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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Does NE3107 Influence Metabolic Inflammation and “Longevity” Relevant to Processes Underlying Dementia?

Are processes of aging pharmacologically mutable?

- The primary goal of our study was to investigate the associations between metabolic inflammation, biological aging, and dementia in a human clinical investigation
- The specific aim tested whether NE3107 could impact physiologic processes consistent with neurocognitive decline and diseases of aging
- Methodology included:
  - Principal component analyses
  - Divergent correlational analyses
  - Epigenetic methylation (clock: Horvath Epigenetic Clock Development Foundation)
  - Inflammation (clock: HURDLE/Chronomics analyses)
- Data from this analysis suggests that it is possible that NE3107 may “unlink” and “realign” these associations between metabolic inflammation, biological aging, and dementia

Background

- NE3107 is an investigative oral anti-inflammatory and insulin sensitizer being evaluated in both AD and PD[1]
  - NE3107 binds ERK and inhibits inflammation-specific ERK, NFκB and TNF signaling, but does not impact their homeostatic functions[1]
  - In obese animal models and subjects with impaired glucose tolerance (IGT) and in Type II Diabetes (T2D), NE3107 decreased pro-inflammatory mediators and insulin resistance[1]
  - NE3107 improved motor activity and decreased neurodegeneration in a PD Marmoset model[2] and improved MDS-UPDRS Part III scores in a Phase 2a PD study[3]
  - Additional Phase 2a data in PD will be presented at this Conference[4]
  - In an open-label 14-week Phase 2 study in MCI and mild AD, NE3107 improved neurological signs and symptoms, neuroimaging outcomes, and CSF/Peripheral biomarkers; these findings were also correlated with changes in several biomarkers and neuroimaging analyses of change[5,6]
  - NE3107 has a well tolerated safety profile to date[3,5]
- We evaluated the efficacy, safety, and tolerability of NE3107, in a larger sample and over a longer duration (30 weeks), in a phase 3, randomized, placebo-controlled trial in subjects aged 60-85 years with probable AD (NCT04669028)

Patient Disposition and Data Source for This Presentation

- The trial started during the COVID-19 pandemic and enrolled a total of 439 subjects through 39 sites
- We previously reported that upon trial completion, the Company found significant deviation from protocol and Good Clinical Practice violations at 15 sites, causing the Company to exclude all subjects from these sites
- After exclusions for GCP violations, 57 subjects remained in the Per-Protocol population; upon unblinding, those assigned to NE3107 were verified to have taken study drug from pharmacokinetics data, and 7 subjects randomized to placebo discontinued before day 150
- Baseline and completion data were available for 50 subjects (NE3107, n=24 and placebo, n=26); and DNA methylation data were available for 33 of this cohort
- This presentation will discuss findings from these subjects

Safety Findings: NE3107 Was Well Tolerated

- Modified intent-to-treat population from sites without Good Clinical Practice violations (n=76)
- NE3107 appeared to be well-tolerated, with no new safety or tolerability findings
- NE3107 group AEs at a rate >5% and > the placebo group were:
  - Blood TSH increased (7.1% vs 2.9%) Headache (9.5% vs 0%)
- Placebo group AEs at a rate >5% and > the NE3107 group were:
  - COVID-19 (17.6% vs 9.5%) Urinary tract infection (8.8% vs 7.1%)
  - Dizziness (5.9% vs 2.4%) Hypertension (5.9% vs 2.4%)
  - Gastroenteritis viral (5.9% vs 2.4%) Rash (5.9% vs 2.4%)
- There were no treatment-related severe adverse reactions

Change From Baseline in Primary and Secondary Endpoints

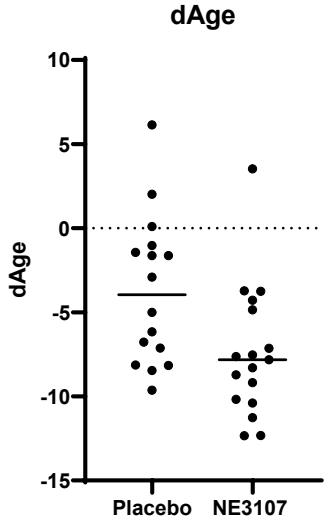
- After the exclusions, the study was no longer powered for endpoints, but week 30 data suggest NE3107 vs placebo is comparable to results reported from clinical trials by approved medications

