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Evaluation of Diffusion Tensor Imaging Biomarkers in Phase 2 PROSPECT-ALZ Study of Ceperognastat in Early Symptomatic Alzheimer’s Disease

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OBJECTIVE

- To investigate the utility of free-water diffusion tensor imaging (FW-DTI) in understanding microstructural changes associated with treatment with ceperognastat and placebo

CONCLUSION

- Observed longitudinal increases in both gray matter (GM) and white matter (WM) FW in placebo groups are consistent with prior studies^{17,18}
- With ceperognastat 3 mg, the high O-GlcNAcase (OGA) occupancy¹⁹ may prolong suppression beyond the pathologic somatodendritic tau^{20,21} affecting GM and WM microstructure through both tau-dependent and tau-independent off-target mechanisms
- FW-DTI detected regionally and temporally distinct microstructural responses to ceperognastat 3 mg—a pattern not captured by volumetric magnetic resonance imaging (MRI) alone—suggesting that FW-DTI provides mechanistic sensitivity beyond conventional structural MRI and DTI¹⁷ in tau-targeting trials

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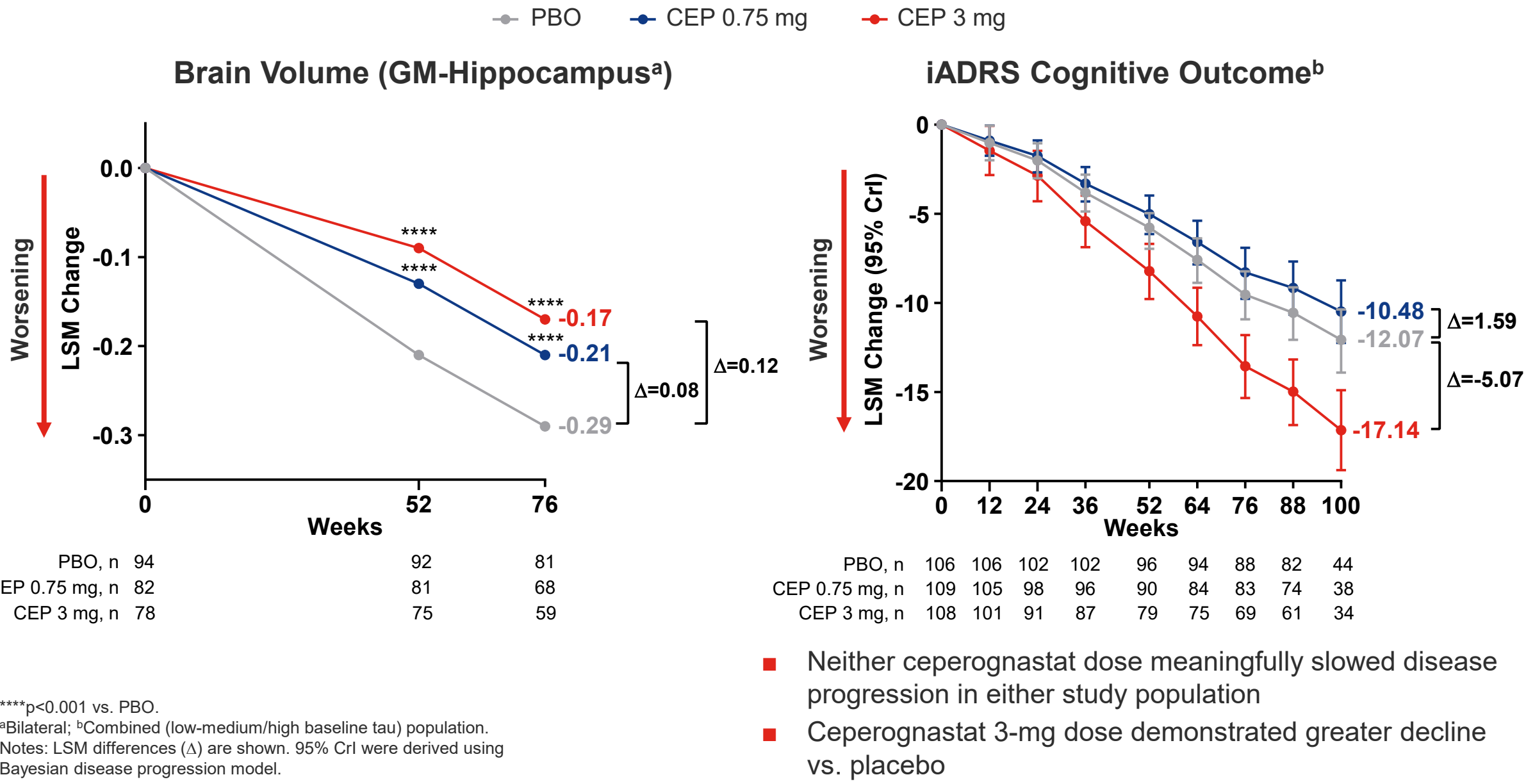


