Fosgonimeton in Mild-to-Moderate Alzheimer's Disease; Efficacy and Safety from the LIFT-AD Trial

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Clinical Trials on Alzheimer's Disease (CTAD) – 17th Annual Conference
Madrid, Spain, and Online
October 29 – Nov 1, 2024

Disclosures

- Anton Porsteinsson reports receiving payment of honoraria from ONO Pharmaceuticals, Eisai, Biogen, IQVIA, WebMD, Lundbeck, Otsuka, Acadia, Functional Neuromodulation, Xenon Pharmaceuticals, Novartis, Cognitive Research Corporation, BMS, Alector, Eli Lilly, Genentech/Roche, Cassava, and Vaccinex

- Kevin J Church, Javier San Martin, and Simon Daggett are employees and stockholders of Athira Pharma, Inc.

- Len B Walt is a former consultant to Athira Pharma, Inc.

- Michael D Hale is a former employee and current stockholder of Athira Pharma, Inc.

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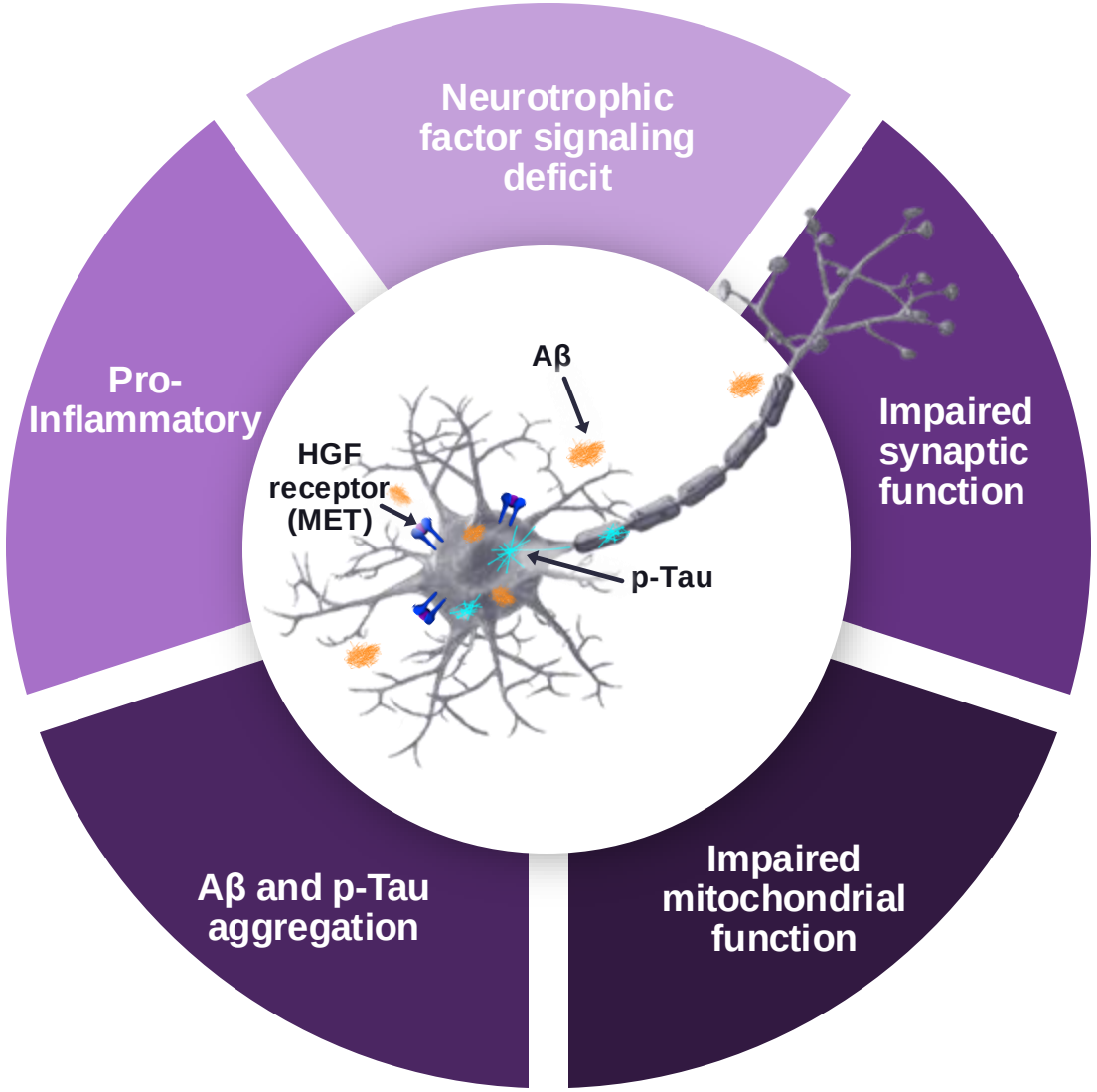
The Pathophysiology of Alzheimer's Disease is Multifactorial and Leads to Neurodegeneration and Dementia



