71981

Treatment-Induced Epigenetic Modifications in MCI and Probable Alzheimer's Disease

Christopher Lewis Reading, PhD[1], Juozas Gordevicius, PhD[2], Jonathan Haroon, BS[3], Kaya Jordan, BS[3], Elisabeth Rindner, BS[3], Clarence N Ahlem, MS[1], Kennedy D Mahdavi[3,4], Rama Surya, BS[3], Victoria Venkatraman[3,4], Harvey Yuan, MS[5], Sergio Becerra, BS[5,6], Bijan Pourat, MD[7], Taylor Kuhn, PhD[3,8], Joseph Palumbo, MD[1], Robert Brooke, MS[2], Sheldon E Jordan[3,5,9]

[1]BioVie Inc., Carson City, NV, USA; [2]Epigenetic Clock Development Foundation, Torrance, CA, USA; [3]The Regenesis Project, Santa Monica, CA, USA; [4]Princeton Pharmatech, Princeton, NJ, USA; [5]Synaptec Network, Inc., Santa Monica, CA, USA; [6]Department of Research and Psychiatry VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA; [7]Pourat, M.D., Beverly Hills, CA, USA; [8]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA; [9]Department of Neurology, University of California, Los Angeles, Los Angeles, CA, USA

BACKGROUND

- Alzheimer's disease (AD) exhibits global and several tissue- and gene-specific alterations in DNA methylation,[1-3] an epigenetic modification generally occurring at CpG sites,[4] as well as an increase in the epigenetic age,[5] a reliable indicator of biological age and overall health[6]
- Chronic inflammation, thought to be instrumental in AD pathogenesis and disease progression,[7] has also been shown to induce extensive and aberrant DNA hypermethylation[8]
- NE3107 is an investigative, oral, small-molecule, blood-brain barrier–permeable compound with potential anti-inflammatory and insulin-sensitizing functions thought to result from binding to ERK and selectively inhibiting ERK-, NF-κB–, and TNF-α–stimulated inflammatory signaling, without affecting homeostasis, and is being evaluated for its ability to slow or prevent progression of MCI and AD[9]
- In a recent exploratory, phase 2, open-label, 3-month clinical trial (NCT05227820) in 23 patients with MCI or mild to moderate dementia, NE3107 treatment was associated with the following clinical improvements:
  - Increased perfusion and functional connectivity in several regions of the brain (primary endpoint)[10]
  - Reduced inflammation (lower TNF-α), CSF AD biomarkers (pTau and pTau:Aβ42 ratio), and oxidative stress (increased brain glutathione)[11]
  - Better neurocognitive functioning (including improved ADAS-Cog11, QDRS, and ADCOMS)[12]
  - Significant improvements in the clinician-, patient-, and caretaker-rated Global Rating of Change (GRC)[12]
  - Reduction in depression severity and improvement of dementia symptoms[13]
- Given the potential roles of inflammation and aberrant DNA methylation (DNAm) in AD pathophysiology, we evaluated the scope of the anti-inflammatory effects of NE3107, including changes in DNA methylation and epigenetic age of the patients in the NCT05227820 trial

OBJECTIVES

- This exploratory, phase 2, open-label, 3-month study explored the potential effects of anti-inflammatory NE3107 treatment on epigenetic modifications, specifically DNA methylation, in addition to neurophysiological health, neurocognitive function, biomarker status, oxidative stress, depression symptoms, and functional improvement (GRC), as well as the overall treatment experience, in patients with dementia
- Here, we report the post-treatment changes in the DNAm-based skin and blood clock[6] profile, gene-specific changes in the DNAm profile, as well as correlations among changes in DNAm and other clinical measures from the study

