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Peer reviewed

A phase 2, open-label study of anti-inflammatory NE3107 in patients with dementias

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Abstract

Background: Alzheimer's disease (AD) is a progressive, multifactorial, neurodegenerative disorder affecting >6 million Americans. Chronic, low-grade neuroinflammation, and insulin resistance may drive AD pathogenesis. We explored the neurophysiological and neuropsychological effects of NE3107, an oral, anti-inflammatory, insulin-sensitizing molecule, in AD.

Methods: In this phase 2, open-label study, 23 patients with mild cognitive impairment or mild dementia received 20-mg oral NE3107 twice daily for 3 months. Primary endpoints assessed changes from baseline in neurophysiological health and oxidative stress (glutathione level) using advanced neuroimaging analyses. Secondary endpoints evaluated changes from baseline in neuropsychological health using cognitive assessments, including the 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog11), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment, Clinical Dementia Rating, Quick Dementia Rating Scale, Alzheimer's Disease Composite Score, and Global Rating of Change (GRC). Exploratory endpoints assessed changes from baseline in neuroinflammation biomarkers (tumor necrosis factor alpha, TNF- α) and AD (amyloid beta and phosphorylated tau [P-tau]).

Results: NE3107 was associated with clinician-rated improvements in cerebral blood flow and functional connectivity within the brain. In patients with MMSE \geq 20 (mild cognitive impairment to mild AD; $n = 17$), NE3107 was associated with directional, but statistically nonsignificant, changes in brain glutathione levels, along with statistically significant improvements in ADAS-Cog11 ($P = .017$), Clinical Dementia Rating ($P = .042$), Quick Dementia Rating Scale ($P = .002$), Alzheimer's Disease Composite Score ($P = .0094$), and clinician-rated GRC ($P < .001$), as well as in cerebrospinal fluid P-tau levels ($P = .034$) and P-tau:amyloid beta 42 ratio ($P = .04$). Biomarker analyses also demonstrated directional, but statistically non-significant, changes in plasma TNF- α , consistent with the expected mechanism of NE3107. Importantly, we observed a statistically significant correlation ($r = 0.59$) between improvements in TNF- α levels and ADAS-Cog11 scores ($P = .026$) in patients with baseline MMSE \geq 20.

Conclusion: Our results indicate that in this study NE3107 was associated with what appear to be positive neurophysiological and neuropsychological findings, as well as evidence of improvement in biomarkers associated with neuroinflammation and AD in patients diagnosed with dementia. Our findings are consistent with previous preclinical and clinical observations and highlight a central role of neuroinflammation in AD pathogenesis.

Abbreviations: AD = Alzheimer's disease, ADAS-Cog11 = 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale, ADCOMS = Alzheimer's Disease Composite Score, ASL = arterial spin labeling, A β = amyloid beta, A β 42 = A β peptide 42, BID = twice per day, BOLD = blood-oxygen-level-dependent, CDR = Clinical Dementia Rating, CNS = central nervous system, CSF = cerebrospinal fluid, DMN = default mode network, ERK = extracellular signal-regulated kinase, FC = functional connectivity, fMRI = functional magnetic resonance imaging, GRC = global rating of change, HC = hippocampus/hippocampal, IL = interleukin, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination, MNI = Montreal Neurological Institute, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, NBM = nucleus basalis of Meynert, NF- κ B = nuclear factor kappa B, P-tau = phosphorylated tau protein, QDRS = Quick Dementia Rating Scale, rCBF = relative cerebral blood flow, ROI = region of interest, TNF- α = tumor necrosis factor alpha.

Keywords: Alzheimer's disease, amyloid beta, anti-inflammatory agent, cognitive function, dementia, glutathione, inflammation, magnetic resonance imaging, mild cognitive impairment, NE3107, phosphorylated tau

JH, KJ, and KM contributed equally to this work.

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All human subjects provided informed consent.

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of Synaptec Network and was responsible for processing of fMRIs on this study. Ms. Zielinski, Ms. Venkatraman, and Dr. Pourat have nothing to disclose. Dr. Zhang has received consulting fees from BioVie Inc. to prepare the data analysis of the manuscript and has stock or stock options with BioVie Inc. Mr. Ahlem and Dr. Reading are employees, stockholders, and have stock options with BioVie Inc. Dr. Palumbo is an employee and stockholder at BioVie Inc.; he has multiple patents filed as a full time compensated employee: formerly—Johnson & Johnson, Mitsubishi Tanabe, and Zynerva Pharmaceuticals; currently—BioVie Inc.; he is also an unpaid voluntary member of Dean's Advisory Council of the George Washington University School of Medicine and Health Sciences, Washington, DC.

1. Introduction

Chronic neuroinflammation is thought to play a significant role in the progression of neurodegenerative disorders, such as Alzheimer's disease (AD).^[1–3] AD pathologies, amyloid beta (A β), and phosphorylated tau (P-tau), are thought to trigger pro-inflammatory responses to drive chronic inflammation, which in turn may contribute to further accumulation of A β and P-tau, accelerating neurodegeneration.^[1,4,5] Tumor necrosis factor- α (TNF- α), a key inflammatory mediator, is capable of inducing oxidative stress through the production of reactive oxygen species and reduction of glutathione, an important antioxidant.^[6–8] Additionally, neuroinflammatory mediators can disrupt insulin signaling via serine phosphorylation of insulin receptor substrate-1, leading to insulin resistance, which can subsequently contribute to increased A β peptide 42 (A β 42) production and neuritic plaques, impaired glucose metabolism, and, eventually, cognitive decline.^[5,9–13] Therefore, anti-inflammatory and insulin-sensitizing drugs are being explored for their potential to slow AD progression and the associated cognitive decline.^[4,5,14]

NE3107 is a chemically modified analog of a physiologic human adrenal sterol, β -androstenetriol, and is an orally bioavailable, metabolically stable, blood-brain barrier-permeable molecule currently being investigated for its potential therapeutic effects in neurodegenerative disorders, including AD.^[5] NE3107 is thought to bind the inflammatory mediator, extracellular signal-regulated kinase (ERK), and selectively inhibit inflammation-stimulated ERK, nuclear factor kappa B (NF- κ B), and TNF- α signaling, without compromising any homeostatic functions of ERK.^[5] In pre-clinical studies, NE3107 was shown to modulate several inflammatory mediators associated with cognitive decline, such as ERK, NF- κ B, TNF- α , and interleukin 1 beta (IL-1 β), as well as monocyte chemoattractant protein-1 and its receptor, chemokine C-C motif receptor 2 (CCR2).^[5,15,16] In humans, NE3107 was associated with decreased C-reactive protein, an inflammatory biomarker implicated in AD.^[5] Given the direct influence of pro-inflammatory mediators on insulin signaling, NE3107 has been proposed to possess insulin sensitizing activity.^[5] Results from phase 1 and 2 clinical trials indicated that NE3107 improved insulin sensitivity and restored metabolic homeostasis in patients with impaired glucose tolerance and type 2 diabetes and inflammation.^[17,18] Importantly, NE3107 was well tolerated and had a favorable safety profile across 6 clinical trials.^[5]

In the present, exploratory investigation, NE3107-treated patients were evaluated for changes in advanced neuroimaging, cognitive performance tests, and central nervous system (CNS) biomarkers of AD, as well as improvements in inflammatory serological and metabolic parameters. Based on NE3107's anti-inflammatory mechanism of action and immunomodulatory effects, it was hypothesized that 20mg of NE3107 administered twice daily (BID) in patients with mild cognitive impairment (MCI) or dementia would lead to (1) changes in neuroimaging consistent with increased brain glutathione (indicating decreased oxidative stress) and enhanced arterial perfusion, as well as increased functional connectivity (FC) of the default mode network (DMN), nucleus basalis of Meynert

(NBM), and hippocampal (HC) networks, (2) improvements in neurocognitive functioning, and (3) reduction in biomarkers associated with inflammation (TNF- α) and AD pathology (A β 42 and P-tau), as well as improvements in biomarkers associated with glucose metabolism.