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BACKGROUND

- FW-DTI is used to probe GM and WM microstructure, as it isolates microstructural tissue-compartment diffusivity (mean diffusivity [MD_T], axial diffusivity [AD_T], radial diffusivity [RD_T], and fractional anisotropy [FA_T]) from extracellular FW, potentially explaining volumetric effects obscured in standard DTI¹⁻³
- Data from PROSPECT-ALZ (NCT05063539), a Phase 2 trial of ceperognastat (an OGA inhibitor) in early symptomatic Alzheimer’s disease (AD) with flortaucipir-confirmed tau pathology,⁴ were used to evaluate FW-DTI metrics as potential biomarkers in tau-targeting therapies
- Ceperognastat prevents O-linked β-N-acetylglucosamine (O-GlcNAc) removal, leading to an increase of O-GlcNAcylation, which competitively reduces tau hyperphosphorylation⁵⁻⁸ and helps maintain tau in a soluble, non-aggregating form⁹⁻¹¹
- In AD, pathological tau accumulates preferentially in the transentorhinal cortex to other medial temporal lobe (MTL) regions and neocortex at early-to-moderate disease stages¹²
 - This is consistent with flortaucipir regional patterns^{13,14} with little frontal lobe involvement, as it is affected at later stages of the disease¹²

Ceperognastat 3 mg Reduced Volumetric Loss vs. Placebo but Worsened Cognition⁴



METHODS

- FW-DTI was used to model extracellular water fraction and FW-corrected tissue properties: MD_T, AD_T, RD_T, and FA_T
- Change from baseline FW-DTI metrics at Week (W) 52 and W76 were analyzed using a mixed-effects model of repeated measures in a subset of participants with baseline and ≥1 follow-up diffusion MRI (baseline: placebo, n=47; low-dose ceperognastat 0.75 mg, n=38; high-dose ceperognastat 3 mg, n=40)
 - Fixed effects: Treatment, visit, treatment-by-visit interaction, baseline measure, age at baseline, and baseline tau-PET category
- Key brain regions of interest were evaluated to assess the sensitivity of FW-DTI in detecting changes in both GM and WM:
 - GM: Hippocampus, MTL, and frontal lobe
 - WM: Periventricular WM tracts, posterior thalamic radiation, and deep WM tracts

