Fosgonimeton Provides Congruent Improvements on Neurodegeneration Biomarkers, Significantly Correlating with Composite Clinical Scores of Cognition and Function in Alzheimer's Disease

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Athira PHARMA

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 a principal investigator on Athira clinical studies and is a neurologist at the Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas

Fosgonimeton: a positive modulator of the HGF/MET neurotrophic system

MULTIMODAL, PROTECTIVE, REGENERATIVE, DISEASE MODIFYING

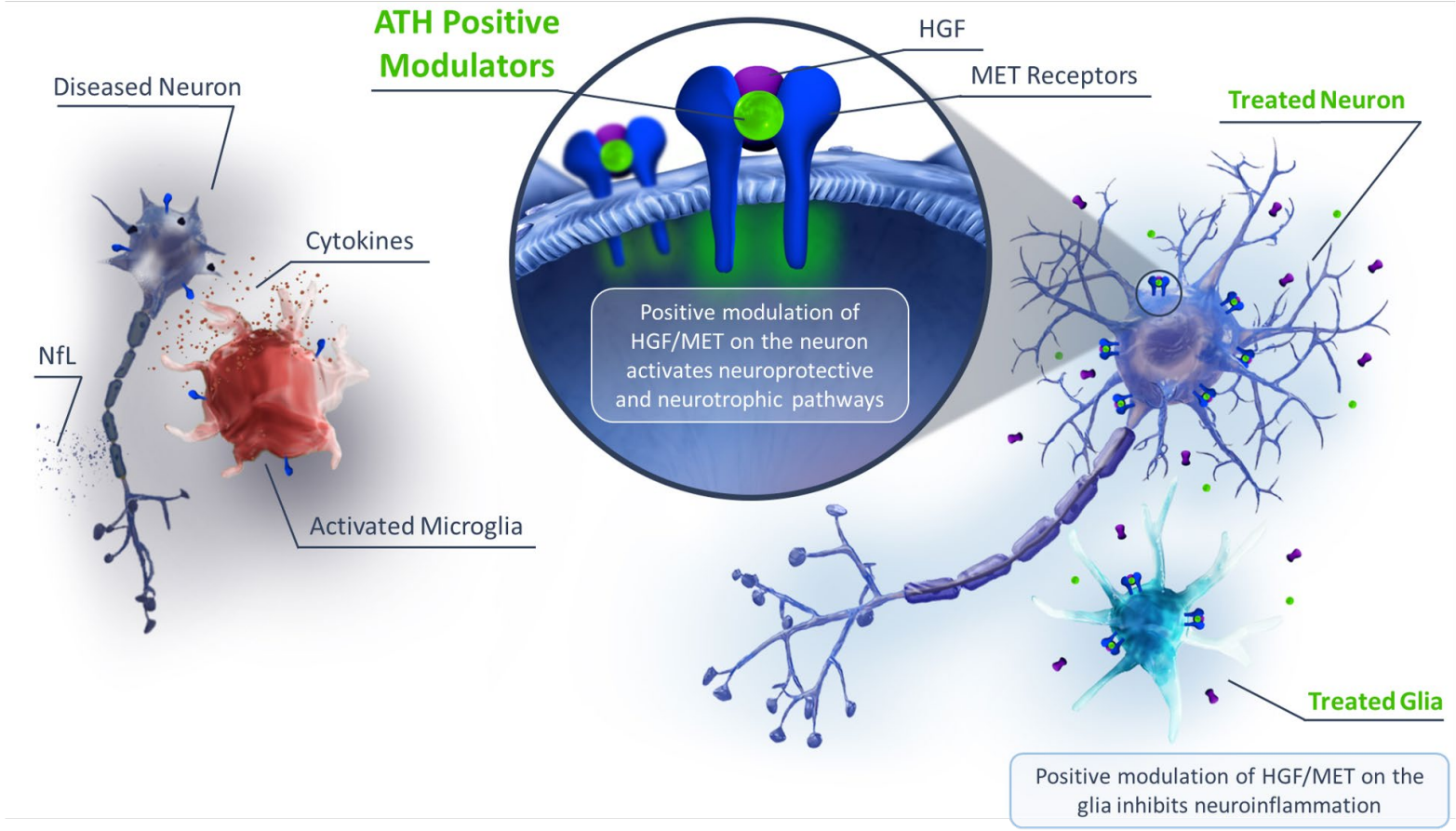
HGF/MET is a critical neurotrophic system[1]

Potential first-in-class small molecule drug candidates

- Able to cross the blood-brain barrier
- Positively modulate HGF/MET

Mechanism of action may

- Reduce inflammation
- Promote regeneration
- Provide neuroprotection
- Modify the course of disease



HGF, hepatocyte growth factor.

1. Desole C et al. *Front Cell Dev Biol*. 2021 Jun 9;9:683609.

Two 6-month trials of fosgonimeton in mild-to-moderate AD

- The exploratory **phase 2 ACT-AD trial**[a] examined the safety and efficacy of fosgonimeton in participants with mild-to-moderate AD
- Ongoing **phase 2/3 LIFT-AD trial**[b] was amended to recruit participants not on concomitant AChEIs

Key learnings from ACT-AD[a]

- Fosgonimeton was well-tolerated with a favorable safety profile
- Prespecified subgroup analysis with and without concomitant AChEIs
- Observed unexpected potential pharmacodynamic interaction with AChEIs
- In the absence of AChEIs, clinical and biomarker effects consistently favor fosgonimeton over placebo

AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease.
[a]ACT-AD (NCT04491006) was a 6-month, randomized, double-blind, placebo-controlled trial (N = 77). [b]LIFT-AD (NCT04488419) is an active 6-month, randomized, double-blind, placebo-controlled trial.
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).

