ACT-AD: Fosgonimeton in Mild-to-Moderate Alzheimer's Disease – First Results of a Randomized, Placebo-Controlled, 26-Week, Phase 2 Proof-of-Concept Trial

Hans J. Moebius, Charles Bernick, Paul Winner, Joyce Maalouf, Kai-Bin Ooi, Samuel Dickson, Suzanne Hendrix, Kevin Church, John M. Olichney

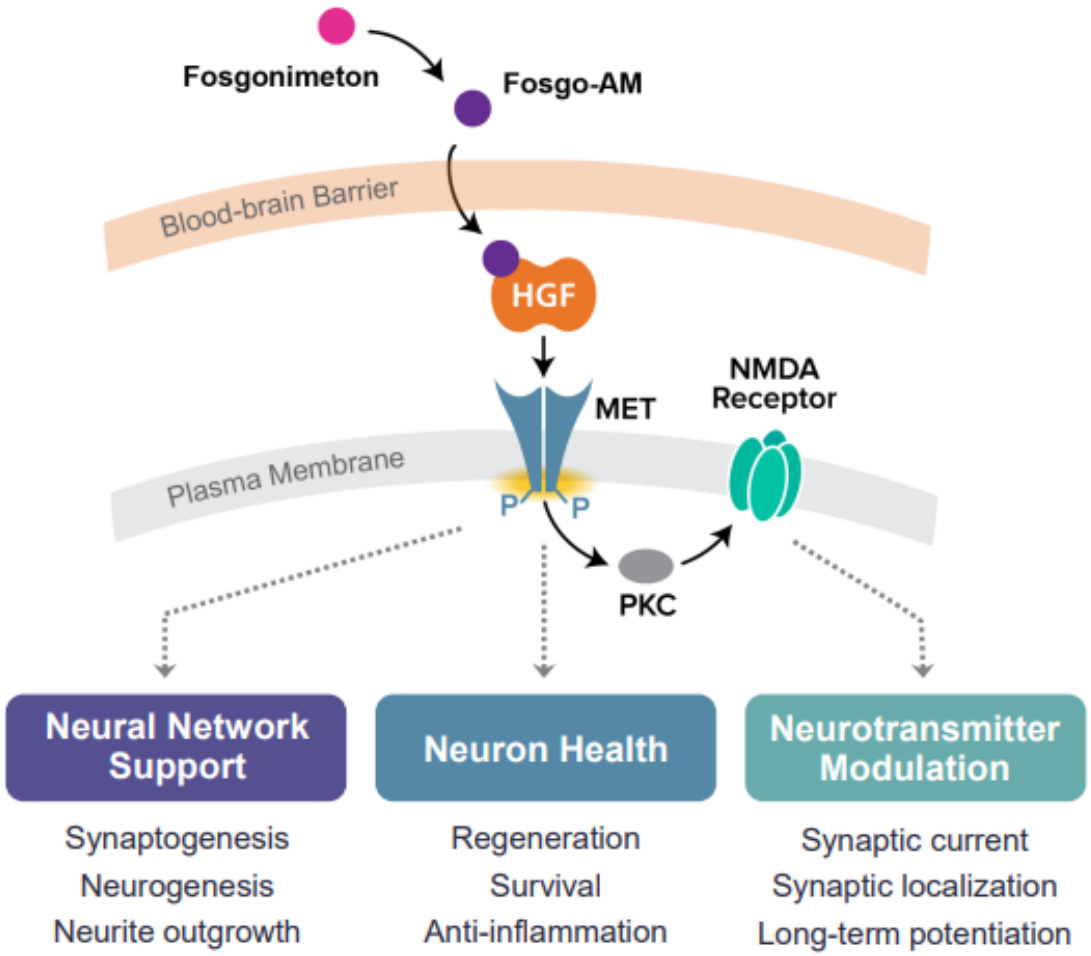
Athira PHARMA

Disclosures

- Hans J. Moebius, Joyce Maalouf, Kai-Bin Ooi, and Kevin Church are employees of Athira Pharma, Inc., with salary and stock compensation
- Charles Bernick is a principal investigator on Athira clinical studies and is clinical professor, University of Washington
- Paul Winner is on the Athira scientific advisory board; a principal investigator on Athira clinical studies; senior director, Premiere Research Institute; and attending neurologist, Palm Beach Neurology
- Sam Dickson and Suzanne Hendrix are employees of Pentara Corporation
- John Olichney is on the Athira scientific advisory board and is Professor Emeritus of Neurology, and Director of the UC Davis Alzheimer’s Disease Center's Clinical Trials Unit

