Phase 2 Drug Development for Alzheimer's Disease: Athira Pharma

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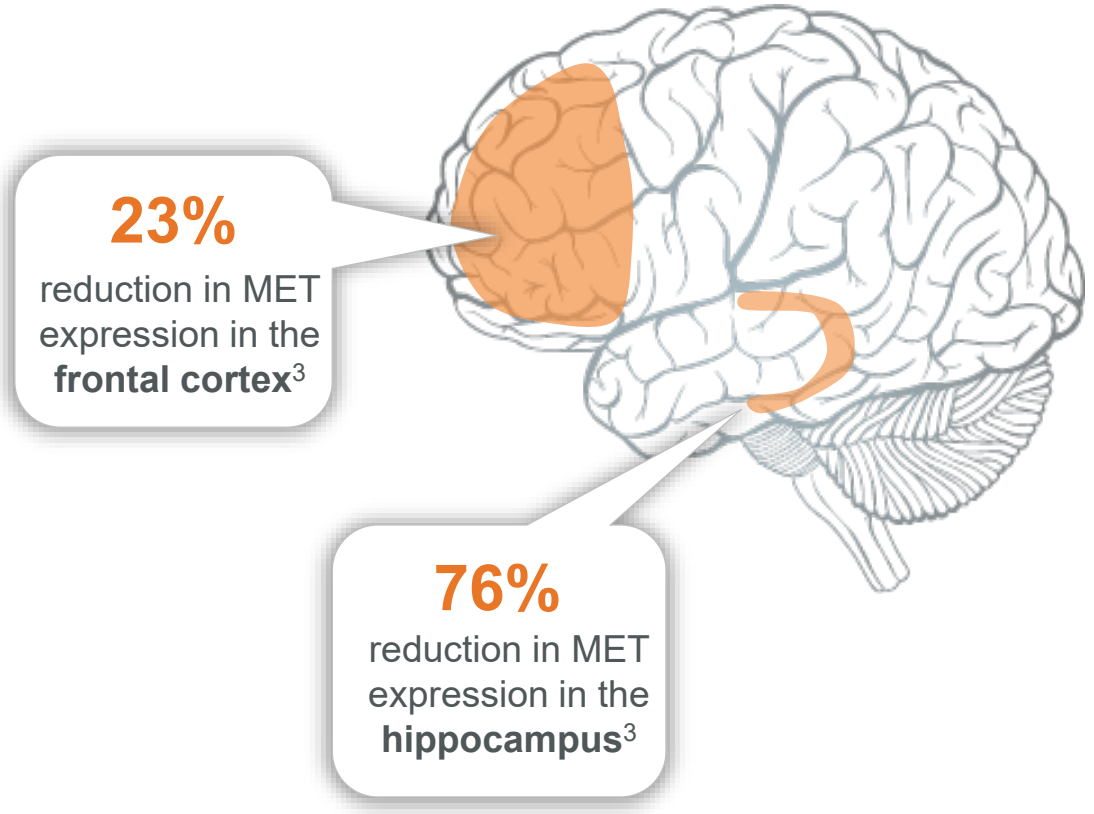
The HGF/MET pathway has not yet been leveraged in neurodegeneration

- The HGF/MET pathway is essential for **brain development and homeostasis**[1]
- In patients with AD, MET is downregulated in the frontal cortex and hippocampus[2,3]

Reduction in MET expression in AD



AD, Alzheimer's disease; HGF, hepatocyte growth factor.

1. Desole C et al. *Front Cell Dev Biol*. 2021;9:683609. 2. Hamasaki H et al. *Neuropathology*. 2014;34:284-290. 3. Hokama M et al. *Cereb Cort*. 2014;24:2476-2488.

