MMSE
- Participants, clinicians, and caregivers reported a GRC upon study completion
- **Depression symptoms: Patient Health Questionnaire (PHQ-9)**
  - The PHQ-9 is a 9-item submodule of the full PHQ, validated as a measure of depression severity, and is scored from 0 to 27, where a score of ≥5 indicates depression, and higher scores indicate more severe depression[11]
- **Dementia symptoms and treatment experience: participant interviews**
  - Evaluated using 60-minute, semi-structured interviews
  - Consisted of open-ended questions to characterize a participant's dementia signs and symptoms prior to the trial, changes experienced during the trial, and experience with the trial medication (NE3107)

RESULTS

- 23 patients were enrolled in the study and received 20-mg oral NE3107 twice daily for 3 months
- **Table 1** shows the demographic and baseline characteristics of the study patients

Neuroimaging analyses

- NE3107 was associated with clinician-rated improvements from baseline in functional connectivity within the NBM, the precuneus, and the hippocampus
- MRS analysis showed that 59% (n=13) of all 22 patients analyzed and 67% (n=12) of patients with MCI or mild dementia (MMSE ≥20) showed increases in the levels of brain glutathione after NE3107 treatment, compared to baseline

Multi-modal correlation analyses

- For the total patient population, we observed statistically significant correlations in changes from baseline between the following parameters:
  - ADCOMS and Aβ42 (r=0.53)
  - ADCOMS and P-tau levels (r=0.49)
  - ADAS-Cog11 scores and brain glutathione levels (r=−0.45)
  - Aβ42 and P-tau levels (r=0.72)
  - Aβ42 and the P-tau:Aβ42 ratio (r=−0.71)
  - P-tau levels and the P-tau:Aβ42 ratio (r=−0.59)
- For patients with MMSE ≥20, we observed statistically significant correlations in changes from baselines between the following parameters:
  - ADAS-Cog11 scores and TNF-α levels (r=0.59)
  - P-tau levels and the P-tau:Aβ42 ratio (r=0.74)
- Improvements in ADAS-Cog11 significantly correlated with clinician-rated improvements in GRC outcomes (r=−0.52; *P*<0.05)

Table 1. Baseline characteristics

Characteristic	All patients (N=23)
Age, mean (SD)	71.1 (9.50)
Gender, n (%) Female Male	 16 (70) 7 (30)
Family history, n (%) AD AD, dementia, unspecified etiology AD, PD Dementia, unspecified etiology PD	 5 (22) 2 (9) 1 (4) 4 (17) 1 (4)
QDRS score, mean	5.07
CDR score, n (%) 0.5 1	 18 (78) 5 (22)
MMSE, n (%) ≥20 (MCI to mild dementia) <20 (moderate dementia)	 18 (78) 5 (22)
PHQ-9, n (%) <5 (none to minimal depression) ≥5 (mild, moderate, or severe depression)	n=22 7 (32) 15 (68)
APOE status ε2/ε3 ε2/ε4 ε3/ε3 ε3/ε4 ε4/ε4	 2 (9) 1 (4) 9 (39) 10 (44) 1 (4)

Changes in depression symptoms

- Out of a total of 22 patients who were evaluated using the PHQ-9, 15 (68%) patients had a baseline score of ≥5, indicating mild, moderate, or severe depression[11] (**Table 1**)
- 64% (n=14) of all 22 patients analyzed had a lower PHQ-9 score after NE3107 treatment, compared with baseline (mean change: −2.9; *P*=0.0203) (**Figure 2**)
  - In patients with a baseline PHQ-9 score of ≥5, the PHQ-9 score decreased by an average of 4.3 points (95% CI: −7.674, −0.993) after treatment with NE3107, compared with baseline (*P*=0.0147)
- Patients with mild to severe depression (baseline PHQ-9 score ≥5) had greater improvement, compared to all patients, in several individual PHQ-9 domains evaluating apathy, depressive symptoms, sleep disturbance, fatigue, eating disorders, and low self-esteem (**Figure 3**)
- At the end of the study, 27% (n=4) of 15 patients with mild to severe depression at baseline had PHQ-9 scores <5, indicating minimal depression[11]
- Post-treatment changes in PHQ-9 scores significantly correlated with changes in ADAS-Cog11 scores (r=−0.5; *P*<0.05) and ADCOMS (r=−0.46; *P*<0.05)