A new approach to AD

- AD is a disorder of synaptic disconnection and degeneration in the brain[1,2]
- HGF signaling through the MET receptor activates neuroprotective and neurotrophic pathways[3-5]
  - MET is expressed in neurons and glia[6]
  - MET expression is reduced in AD brains[7]
- Fosgonimeton is a small-molecule positive modulator of HGF/MET
  - Significantly reduced ERP P300 latency in prior phase 1b study over 8 days[8]
  - Exhibited MET pathway–mediated neuroprotective effects in cultured neurons (see poster No. 65874)[9,10]



AD, Alzheimer's disease; ERP, event-related potential; fosgo-AM, active metabolite of fosgonimeton; HGF, hepatocyte growth factor; NMDA receptor, *N*-methyl-D-aspartate receptor; P, phosphorylation; PKC, protein kinase C.

1. Jackson J. et al. *Front Neurosci.* 2019;13:735. 2. Forner S, et al. *Trends Neurosci.* 2017;40:347-357. 3. Ebens A et al. *Neuron.* 1996;17:1157-1172. doi:10.1016/s0896-6273(00)80247-0. 4. Maina F, Klein R. *Nat Neurosci.* 1999;2:213-17. doi:10.1038/6310. 5. Shang J et al. *J Neurosci Res*. 2011;89:86-95. doi:10.1002/jnr.22524. 6. Yamada T, et al. *Brain Res.* 1994;637:308-312. 7. Hamasaki et al, *Neuropathology.* 2014;34:284-290. 8. Hua X, et al. *J Alzheimer's Dis.* 2022;86:1399-1413. doi:10.3233/JAD-21511. 9. Reda S et al. Poster presented at: Alzheimer's Association International Conference; (AAIC 2022) July 31-August 3, 2022; San Diego, CA. 10. Johnston J, et al. Presentation at ASENT Annual Meeting, February 28-March 3, 2022.

Athira PHARMA

Fosgonimeton phase 2: ACT-AD objectives

- In subjects with mild-to-moderate AD dementia[1]:
  - Evaluate the effects of fosgonimeton treatment on ERP P300 latency (using MMRM) — Primary
  - Assess the safety and tolerability of fosgonimeton — Primary
  - Change from baseline in assessment scores: ADAS-Cog11, ADCS-CGIC, and ADCS-ADL23 — Secondary
  - Evaluate effects of fosgonimeton by composite score (GST)
  - Analysis by subgroups:
    - Severity (mild or moderate)
    - ApoE (carriers or non-carriers)
    - With and without add-on cholinergic therapy

ADAS-Cog11, Alzheimer's Disease Assessment Scale—Cognitive subscale; ADCS-ADL23, Alzheimer's Disease Cooperative Study—Activities of Daily Living, 23-item version; ADCS-CGIC, Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; ApoE, apolipoprotein E; GST, global statistical test; MMRM, mixed-model repeated measures.

