Fosgonimeton Provides Congruent Benefit on Diverse Biomarkers of Neurodegeneration, Significantly Correlating With a Composite Clinical Score of Cognition and Function in Alzheimer's Disease

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CONCLUSIONS

1 Evidence from the double-blind placebo-controlled ACT-AD study suggests that baseline plasma NfL, a marker of ongoing neurodegeneration, may predict decline in subjects with mild-to-moderate AD

2 NfL showed a statistically significant reduction from baseline with fosgonimeton treatment at 26 weeks, indicating reduced neurodegeneration versus placebo. All assessed plasma biomarkers, NfL (neurodegeneration), GFAP, and YKL-40 (neuroinflammation), may reflect the neuroprotective potential of fosgonimeton[a]

3 Directional changes in pathological biomarkers (Aβ 42/40 ratio and p-Tau181) with fosgonimeton suggest its potential as a disease-modifying therapy for mild-to-moderate AD[a]

[a]These results need to be confirmed in larger studies.

KEY TAKEAWAY

Fosgonimeton-related reductions in NfL and GFAP significantly correlated with improvements in clinical outcomes at week 26, as assessed by the GST, a composite score of ADAS-Cog11 and ADCS-ADL23

INTRODUCTION

- HGF signaling through the MET receptor activates neuroprotective and neurotrophic pathways[1-3]
- MET expression is markedly reduced in AD,[4] and positive modulation of the HGF/MET system may be beneficial for patients with AD
- The randomized, double-blind, phase 2 ACT-AD study (NCT04491006) compared the safety and efficacy of fosgonimeton, a small-molecule positive modulator of HGF/MET, with that of placebo in subjects with mild-to-moderate AD[5]
- Among subjects without concomitant AChEI therapy, treatment with fosgonimeton maintained a favorable safety profile over 26 weeks of the double-blind study and descriptively showed:
  - Reduced ERP P300 latency
  - Improved cognition as measured by ADAS-Cog11
  - Improved function as measured by ADCS-ADL23
- In addition, fosgonimeton showed a statistically significant improvement in plasma NfL levels ($p = 0.0241$) compared with placebo
- We present results from additional plasma biomarker analyses from ACT-AD

OBJECTIVES

- **To explore the potential utility of plasma biomarkers from ACT-AD in predicting clinical outcomes**
- **To determine the effect of fosgonimeton on biomarkers of neurodegeneration (NfL), neuroinflammation (GFAP, YKL-40), and protein pathology (Aβ 42/40 ratio, p-Tau181)**
- **To assess the relationship between plasma biomarkers and clinical outcomes as measured by the GST, a composite score of ADAS-Cog11 and ADCS-ADL23**