Plasma biomarker analyses in ACT-AD

Objectives

- Explore the potential utility of plasma biomarkers and association with clinical outcomes[a]
- Assess the relationship between plasma biomarkers and clinical outcomes
- Complement ADAS-Cog11 results with MMSE scores

Biomarkers

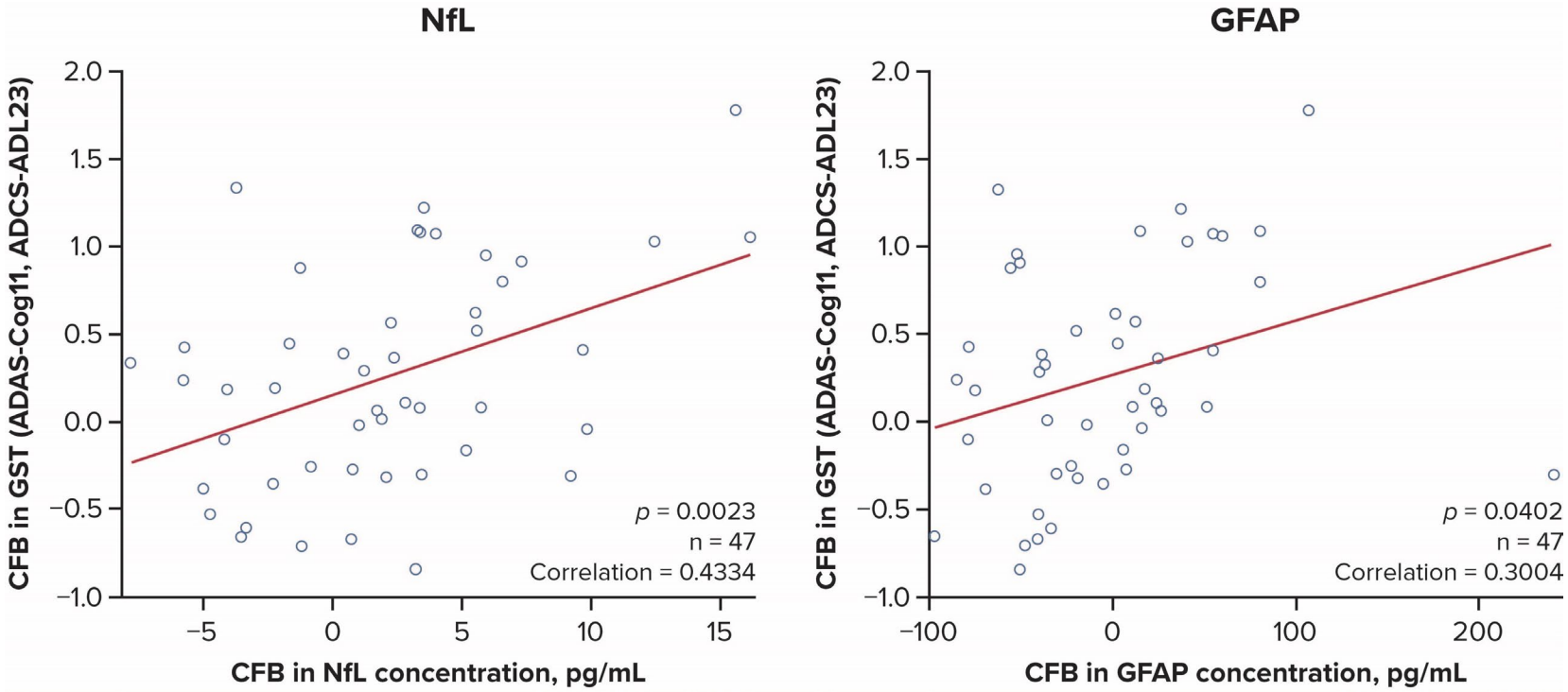
- NfL (neurodegeneration)
- GFAP (neuroinflammation)
- YKL-40 (neuroinflammation)
- Aβ 42/40 ratio (protein pathology)
- p-Tau181 (protein pathology)

Results are presented as pooled fosgonimeton dose arms (40 mg and 70 mg daily) versus placebo

Aβ, amyloid beta; ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; GFAP, glial fibrillary acidic protein; MMSE, mini-mental state examination; NfL, neurofilament light chain; p-Tau181, tau phosphorylated at threonine-181; YKL-40, chitinase-3–like protein 1.
[a]Differential population is based on available data, relative to specific endpoints.