2. Methods

2.1. Patient recruitment

This study (Clinical Trial Identifier #NCT05227820) was reviewed and approved by Advarra Institutional Review Board (Protocol Identifier: Pro00058626). The most recent approval number is CR00403211. Twenty-three patients were enrolled from Los Angeles neurology clinics. All patients provided written, signed informed consent.

Participants were recruited through a network of neurology clinics in Los Angeles. When patients expressed interest, study staff informed participants and their caregivers about the protocol, potential risks and benefits, follow-up procedures, and expenses. Participants and caregivers were given the opportunity to ask any questions they might have had after an extensive perusal of the informed consent. To ensure commitment and attention to follow-up procedures, caregivers were involved in the consenting process. Each participant gave their written, signed consent.

Inclusion criteria required patients to (1) have a clinical diagnosis of cognitive decline due to degenerative dementia, (2) be aged from 50 to 89 years old, and (3) have a Quick Dementia Rating Scale (QDRS) score ranging from 1.5 to 12.5 with a converted Clinical Dementia Rating (CDR) score of 0.5 (MCI) to 1 (mild dementia). Diagnoses were established by the principal investigator who is a board-certified neurologist.

Patients were excluded from consideration if any of the following criteria were met: contraindication to lumbar puncture, contraindication to magnetic resonance imaging (MRI), women who were pregnant or could have become pregnant, diagnosis of a reversible cause of cognitive impairment that explained the clinical status entirely (e.g., depression, hypothyroidism), advanced stages of terminal illness or active cancer requiring chemotherapy, or a history of breast cancer. Women with child-bearing potential who were not willing to use a double-barrier birth control method were excluded from enrollment, as were males not willing to use a double-barrier birth control method with female sex partners with child-bearing potential. Individuals with hepatic or renal impairment were excluded from enrollment as well.

2.2. Study procedures

Patients received 20-mg oral NE3107 (BioVie Inc., Encinitas, CA) BID approximately 12 hours apart for 3 months. The dose was kept stable for the duration of the study intervention and was the same for all patients.

Following confirmation of the inclusion and exclusion criteria, patients underwent baseline testing to include the following: advanced MRI of the brain, lumbar puncture, apolipoprotein E

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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genotyping, epigenetic analysis, cognitive testing, and serological analysis.

2.3. Study endpoints

Primary endpoints involved a comparison of neurophysiological health as evaluated by multimodal brain MRIs obtained at baseline and post intervention termination (3 months). Specifically, multimodal MRI endpoints included: (1) an increase or stabilization in glutathione levels (as measured by magnetic resonance spectroscopy, MRS) compared to baseline; patients with cognitive decline often show a characteristic change in MRS or volumetric evaluation compared to age-matched controls.^[19] (2) Enhancement of arterial perfusion compared to baseline (as quantified by arterial spin labeling, ASL); patients with cognitive decline often have decreased perfusion in temporal-parietal or frontal regions of the brain, as detected with ASL perfusion.^[19] (3) Increased FC of the NBM with both hippocampi as well as between both hippocampi compared to baseline, as visualized by seed analysis of blood-oxygen-level-dependent (BOLD) imaging. (4) Increased neurovascular coupling as visualized by BOLD imaging compared to baseline. (5) Stabilized and/or improved dendritic density compared to baseline (as measured by diffusion tensor imaging, DTI-NODDI).

Secondary endpoints assessed several neuropsychological testing measures and included the QDRS, CDR score as estimated by the QDRS, the 11-item Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog11), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), AD Composite Score (ADCOMS), and Global Rating of Change (GRC). Exploratory endpoints included a longitudinal comparison of metabolic and serological analyses, specifically, measures of inflammation, AD pathology, and glucose metabolism.

2.4. Primary endpoint: neuroimaging

Each prospective patient underwent advanced magnetic resonance neuroimaging during the study screening period, prior to treatment administration, to obtain baseline measurements. The MRI included volumetric analysis of the HC and lobes of the brain, perfusion values (relative cerebral blood flow, rCBF) quantified by ASL, neuronal FC (visualized by BOLD imaging), and MRS of the precuneus.

Patient scans were conducted at a single imaging center in Beverly Hills, CA. All magnetic resonance data were quality-controlled prior to being processed and reviewed. Post-processing was done using the Functional Magnetic Resonance Imaging of the Brain Software Library (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) with standardized parameters for all patients. Identical follow-up MRI scans were done at the same imaging center where baseline scans were conducted. MRS post-processing was completed using Tarquin analysis (<https://tarquin.sourceforge.net/>). During the MRI data processing and pre-processing phase, there were several quality checks employed to ensure accuracy. These checks involved image and alignment co-registration, bias field correction, and skull stripping. Additionally, there were functional MRI (fMRI) quality checks specifically focused on motion correction to guarantee reliable results for the functional data, including removal of movement artifact in BOLD imaging and ASL.

2.5. Blinded review

fMRI data were qualitatively judged by 2 trained, blinded investigators: a board-certified neurologist with expertise in

neuroradiology and a neuropsychologist with expertise in fMRI and subsequent statistical analysis. In the event of disagreement between raters, data were subjected to additional review and ultimately scored by consensus.

Baseline scans were rated as abnormal or normal according to the following criteria: for perfusion, measured by rCBF, a 30% decrease in signal intensity in the temporal, parietal, or occipital lobes (in at least 1 hemisphere) was scored as abnormal; for BOLD, seed-based FC, a cluster >1cm³ shown on a statistical map would be scored as abnormal for the following connectivity patterns: for a seed placed in the NBM, abnormal regions for cluster included contralateral and/or ipsilateral NBM (beyond the area of the seed), inferior frontal lobe, temporal lobe, and basal forebrain; for a seed placed in the HC, abnormal regions for cluster included contralateral and/or ipsilateral HC (beyond the area of the seed) and anterior mid-temporal lobe; for a seed placed in the precuneus, abnormal regions for cluster included prefrontal midline region (excluding the interhemispheric fissure) and parietal lobe. Follow-up scans were rated as improved: no longer meets criteria for abnormality; declined: previously “normal” scan met criteria for abnormality at follow-up or abnormality became more extensive in an abnormal patient; or stable: no significant change between baseline and follow-up scans.

