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

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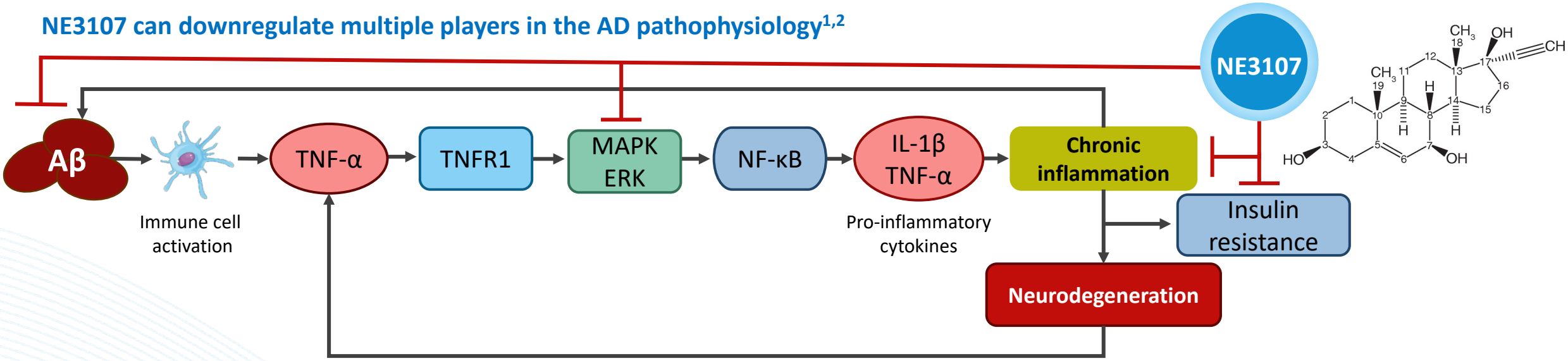
DG and BP have nothing to disclose

CA, CR, and JP are employees of BioVie Inc.

Background

NE3107 can downregulate multiple players in the AD pathophysiology[1,2]



For details, see Jung et al, 2019[1] and Reading et al, 2021[2]

- Disrupting the feed-forward loop formed by neuroinflammation, insulin resistance, and AD pathologies may be an effective strategy to limit AD progression[3]
- NE3107 is a metabolically stabilized, blood-brain barrier–permeable, orally bioavailable molecule derived from DHEA, an abundant and naturally occurring steroid hormone in humans[2,4]
- Previously, NE3107 was shown to bind ERK, inhibit key inflammatory mediators such as NF-κB, lower proinflammatory cytokines such as TNF-α and IL-6, improve insulin signaling, and have a favorable safety profile[2]
- MRI-based neuroimaging can reveal several AD-specific brain changes such as reduced glutathione levels, decreased arterial hypoperfusion, and diminished functional connectivity[5-7]

AD, Alzheimer's disease; Aβ, amyloid β; DHEA, dehydroepiandrosterone; ERK, extracellular regulated-kinase; IL-6, interleukin-6; MAPK, mitogen-activated protein kinases; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor-α; TNFR, TNF-α receptor.

Hypothesis-Driven Study

Proposed mechanism of action

Reduced neuroinflammation via a reduction of key inflammatory mediators, such as TNF-α

Proposed clinical effects of NE3107

Improvements in insulin signaling

Reduction of AD biomarkers

Increase in brain glutathione, a neuroprotective antioxidant

Improvements in neurocognitive functioning

Changes in neuroimaging consistent with increased functional connectivity in the default mode network, nucleus basalis of Meynert, and hippocampal networks without changes in structural connectivity or volumetrics

- **NE3107's effects on these key parameters may help to decrease the progression of AD**

Objectives

- **A phase 2, open-label study** to evaluate the potential efficacy of NE3107 in patients with mild cognitive impairment (MCI) or mild dementia using advanced neuroimaging endpoints, AD and inflammatory biomarkers, changes in glucose metabolism, and cognitive performance testing

