PROSPECT-ALZ: Results of the phase 2 study of ceperognastat, an orally available O-linked N-acetyl glucosaminidase inhibitor for the treatment of early symptomatic Alzheimer's disease

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DISCLOSURES

- Adam S. Fleisher, Leanne Munsie, Michele Mancini, Eden Yun-Ju Cheng, Sergey Shcherbinin, Tomomi Nakamura, William Kielbasa, Hugh Nuthall, Dustin Mergott, Mark Mintun, and Miroslaw Brys are employees and minor shareholders of Eli Lilly and Company

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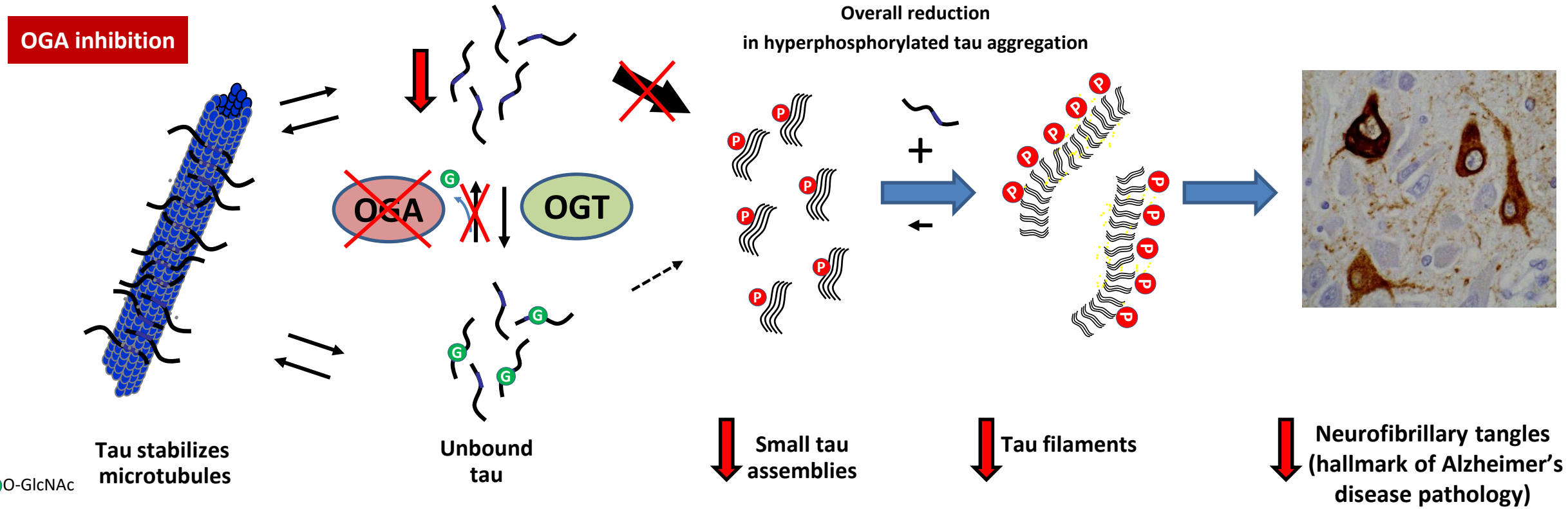
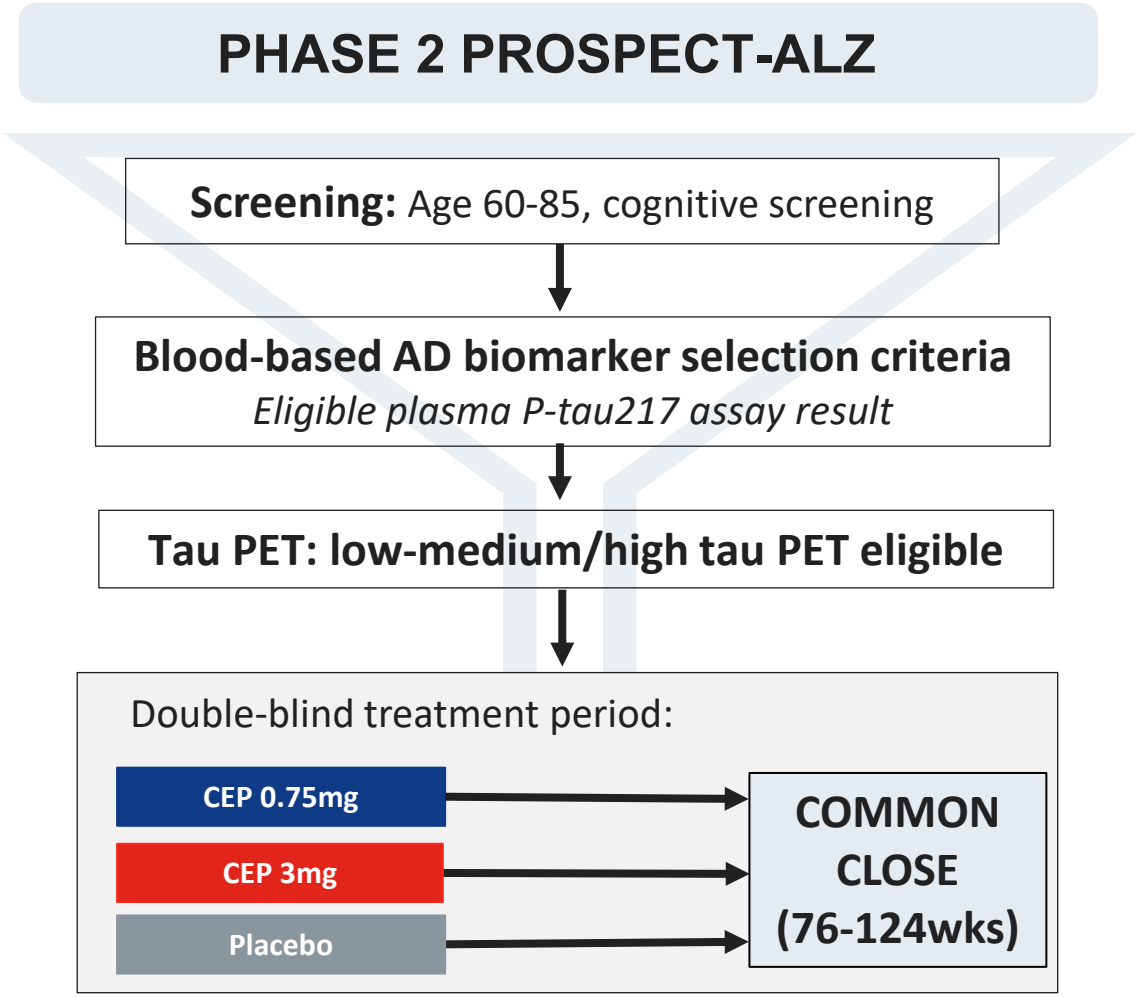
CEPEROGNASTAT (CEP) IS AN INHIBITOR OF AN INTRACELLULAR ENZYME THAT REGULATES PROTEIN O-GLCNAC MODIFICATION