1. McKhann G, et al. *Alzheimers Dement.* 2011;7:263-269.

Athira PHARMA

Study design: double-blind, placebo-controlled, 26 weeks

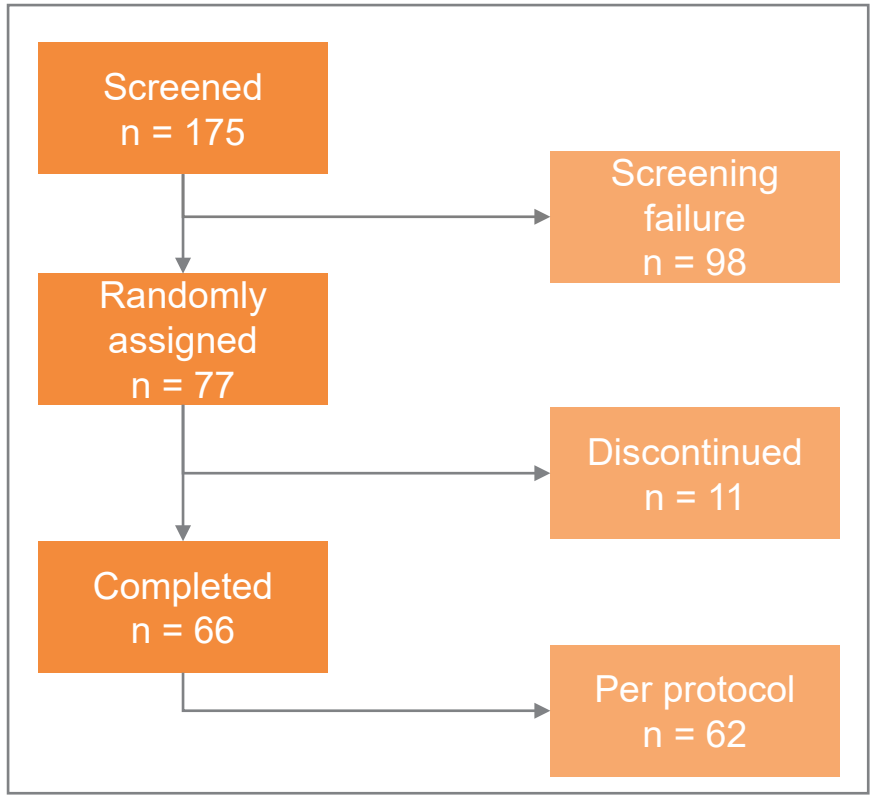
Patients (N = 77)

- 55–85 years
- Mini-Mental State Examination (MMSE) score: 14-24
- Clinical Dementia Rating (CDR) global score 1 or 2
- Clinical diagnosis of dementia, probably due to AD[1]
- Could receive prior or concomitant AChEI[a]
- Reliable and capable support person/caregiver

R
1:1:1

Double-blind

- Fosgonimeton (40 mg, QD, SC)
- Fosgonimeton (70 mg, QD, SC)
- Placebo (QD, SC)



Observation time points:

Week 2 | Week 6 | Week 12 | Week 16 | Week 20 | Week 26 | OLEX[b]

[a]Stable AChEI treatment defined as: stable AChEI dose for 3 months prior to screening with no changes during the study or discontinuation of AChEI ≥4 weeks prior to screening.
[b]OLEX duration is 18 months with the goal of assessing long-term safety.
AChEI, acetylcholinesterase inhibitor; CDR, clinical dementia rating; MMSE, mini-mental state examination; OLEX, open-label extension; R, randomization; QD, once daily; SC, subcutaneous.
1. McKhann GM et al. *Alzheimers Dement*. 2011;7:263-269.

Athira PHARMA

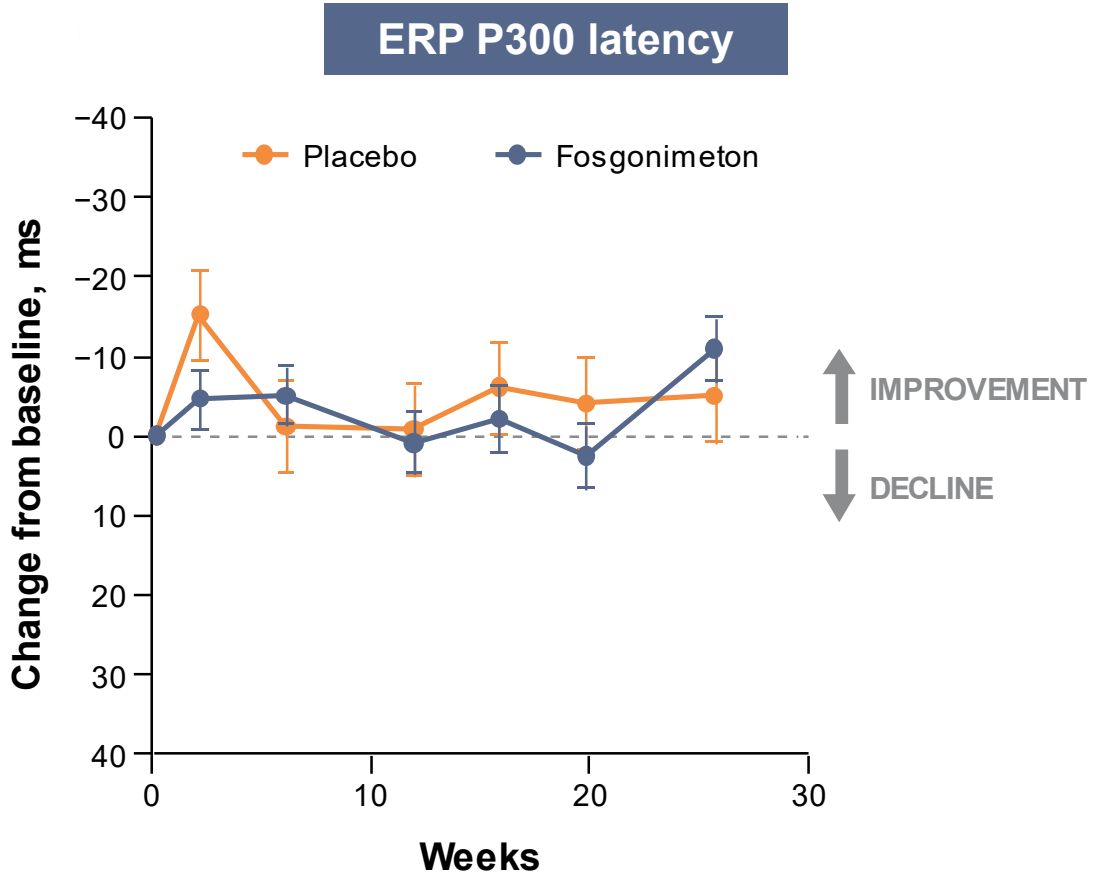
Demographics and baseline characteristics