RESULTING NEURODEGENERATION

Loss of network connectivity

Neuronal death

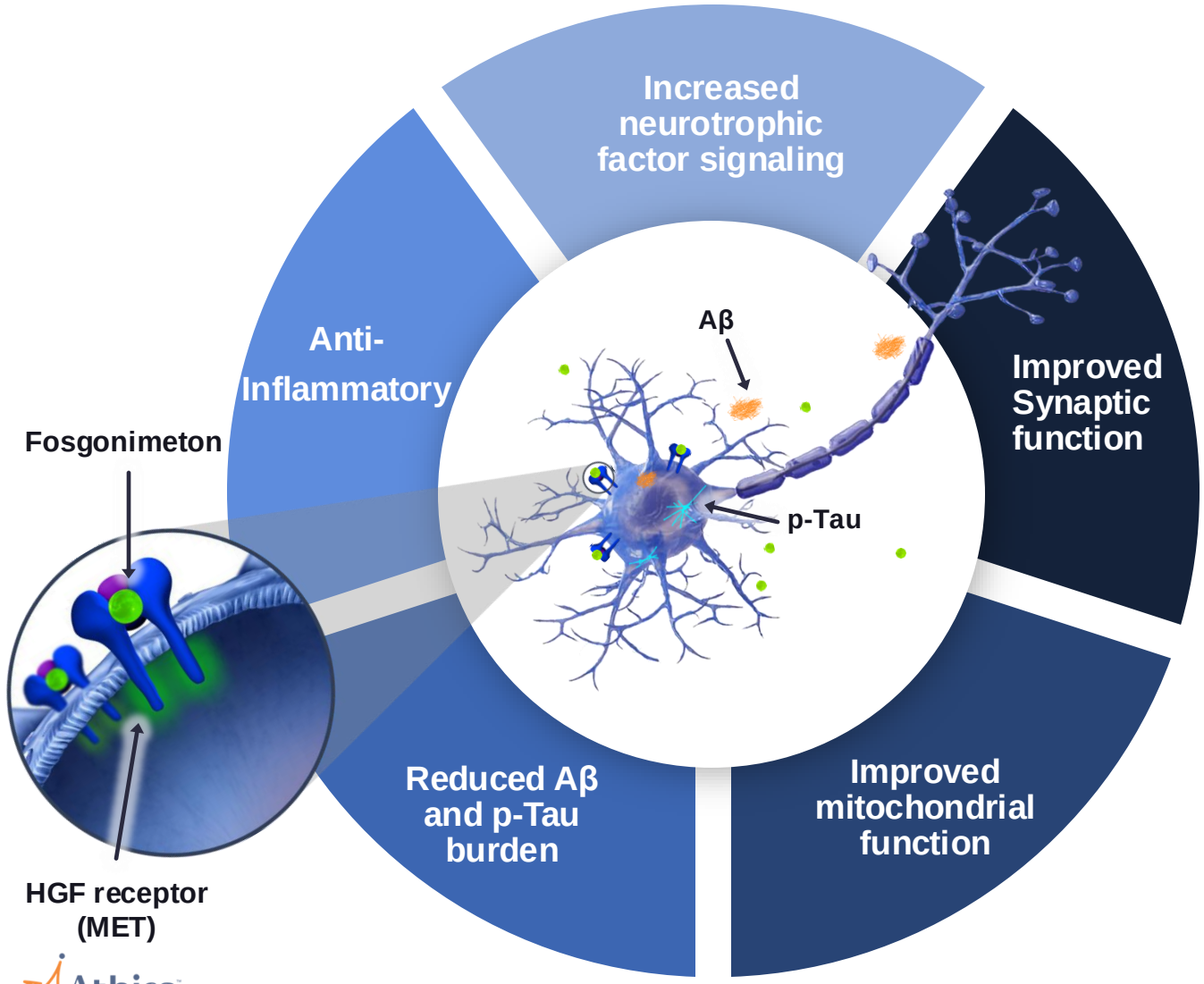
Brain atrophy

Cognitive decline

Loss of independence

Aβ, amyloid beta; AD, Alzheimer's disease; HGF, hepatocyte growth factor; p-Tau, phosphorylated tau

Fosgonimeton Positively Modulates the Neurotrophic Hepatocyte Growth Factor System to Prevent Neurodegeneration and Preserve Neuronal Health



GOAL OF TREATMENT

Increased neuronal survival

Preserved network connectivity

Improved cognitive function

Aβ, amyloid beta; AD, Alzheimer's disease; p-Tau, phosphorylated tau

LIFT-AD Timelines and Major Amendments

- Study initiated
- 1:1:1 (placebo, fosgonimeton 40 mg or 70 mg)
- AChEI not excluded

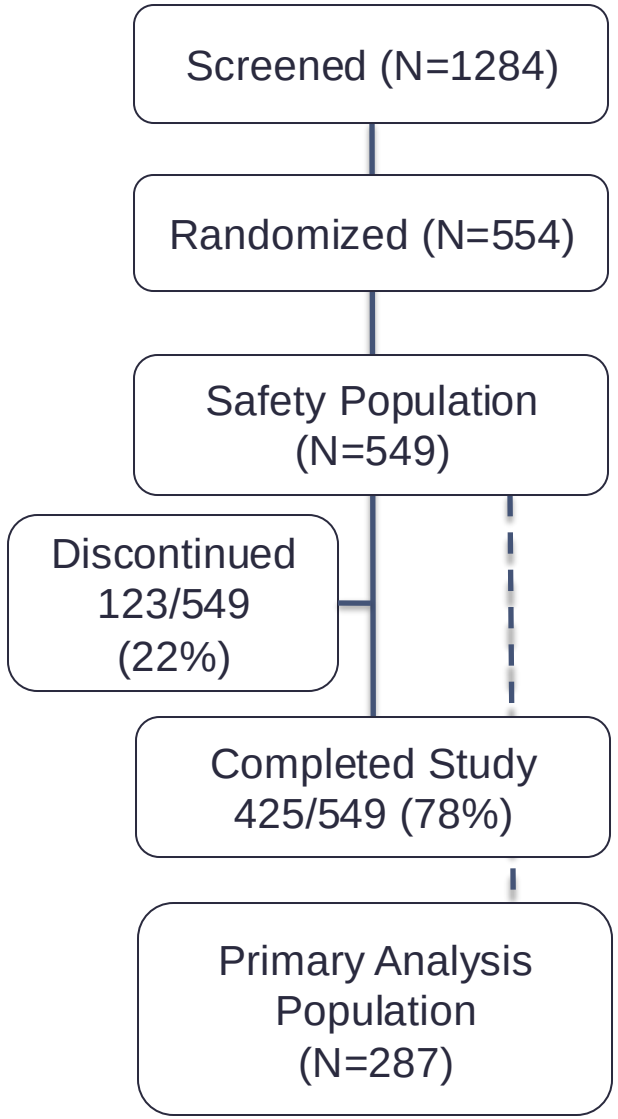
- **70 mg dose discontinued**
- 40 mg dose selected (better tolerability)

2020 | 2021 | 2022 | 2023 | 2024

- **Excluded concomitant AChEI use** (4 weeks prior to Screening)
- Interim analysis independently assessed 100 patients without AChEI
- **Sample size reestimation** of patients without AChEI to 300

2024

- Study completed



AChEI, acetylcholinesterase inhibitor

LIFT-AD Study Design in Mild-to-Moderate Alzheimer's Disease

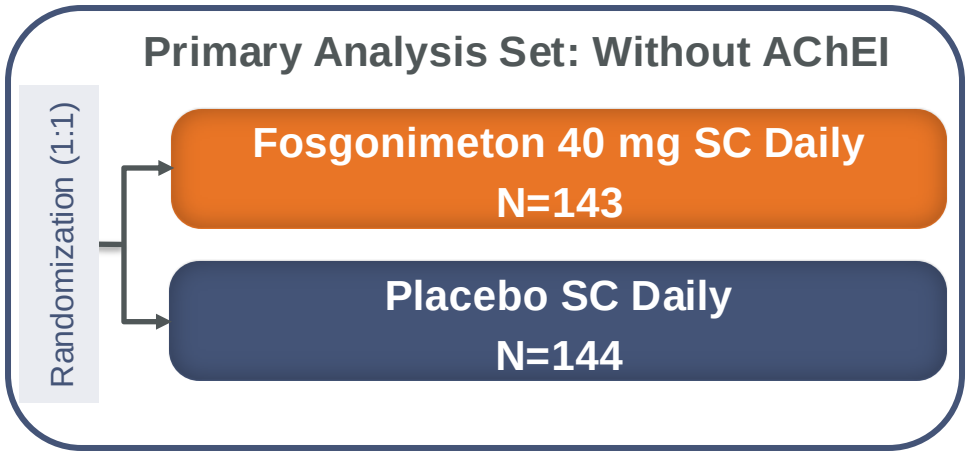
Randomized, Double-blind, Placebo-controlled, 26-week Trial

KEY INCLUSION CRITERIA

- 55-88 years of age
- Clinical diagnosis of probable AD
- Mild-to-moderate dementia
  - MMSE score of 14-24
  - CDR global score of 1 or 2

ANALYSIS POPULATION

- **Primary analysis**: 312 enrolled 287 evaluable participants without concomitant AChEI
- **Safety analysis**: 549 participants



ENDPOINTS

PRIMARY

- Global Statistical Test Score - composite of ADAS-Cog11 and ADCS-ADL23
- Safety

