Clinical Outcomes From a Phase 3, Randomized, Placebo-Controlled Trial of NE3107 in Subjects With Mild to Moderate Probable Alzheimer's Disease

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Disclosures

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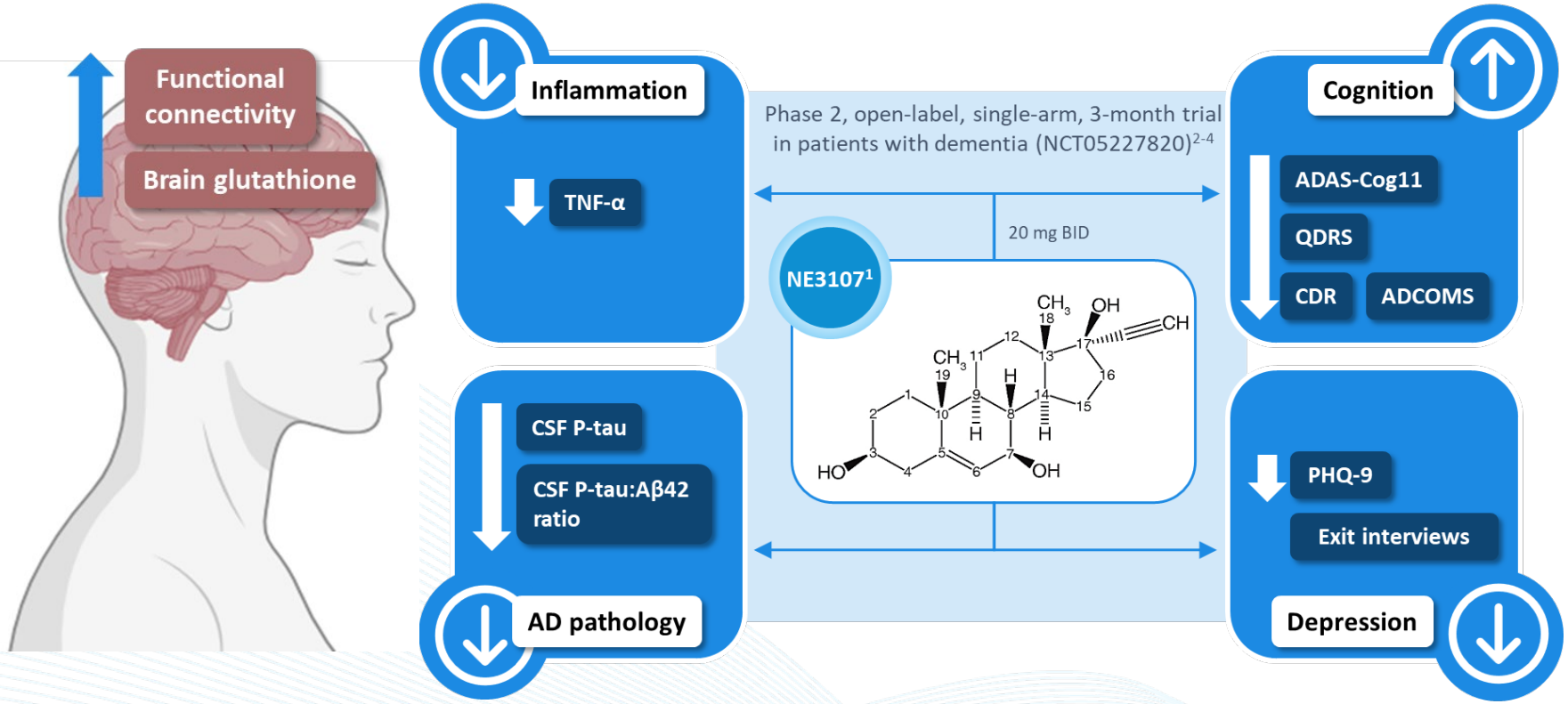
DCS has nothing to disclose.

NE3107: an oral, BBB-permeable, small molecule that inhibits ERK, NF-κB, and TNF-α signaling and acts as an insulin sensitizer[1]



- **In a placebo-controlled phase 2a PD study[5]:**

NE3107 was associated with:

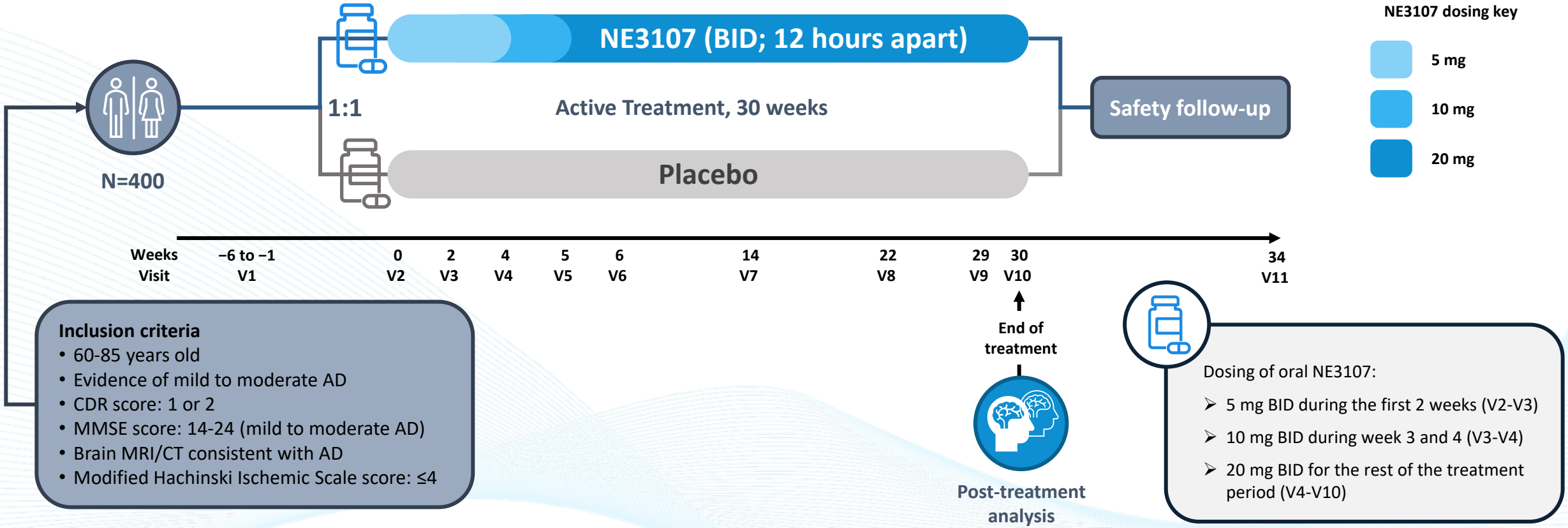
- Improved levodopa activity
- Sleep

ADAS-Cog11, 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCOMS, Alzheimer's disease composite score; BID, twice per day; CDR, Clinical Dementia Rating; PHQ-9, 9-item submodule of the Patient Health Questionnaire; P-tau, phosphorylated tau protein; QDRS, Quick Dementia Rating System.

1. Reading CL, et al. *Neurodegener Dis Manag*. 2021;11(4):289-298 . 2. Haroon J, et al. 2022. 3. Rindner et al. 2022. 4. Palumbo J, et al. 2023. 5. Aldred J, et al. 2023.

NM101 trial (NCT04669028): NE3107 in patients with mild to moderate AD

- Phase 3
- Placebo-controlled
- 40 weeks
- Safety, tolerability, and efficacy
- Double-blind
- Multicenter
- Probable AD



Inclusion criteria
- 60-85 years old
- Evidence of mild to moderate AD
- CDR score: 1 or 2
- MMSE score: 14-24 (mild to moderate AD)
- Brain MRI/CT consistent with AD
- Modified Hachinski Ischemic Scale score: ≤4

Dosing of oral NE3107:
- 5 mg BID during the first 2 weeks (V2-V3)
- 10 mg BID during week 3 and 4 (V3-V4)
- 20 mg BID for the rest of the treatment period (V4-V10)

BID, twice per day; CT, computed tomography; MRI, magnetic resonance imaging.

Reading CL, et al. *Neurodegener Dis Manag*. 2021;11(4):289-298.

Study endpoints

Efficacy assessments:

Co-primary endpoints – change from baseline to treatment completion (week 30)

- Cognitive impairment and global change: ADAS-Cog12 and ADCS-CGIC

Secondary endpoints – change from baseline to treatment completion (week 30)

- Neurocognitive functioning: MMSE, ADCOMS, and CDR
- Neuropsychiatric health: NPI
- Functional outcome: ADCS-ADL
- Glycemic control: Insulin, HOMA2, MAGE, and fasting blood glucose

Exploratory endpoints – change from baseline to treatment completion (week 30)

- Inflammation, metabolic and neurodegeneration biomarkers – including CRP, MCP-1, TNFα, Leptin, Adiponectin, NfL, GFAP, Aβ42, Aβ40 and P-tau
- Two Neuroimaging Sub-studies: vMRI and FDG-PET
- Epigenetic aging clock: DNA methylation status

Safety and tolerability: Incidence and severity of TEAEs; vital signs; physical examinations; C-SSRS; 12-lead ECGs; clinical laboratory assessments (hematology, chemistry, and urinalysis)

