P034 Clinical Outcomes From a Phase 2, Open-Label Study of NE3107 in Patients With Cognitive Decline Due to Degenerative Dementias

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BACKGROUND

- Core features of AD include inflammatory brain changes, such as the accumulation of Aβ and p-tau, which may result in neurodegeneration and a decline in cognitive function[1,2]
- The earliest symptomatic phase of the AD continuum, MCI, may manifest as subtle cognitive deficiencies, such as aberrant episodic memory and language
- About one-third of MCI patients are likely to progress to AD dementia within 5 years[1]
- Chronic neuroinflammation can promote Aβ and p-tau synthesis and impair insulin signaling (insulin resistance [IR]) consequently promoting Aβ accumulation and exacerbating cognitive and memory deficits[3-5]
- Insulin-sensitizing and anti-inflammatory drugs represent a promising strategy for slowing AD progression and the associated cognitive decline[5-7]
- NE3107 is a small, oral, blood-brain barrier–permeable molecule that exerts anti-inflammatory and insulin-sensitizing actions by binding to ERK and inhibiting key inflammatory mediators, such as ERK, NF-κB, and TNF-α[7]
- This 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 mild dementia

OBJECTIVES

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

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 (clinical outcomes)
- To evaluate changes in 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

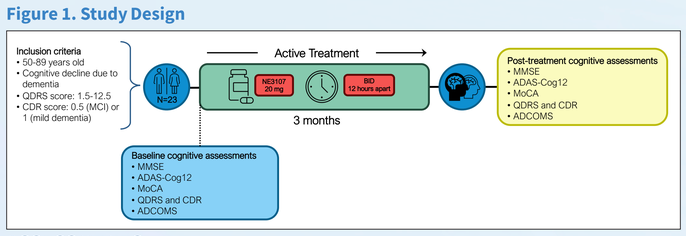
- This was a single-arm, open-label, phase 2 trial evaluating the efficacy and safety of 20 mg oral NE3107 administered twice daily (approximately 12 hours apart) to 23 patients with MCI or dementia **(Figure 1)**

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 (3 MONTHS)

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

SECONDARY – CHANGES FROM BASELINE TO TREATMENT COMPLETION

- Cognitive performance assessments included:
  - **ADAS-Cog12:** Measures memory, orientation, and other functions – positive change in scores indicate cognitive impairment
  - **MMSE:** Evaluates memory, language, and visual-spatial skills, etc, and a positive change in score indicates improved cognition
  - **MoCA:** Specially designed to test executive function, highly sensitive to MCI, and a positive change in score indicates improved cognition
  - **QDRS:** Cognitive and functional assessments, scored from 0 (normal) to 3 (severe impairment), based on caregiver interviews
  - **CDR:** Based on QDRS and depicts the severity of dementia, ranging from 0 (normal) to 3 (severe dementia)
  - **ADCOMS:** Combines ADAS-Cog, MMSE, and CDR items, and it is sensitive to clinical decline in patients with MCI and mild AD
- Participants, clinicians, and caretakers reported a Global Rating of Change (GRC) upon study completion
  - The GRC was assessed using an 11-point scale to track changes in a patient's conditions, abilities, and overall sense of well-being, where 0 indicated "no change," +5 indicated "significantly better," and −5 indicated "significantly worse"
- Serological inflammatory markers
- Serological glucose homeostasis markers
- AD CSF biomarkers

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

- Repeated Measures ANOVAs (RMANOVAs) were used to determine whether participants who successfully completed the treatment protocol demonstrated differential improvement in cognition over time, with global and domain level mean T-scores as the outcome variable of interest
- Age, sex, and education, as statistically indicated, were included as additional regressors
- Correlation analyses were conducted to determine whether absolute change in domain level, as measured by neuropsychological evaluation and global cognitive performance, is associated with absolute change in the imaging parameters
- Paired sample t-tests were used for statistical analyses of the cognitive assessments