2.6. Group analysis

After preprocessing (motion correction, artifact removal, spatial smoothing) the resting-state fMRI, FC analysis was performed with a seed set for the following regions of interest (ROIs): the precuneus (Fig. S1A, Supplemental Digital Content, <http://links.lww.com/MD/N250>), the left and right NBM, and the left and right HC (Fig. S1B, Supplemental Digital Content, <http://links.lww.com/MD/N250>). The NBM seeds were drawn in Montreal Neurological Institute (MNI) standard space and transformed to functional space for first-level analysis, the HC seed was taken from the Functional Magnetic Resonance Imaging of the Brain Software Library subcortical segmentation tool (Functional Magnetic Resonance Imaging of the Brain's Integrated Registration and Segmentation Tool), and the precuneus was taken from MNI standard space as well. The HC and NBM seeds were also in probabilistic tractography to map out the white matter connections. Glutathione concentrations in the precuneus were measured using MRS analysis (Fig. S1C, Supplemental Digital Content, <http://links.lww.com/MD/N250>). Group analysis was performed in standard MNI space using a mixed effects model with age and sex as additional covariates.

2.7. Secondary endpoints: neuropsychological testing

Secondary endpoints also evaluated changes in cognitive functioning using the QDRS, CDR score (estimated by the QDRS), ADAS-Cog11 (scored from 0–70), MMSE, MoCA, and ADCOMS. The QDRS form consists of 10 categorical questions, 5 of which are cognitive and 5 of which are functional. Each question has 5 detailed answers, each of which represents an impairment level of 0 (normal), 0.5, 1, 2, or 3 (severe impairment). The person designated as the caregiver at baseline consented to do the QDRS interview at completion to maintain consistency. Total QDRS scores were converted to CDR scores ranging from 0 (normal aging), 0.5 (MCI), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia).^[20] The ADAS-Cog11 consists of 11 components that assess spoken language, comprehension, word-finding difficulties, object/figure naming, command following, constructional praxis, ideational praxis, orientation, word recognition, and test direction recall.^[21] The MMSE is a 30-point test that assesses cognitive ability.^[22] Specific tasks that measure orientation, attention, memory, language, and visuospatial abilities

are part of the MMSE. The MoCA was used to assess general cognitive function.^[23] It measures immediate and delayed memory, attention, language, visuospatial construction, orientation to time and place, and frontal executive skills. Scores on the MoCA scale range from 0 to 30; 26 or more is regarded as reflecting normal cognitive status.^[24] To minimize practice effects between baseline and completion testing, different MoCA iterations were administered. ADCOMS was used to ascertain treatment effects and is composed of 4 ADAS-Cog items, 2 MMSE items, and all 6 items of the CDR—Sum of Boxes.^[25]

Patients, clinicians, and caretakers also reported a GRC upon study completion.^[26] 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."

2.8. Exploratory endpoints: biomarkers

Secondary endpoints evaluated changes in glucose metabolism markers (hemoglobin A1c and urinary glucose levels), changes in inflammatory markers (high-sensitivity C-reactive protein, erythrocyte sedimentation rate, and transforming growth factor beta), and changes in levels of several cytokines (TNF- α , IL-1 β , IL-6, and IL-12).

All patients underwent apolipoprotein E swab testing and a lumbar puncture to assess A β 42 and Tau proteins for AD spectrum. The lumbar puncture was performed at baseline and after completion of the study protocol. Table 1 summarizes all biomarkers assessed and the assays used. These assessments were carried out by commercial laboratories. Additional procedures included blood and serum samples collected at baseline and completion to ensure patient safety and the effect of NE3107 on the laboratory values listed above. Clinical laboratory tests for safety were collected at baseline, 2 weeks, 4 weeks, 8 weeks, and completion, while laboratory tests for efficacy were collected at baseline and completion. Epigenetic analyses are in progress and will be reported at a later time.

2.9. Statistical analysis

Paired sample t-tests were used for statistical analyses of the secondary endpoints, including biomarkers and neuropsychological testing, which compared the change from baseline at the post-intervention termination follow-up (3 months after baseline) using a level of significance of 0.05. Software for statistical analyses included SAS (version 9.4; SAS Institute Inc., Cary, NC) and R (version 4.0). Since this was an exploratory investigation, the study was not formally powered for any endpoint. The protocol was designed to examine MCI and mild dementia. Since

the conventional CDR sum of boxes was not used to determine the Global CDR score, the standard MMSE was used to define mild (MMSE \geq 20) versus moderate (MMSE $<$ 20) impairment. For exploratory analyses, *P* values were not adjusted for multiple determinations.

3. Results

Patients were enrolled from January 2022 through April 2022. A total of 23 patients completed the study and received NE3107 over the course of 3 months (Fig. 1). At baseline, all patients had a QDRS score ranging from 1.5 to 12.5, with a converted CDR score of 0.5 (MCI) to 1 (mild dementia). A description of patient demographics, including patient baseline demographics and dispositions, can be found in Table 2.

3.1. Primary endpoint: neuroimaging

3.1.1. Blinded review. Functional MRI modalities, including rCBF and BOLD, seed analysis of the NBM, HC networks, and DMN, were subjected to blinded review by 2 independent clinicians with a predetermined rubric. The average inter-rater reliability for all functional MRI modalities was 96%. The DMN had the highest abnormality at baseline with 86% (19/22) of patients demonstrating abnormality in DMN FC. This was followed by the HC networks where 77% (17/22) of patients demonstrated an abnormality in the left HC network, 82% (18/22) in the right. The greatest improvement was seen in the HC networks, with 45% (10/22) of patients demonstrating improved FC at follow-up for the left HC, 54% (12/22) for the right (Table 3). DTI-NODDI analyses are still in progress.

3.2. ROI group analysis

With an ROI in the precuneus, there was a statistically significant (*z*-score $>$ 2.3) increase in FC compared to other areas of the DMN, including the prefrontal cortex (Fig. 2A). With an ROI placed in either HC or NBM, there was a statistically significant increase in connectivity between the hippocampi and NBM, respectively (Fig. 2B–E).

3.3. Magnetic resonance spectroscopy

Brain glutathione levels in the precuneus were assessed using MRS. For patients with MCI or mild AD (MMSE \geq 20), 11/17 (69%) improved, with a 59% increase in brain glutathione levels (Fig. 2F and Table 4).

3.4. Secondary outcomes: neuropsychological testing

The co-secondary endpoint of this study was to evaluate the effect of NE3107 treatment on neuropsychological health as assessed by cognitive performance testing administered at baseline and treatment completion using ADAS-Cog11, MMSE, MoCA, and ADCOMS. Fifty-seven percent (*n* = 13) of all 23 patients and 72% (*n* = 13) of 18 patients with MMSE \geq 20 had an improved (lower) ADAS-Cog11 score at completion compared with baseline (Fig. 3A and Table 4). Thirty-five percent (*n* = 8) of all 23 patients and 44% (*n* = 8) of 18 patients with MMSE \geq 20 had an improved (higher) MMSE score at completion compared with baseline (Fig. 3B and Table 4). Thirty-nine percent (*n* = 9) of all 23 patients and 50% (*n* = 9) of 18 patients with MMSE \geq 20 had improved (higher) MoCA scores at completion compared with baseline (Fig. 3C and Table 4). Fifty-seven percent (*n* = 13) of all 23 patients and 72% (*n* = 13) of 18 patients with MMSE \geq 20 had improved (lower) ADCOMS at completion compared with baseline (Table 4).

