Metabolic Dysregulation in Probable Alzheimer's Disease

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Background

- Alzheimer's disease (AD) is a multifactorial disease[1], and several risk factors, such as obesity, chronic inflammation, insulin resistance (IR), oxidative stress, and dyslipidemia, may contribute to neurodegeneration, AD progression, and subsequent cognitive decline[2]
  - Obesity is associated with chronic low-grade inflammation[1] involving pro-inflammatory cytokines such as TNF-α,[3] a key modulator of inflammatory responses[4] that has been implicated in the development of IR[2] and oxidative stress[2,5]
  - Anti–TNF-α therapies have been shown to reduce the risk of developing AD in patients with autoimmune disease[4]
- Given the integral role TNF-α plays in the pathophysiology of neurodegenerative disorders,[6] bezisterim (NE3107), an investigative oral, anti-inflammatory and insulin-sensitizing agent, is being evaluated for its ability to slow or prevent progression of MCI and AD[7]
  - Bezisterim's binds to the inflammatory mediator ERK and selectively inhibits inflammation-specific ERK, NF-κB, and TNF-α signaling, without affecting their homeostatic functions[7]
  - Bezisterim lowered pro-inflammatory mediators in rodent models of inflammation[8] and improved insulin sensitivity in diabetic rats[9]
  - In obese patients with T2D and inflammation, bezisterim improved insulin sensitivity and normalized HbA1C[7]
- In a recent phase 2, open-label, single-arm, 3-month trial (NCT05227820), bezisterim treatment was associated with neurophysiological, neurocognitive, and neuropsychiatric improvements, significant reductions in CSF P-tau and P-tau:Aβ42 ratio, and trending improvements in the levels of plasma TNF-α and brain glutathione, a marker of oxidative stress,[10] in patients with MCI or mild dementia (MMSE ≥20; n=18), and demonstrated a favorable safety profile
  - Significant correlations between changes from baseline in cognitive performance and brain glutathione levels, CSF P-tau, or CSF P-tau:Aβ42 ratio were observed in patients with mild to moderate dementia (N=23)
  - Improvement in ADAS-Cog11 scores significantly correlated with reduction in TNF-α in patients with MMSE ≥20
- We are evaluating the efficacy, safety, and tolerability of bezisterim in a larger sample and over a longer duration, in a phase 3, randomized, placebo-controlled trial in approximately 400 patients aged 60-85 years with probable AD (NCT04669028)[7]

Aβ, amyloid beta; ADAS-Cog11, 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale; CSF, cerebrospinal fluid; ERK, extracellular signal-regulated kinase; HbA1C, hemoglobin A1C; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NF-κB, nuclear factor kappa B; P-tau, phosphorylated tau protein; T2D, type 2 diabetes; TNF-α, tumor necrosis factor alpha.

Study endpoints

Efficacy assessments:

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

- Cognitive impairment: CDR-SB

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

- Neurocognitive functioning: ADAS-Cog12, MMSE, ADCOMS, and CDR
- Global assessment of clinical change: ADCS-CGIC
- 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)