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
- We assessed the neuropsychological effects of NE3107 using the ADAS-Cog12, MMSE, and MoCA cognitive performance tests **(Figure 2)**
  - 57% (n=13) of all 23 patients and 72% (n=13) of 18 patients with MMSE ≥20 had a lower ADAS-Cog12 score, compared with baseline, suggesting improved cognition
  - 35% (n=8) of all 23 patients and 44% (n=8) of 18 patients with MMSE ≥20 had higher MMSE scores at treatment completion, compared with baseline, consistent with cognitive improvements
  - 39% (n=9) of all 23 patients and 50% (n=9) of 18 patients with MMSE ≥20 had higher MoCA scores at treatment completion, compared with baseline, consistent with cognitive improvements

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)

Figure 2. Mean Change Plots for ADAS-Cog12, MMSE, and MoCA Assessments

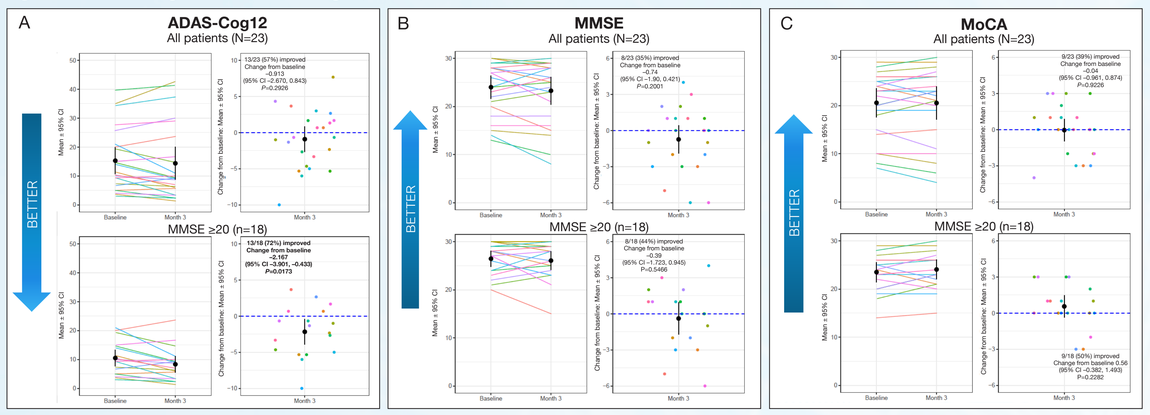


Figure 3. Mean Change Plots for Cognitive Subtotal Score Assessments

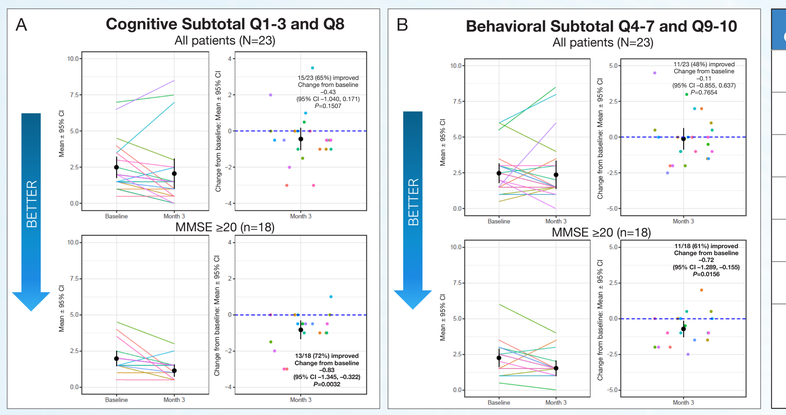


Table 2. Statistically Significant Correlations

Characteristic	All patients	MMSE ≥20
ADAS-Cog12		
TNF-α		r=0.59
Brain glutathione	r=−0.45	
ADCOMS		
Aβ42	r=0.53	
P-tau	r=0.49	

ADCOMS was also significantly improved in subjects with abnormal scans at baseline in the precuneous (5/5, *P*=0.024) and nucleus basalis of Meynert (7/8, *P*=0.014).