	Placebo	NE3107	NE3107 vs placebo	Comparator[a]
Co-Primary				
CDR-SB (Lower=improvement)	+1.39 p=0.0125 (n=26)	+0.44 P=0.4522 (n=24)	−0.95 (68%)	−0.45 (27%)[7] −0.39 (22%)[8]
ADAS-Cog12 (Lower=improvement)	+3.64 p=0.0545 (n=23)	+2.70 p=0.1618 (n=24)	−0.94 (26%)	+1.44 (25%)[7] +1.40 (27%)[8]
Secondary				
MMSE (Higher=improvement)	−2.54 p=0.0007 (n=26)	−1.52 p=0.0547 (n=24)	+1.02 (40%)	+0.6 (18%)[8]
ADCS-ADL (Higher=improvement)	−6.54 p<0.0001 (n27)	−3.46 p=0.0435 (n=24)	+3.08 (47%)	+2.0 (36%)[7]
ADCS-CGIC (Lower=improvement)	+0.31 p=0.2733 (n=26)	−0.12 p=0.6951 (n=24)	−0.43 (139%)	
ADCOMS (Lower=improvement)	+0.11 p=0.0358 (n=22)	+0.09 p=0.1094 (n=24)	−0.03 (27%)	−0.05 (23%)[8]

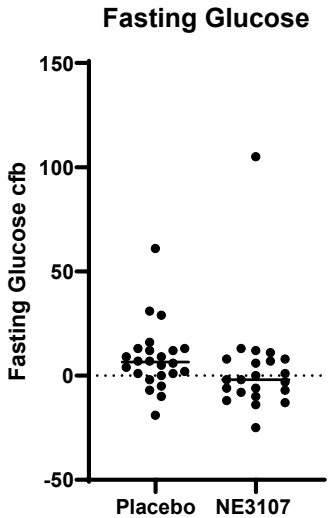
[a]Other published data at 18 months data for lecanemab[7] and aducanumab.[8]

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.

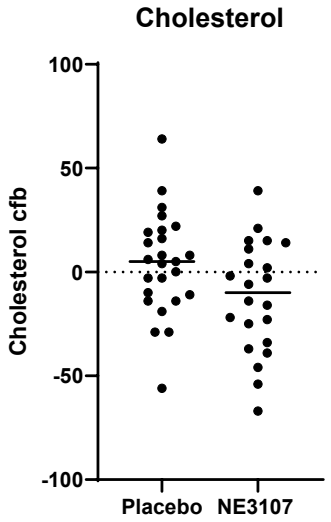
Distributions[a] for NE3107 and Placebo Show Epigenetic, Metabolic and Inflammatory Differences



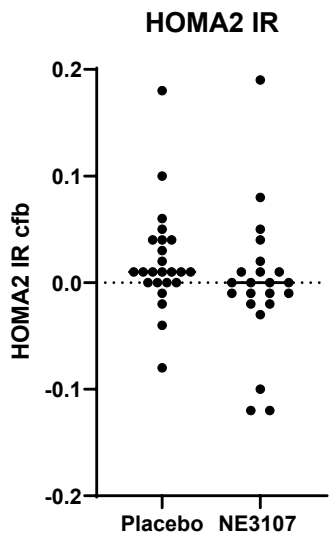
median -3.95, -7.82
n 16, 17
difference -3.87 years
p 0.012



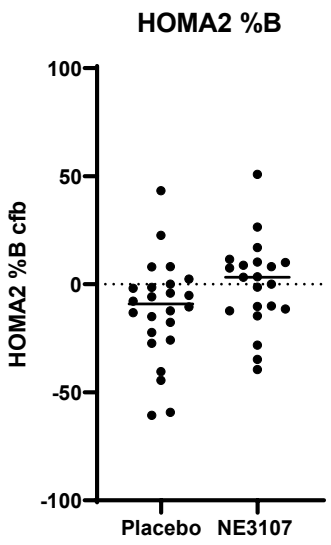
median +6.50, -2.00
n 24, 22
difference -8.50 mg/dL
p 0.036



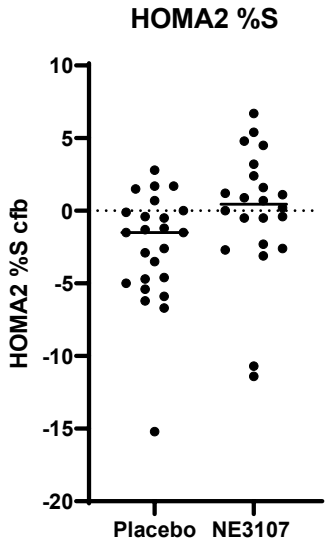
median +5.00, -10.0
n 25, 22
difference -15 mg/dL
p 0.049