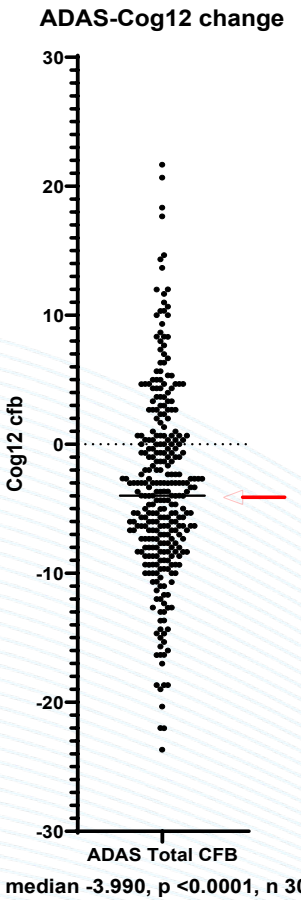
ADAS-Cog12, 12-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCOMS, Alzheimer's Disease Composite Score; ADCS-ADL, Alzheimer's Disease Cooperative Study—Activities of Daily Living; ADCS-CGIC, Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; CDR, Clinical Dementia Rating; CRP, C-reactive protein; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; FDG-PET, fluorodeoxyglucose–positron emission tomography; HOMA2-IR, The Homeostasis Model Assessment of insulin resistance; IL-6, interleukin 6; MAGE, Mean Amplitude of Glycemic Excursions; NPI, Neuropsychiatric Inventory; TEAE, treatment-emergent adverse event; vMRI, volumetric magnetic resonance imaging.

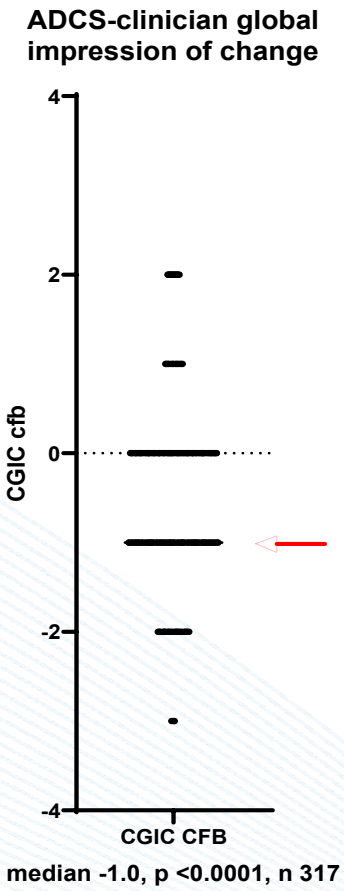
Disclosures regarding current data analyses

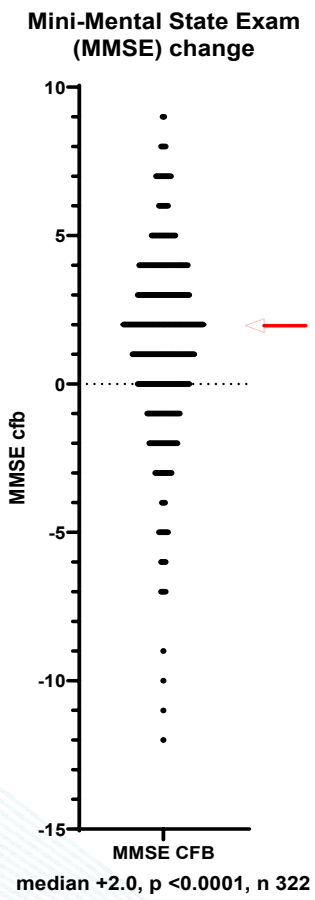
- Data presented in the following slides are based on evaluable blinded data as of October 18, 2023
- Data for Adiponectin, Leptin, p-Tau 217, NfL, GFAP and DNAm are pending
- The blinded analyses presented in these slides do not necessarily imply a treatment effect
- The data presented are currently undergoing cleaning and verification
- The results may change post cleaning and database lock

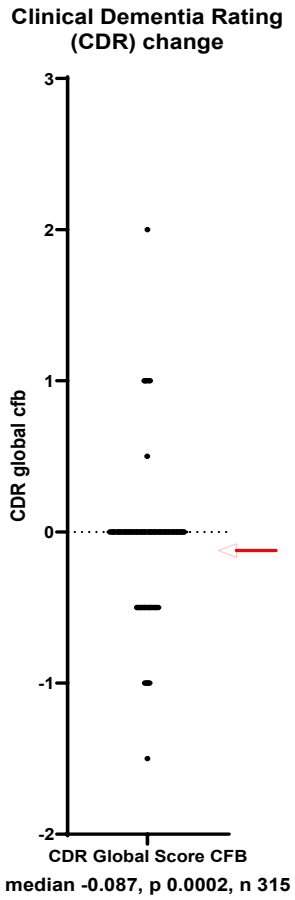
Consistent population changes from baseline (cfb)