Positive biomarker data associates with clinical endpoints

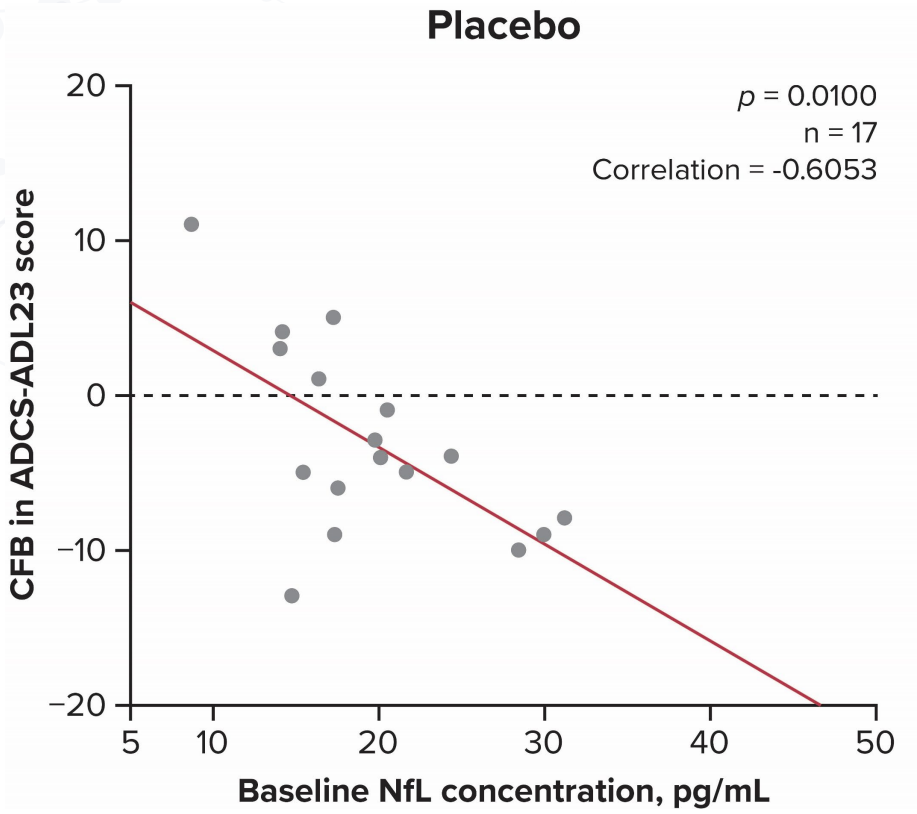
- Decreases in biomarkers of neurodegeneration and neuroinflammation significantly correlate with improvements in cognitive and functional measures (mITT population, in placebo- and fosgonimeton-treated participants)
- Validated biomarker associations with clinical endpoints are supported by the literature[1-3]

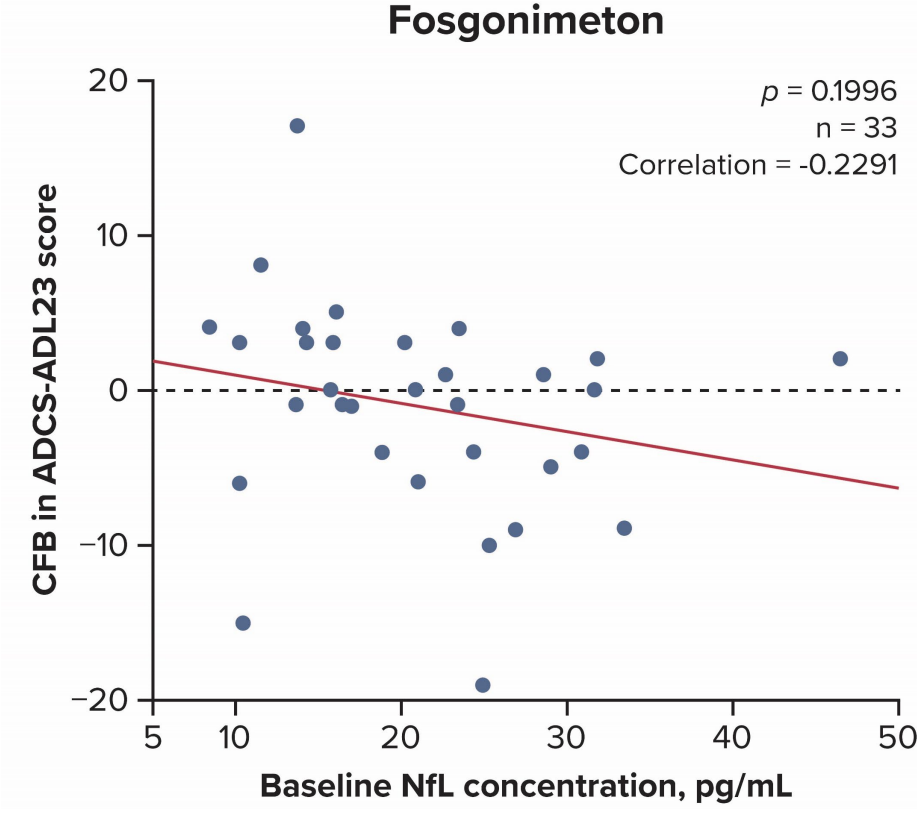


ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL23, Alzheimer's Disease Cooperative Study–Activities of Daily Living, 23-item version; CFB, change from baseline; GFAP, glial fibrillary acidic protein; GST, global statistical test; mITT, modified intention-to-treat; NfL, neurofilament light chain.

1. Mattson N et al. *JAMA Neurol* 2019;76:872. 2. Götze K et al. *Neurobiol of Dis* 2023;176:105937. 3. Lin YS et al. *Sci Rep.* 2018; 8:17368.

Fosgonimeton decouples the predictive relationship between baseline NfL and CFB in ADCS-ADL23[1,2]