METHODS

Study Design

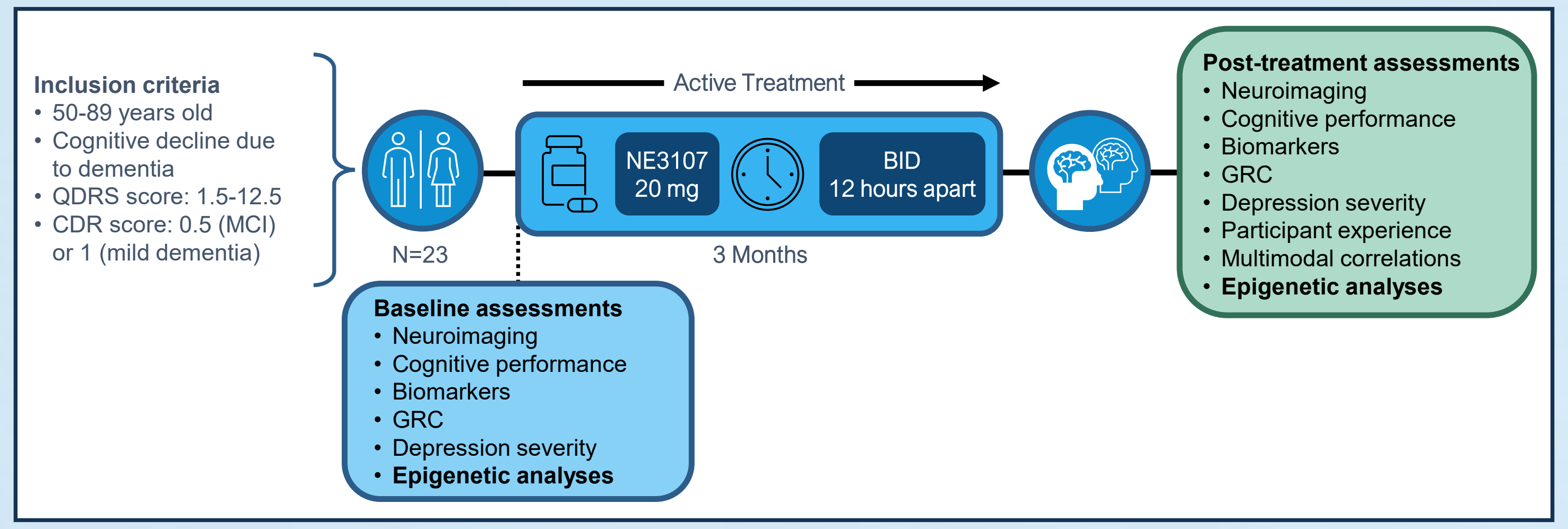
- This was a single-arm, open-label, phase 2 trial evaluating the efficacy and safety of 20-mg oral NE3107 administered twice daily (approximately 12 hours apart) to patients with clinical dementia over a duration of 3 months (**Figure 1**)

Study Population

Key inclusion criteria

- Age 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



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)

N=23

Active Treatment

NE3107 20 mg

BID 12 hours apart

3 Months

Baseline assessments
- Neuroimaging
- Cognitive performance
- Biomarkers
- GRC
- Depression severity
- **Epigenetic analyses**

Post-treatment assessments
- Neuroimaging
- Cognitive performance
- Biomarkers
- GRC
- Depression severity
- Participant experience
- Multimodal correlations
- **Epigenetic analyses**

Assessments

Primary – change from baseline to treatment completion

- 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

- Serological inflammatory marker: TNF-α
- AD CSF biomarkers: Aβ42, pTau, pTau:Aβ42 ratio, and total Tau
- Cognitive performance assessments, including ADAS-Cog11, MoCA, and MMSE
- Participants, clinicians, and caregivers reported a GRC upon study completion
- Depression symptoms: Patient Depression Questionnaire (PDQ-9)
- Dementia symptoms and treatment experience: 60-minute semi-structured participant interviews
- **Skin and blood clock analyses**
- **Gene-specific DNAm alterations**
  - Illumina 850K array DNA methylation changes following 14 weeks of NE3107 treatment were sorted and the top 400 CpGs with decreased methylation (decreases >50%) were explored for correlations with changes in clinical results following treatment
  - In addition, changes in MCI/AD clinical measures from baseline to 14 weeks were compared with changes in all individual CpG residues in the Illumina 850K array