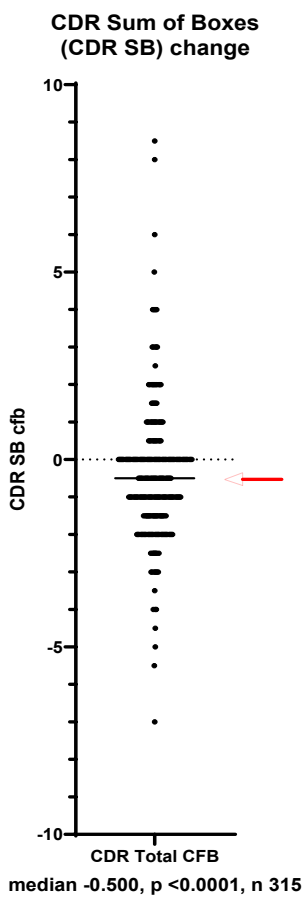
Blinded data

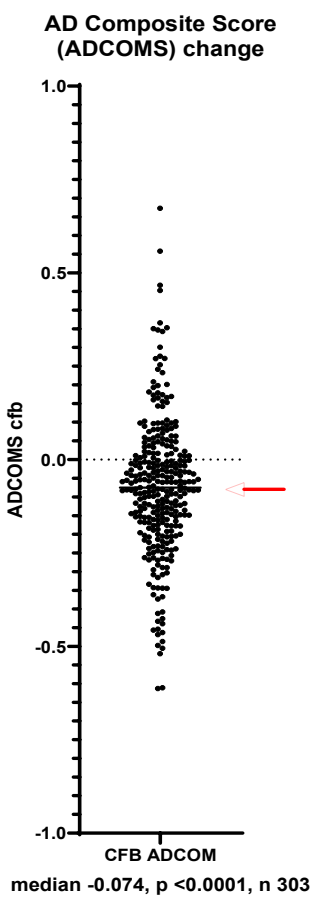


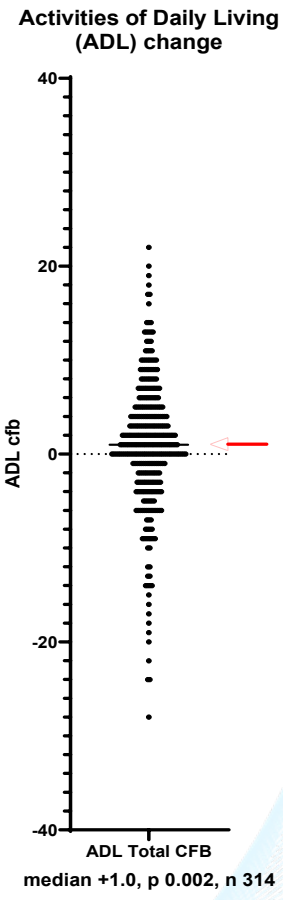












Spearman r *	CGIC	MMSE	CDR	CDR SB	ADCOMS	ADL
Cog12	+0.24	-0.46	+0.23	+0.23	+0.51	-0.40
CGIC		-0.50			+0.46	-0.40
MMSE			-0.38	-0.42	-0.63	+0.34
CDR SB					+0.79	-0.21
ADCOMS						-0.23

APOE, apolipoprotein E; CFB, change from baseline.