Table 1

Biomarkers assessed in the trial.

Biomarker	Assay
HbA1c	Enzymatic assay
Urinary glucose levels	Reagent strip and light microscopy
hsCRP	Immunoturbidimetric assay
ESR	Westergren
TGF- β	Enzyme Linked Immunosorbent Assay (ELISA)
IL-1 β	Enzyme Linked Immunosorbent Assay (ELISA)
IL-6	Immunoassay
IL-12	Immunoassay
TNF- α	Immunoassay
APOE	Single nucleotide polymorphism (SNP) genotyping
AB42/tau ratio	Electrochemiluminescent Immunoassay (ECLIA)

APOE = apolipoprotein E, HbA1c = hemoglobin A1c, TGF- β = transforming growth factor beta.

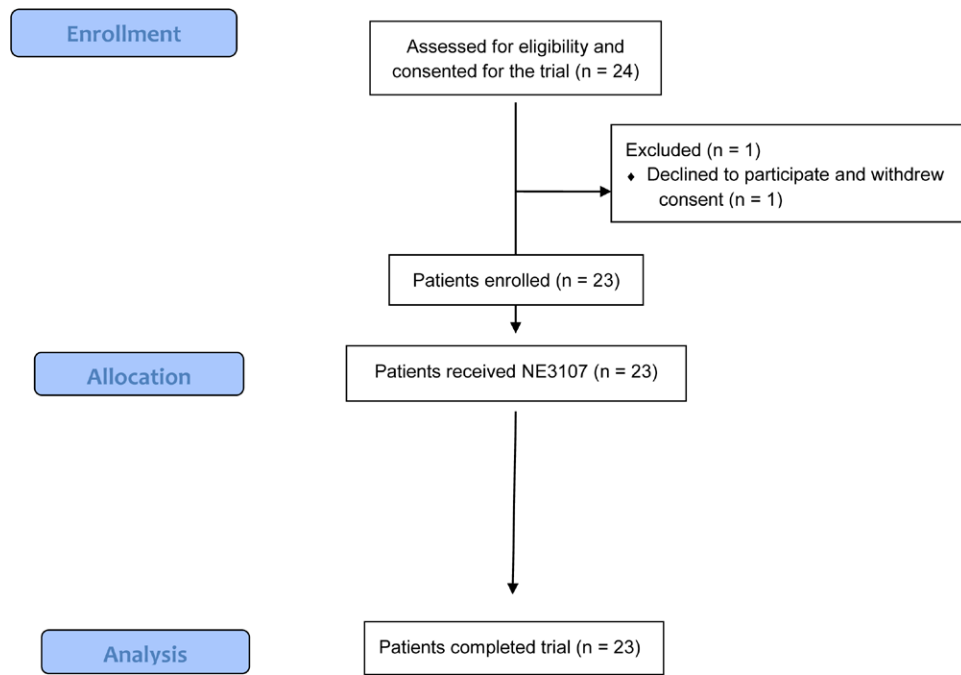


Figure 1. Flowchart of the study selection process.

Characteristic	All patients (N = 23)
Age, mean (SD), years	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 AD)	18 (78)
<20 (moderate AD)	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)

AD = Alzheimer’s disease; APOE = apolipoprotein E; CDR = Clinical Dementia Rating; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PD = Parkinson disease; QDRS = Quick Dementia Rating System.

Neuropsychological effects of NE3107 were also measured by evaluating changes in the QDRS, as well as changes in QDRS-derived CDR levels. Sixty-one percent (n = 14) of all 23 patients and 72% (n = 13) of 18 patients with MMSE ≥ 20 had improved (lower) QDRS scores at treatment completion compared with baseline (Fig. 3D and Table 4). Additionally, 17% (n = 4) of all 23 patients and 22% (n = 4) of 18 patients with MMSE ≥ 20 had a reduction in CDR level at treatment completion compared with baseline, indicating improved cognitive function (Fig. 3E and Table 4).

Overall, NE3107 treatment was associated with statistically significant improvements in the clinician-reported (mean change: 1.7; P = .0038), patient-reported (mean change: 2.2; P < .001), and caretaker-reported (mean change: 1.07; P = .038) GRC (Table 5). Similarly, in patients with MMSE ≥ 20, NE3107 treatment was associated with statistically significant improvements in the clinician-reported (mean change: 2.67; P < .001), patient-reported (mean change: 2.08; P = .0012), and caretaker-reported (mean change: 1.69; P = .0011) GRC (Table 5).

3.5. Correlation of neuroimaging and neuropsychological testing results

Improvements in ADCOMS were correlated with the clinician-rated imaging results for patients with MCI or mild AD (MMSE ≥ 20). For this group, an abnormal score on any of the functional imaging modalities (rCBF, DMN, HC networks, NBM) at baseline and improvement at follow-up was associated with improved ADCOMS (P < .05) (Fig. 3F).

3.6. Exploratory endpoints: biomarkers

The exploratory endpoints of this study investigated the anti-inflammatory and insulin-sensitizing effects of 20-mg oral NE3107 administered BID for 3 months; these effects were measured via serological biomarkers and cerebrospinal fluid (CSF) biomarkers.

3.7. Serological biomarker results

Plasma TNF-α levels were analyzed at baseline and study completion in 18 out of 23 patients. Of these, 61% (n = 11) had reduced plasma TNF-α levels at study completion compared with baseline. Additionally, 64% (n = 9) of the 14 patients with MMSE ≥ 20 showed a reduction over the course of the 3-month treatment (Fig. 4A and Table 4). At baseline, only 4% (n = 1) of the study patients were diabetic, and hence any apparent effects of NE3107 on glucose metabolism were not ascertained in this study.

Table 3**Clinician-rated scores of functional magnetic resonance imaging at baseline and follow-up.**

Functional MRI modality	Follow-up		
	Declined n (%)	No change n (%)	Improved n (%)
rCBF			
Total, 22 (100%)	2 (9%)	17 (77%)	3 (14%)
Normal, 6 (27%)	1 (17%)	5 (83%)	0 (0%)
Abnormal, 16 (73%)	1 (6%)	12 (75%)	3 (19%)
BOLD left NBM			
Total, 22 (100%)	2 (9%)	12 (55%)	8 (36%)
Normal, 14 (64%)	2 (14%)	10 (72%)	2 (14%)
Abnormal, 8 (36%)	0 (0%)	2 (25%)	6 (74%)
BOLD right NBM			
Total, 22 (100%)	3 (14%)	12 (55%)	7 (32%)
Normal, 13 (59%)	3 (23%)	9 (69%)	1 (8%)
Abnormal, 9 (41%)	0 (0%)	3 (33%)	6 (67%)
BOLD DMN			
Total, 22 (100%)	6 (27%)	9 (41%)	7 (32%)
Normal, 3 (14%)	1 (33%)	2 (67%)	0 (0%)
Abnormal, 19 (86%)	5 (26%)	7 (37%)	7 (37%)
BOLD left HC network			
Total, 22 (100%)	5 (23%)	7 (32%)	10 (46%)
Normal, 5 (23%)	1 (20%)	3 (60%)	1 (20%)
Abnormal, 17 (77%)	4 (24%)	4 (24%)	9 (52%)
BOLD right HC network			
Total, 22 (100%)	5 (23%)	5 (23%)	12 (55%)
Normal, 4 (18%)	1 (25%)	2 (50%)	1 (25%)
Abnormal, 18 (82%)	4 (22%)	3 (17%)	11 (61%)

BOLD = blood-oxygen-level-dependent; DMN = default mode network; HC = hippocampal; MRI = magnetic resonance imaging; NBM = nucleus basalis of Meynert; rCBF = relative cerebral blood flow.