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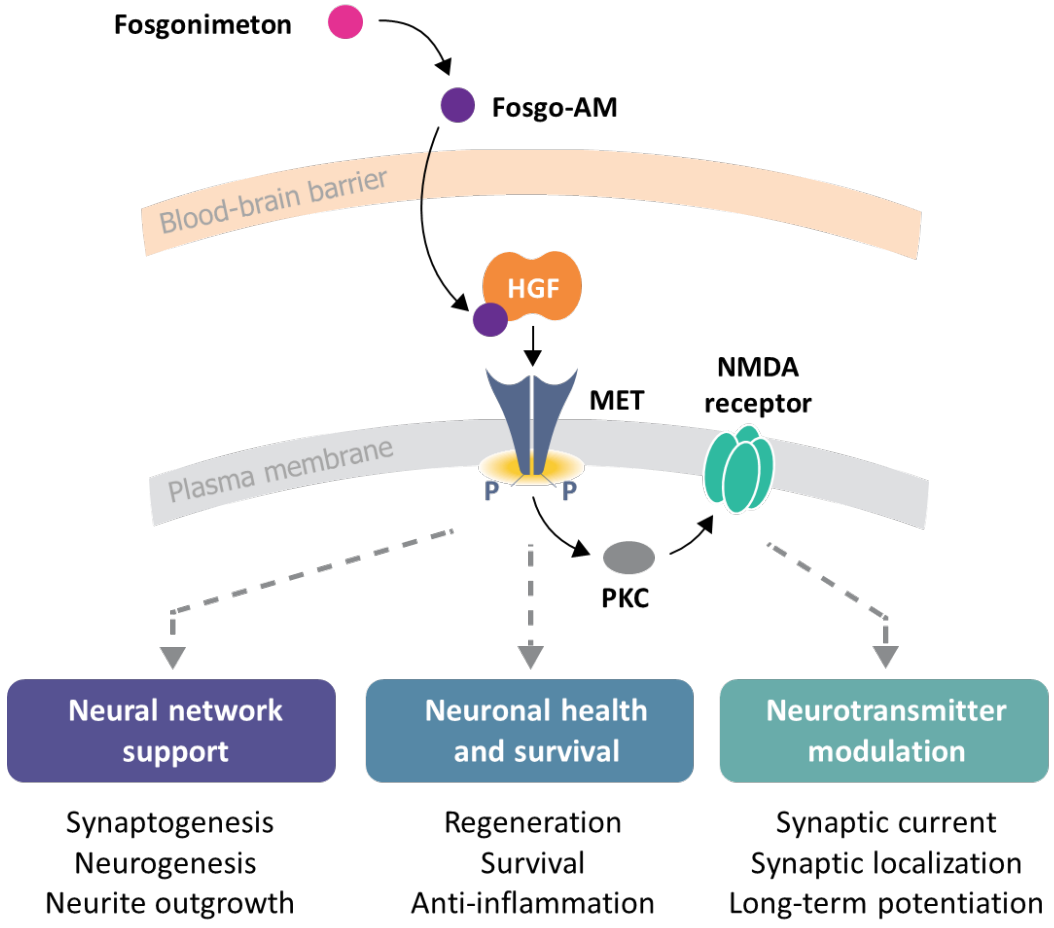
Fosgonimeton has a novel, multimodal mechanism of action