Patient characteristic[a]	Placebo n = 23	Fosgonimeton 40 mg n = 27	Fosgonimeton 70 mg n = 25
Age, mean ± SD, y	70.0 ± 8.20	70.6 ± 6.54	73.8 ± 7.08
BMI, mean ± SD, kg/m^2	24.0 ± 3.11	26.5 ± 4.26	25.4 ± 3.25
Sex, n (%)			
Female	11 (47.8)	15 (55.6)	11 (44.0)
Male	12 (52.2)	12 (44.4)	14 (56.0)
Years of education, mean ± SD	15.0 ± 2.58	14.3 ± 2.65	15.3 ± 3.16
Baseline MMSE score, mean ± SD	19.1 ± 2.73	19.2 ± 2.69	18.8 ± 3.50
ApoE4 carriers, n (%)			
E2/E3	0 (0.0)	1 (3.7)	1 (4.0)
E2/E4	2 (8.7)	0 (0.0)	0 (0.0)
E3/E3	7 (30.4)	13 (48.1)	9 (36.0)
E3/E4	9 (39.1)	6 (22.2)	11 (44.0)
E4/E4	5 (21.7)	6 (22.2)	4 (16.0)
Unknown	0 (0.0)	1 (3.7)	0 (0.0)
Concomitant AChEI, n (%)	15 (65.2)	15 (55.6)	16 (64.0)
P300 latency, mean ± SD, ms	361.5 ± 32.23	385.6 ± 42.98	375.3 ± 35.77

[a]mITT population.
BMI, body mass index; mITT, modified intent-to-treat; SD, standard deviation.

Athira PHARMA

Primary endpoint ERP P300 latency (n.s.) by protocoled mITT, specific MMRM analysis



mITT population by an MMRM analysis. Data presented as unadjusted mean ± SEM.
n.s., not significant; SEM, standard error of the mean.

Athira PHARMA

Fosgonimeton demonstrated a favorable safety profile, with no treatment-related serious AEs

MedDRA term	Placebo n = 24 n (%)	Fosgonimeton 40 mg n = 27 n (%)	Fosgonimeton 70 mg n = 26 n (%)	Overall n = 77 n (%)
Any AE	17 (70.8)	24 (88.9)	26 (100.0)	67 (87.0)
General disorders and administration site conditions	4 (16.7)	22 (81.5)	25 (96.2)	51 (66.2)
Injection site reaction	1 (4.2)	17 (63.0)	21 (80.8)	39 (50.6)
Nervous system disorders	5 (20.8)	11 (40.7)	8 (30.8)	24 (31.2)
Dizziness	2 (8.3)	2 (7.4)	4 (15.4)	8 (10.4)
Blood and lymphatic system disorders	2 (8.3)	10 (37.0)	7 (26.9)	19 (24.7)
Eosinophilia	1 (4.2)	7 (25.9)	5 (19.2)	13 (16.9)
Injury, poisoning, and procedural complications	2 (8.3)	8 (29.6)	5 (19.2)	15 (19.5)
Gastrointestinal disorders	4 (16.7)	4 (14.8)	6 (23.1)	14 (18.2)