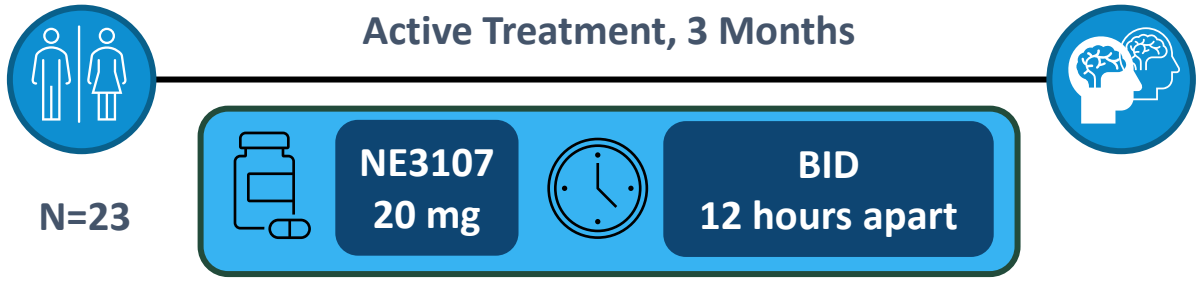
Primary Objective	To evaluate changes in neurophysiological health using multi-modal brain MRIs obtained at baseline and treatment termination (3 months)
Secondary Objective	To include a longitudinal comparison of cognitive impairment as defined by neuropsychological testing and AD and inflammatory markers

Study Design

Phase 2 Open-Label Single-Arm 3-Month Study

Inclusion criteria
- 50-89 years old
- Cognitive decline due to dementia
- QDRS score: 1.5-12.5
- CDR score: 0.5 (MCI) or 1 (mild dementia)

Exclusion criteria
- Prior imaging inconsistent with AD
- History of stroke that resulted in cognitive or motor deficits
- MRI/CT evidence of moderate/large cerebral infract



Change from baseline assessments

Neuroimaging	Clinical Assessments	Biomarker Assessments
MRS	MMSE	Plasma TNF-α
Relative CBF	ADAS-Cog12	CSF Aβ42
Anatomical imaging	MoCA	CSF p-tau
BOLD imaging*	QDRS and CDR	P-tau:Aβ42 ratio
DTI-NODDI†	ADCOMS	Brain glutathione (by MRS)

*Preliminary data; †Data analysis ongoing.
ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, AD Composite Score; ASL, arterial spin labeling; BID, twice per day; BOLD, blood-oxygen level dependent; CBR, cerebral blood flow; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; DTI-NODDI, diffusion tensor imaging – neurite orientation dispersion and density imaging; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRS, magnetic resonance spectroscopy; NMR, nuclear magnetic resonance; QDRS, Quick Dementia Rating Scale.

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 or mild dementia)	18 (78)
<20 (moderate dementia)	5 (22)
APOE status	
ε2/ε3	2 (9)
ε2/ε4	1 (4)
ε3/ε3	9 (39)
ε3/ε4	10 (44)
ε4/ε4	1 (4)

APOE, apolipoprotein E gene; PD, Parkinson's disease.

Clinical Assessment Outcomes

NE3107 Was Associated With Improvements From Baseline in Clinical Outcomes of Neuropsychological and Cognitive Assessments after 3 months of Treatment

Changes from Baseline in Clinical Assessments

Assessment	All Patients (N=23)	MCI/Mild AD (n=18)
ADAS-Cog12	−0.913	**−2.167***
MMSE	−0.74	−0.39
MoCA	−0.04	0.56
QDRS	−0.54	**−1.56***
CDR	0.04	**−0.11***
ADCOMS	0.0049	**−0.07***

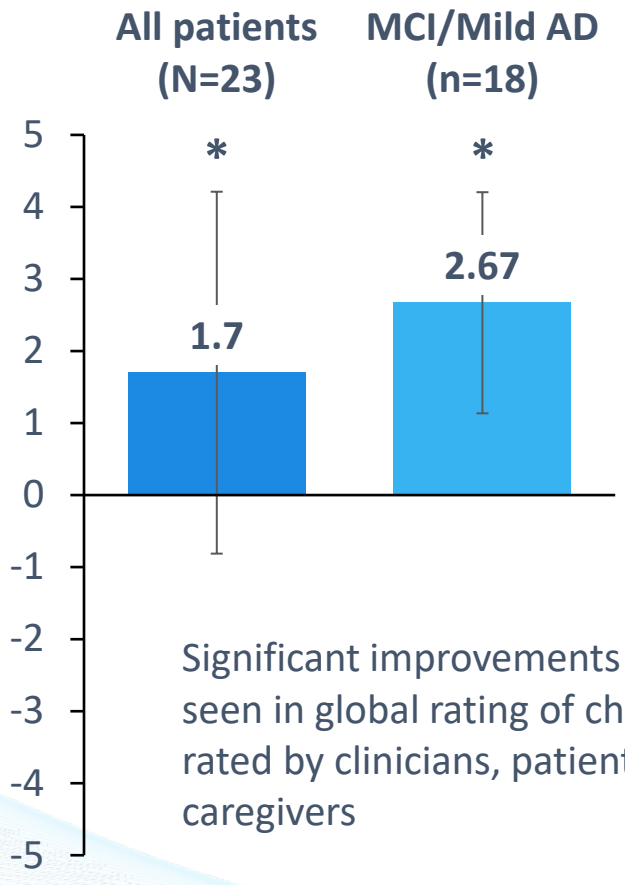
In the patients with baseline MMSE ≥20 (indicating MCI or mild dementia), NE3107 was associated with statistically significantly improved cognitive functioning vs baseline, in ADAS-Cog12, QDRS, CDR, ADCOMS,