SECONDARY

- ADAS-Cog11
- ADCS-ADL23
- Plasma NfL

EXPLORATORY PLASMA BIOMARKERS

- Aβ42/40, p-Tau181, p-Tau217, and GFAP

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; CDR, clinical dementia rating; GFAP, glial fibrillary acidic protein; MMSE, Mini Mental State Examination; NfL, neurofilament light chain; p-Tau, phosphorylated tau; Aβ, Amyloid-ß; SC, subcutaneous

Baseline Characteristics and Demographics Are Well Balanced

Characteristic	Primary Analysis Population (No Concomitant AChEI)	
	Placebo (N=144)	**Fosgonimeton 40 mg** (N=143)
Mean (SD) age, years	73.4 (7.1)	72.6 (6.9)
Female, n (%)	82 (56.9)	76 (53.1)
White, n (%)	118 (81.9)	116 (81.1)
APOE4 carriers, n (%)	74 (51.4)	74 (51.7)
Heterozygotes	59 (41.0)	59 (41.3)
Homozygotes	15 (10.4)	15 (10.5)
Concomitant AChEI, n (%)	0 (0)	0 (0)
Mean (SD) MMSE Score	19.3 (3.4)	19.9 (3.5)
MMSE ≥20 (mild), n (%)	74 (51.4)	81 (56.6)
MMSE <20 (moderate), n (%)	70 (48.6)	61 (42.7)
CDR Global Score, n (%)		
0.5	1 (0.7)	1 (0.7)
1	123 (85.4)	122 (85.3)
2	19 (13.2)	20 (14.0)
Mean (SD) ADAS-Cog 11	22.3 (7.6)	20.7 (7.8)
Mean (SD) ADCS-ADL23	62.3 (10.0)	62.5 (9.9)
Mean (SD) NfL, pg/mL	27.7 (16.4)	26.3 (25.5)
Mean (SD) pTau217, pg/mL	1.0 (0.6)	0.8 (0.8)

AChEI, acetylcholinesterase inhibitor; ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL23, Alzheimer's Disease Cooperative Study–Activities of Daily Living; CDR, clinical dementia rating; MMSE, Mini Mental State Examination; NfL, neurofilament light chain; APOE, Apolipoprotein E; SD, standard deviation

Summary of Primary and Secondary Endpoints

Primary and secondary endpoints did not reach statistical significance

Measure (Direction of Improvement)	**LS Mean Change (SE) [a] from Baseline at Week 26** (Primary Analysis Population)		
	Placebo (N=144)	**Fosgonimeton 40 mg** (N=143)	**Difference vs Placebo** (N=287)
GST ↓	-0.13 (0.07)	-0.21 (0.07)	-0.08 (0.10) p=0.70
ADAS-Cog11 ↓	-0.39 (0.54)	-1.09 (0.56)	-0.70 (0.77) p=0.35
ADCS-ADL23 ↑	-0.02 (0.65)	0.65 (0.67)	0.67 (0.92) p=0.61
NfL (pg/mL) ↓	2.95 (2.49)	-0.96 (2.48)	-3.91 (3.46) p=0.26*

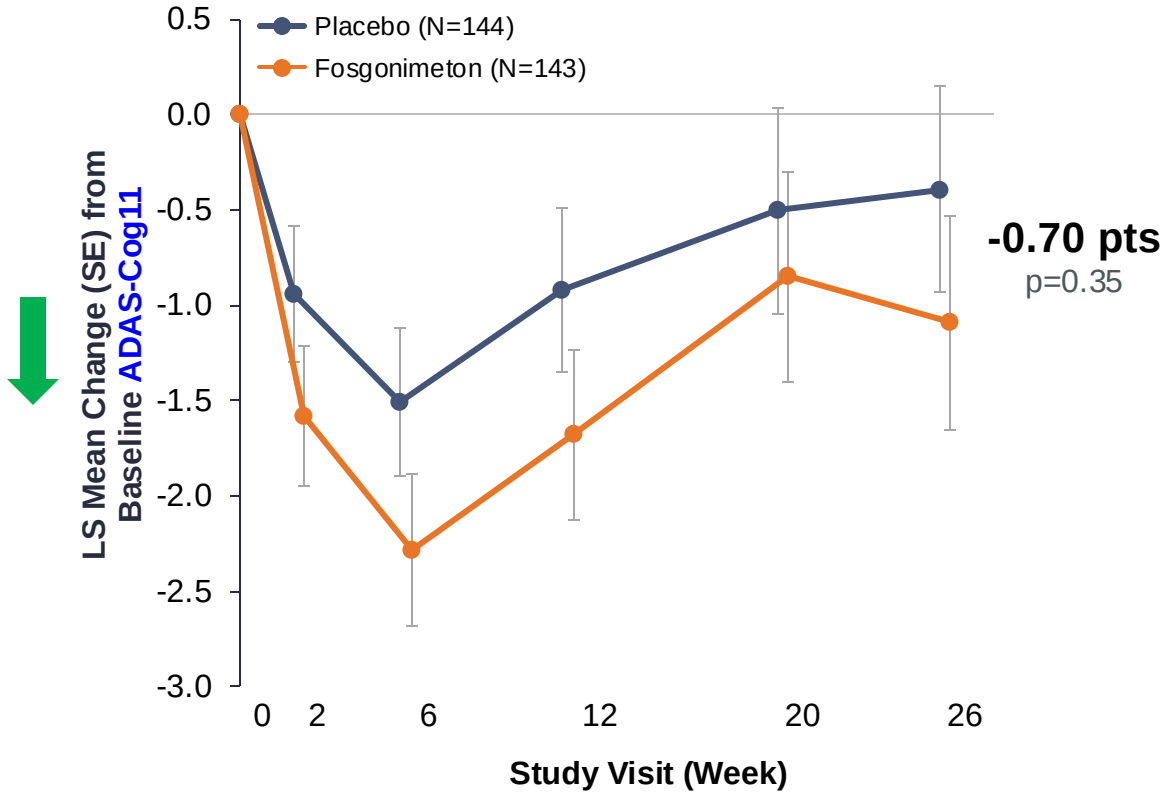
GST, global statistical test score; ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL23, Alzheimer's Disease Cooperative Study–Activities of Daily Living; NfL, neurofilament light chain; LS mean, least squares mean; SE, standard error

[a] Estimates from MMRM analysis

*Weighted model p-value not reported due to lack of model convergence; Non-weighted analysis p-value shown

