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Biomarker Analyses From the Phase 2, Randomized, Placebo-Controlled ACT-AD and Open-Label Extension Clinical Trials of Fosgonimeton in Patients With Mild-to-Moderate Alzheimer's Disease

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CONCLUSIONS

1. Improvements in plasma biomarkers of neurodegeneration (NfL) and neuroinflammation (GFAP) independently correlate with improvements in clinical measures of cognition and function
2. NfL and GFAP measures significantly correlate with a composite score of cognition and function, further supporting potential clinical relevance

KEY TAKEAWAY

Linear correlation analyses of a composite score of cognition and function with NfL and GFAP support their clinical utility as candidate plasma biomarkers for AD-related neurodegeneration and neuroinflammation

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Disclosures

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Disclaimer

Fosgonimeton is an investigational therapy that has not received FDA approval and has not been demonstrated to be safe or effective for any use.

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INTRODUCTION

- Positive modulation of the HGF/MET system induces neuroprotective and neurotrophic pathways,[1,3] which have the potential to address multiple facets of AD pathology[4]
- Fosgonimeton, a small-molecule positive modulator of the HGF/MET system, was evaluated in participants with mild-to-moderate AD in a randomized, double-blind, placebo-controlled, exploratory, phase 2 trial (ACT-AD; NCT04491006) and its open-label extension (NCT04886063)[5]
  - Topline results for ACT-AD were announced in June 2022, and the primary endpoint was not met by protocoled analysis
- In the subgroup of participants not receiving AChEIs, post hoc analysis showed descriptive improvements following fosgonimeton treatment, including:
  - Reduced ERP P300 latency (prespecified analysis)[5]
  - Improved cognition and function (ADAS-Cog11, MMSE, ADCS-ADL23[a])[6,7]
  - Improvements in diverse plasma biomarkers (NfL,[b] GFAP, YKL-40, Aβ 42/40, p-Tau181)[7]
- Neurodegeneration leads to increasing AD severity and cognitive decline and is the only known source of elevated NfL levels in fluids (eg, plasma, CSF)[8-10]
- Plasma GFAP, an indicator of neuroinflammation seen at sites of astrogliosis surrounding Aβ plaques,[11] has been observed at significantly higher levels in people with AD when compared to healthy volunteers[12]
- NfL and GFAP could therefore be clinically meaningful biomarkers of AD-related neurodegeneration and neuroinflammation

[a]Improvement shown in the mITT population.
[b]Statistically significant ($p = 0.0222$).

OBJECTIVE

To assess the relationship between plasma biomarkers and clinical measures of cognition (ADAS-Cog11, MMSE) and function (ADCS-ADL23)

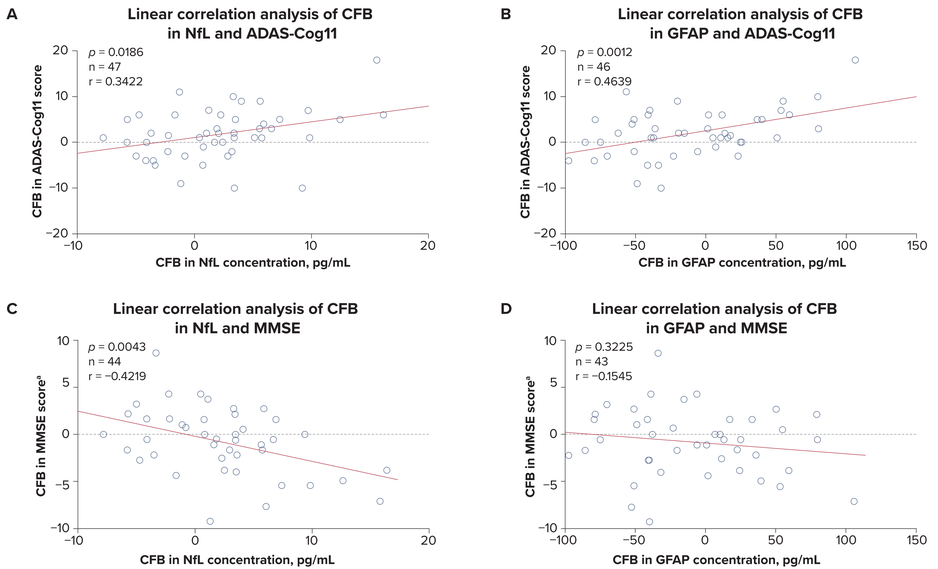
METHODS

- Participants with mild-to-moderate AD were randomly assigned (1:1:1) to receive once-daily subcutaneous fosgonimeton 40 mg, fosgonimeton 70 mg, or placebo for 26 weeks
- Blood samples were collected at baseline and week 26 from participants who consented to plasma biobanking
  - Biomarkers analyzed to date include: NfL, GFAP, YKL-40, Aβ 42/40, and p-Tau181[13-15]
- CFB in plasma biomarkers for fosgonimeton (pooled 40 mg and 70 mg arms) were compared with placebo in post hoc analyses[c]
- Linear regression analyses were performed to assess the relationship between CFB in plasma biomarkers (NfL and GFAP) and CFB in clinical outcomes (ADAS-Cog11, MMSE, ADCS-ADL23)

[c]One CFB GFAP value was about five standard deviations above the mean of the remaining values and was excluded from analysis due to its large impact on the reported estimates; inclusion of this value did not impact overall conclusions regarding this relationship.