Green=Improvement

*$P<0.05$

Poster P034

Clinician-Rated Global Rating of Change



Significant improvements were seen in global rating of change as rated by clinicians, patients, and caregivers

Biomarkers

NE3107 Was Associated With Reduction in Neuroinflammation as Assessed by TNF-α Levels, Improvements in Biomarkers, and Correlations Between Biomarkers and Clinical Outcomes

Changes from baseline in biomarkers

Assessment	All Patients (N=23)	MCI/Mild AD (n=18)
TNF-α, pg/mL	−0.452	−0.563
CSF p-tau, pg/mL	−1.1	**−1.66***
P-tau:Aβ42 ratio	−0.0033	**−0.0024***

In the MMSE ≥20 patients, NE3107 was associated with statistically significant improvements in p-tau and the p-tau:Aβ42 ratio

Correlations between biomarkers and clinical outcomes

	All Patients	MMSE ≥20 n=18
ADAS-Cog12		
TNF-α	r=0.46	**r=0.59***
ADCOMS		
Aβ42	**r=0.53***	r=0.31
P-tau	**r=0.49***	r=0.37

NE3107 was associated with statistically significant correlations between several clinical assessments and biomarkers

*$P<0.05$

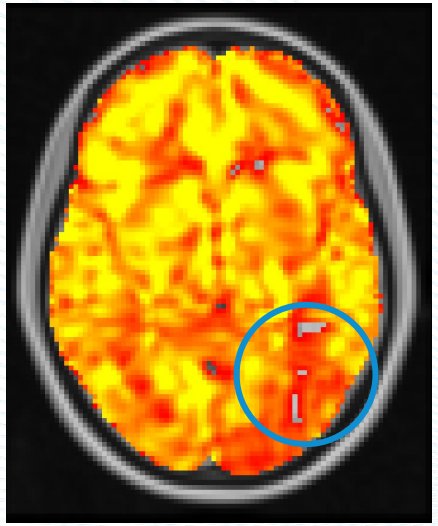
Green=Improvement

Posters P034 and P095

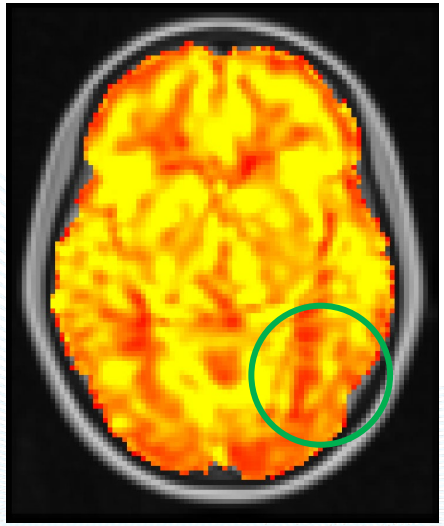
Neuroimaging Methodology

Clinician Blinded Review Methods: Functional MRI data were submitted to blinded review and scoring by two independent clinician-readers. Inter-rater reliability was 96%; in the event of disagreement between raters, the data were subjected to additional review and ultimately scored by consensus

Criteria for Abnormality: Perfusion/Relative cerebral blood flow (CBF): 30% decrease in signal intensity in the temporal, parietal, or occipital lobes (in at least 1 hemisphere) was scored as abnormal