3.8. CSF biomarker results

Patients with MCI and AD have been shown to have lower CSF A β 42 levels and increased CSF P-tau levels compared to cognitively unimpaired individuals.^[27–30] In this study, 63% (n = 10) of 16 total patients and 64% (n = 7) of 11 patients with MMSE \geq 20 had a lower P-tau:A β 42 ratio at study completion compared with baseline (Fig. 4B and Table 4). CSF P-tau levels were reduced in 62% (n = 13) of 21 patients and 63% (n = 10) of 16 patients with MMSE \geq 20, compared with baseline (Fig. 4C and Table 4). CSF A β 42 levels decreased in 61% (n = 11) of 18 total patients and in 69% (n = 9) of 13 patients with MMSE \geq 20, compared with baseline (Fig. 4D and Table 4).

3.9. Multimodal correlation analyses

3.9.1. Correlations between changes in cognitive performance and biomarkers. Since AD is thought to be a multifactorial disease,^[31] we sought to demonstrate correlations among improvements in cognitive performance and various biomarkers, as well as between different cognitive performance or biomarker assessments.

For the total patient population, we observed statistically significant correlations between posttreatment improvements in QDRS scores and ADCOMS ($r = 0.91$; $P < .001$); ADAS-Cog11 scores and brain glutathione levels ($r = -0.45$; $P = .034$); ADCOMS and A β 42 levels ($r = 0.53$; $P = .025$); ADCOMS and P-tau levels ($r = 0.49$; $P = .024$); A β 42 and P-tau levels ($r = 0.72$; $P = .0016$); A β 42 levels and the P-tau:A β 42 ratio ($r = -0.71$; $P = .0021$); and P-tau levels and the P-tau:A β 42 ratio ($r = -0.59$; $P = .016$) (Table S1, Supplemental Digital Content, <http://links.lww.com/MD/N249>). We also observed statistically non-significant correlations between posttreatment improvements from baseline in ADAS-Cog11 scores and TNF- α levels ($r = 0.46$; $P = .054$) and TNF- α and brain glutathione levels ($r = -0.44$; $P = .076$).

For patients with MCI to mild dementia (MMSE \geq 20; n = 18), we found statistically significant correlations between posttreatment improvements in ADAS-Cog11 scores and TNF- α levels ($r = 0.59$; $P = .026$); QDRS scores and ADCOMS ($r = 0.76$; $P < .001$); and P-tau levels and the P-tau:A β 42 ratio ($r = 0.74$; $P = .0086$) (Table S1, Supplemental Digital Content, <http://links.lww.com/MD/N249>). We also observed statistically non-significant correlations between posttreatment improvements from baseline in ADCOMS and brain glutathione levels ($r = 0.45$; $P = .059$); TNF- α and brain glutathione levels ($r = -0.53$; $P = .05$); and A β 42 and brain glutathione levels ($r = 0.50$; $P = .084$).

4. Discussion

Old age is the greatest risk factor for AD, and expanding geriatric populations are likely to exacerbate the already substantial healthcare costs associated with AD. Hence, there is an urgent medical need for drugs that can alter the progression of AD.^[32,33] In the present phase 2, open-label, exploratory study, we evaluated the potential scope of treatment-related improvements in patients with mild-to-moderate dementia using neuroimaging endpoints (neurophysiology), cognitive performance tests (neuropsychology), and biomarkers of AD pathology, inflammation, and oxidative stress following treatment with the anti-inflammatory and insulin-sensitizing agent, NE3107. Overall, treatment with 20 mg oral NE3107 BID for 3 months appeared to be associated with improvements in neurophysiology, oxidative stress, cognition, and biomarkers related to neuroinflammation and AD. Importantly, we demonstrated statistically significant correlations among improvements in neuroimaging endpoints, cognitive performance, and AD-related biomarkers (Table S1, Supplemental Digital Content, <http://links.lww.com/MD/N249>).

NE3107 was originally found while screening for synthetic analogs of a naturally occurring dehydroepiandrosterone derivative with potent anti-inflammatory properties.^[34,35] NE3107 is

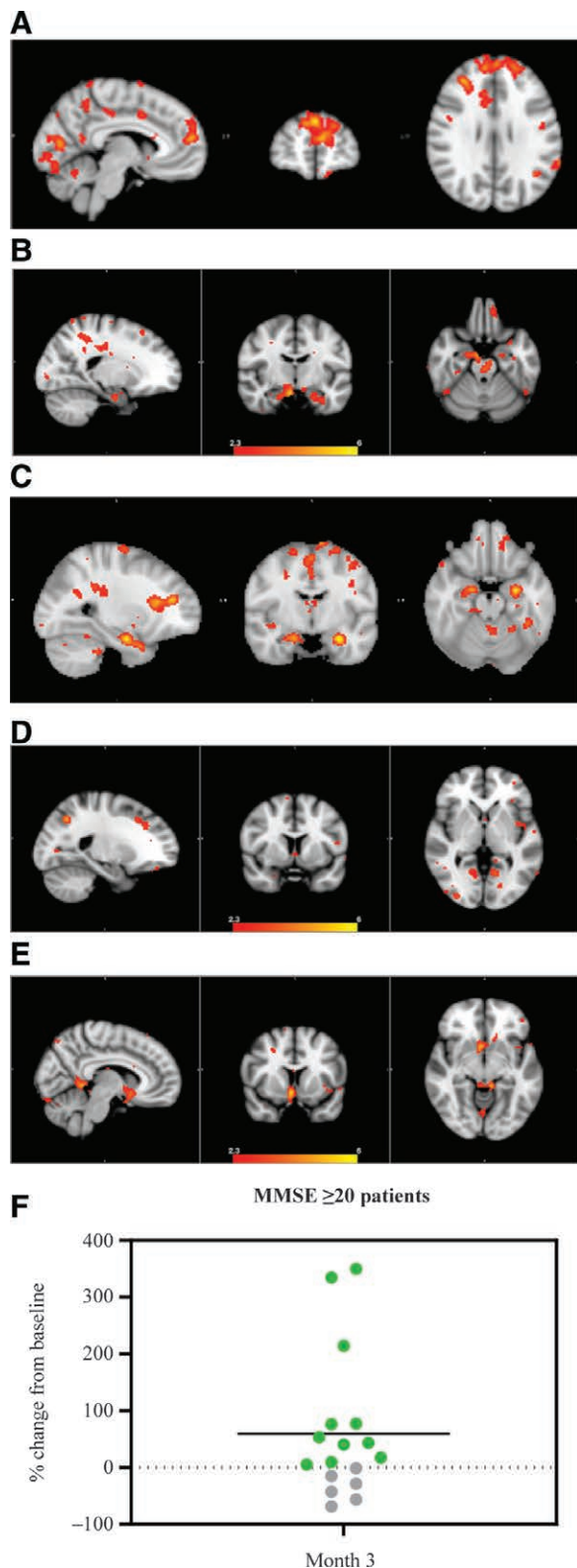


Figure 2. The neurophysiological health of patients before and after treatment with NE3107 was evaluated using advanced MRI of the brain. (A–E) Statistically significant regions of increased connectivity for (A) precuneus ROI (z-score > 3.1), (B) left HC ROI (z-score > 2.3), (C) right HC ROI (z-score > 2.3), (D) left NBM ROI (z-score > 2.3), and (E) right NBM ROI (z-score > 2.3); (F) Percent change from baseline in glutathione levels in the precuneus as measured by MRS ($P = .069$). HC = hippocampus; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; NBM = nucleus basalis of Meynert; ROI = region of interest.