- OGT/OGA regulate O-GlcNAc on 100+ substrates involved in transcription, metabolism, proteasome degradation & other processes
- In animal models:
  - Tau O-GlcNAc modification is inversely related to the levels of insoluble, hyperphosphorylated tau
  - OGA inhibition leads to reduction in aggregated tau neurofibrillary tangle accumulation



Abbreviations:OGA = O-linked N-acetyl glucosaminidase = O-GlcNAcase; OGT = O-GlcNAc transferase.

PROSPECT-ALZ STUDY DESIGN



Key eligibility criteria

- Geographies: USA, Canada, Poland, Japan, Australia
- 60-85 years, early symptomatic AD
- MMSE 22-30 & CDR-GS 0.5-1.0 (CDR memory box score of ≥0.5)
- Plasma P-tau217 assay eligible
- Tau PET eligible: stratified by low-medium and high baseline tau

Primary outcome

- Integrated Alzheimer's Disease Rating Scale (iADRS): a combination of cognitive (ADAS-Cog_{13}) and functional (ADCS-iADL) scales

Treatment period and statistical design

- CEP 0.75mg, CEP 3mg, or placebo, once daily, oral with 1:1:1 allocation
- Common close design with 76-124 week treatment period
- **Primary Outcome:** Bayesian Disease Progression Model
- **Secondary/Exploratory outcomes**: Natural Cubic Spline model from baseline to 76 weeks

Abbreviations: AD = Alzheimer's disease; CDR-GS = Clinical Dementia Rating Scale – Global Score; CEP = ceperognastat; MMSE = Mini-Mental State Examination; PET = positron emission tomography.

