P095

Biomarker Assessments From a Phase 2, Open-Label Study of NE3107 in Patients With Cognitive Decline Due to Degenerative Dementias

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BACKGROUND

- TNF-α, an important inflammatory regulator, is frequently overexpressed in neurodegenerative disorders, including MCI and AD, and significantly contributes to AD pathophysiology[1,2]
- TNF-α–mediated signaling activates several key inflammatory pathways (including the MAPK/ERK and IKK/NF-κB pathways), triggers the release of pro-inflammatory cytokines (including TNF-α and IL-1β), and increases Aβ synthesis[2-4]
  - Patients with MCI and AD were shown to have lower CSF Aβ42 levels and increased CSF p-tau levels compared to cognitively unimpaired individuals[5]
- Anti–TNF-α therapies were shown to significantly reduce the risk of AD in patients with RA and psoriasis and improve cognitive function in a small study of patients with RA[1,6,7]
- NE3107 is an oral, blood-brain–permeable molecule that binds ERK and has anti-inflammatory and insulin-sensitizing activities via inflammation pathway–specific inhibition of ERK and NF-κB activation, and decreased TNF-α signaling, without disrupting homeostasis[8]
- An ongoing phase 3 clinical trial is investigating the cognitive benefits and safety of NE3107 in patients with mild-to-moderate AD[8]
- Our phase 2, open-label study utilized multi-modal brain MRIs, cognitive performance assessments, and biomarker analyses to evaluate the efficacy and safety of NE3107 in patients with MCI or dementia
- Here, we report the post-treatment changes in the levels of the master inflammatory mediator, TNF-α, and several key CSF AD biomarkers

OBJECTIVES

- The overall objective of this 3-month study was to assess neurophysiological and neuropsychological benefits, ascertain improvements in glucose metabolism, and assess biomarker alterations in patients with dementia treated with NE3107

PRIMARY OBJECTIVE

- To evaluate the effect of NE3107 treatment on neurophysiological health as assessed by multi-modal brain MRIs obtained at baseline and treatment completion (3 months)

SECONDARY OBJECTIVES

To evaluate the effect of NE3107 treatment on neuropsychological health as assessed by cognitive performance testing administered at baseline and treatment completion

- To evaluate changes in CSF and serological inflammatory, glucose homeostasis, and AD biomarkers at baseline and treatment completion
- To determine the safety and tolerability of NE3107 during the study period

METHODS

STUDY DESIGN

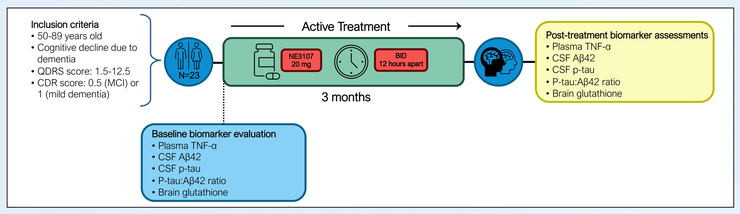
- This was a single-arm, open-label, phase 2 trial evaluating the efficacy and safety of 20 mg oral NE3107 administered twice daily (approximately 12 hours apart) to patients with clinical dementia **(Figure 1)**

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 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
- Serological glucose homeostasis
- 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 METHODS

ANALYSIS SET

- Statistics for efficacy and safety analyses included all study participants who received at least 1 dose of NE3107

SAMPLE SIZE DETERMINATION

- The study was not formally powered. 23 patients were enrolled assuming, from prior experience, that approximately 20 patients would complete the study

STATISTICAL ANALYSES

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

RESULTS

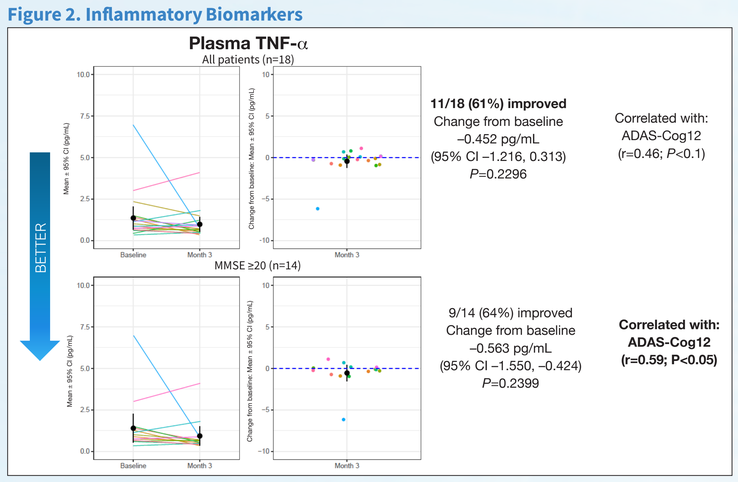
- 23 patients were enrolled in the study and received 20 mg oral NE3107 twice daily for 3 months
- **Table 1** shows the demographic and baseline characteristics of the study patients