thought to bind to ERK and prevent its activation within specific signaling complexes associated only with pathological inflammation, without perturbing ERK's homeostatic activity, which is mediated by the Ras-Raf-MEK-ERK pathway. NE3107 inhibits downstream signal transduction events involving NF- κ B that typically lead to pro-inflammatory responses, apoptosis, and insulin resistance.^[36,37] In murine models of arthritis, NE3107 was associated with anti-inflammatory effects, such as reduced production of several key inflammatory mediators (e.g., TNF- α and IL-6), without being immune suppressive.^[34,38] TNF- α is thought to play a central role in neuroinflammation and AD pathogenesis, and suppressing this pro-inflammatory mediator may improve cognition and slow AD-associated cognitive decline, as demonstrated by improvements in brain pathology and cognitive function in rodent AD models after treatment with anti-TNF- α therapies. Moreover, patients with rheumatoid arthritis or psoriasis who were taking anti-TNF therapies showed a decreased risk of developing AD.^[14,32,39] Indeed, neuroinflammation is believed to be a founding event in AD, perhaps occurring even prior to A β plaque deposition.^[40] Consistent with these findings, we showed that NE3107 treatment was associated with marked, albeit statistically non-significant, reductions in plasma TNF- α levels from baseline. Statistically significant correlations among improvements in neuroimaging endpoints, cognitive performance, and AD-related biomarkers support this hypothesis and should be further studied (Table S1, Supplemental Digital Content, <http://links.lww.com/MD/N249>).

Oxidative stress is thought to play an important role in the development of MCI and AD, and reduced CNS glutathione, an antioxidant buffer in the brain, has been implicated in AD-related neurodegeneration.^[8] Additionally, reduced brain glutathione levels were significantly correlated with diminished cognitive function, as measured by MMSE and CDR, in patients with MCI and AD.^[41] Inflammation and oxidative stress are mutually exacerbating; specifically, TNF- α , via the activation of the MAPK and NF- κ B pathway, can increase reactive oxygen species levels and reduce glutathione levels.^[6,7] In turn, depletion of intracellular glutathione can induce a neuroinflammatory response involving NF- κ B and ERK in microglia and astrocytes, leading to the release of pro-inflammatory cytokines, such as TNF- α and IL-6.^[42] Consistent with the anti-inflammatory effects of NE3107, we demonstrated an increase in brain glutathione levels in patients with MCI or dementia after 3 months of NE3107 treatment. Moreover, we found statistically significant correlations between increases in brain glutathione and reductions in plasma TNF- α (indicating decreased inflammation; $r = -0.53$; $P = .05$) in patients with MCI or mild dementia (MMSE ≥ 20) and reductions in ADAS-Cog11 scores (indicating improved cognition; $r = -0.45$; $P = .034$) in all 23 patients.

P-tau and A β 42 plaques are considered to be pathological hallmarks of AD and are pro-inflammatory, forming feedback loops with neuroinflammation in AD pathogenesis.^[4,5,43] Moreover, they can be detected several years prior to the onset of clinical symptoms of AD,^[40,44] and the CSF ratio of P-tau:A β 42 (elevated levels of P-tau and low levels of A β 42) was shown to be a preclinical and predictive biomarker of cognitive impairment and dementia.^[45] In line with the anti-TNF- α effect of NE3107, we saw statistically significant reductions in CSF P-tau levels and the P-tau:A β 42 ratio in patients with baseline MMSE ≥ 20 . Additionally, we noted a statistically significant correlation ($r = 0.49$; $P = .024$) between changes from baseline in the CSF P-tau level and ADCOMS.

The predefined hypotheses of this study were based on the previously demonstrated anti-inflammatory and insulin-sensitizing properties of NE3107. Accordingly, the primary objective of this study was to demonstrate improvements in the neurophysiology (using neuroimaging) of patients after treatment with NE3107. After 3 months of treatment, NE3107 was descriptively associated with clinician-rated, statistically significant improvements

Table 4
Summary of results from cognitive performance and biomarker assessments.

Endpoint	All patients				Patients with MMSE ≥ 20					
	Baseline, mean (95% CI)	Posttreatment, mean (95% CI)	Patients with improvement (%)	Mean change from baseline (95% CI)	P value*	Baseline, mean (95% CI)	Posttreatment, mean (95% CI)	Patients with improvement (%)	Mean change from baseline (95% CI)	P value*
Cognitive assessment										
ADAS-Cog11	15.28 (10.59, 19.96)	14.36 (8.74, 19.98)	13/23 (57)	-0.91 (-2.67, 0.84)	.29	10.50 (7.64, 13.36)	8.33 (5.51, 11.15)	13/18 (72)	-2.17 (-3.90, -0.43)	.017 [†]
MMSE	24.00 (21.57, 26.43)	23.26 (20.39, 26.14)	8/23 (35)	-0.74 (-1.90, 0.42)	.20	26.44 (24.80, 28.09)	26.06 (24.12, 27.99)	8/18 (44)	-0.39 (-1.72, 0.95)	.55
MoCA	20.57 (17.59, 23.54)	20.52 (17.14, 23.91)	9/23 (39)	-0.04 (-0.96, 0.87)	.92	23.50 (21.44, 25.56)	24.06 (22.03, 26.08)	9/18 (50)	0.56 (-0.38, 1.49)	.23
QDRS	4.98 (3.74, 6.22)	4.44 (2.503, 6.37)	14/23 (61)	-0.54 (-1.77, 0.69)	.37	4.22 (3.16, 5.29)	2.67 (1.97, 3.36)	13/18 (72)	-1.56 (-2.46, -0.65)	.002 [†]
CDR	0.61 (0.52, 0.70)	0.65 (0.41, 0.90)	4/23 (17)	0.04 (-0.14, 0.23)	.63	0.56 (0.48, 0.64)	0.44 (0.33, 0.56)	4/18 (22)	-0.11 (-0.22, -0.005)	.042 [†]
ADCOMS	0.34 (0.22, 0.46)	0.35 (0.16, 0.53)	13/23 (57)	0.0049 (-0.079, 0.089)	.90	0.23 (0.16, 0.30)	0.17 (0.101, 0.21)	13/18 (72)	-0.07 (-0.12, -0.019)	.0094 [†]
	All patients				Patients with MMSE ≥ 20					
Biomarker	Baseline, mean (95% CI)	Posttreatment, mean (95% CI)	Patients with improvement (%)	Mean change from baseline (95% CI)	P value*	Baseline, mean (95% CI)	Posttreatment, mean (95% CI)	Patients with improvement (%)	Mean change from baseline (95% CI)	P value*
Brain glutathione, mM	1.25 (0.92, 1.57)	1.35 (1.088, 1.62)	13/22 (59)	0.11 (-0.23, 0.45)	.54	1.12 (0.76, 1.48)	1.35 (1.051, 1.65)	12/18 (67)	0.23 (-0.15, 0.61)	.22
Plasma TNF- α , pg/mL	1.33 (0.73, 1.94)	0.93 (0.56, 1.304)	11/18 (61)	-0.45 (-1.22, 0.31)	.23	1.43 (0.67, 2.19)	0.91 (0.43, 1.402)	9/14 (64)	-0.56 (-1.55, 0.42)	.24
CSF P-tau:A β 42 ratio	0.047 (0.0304, 0.063)	0.044 (0.028, 0.059)	10/16 (63)	-0.0033 (-0.008, 0.002)	.18	0.033 (0.019, 0.046)	0.0304 (0.019, 0.042)	7/11 (64)	-0.0024 (-0.005, 0.00)	.04 [†]
CSF P-tau, pg/mL	31.87 (23.49, 40.25)	30.78 (22.72, 38.83)	13/21 (62)	-1.1 (-3.04, 0.85)	.26	26.46 (19.40, 33.52)	24.80 (18.49, 31.11)	10/16 (63)	-1.66 (-3.17, -0.14)	.033 [†]
CSF A β 42, pg/mL	842.3 (696.6, 987.9)	852.0 (709.2, 994.8)	11/18 (61)	9.72 (-60.72, 80.17)	.77	939.5 (770.6, 1108)	930.8 (750.8, 1111)	9/13 (69)	-8.69 (-80.95, 63.56)	.80