Baseline



Follow-up

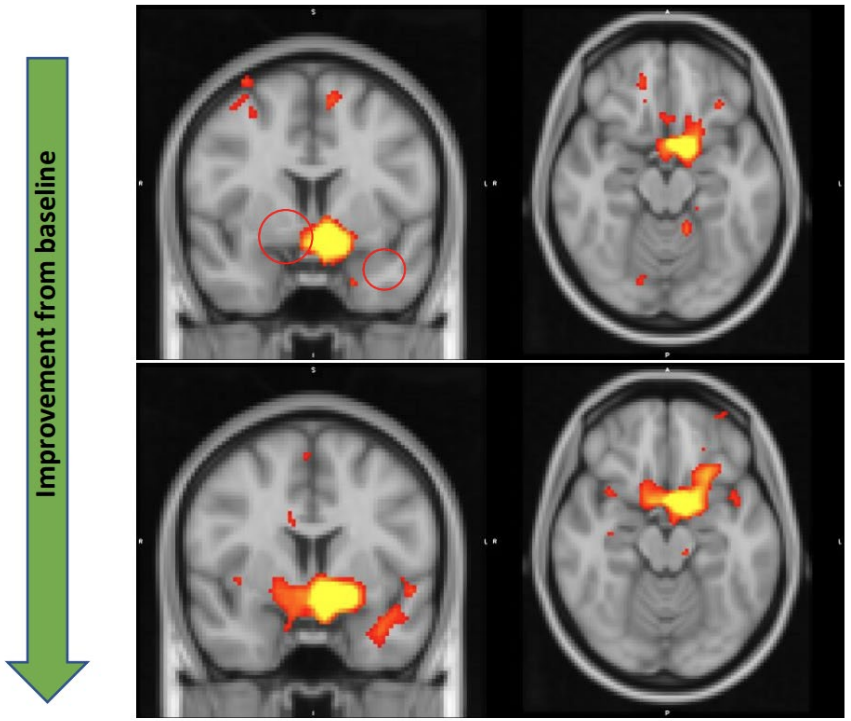
Examples show a subject that had decreased perfusion (abnormal) that improved at follow-up

Neuroimaging Methodology

Criteria for Abnormality: A cluster >1 cm^3 shown on a statistical map would be scored as abnormal for the following connectivity patterns:

For a seed placed in the Nucleus Basalis of Meynert (NBM), abnormal regions for cluster include:

- Contralateral and/or ipsilateral NBM (beyond the area of the seed)
- Inferior frontal lobe
- Temporal lobe
- Basal forebrain

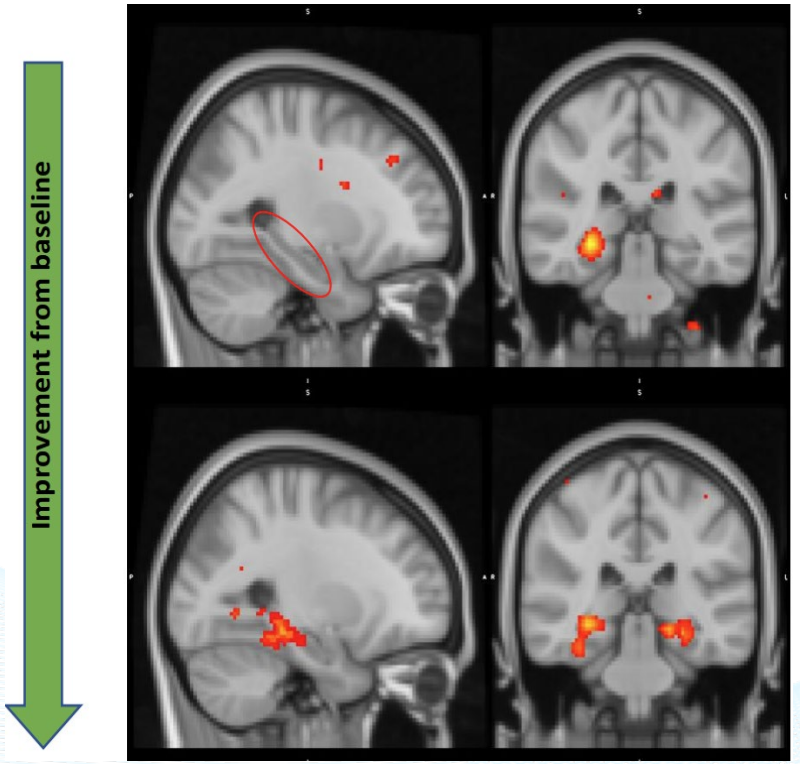


Lack of contralateral connectivity, lack of connectivity to temporal lobe

Contralateral connectivity is recovered at follow-up and temporal lobe connectivity is also seen.