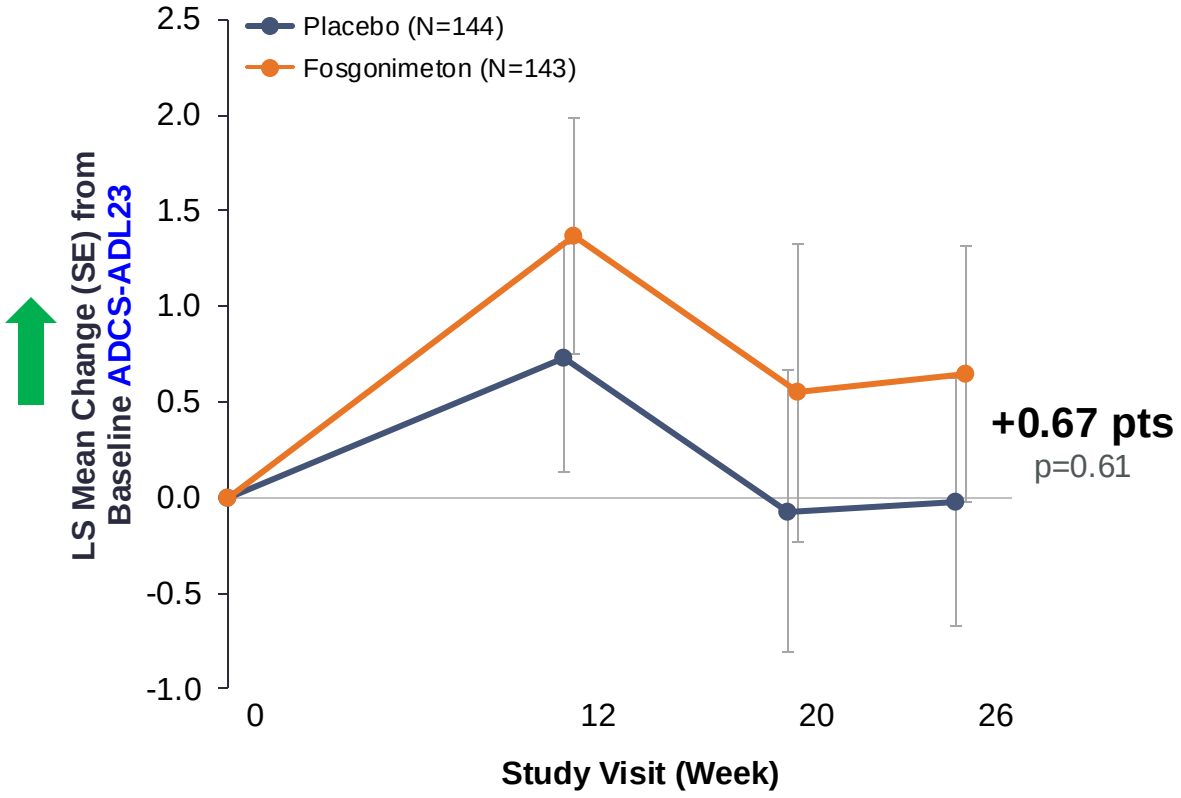
Changes in Cognition and Activities of Daily Living Over Time

ADAS-Cog11



	Placebo (N=144)	Fosgonimeton (N=143)
Baseline, Mean (SD)	22.3 (7.6)	20.7 (7.8)
CFB at Week 26, Mean (SE)	-0.39 (0.54)	-1.09 (0.56)

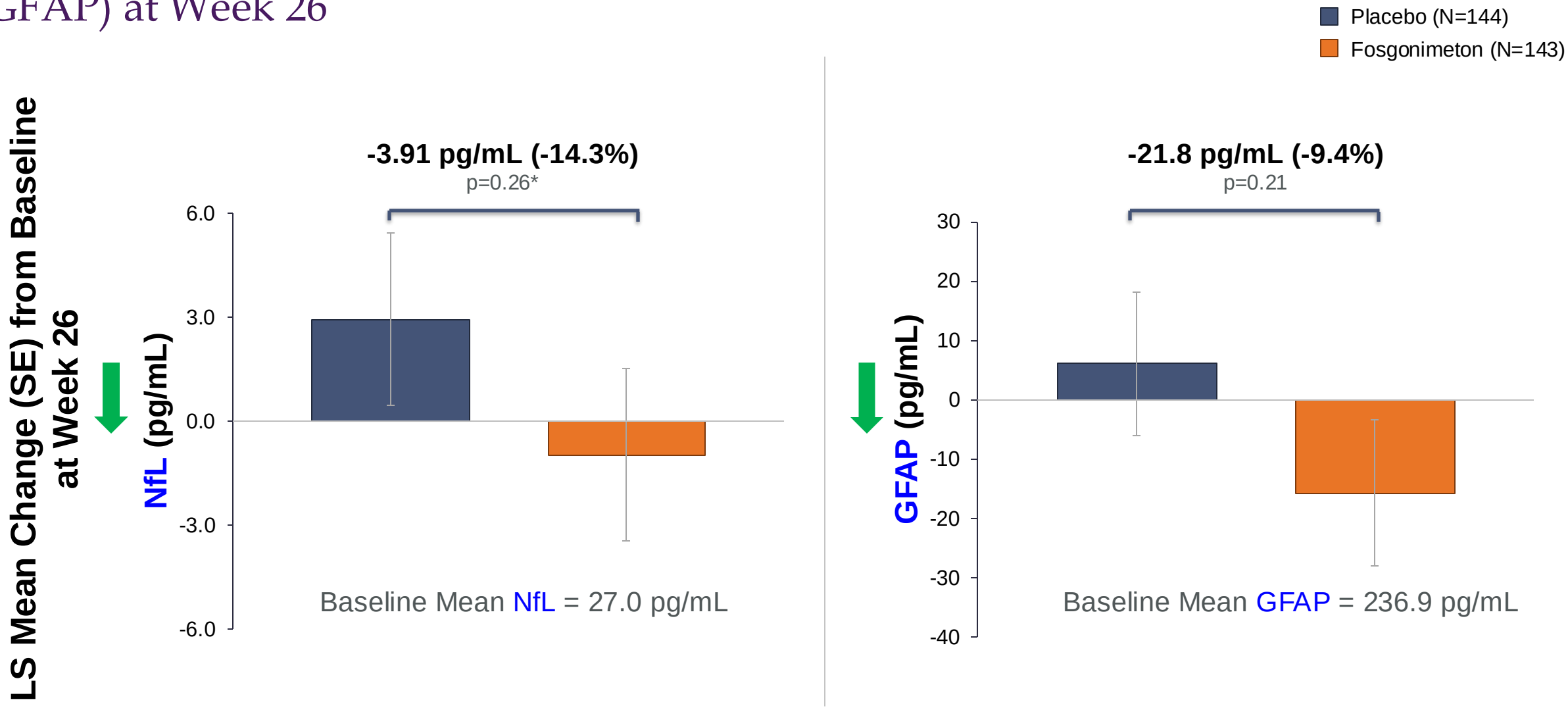
ADCS-ADL23



	Placebo (N=144)	Fosgonimeton (N=143)
Baseline, Mean (SD)	62.3 (10.0)	62.5 (9.9)
CFB at Week 26, Mean (SE)	-0.02 (0.65)	0.65 (0.67)

ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL23, Alzheimer's Disease Cooperative Study–Activities of Daily Living; CFB, change from baseline; LS mean, least squares mean; SE, standard error; SD, standard deviation

