**1520-P** 

## BACKGROUND

- Alzheimer's disease (AD) is a multifactorial disease,<sup>1</sup> 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<sup>2</sup>
- Obesity is associated with chronic low-grade inflammation<sup>1</sup> involving pro-inflammatory cytokines such as TNF-α,<sup>3</sup> a key modulator of inflammatory responses<sup>4</sup> that has been implicated in the development of IR<sup>2</sup> and oxidative stress<sup>2,5</sup>
- Anti–TNF-α therapies have been shown to reduce the risk of developing AD in patients with autoimmune disease<sup>4</sup>
- Given the integral role TNF-α plays in the pathophysiology of neurodegenerative disorders,<sup>6</sup> bezisterim (NE3107), an investigative oral, anti-inflammatory and insulinsensitizing agent, is being evaluated for its ability to slow or prevent progression of MCI and AD<sup>7</sup>
- Bezisterim binds to the inflammatory mediator ERK and selectively inhibits inflammation-specific ERK, NF-κB, and TNF-α signaling, without affecting their homeostatic functions<sup>7</sup>
- Bezisterim lowered pro-inflammatory mediators in rodent models of inflammation<sup>8</sup> and improved insulin sensitivity in diabetic rats<sup>9</sup> • In obese patients with T2D and inflammation, bezisterim improved insulin sensitivity and normalized HbA1C<sup>7</sup>
- 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-a and brain glutathione,
- a marker of oxidative stress,<sup>10</sup> 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)<sup>7</sup>

# **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, TNF-α, 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)



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# Metabolic Dysregulation in Probable Alzheimer's Disease Christopher L. Reading<sup>1</sup>, Clarence Ahlem<sup>1</sup>, Joseph M. Palumbo<sup>1</sup>, Marcia A. Testa<sup>2</sup>, Donald C. Simonson<sup>3</sup>

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# RESULTS





>ABCOMS, Alzheimer's Disease Cooperative subscale of the Alzheimer's Disease Cooperative study—Clinical Global Impression of Change; CDR, Clinical State Examination; NF-kB, nuclear factor kappa B; P-tau, phosphorylated tau protein; T2D, type 2 diabetes; TNF-a, tumor necrosis factor alpha. ADAS-Cog 12, 12-item cognitive subscale of the Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; CDR, Clinical State Examination; NF-kB, nuclear factor kappa B; P-tau, phosphorylated tau protein; T2D, type 2 diabetes; TNF-a, tumor necrosis factor alpha. ADAS-Cog 12, 12-item cognitive subscale of the Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; CDR, Clinical State Examination; NF-kB, nuclear factor kappa B; P-tau, phosphorylated tau protein; T2D, type 2 diabetes; TNF-a, tumor necrosis factor alpha. ADAS-Cog 12, 12-item cognitive subscale of the Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; CDR, Clinical State Examination; NF-kB, nuclear factor kappa B; P-tau, phosphorylated tau protein; T2D, type 2 diabetes; TNF-a, tumor necrosis factor alpha. ADAS-Cog 12, 12-item cognitive subscale of the Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; CDR-SB, nuclear factor kappa B; P-tau, phosphorylated tau protein; T2D, type 2 diabetes; TNF-a, tumor necrosis factor kappa B; P-tau, phosphorylated tau protein; T2D, type 2 diabetes; TNF-a, tumor necrosis factor kappa B; P-tau, phosphorylated tau protein; T2D, type 2 diabetes; TNF-a, tumor necrosis factor kappa B; P-tau, phosphorylated tau protein; T2D, type 2 diabetes; TNF-a, tumor necrosis factor kappa B; P-tau, phosphorylated tau protein; T2D, type P-tau, phosphorylated tau protein; T2D, type 2 diabetes; TNF-a, tumor necrosis factor kappa B; P-tau, phosphorylated tau protein; T2D, type P-tau, phosphorylated tau protein; T2D, type P-tau protein; T2D, type P 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.