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

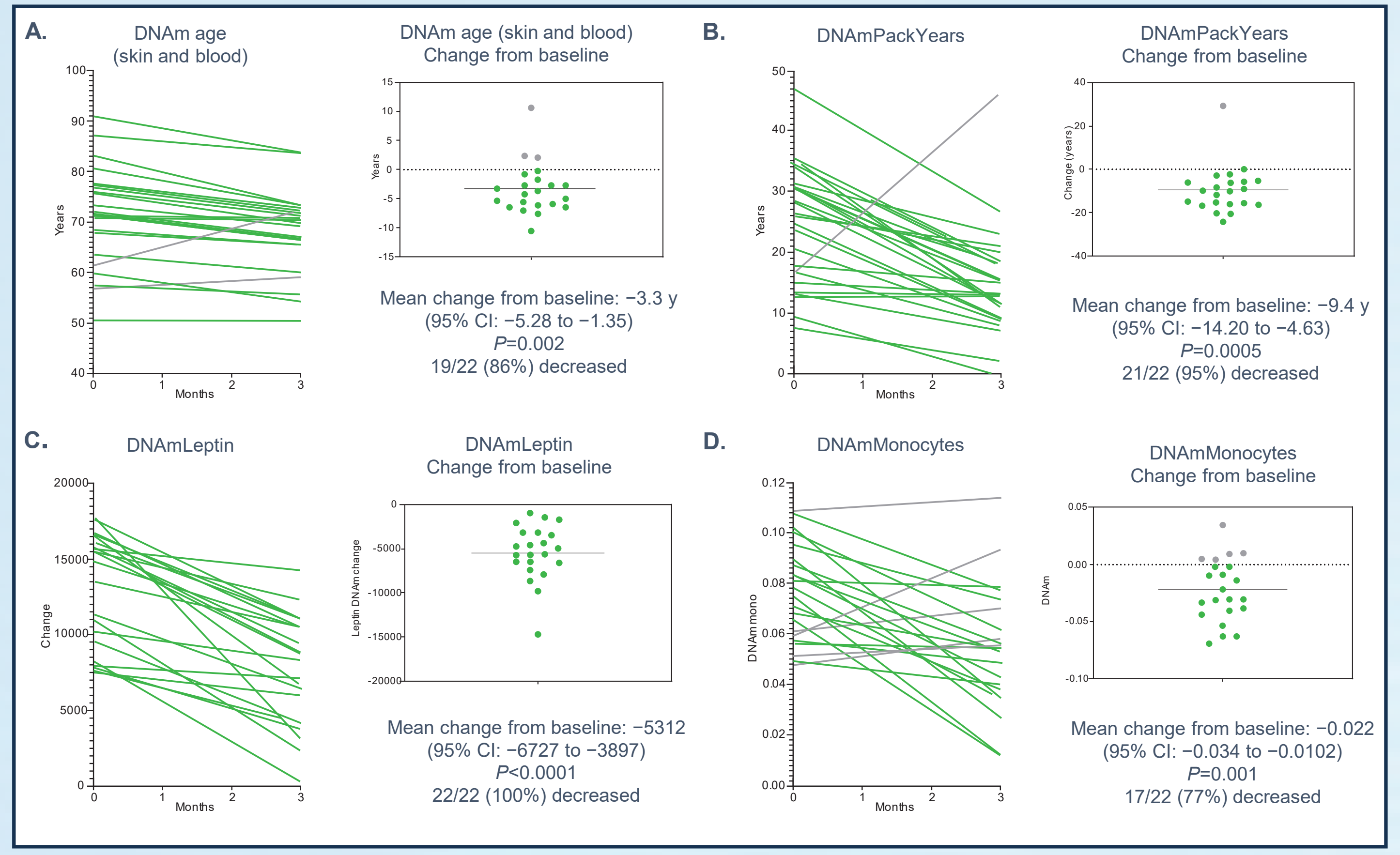
Skin and blood clock analysis

- At baseline, patients' epigenetic age (estimated using the DNAm-based skin and blood clock) closely matched their chronological age (+0.3 y; **Tables 1** and **2**)
- Several statistically significant improvements in the DNAm-based outcomes were seen after 3 months of NE3107 treatment (**Figure 2** and **Table 2**):
  - The epigenetic age decreased by 3.3 years, indicating a younger biological age compared to baseline
  - DNAmPackYears, a DNAm-based estimation of smoking pack-years,[14] was reduced by 9.4 years or 39%
  - DNAmLeptin was reduced by 40% after NE3107 treatment
  - DNAmMonocyte correlated with monocyte frequency at baseline, and while monocyte frequency did not change significantly over 3 months, DNAmMonocyte was reduced by 29%
- There were no significant changes in DNAm of T cells, NK cells, or granulocytes (**Table 2**)

Table 1. Baseline characteristics

Characteristic	All patients (N=23)
Age, mean (SD)	71.1 (9.50)
Gender, n (%) Female Male	 16 (70) 7 (30)
Family history, n (%) AD AD, dementia, unspecified etiology AD, PD Dementia, unspecified etiology PD	 5 (22) 2 (9) 1 (4) 4 (17) 1 (4)
QDRS score, mean	5.07
CDR score, n (%) 0.5 1	 18 (78) 5 (22)
MMSE, n (%) ≥20 (MCI to mild dementia) <20 (moderate dementia)	 18 (78) 5 (22)
PDQ-9, n (%) <5 (none to minimal depression) ≥5 (mild, moderate, or severe depression)	n=22 7 (32) 15 (68)
APOE status ε2/ε3 ε2/ε4 ε3/ε3 ε3/ε4 ε4/ε4	 2 (9) 1 (4) 9 (39) 10 (44) 1 (4)