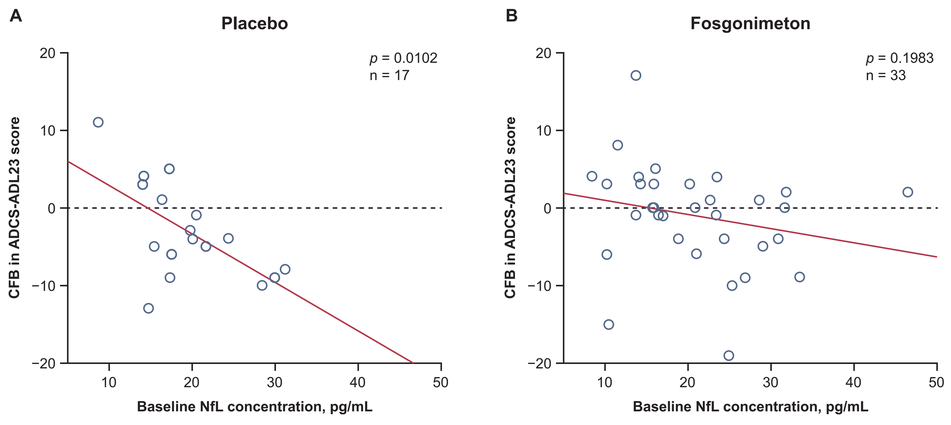
METHODS

- Subjects with mild-to-moderate AD were randomly assigned (1:1:1) to receive fosgonimeton 40 mg, fosgonimeton 70 mg, or placebo subcutaneously once daily for 26 weeks
- Blood samples, collected at baseline and at week 26 from subjects who consented to plasma biobanking, were analyzed for the following plasma biomarkers: NfL, GFAP, YKL-40, Aβ 42, Aβ 40, and p-Tau181
  - Additional details on the methods for biomarker analysis are provided in the **Supplemental Information** (**QR Code**)
- Several exploratory baseline factors and covariates were considered in the studied plasma biomarkers, including AChEI use, *ApoE4* carrier status, sex, age, body mass index, MMSE score, educational level, age at AD diagnosis, years from AD diagnosis to start of study, Clinical Global Impression–Severity, and Clinical Dementia Rating–Sum of Boxes
- LSM ± SEM differences were calculated for CFB in biomarker levels to week 26, and treatment effect was determined using ANOVA; *p*-values were not adjusted for multiplicity

RESULTS

- 66 subjects completed the ACT-AD study; after excluding missing subjects, samples, or data among subjects who did not provide prior consent for plasma biobanking, biomarker data were available for up to 61 subjects (**Supplemental Table S1, QR code**)
- For subjects treated with fosgonimeton, results are presented as pooled fosgonimeton arms (40 mg and 70 mg)

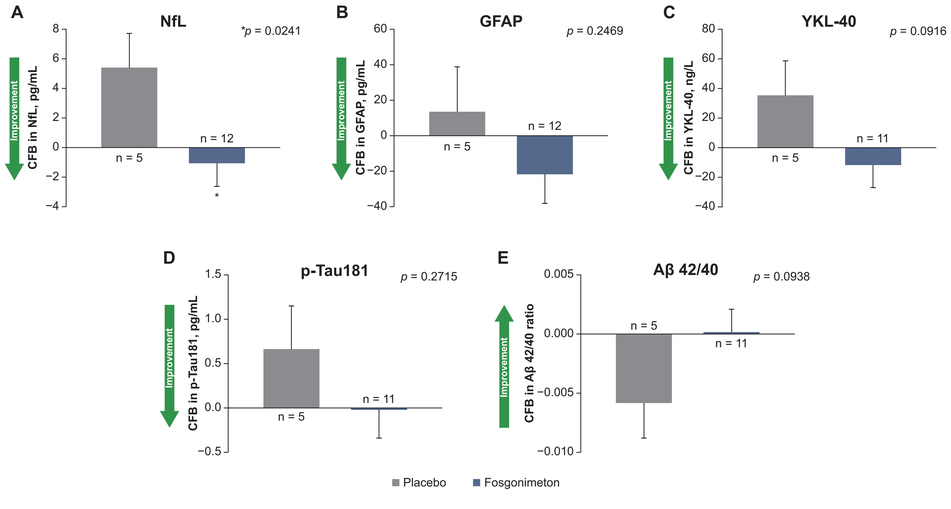
Figure 1. Baseline NfL is significantly associated with the course of decline in subjects who received placebo; fosgonimeton appears to favorably mitigate the expected decline



Linear regression analysis showed that (A) in placebo-treated subjects, baseline NfL levels significantly negatively correlated with clinical decline from baseline to week 26 in ADCS-ADL23 (p = 0.0102); such biomarkers are useful for determining the expected course of disease if untreated. (B) No such relationship was found in fosgonimeton-treated subjects.

- To understand whether baseline NfL is a predictor of treatment response, its correlation with CFB in ADCS-ADL23 scores was calculated in both placebo and fosgonimeton-treated subjects. The correlation was not significant ($p = 0.1983$), suggesting that baseline NfL loses its predictive utility for decline in subjects receiving fosgonimeton, supporting a potential treatment benefit

Figure 2. Fosgonimeton treatment consistently improves biomarkers of neurodegeneration and neuroinflammation, compared with placebo, among subjects not taking concomitant AChEIs