For a seed placed in the hippocampus (HC), abnormal regions for cluster include:

- Contralateral and/or Ipsilateral HC (beyond the area of the seed)
- Anterior mid-temporal lobe



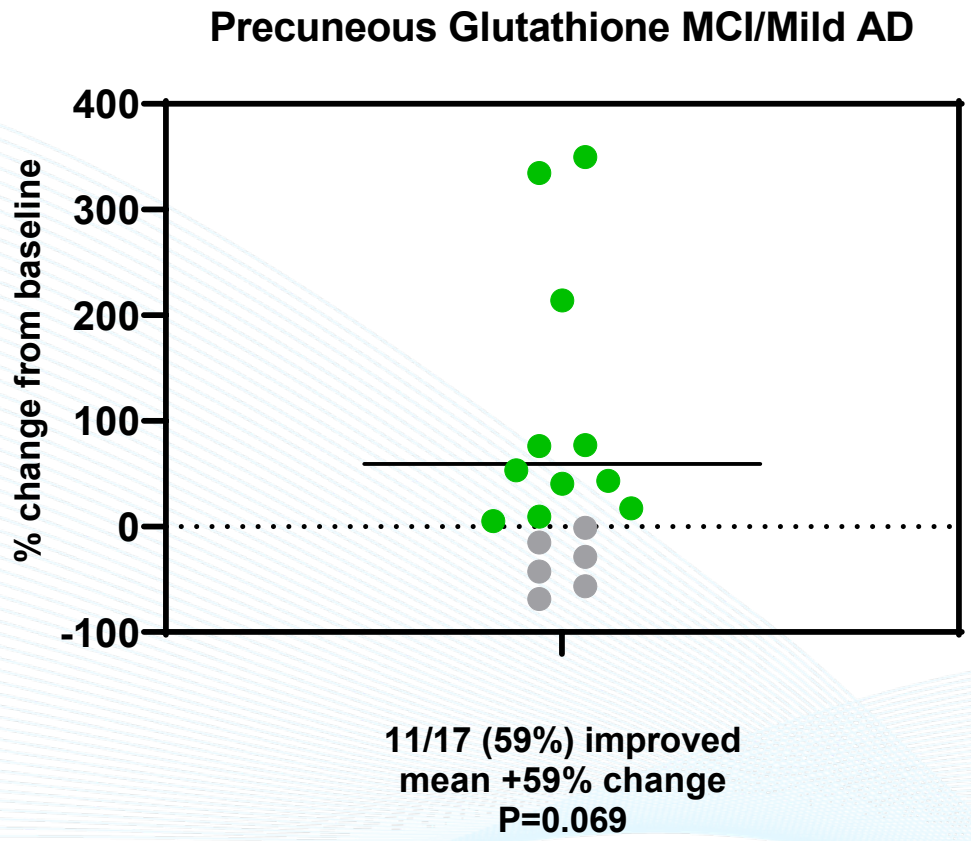
Lack of contralateral connectivity

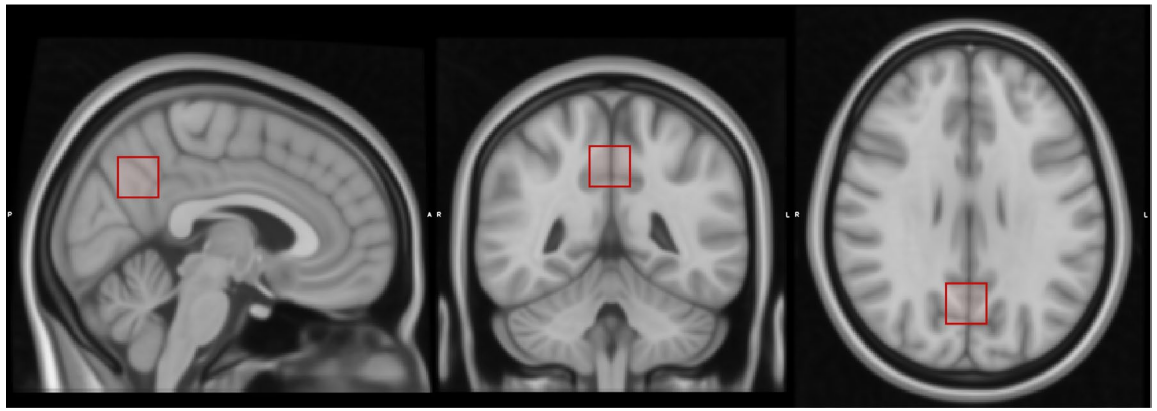
Hippocampal connectivity on the contralateral side is recovered at follow-up