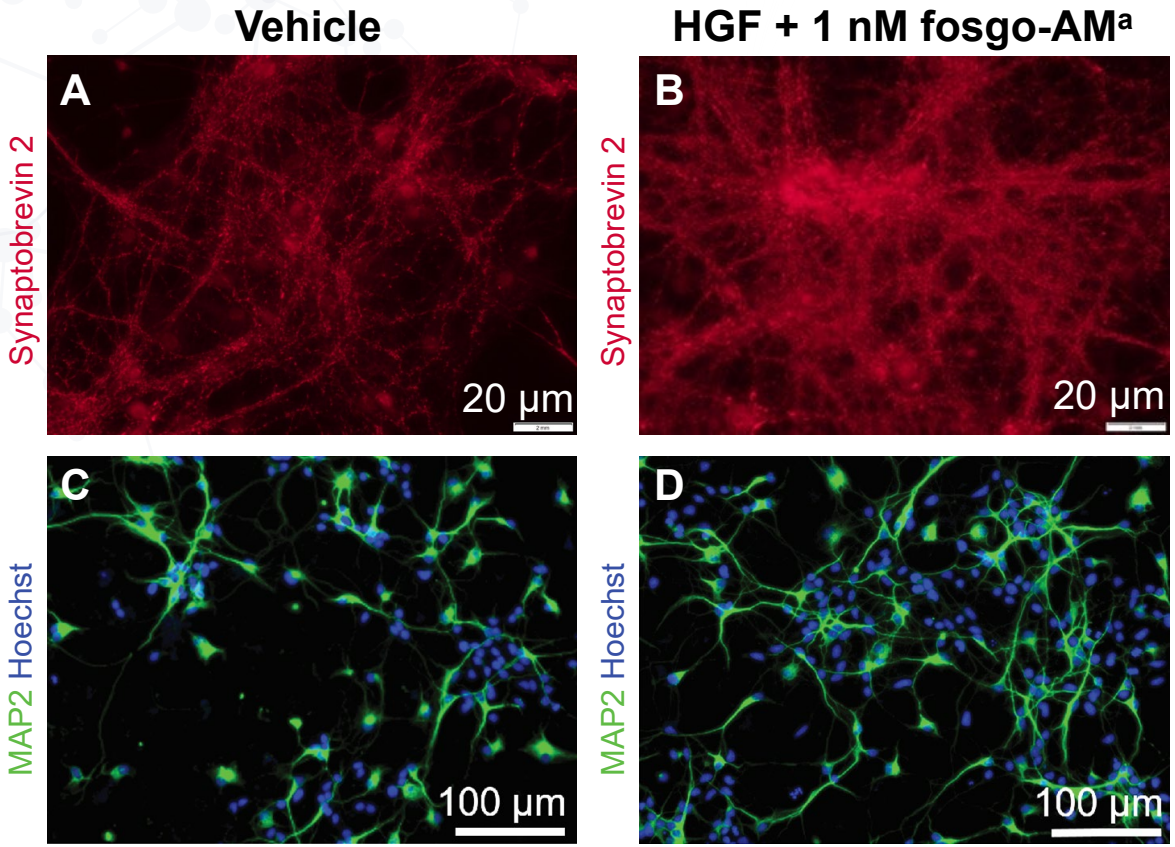
- Rapidly converts in plasma to a brain-penetrant active metabolite (fosgo-AM)
- Small-molecule **positive modulator** of the HGF/MET pathway
- Downstream **neuroprotective** and **neurotrophic** effects
- Promotes **synaptogenesis**
- In preclinical studies, fosgo-AM restored neuronal health and protected against neurodegeneration (poster 65874)[1]



Fosgo-AM, active metabolite of fosgonimeton; HGF, hepatocyte growth factor; NMDA receptor, *N*-methyl-D-aspartate receptor; P, phosphorylation; PKC, protein kinase C.

1. Reda S et al. Poster presented at: Alzheimer's Association International Conference (AAIC 2022); July 31-August 3, 2022; San Diego, CA.

Fosgonimeton enhanced synaptogenesis and neurite outgrowth, and provided neuroprotection[1]



- A, B: In primary cultures, the **number of synapses and synaptic strength** (relative abundance of presynaptic vesicles per synapse) were significantly increased with fosgo-AM
- C, D: **Neurite outgrowth** was significantly increased after exposure to fosgo-AM

Fosgo-AM also protected cells against neurotoxic insults: LPS, H_2O_2, glutamate, and MPP^+ (data not shown)

Fosgo-AM, active metabolite of fosgonimeton; H_2O_2, hydrogen peroxide; HGF, hepatocyte growth factor; LPS, lipopolysaccharide; MAP2, microtubule-associated protein 2; MPP+, 1-methyl-4-phenylpryidinium.

[a]HGF alone was also assessed and did not show statistically significant effects on synaptogenesis or neurite outgrowth.

1. Reda S et al. Poster presented at: Alzheimer's Association International Conference (AAIC 2022); July 31-August 3, 2022; San Diego, CA.