Ap42 = amyloid beta peptide 42; ADAS-Cog11 = 11-item Alzheimer’s Disease Assessment Scale-Cognitive Subscale; ADCOMS = Alzheimer’s Disease Composite Score; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; P-tau = phosphorylated tau protein; QDRS = Quick Dementia Rating Scale; TNF- α = tumor necrosis factor alpha.
 *1-way t-test.
[†]Statistical significance ($P < .05$).

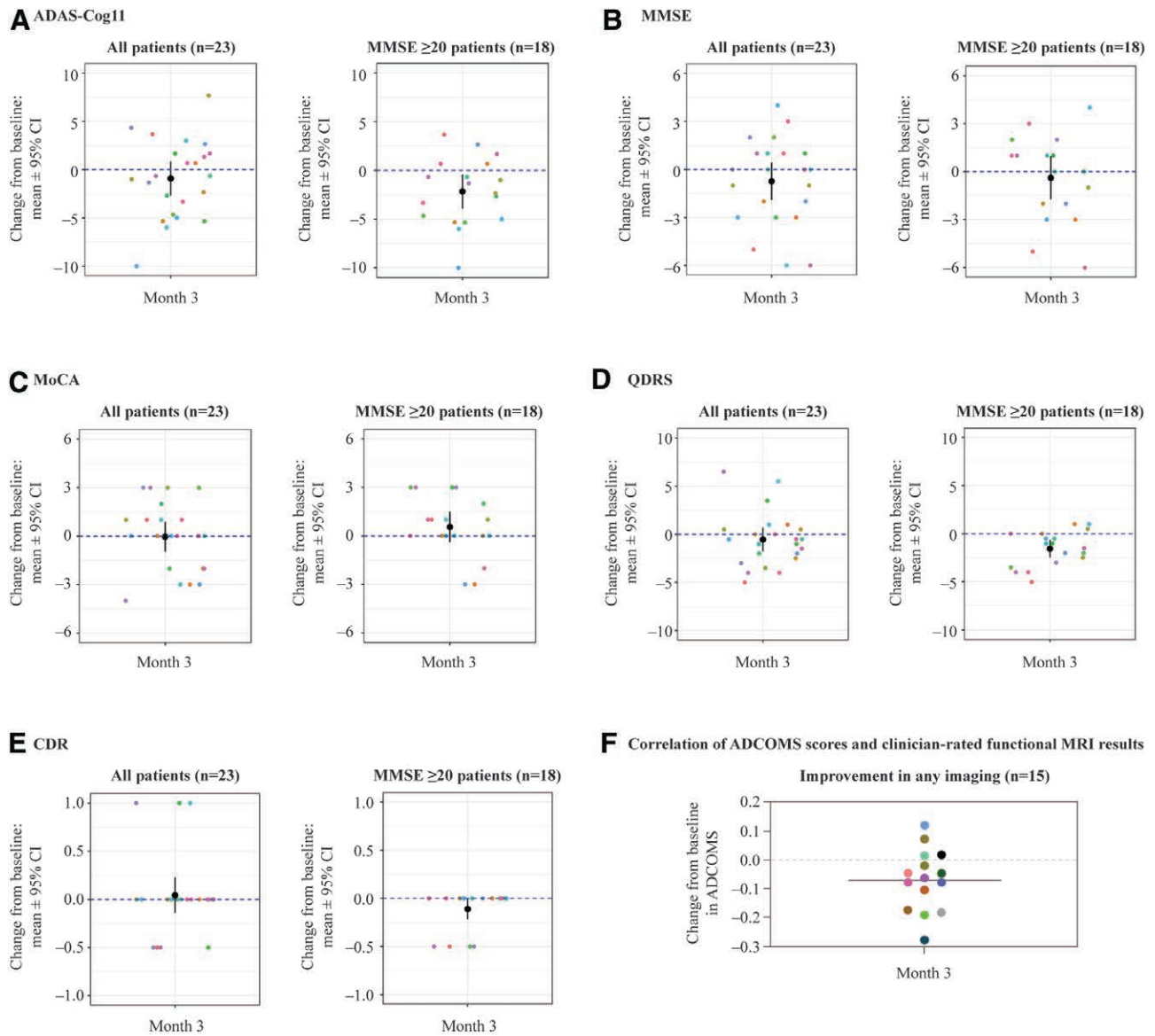


Figure 3. Secondary endpoints evaluated changes, after treatment with NE3107, in neuropsychological health using various cognitive assessments. (A–E) Change from baseline in (A) ADAS-Cog11 scores (all patients, $P = .29$; MMSE ≥ 20 patients, $P = .017$); (B) MMSE scores (all patients, $P = .20$; MMSE ≥ 20 patients, $P = .55$); (C) MoCA scores (all patients; $P = .92$; MMSE ≥ 20 patients, $P = .23$); (D) QDRS scores (all patients, $P = .37$; MMSE ≥ 20 patients, $P = .002$); (E) CDR scores (all patients, $P = .63$; MMSE ≥ 20 patients, $P = .042$). (F) Change from baseline in ADCOMS in patients with clinician-rated improvements in any fMRI analyses. ADAS-Cog11 = 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS = Alzheimer's Disease Composite Score; CDR = Clinical Dementia Rating; fMRI = functional magnetic resonance imaging; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; QDRS = Quick Dementia Rating Scale.