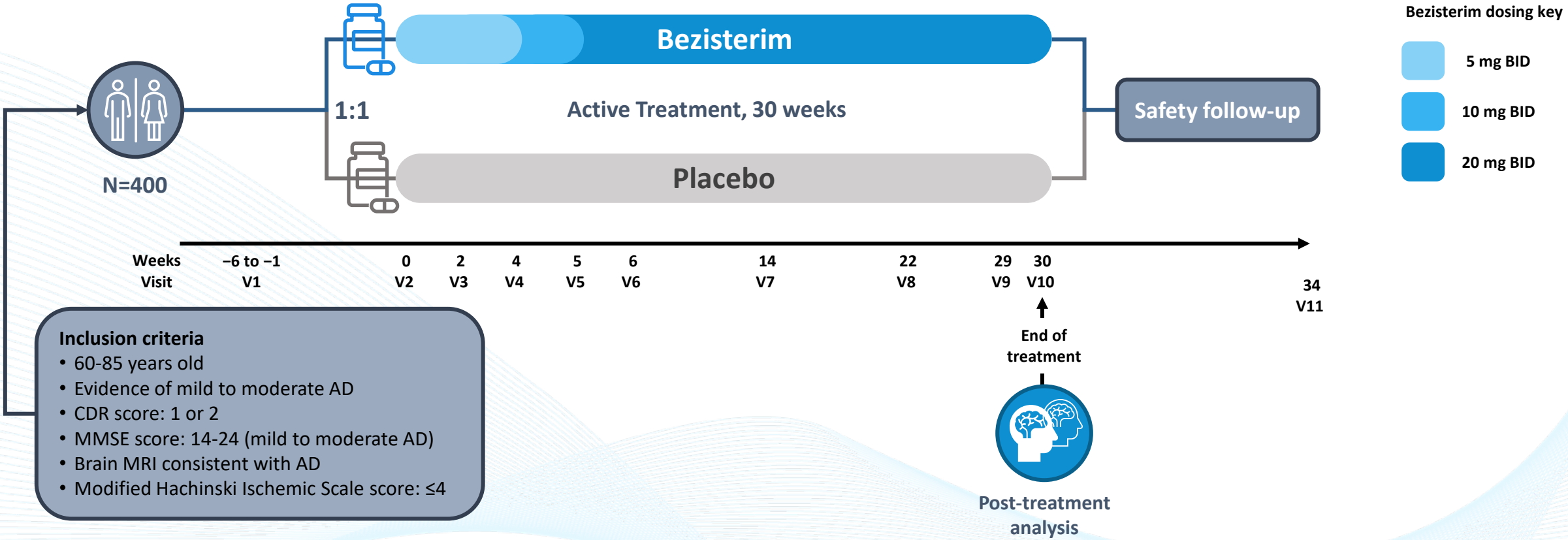
- Inflammatory and neurodegeneration biomarkers – including CRP, IL-6, TNFα, and P-tau
- Neuroimaging: vMRI and FDG-PET
- Epigenetic aging clock: DNA methylation status
- Exit interviews

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

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; CDR-SB, Clinical Dementia Rating—Sum of Boxes; 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.

Study design

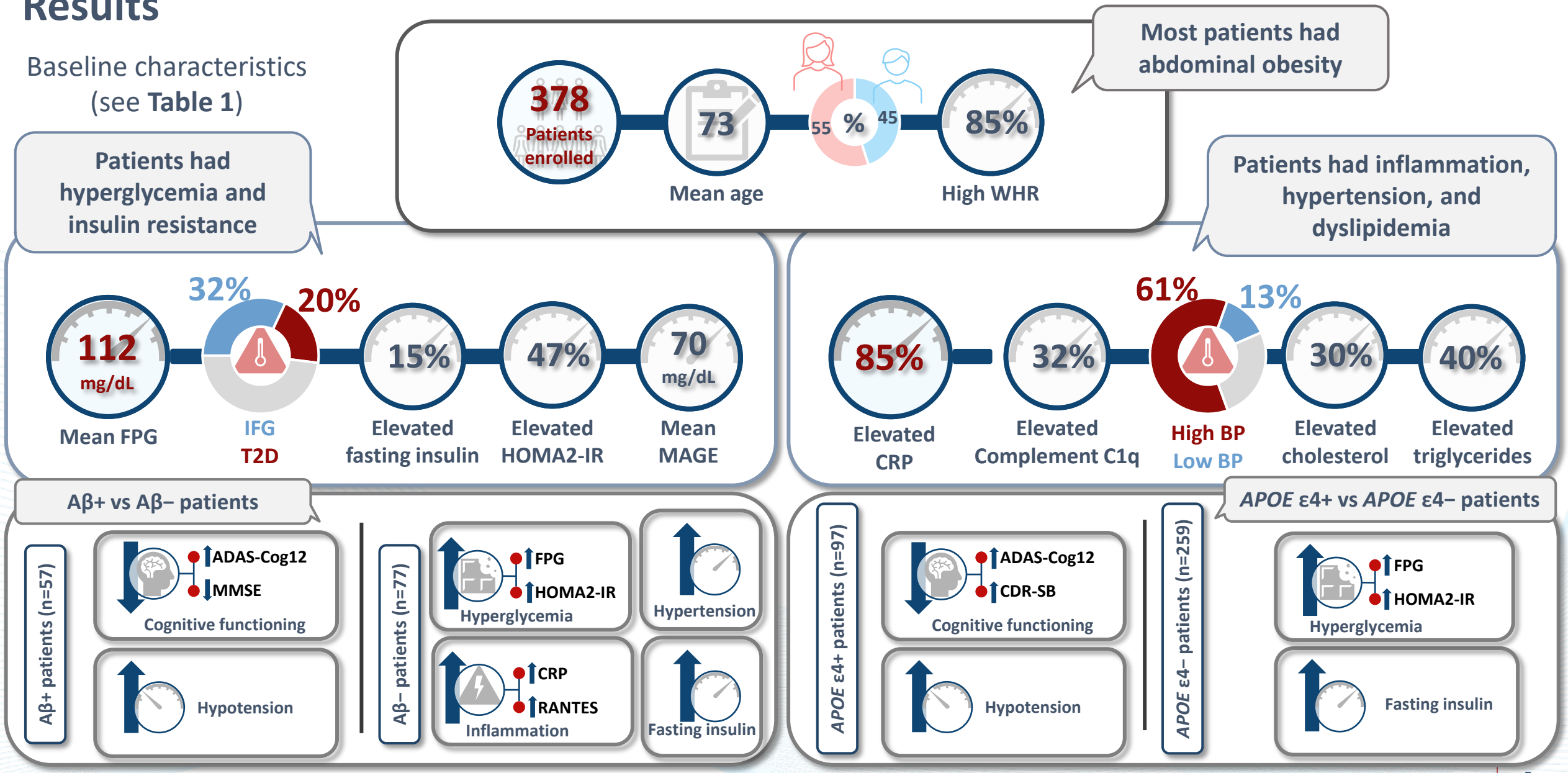
- This is a phase 3, double-blind, placebo-controlled, parallel group, multicenter 40-week study of bezisterim to evaluate the safety, tolerability, and efficacy of oral bezisterim administered twice daily (BID; approximately 12 hours apart) in patients with mild to moderate probable AD, compared with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