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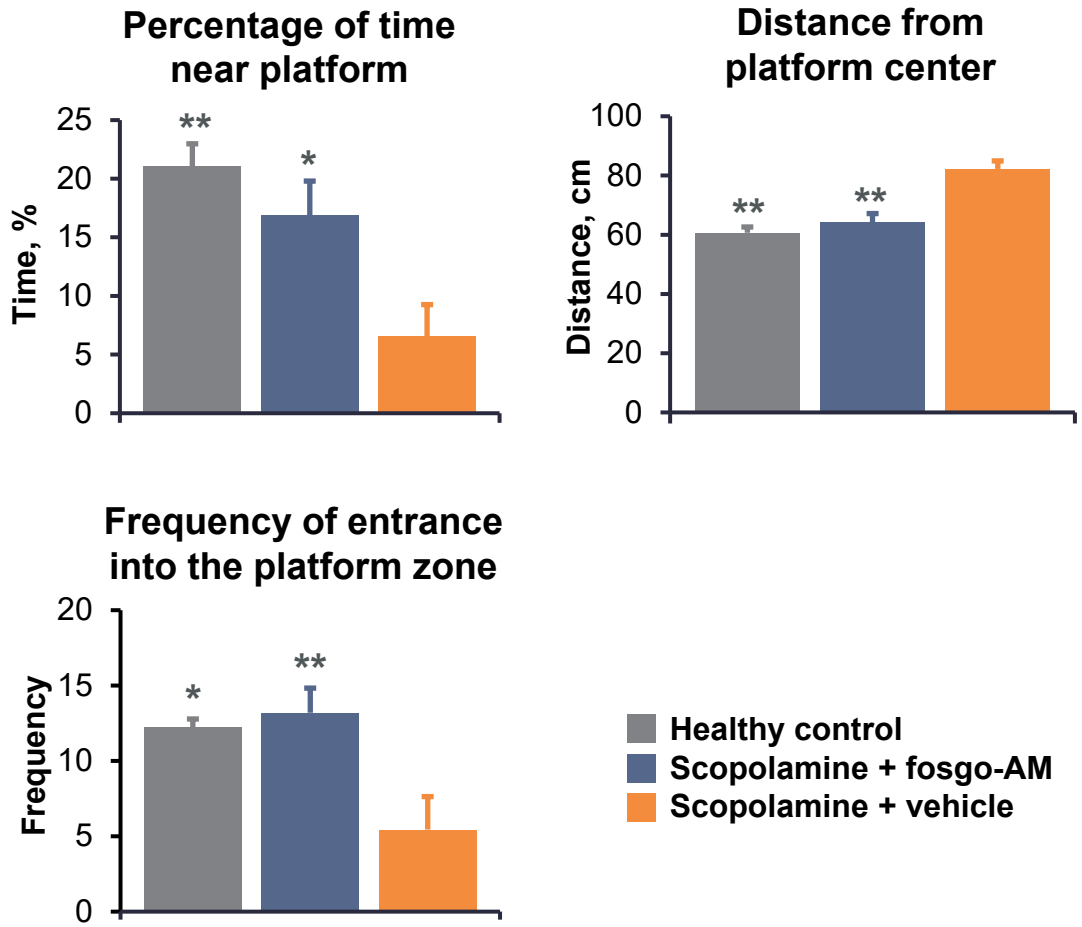
Fosgonimeton prevented spatial memory deficits[1]

- Healthy control animals (**gray**) quickly located a hidden platform in the Morris water maze
- Treatment with a cholinergic antagonist, scopolamine, led to spatial memory deficits (**orange**)
- When administered 40 minutes before scopolamine, treatment with **fosgo-AM prevented this memory deficit** (**blue**)



ANOVA, analysis of variance; fosgo-AM, active metabolite of fosgonimeton; SEM, standard error of the mean.
Data presented are mean ± SEM. Data collected during the probe trials were analyzed using 1-way ANOVA with Bonferroni post hoc tests compared with scopolamine + vehicle controls.
*$P < 0.05$, ** $P < 0.01$.

1. Taylor R et al. Poster presented at: Alzheimer's Association International Conference (AAIC 2022); July 31-August 3, 2022; San Diego, CA.