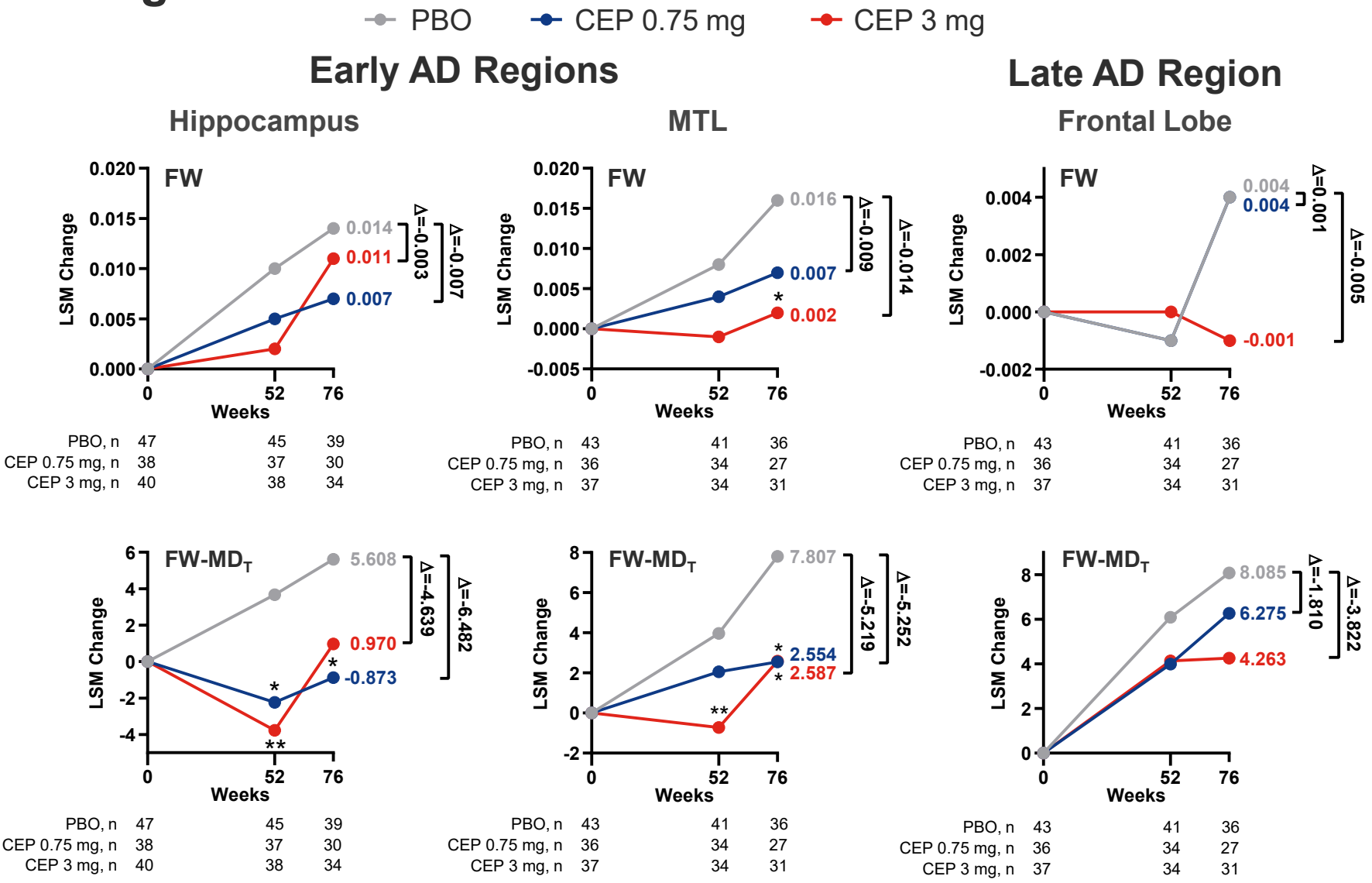
RESULTS

Baseline Demographics and Characteristics

Characteristic	Placebo (n=47)	Low Dose (CEP 0.75 mg) (n=38)	High Dose (CEP 3 mg) (n=40)
Female	59.6	73.7	60.0
Age, mean (SD), years	72.9 (5.1)	72.4 (5.7)	73.3 (5.3)
Race			
Asian	8.5	7.9	7.5
Black or African American	6.4	7.9	0
White	85.1	84.2	92.5
Ethnicity			
Non-Hispanic/Latino	100.0	97.4	100.0
BMI, mean (SD), kg/m ²	25.6 (5.0)	26.1 (5.3)	24.3 (5.0)
Time since onset of AD symptoms, mean (SD), years	3.4 (2.5)	3.6 (2.3)	3.8 (2.5)
APOE ε4, carrier	76.6	67.6	80.0
APOE ε4/ε4	10.6	21.6	10.0
AChEI and/or memantine use	55.3	55.3	62.5

Notes: Data are % unless stated otherwise. Participants with a baseline measurement and ≥1 complete post-baseline measurement for any DTI assessment. Percentages are based on the number of non-missing values (n).

GM: Ceperognastat 3 mg Showed Reduced Change From Baseline in MD_T at W52 vs. Placebo in Early AD Regions



*p<0.1 (trending, marginal), **p<0.05 (statistically significant) vs. PBO. Notes: LSM differences (Δ) are shown. MTL: Entorhinal cortex, parahippocampal gyrus, hippocampus. Frontal lobe: Caudal middle frontal, frontal pole, lateral orbito-frontal, medial orbito-frontal, paracentral, pars opercularis, pars orbitalis, pars triangularis, precentral, rostral middle frontal, and superior frontal.