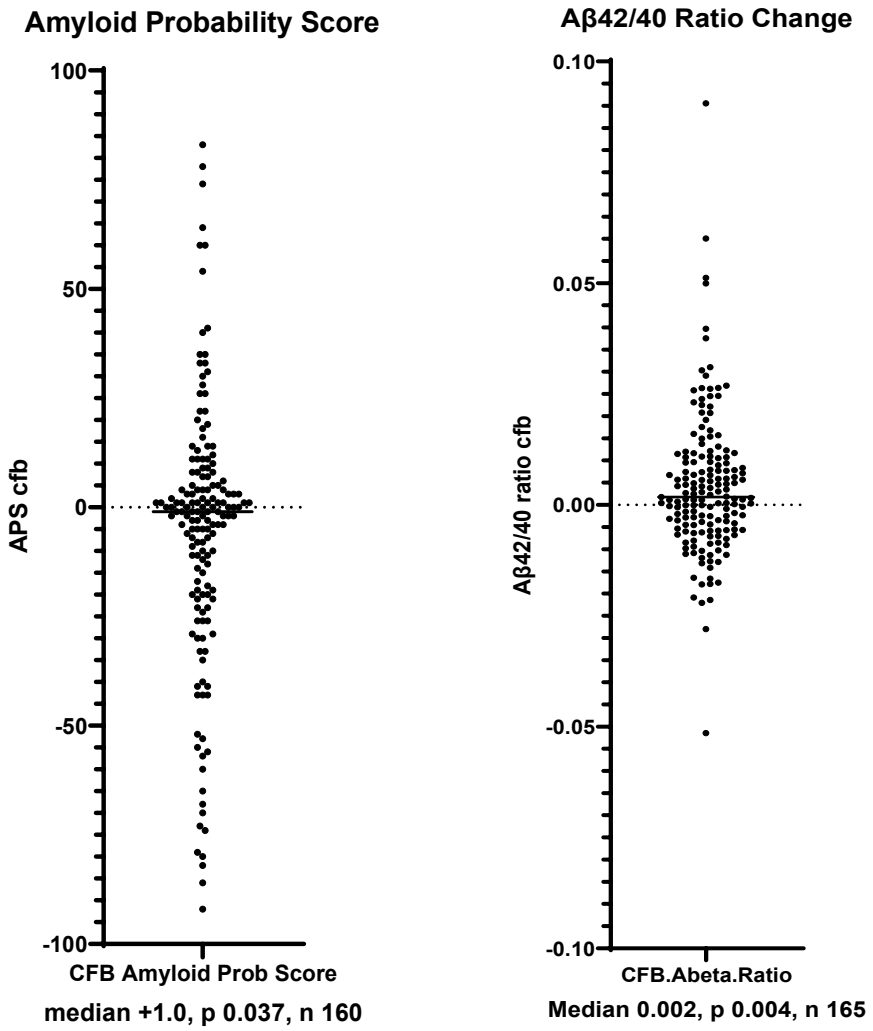
*All *P* <0.0001

Similar distributions for

- APOE4+/-
- Mild/Moderate
- Male/Female
- Older/Younger

Reduced Amyloid Burden

Blinded data



The PrecivityAD® test identifies whether a patient is likely to have the presence or absence of amyloid plaques in the brain, a pathological hallmark of Alzheimer's disease. The test relies on precise and robust quantitation of Amyloid Beta 42/40 ratio (Aβ 42/40) and detection of Apolipoprotein E proteotype (equivalent to ApoE genotype) in blood samples, using C_2N's proprietary mass spectrometry platform.

Baseline	Week 30
Positive n=63	Positive n=40 (63.5%)
	Negative n=23 (36.5%
Negative n=103	Positive n=15 (14.4%)
	Negative n=88 (85.6%)

Fisher Exact Test p=0.0002

Potential evidence of target engagement

Blinded data

- Many of the genes associated with Late Onset AD are related to cholesterol metabolism, which is decreased in AD neuron membranes
- Insulin and glycemic control are known to be involved in neurodegeneration. Increased Insulin and HOMA2-% β cell function and decreased HOMA2% Insulin Sensitivity resulted in no cases of hypoglycemia
- Increased mean amplitude of glycemic excursion (MAGE from CGM) increases risk of AD progression
- If unblinded data concur, this would be evidence of target engagement.

	Cholesterol	Insulin	HOMA2-%B	HOMA2-%S	MAGE
Change from Baseline	+3.0 mg/dL	+1.9 mIU/mL, *	+13.5%, *	-21.2%, *	-0.57 mg/dL
V10 median					