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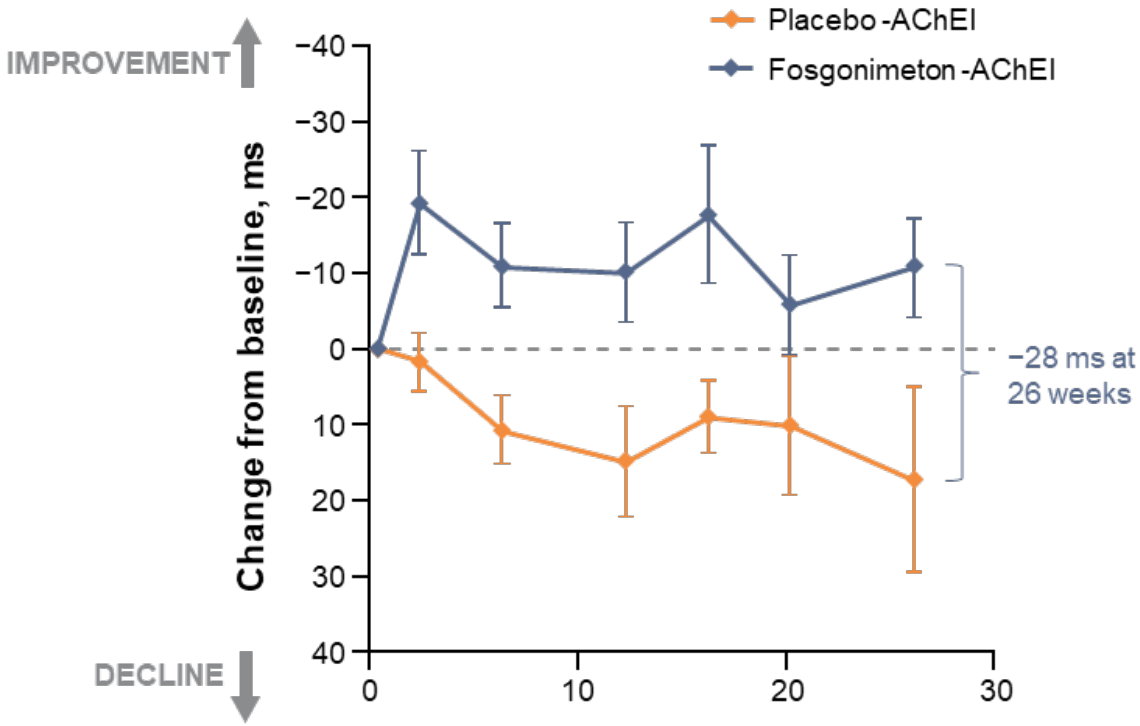
ACT-AD was the first interventional, double-blind, 26-week trial of fosgonimeton

- First results from phase 2 ACT-AD presented at AAIC (presentation 61572)
- Fosgonimeton had a favorable safety profile, with few CNS-specific AEs

In the monotherapy group:

- Primary endpoint ERP P300 latency showed a directional change favoring fosgonimeton over placebo
- Fosgonimeton monotherapy showed congruent descriptive benefit (ADAS-Cog11, ADCS-ADL23)