Figure 2. Change from baseline in PHQ-9 scores

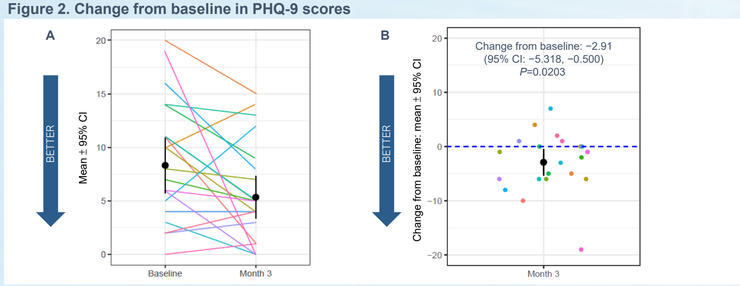
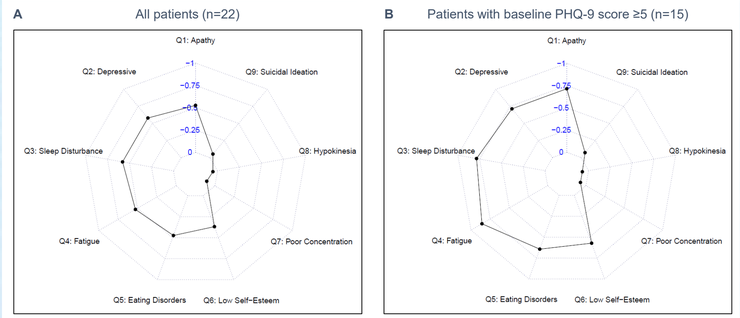


Figure 3. Change from baseline in individual domains of the PHQ-9



Outcomes of exit interviews

- 48% (n=11 of 23) of patients completed an exit interview; their baseline demographics and clinical characteristics are shown in **Table 2**
  - Average age and family history of AD or dementia were similar to the overall study population
  - Slightly more females were represented in the exit interview sample than the main study
  - 64% (n=7) of the 11 patients completed interviews with a study partner; 36% (n=4) participated independently
- Patients reported an average of 4.6 (SD=2.02; range: 1-7) problems related to their degenerative dementia prior to NE3107 treatment
  - These included memory difficulties/brain freezes (n=11; 100%), difficulty thinking clearly (n=7; 64%), frustration/depression (n=6; 55%), and feeling tired or lacking energy (n=5; 46%)
- The biggest pre-trial challenges for patients were difficulties with memory (n=7; 64%), ability to think clearly (n=3; 27%), and mood (n=2; 18%)
- Study partners (n=7) reported an average of 4 (SD=1.53; range 2-6) problems related to the patient's degenerative dementia prior to NE3107 treatment
  - These included mood problems (n=7; 100%), cognitive difficulties (n=7; 100%), ability of the patient to think clearly (n=6; 86%), and memory problems (n=5; 71%)
- The biggest pre-trial challenges for study partners were difficulties with the patient's mood (n=4; 57%), ability to think clearly (n=3; 42%), and memory (n=2; 29%)
- Most (n=9; 82%) patients reported improvements (mean [SD]: 4.7 [1.86]; range: 1-7) after treatment with NE3107; all of these patients reported that these changes made a meaningful difference to them (**Table 3**)
- Almost all (n=6; 86%) study partners reported improvements (mean [SD]: 4.0 [1.53]; range: 2-6) in the patient after treatment with NE3107; all of these study partners reported that these changes were meaningful to them (**Table 3**)

Table 2. Baseline characteristics of patients who completed the exit interviews

Characteristic	All patients (n=11)
Demographic	
Age, y, mean (SD)	70.4 (6.32)
Gender, n (%) Female Male	 9 (82) 2 (18)
Family history[a], n (%) AD Dementia, unspecified etiology	 4 (36) 3 (27)
Ethnicity, n (%) Non-Hispanic	 11 (100)
Race, n (%) White	 11 (100)
Clinical, n (%)	
Traumatic brain injury	1 (9)
Concussion	2 (18)
Stroke	1 (9)
High blood pressure	2 (18)
High cholesterol	2 (18)
Sleep apnea	2 (18)
Major depressive disorder	2 (18)

[a]Not mutually exclusive.