BASELINE DEMOGRAPHICS GENERALLY BALANCED ACROSS STUDY ARMS

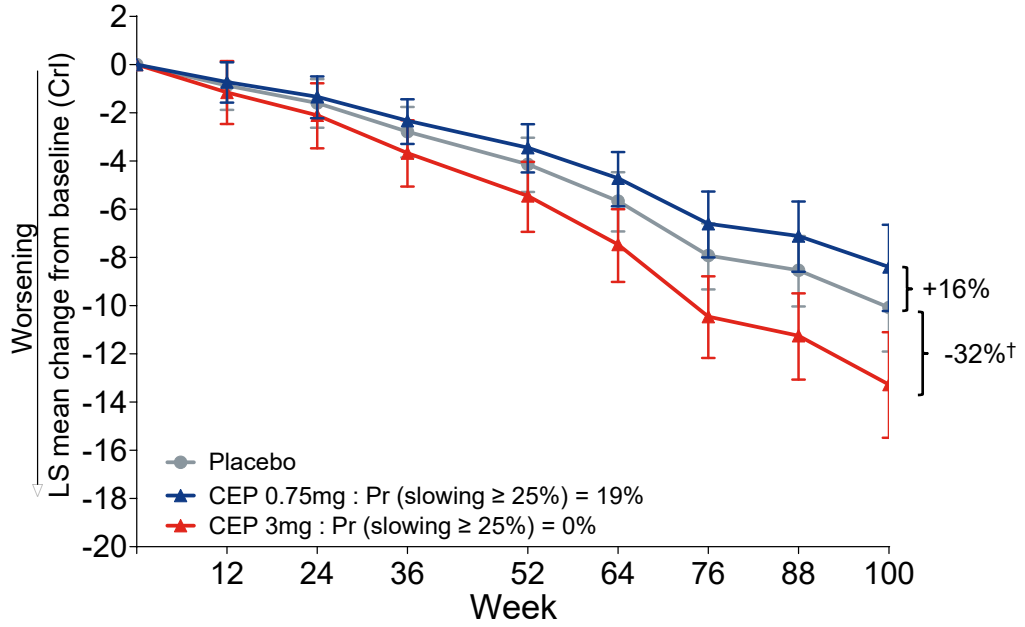
	Primary Population (N= 259) (Low-medium Baseline Tau)			Combined Population (N= 327) (Low-medium/ High Baseline Tau)		
Demographic	**Placebo** (n= 86)	**CEP 0.75mg** (n= 87)	**CEP 3mg** (n= 86)	**Placebo** (n= 108)	**CEP 0.75mg** (n= 110)	**CEP 3mg** (n= 109)
Sex, % female	65.1	63.2	58.1	63.0	63.6	57.8
Age, mean	74.8	74.0	74.0	73.4	73.3	73.4
Race, % Asian	10.5	11.5	14.0	10.2	10.9	12.8
% Black or AA	2.3	3.4	1.2	2.8	2.7	0.9
% White	87.2	85.1	84.9	87.0	86.4	86.2
Ethnicity, % Hispanic/Latino	2.3	3.4	4.7	1.9	3.6	3.7
Education, mean, yrs	15.0	14.7	14.5	15.1	14.8	14.6
***APOE* ε4, % carrier**	69.8	60.5	67.4	70.4	63.3	67.0
***APOE* ε4/ε4, %**	4.7	17.4	10.5	7.4	16.5	10.1
AChEI and/or memantine use, %	51.2	46.0	52.3	56.5	50.0	56.9

Abbreviations: AA = African American; AChEI = acetylcholinesterase inhibitors; CEP = ceperognastat; yrs = years; N/n = number.

PRIMARY OUTCOME MEASURE FAILED TO MEET STUDY SUCCESS CRITERIA AT EITHER DOSE

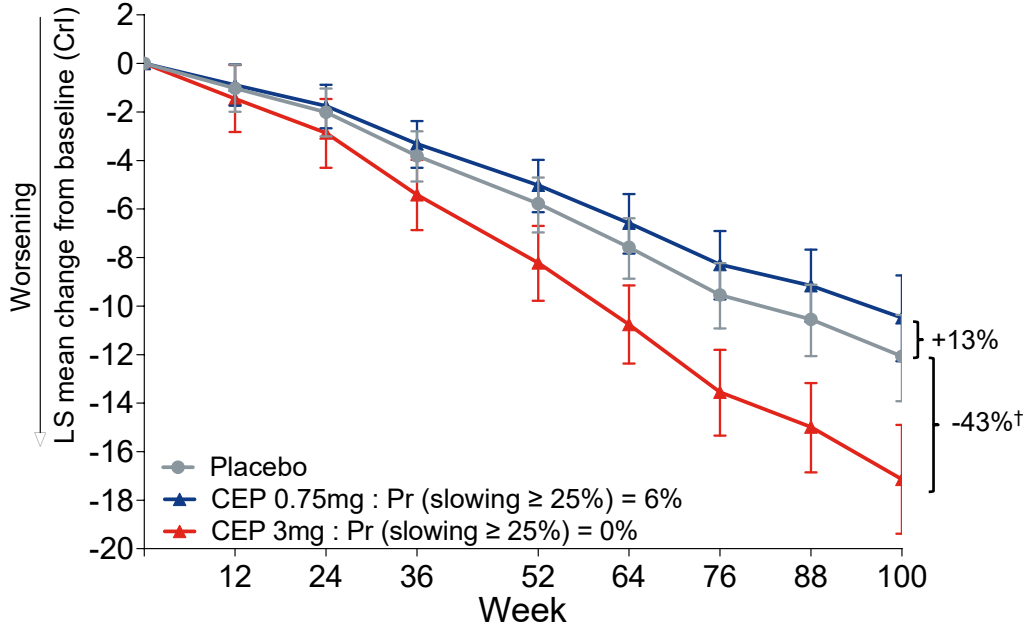
Integrated Alzheimer's Disease Rating Scale (iADRS) Change from Baseline to Week 100 Analyzed by Disease Progression Model (DPM)*

Primary Population (Low-medium Baseline Tau)



● Placebo n=84	84	80	80	76	76	71	64	34
▲ CEP 0.75mg n=86	83	77	75	72	69	69	61	30
▲ CEP 3mg n=85	79	72	69	62	60	56	51	28

Combined Population (Low-medium/ High Baseline Tau)



● Placebo n=106	106	102	102	96	94	88	82	44
▲ CEP 0.75mg n=109	105	98	96	90	84	83	74	38
▲ CEP 3mg n=108	101	91	87	79	75	69	61	34

Success defined as: >60% probability of ≥ 25% slowing of progression compared to placebo: Pr (slowing ≥ 25%) > 60%