ERP P300 latency



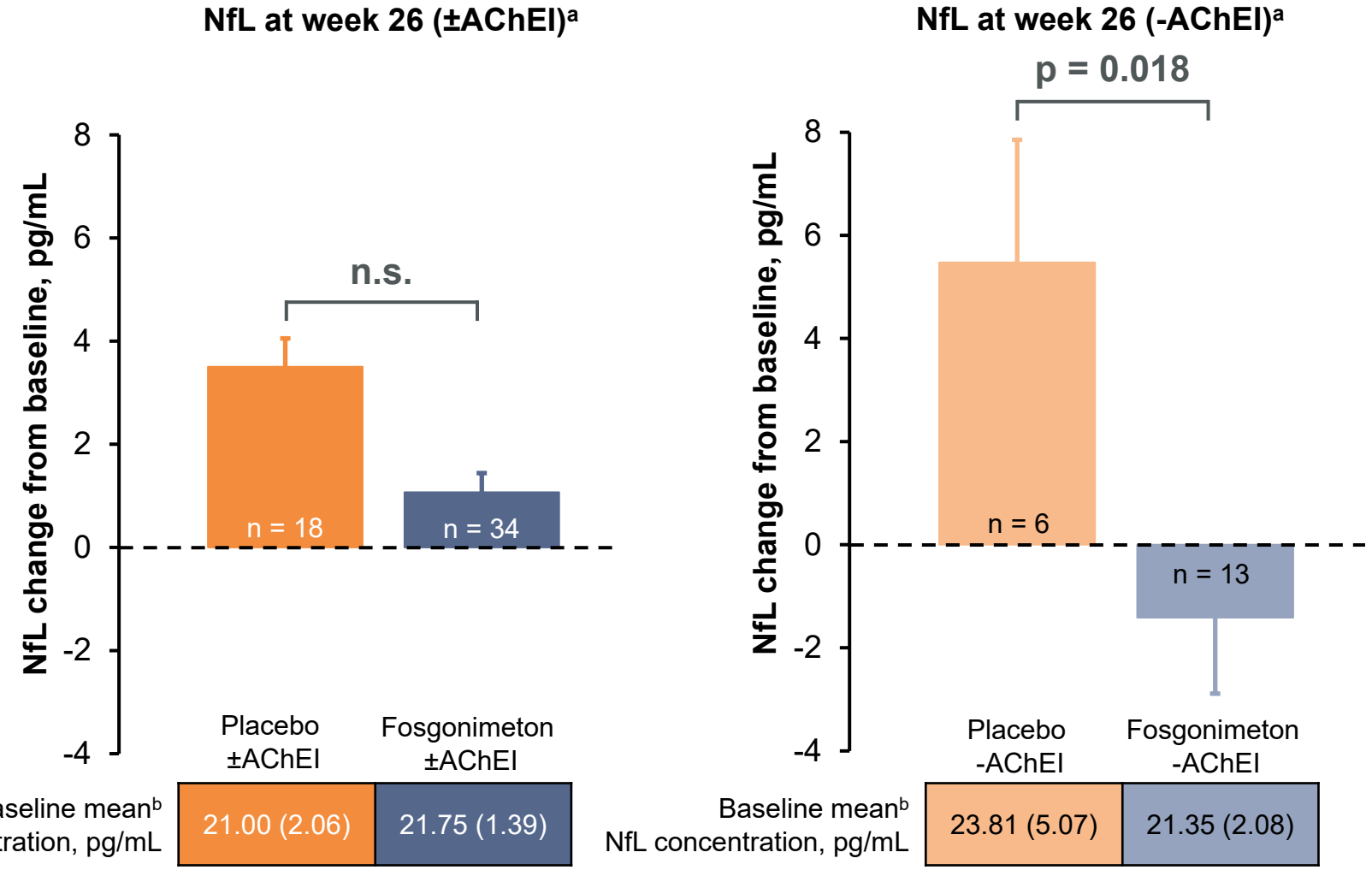
n at each visit	W2	W6	W12	W16	W20	W26
Placebo	8	8	6	6	7	6
Fosgonimeton	20	19	18	15	16	17

AChEI, acetylcholinesterase inhibitor; ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL23, Alzheimer's Disease Cooperative Study Activities of Daily Living Scales; AEs, adverse events; CNS, central nervous system; ERP, event-related potential.

Data presented are mean ± SEM. 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.