Table 3. Changes after NE3107 treatment

Concept	Patient-Elicited		Study Partner–Elicited	
	Improvement, n (%) n=11	Meaningful Difference, n (%) n=9	Improvement, n (%) n=7	Meaningful Difference, n (%) n=6
Memory	8 (73)	7 (78)	5 (71)	3 (50)
Clarity	6 (55)	5 (56)	4 (57)	3 (50)
Engagement	6 (55)	5 (56)	4 (57)	2 (33)
Mood	7 (64)	4 (44)	6 (86)	6 (100)
Energy	4 (36)	3 (33)	2 (29)	1 (17)
Headaches	2 (18)	2 (22)	2 (29)	1 (17)
Feelings of hope	4 (36)	2 (22)	2 (29)	1 (17)
Movement	1 (9)	1 (11)	1 (14)	1 (17)
Weight loss	1 (9)	1 (11)	-	-
Independence	1 (9)	-	4 (57)	2 (33)
Self-care	-	-	3 (43)	0 (0)
No improvement	2 (18)	-	1 (14)	-

- All patients (n=11; 100%) who completed the exit interviews noted that the study medication was easy to take
  - Most of the patients (n=10; 91%) had no issues taking the study medication at the frequency directed (BID) and noted that it was easy to remember to take the medication at that frequency (n=8; 73%)

CONCLUSIONS

- In this phase 2, single-arm, open-label study, we investigated the anti-inflammatory effects of oral NE3107 treatment on the neurophysiology and neuropsychology of 23 patients with mild to moderate dementia over 3 months. We qualitatively characterized the pre-trial disease burden and patient experience with NE3107 and evaluated its ability to reduce the severity of depression in these patients
- Our study demonstrated post-treatment improvements in the neurophysiological health (functional connectivity within the brain) of patients, meeting its primary objective
- We hypothesized that the modulation of TNF-α levels and other inflammatory mediators would collectively lead to improvements in neuronal health and cognition in patients
  - In support of this, our findings demonstrated that NE3107's ability to reduce TNF-α significantly correlated with improvements in cognition
- For most patients, NE3107 was associated with a reduction in PHQ-9 scores, with greater improvements observed in patients with moderate to severe depression at baseline (PHQ-9 score ≥5). Consequently, more than 25% of patients with mild to severe depression at baseline had scores indicating minimal depression (PHQ-9 score <5) after treatment with NE3107
- Our exit interviews revealed that NE3107 treatment was associated with several benefits for patients, such as improvements in memory and clarity (cognition), mood (psychology), and engagement, and these improvements were meaningful to patients and their study partners
- Given its oral, twice-daily regimen, most patients agreed that NE3107 was easy to take and adhere to
- Thus, we demonstrated changes indicative of an overall reduction in depression symptoms after treatment with NE3107 and successfully characterized treatment benefits that are most meaningful to patients and their caregivers
- Our findings encourage further investigation of NE3107 in longer-term, placebo-controlled studies with patients with dementia and depression
- A randomized, placebo-controlled, phase 3 study of NE3107 in patients with mild to moderate AD is ongoing [NCT04669028]

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ACKNOWLEDGEMENTS

p-value communications provided editorial support. Funded by BioVie Inc.

DISCLOSURES

JP, NO, CA, and **CR** are employees of BioVie Inc.
JJ and **EM** are employees of Labcorp Drug Development.
JH, EM, KJ, ER, KM, VV, SB, JRS, and **SJ** have received grant support from BioVie Inc.
DG, KH, and **BP** have nothing to declare.

Aβ42, 42-amino acid beta amyloid peptide; ADAS-Cog11, the 11-component Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; *APOE*, apolipoprotein E; BID, twice daily; CDR, Clinical Dementia Rating; CI, confidence interval; CSF, cerebrospinal fluid; ERK, extracellular signal-regulated kinase; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NBM, nucleus basalis of Meynert; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; P-tau, phosphorylated tau protein; QDRS, Quick Dementia Rating System; SD, standard deviation; TNF-α, tumor necrosis factor alpha.

Presented at the 2023 Society of Biological Psychiatry Annual Meeting | April 27-29, 2023 | San Diego, CA