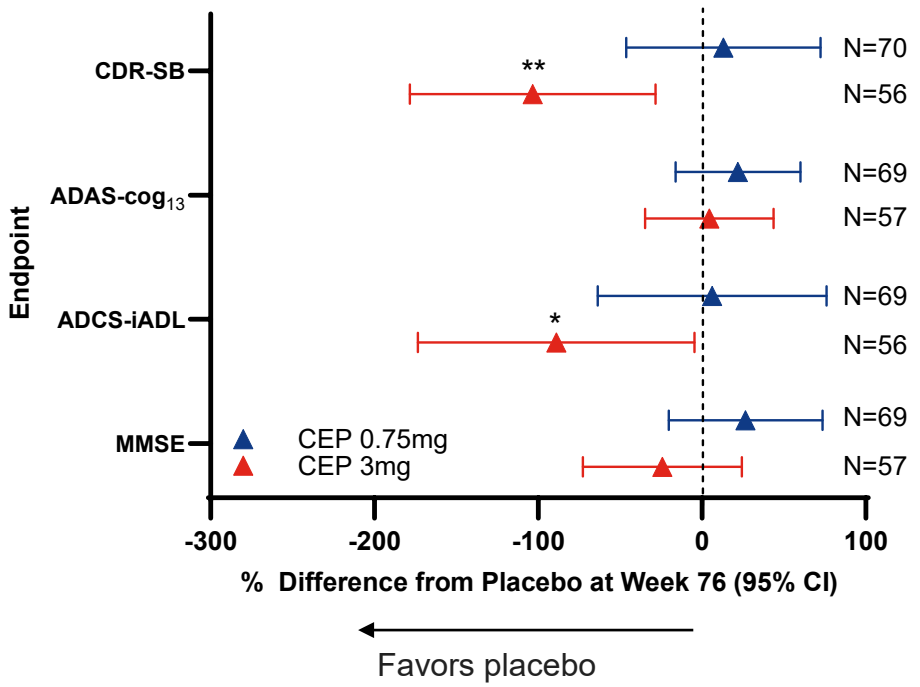
- **Neither CEP dose meaningfully slowed disease progression in either study population**
- **CEP 3mg dose demonstrated greater decline compared to placebo**

*The model was adjusted for age at baseline, AChEI/Memantine use at baseline, and pooled investigator.
†95% probability of separating from placebo.
Abbreviations: AChEI = acetylcholinesterase inhibitors CEP = ceperognastat; LS = least squares; yrs = years.

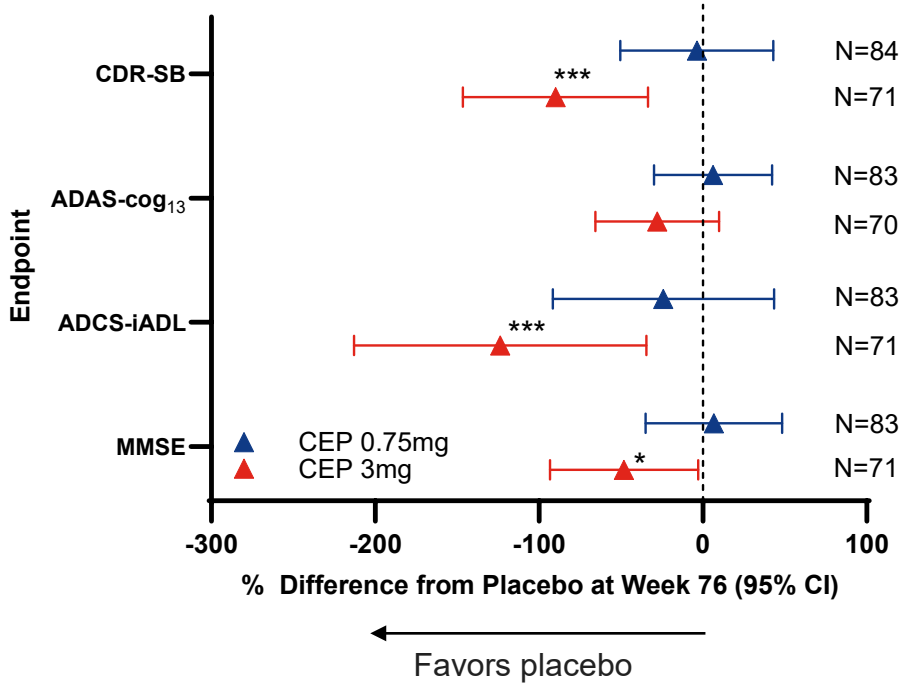
SECONDARY CLINICAL OUTCOMES INDICATE GREATER DECLINE IN CEP 3MG DOSE ARM

Percent Difference Relative to Placebo at Week 76 Across Clinical Endpoints Analyzed by Natural Cubic Spline†

Primary Population (Low-medium Baseline Tau)



Combined Population (Low-medium/ High Baseline Tau)



* p<0.05
** p<0.01
*** p<0.001

† NCS model adjusted for pooled investigator site, age at baseline, AChEI/Memantine use at baseline (and baseline tau category for Combined population).