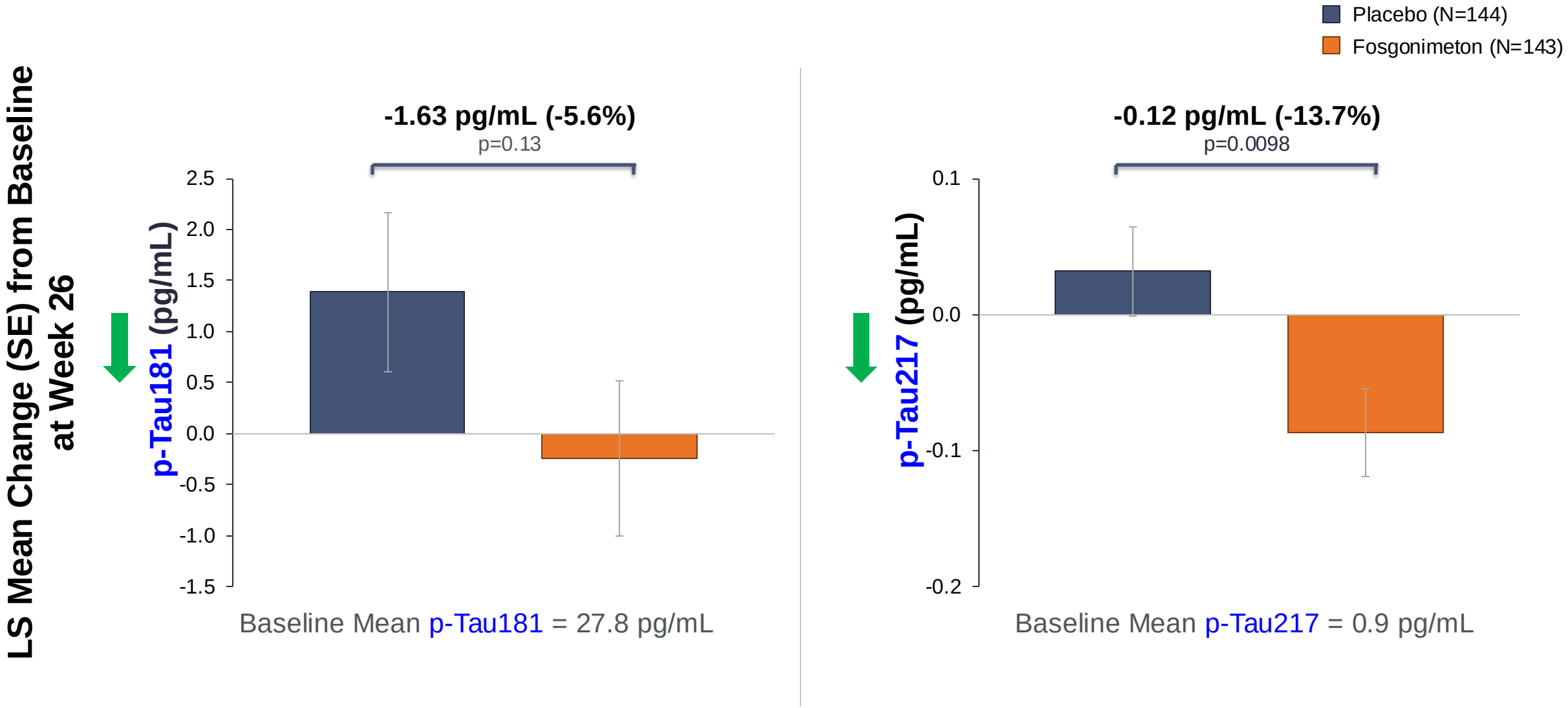
Changes in Plasma Biomarkers of Neurodegeneration (NfL) and Neuroinflammation (GFAP) at Week 26



NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; Aβ, Amyloid-β; LS mean, least squares mean; SE, standard error

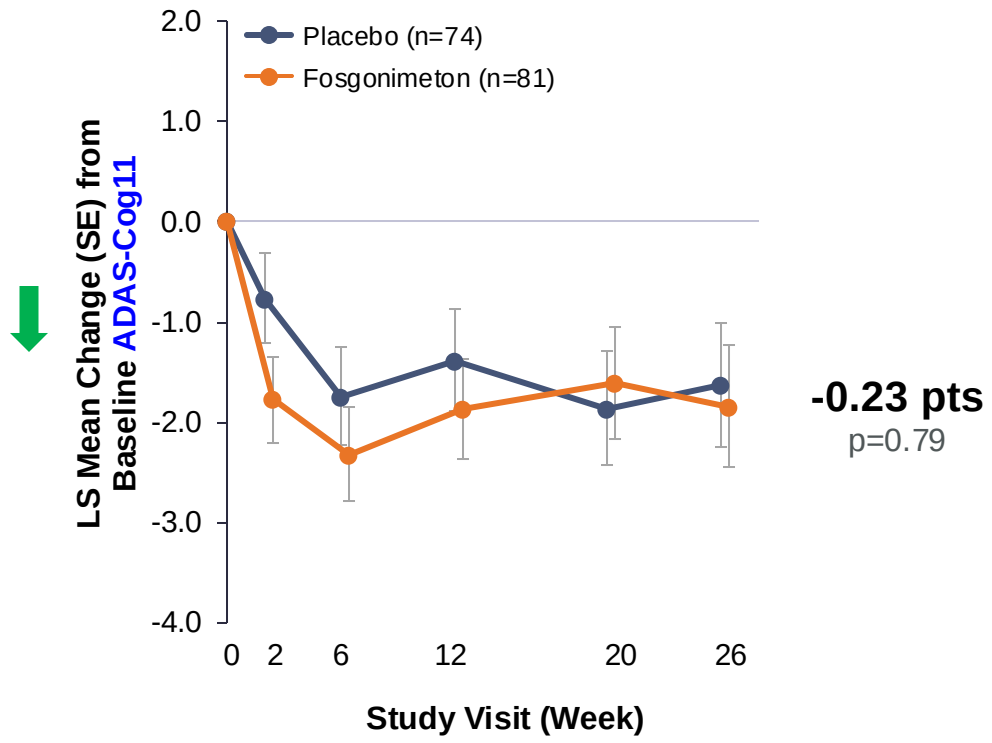
**Weighted model p-value not reported due to lack of model convergence; Non-weighted analysis p-value = 0.26*

Changes in Plasma Biomarkers of Protein Pathology (p-Tau) at Week 26



Changes in Cognition in Mild and Moderate Alzheimer's Disease by MMSE Over Time

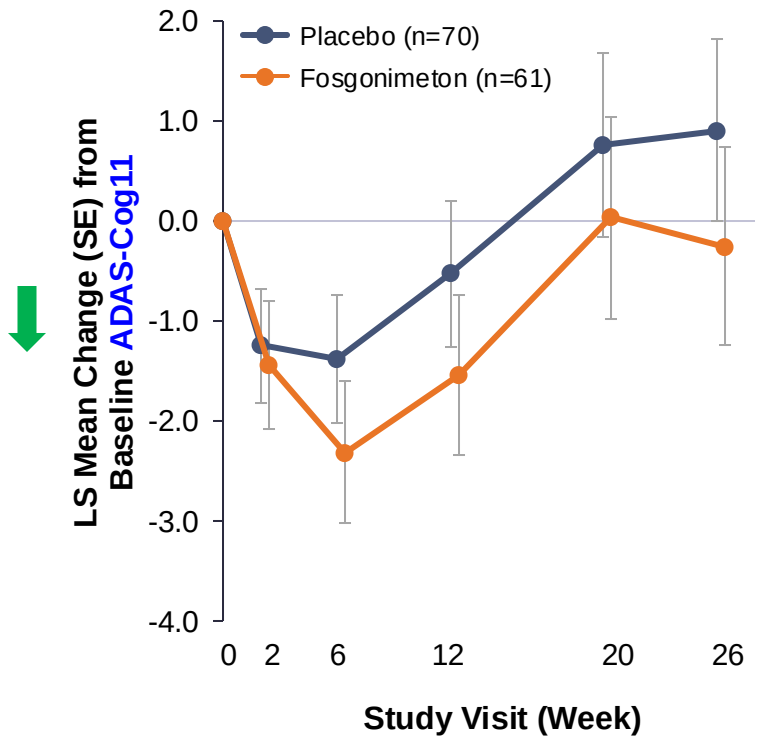
Mild Baseline MMSE (20 – 24)