Figure 2. Change from baseline in DNAm (skin and blood clock analysis)



A. Mean change from baseline: −3.3 y (95% CI: −5.28 to −1.35) *P*=0.002 19/22 (86%) decreased

B. Mean change from baseline: −9.4 y (95% CI: −14.20 to −4.63) *P*=0.0005 21/22 (95%) decreased

C. Mean change from baseline: −5312 (95% CI: −6727 to −3897) *P*<0.0001 22/22 (100%) decreased

D. Mean change from baseline: −0.022 (95% CI: −0.034 to −0.0102) *P*=0.001 17/22 (77%) decreased

Table 2. Skin and blood clock analysis

Parameter	Baseline, mean (SD)	3 months, mean (SD)	Change, mean (%)	*P*[a]	Patients experiencing improvement, n (%) (N=22)
Epigenetic age[a], y	70.8 (10.6)	67.5 (8.5)	−3.3 (−4.7%) 95% CI: −5.3 to −1.4	0.002	19 (86)
DNAmPackYears	24.1 (9.7)	14.6 (9.5)	−9.4 (−39%) 95% CI: −14.2 to −4.6	0.005	21 (95)
DNAmLeptin (CpGs)	13141 (3634)	7829 (3595)	−5312 (−40%) 95% CI: −6727 to −3897	<0.0001	22 (100)
Blood Cell Frequency (Freq)					
DNAmMonocytes (Freq)	0.076 (0.019)	0.054 (0.024)	−0.022 (−29%) 95% CI: −0.034 to −0.0102	0.001	17 (77)
Monocytes (Freq)	0.046 (0.124)	0.044 (0.104)	−0.002 (−4.9%)	ns	–
Correlation[b], mean (*P*)	0.156 (0.076)	0.00047 (0.928)			
DNAmCD8Tcell	0.014 (0.019)	0.013 (0.021)	−0.002 (−12%)	ns	–
DNAmCD4Tcell	0.185 (0.105)	0.152 (0.069)	−0.033 (−18%)	ns	–
DNAmNKcell	0.0629 (0.039)	0.0632 (0.054)	0.0003 (0.5%)	ns	–
DNAmGranulocyte	0.667 (0.131)	0.653 (0.103)	−0.015 (−2.2%)	ns	–

[a]t-test; [b]R² (t distribution).

Gene-specific DNAm analysis

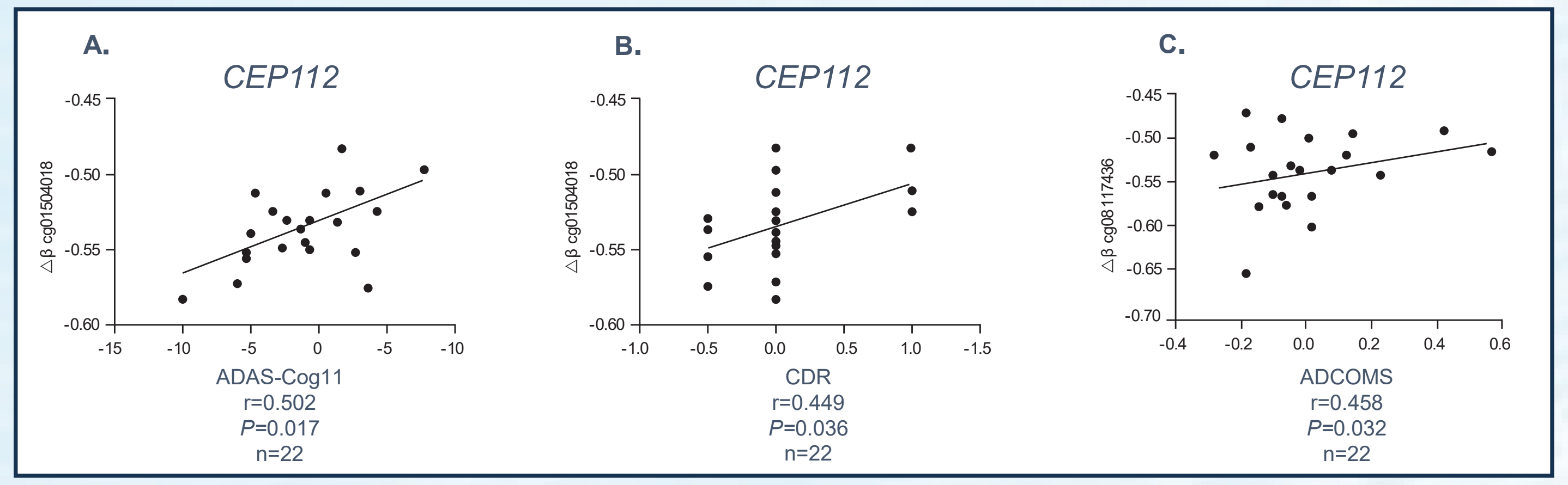
- The top 400 CpGs with decreased methylation (decreases >50%) were explored for correlations with changes in clinical results following treatment
  - 366/400 CpGs were associated with identified genes
  - Changes for CpGs that showed Spearman correlations ($P<0.05$) with individual clinical changes (biomarker, cognition, function, and imaging) were highly intercorrelated and were predominantly related to genes for which decreased expression has been implicated in AD
- A total of 167 of these genes showed significant Spearman correlations with changes in at least 1 clinical measure from the study
  - 42 of these correlated with ≥2 clinical measures, with correlations in the direction of improvement for the clinical measures (**Table 3**)
  - One such gene, *CEP112*, which encodes centrosomal protein 112, important for cell division and cell cycle progression,[15] and is downregulated in AD,[16] showed significant reduction in DNAm which was correlated with several measures of cognition, specifically ADAS-Cog11, CDR, and ADCOMS (**Figure 4**)
- CpG residues with a significant median decrease in the change from baseline were individually correlated with each clinical measure evaluated as part of the clinical trial
  - The frequency of significant Spearman correlations for changes in all 850K CpGs within representative genes involved in insulin signaling; anti-oxidant, anti-inflammatory, anti-apoptotic, and anti-amyloid responses; and neurostimulation was calculated for each clinical measure (**Table 4**)