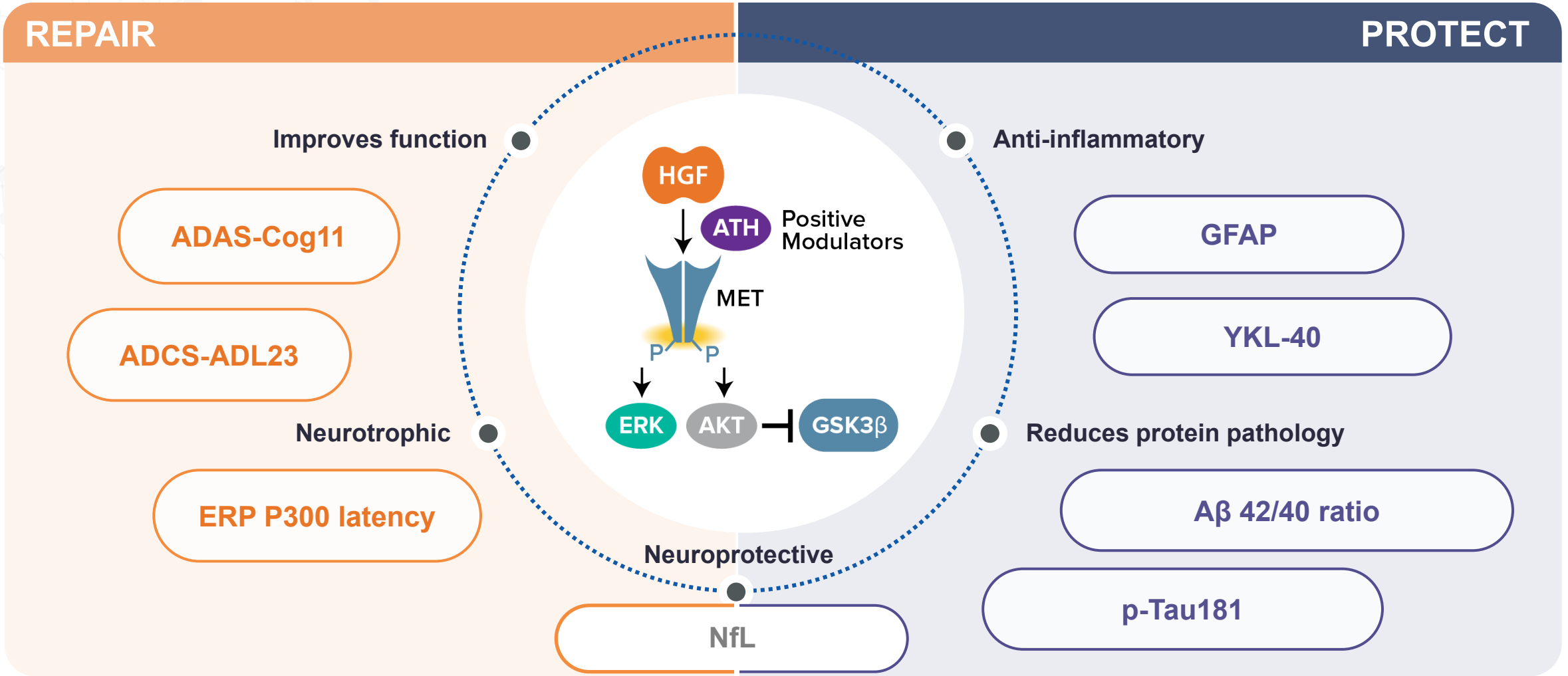


Baseline NfL is predictive of decline in ADL23 scores

Fosgonimeton treatment disrupts the decline in ADL23 scores

ADCS-ADL23, Alzheimer's Disease Cooperative Study–Activities of Daily Living, 23-item version; CFB, change from baseline; NfL, neurofilament light chain.
Data are from mITT population (n = 50). Differential population is based on available data, relative to specific endpoints.
1. Li D et al. *J Alzheimer's Dis Rep.* 2021;5:601-611. 2. Lin YS et al. *Sci Rep.* 2018; 8:17368.

Clinical findings support therapeutic potential of fosgonimeton

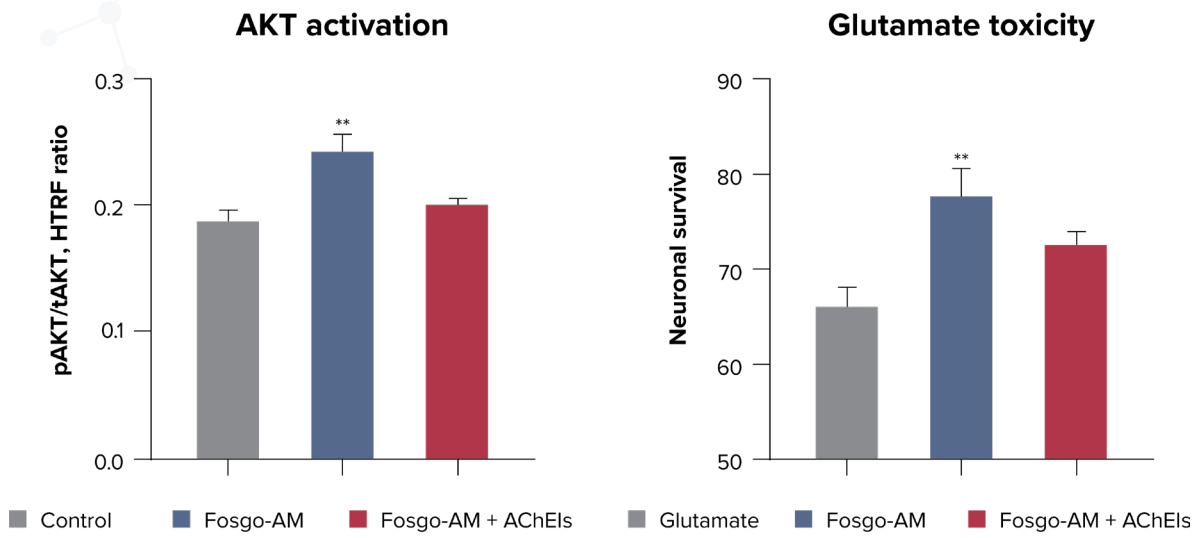


Aβ, amyloid beta; ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL23, Alzheimer's Disease Cooperative Study–Activities of Daily Living; AKT, protein kinase B; ERK, extracellular-signal regulated kinase; ERP, event-related potential; GFAP, glial fibrillary acidic protein; GSK3β, glycogen synthase kinase-3β; HGF, hepatocyte growth factor; NfL, neurofilament light chain; p-Tau181, tau phosphorylated at threonine-181; YKL-40, chitinase-3–like protein 1.
Data are from ACT-AD phase 2 trial.