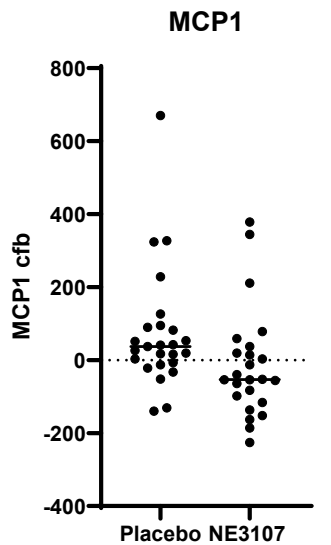
median +0.010, -0.010
n 24, 22
difference -0.020
p 0.063



median -9.150, +3.20
n 24, 21
difference +12.4
p 0.040



median -1.50, +0.450
n 24, 22
difference +1.95
p 0.018



median +37.0, -53.5
n 24, 24
difference -90.5 pg/mL
p 0.007

dAge = Horvath SkinBlood Clock
Biological age - Chronological Age

- Significant[a] improvements for NE3107 vs Placebo in dAge, glucose, cholesterol, HOMA2 beta cell function, HOMA2 Insulin Sensitivity, and MCP1
- There were no significant differences in pTau, GFAP, NfL or Aβ42/40 ratio
- Non-significant directional improvements were observed for fasting insulin and triglycerides, fructosamine, adiponectin, leptin, systolic and diastolic BP and weight

[a]For exploratory analyses, α was not conserved.

Correlations and Principal Component Analyses Appear to Differ Between NE3107 and Placebo

Active Treatment with NE3107 Appears to Decrease Inflammatory and Metabolic Processes Typically Linked to Clinical Deterioration

- Differences were observed between NE3107 and placebo for clinical correlations[a], and these were evident in Principal Component Analysis (PCA)
  - Placebo showed correlations of neurological assessments and biological age acceleration with
    - Increased metabolic syndrome measures
    - Traditional AD biomarkers (GFAP, NfL, Aβ42/40, pTau217)
  - NE3107 showed correlations of neurological assessments and biological age acceleration with
    - Improved metabolic and glycemic control
    - Improved neuropsychiatric indices
    - Chemokines associated with microglial attraction to and digestion of Aβ plaques

[a]For principal component analyses, data was normalized by Z' scores, and Bayesian imputation was applied for missing data; for clinical correlations, outliers were removed using Grubbs test ($\alpha < 0.05$).

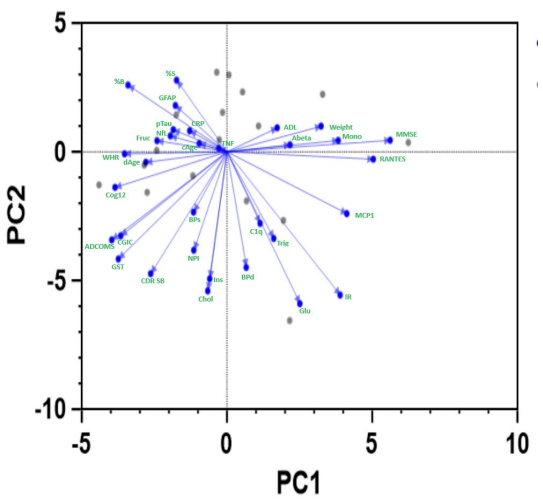
PCA, Principal Component Analysis.

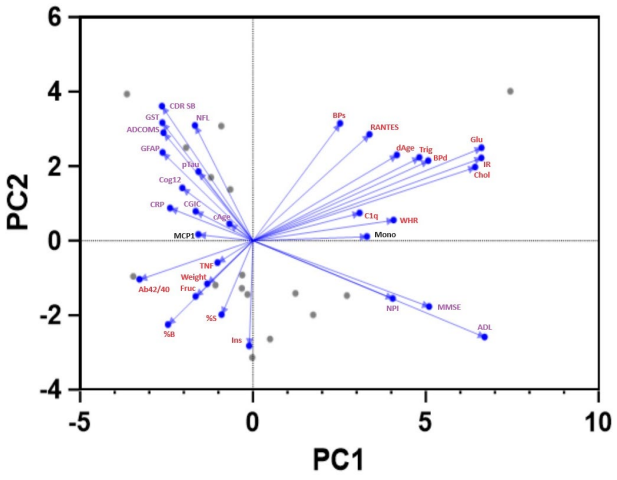
Divergent Correlations of Changes in Placebo and NE3107

	Placebo	NE3107
dAge (low better)	(+) BP, Trig, Chol	(+) CGIC, pTau217, (–) MMSE, MCP1, Mono
GST (low better)	(+) TNF, pTau217, GFAP, NfL	(–) MCP1, (+) NPI
MMSE (high better)	(–) GFAP, NfL	(+) RANTES, (–) CRP, Fructosamine, NPI
CDR SB (low better)	(+) BP, TNF, RANTES, pTau217, GFAP, NfL	(–) MCP1, HOMA2 %S, NPI
ADCOMS (low better)	(+) GFAP, NfL	(–) MCP1, HOMA2 %B, Aβ42/40
Cog12 (low better)	(+) GFAP, Aβ42/40 (–) Chol, cAge	(+) Fructosamine, (–) MCP1
CGIC (low better)	(–) C1q, Chol	(+) NPI
ADL (high better)	(+) Insulin, (–) CRP, GFAP, NfL	(–) BP, NPI, (+) cAge