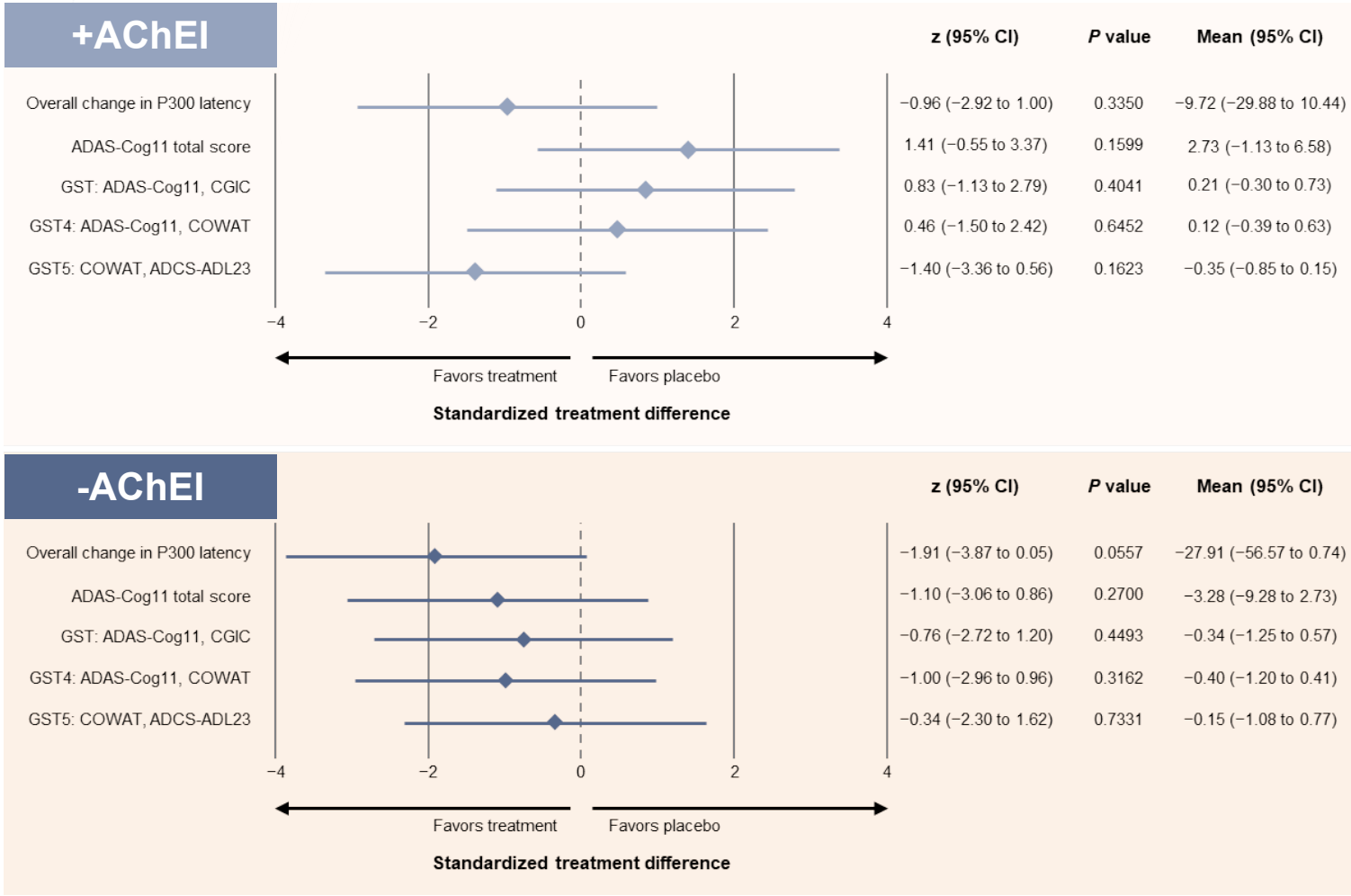
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

Descriptive changes in secondary end points (mITT, MMRM)

- ADAS-Cog11
  - Mean difference: +0.71 points compared to placebo at Week 26 (n.s.)
- ADCS-CGIC
  - Mean difference: +0.04 points compared to placebo at Week 26 (n.s.)
- ADCS-ADL23
  - Mean difference: +2.12 points compared to placebo at Week 26 (n.s)
- COWAT
  - Mean difference: +1.14 points compared to placebo at Week 26 (n.s.)