Neuroprotective effects of fosgonimeton are reduced with exposure to AChEIs

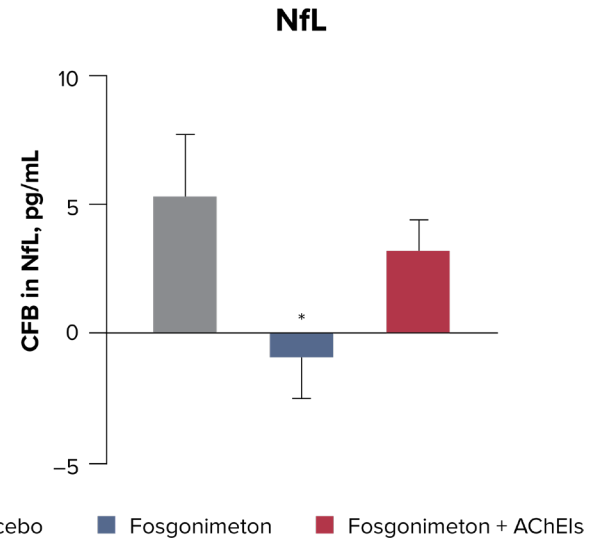
Preclinical

- Combination of fosgo-AM with donepezil interfere with fosgo-AM-induced AKT activation
- Neuroprotective effects of fosgo-AM are reduced when combined with donepezil
  - Likely the result of observed decrease in fosgo-AM-induced AKT activation



Clinical

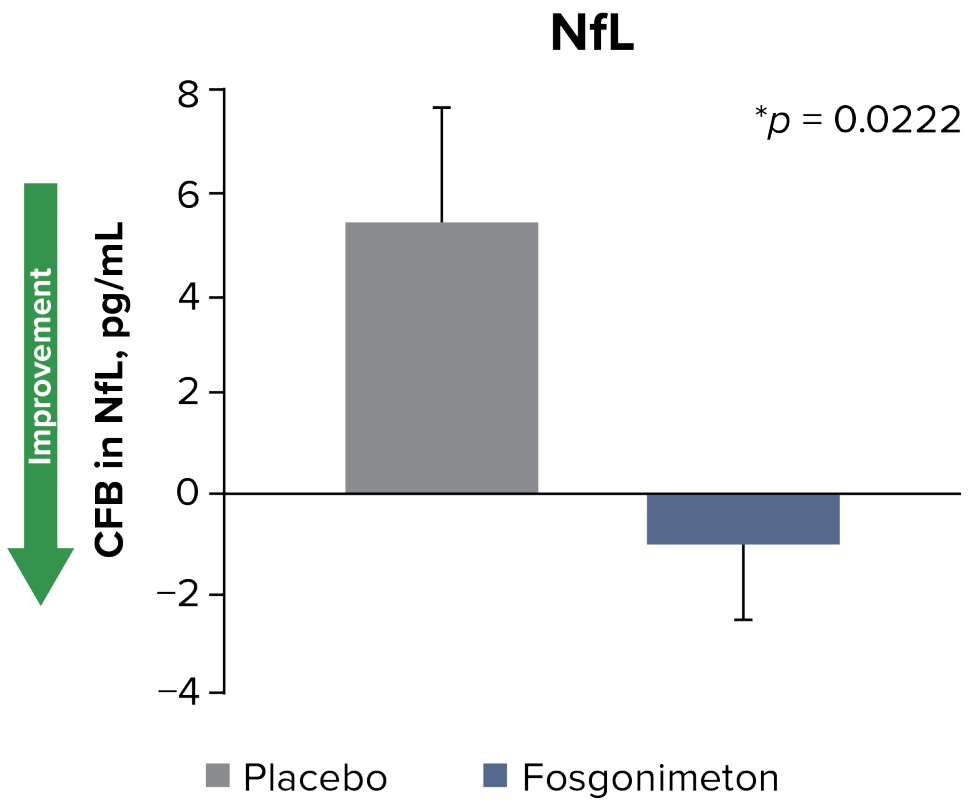
- Fosgonimeton significantly reduced NfL, a biomarker of neurodegeneration, in the ACT-AD study
- When combined with AChEIs, NfL increased, suggesting a loss of the neuroprotective effect
- This result is consistent with preclinical findings of reduced neuroprotection in combination with AChEIs



AChEIs, acetylcholinesterase inhibitors; AKT, protein kinase B; ANOVA, analysis of variance; CFB, change from baseline; NfL, neurofilament light chain; SEM, standard error of the mean.
For in vitro assays, fosgonimeton was administered as the active metabolite, fosgo-AM. AKT assay: one-way ANOVA with Dunnett's post-test; **p<0.01 vs. control; n = 6 (control), 5 (fosgo-AM), 3 (fosgo-AM + AChEIs), mean + SEM. Glutamate assay: one-way ANOVA with Dunnett's post-test; **p<0.01 vs. glutamate; n = 6 (glutamate), 6 (fosgo-AM), 5 (fosgo-AM + AChEIs); mean + SEM.
For clinical data, NfL data are least squares means from an ANOVA model with CFB as the dependent variable with the following in the model: treatment group, AChEI use, baseline biomarker value, and the interaction of treatment and AChEI use. Error bars are ± SE. n = 5 (placebo); n= 12 (fosgonimeton − AChEIs), n = 22 (fosgonimeton + AChEI).