- We evaluated the neuropsychological effects of NE3107 using the cognitive subtotal scores Q1-10 **(Figure 3)**
  - 65% (n=15) of all 23 patients and 72% (n=13) of 18 patients with MMSE ≥20 showed reduced Cognitive Subtotal Scores Q1-3 and Q8 at treatment completion (improved), compared to baseline
  - 48% (n=11) of all 23 patients and 61% (n=11) of 18 patients with MMSE ≥20 showed reduced Behavioral Subtotal Scores Q4-7 and Q9-10 at treatment completion (improved), compared to baseline
- We assessed the neuropsychological effects of NE3107 by evaluating changes in the QDRS and CDR cognitive scales from baseline **(Figure 4)**
  - 61% (n=14) of all 23 patients and 72% (n=13) of 18 patients with MMSE ≥20 had lower QDRS scores at treatment completion, compared with baseline, consistent with lower cognitive impairment
  - 17% (n=4) of all 23 patients and 22% (n=4) of 18 patients with MMSE ≥20 had reduced CDR scores at treatment completion, compared with baseline, suggesting lower cognitive impairment
- NE3107 was associated with reductions in the ADCOMS scores, suggesting lower cognitive impairment **(Figure 5)**
  - 57% (n=13) of all 23 patients and 72% (n=13) of 18 patients with MMSE ≥20 had reduced ADCOMS scores at treatment completion (improved), compared with baseline
- NE3107 was associated with improvements in the patients' daily abilities and overall sense of well-being **(Figure 6)**
  - Overall (N=23 patients), doctors, patients, and caretakers reported a mean change of 1.7, 2.2, and 1.07 points, respectively
  - Among the subset of patients with baseline MMSE ≥20, doctors, patients, and caretakers reported a mean change of 2.67, 2.08, and 1.69 points, respectively

Figure 4. Mean Change Plots for QDRS and CDR Scores

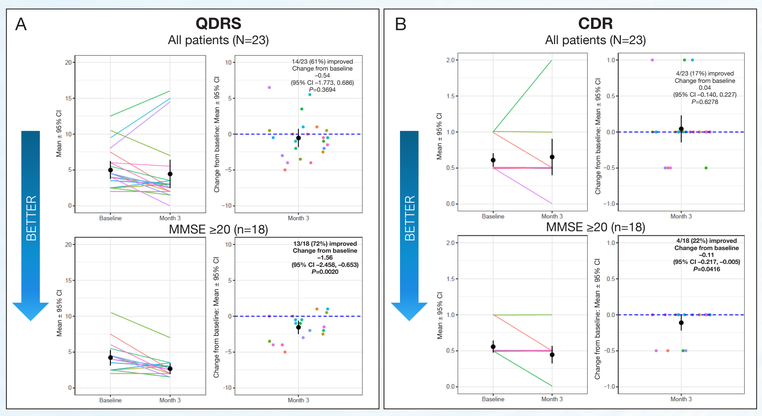
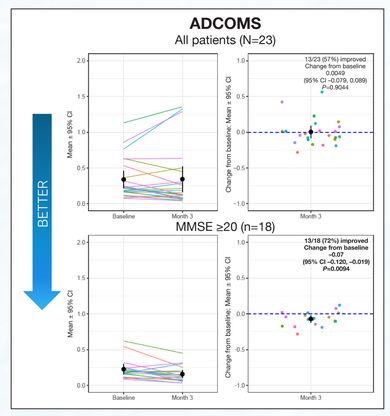
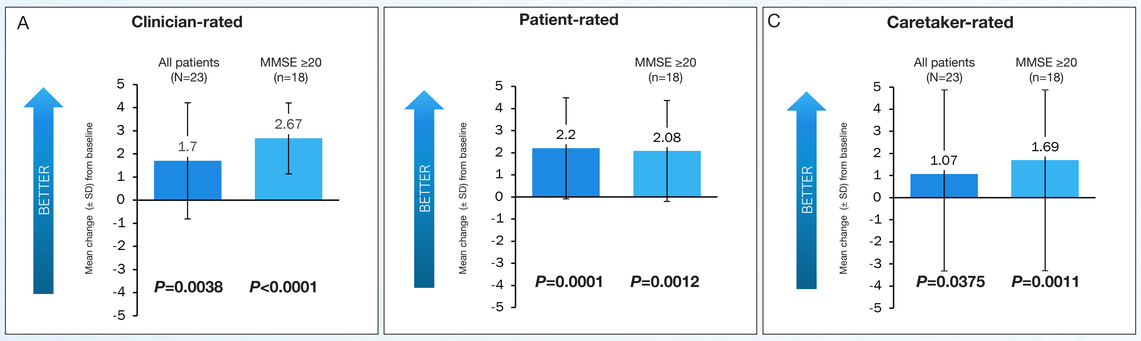