Oxidative Stress

NE3107 May Be Associated With Reduced Oxidative Stress in the Brain

% change from baseline in brain glutathione assessed by MRS of precuneus



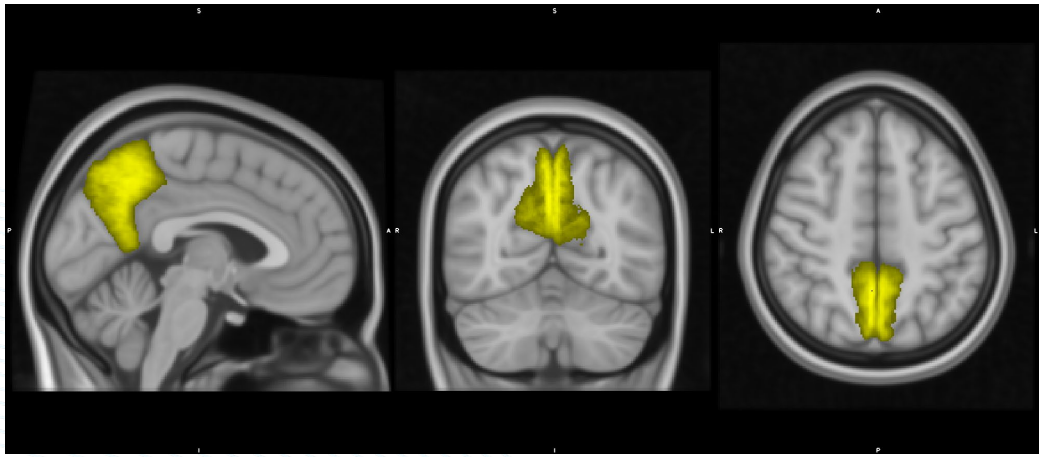


For all patients, there were significant correlations between glutathione and TNF-α (r=−0.44) and glutathione and ADAS-Cog12 (r=−0.45)

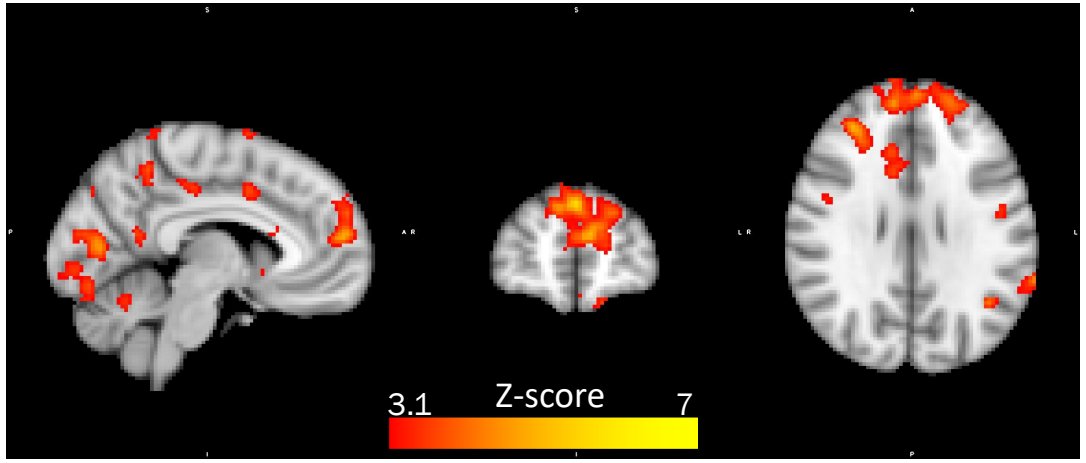
Functional Connectivity

NE3107 Was Associated With Increased Functional Connectivity from Baseline in Group Analysis Using BOLD Imaging

