M183

Metabolic Dysregulation in Probable Alzheimer's Disease

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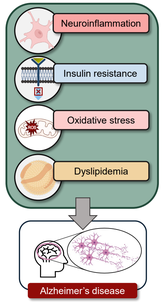
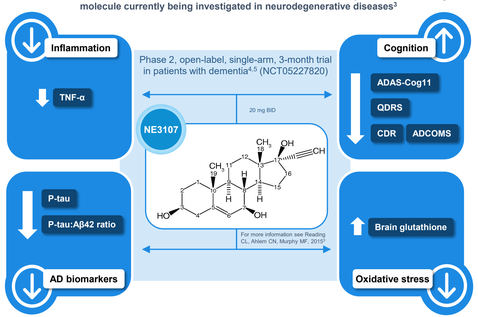
BACKGROUND

Alzheimer's disease (AD) is a multifactorial and progressive neurodegenerative disorder[1,2]



For more information see Iqbal K, Grundke-Iqbal I, 2010[1]; and Verdile G, Keane KN, Cruzat VF, et al., 2015[2]

NE3107 is a small, oral, blood-brain barrier-permeable, anti-inflammatory, insulin-sensitizing molecule currently being investigated in neurodegenerative diseases[3]



STUDY ENDPOINTS

Efficacy assessments:

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

- Cognitive impairment: 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: HOMA2-IR, MAGE, fasting blood glucose

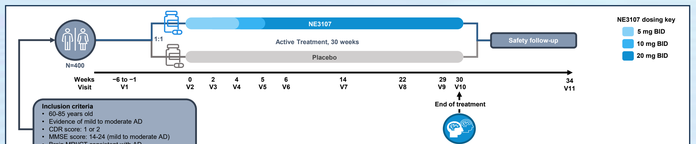
Exploratory endpoints – change from baseline to treatment completion (week 30)

- Inflammatory and neurodegeneration biomarkers – including CRP, IL-6, TNFα, and P-tau
- Neuroimaging: vMRI and FDG-PET
- Epigenetic aging clock: DNA methylation status
- Exit interviews

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

STUDY DESIGN

- This is a phase 3, double-blind, placebo-controlled, parallel group, multicenter, 40-week clinical trial (NCT04669028) to evaluate the safety, tolerability, and efficacy of oral NE3107 administered twice daily (BID; approximately 12 hours apart) in patients with mild to moderate probable AD, compared with matching placebo[3]
  - The dose of oral NE3107 was 5 mg BID during the first 2 weeks (V2-V3), 10 mg BID during weeks 3 and 4 (V3-V4), and then 20 mg BID for the rest of the treatment period (V4-V10)



Aβ, amyloid beta; ADAS-Cog11, 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale; 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; BID, twice per day; BP, blood pressure; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating—Sum of Boxes; CRP, C-reactive protein; C-SSRS, Columbia-Suicide Severity Rating Scale; CT, computed tomography; ECG, electrocardiogram; FDG-PET, fluorodeoxyglucose–positron emission tomography; FPG, fasting plasma glucose; HOMA2-IR, The Homeostasis Model Assessment of insulin resistance; IFG, impaired fasting glucose; IL-6, interleukin 6; MAGE, Mean Amplitude of Glycemic Excursions; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NPI, Neuropsychiatric Inventory; P-tau, phosphorylated tau protein; QDRS, Quick Dementia Rating System; RANTES, regulated upon activation, normal T cell expressed and secreted; ROS, reactive oxygen species; T2D, type 2 diabetes; TEAE, treatment-emergent adverse event; TNF-α, tumor necrosis factor alpha; vMRI, volumetric magnetic resonance imaging; WHR, waist-to-hip ratio.