Fosgonimeton treatment significantly reduces plasma NfL, a biomarker of neurodegeneration

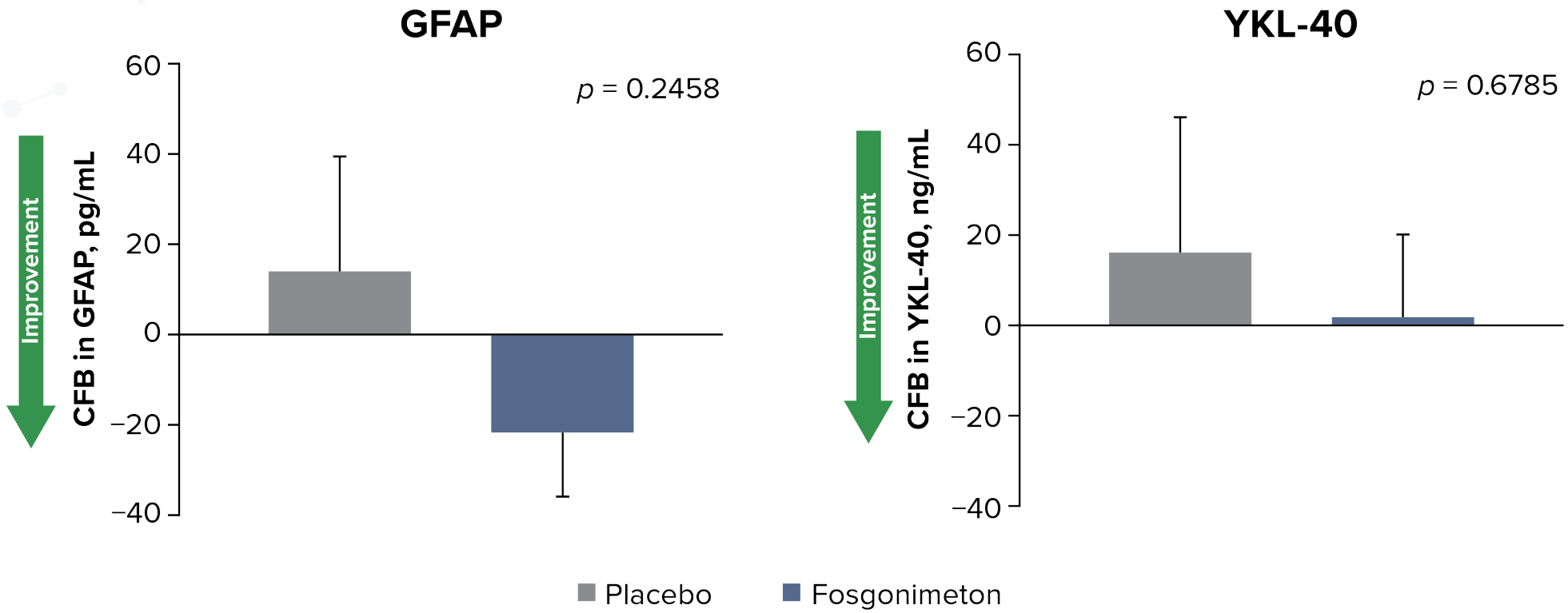
- Fosgonimeton showed a statistically significant decrease in plasma NfL levels compared with placebo (-6.48 pg/mL, $p = 0.0222$)
- Suggests protection against progressive neurodegeneration



AChEI, acetylcholinesterase inhibitors; CFB, change from baseline; mITT, modified intention-to-treat; NfL, neurofilament light chain.
Data are least square means from an ANOVA model with CFB as the dependent variable with the following in the model from mITT population: treatment group, AChEI use, baseline biomarker value and the interaction of treatment and AChEI use. Error bars are ± SE.
*Placebo (n = 5) vs fosgonimeton (n = 12), without concomitant AChEIs.

Fosgonimeton treatment shows directional improvements in plasma biomarkers of neuroinflammation, GFAP and YKL-40