Figure 5. Mean Change Plots for ADCOMS Scores



- NE3107 was associated with improvements in the QDRS and CDR cognitive scales from baseline **(Figure 4)**
  - 61% (n=14) of all 23 patients and 72% (n=13) of 18 patients with MMSE ≥20 had lower QDRS scores at treatment completion, compared with baseline, consistent with lower cognitive impairment
  - 17% (n=4) of all 23 patients and 22% (n=4) of 18 patients with MMSE ≥20 had reduced CDR scores at treatment completion, compared with baseline, suggesting lower cognitive impairment

Figure 6. Mean Change Plots for Global Rating of Change



CORRELATION ANALYSIS

- Improvements in QDRS scores were statistically significantly correlated with improvements on the ADCOMS assessment
  - The correlation coefficient was r=0.91 for all patients and r=0.76 for patients with MMSE ≥20
- Clinical outcomes were also correlated with several biomarkers and with neuroimaging analyses performed in these patients **(Table 2)**; for more information, please see the poster and oral presentation listed below
  - Biomarker data are reported in poster P095, "Biomarker Assessments 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"

SAFETY

- No serious adverse events or treatment-emergent adverse events were observed over the duration of 3 months

CONCLUSIONS

- We investigated the efficacy and safety of 20 mg oral NE3107 administered twice a day for 3 months in 23 patients with MCI or mild-to-moderate dementia
- In this small cohort of patients with dementia, NE3107 appeared to be associated with improvements in several neuropsychological and cognitive assessments after 3 months of treatment
- In the patients with baseline MMSE ≥20 (indicating MCI or mild dementia), NE3107 was associated with statistically significantly improved cognitive functioning vs baseline, indicated by changes in ADAS-Cog12, QDRS, CDR, and ADCOMS
- NE3107 appeared to be associated with statistically significant improvements vs baseline in the overall impression of the patients' daily abilities, observable by clinicians, caregivers, and patients
- NE3107 was well tolerated and was not associated with any serious adverse events
- These data appear to support the hypothesis that the anti-inflammatory effects of NE3107 can decrease cognitive impairment associated with MCI and AD
- Correlations among clinical measures, biomarkers, and neuroimaging provide evidence to support the highlighted hypothesized role of neuroinflammation in AD pathogenesis and may indicate important drug effects associated with NE3107 in this open-label study
- 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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DISCLOSURES

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Aβ, amyloid β; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ANOVA, Analysis of Variance; *APOE*, apolipoprotein E gene; BID, twice per day; CDR, clinical dementia rating; CSF, cerebrospinal fluid; ERK, extracellular signal-regulated kinase; IR, insulin resistance; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NF-κB, nuclear factor kappa B; p-tau, phosphorylated tau protein; PD, Parkinson's disease; TNF-α, tumor necrosis factor-α; QDRS, Quick Dementia Rating Scale.