RESULTS

Baseline characteristics (see **Table 1**)

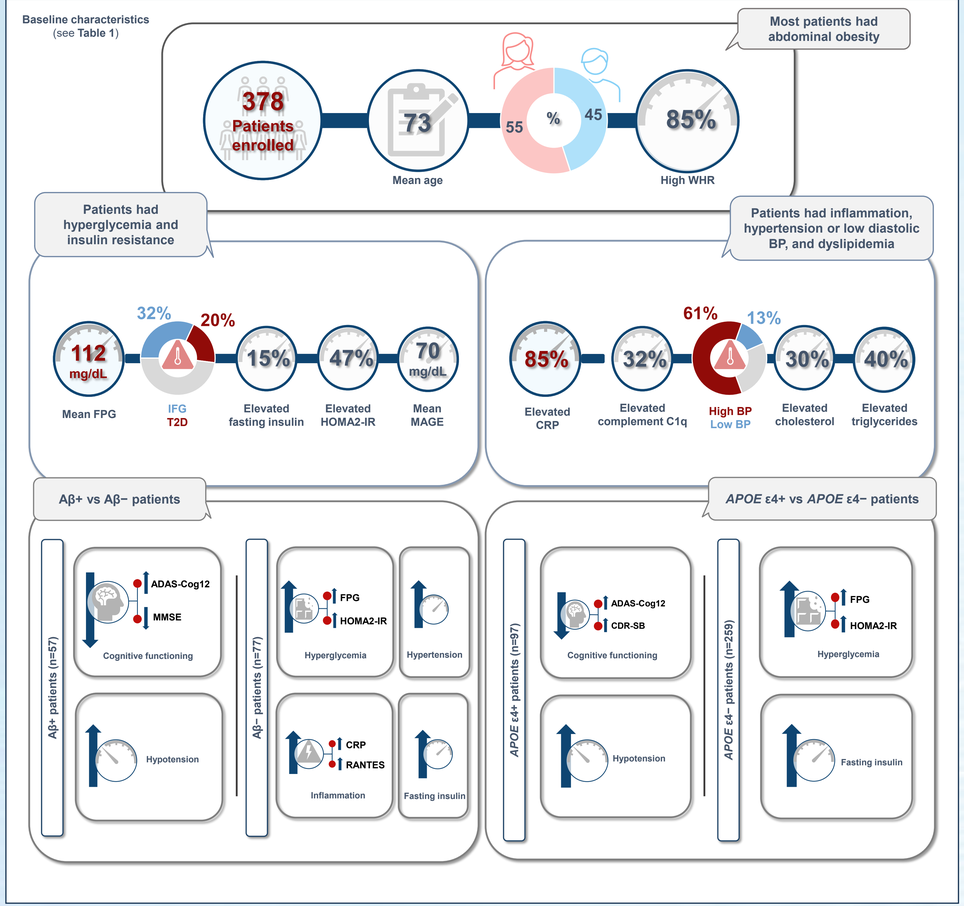


Table 1. Baseline characteristics

Characteristic	All N=378	Aβ+[a] n=57	Aβ−[b] n=77	*P*	*APOE* ε4+ n=97	*APOE* ε4− n=259	*P*
Age, mean (SE) y	73 (0.3)	76 (0.8)	72 (0.6)	**	73 (0.6)	73 (0.4)	-
Female, %	55	53	67	-	64	64	-
High WHR[c], %	85	84	84	-	81	82	-
FPG, mean, mg/dL IFG, % T2D, %	112 32 20	100 18 14	112 35 22	* # -	106 25 17	115 36 25	* - -
Fasting insulin, mean (SE), µIU/mL High (>23), %	16 (1.1) 15	10 (1.0) 9	15 (2.4) 15	* -	12 (1.1) 10	17 (1.6) 17	* -
HOMA2-IR, mean (SE) 1.4-2.5, % >2.5, %	1.8 (0.1) 27 20	1.3 (0.2) 13 15	1.9 (0.2) 29 21	* ## -	1.5 (0.1) 24 15	1.9 (0.1) 27 22	* - -
MAGE, mean (SE), mg/dL	70 (2.5)	62 (3.4)	68 (4.6)	-	68 (4.2)	71 (3.1)	-
CRP, mean (SE), mg/L >3, % >10, %	4.1 (0.4) 67 18	1.8 (0.2) 13 0	6.3 (1.2) 28 18	** # ##	3.6 (0.8) 20 4	4.3 (0.4) 32 21	 -
C1q, mean (SE), mg/dL High (>22), %	22 (0.2) 32	21 (0.4) 28	44 (0.5) 33	- -	21 (0.3) 34	22 (0.2) 31	- -
RANTES, mean (SE), pg/mL	28 (1.6)	23 (2.0)	33 (2.8)	**	26 (2.8)	29 (2.0)	-
Cholesterol, mean (SE), mg/dL High (>199), %	189 (4) 30	174 (5) 22	175 (5) 26	- -	183 (4) 30	180 (3) 30	- -
Triglycerides, mean (SE), mg/dL High (>149), %	143 (4) 40	130 (9) 27	143 (8) 36	- -	132 (5) 36	148 (5) 41	- -
High BP (>130/80), % Low BP (<66 diastolic), %	61 13	47 12	71 2.5	## ##	54 15	63 4.1	- ##
CDR-SB, mean (SE)	6.3 (0.1)	6.6 (0.3)	6.2 (0.2)	-	6.6 (0.2)	6.1 (0.1)	**
MMSE, mean (SE)	20 (0.1)	20 (0.1)	21 (0.2)	**	20 (0.2)	20 (0.1)	-
ADAS-Cog12, mean (SE)	28 (0.4)	31 (1.4)	25 (0.7)	**	30 (0.9)	27 (0.5)	**
ADCS-ADL, mean (SE)	55 (0.6)	57 (1.4)	57 (1.2)	-	56 (1.0)	55 (0.5)	-
Aβ42/40 ratio, mean (SE)	0.095 (0.001)	0.085 (0.001)	0.107 (0.001)	**	0.089 (0.002)	0.098 (0.001)	**

[a]Positive Precivity test; [b]Negative Precivity test; [c]For females WHR>0.8 and for males WHR>0.95; Mann-Whitney *P <0.05, **P<0.01; Fisher's Exact Test ##<0.05, ## <0.01.

CONCLUSIONS

- To our knowledge, NE3107 is the only oral, anti-inflammatory agent currently in phase 3 development for AD[6], and this is the largest study to date to evaluate its safety and efficacy in patients with AD