Table 3. Gene-specific DNAm analysis

Gene	Probe	Median DNAm change	Significant Spearman correlations with clinical measures[a]
CEP85L	cg14346555	−0.590	↓ADAS-Cog11, ↑grey matter
SPDYE4	cg21610999	−0.5568	↓ADAS-Cog11, ↑precuneus glutathione
VRK2	cg13118287	−0.568	↓ADAS-Cog11, ↑GRC
CEP112	cg01504018	−0.531	↓ADAS-Cog11, ↓CDR, ↓ADCOMS, ↑GRC
ILKAP	cg20598555	−0.539	↓ADCOMS, ↓QDRS
DBNDD2	cg01373262	−0.561	↓CDR, ↓ADCOMS
CAB39L	cg00467160	−0.544	↓ADCOMS, ↓QDRS, ↑GRC, ↓CSF Tau
SLC37A1	cg11453546	−0.546	↓ADCOMS, ↑CSF glucose
SLC26A1	cg23958868	−0.573	↓ADCOMS, ↓QDRS
NPHP4	cg15324288	−0.528	↓ADCOMS, ↓QDRS
IQGAP1	cg23480821	−0.515	↓ADCOMS, ↓CSF Aβ42
OR10G7	cg18910882	−0.525	↑GRC, ↓QDRS-behavior
WDR59	cg00519320	−0.514	↓PDQ-9, ↑frontal lobe
CXCR7	cg15650509	−0.549	↓CSF pTau, ↓CSF pTau/Aβ42, ↓CSF Tau
KIR2DL3	cg01171428	−0.550	↑precuneus glutathione, ↓CSF Aβ42, ↓systolic BP
PAIP2B	cg16116663	−0.538	↓CSF Aβ42, ↓CSF Tau
SRSF4	cg01993027	−0.564	↓CSF pTau/Aβ42, ↑grey matter, ↑frontal lobe, ↑CSF Aβ42
SELT	cg00832928	−0.593	↑frontal lobe, ↑grey matter
PELP1	cg13593809	−0.578	↑frontal lobe, ↑grey matter, ↓weight
MCM10	cg01490296	−0.572	↑grey matter, ↓systolic BP
EMC2	cg13442241	−0.552	↑grey matter, ↓systolic BP
DHFR	cg04272309	−0.543	↑precuneus glutathione, ↑frontal lobe, ↑grey matter
LRRC69	cg09339848	−0.534	↓CSF pTau/Aβ42, ↑precuneus glutathione, ↑frontal lobe, ↑grey matter
FAM184A	cg24402990	−0.516	↑precuneus glutathione, ↑grey matter
RBPJL	cg27133230	−0.559	↑precuneus glutathione, ↑frontal lobe
INO80	cg00470768	−0.548	↑precuneus glutathione, ↓systolic BP
SLC41A2	cg24073653	−0.533	↑precuneus glutathione, ↓systolic BP

[a]Arrows indicate the direction of change with decreased DNAm.