* *P* <0.0001

Spearman r	CGIC	ADL	Cog12
cholesterol	-0.142*	+0.130*	-0.146*
MAGE	+0.265**		

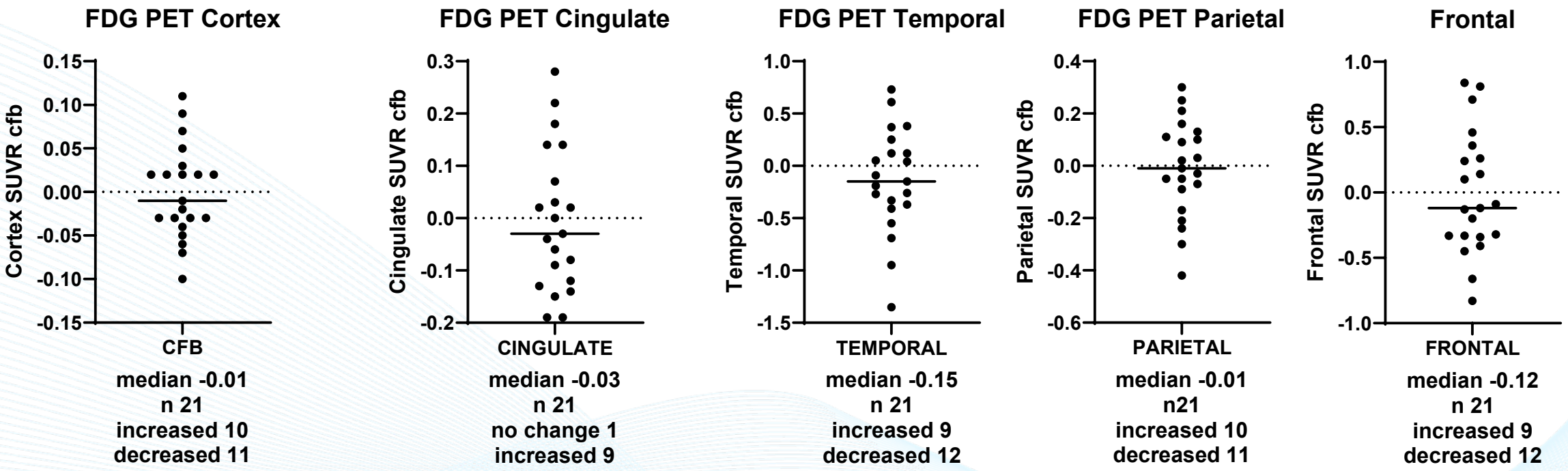
* *P* <0.05, ** *p* 0.01

LOAD, late onset Alzheimer's disease.

Imaging sub-study: FDG-PET

Blinded data

- FDG PET was analyzed in 21 evaluable subjects with baseline and week 30 data
- Sum of ROIs in regional cortical FDG-PET standard uptake value ratios (SUVR) **INCREASED** in 10/21 subjects
  - If unblinded data concur with this, it would also be evidence of target engagement

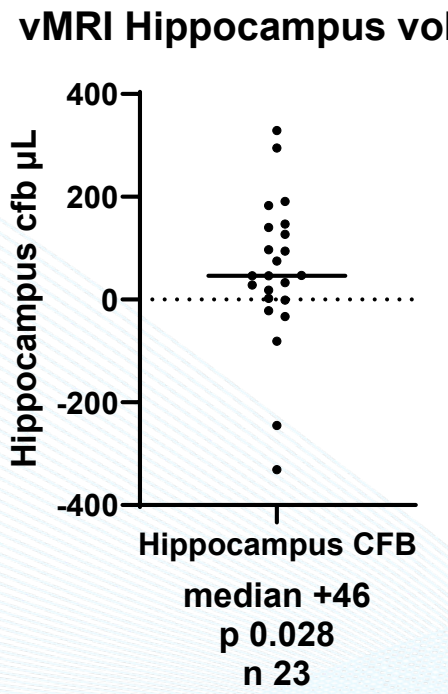


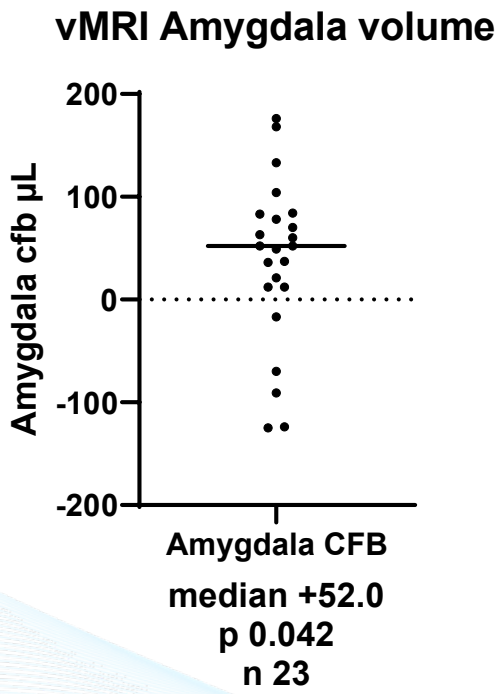
SUVR, standard uptake value ratio.