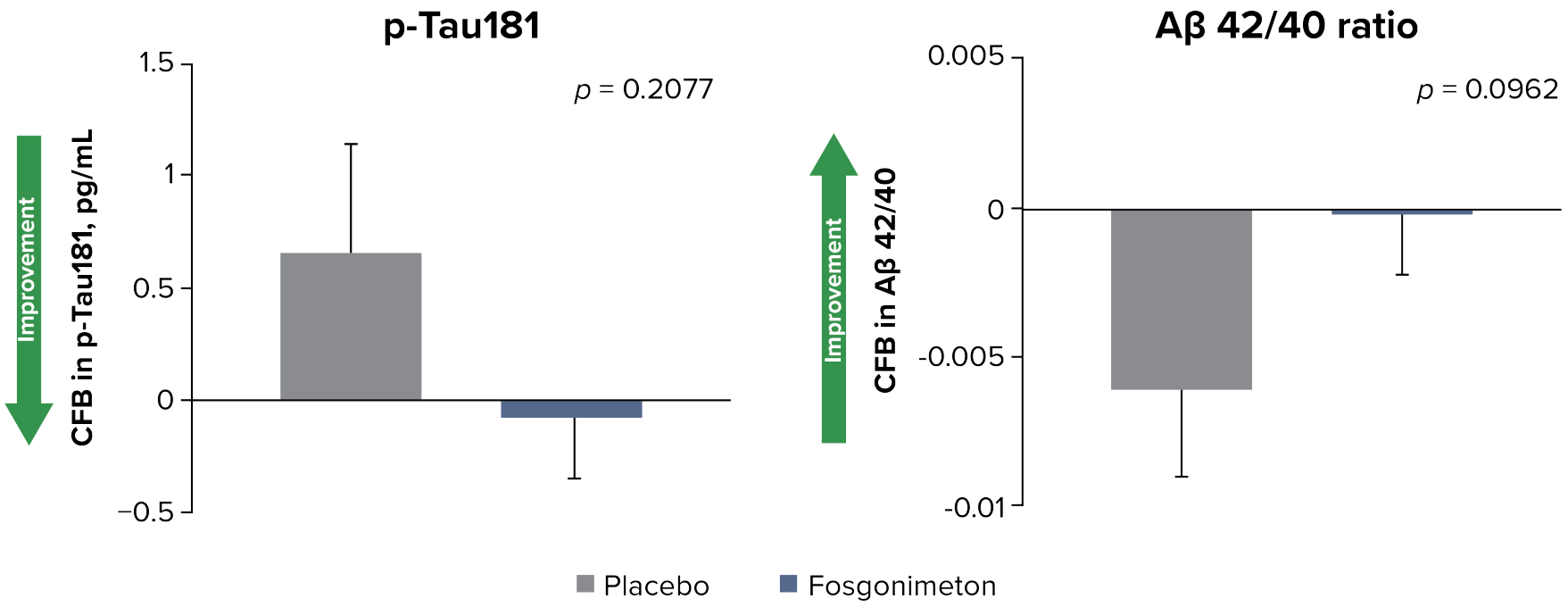
- Descriptive reduction vs placebo is supportive of a potential anti-inflammatory mechanism of action of fosgonimeton



AChEI, acetylcholinesterase inhibitors; CFB, change from baseline; GFAP, glial fibrillary acidic protein; mITT, modified intention-to-treat; YKL-40, chitinase-3–like protein 1.
Data are least square means from an ANOVA model with CFB as the dependent variable with the following in the model from mITT population: treatment group, AChEI use, baseline biomarker value, and the interaction of treatment and AChEI use. Error bars are ± SE. Placebo (n = 5); fosgonimeton (n = 12), without concomitant AChEIs.

Fosgonimeton treatment induces directional improvements in plasma biomarkers of AD-related protein pathology

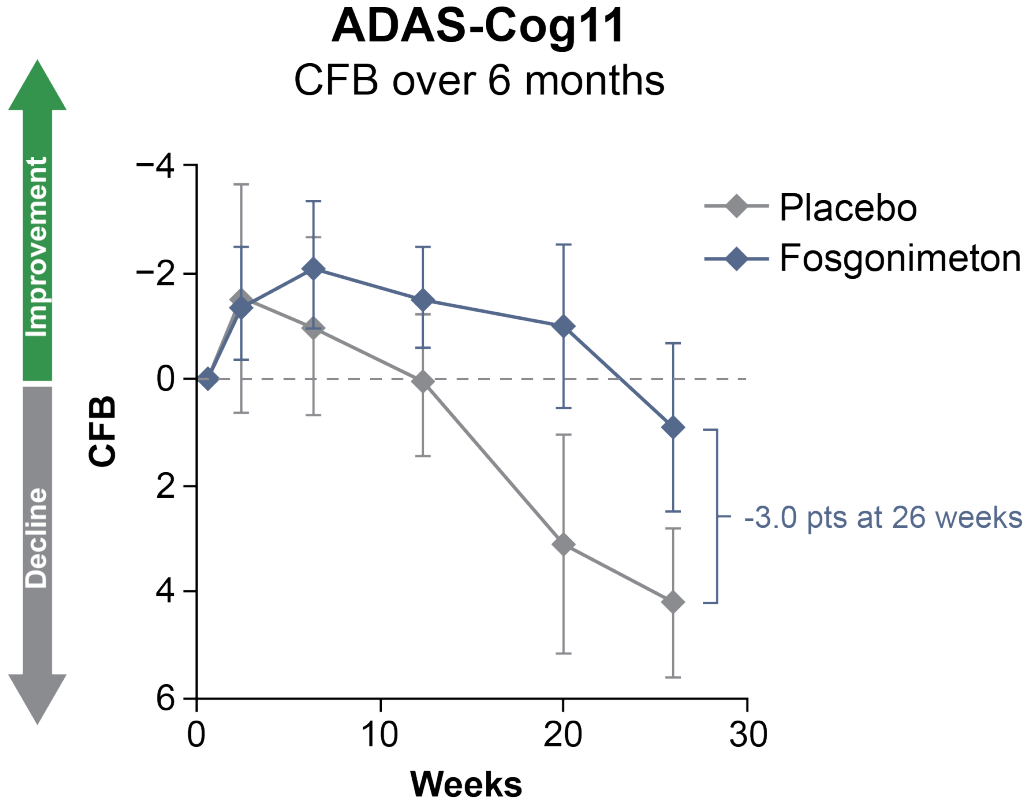
- Decreased Aβ 42/40 ratio and increased absolute p-Tau181 values are hallmarks of AD
- Supportive of disease modifying potential of fosgonimeton



Aβ, amyloid beta; AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; CFB, change from baseline; mITT, modified intention-to-treat; p-Tau181, tau phosphorylated at threonine-181.
Data are least square means from an ANOVA model with CFB as the dependent variable with the following in the model from mITT population: treatment group, AChEI use, baseline biomarker value, and the interaction of treatment and AChEI use. Error bars are ± SE. Placebo (n = 5); fosgonimeton (n = 11 or 12), without concomitant AChEIs.