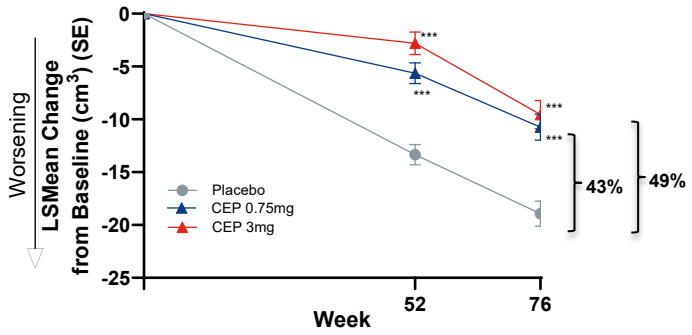
Abbreviations: AChEI = acetylcholinesterase inhibitors; ADAS-cog$_{13}$ = Alzheimer's Disease Assessment Scale – Cognitive Subscale 13; ADCS-iADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; CDR-GS = Clinical Dementia Rating Scale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CI = confidence interval; CEP = ceperognastat; MMSE = Mini-Mental State Examination.

LESS VOLUME LOSS (HIPPOCAMPUS, WHOLE BRAIN) AND REDUCED VENTRICULAR VOLUME INCREASE IN CEPEROGNASTAT ARMS

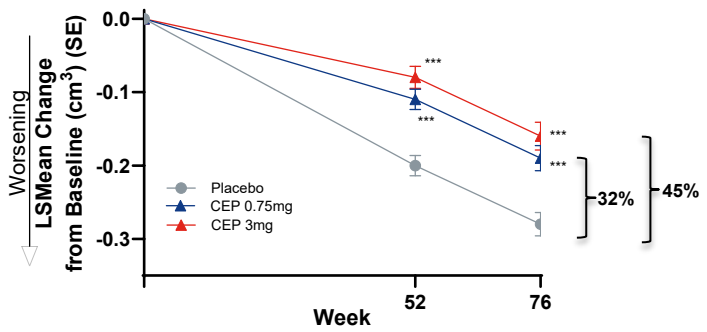
Volumetric MRI Change (cm^3) from Baseline to Week 76 Analyzed by Mixed Model Repeated Measures (MMRM)†

Primary Population (Low-medium Baseline Tau)

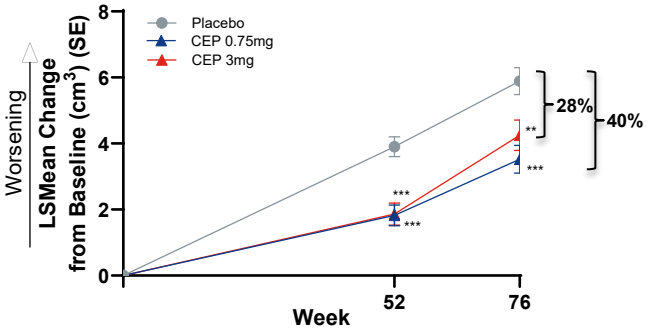
Bilateral Whole Brain



Bilateral Hippocampus

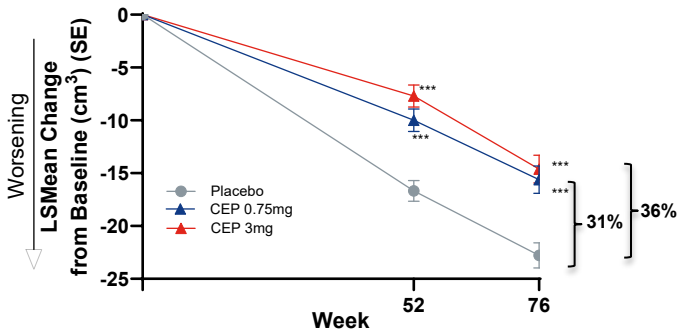


Bilateral Whole Lateral Ventricles

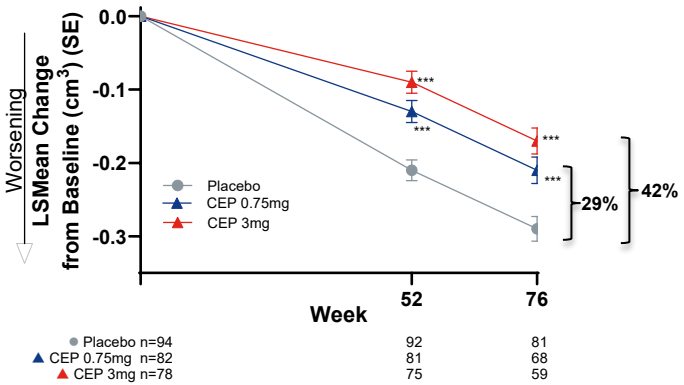


Combined Population (Low-medium/ High Baseline Tau)