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	18 (78)
<20	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)

- NE3107 was associated with decreased plasma TNF-α levels **(Figure 2)**
  - 61% (n=11) of all 18 patients analyzed and 64% (n=9) of 14 patients with MMSE ≥20 had reduced plasma TNF-α, compared with baseline

Figure 2. Inflammatory Biomarkers



- NE3107 was associated with improvements in core AD biomarkers **(Figure 3)**
  - 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 in 69% (n=9) of 13 patients with MMSE ≥20, compared with baseline. The data were not normally distributed due to 2 outliers in the total patients and 1 in patients with MMSE ≥20
    - Soluble Aβ42 in CSF is a reflection of both synthesis and aggregation into plaques; anti-inflammatory activity reduces its synthesis

Figure 3. CSF AD Biomarkers

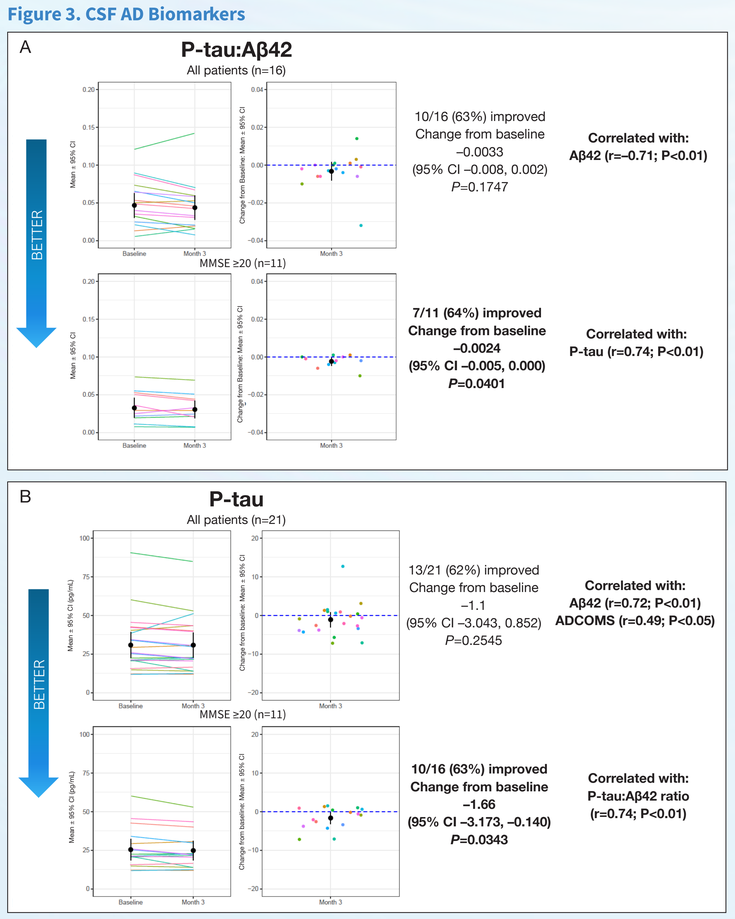


Figure 3. CSF AD Biomarkers (cont.)

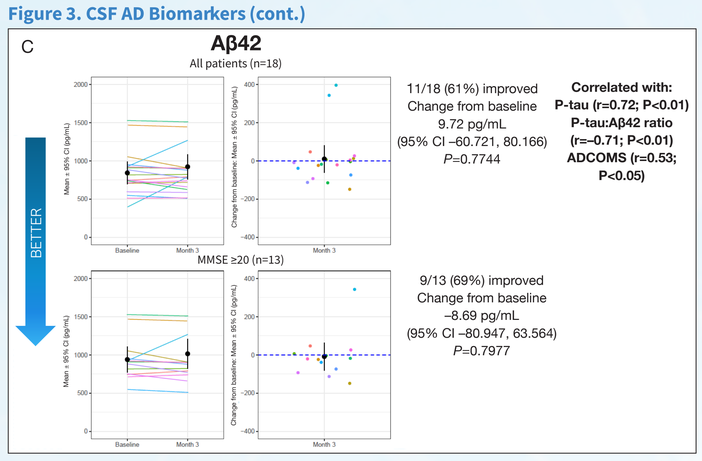
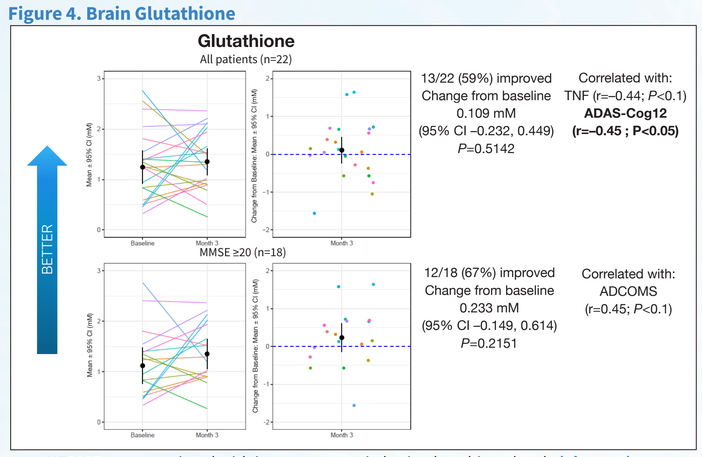