Figure 4. Correlations between changes in *CEP112* DNAm and cognitive outcomes



A. ADAS-Cog11 r=0.502 *P*=0.017 n=22

B. CDR r=0.449 *P*=0.036 n=22

C. ADCOMS r=0.458 *P*=0.032 n=22

Post-treatment improvements in correlations

- The number of significant positive correlations between CDR and the genes with >50% DNAm reduction increased from 11 at baseline to 38 after NE3107 treatment (Fisher exact test $P<0.0001$)
- Similar increases in the number of significant positive correlations were seen with other clinical measures, including QDRS, PDQ-9, and GRC, suggesting a re-establishment of homeostasis

Table 4. Frequency of significant Spearman correlations between changes in DNAm (individual CpG residues) and clinical measures after 14 weeks of NE3107 treatment

Clinical measure	Insulin signaling[a]	Anti-oxidant[b]	Anti-inflammatory[c]	Anti-apoptotic[d]	Anti-amyloid[e]	Neuro-stimulatory[f]
MRI neuroimaging						
Hippocampus	16	24	9	4	3	1
Grey matter[g]	91	78	24	24	22	26
Frontal lobe	238	152	44	49	36	69
Temporal lobe	181	112	26	28	13	49
Parietal lobe	91	154	40	47	14	74
Occipital lobe	42	28	9	2	2	5
Glutathione	67	43	27	14	8	20
Cognitive assessments						
CDR	15	23	13	5	5	10
MMSE	31	29	18	7	3	5
ADAS-Cog11	26	16	12	4	9	8
ADCOMS	13	17	4	3	5	8
MoCA	23	8	8	2	2	6
QDRS	10	19	6	3	1	8
PDQ-9	71	49	22	6	17	18
Biomarkers						
pTau	22	26	6	6	3	12
pTau/Aβ42	46	43	19	6	5	15
Aβ42	11	24	9	7	1	15
Tau	34	38	10	2	2	15
TNF-α	23	17	14	7	8	8

[a]*INS, INSR, IGF, IGFR, IRS, AKT,* and *PI3K*; [b]*GST, GPX, GSS, GSR, AATF, ARSB, ATM, NEDD4, ZMAT, TXN, TXNRD,* and *PRDX*; [c]*IL6, IL4, IL10, IL13, NFKBIB, SIRT,* and *LRRFIP1*; [d]*IAP* and *BIRC*; [e]*SORL1, PIGK, UBA1,* and *ZNF331*; [f]*NEUROD1, BDNF, NGF, NTRK, NTF3,* and *CEP112*; [g]Subcortical grey matter.

CONCLUSIONS

- Overall, NE3107 treatment significantly decreased the epigenetic (biological) age compared to the chronological age and was associated with significant reductions in DNAmPackYears, DNAmLeptin, and DNAmMonocytes
- NE3107 treatment was also associated with >50% reduction in DNAm of 400 CpGs, 366 of which had identifiable genes
- When correlations were examined for the entire 850K array, potentially functional correlations were observed between clinical and epigenetic changes
- Increases in precuneus glutathione levels (measured by MRS) significantly correlated with reductions in the DNAm of 43 CpGs related to anti-oxidant genes, including those encoding glutathione and thioredoxin enzymes
  - Decreased glutathione levels have been shown to be associated with cognitive decline in humans[17]
  - Thioredoxin has been shown to be associated with AD progression and cognitive changes in human tissue and human subjects[18,19]
- Reduction in plasma TNF-α levels significantly correlated with reductions in the DNAm of 14 CpGs related to anti-inflammatory genes, including *IL6*, *IL10*, and also *LRRFIP1*, whose protein product represses TNF-α expression[20]
  - Experimental therapies targeting TNF-α in humans have been associated with improved cognitive function[21]
- Volumetric changes in the hippocampus, subcortical grey matter, as well as frontal, temporal, parietal, and occipital lobes significantly correlated with reductions in the DNAm of numerous CpGs associated with genes related to insulin signaling and anti-oxidant responses
  - Volumetric changes in the brain have been associated with alterations in cognitive function in patients with MCI and dementia[22]
- NE3107 may trigger epigenetic changes that alleviate inflammation and oxidative stress, restoring homeostatic regulation and enabling the recovery of gene expression that may improve several clinical measures of MCI and AD; transcriptomic analyses in future studies may help validate this hypothesis
- Metabolic dysregulation is a cardinal feature of AD,[23] and findings from this study suggest that NE3107 may help to restore metabolic homeostasis through extensive epigenetic remodeling and increased correlations between clinical measures and genes with reduced DNAm, consistent with its pro-homeostatic effects in obese patients with diabetes[24]
- Taken together, NE3107 treatment-associated changes may be indicative of broad and multisystemic regulatory activities within mechanisms associated with the diagnosis and progression of cognitive disorders, MCI, and dementia[22,25]
- These data suggest that NE3107 may have broader anti-inflammatory functions than previously thought and support further investigation of NE3107 in AD
- An ongoing phase 3, placebo-controlled study (NCT04669028) is evaluating the safety and efficacy of NE3107 in ~400 patients with probable AD