Biomarker results align with data showing descriptive cognitive benefits with fosgonimeton

- Compared with placebo treatment, fosgonimeton improved cognition per ADAS-Cog11 in participants without concomitant AChEIs
- At 26 weeks, CFB in fosgonimeton-treated participants was -3.0 pts compared with placebo (74% improvement, not significant)

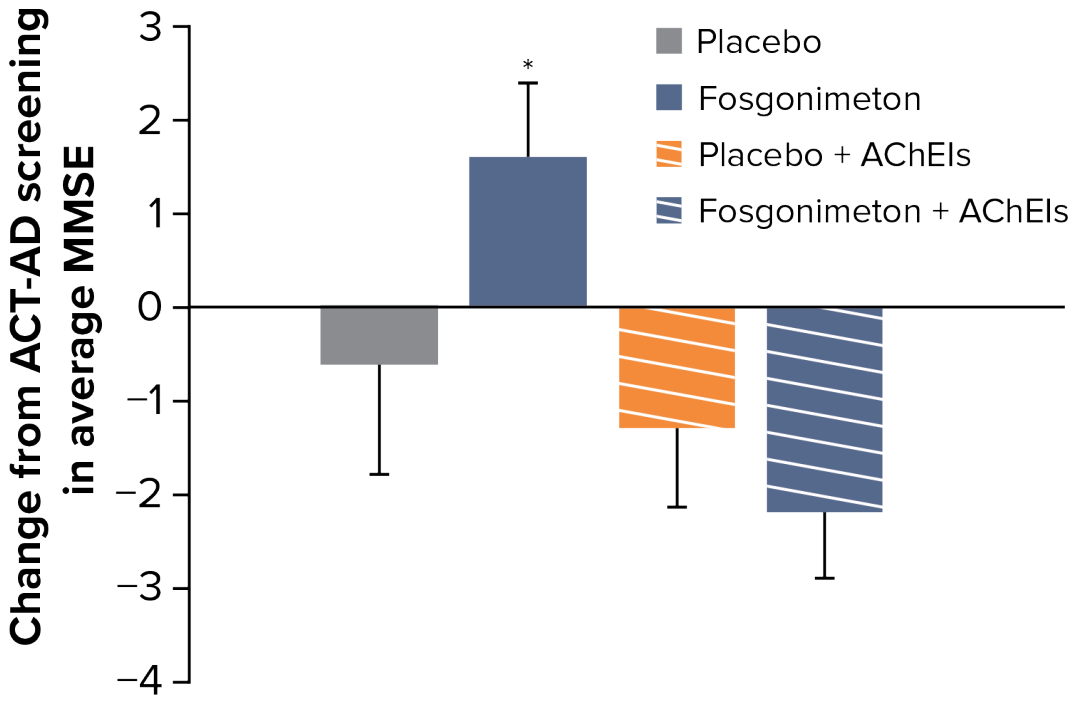


n at each visit	W2	W6	W12	W20	W26
Placebo	8	8	7	7	6
Fosgonimeton	19	19	17	16	17

AChEI, acetylcholinesterase inhibitor; ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; CFB, change from baseline; mITT, modified intention-to-treat; pts, points; W, week.
Data are summary statistics from mITT population without concomitant AChEIs. Error bars are ± SE.

Pro-cognitive effect suggested by ADAS-Cog11 is replicated by MMSE analysis

- MMSE scores were recorded at ACT-AD screening and at the start of the OLEX[a]
- Fosgonimeton led to a significant improvement in MMSE scores from screening (+1.6 pts, p = 0.035)
  - Improvement in MMSE was potentially negated by concomitant AChEIs
- Trending improvement with fosgonimeton (+2.2 pts) vs placebo (p = 0.120)



AChEIs, acetylcholinesterase inhibitors; MMRM, mixed model for repeated measure; MMSE, mini-mental state examination; OLEX, open label extension; pts, points.
[a]Eligible participants could voluntarily enroll in the 18-month open label extension following completion of ACT-AD. Statistics are obtained from a MMRM, with treatment group, AChEI usage, AChEI usage by treatment group interaction, period, period by treatment interaction, period by AChEI usage interaction, and period by AChEI usage by treatment interaction as fixed effects, subject as a random effect. A compound symmetry covariance matrix is used. Each statistical test was a contrast from MMRM using a 2-sided test. Placebo (n = 7); fosgonimeton (n = 16); placebo + AChEIs (n = 15); fosgonimeton + AChEIs (n = 20). Data are post-hoc exploratory analysis presented as least mean square ± SE.
*p = 0.035 fosgonimeton mean MMSE from screening to start of OLEX.

Conclusions

- Fosgonimeton is a novel treatment approach to neurodegeneration
- Concomitant AChEI treatment leads to a reduction of the effects of fosgonimeton
  - Likely due, in part, to an interference on neuroprotective AKT signaling
- In the ACT-AD trial subgroup without AChEIs, fosgonimenton showed congruent effects:
  - Improvement in cognition (ADAS-Cog11, MMSE)
  - Significant reduction in a biomarker of neurodegeneration (NfL)
  - Reduction in AD protein pathology (p-Tau181, Aβ 42/40 ratio)
  - Reduction in biomarkers of neuroinflammation (GFAP, YKL-40)

Clinical and biomarker findings support therapeutic potential of fosgonimeton

Aβ, amyloid beta; AChEI, acetylcholinesterase inhibitors; AD, Alzheimer's disease; ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; GFAP, glial fibrillary acidic protein; MMSE, mini-mental state examination; NfL, neurofilament light chain; p-Tau181, tau phosphorylated at threonine-181; YKL-40, chitinase-3–like protein 1.

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For more information:

http://bit.ly/3U7ohVJ

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