Imaging sub-study: vMRI

Blinded data

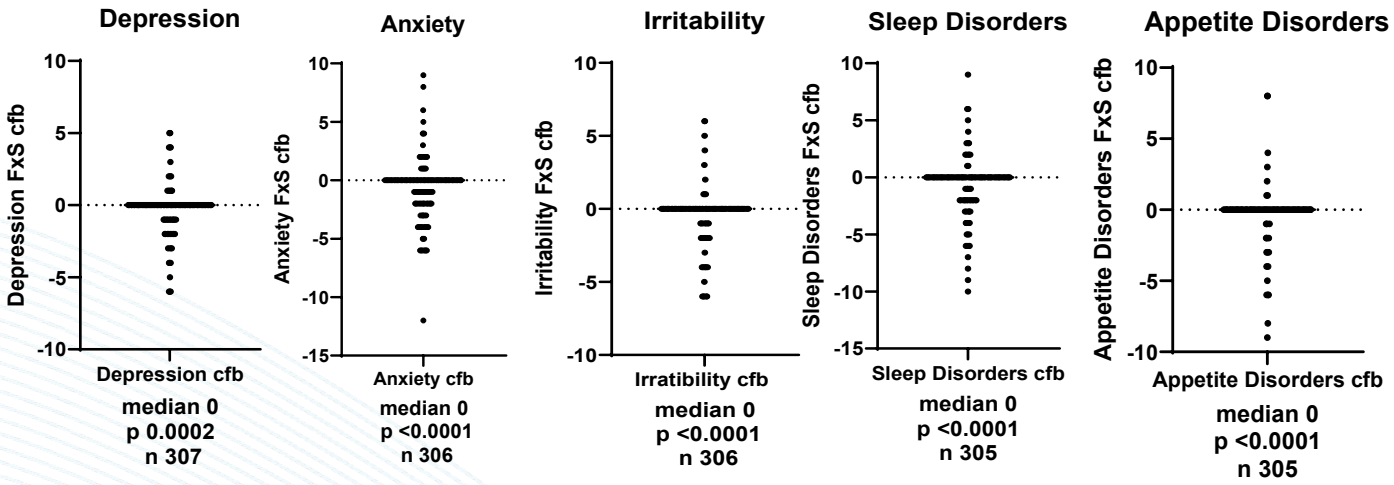
- vMRI was analyzed in 23 evaluable subjects with baseline and V10 data
  - Median volumes **INCREASED** in hippocampus and amygdala