Table 5
Summary of results from Global Rating of Change assessments.

GRC assessment	All patients (N = 23)		Patients with MMSE ≥ 20 (n = 18)	
	Mean (95% CI)	P value*	Mean (95% CI)	P value*
Clinician-reported	1.7 (0.61, 2.78)	.0038	2.67 (1.90, 3.43)	<.001
Patient-reported	2.2 (1.21, 3.18)	<.001	2.08 (0.95, 3.22)	.0012
Caretaker-reported	1.07 (0.067, 2.063)	.038	1.69 (0.78, 2.61)	.0011

CI = confidence interval; GRC = Global Rating of Change.
 *1-way *t*-test.

from baseline in rCBF within the temporo-parieto-occipital lobe (measured using ASL) and FC (measured using BOLD imaging) within the DMN, as well as the NBM and HC networks. Present in the parietal lobe, the precuneus has integral functions within

the DMN and is important for episodic and autobiographical memory. Consistent with its importance, the precuneus is thought to consume more glucose than any other region of the human brain, and compromised CBF activity within this region

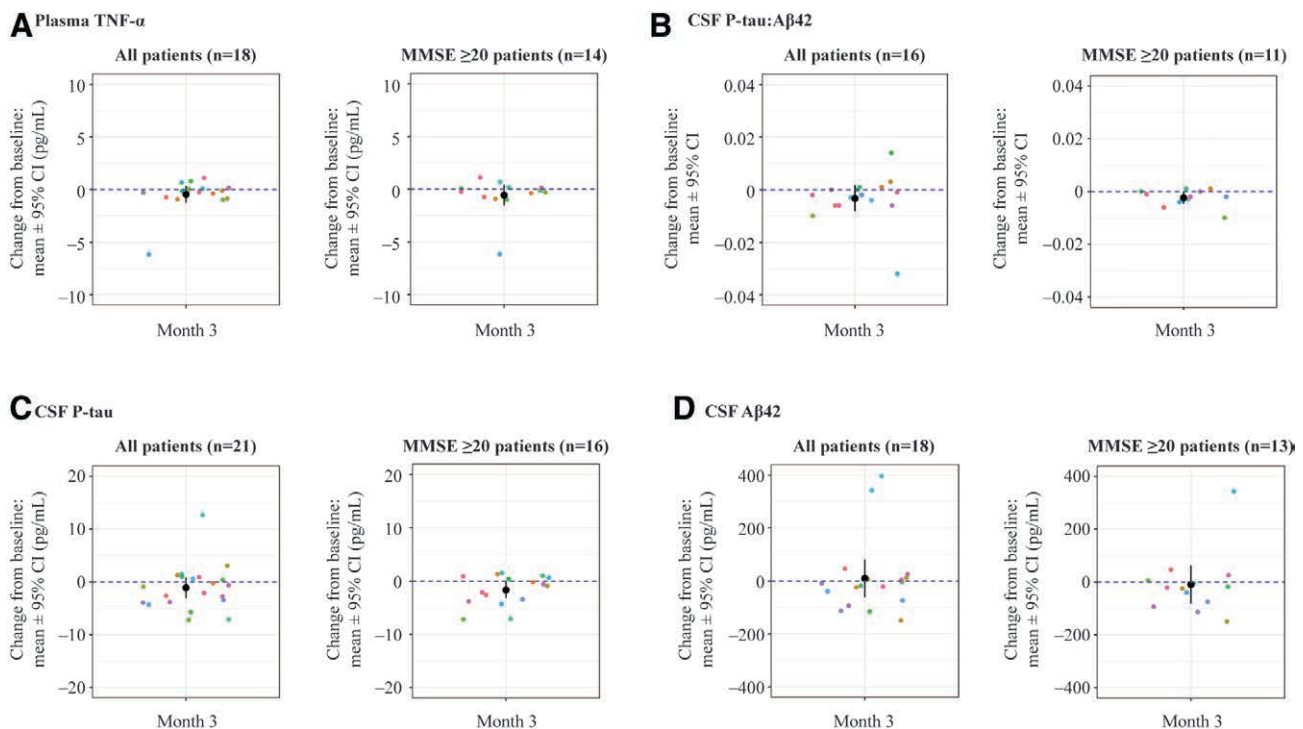


Figure 4. Exploratory endpoints assessed changes in biomarkers associated with neuroinflammation and AD in patients after treatment with NE3107. (A) Change from baseline in plasma TNF- α for all patients ($P = .23$) and patients with MMSE ≥ 20 ($P = .24$). (B–D) Change from baseline in CSF levels of B. P-tau:A β 42 ratio (all patients, $P = .18$; MMSE ≥ 20 patients, $P = .04$); (C) P-tau levels (all patients, $P = .26$; MMSE ≥ 20 patients, $P = .034$); (D) A β 42 levels (all patients, $P = .77$; MMSE ≥ 20 patients, $P = .80$). A β 42 = amyloid beta peptide 42; CSF = cerebrospinal fluid; MMSE = Mini-Mental State Examination; P-tau = phosphorylated tau protein; TNF- α = tumor necrosis factor alpha.

may be associated with AD progression.^[39] ASL-MRI-derived changes in perfusion strongly correlate with changes in glucose metabolism measured using fluorodeoxyglucose positron emission tomography. Thus, improvements in perfusion (rCBF) are expected to correspond to improvements in brain glucose and energy utilization.^[46–48]

Our study had several limitations. First, our sample size, while appropriate for an exploratory study, was relatively small, and the duration of active treatment was short. Despite the short duration, several of the observed effects associated with NE3107 for the primary and secondary endpoints were in the direction of therapeutic benefit. Second, there was a lack of peripheral glycemic dysregulation in the study patients—only 4% ($n = 1$) of the study patients were diabetic—precluding any apparent effects of NE3107 on glucose metabolism in this study. Additionally, our study did not employ any surrogate endpoints to measure changes in insulin signaling in the CNS of the study patients. Fourth, the open-label study design limited our ability to isolate potential placebo effects. However, this study served as an exploratory precursor to inform the design of subsequent larger, placebo-controlled confirmatory trials. Fifth, given the exploratory nature of this study, we utilized multiple comparisons to gain an understanding of the scope of treatment effects associated with NE3107, which may have affected the accuracy of the conclusions. Lastly, we acknowledge a lack of ethnic and racial diversity in our study patients. Future studies with NE3107 will aim to include racially and ethnically diverse groups of patients.

An important finding of this study was that patients with MCI or mild dementia (MMSE ≥ 20 at baseline) showed greater improvements in several endpoints (Figs. 3 and 4 and Table 4), suggesting that the potential extent of the therapeutic effects of NE3107 may be more pronounced in patients who are in the prodromal or early stages of dementia. Compelling evidence suggests that AD progression may follow a more

intricate, rather than unidirectional, path, its pathophysiology comprising several aberrant positive feedback loops that may form several years prior to disease manifestation.^[40,44,49] Therefore, early intervention with an immunomodulatory, and possibly, multipotent, therapeutic such as NE3107 may be a valuable line of defense and could alter the clinical course of AD.^[49,50] Subsequent longer-term, placebo-controlled studies are required to validate the potential of NE3107 in patients in the early stages of dementia.

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