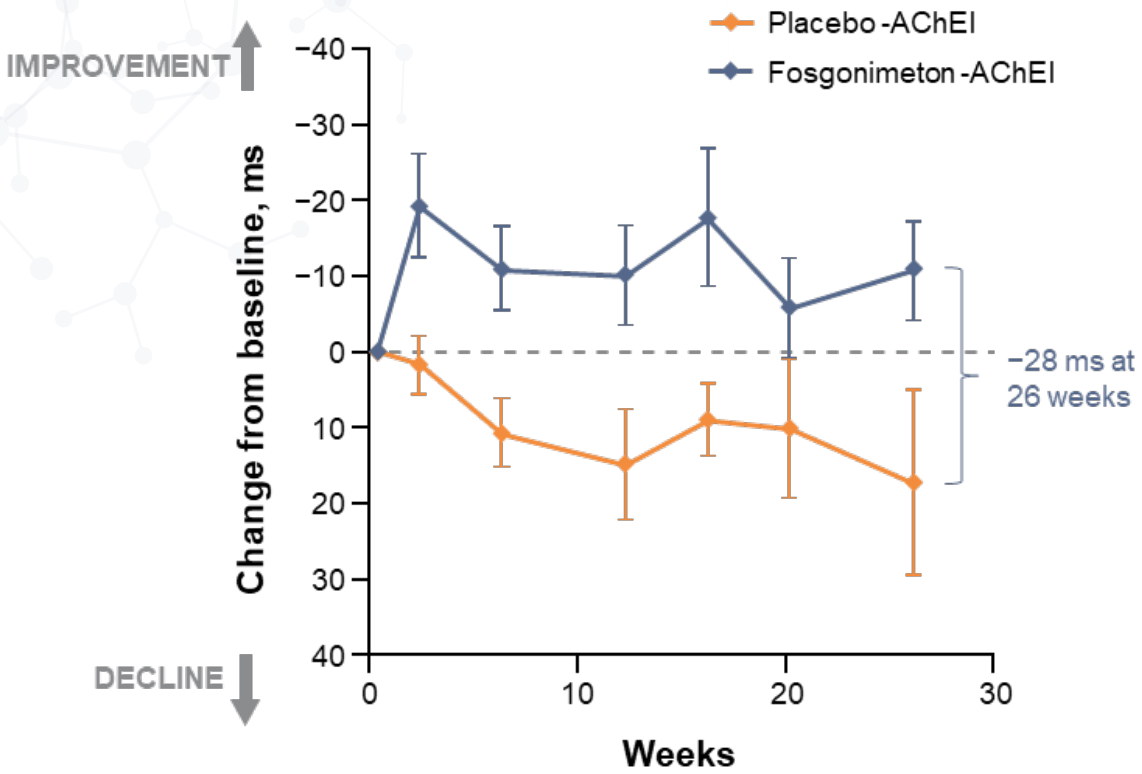
COWAT, Controlled Oral Word Association Test.