-0.23 pts
p=0.79

Baseline Mean ADAS-Cog11 = 18

Moderate Baseline MMSE (14 – 19)



-1.16 pts
p=0.39

Baseline Mean ADAS-Cog11 = 25

ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE, Mini Mental State Examination; LS mean, least squares mean; SE, standard error

Summary of Treatment-Emergent Adverse Events (Safety Analysis Population)

Subject Incidence, n (%)	Placebo (N=218)	Fosgonimeton 40 mg (N=224)	Fosgonimeton 70 mg (N=107)
Any AE	136 (62.4)	177 (79.0)	94 (87.9)
TEAEs	132 (60.6)	175 (78.1)	94 (87.9)
TEAEs occurring in ≥ 4% in any group			
Injection site reactions HLT	31 (14.2)	128 (57.1)	78 (72.9)
Fall	9 (4.1)	10 (4.5)	5 (4.7)
COVID-19	12 (5.5)	10 (4.5)	2 (1.9)
Eosinophilia	0	16 (7.1)	8 (7.5)
Pruritus	4 (1.8)	10 (4.5)	6 (5.6)
Headache	9 (4.1)	6 (2.7)	3 (2.8)
Urinary tract infection	9 (4.1)	5 (2.2)	2 (1.9)
Treatment-related TEAEs	54 (24.8)	155 (69.2)	86 (80.4)
Serious TEAEs	15 (6.9)	11 (4.9)	3 (2.8)
Treatment-related serious TEAEs	0	3 (1.3)	2 (1.9)
TEAEs leading to study withdrawal	10 (4.6)	24 (10.7)	23 (21.5)
Deaths	0	0	0

AE, adverse event; HLT, high-level terms; TEAE, treatment-emergent adverse event
Most TEAE discontinuations were due to injection site reactions

Summary of LIFT-AD Trial Results

- LIFT-AD did not meet the primary endpoint (composite GST score) or its secondary endpoints
- All primary and secondary endpoints favored fosgonimeton but did not reach statistical significance
  - A larger effect size was seen with fosgonimeton in those with more severe cognitive impairment at baseline
  - All biomarkers of neurodegeneration, inflammation, and protein pathology consistently favored fosgonimeton
- Fosgonimeton was generally well tolerated with an acceptable safety profile
  - ISRs of mild-to-moderate severity were the most frequently reported related adverse events
- Potential limitations: 26-week study duration, milder-than expected population, lack of decline in the placebo group

The consistent directional improvement in clinical and biomarker endpoints in LIFT-AD suggests that positive modulation of HGF signaling may have a beneficial effect in neurodegenerative diseases

Acknowledgement

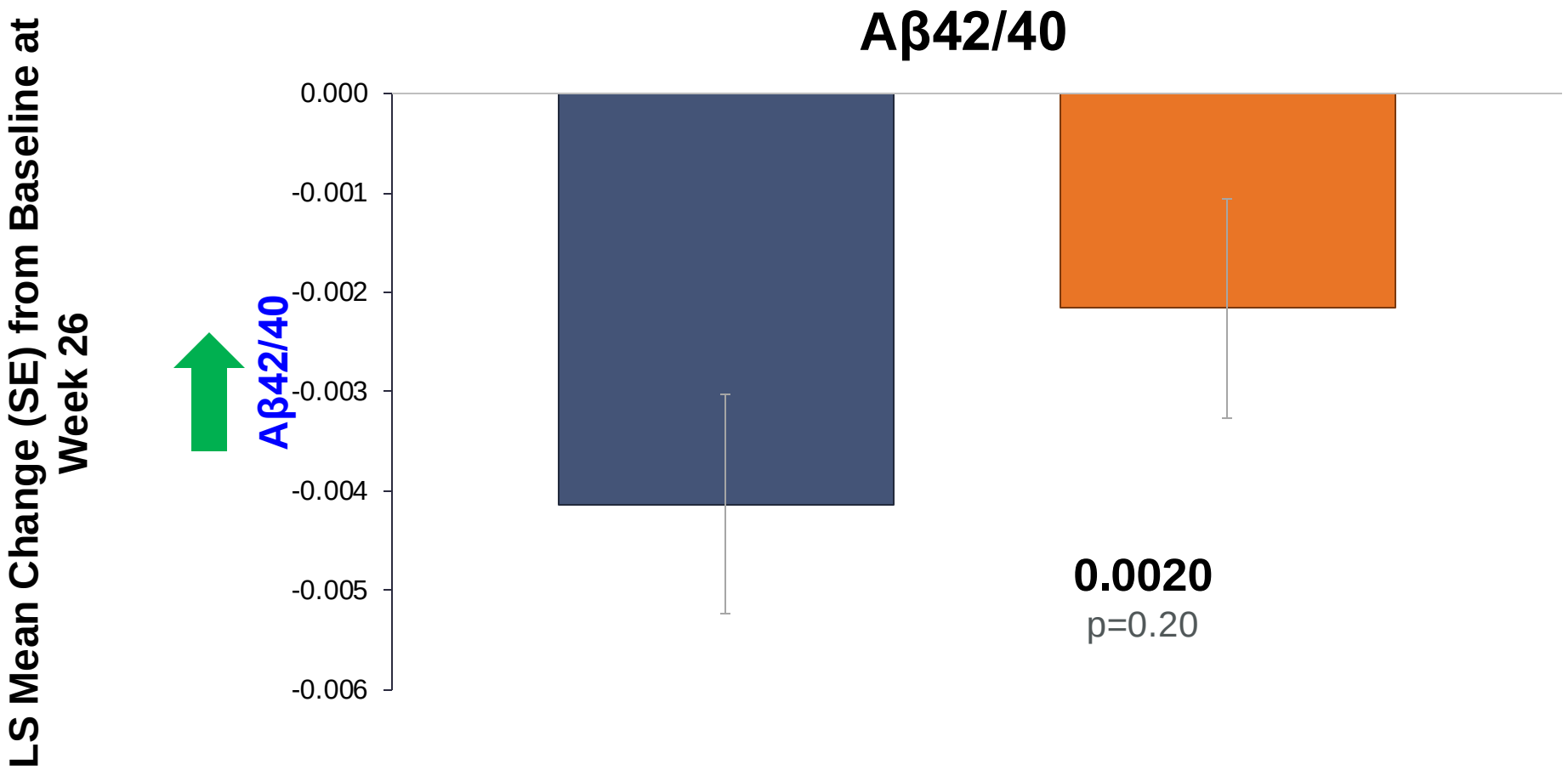
The authors and Athira would like to thank the following:

- Trial participants, their families, and caregivers
- Trial investigators and site staff
- Data monitoring committee
- Athira Pharma staff
- Clinical research organizations