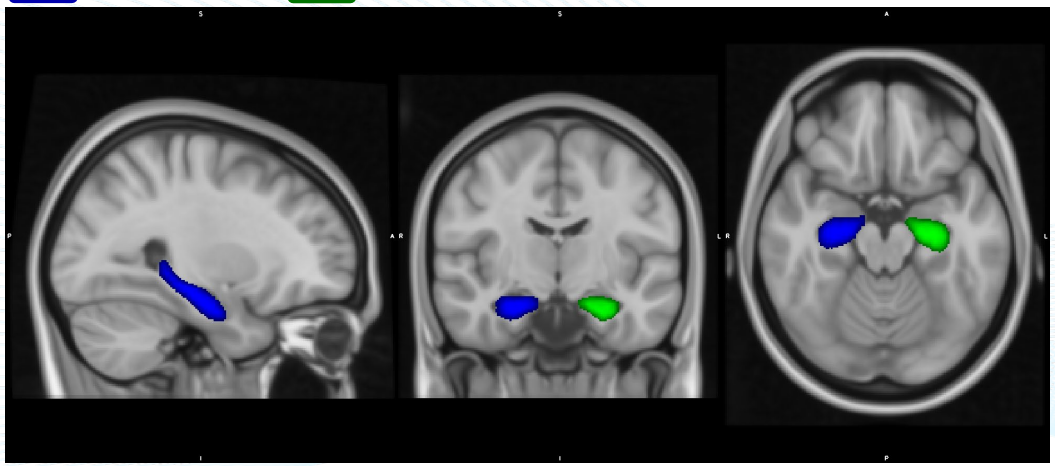
Default mode network

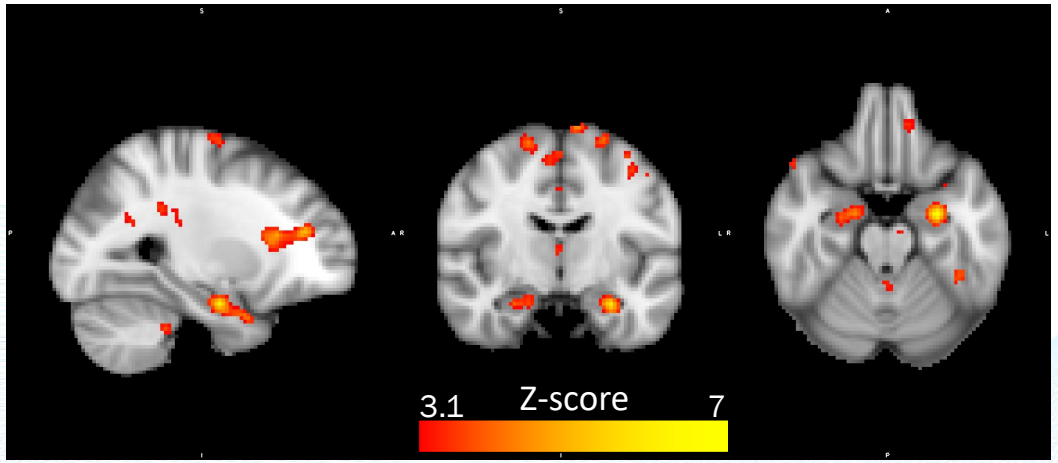


Statistically significant regions of increased connectivity



Right and left hippocampus ROI (memory and learning)



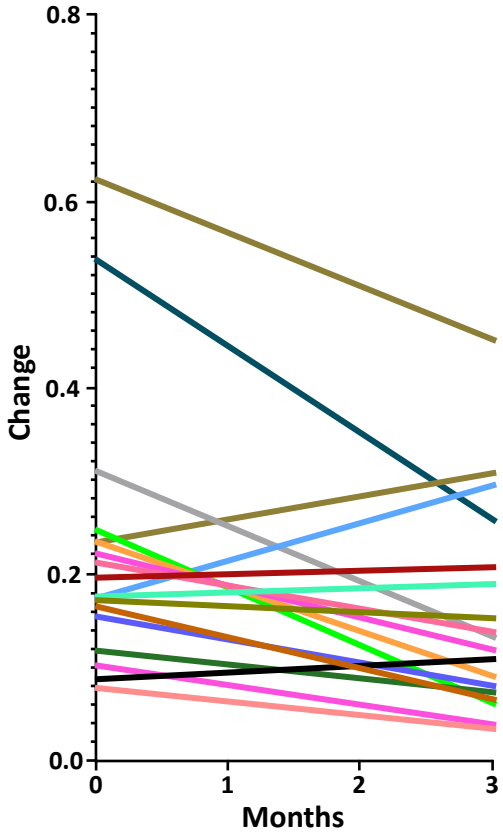


ROI, region of interest.