BID, twice per day; MRI, magnetic resonance imaging.

Results

Baseline characteristics (see **Table 1**)



BP, blood pressure; FPG, fasting plasma glucose; IFG, impaired fasting glucose; RANTES, regulated upon activation, normal T cell expressed and secreted; WHR, waist-to-hip ratio.

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	112	100	112	*	106	115	*
IFG, %	32	18	35	#	25	36	
T2D, %	20	14	22	-	17	25	-
Fasting insulin, mean (SE), µlU/mL	16 (1.1)	10 (1.0)	15 (2.4)	*	12 (1.1)	17 (1.6)	*
High (>23), %	15	9	15	-	10	17	-
HOMA2-IR, mean (SE)	1.8 (0.1)	1.3 (0.2)	1.9 (0.2)	*	1.5 (0.1)	1.9 (0.1)	*
1.4-2.5, %	27	13	29	##	24	27	-
>2.5, %	20	15	21	-	15	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	4.1 (0.4)	1.8 (0.2)	6.3 (1.2)	**	3.6 (0.8)	4.3 (0.4)	
>3, %	67	13	28	#	20	32	
>10, %	18	0	18	##	4	21	-
C1q, mean (SE), mg/dL	22 (0.2)	21 (0.4)	44 (0.5)	-	21 (0.3)	22 (0.2)	-
High (>22), %	32	28	33	-	34	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	189 (4)	174 (5)	175 (5)	-	183 (4)	180 (3)	-
High (>199), %	30	22	26	-	30	30	-
Triglycerides, mean (SE), mg/dL	143 (4)	130 (9)	143 (8)	-	132 (5)	148 (5)	-
High (>149), %	40	27	36	-	36	41	-
High BP (>130/80), %	61	47	71	##	54	63	-
Low BP (<66 diastolic), %	13	12	2.5	##	15	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

- This is the largest study to date to evaluate the safety and efficacy of bezisterim in patients with AD; bezisterim is the only anti-inflammatory agent currently in phase 3 development for AD[11]
- At baseline, the majority of patients had a high WHR (85%), hypertension (61%), and impaired glucose metabolism (IFG/T2D; 52%); almost half of all patients (47%) had some degree of insulin resistance; 40% and 30% of patients had hypertriglyceridemia and hypercholesterolemia, respectively; and patients had elevated inflammatory markers
- 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 had significantly higher inflammation, insulin resistance, IFG, and hypertension, compared to their Aβ+ counterparts
- Additional subgroup analysis revealed higher degrees of impaired glucose metabolism and insulin resistance among the *APOE* ε4− patients compared to their *APOE* ε4+ counterparts and comparable baseline MMSE scores, indicating that both groups had mild to moderate cognitive impairment
- Thus, even in the absence of classical risk markers, such as Aβ+ and *APOE* ε4+, central obesity (high WHR) and age-related systems dysregulation, involving inflammation (elevated CRP, RANTES, and C1q), hyperglycemia, insulin resistance, dyslipidemia, and hypertension, may contribute to probable AD and disease progression
- Consistent with the proposed anti-inflammatory and insulin-sensitizing properties of bezisterim, this phase 3 study was designed to confirm the efficacy and safety of bezisterim treatment in patients with probable AD

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