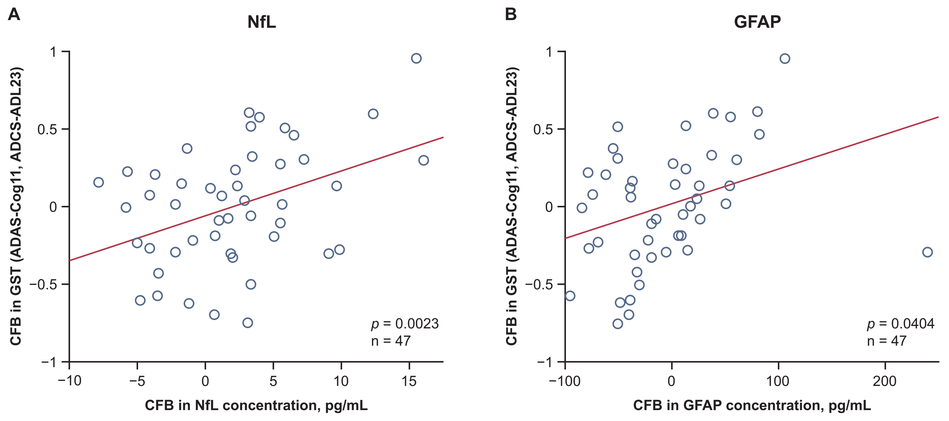


A significant improvement in (A) NfL was seen after 26 weeks of fosgonimeton treatment compared with placebo; CFB in (B) GFAP, (C) YKL-40, (D) p-Tau181, and (E) Aβ 42/40 ratio all showed directional effects (ANOVA with terms for treatment, AChEI, treatment AChEI interaction, and baseline biomarker value).

Data presented as LSM ± SEM.

- These clinical results are corroborated by additional neuroinflammatory findings from a preclinical model of AD (**Supplemental Figure S1, QR code**)

Figure 3. Decreases in biomarkers of neurodegeneration and neuroinflammation (NfL and GFAP) correlate with improvements in cognitive and functional measures (GST composite score of ADAS-Cog11 and ADCS-ADL23)



In all subjects, CFB in (**A**) NfL and (**B**) GFAP concentrations at week 26 significantly correlated with CFB in GST (combined ADAS-Cog11 plus ADCS-ADL23 composite scores). The relationship between the studied biomarkers and GST was determined in the modified intention-to-treat population.

- In current practice, evidence for therapeutic benefit in symptomatic AD is ideally based on effects on cognitive plus functional measures (typically reductions in the rate of decline) that are congruent with changes in biomarkers of the underlying disease process[6]
- The correlation between CFB in clinical assessments and plasma biomarkers was calculated to evaluate their relationship in subjects with AD; improvements in ADAS-Cog11 and ADCS-ADL23 scores (per the composite GST score) significantly correlated with decreases in plasma NfL ($p = 0.0023$) and GFAP ($p = 0.0404$) levels
- This association was not altered by any of the covariates examined in the study. These findings support the utility of NfL and GFAP as markers of disease status as quantified by the GST; NfL and GFAP thus lend supporting evidence to the composite score (GST) results

Abbreviations:
Aβ, amyloid beta; **AChEI**, acetylcholinesterase inhibitor; **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; **ANOVA**, analysis of variance; ***ApoE4***, apolipoprotein E4; **CFB**, change from baseline; **ERP**, event-related potential; **GFAP**, glial fibrillary acidic protein; **GST**, global statistical test; **HGF**, hepatocyte growth factor; **LSM**, least squares mean; **MMSE**, Mini-Mental State Examination; **NfL**, neurofilament light chain; **p-Tau181**, tau phosphorylated at threonine-181; **SEM**, standard error of the mean; **YKL-40**, chitinase-3–like protein 1.

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Acknowledgments

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The information presented here is solely the responsibility of Athira and does not necessarily represent the official views of the National Institutes of Health.

Disclosures

Hans J. Moebius, Kai-Bin C. Ooi, Michael D. Hale, Sharay E. Setti, and Kayla N. Kleist are employees of Athira Pharma, Inc. with salary and stock compensation.
Charles Bernick is an employee of Cleveland Clinic Lou Ruvo Center for Brain Health - Las Vegas.