Neuropsychiatric inventory

Blinded data

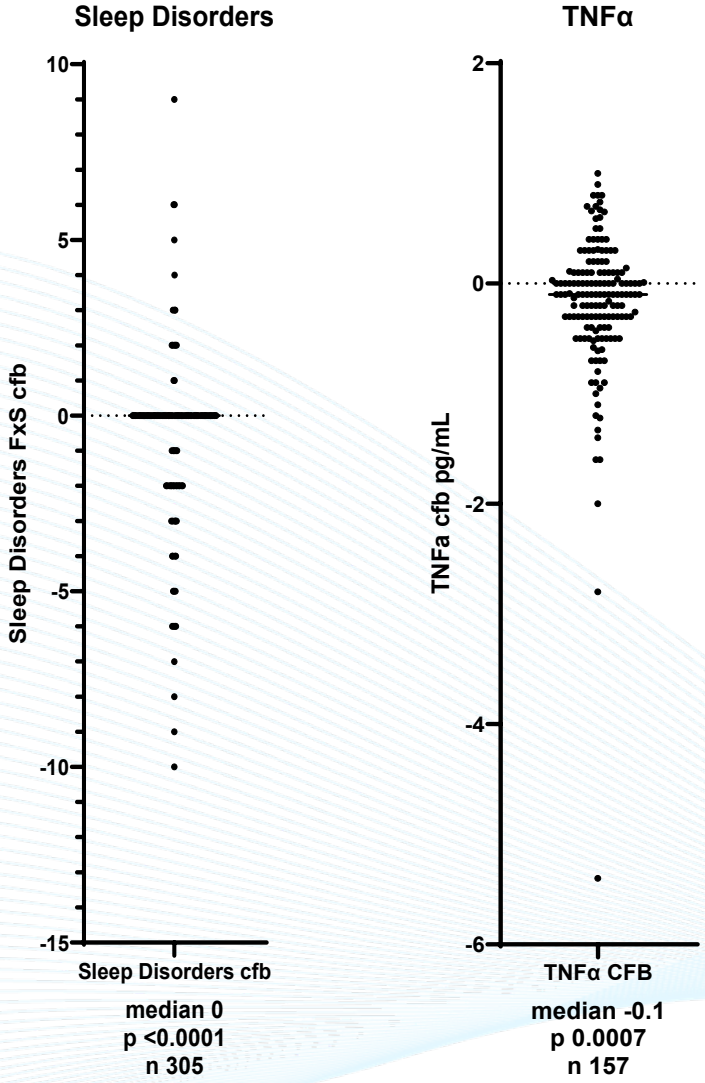


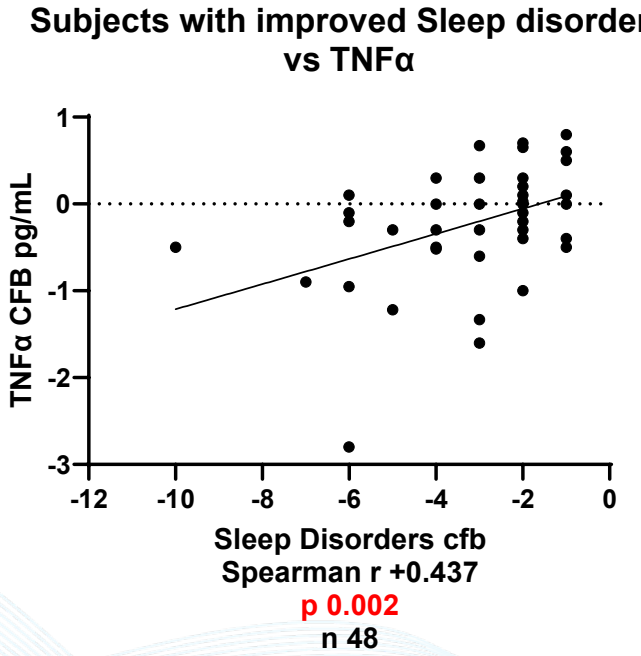
Spearman r	Cog12	CGIC	CDR SB	MMSE	ADCOMS	ADL
Anxiety	+0.116*	+0.115*	+0.146*	-0.172**	+0.163 **	
Irritability		+0.123*	+0.211**	-0.228***	+0.191**	
Sleep	+0.118 **	+0.240***	+0.156**		+0.183 **	-0.258***
Appetite	+0.115*	+0.184***				-0.129*

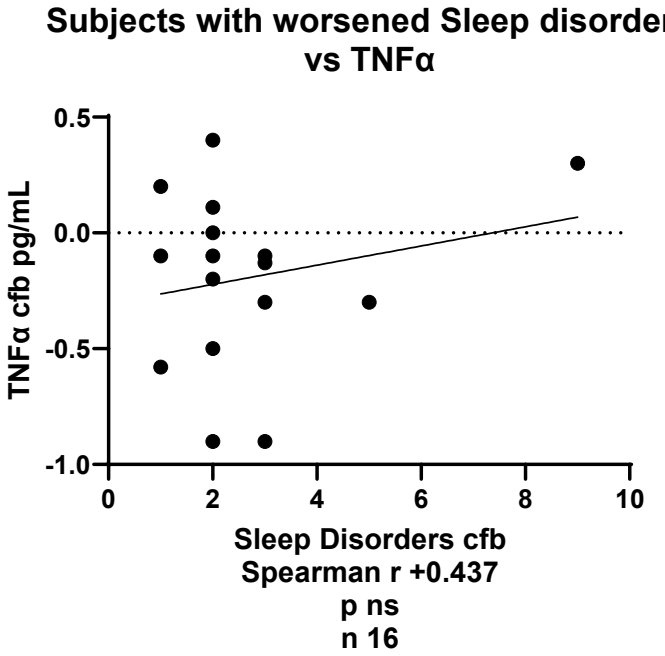
*<0.05, **<0.01, ***<0.0001

Decreased TNF-α correlated with improved sleep

Blinded data







Conclusions

- The study overall had a very low rate of AEs reported and only 10 subjects discontinued due to a reported AE (2.3%, blinded)
- There were observed blinded changes between baseline and week 30 for Aβ42/40, and APS
- There were observed correlations in the blinded analysis for the cognitive scales with metabolic and inflammatory AD biomarkers
- The blinded analysis may be consistent with the hypothesis that metabolic inflammation contributes to AD progression, and with Phase 2a findings of NE3107's potential anti-inflammatory and insulin sensitizing activity in mild/moderate AD
- We anticipate announcing topline data from this trial in the November/December timeframe
- Slides will be on www.BioViePharma.com after presentation

References

1. Reading CL, Ahlem CN, Murphy MF. NM101 phase III study of NE3107 in Alzheimer's disease: rationale, design and therapeutic modulation of neuroinflammation and insulin resistance. *Neurodegener Dis Manag*. 2021;11(4):289-298.
2. Haroon J, Mahdavi K, Jordan K, et al. Biomarker assessments from a phase 2, open-label study of NE3107 in patients with cognitive decline due to degenerative dementias. Poster presented at: Clinical Trials on Alzheimer's Disease (CTAD) Conference; November 29-December 2, 2022; San Francisco, CA.
3. Rindner E, Mahdavi K, Haroon J, et al. Clinical outcomes from a phase 2, open-label study of NE3107 in patients with cognitive decline due to degenerative dementias. Poster presented at: Clinical Trials on Alzheimer's Disease (CTAD) Conference; November 29-December 2, 2022; San Francisco, CA.
4. Palumbo J, Johnston K, Haroon J, et al. Effects of NE3107 on depression and multi-modal outcomes in a phase 2, open-label study in patients with cognitive decline due to degenerative dementias. Poster presented at: Society of Biological Psychiatry (SOBP) Annual Meeting; April 27-29, 2023; San Diego, CA.
5. Aldred J, Rodriguez R, Rivera-Rivera J, et al. A randomized, phase 2a, double-blind, placebo-controlled clinical trial with NE3107 adjunctive to carbidopa/levodopa in patients with Parkinson's disease. Poster presented at: International Congress of Parkinson's Disease and Movement Disorders (MDS); August 27-31, 2023; Copenhagen, Denmark.