|     | All<br>N=278 | Aβ+ <sup>a</sup><br>n=57 | Aβ- <sup>b</sup>          | D   | <i>APOE</i> ε4+ | APOE ε4-                           | D   |
|-----|--------------|--------------------------|---------------------------|-----|-----------------|------------------------------------|-----|
|     | 73 (0.3)     | 76 (0.8)                 | 72 (0.6)                  | **  | 73 (0.6)        | 73 (0.4)                           |     |
|     | 55           | 53                       | 67                        |     | 6/              | Г <u></u> (0. <del>т</del> )<br>64 |     |
|     | 05           | 01                       | 07                        |     | 04              | 04                                 | -   |
|     | 00   110     | 100                      | 110                       | - * |                 | 02                                 | - * |
|     |              | 100                      |                           |     | 106             |                                    |     |
|     | 32           |                          | 35                        | #   | 25              | 36                                 |     |
| /ml | 16 (1 1)     | 10(10)                   | $\frac{22}{15(2\Lambda)}$ | - * | 12(11)          | 17(16)                             | - * |
| /   |              |                          | 15 (2.4)                  |     |                 |                                    |     |
|     |              |                          |                           | - * |                 |                                    | - * |
|     |              | 1.3 (0.2)                | 1.9 (0.2)                 |     | 1.5 (0.1)       |                                    |     |
|     | 27           |                          | 29                        | ##  | 24              | 27                                 | -   |
|     | 20           | 15                       | 21                        | -   | 15              | 22                                 | -   |
|     | 70 (2.5)     | 62 (3.4)                 | 68 (4.6)                  | -   | 68 (4.2)        | 71 (3.1)                           | -   |
|     | 4.1 (0.4)    | 1.8 (0.2)                | 6.3 (1.2)                 | **  | 3.6 (0.8)       | 4.3 (0.4)                          |     |
|     | 67           | 13                       | 28                        | #   | 20              | 32                                 |     |
|     | 18           | 0                        | 18                        | ##  | 4               | 21                                 | -   |
|     | 22 (0.2)     | 21 (0.4)                 | 44 (0.5)                  | -   | 21 (0.3)        | 22 (0.2)                           | -   |
|     | 32           | 28                       | 33                        | _   | 34              | 31                                 | -   |
|     | 28 (1.6)     | 23 (2.0)                 | 33 (2.8)                  | **  | 26 (2.8)        | 29 (2.0)                           | -   |
|     |              |                          |                           |     |                 |                                    |     |
|     | 189 (4)      | 174 (5)                  | 175 (5)                   | -   | 183 (4)         | 180 (3)                            | -   |
|     | 30           | 22                       | 26                        | -   | 30              | 30                                 | -   |
|     |              |                          |                           |     |                 |                                    |     |
|     | 143 (4)      | 130 (9)                  | 143 (8)                   | -   | 132 (5)         | 148 (5)                            | -   |
|     | 40           | 27                       | 36                        | _   | 36              | 41                                 | _   |
|     | 61           | 47                       | 71                        | ##  | 54              | 63                                 | -   |
|     | 13           | 12                       | 2.5                       | ##  | 15              | 4.1                                | ##  |
|     | 6.3 (0.1)    | 6.6 (0.3)                | 6.2 (0.2)                 |     | 6.6 (0.2)       | 6.1 (0.1)                          | **  |
|     | 20 (0 1)     | 20 (0 1)                 | 21 (0 2)                  | **  | 20 (0 2)        | 20 (0 1)                           | -   |
|     | 28 (0.1)     | 20(0.1)                  | 25 (0.7)                  | **  | 30 (0.9)        | 27 (0.5)                           | **  |
|     |              |                          |                           |     |                 |                                    |     |
|     |              |                          |                           | -   |                 |                                    | -   |
|     | 0.095        | 0.085 (0.001)            | 0.107 (0.001)             | **  | 0.089           | 0.098                              | **  |
|     | (0.001)      |                          |                           |     | (0.002)         | (0.001)                            |     |

Positive Precivity test; <sup>b</sup>Negative Precivity test; <sup>c</sup>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, ##<0.0

• 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

• 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,

 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

• 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

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