Thank You

Appendix

Changes in Plasma Biomarkers of Protein Pathology (Aβ42/40) at Week 26



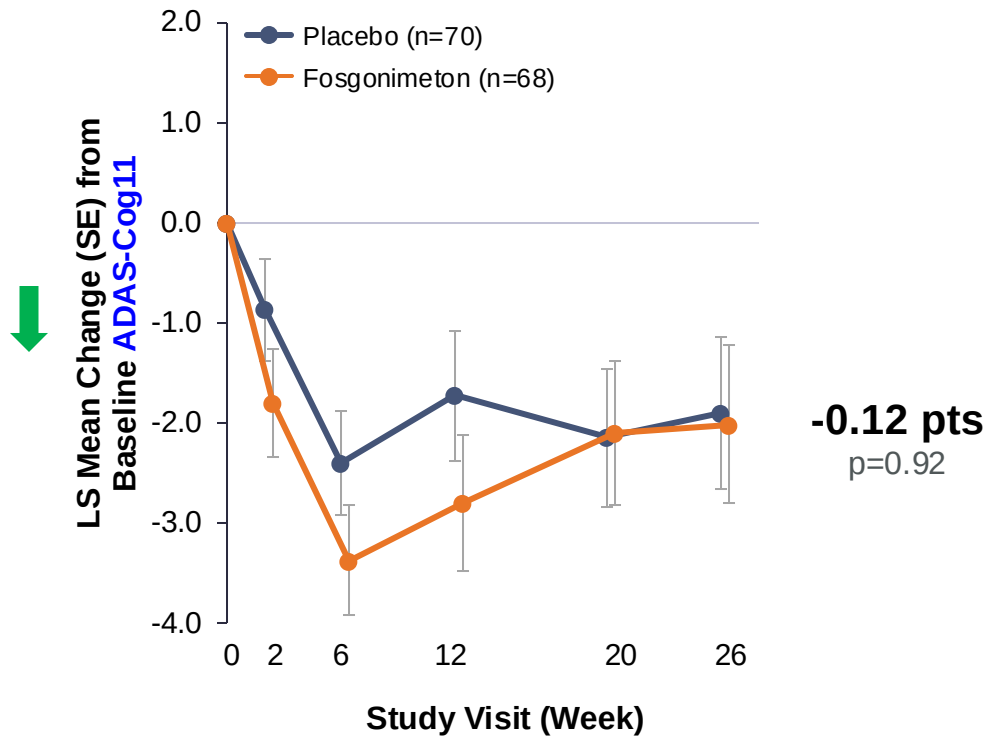
Baseline Characteristics of Subjects with More Severe vs Less Severe Cognitive Impairment (by Highest and Lowest ADAS-Cog11 Tertiles)

Characteristic	Less Severe Subgroup (Baseline ADAS-Cog11 ≤ 18)		More Severe Subgroup (Baseline ADAS-Cog11 ≥ 25)	
	Placebo (N=46)	Fosgonimeton 40 mg (N=59)	Placebo (N=52)	Fosgonimeton 40 mg (N=42)
Mean (SD) age, years	73.6 (6.6)	73.1 (6.7)	73.3 (7.8)	71.5 (7.9)
Mean (SD) MMSE Score	21.6 (2.2)	22.1 (2.7)	16.6 (3.0)	16.8 (2.7)
Mean (SD) ADAS-Cog 11	14.4 (3.1)	13.6 (3.3)	30.2 (5.6)	29.8 (5.9)
Mean (SD) ADCS-ADL23	64.7 (8.3)	65.4 (8.2)	58.5 (11.5)	57.8 (11.0)
Mean (SD) NfL, pg/mL	25.3 (11.8)	24.3 (13.8)	32.2 (22.3)	30.7 (40.8)
Mean (SD) GFAP, pg/mL	234 (112)	206 (103)	268 (104)	241 (162)
Mean (SD) pTau181, pg/mL	25.7 (12.7)	21.4 (9.7)	32.4 (13.9)	30.8 (18.4)
Mean (SD) pTau217, pg/mL	0.8 (0.6)	0.6 (0.4)	1.0 (0.5)	1.1 (1.1)

ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL23, Alzheimer's Disease Cooperative Study–Activities of Daily Living; GFAP, glial fibrillary acidic protein; MMSE, Mini Mental State Examination; NfL, neurofilament light chain; SD, standard deviation

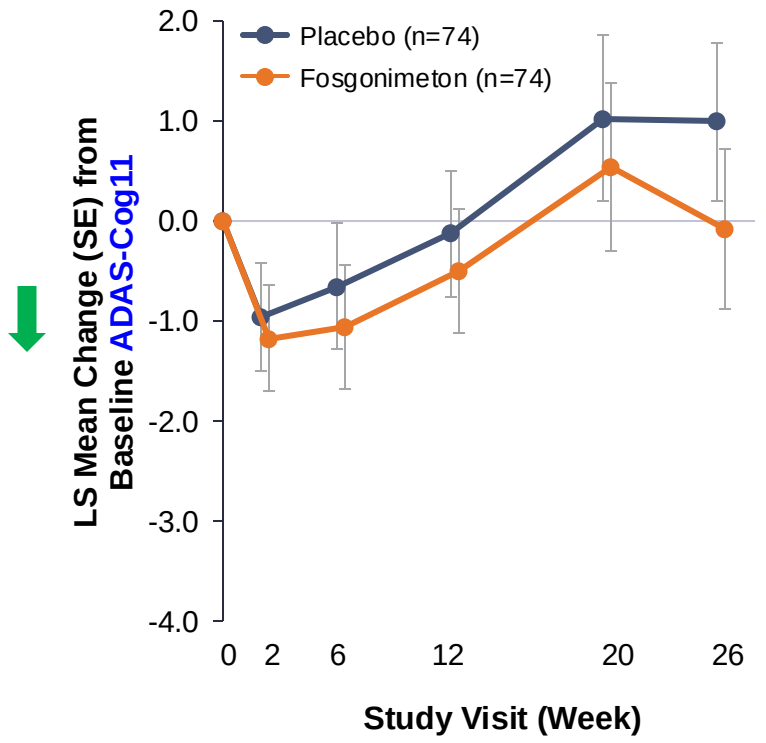
Change Over Time in Cognition Assessed by APOE4 Status