References: 1. Assaf Y, Pasternak O. *J Mol Neurosci*. 2008;34:51-61. 2. Ofori E, et al. *NeuroImage Clin*. 2019;24:101985. 3. Raghavan S, et al. *Brain Commun*. 2021;3:fab106. 4. Fleisher AS, et al. Poster presented at: CTAD 2024. Abstract OC10. 5. Liu F, et al. *Proc Natl Acad Sci U S A*. 2004;101:10804-10809. 6. Arnold CS, et al. *J Biol Chem*. 1996;271:28741-28744. 7. Smet-Nocca C, et al. *Mol Biosyst*. 2011;7:1420-1429. 8. Bourré G, et al. *Front Endocrinol*. 2018;9:595. 9. Yuzva SA, et al. *Nat Chem Biol*. 2008;4:483-490. 10. Yuzva SA, et al. *Nat Chem Biol*. 2012;8:383-389. 11. Yuzva SA, Vocadlo DJ. *Curr Alzheimer Res*. 2009;6:451-454. 12. Braak H, Braak E. *Acta Neuropathol*. 1991;82:239-259. 13. Marique M, et al. *Ann Neurol*. 2015;78:787-800. 14. Lowe VJ, et al. *Alzheimers Dement*. 2020;16:561-571. 15. Fligley CR, et al. *Front Hum Neurosci*. 2023;17:1196624. 16. Sintani I, et al. *Hum Brain Mapp*. 2018;40:1618-1631. 17. Bergamino M, et al. *Sci Rep*. 2021;11:6990. 18. Wang W, et al. *Neurobiol Aging*. 2023;121:166-178. 19. Kiebasa W, et al. *Alzheimers Dement Transl Res Clin Interv*. 2024;10:e70020. 20. Sohn PD, et al. *Mol Neurodegener*. 2016;11:47. 21. Le LTHL, et al. *Adv Sci (Wein)*. 2023;10:e2302035.

Abbreviations: AChEI=acetylcholinesterase inhibitor; AD=Alzheimer’s disease; AD_T=axial diffusivity; APOE=apolipoprotein E; Assoc.=association; BMI=body mass index; CC=corpus callosum; CEP=ceperognastat; CFB=change from baseline; CI=confidence interval; CrI=credible interval; DTI=diffusion tensor imaging; FA=fractional anisotropy; FW=free water; GM=gray matter; iADRS=Integrated Alzheimer’s Disease Rating Scale; LSM=least squares mean; MD=squares mean; MD_T=mean diffusivity; MTL=medial temporal lobe; ns=not significant; O-GlcNAc=O-linked β-N-acetylglucosamine; OGA=O-GlcNAcase; PBO=placebo; PET=positron emission tomography; Proj.=projection; PTR=posterior thalamic radiation; RD=radial diffusivity; Sag.=sagittal; SD=standard deviation; SE=standard error; SFOF=superior fronto-occipital fasciculus; SLF=superior longitudinal fasciculus; W=Week; WM=white matter

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KEY RESULTS

WM: Ceperognastat 3 mg Showed Increased MD_T Change From Baseline vs. Placebo in Non-periventricular Deep WM Tracts

FW and FW-Corrected DTI Metrics: Significance of Changes From Baseline in the Ceperognastat 3-mg Arm

Non-periventricular Deep WM	Projection Fibers	Association Fibers	SLF	PTR (Tau-Vulnerable)
Metric	p-Values (W52 / W76)	p-Values (W52 / W76)	p-Values (W52 / W76)	p-Values (W52 / W76)
FW	ns / ns	ns / ns	ns / ns	ns / ns
FW-corrected MD _T	<0.05 / <0.05	<0.05 / <0.05	ns / <0.05	<0.05 / <0.1
FW-corrected RD _T	ns / ns	ns / ns	ns / ns	ns / ns
FW-corrected AD _T	ns / ns	ns / ns	ns / ns	<0.05 / <0.1
FW-corrected FA _T	ns / ns	ns / ns	ns / ns	ns / ns

- FW-corrected AD_T in the posterior thalamic radiation (PTR) declined progressively from baseline in placebo, while ceperognastat 3 mg maintained near-baseline values through W52 and W76 (p=0.034 and p=0.063 vs. placebo, respectively)