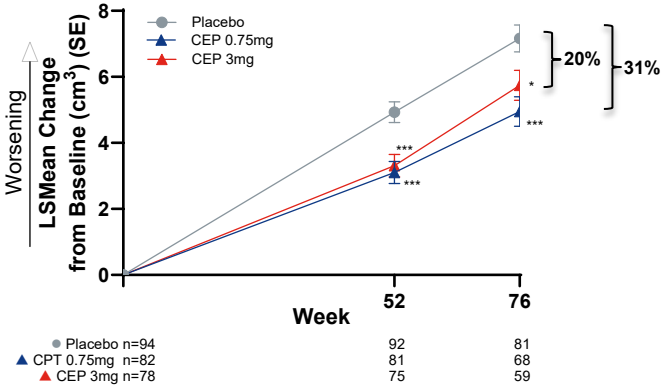
Bilateral Whole Brain



Bilateral Hippocampus



Bilateral Whole Lateral Ventricles



* p<0.05
** p<0.01
*** p<0.001

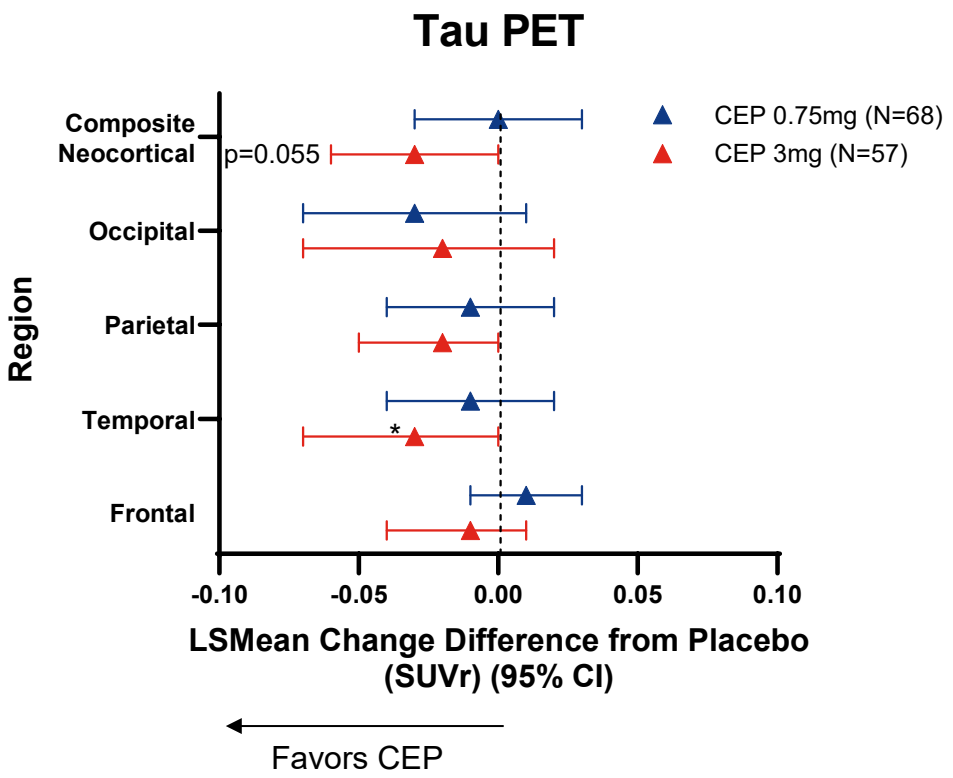
†MMRM adjusted for baseline volume, age (and baseline tau category for Combined population).

Abbreviations: CEP = ceperognastat; LS = least squares; MRI = Magnetic resonance imaging; SE = standard error.

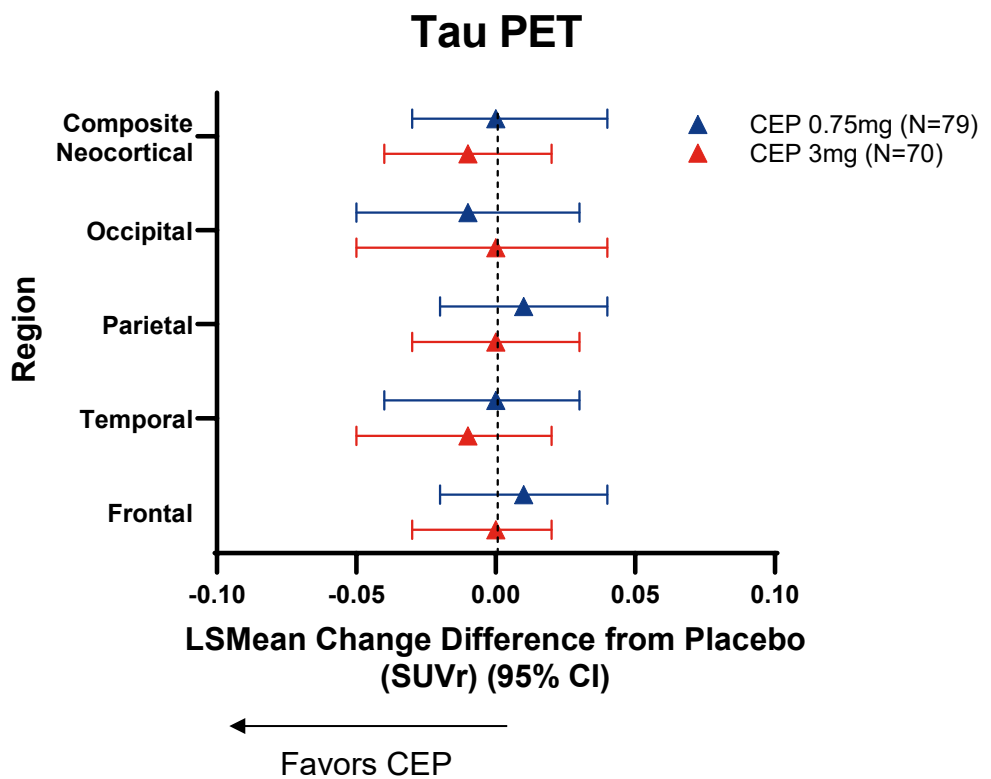
TAU PET SUGGESTS 3MG DOSE ARM SLOWED TAU ACCUMULATION WITHIN THE PRIMARY POPULATION

