Multi-Modal Correlation Analyses From a Phase 2, Open-Label Study of NE3107 in Patients With Cognitive Decline Due to Degenerative Dementias

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BACKGROUND

- Alzheimer's disease (AD) is characterized by increased TNF-α (indicating increased inflammation),[1] decreased CSF Aβ42 (due to incorporation into plaques),[2,3] increased CSF P-tau,[2] reduced brain glutathione (indicating elevated oxidative stress),[4] and impaired insulin signaling[5,6]
  - These pathologies drive AD progression and contribute to cognitive decline
- TNF-α is thought to play a central role in AD pathophysiology, and treatment with anti–TNF-α therapies was shown to reduce AD pathologies, improve cognition, and lower the likelihood of developing AD[1,7]
- 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[8]
- 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[8]
- In an exploratory, 3-month, phase 2 trial, NE3107 treatment was associated with improved cognitive performance, including significant improvements in ADAS-Cog12 and CDR scores and ADCOMS, in patients with MCI to mild dementia (MMSE ≥20) [poster#007 in Neighborhood 6]
- This phase 2 trial also assessed improvements in neurophysiological health and in several AD-related biomarkers after NE3107 treatment as well as correlations between the anti-inflammatory effects and meaningful clinical outcomes

OBJECTIVES

- The objectives of this 3-month study were to assess the effects of anti-inflammatory NE3107 treatment on the neurophysiological and neuropsychological health and biomarker status of patients with dementia
- Here, we report the post-treatment changes in neuroimaging, the levels of the master inflammatory mediator, TNF-α, the brain oxidative stress marker, glutathione, and several key CSF AD biomarkers, as well as the outcomes of multi-modal correlation analyses

METHODS

Study Design

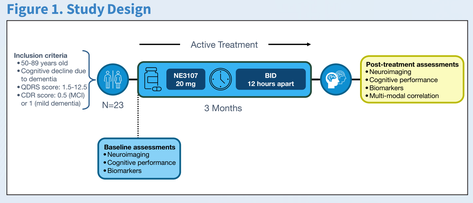
- This was a single-arm, open-label, phase 2 trial evaluating the efficacy and safety of 20 mg oral NE3107 administered twice daily (approximately 12 hours apart) to patients with clinical dementia over a duration of 3 months **(Figure 1)**

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



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
  - Changes in functional connectivity were assessed using BOLD imaging
  - Changes in glutathione levels were assessed using MRS

Secondary – changes 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-Cog12, MoCA, and MMSE
- Participants, clinicians, and caregivers reported a Global Rating of Change upon study completion

Safety Assessments

- Safety and tolerability were assessed using incidence reports, vital sign measurements, physical examinations, and clinical laboratory assessments
- Treatment-emergent adverse reactions were recorded throughout the study period

Statistical Analyses

- Paired sample t-tests were used for statistical analyses of the secondary endpoints including cognitive measures and changes in serological markers

RESULTS

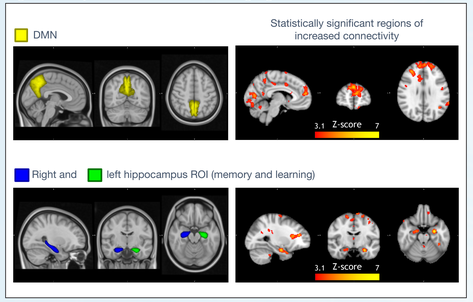
- Twenty-three patients were enrolled in the study and received 20 mg oral NE3107 twice daily for 3 months
- **Table 1** shows the demographic and baseline characteristics of the study patients

Table 1. Baseline Characteristics

Characteristic	All patients (N=23)
Age, mean (SD)	71.1 (9.50)
Gender, n (%)	
Female	16 (70)
Male	7 (30)
Family history, n (%)	
AD	5 (22)
AD, dementia, unspecified etiology	2 (9)
AD, PD	1 (4)
Dementia, unspecified etiology	4 (17)
PD	1 (4)
QDRS score, mean	5.07
CDR score, n (%)	
0.5	18 (78)
1	5 (22)
MMSE, n (%)	
≥20 (MCI to mild dementia)	18 (78)
<20 (moderate dementia)	5 (22)
APOE status, n (%)	
ε2/ε3	2 (9)
ε2/ε4	1 (4)
ε3/ε3	9 (39)
ε3/ε4	10 (44)
ε4/ε4	1 (4)

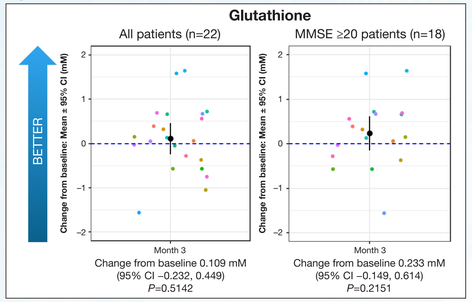
- ROI group analysis demonstrated that NE3107 was associated with increased functional connectivity from baseline in the default mode network (DMN) and either hippocampi using BOLD imaging **(Figure 2)**