Apparent difference by background therapy status



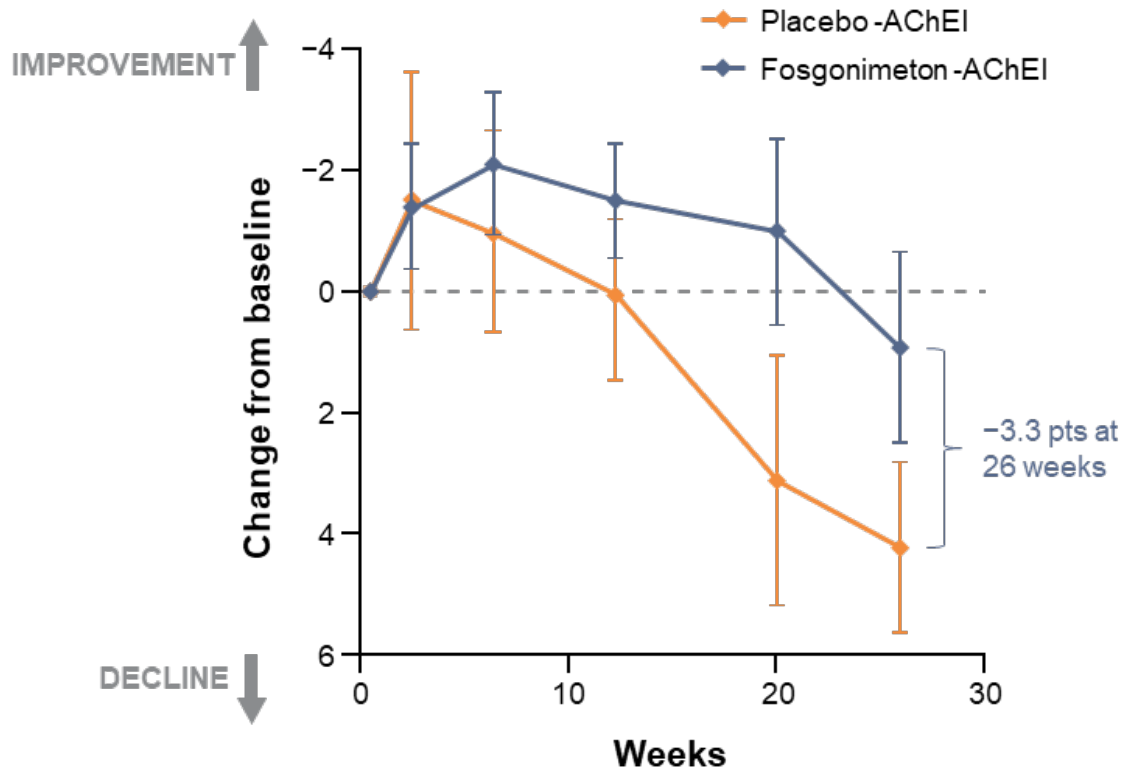
Congruent directional change (n.s.) in P300 latency and ADAS-Cog11 with fosgonimeton vs. placebo, -AChEI population

ERP P300 latency



n at each visit	W2	W6	W12	W16	W20	W26
Placebo	8	8	6	6	7	6
Fosgonimeton	20	19	18	15	16	17

ADAS-Cog11



n at each visit	W2	W6	W12	W20	W26
Placebo	8	8	7	7	6
Fosgonimeton	20	20	18	17	18

mITT population. Data presented as unadjusted mean ± SEM.
W, week

Athira PHARMA

Current observations and conclusions

- Phase 2 ACT-AD provided insights to inform conduct of the larger LIFT-AD trial
- Baseline P300 latency was imbalanced across 3 parallel arms with limited numbers of patients
- Primary endpoint P300 latency was not statistically significant by mITT, MMRM analysis
- Potential drug-drug interaction between fosgonimeton and cholinergic therapy was unexpected and appears to impact protocoled study outcomes

Fosgonimeton was well tolerated, with a **favorable safety** profile over 26 weeks' double-blind treatment

Fosgonimeton may have **potential benefit as monotherapy**,
with congruent directional changes in ERP P300 and ADAS-Cog11

Acknowledgments

Athira Pharma thanks the patients and caregivers who participated in clinical trials of fosgonimeton.

This presentation was developed with medical writing and editorial support from Katie Henderson, PhD, and Eileen McIver, PhD, of ApotheCom (San Francisco, CA), and was sponsored by Athira Pharma.

ACT-AD was sponsored and designed by Athira Pharma.

The ACT-AD trial is supported by a grant from the National Institute on Aging of the National Institutes of Health under Award Number R01AG06268. The information presented in this presentation is solely the responsibility of Athira and does not necessarily represent the official views of the National Institutes of Health.

- For more information about fosgonimeton and the Athira pipeline, please visit our other presentations at AAIC
  - Poster 65874: Fosgonimeton, a novel, small-molecule positive modulator of the HGF/MET system, is neuroprotective in primary neuron culture
  - Poster 63440: Development of stable, orally bioavailable small-molecule positive modulators of HGF/MET signaling for the treatment of cognitive impairment
  - Featured research symposium (August 4, 8:00-9:15am PT): Integrative systems biology of Alzheimer's disease
- A plain language summary of this presentation is available online

Athira PHARMA