Figure 4. Brain Glutathione



- NE3107 was associated with improvements in brain glutathione levels **(Figure 4)**
  - 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

CORRELATION ANALYSIS

- Statistically significant correlations for each of the biomarkers are listed in each of the figures
  - Change from baseline in ADCOMS scores and Aβ42 (r=0.53) and p-tau levels (r=0.49)
  - Change from baseline in Aβ42 and p-tau levels (r=0.72) and p-tau:Aβ42 ratio (r=–0.71)
  - Change from baseline in p-tau levels and the p-tau:Aβ42 ratio (r=–0.59)
- Biomarkers were also correlated with clinical measures and neuroimaging analyses performed in these patients; for more information, please see the poster and the oral presentation listed below
  - Clinical outcomes data are reported in poster P034, "Clinical Outcomes From a Phase 2, Open-Label Study of NE3107 in Patients With Cognitive Decline Due to Degenerative Dementias"
  - Neuroimaging and correlational analyses are reported in oral presentation OC24, "Neuroimaging Data From a Phase 2, Open-Label Study of NE3107 in Patients With Cognitive Decline Due to Degenerative Dementias"

CONCLUSIONS

- We investigated the anti-inflammatory effects of 20 mg oral NE3107 administered twice a day for 3 months to 23 patients with MCI or mild dementia
- Because neurofibrillary tangles and Aβ plaques form a positive feedback loop with chronic neuroinflammation[9] our observations of improvements in the total p-tau and p-tau to Aβ42 ratio[10] suggest that NE3107 anti-inflammatory activity may have reduced CNS plaques and tangles in these patients
- Our results showed that NE3107 was associated with trending improvements in plasma TNF-α and brain glutathione levels, suggesting an effective lowering of pro-inflammatory responses[1-4] and lower oxidative stress in the brain[11]
- In this study, NE3107 was associated with lower CSF p-tau levels and p-tau:Aβ42 ratios for the majority of patients, compared with baseline
  - Patients with MCI to mild dementia (MMSE ≥20) appeared to show statistically significant improvement in these parameters
  - Reductions in the p-tau:Aβ42 ratio were driven by reductions in p-tau rather than an increase in Aβ42 levels
- Thus, in this small cohort of patients with dementia, the data describe NE3107's association with: (a) a lowering of TNF-α, a master regulator of inflammatory pathways in AD pathogenesis[1-4]; (b) an increase in the major brain antioxidant, glutathione; and (c) a reduction in p-tau protein levels, a significant neuropathological component of AD[9]
- The CSF ratio of p-tau:Aβ42 has been shown to predict cognitive decline in patients with MCI and AD.[12] Given this study's documentation of a reduction of the CSF ratio of p-tau:Aβ42 in association with the open-label administration of NE-3107, it is possible to suggest that NE3107 may have promise to perhaps prevent or slow AD progression
- Additionally, correlations of change among biomarkers, clinical measures, and neuroimaging that occur concomitantly with the administration of the study drug may also suggest potential drug effects of NE3107 in dementia, and these findings appear to highlight the role of neuroinflammation in AD pathogenesis
- Subsequent longer-term, placebo-controlled studies are required to assess the potential of NE3107 in 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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AD, Alzheimer's disease; Aβ, amyloid β; ADCOMS, Alzheimer's Disease Composite Score; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; *APOE*, apolipoprotein E gene; BID, twice per day; CDR, clinical dementia rating; CSF, cerebrospinal fluid; ERK, extracellular signal-regulated kinases; IKK, inhibitor of kappa B kinase; IL, interleukin; IR, insulin resistance; MAPK, mitogen-activated protein kinase; 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; RA, rheumatoid arthritis; TNF-α, tumor necrosis factor-α; QDRS, Quick Dementia Rating Scale.