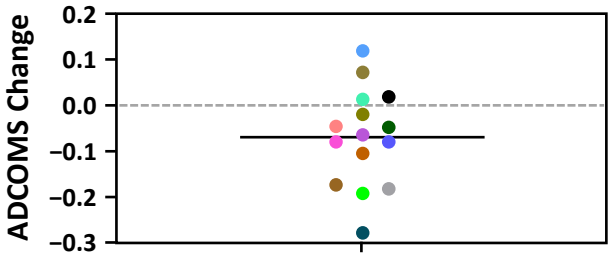
Neurocognition

Changes from baseline in ADCOMS for patients who had abnormal MRI signals at baseline and improved after treatment with NE3107

ADCOMS MCI/Mild AD

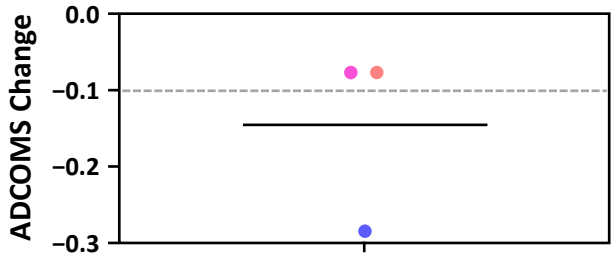


Any Imaging MCI/Mild AD



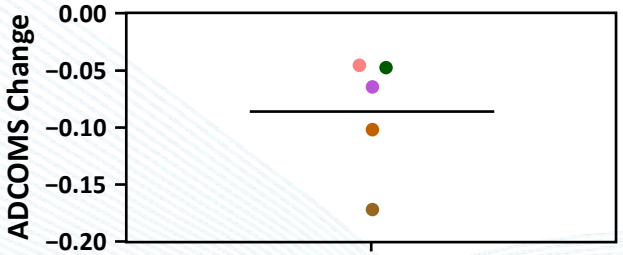
Mean: −0.068
***P*=0.028**
11/15 (67%) decreased

Temporal Parietal Occipital CBF



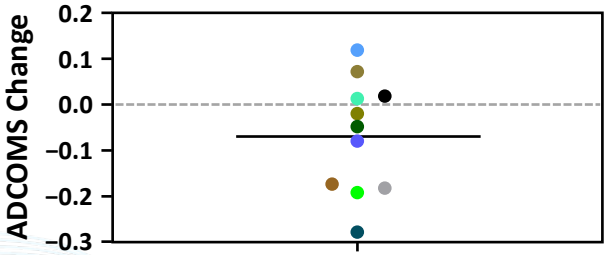
Mean: −0.145
P=NS
3/3 (100%) decreased

Precuneus MCI/Mild AD



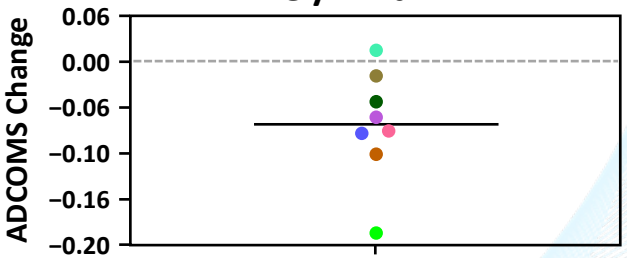
Mean: −0.085
***P*=0.024**
5/5 (100%) decreased

Hippocampus



Mean: −0.067
P=0.109 (NS)
7/11 (64%) decreased

Nucleus basalis of Meynert MCI/Mild AD



Mean: −0.069
***P*=0.014**
7/8 (88%) decreased

Improvements in ADCOMS were observed in patients who had improved neuroimaging results

*$P<0.05$

Each line or dot represents one patient

Conclusion

- In this open-label study, NE3107 appeared to be associated with improvements in cognitive assessments and biomarkers related to neuroinflammation and AD
- NE3107 was also descriptively associated with clinician-rated improvements from baseline in relative CBF and functional connectivity within the nucleus basalis of Meynert, the precuneus, and the hippocampus
- Correlations of change among neuroimaging, clinical measures, and biomarkers, which occur concomitantly with the administration of the study drug, may suggest potential drug effects of NE3107 in dementia, and these findings may appear to highlight the hypothesized role of neuroinflammation in AD pathogenesis

➢ The conclusions and observations of this study appear to align with the pre-defined hypotheses of the study, based on predicted MOA and function

Next Steps

- 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]

Acknowledgments and References

Acknowledgments

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