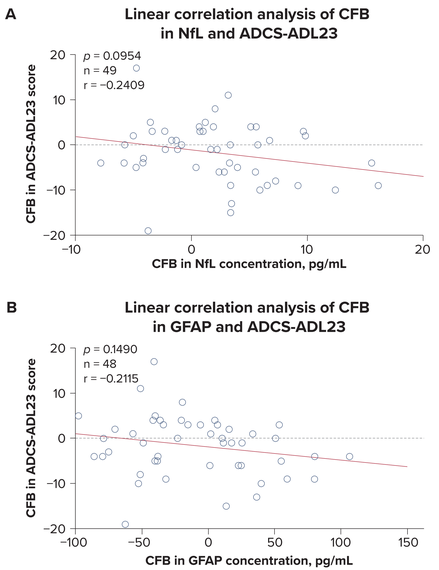
RESULTS

Figure 1. Reductions in biomarkers of neurodegeneration (NfL) and neuroinflammation (GFAP) correlate with improvements in cognition (ADAS-Cog11; MMSE)



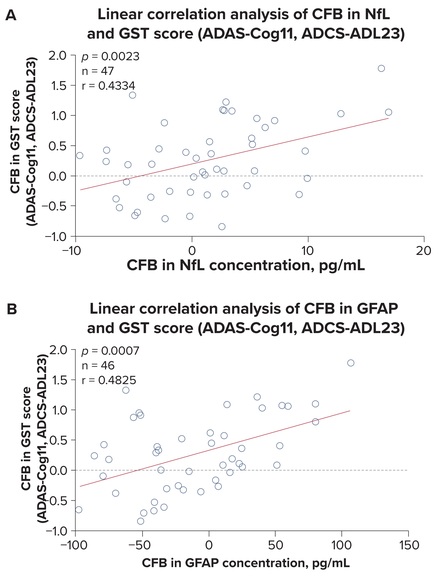
CFB in (A) NfL and (B) GFAP concentrations at week 26 significantly correlated with improvements in ADAS-Cog11 CFB scores. CFB in (C) NfL concentrations significantly correlated with improvements in MMSE scores. (D) CFB in GFAP trended toward correlation with improvements in MMSE scores.
[a]Change in MMSE measured between baseline (average of two screening measures) ACT-AD and screening for the open-label extension.

Figure 2. Reductions in biomarkers of neurodegeneration (NfL) and neuroinflammation (GFAP) trend toward correlation with improvements in function (ADCS-ADL23)



CFB in (A) NfL and (B) GFAP concentrations at 26 weeks trended toward correlations with improvements in ADCS-ADL23 CFB scores.

Figure 3. Reductions in biomarkers of neurodegeneration (NfL) and neuroinflammation (GFAP) significantly correlate with improvements in a composite score of cognition and function



CFB in (A) NfL and (B) GFAP concentrations at 26 weeks significantly correlated with improvements in GST composite score of ADAS-Cog11 and ADCS-ADL23.

Abbreviations **Aβ**, amyloid beta; **AChEI**, acetylcholinesterase inhibitors; **AD**, Alzheimer's disease; **ADAS-Cog11**, Alzheimer's Disease Assessment Scale–Cognitive Subscale; **ADCS-ADL23**, Alzheimer's Disease Cooperative Study–Activities of Daily Living, 23-item version; **CFB**, change from baseline; **CSF**, cerebrospinal fluid; **ERP**, event-related potential; **GFAP**, glial fibrillary acidic protein; **GST**, global statistical test; **HGF**, hepatocyte growth factor; **mITT**, modified intention-to-treat; **MMSE**, Mini-Mental State Examination; **NfL**, neurofilament light chain; **p-Tau181**, tau phosphorylated at threonine-181; **YKL-40**, chitinase-3–like protein 1.

References **1.** Ebens A et al. *Neuron*. 1996;17:1157-1172. **2.** Maina F, Klein R. *Nat Neurosci*. 1999;2:213-217. **3.** Shang J et al. *J Neurosci Res*. 2011;89:86-95. **4.** Moebius HJ, Church KJ. *J Alzheimers Dis*. 2023;92:1-12. **5.** Moebius HJ et al. Presented at: Alzheimer's Association International Conference (AAIC) 2022; July 31-August 4, 2022; San Diego, CA (HFS-5-09 AAIC). **6.** Moebius HJ et al. Presented at: Clinical Trials on Alzheimer's Disease (CTAD) 2022; November 29-December 2, 2022; San Francisco, CA (LP79 CTAD). **7.** Moebius HJ et al. Presented at: American Academy of Neurology (AAN) 2023; April 22-27, 2023; Boston, MA. **8.** Olsson, B et al. *JAMA Neurol*. 2019;76(3):318-325. **9.** Bacioglu M et al. *Neuron*. 2016;91:56-66. **10.** Zetterberg H et al. *JAMA Neurol*. 2016;73:60-67. **11.** Osborn, LM et al. *Prog Neurobiol*. 2016;144:121-141. **12.** Chatterjee P et al. *Alzheimers Dement*. 2023;19:1117-1134. **13.** Mattson N et al. *JAMA Neurol*. 2019;76:791-799. **14.** Götze K et al. *Neurobiol of Dis*. 2023;176:105937. **15.** Lin YS et al. *Sci Rep*. 2018;8:17368.