- For the parameters listed, significant and trending changes were unique to either placebo or NE3107. RED placebo measures have reversed correlations with NE3107
- MCP1 and RANTES may contribute to Astroglia-derived microglia M1 to M2 transition[9-12]and migration to and digestion of Aβ plaques[13]

Principal Component Analyses (PCA)





NE3107

dAge & Assessments

%B
%S
GFAP
pTau
NfL
CRP
Fruc
cAge
WHR
TNF
dAge
Cog12
ADCOMS
CGIC
GST
CDR SB
BPs
NPI
Ins
Chol
ADL
Weight
Ab42/40
Mono
MMSE
RANTES
MCP1
C1q
Trig
BPd
Metabolic & Inflammation
Glu
IR

Placebo

dAge & Metabolic Inflammation

CDR SB
GST
NFL
ADCOMS
GFAP
pTau
Cog12
CRP
CGIC
cAge
MCP1
TNF
Weight
Fruc
Ab42/40
%S
%B
Ins
BPs
RANTES
dAge
Trig
BPd
Glu
IR
Chol
C1q
WHR
Mono

AD biomarkers & Assessments

NPI
MMSE
ADL

In the Context of Dementia, NE3107 May Show Pro-homeostatic Effects Related to Cognition and Aging

- Previously we reported that NE3107 appeared to decrease metabolic inflammation-driven systems dysregulation[5]
- Principal component analysis, divergent correlations, and epigenetic analysis suggest
  - Metabolic inflammation may be a driver of biological aging and AD
  - NE3107 might realign physiological processes associated with decreased neurocognitive decline and diseases of aging

An additional trial in mild to moderate AD could determine if the hypotheses generated from this small sample size are correct

What Has Been Learned About NE3107 and the Biology of Dementia?

- The strongest risk factor for AD is age
  - Age biology may be modifiable in ways relevant to the onset and progression of dementia
- In probable AD placebo subjects
  - Neurologic assessments are correlated with biomarkers known to be associated with chronological aging, hematologic findings, metabolic inflammation, and cognitive decline
- In probable AD NE3107 subjects
  - Neurologic assessments no longer appear to be correlated with biomarkers known to be associated with chronological aging, metabolic inflammation, and cognitive decline
  - This may suggest a change in systems biology and regulation of homeostasis with NE3107 treatment
- NE3107 appeared to be related to a change in “biologic age” minus “chronologic age” compared to placebo
  - Magnitude of change was approximately four years in seven months of treatment
    - i.e. “biological age” mean change of approximately 6 months per month of drug exposure, versus placebo

Sources:
EPIGENETICS: Horvath Epigenetic Clock Development Foundation data, NE3107 significantly improved the SkinBlood, PhenoAge, and PackYears clocks compared to placebo
INFLAMMATION CLOCK: Based on HURDLE/Chronomics analyses, NE3107 significantly improved the inflammation clock14, as well as the PhenoAge, GrimAge and Age Hannum clocks compared to placebo

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Quanterix
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Matt Polak
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BWH HARVARD MEDICAL SCHOOL AND BRIGHAM AND WOMEN'S HOSPITAL

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Abbreviations

- Aβ42/40, ratio of amyloid β 42 to amyloid β 40
- AD, Alzheimer's disease
- ADAS-Cog12CDR-SB, 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
- BP, blood pressure
- cAge, chronological age
- CDR, Clinical Dementia Rating
- Chol, cholesterol
- COVID-19, coronavirus 2019
- CRP, C-reactive protein
- CSF, cerebrospinal fluid
- dAge, difference in Biological Age – chronological age
- ERK, extracellular signal-regulated kinase
- GFAP, glial fibrillary acidic protein
- GST, Glutathione S-transferases
- HOMA2, Homeostatic Model Assessment 2
- IGT, impaired glucose tolerance
- IR, insulin resistance
- MCP1, monocyte chemoattractant protein-1
- MMSE, mini-mental state exam
- Mono, monocytes
- NFkB, nuclear factor kappa B
- NfL, neurofilament light chain
- MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale
- NPI, Neuropsychiatric Inventory
- PCA, Principal Component Analysis
- PD, Parkinson's disease
- pTau217, phosphorylated tau
- RANTES, Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted; also known as Chemokine (C-C motif) ligand 5 (also CCL5)
- TNF, tumor necrosis factor
- Trig, triglycerides
- TSH, thyroid-stimulating hormone