REFERENCES

1. Yokoyama AS, Rutledge JC, Medici V. DNA methylation alterations in Alzheimer's disease. *Environ Epigenet.* 2017;3(2):dvx008. doi:10.1093/eep/dvx008
2. Milicic L, Porter T, Vacher M, Laws SM. Utility of DNA methylation as a biomarker in aging and Alzheimer's disease. *J Alzheimers Dis Rep.* 2023;7(1):475-503.
3. Zhang W, Young JI, Gomez L, et al. Distinct CSF biomarker-associated DNA methylation in Alzheimer's disease and cognitively normal subjects. *Alzheimers Res Ther.* 2023;15(78):1-19. doi:10.1186/s13195-023-01216-7
4. Xie H, Liu X, Zhou Q, et al. DNA methylation modulates aging process in adipocytes. *Aging Dis.* 2022;13(2):433-446.
5. Coninx E, Chew YC, Yang X, et al. Hippocampal and cortical tissue-specific epigenetic clocks indicate an increased epigenetic age in a mouse model for Alzheimer's disease. *Aging (Albany NY).* 2020;12(20):20817-20834.
6. Horvath S, Oshima J, Martin GM, et al. Epigenetic clock for skin and blood cells applied to Hutchinson Gilford Progeria Syndrome and ex vivo studies. *Aging (Albany NY).* 2018;10(7):1758-1775.
7. Jung YJ, Tweedie D, Scerba MT, Greig NH. Neuroinflammation as a factor of neurodegenerative disease: thalidomide analogs as treatments. *Front Cell Dev Biol.* 2019;7:313. doi:10.3389/fcell.2019.00313
8. Yamashita S, Nanjo S, Rehnberg E, et al. Distinct DNA methylation targets by aging and chronic inflammation: a pilot study using gastric mucosa infected with Helicobacter pylori. *Clin Epigenetics.* 2019;11(1):191. doi:10.1186/s13148-019-0789-8
9. 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.
10. Jordan K, Mahdavi K, Haroon J, et al. Neuroimaging data from a phase 2, open-label study of NE3107 in patients with cognitive decline due to degenerative dementias. Oral presentation at: Clinical Trials on Alzheimer's Disease (CTAD) Conference; November 29-December 2, 2022; San Francisco, CA.
11. 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.
12. 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.
13. 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 Annual Meeting; April 27-29, 2023; San Diego, CA.
14. Lu AT, Quach A, Wilson JG, et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging (Albany NY).* 2019;11(2):303-327.
15. Homann J, Osburg T, Ohlei O, et al. Genome-wide association study of Alzheimer's disease brain imaging biomarkers and neuropsychological phenotypes in the European Medical Information Framework for Alzheimer's Disease Multimodal Biomarker Discovery dataset. *Front Aging Neurosci.* 2022;14:840651. doi:10.3389/fnagi.2022.840651
16. Zhang Y, Wang J, Liu X, Liu H. Exploring the role of RALYL in Alzheimer's disease reserve by network-based approaches. *Alzheimers Res Ther.* 2020;12(1):165. doi:10.1186/s13195-020-00733-z
17. Song T, Song X, Zhu C, et al. Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: A meta-analysis of in vivo magnetic resonance spectroscopy studies. *Ageing Res Rev.* 2021;72:101503. doi:10.1016/j.arr.2021.101503
18. Goikolea J, Gerenu G, Daniilidou M, et al. Serum Thioredoxin-80 is associated with age, ApoE4, and neuropathological biomarkers in Alzheimer's disease: a potential early sign of AD. *Alzheimers Res Ther.* 2022;14(1):37. doi:10.1186/s13195-022-00979-9
19. Jia J, Zeng X, Xu G, Wang Z. The potential roles of redox enzymes in Alzheimer's disease: focus on thioredoxin. *ASN Neuro.* 2021;13:17590914211994351. doi:10.1177/17590914211994351
20. Suriano AR, Sanford AN, Kim N, et al. GCF2/LRRFIP1 represses tumor necrosis factor alpha expression. *Mol Cell Biol.* 2005;25(20):9073-9081.
21. Torres-Acosta N, O'Keefe JH, O'Keefe EL, Isaacson R, Small G. Therapeutic potential of TNF-α inhibition for Alzheimer's disease prevention. *J Alzheimers Dis.* 2020;78(2):619-626.
22. Talwar P, Kushwaha S, Chaturvedi M, Mahajan V. Systematic review of different neuroimaging correlates in mild cognitive impairment and Alzheimer's disease. *Clin Neuroradiol.* 2021;31(4):953-967.
23. Yan X, Hu Y, Wang B, Wang S, Zhang X. Metabolic dysregulation contributes to the progression of Alzheimer's disease. *Front Neurosci.* 2020;14:530219. doi:10.3389/fnins.2020.530219
24. Reading CL, Flores-Riveros J, Stickney DR, Frincke JM. An anti-inflammatory sterol decreases obesity-related inflammation-induced insulin resistance and metabolic dysregulation. *Mediators Inflamm.* 2013;2013:814989. doi:10.1155/2013/814989
25. Jia T, Chu C, Liu Y, et al. Epigenome-wide meta-analysis of blood DNA methylation and its association with subcortical volumes: findings from the ENIGMA Epigenetics Working Group. *Mol Psychiatry.* 2021;26(8):3884-3895.