- Patients enrolled in this study had baseline characteristics consistent with metabolic syndrome
  - Most patients had a high WHR (85%), indicating abdominal obesity, hypertension (61%), and impaired glucose metabolism (IFG/T2D; 52%)
  - Nearly half of all patients (47%) had some degree of insulin resistance
  - Forty percent and 30% of patients had hypertriglyceridemia and hypercholesterolemia, respectively, indicating dyslipidemia
  - Almost all patients had elevated CRP (85%), indicating an elevated inflammatory status
- Both Aβ+ and Aβ− patients with AD were enrolled in this study and had comparable CDR-SB scores indicative of mild dementia, but while Aβ+ patients had worse ADAS-Cog12 and MMSE scores, indicating lower cognitive functioning, Aβ− patients were younger and had significantly higher inflammation, insulin resistance, IFG, and hypertension, compared with their Aβ+ counterparts
- Patients who were *APOE* ε4− demonstrated higher degrees of impaired glucose metabolism and insulin resistance compared with their *APOE* ε4+ counterparts; *APOE* ε4− and *APOE* ε4+ patients had comparable baseline MMSE scores, indicating that both groups exhibited mild to moderate cognitive impairment
- Our in-depth analysis of the patients enrolled in this phase 3 trial suggests that even in the absence of classical risk markers, such as Aβ+ and *APOE* ε4+, central obesity and age-related systems dysregulation, involving inflammation (elevated CRP, RANTES, and C1q), hyperglycemia, insulin resistance, dyslipidemia, and hypertension, may contribute to the development and progression of AD and related dementias
- Consistent with the proposed anti-inflammatory and insulin-sensitizing properties of NE3107, this phase 3 study was designed to confirm the efficacy and safety of NE3107 treatment in patients with probable AD

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DISCLOSURES

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