APOE4 Non-Carrier



-0.12 pts
p=0.92

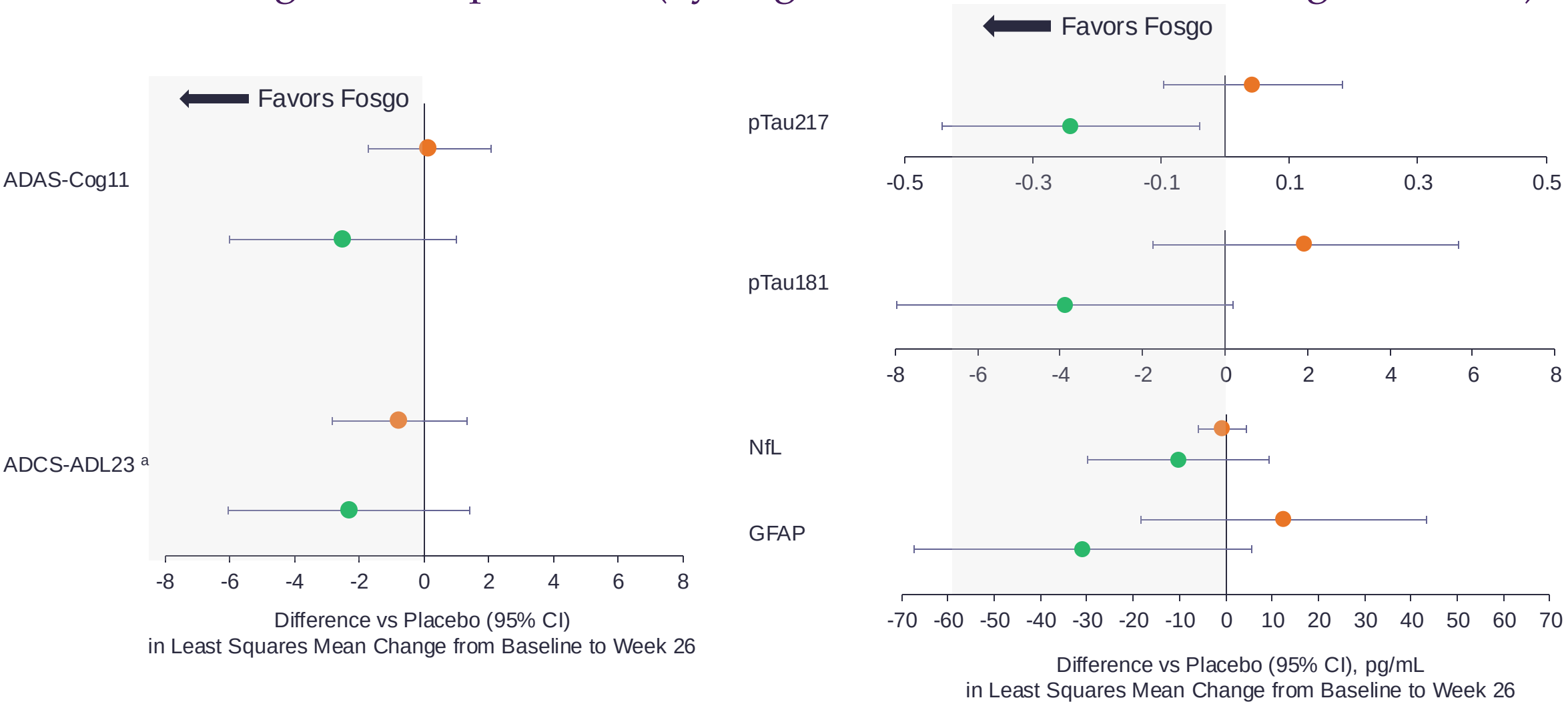
APOE4 Carrier



-1.07 pts
p=0.33

ADAS-Cog11, Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE, Mini Mental State Examination; APOE, Apolipoprotein E; LS mean, least squares mean; SE, standard error

Subgroup Analysis by ADAS-Cog11: Comparison of Subjects with More Severe vs Less Severe Cognitive Impairment (by Highest and Lowest ADAS-Cog11 Tertiles)

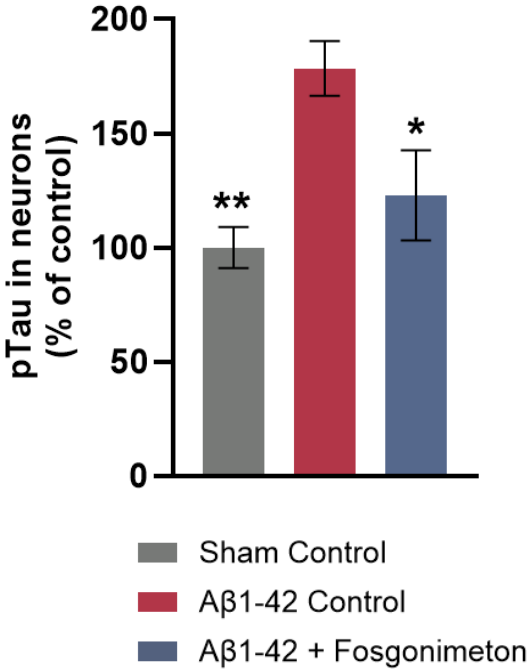


[a] ADCS-ADL23 scores multiplied by -1 to match direction of ADAS-Cog11

Preclinical Movement of Biomarkers

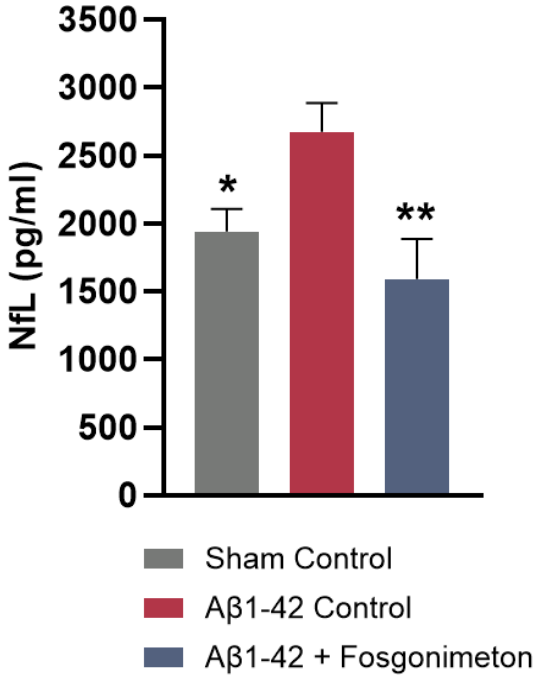
Protein pathology

P-Tau in Aβ1-42 aged mouse model



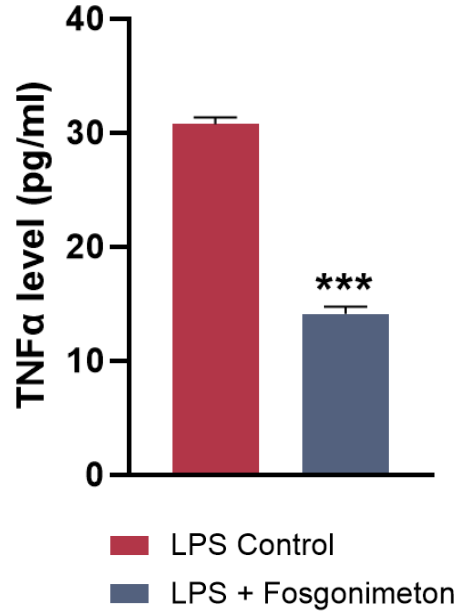
Neurodegeneration

NfL in Aβ1-42 aged mouse model



Neuroinflammation

TNF-α in brain homogenates from LPS mouse model



Aβ, amyloid-beta; LPS, lipopolysaccharide; NfL, neurofilament light chain; P-Tau, phospho-Tau 212/214; TNFα, tumor necrosis factor alpha

Protein pathology: P-Tau measured in hippocampal slices from intrahippocampal Aβ1-42 aged mouse model following 28-day fosgonimeton treatment One-way ANOVA with Fisher's LSD; *p<0.05, **p<0.01 vs. Aβ1-42 control; n = 12 mice per group mean + SEM.

Neurodegeneration: NfL measured in CSF from intrahippocampal Aβ1-42 aged mouse model following 28-day fosgonimeton treatment. One-way ANOVA with Fisher's LSD; *p< 0.05, **p<0.01 vs. Aβ1-42 control; n = 12 mice per group mean + SEM

Neuroinflammation: TNFα measured in brain homogenates 1.5h post LPS intraperitoneal administration. Fosgonimeton was administered 20 minute prior to LPS administration. One-way ANOVA with Dunnett's post-test; ***p<0.001 vs. LPS control; n = 10 mice per group mean + SEM