ACKNOWLEDGEMENTS

p-value communications provided editorial support. Funded by BioVie Inc.

DISCLOSURES

CR, CA, and **JP** are employees of BioVie Inc.
JH, KJ, ER, KM, RS, VV, SB, TK, and **SJ** have received grant support from BioVie Inc.
JG, HY, RB, and **BP** have nothing to disclose.

AATF, apoptosis antagonizing transcription factor; Aβ, amyloid beta; AD, Alzheimer's disease; ADAS-Cog11, the 11-component Alzheimer's Disease Assessment Scale -Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; *AKT*, AKT serine/threonine kinase; APOE, apolipoprotein E; *ARSB*, arylsulfatase B; *ATM*, Ataxia-Telangiesctasia mutated; *BDNF*, brain-derived neurotrophic factor; BID, twice daily; *BIRC*, baculoviral IAP repeat-containing; BP, blood pressure; CDR, Clinical Dementia Rating; CI, confidence interval; CpG, cytosine-phosphate-guanine; CSF, cerebrospinal fluid; ERK, extracellular signal-regulated kinase; *GPX*, glutathione peroxidase; *GSR*, glutathione-disulfide reductase; *GSS*, glutathione synthetase; *GST*, glutathione S-transferase; *IAP*, inhibitors of apoptosis; *IGF*, insulin-like growth factor; *IGFR*, insulin-like growth factor receptor; *IL*, interleukin; *INS*, insulin; *IR*, insulin receptor; *IRS*, insulin receptor substrate; *LRRFIP1*, leucine-rich repeat flightless-interacting protein 1; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NBM, nucleus basalis of Meynert; *NEDD4*, neural precursor cell expressed, developmentally down-regulated protein 4, E3 ubiquitin protein ligase; *NEUROD1*, neuronal differentiation 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; *NFKBIB*, NF-κB inhibitor beta; *NGF*, nerve growth factor; NK, natural killer; ns, not significant; *NTF3*, neurotrophin 3; *NTRK*, neurotrophic tyrosine receptor kinase; PD, Parkinson's disease; PHQ, Patient Health Questionnaire; *PI3K*, phosphoinositide 3-kinase; *PIGK*, phosphatidylinositol glycan anchor biosynthesis class K; *PRDX*, peroxiredoxin; pTau, phosphorylated tau protein; QDRS, Quick Dementia Rating System; SD, standard deviation; *SIRT*, sirtuin; *SORL1*, sortilin related receptor 1; TNF-α, tumor necrosis factor alpha; *TXN*, thioredoxin; *TXNRD*, thioredoxin reductase; *UBA1*, ubiquitin-like modifier activating enzyme 1; *ZMAT*, zinc finger matrin-type 3; *ZNF331*, zinc finger protein 331.

Presented at the 2023 Alzheimer's Association International Conference | July 16-20, 2023 | Amsterdam, Netherlands