Figure 2. Improvements in Neuroimaging



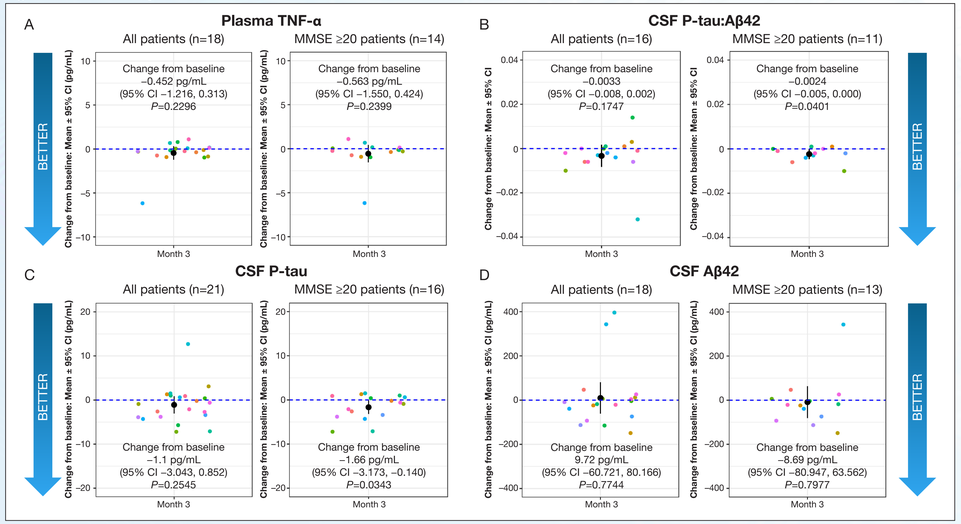
- MRS analyses revealed that NE3107 was associated with improvements in brain glutathione levels **(Figure 3)**
  - 59% (n=13) of 22 total patients and 67% (n=12) of 18 patients with MMSE ≥20 had increased brain glutathione levels, compared with baseline

Figure 3. Results – Brain Glutathione



- NE3107 was associated with improvements in plasma TNF-α levels and core CSF AD biomarkers **(Figure 4)**
  - 61% (n=11) of all 18 patients analyzed and 64% (n=9) out of 14 patients with MMSE ≥20 had reduced plasma TNF-α, compared with baseline
  - 63% (n=10) of 16 total patients and 64% (n=7) of 11 patients with MMSE ≥20 had a lower P-tau:Aβ42 ratio, compared with baseline
  - CSF P-tau levels were reduced in 62% (n=13) of 21 patients and 63% (n=10) of 16 patients with MMSE ≥20, compared with baseline
  - CSF Aβ42 levels decreased in 61% (n=11) of 18 total patients and 69% (n=9) of 13 patients with MMSE ≥20, compared with baseline
    - Soluble Aβ42 in CSF is a reflection of both synthesis and aggregation into plaques; anti-inflammatory activity reduces its synthesis

Figure 4. Inflammatory and AD Biomarkers



Multi-Modal Correlation Analyses

- For the total patient population, we observed statistically significant correlations between the following parameters:
  - Change from baseline in ADCOMS and Aβ42 (r=0.53)
  - Change from baseline in ADCOMS and P-tau levels (r=0.49)
  - Change from baseline in ADAS-Cog12 scores and brain glutathione levels (r=−0.45)
  - Change from baseline in Aβ42 and P-tau levels (r=0.72)
  - Change from baseline in Aβ42 and the P-tau:Aβ42 ratio (r=−0.71)
  - Change from baseline in P-tau levels and the P-tau:Aβ42 ratio (r=−0.59)
- For patients with MMSE ≥20, we observed statistically significant correlations between the following parameters:
  - Change from baseline in ADAS-Cog12 scores and TNF-α levels (r=0.59)
  - Change from baseline in P-tau levels and the P-tau:Aβ42 ratio (r=0.74)

CONCLUSIONS

- In this phase 2, single-arm, open-label study, we investigated the anti-inflammatory effects of oral NE3107 treatment in 23 patients with MCI or mild-to-moderate dementia over 3 months
- NE3107 was descriptively associated with clinician-rated improvements from baseline in functional connectivity within the DMN and both hippocampi
- In this small cohort of patients with dementia, NE3107 treatment was descriptively associated with: (a) a lowering of TNF-α, a master regulator of inflammatory pathways in AD pathogenesis, suggesting a lowering of pro-inflammatory responses[7]; (b) an increase in glutathione, a major brain antioxidant[4]; and (c) a reduction in P-tau protein levels, a significant neuropathological component of AD[2]
- Neurofibrillary tangles and Aβ plaques form a positive feedback loop with chronic neuroinflammation[7,9]; patients with MCI or mild dementia (MMSE ≥20) appeared to show statistically significant improvements from baseline in CSF P-tau levels and P-tau:Aβ42 ratio in this study
  - Reductions in the P-tau levels, rather than an increase in Aβ42 levels, were responsible for the overall reductions in the CSF P-tau:Aβ42 ratio
  - Since patients with MCI and AD have increased CSF P-tau:Aβ42 ratio,[2] it is possible to suggest that NE3107 may potentially prevent or slow cognitive decline and AD progression
- The observed statistically significant correlations of change among biomarkers, cognitive performance, and neuroimaging analyses in this study suggest potential drug effects of NE3107 and appear to highlight the multifaceted role of neuroinflammation in AD pathogenesis
- These data encourage further investigation of NE3107 in longer-term, placebo-controlled studies with patients with dementia
- A randomized, placebo-controlled, phase 3 study of NE3107 in patients with mild-to-moderate AD is ongoing [NCT04669028]

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Disclosures

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Aβ42, 42-amino acid beta amyloid peptide; ADAS-Cog12, the 12-component Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; BID, twice daily; BMI, body mass index; BOLD, blood-oxygen level dependent; CDR, Clinical Dementia Rating; CRP, C-reactive protein; CSF, cerebrospinal fluid; ERK, extracellular signal-regulated kinases; HbA1c, hemoglobin A1c; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NF-κB, nuclear factor kappa B; P-tau, phosphorylated tau protein; QDRS, Quick Dementia Rating System; ROI, region of interest; T2D, type 2 diabetes; TNF-α, tumor necrosis factor alpha.