Tau PET (SUVr†) Change Relative to Placebo at Week 76 Analyzed by ANCOVA‡

Primary Population (Low-medium Baseline Tau)



Combined Population (Low-medium/ High Baseline Tau)



* p<0.05; †SUVr reference region = cerebellar gray; ‡ANCOVA model: change from baseline = baseline + treatment + age (+ baseline tau PET category for combined population analysis).

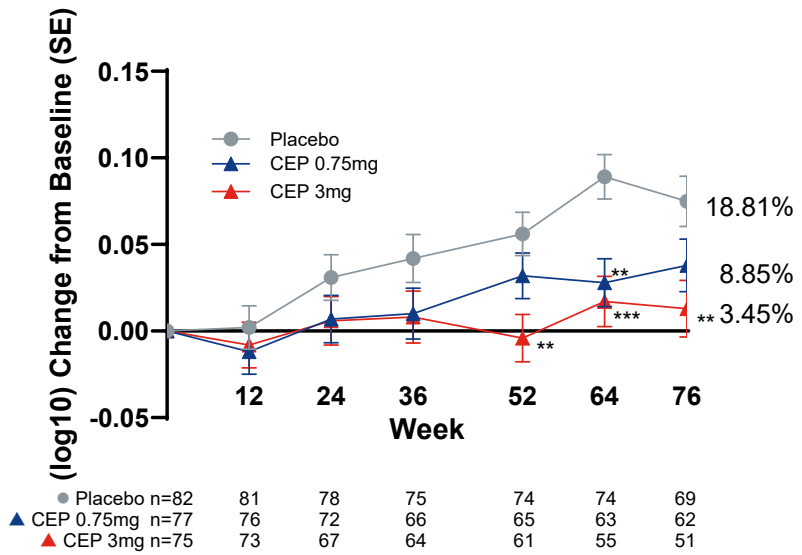
Abbreviations: CI = confidence interval; CEP = ceperognastat; LS = least squares; MRI = Magnetic resonance imaging; N = number; PET = positron emission tomography; SE = standard error; SUVr = standardized uptake value ratio

PLASMA BIOMARKERS SUGGEST TREATMENT EFFECT ON PHOSPHORYLATED TAU AND MARKER OF INFLAMMATION

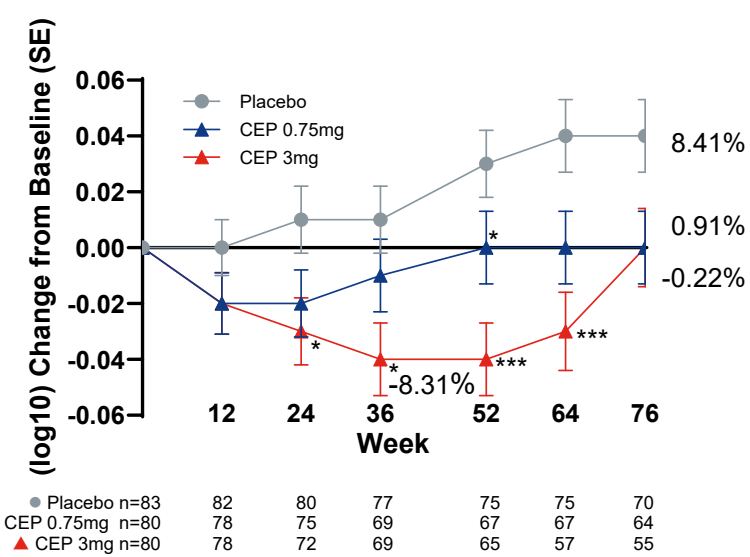
Primary Population (Low-medium Baseline Tau)

Plasma Biomarkers from Baseline to Week 76 Analyzed by Mixed Model Repeated Measures†

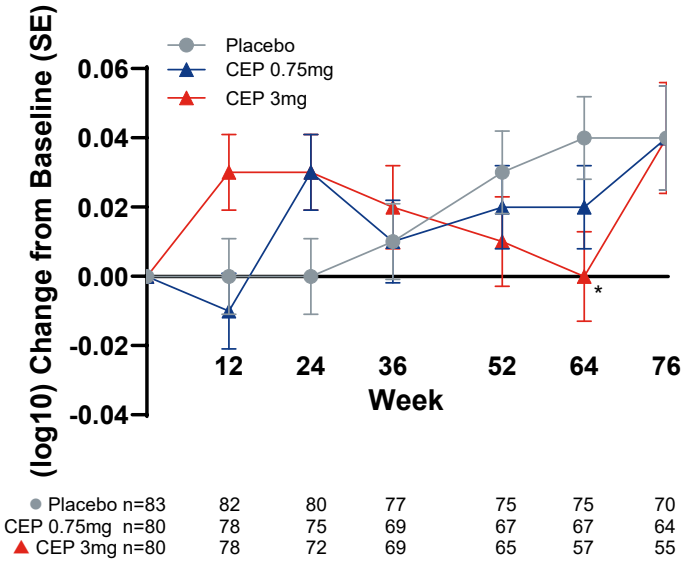
Plasma P-tau217 Assay



GFAP



Plasma NfL



* p<0.05
** p<0.01
*** p<0.001
†MMRM adjusted for baseline value, age.