NfL biomarker analysis supported descriptive benefits

- Neurofilament light chain (NfL) is a validated fluid biomarker that measures ongoing neurodegeneration (CSF or plasma)
- Analysis of NfL levels showed improvements with fosgonimeton monotherapy from baseline to week 26
- Additional fluid biomarker analyses are ongoing



CSF, cerebrospinal fluid; NfL, neurofilament light chain; SE, standard error; SEM, standard error of the mean.
[a]Data presented are least squares mean ± SE. [b]Data shown as mean NfL concentration (SEM).
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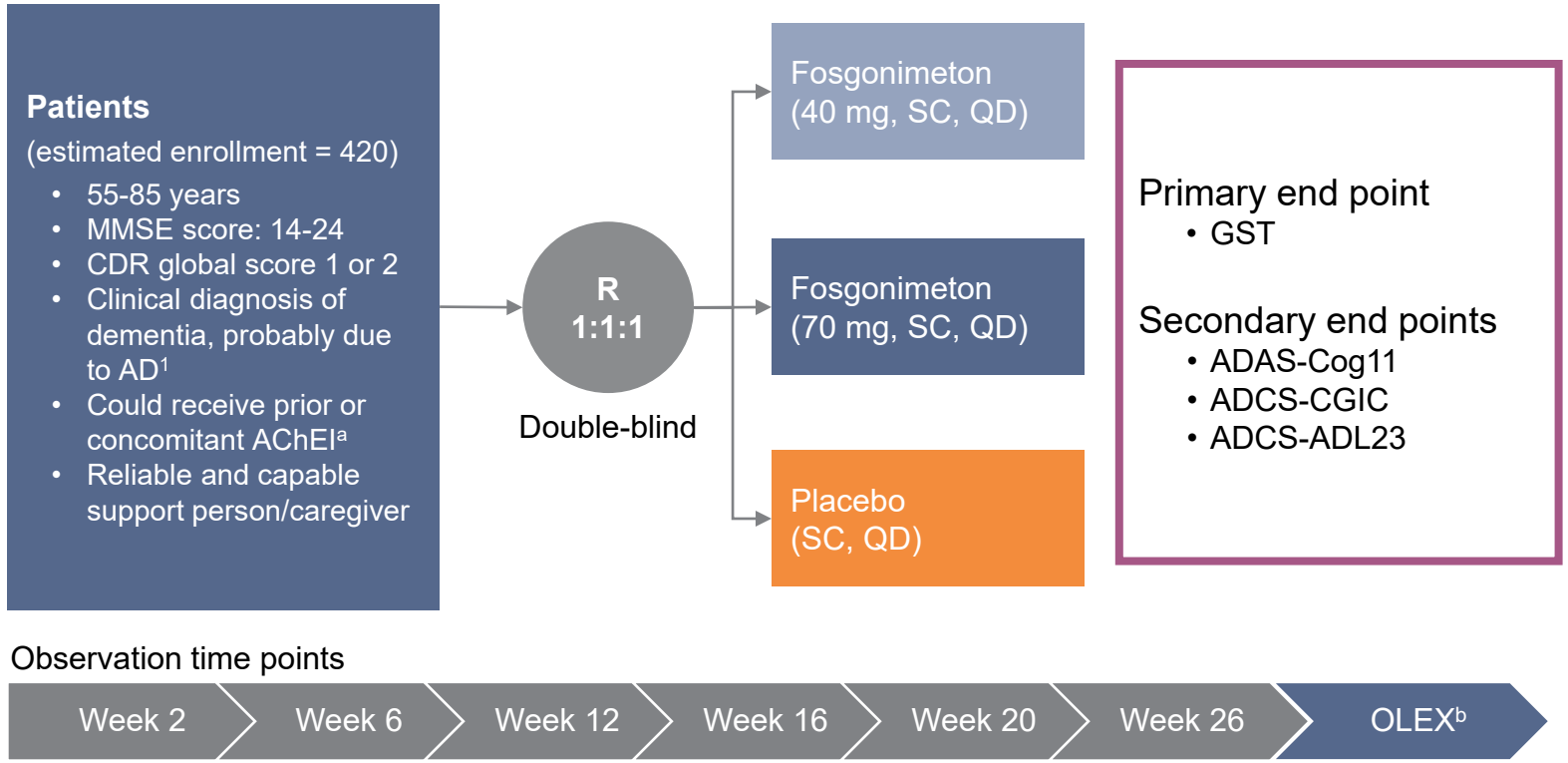
ACT-AD readout was timed to inform LIFT-AD