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SUPPLEMENTAL INFORMATION

Methods

Biomarker analysis

- NfL was assessed using the Simoa NF-light Advantage assay (103186, Quanterix, Billerica, MA, USA)
- GFAP, Aβ 40, and Aβ 42 were measured using the Simoa Neurology 4-Plex E assay (103670, Quanterix, Billerica, MA, USA)
- YKL-40 was measured using the U-PLEX Human YKL-40 assay (K151VLK, Meso Scale Diagnostics, Rockville, MD, USA)
- p-Tau181 was measured using the Simoa p-Tau181 V2 Advantage assay (103714, Quanterix, Billerica, MA, USA)

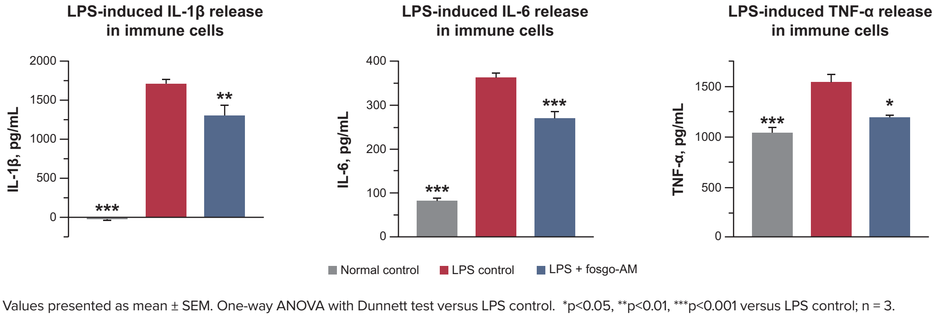
Biomarker analysis in vitro

- THP-1–differentiated macrophages were challenged with LPS in the presence or absence of fosgo-AM
- 24 hours after the LPS challenge, cytokine levels in the supernatant were quantified using HTRF kits to assess the levels of IL-1β (Human IL-1β kit, 62HIL1BPEG, Cisbio, Codolet, France) and IL-6 (Human IL-6 kit, 62HIL06PET, Cisbio, Codolet, France); TNF-α was quantified using ELISA (Human TNF-α ELISA kit, KHC3011, Thermo Fisher, Waltham, MA, USA)
- Data for each group were averaged and presented as mean ± SEM
- Statistical significance was determined by one-way ANOVA with Dunnett multiple comparison post-test; comparisons were considered statistically significant when $p < 0.05$

Supplemental Table S1. Baseline plasma biomarker values from patients in ACT-AD

	NfL pg/mL n = 61	GFAP pg/mL n = 61	YKL-40 ng/L n = 59	p-Tau181 pg/mL n = 59	Aβ 42/40 ratio n = 59
Mean ± SD	20.93 ± 7.84	216.96 ± 77.25	90.75 ± 81.74	3.81 ± 1.68	0.05 ± 0.01
Median (min-max)	19.90 (8.48-46.50)	203.00 (70.00-408.00)	55.41 (21.16-40.20)	3.56 (1.34-11.63)	0.06 (0.02-0.08)

Supplemental Figure S1. Enhancing HGF/MET pathway with fosgo-AM significantly reduces inflammatory markers implicated in neurodegeneration in vitro



Values presented as mean ± SEM. One-way ANOVA with Dunnett test versus LPS control. *p<0.05, **p<0.01, ***p<0.001 versus LPS control; n = 3.

Abbreviations: **Aβ**, amyloid beta; **ANOVA**, analysis of variance; **ELISA,** enzyme-linked immunosorbent assay; **fosgo-AM**, fosgonimeton active metabolite; **GFAP**, glial fibrillary acidic protein; **HGF**, hepatocyte growth factor; **HTRF**, homogenous time-resolved fluorescence; **IL-1β**, interleukin 1 beta; **IL-6**, interleukin 6; **LPS**, lipopolysaccharide; **NfL**, neurofilament light chain; **p-Tau181**, tau phosphorylated at threonine-181; **SD**, standard deviation; **SEM**, standard error of the mean; **TNF-α**, tumor necrosis factor α; **YKL-40**, chitinase-3–like protein 1.

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