Abbreviations: CEP = ceperognastat; GFAP = glial fibrillary acidic protein; MMRM = mixed model repeated measures; N = number; NfL = neurofilament light chain; P-tau = Phosphorylated tau; SE = standard error; SUVr = standardized uptake value ratio.

OVERVIEW OF ADVERSE EVENTS

Overview of AEs, n (%)	Placebo (N= 108)	CEP 0.75mg (N= 110)	CEP 3mg (N= 109)
Death	1 (0.9)	0	2 (1.8)
Pneumonia			1
Hematological malignancy			1*
Meningoencephalitis	1		
Study discontinuations	19 (17.6)	24 (21.8)	39 (35.8)
Study discontinuations reported as due to AEs	1 (0.9)	1 (0.9)	2 (1.8)
Treatment discontinuation reported as due to AEs	3 (2.8)	4 (3.6)	6 (5.5)
Participants with ≥1 SAE	17 (15.7)	13 (12.0)	29 (26.4)
Participants with ≥1 TEAE	99 (91.7)	99 (91.7)	101 (91.8)
Mild	37 (34.3)	42 (38.9)	28 (25.5)
Moderate	55 (50.9)	50 (46.3)	58 (52.7)
Severe	7 (6.5)	7 (6.5)	15 (13.6)

*One subject (CEP 3mg) discontinued due to SAE of hematological malignancy and died 17 days after discontinuing from the study

Abbreviations: AE = adverse event; CEP = ceperognastat; N/n = number; SAE = serious adverse event; TEAE = treatment emergent adverse event.

MOST COMMON TREATMENT EMERGENT ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS WITH CEPEROGNASTAT TREATMENT

TEAEs with OR>2 in either CEP arm versus placebo and n≥10 in combined CEP arm (approximate incidence of 5% or more)

Treatment Emergent Adverse Events

Preferred Term	Placebo (N= 108) n (%)	CEP 0.75mg (N= 108) n (%)	CEP 3mg (N= 110) n (%)	Odds Ratio CEP 0.75mg vs. placebo	Odds Ratio CEP 3mg vs. placebo
Headache	6 (5.6)	16 (14.8)	13 (11.8)	2.96	2.28
ECG QT prolonged	5 (4.6)	8 (7.4)	10 (9.1)	1.65	2.06
Weight decreased	4 (3.7)	6 (5.6)	8 (7.3)	1.53	2.04
Muscle spasms	3 (2.8)	4 (3.7)	6 (5.5)	1.35	2.02
Tremor	2 (1.9)	4 (3.7)	6 (5.5)	2.04	3.06

SAEs with OR>2 in either CEP arm (if applicable) and >1% incidence in either CEP arm

Serious Adverse Events

Cardiac disorders	1 (0.9)	1 (0.9)	5 (4.5)	1.00	5.10
Nervous system disorders	1 (0.9)	3 (2.8)	3 (2.7)	3.06	3.00
Neoplasms benign, malignant and unspecified	1 (0.9)	2 (1.9)	2 (1.8)	2.02	1.98
Psychiatric disorders	0 (0)	1 (0.9)	3 (2.7)	-	-
Vascular disorders	0 (0)	2 (1.9)	1 (0.9)	-	-
General disorders and administration site conditions	0 (0)	1 (0.9)	2 (1.8)	-	-

Abbreviations: AE = adverse event; CEP = ceperognastat; ECG = electrocardiogram; N/n = number; OR = odds ratio; SAE = serious adverse event; TEAE = treatment emergent adverse event.

STUDY CONCLUSIONS

- Neither the 0.75mg or 3mg doses of ceperognastat slowed clinical decline in early symptomatic AD
- Greater clinical decline was observed in the 3mg arm
- Severe and serious adverse events were more common in ceperognastat arms
- Biomarker data suggests slowing of tau pathology (tau PET, plasma P-tau217 assay) most evident in the 3mg arm
- Less brain volume loss observed in both dose arms
- Ceperognastat possibly reduced neuroinflammation (GFAP)

Six-month post-treatment safety follow-up study extension is currently underway.

PROSPECT-ALZ is an ongoing clinical trial, with anticipated further learnings to inform future development.
We are committed to pursuing tau as a promising AD therapeutic target.

Abbreviations: AD = Alzheimer's disease; GFAP = glial fibrillary acidic protein; PET = positron emission tomography

ACKNOWLEDGEMENTS

We gratefully acknowledge the contribution and dedication of all the trial participants with AD, their families, and their caregivers who participated in this study, along with trial site investigators and personnel, and members of the data monitoring committee.

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