- Ongoing late-stage trial (NCT04488419)
- >300 patients recruited
- No drug-related SAEs; 20% early termination rate
- 90% transition to the open-label extension (OLEX)



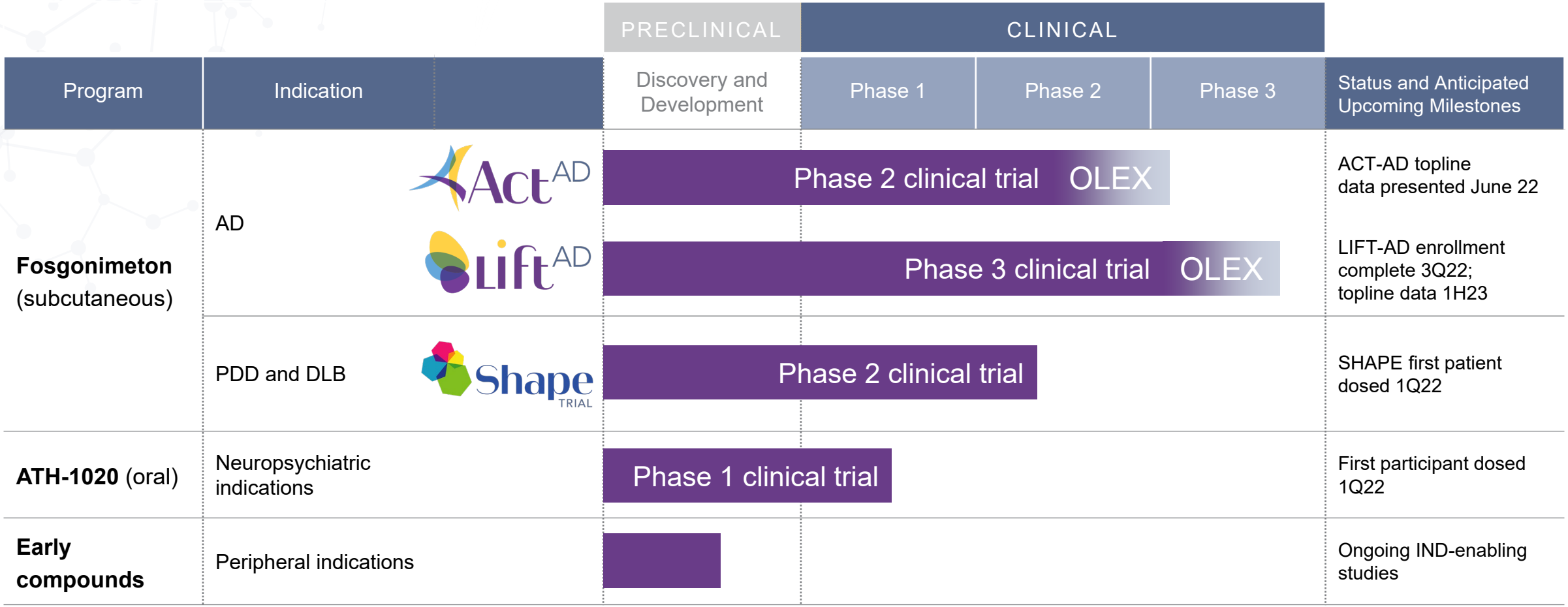
AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-CGIC, Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change; ADCS-ADL23, Alzheimer's Disease Cooperative Study–Activities of Daily Living; CDR, clinical dementia rating; GST, global statistical test; MMSE, mini-mental state examination; OLEX, open-label extension; QD, once daily; R, randomization; SAEs, serious adverse events; SC, subcutaneous.

[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 26 weeks, with the goal of assessing long-term safety.

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

Athira pipeline leverages the HGF/MET pathway in neurodegenerative diseases



1H23, first half 2023; 1Q22, first quarter 2022; 3Q22, third quarter 2022; AD, Alzheimer's disease; DLB, dementia with Lewy bodies; HGF, hepatocyte growth factor; IND, investigational new drug; OLEX, open-label extension; PDD, Parkinson's disease dementia.

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Thank you!