Overall Summary

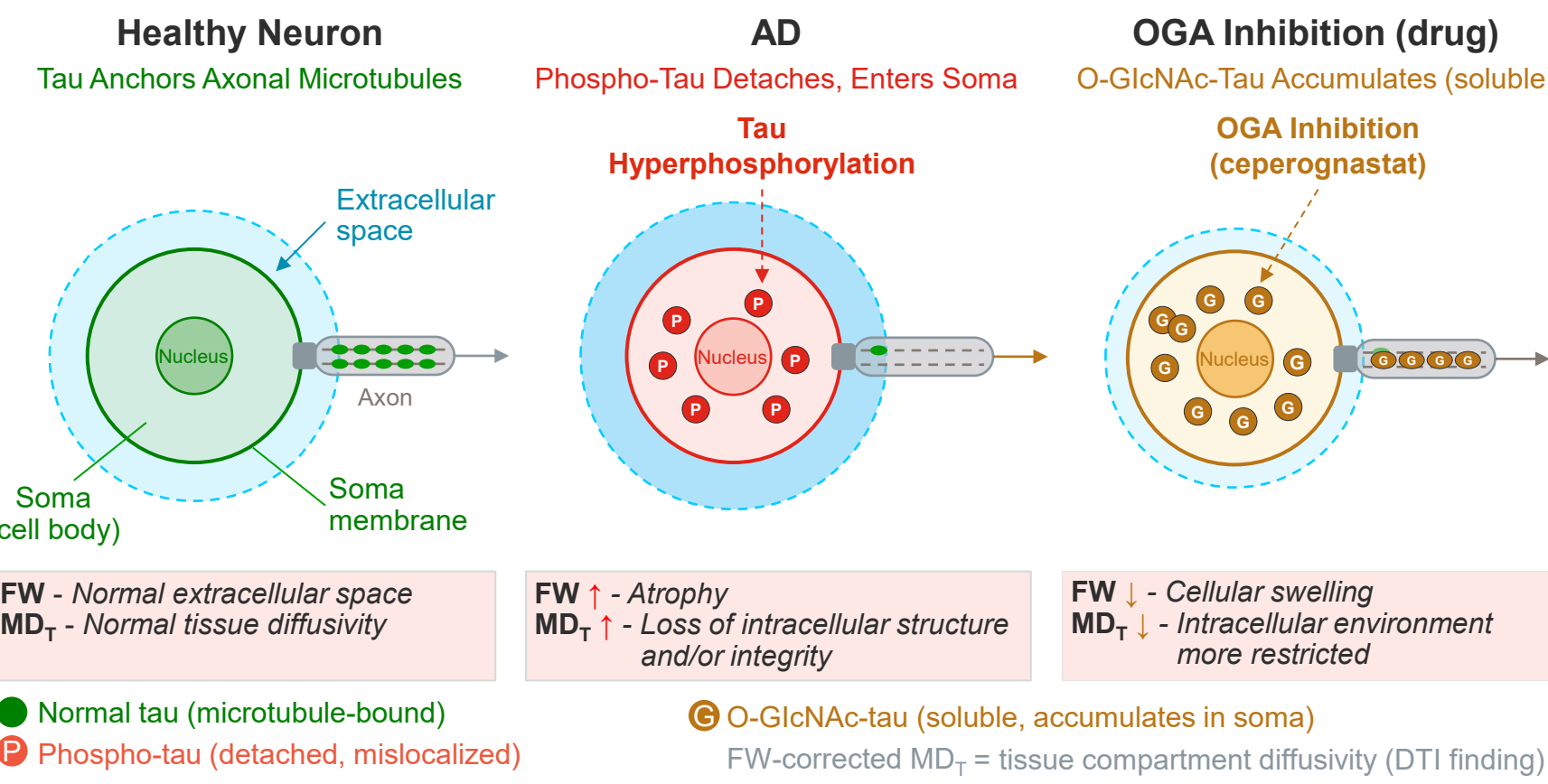
Gray Matter

- Ceperognastat 3 mg reduced MD_T in the hippocampus and MTL at W52, with subsequent signal reversal and concurrent FW elevation by W76, consistent with initial intracellular diffusion restriction followed by loss of cellular integrity and accelerated atrophy
- The W52 MD_T reduction and its subsequent accelerated reversal paralleled the pattern of initial volume preservation followed by steepening atrophy rate between W52 and W76
- The frontal lobe showed no significant FW-DTI changes in the ceperognastat arms vs. placebo at either timepoint, consistent with its late-stage AD vulnerability outside the enrolled disease stage

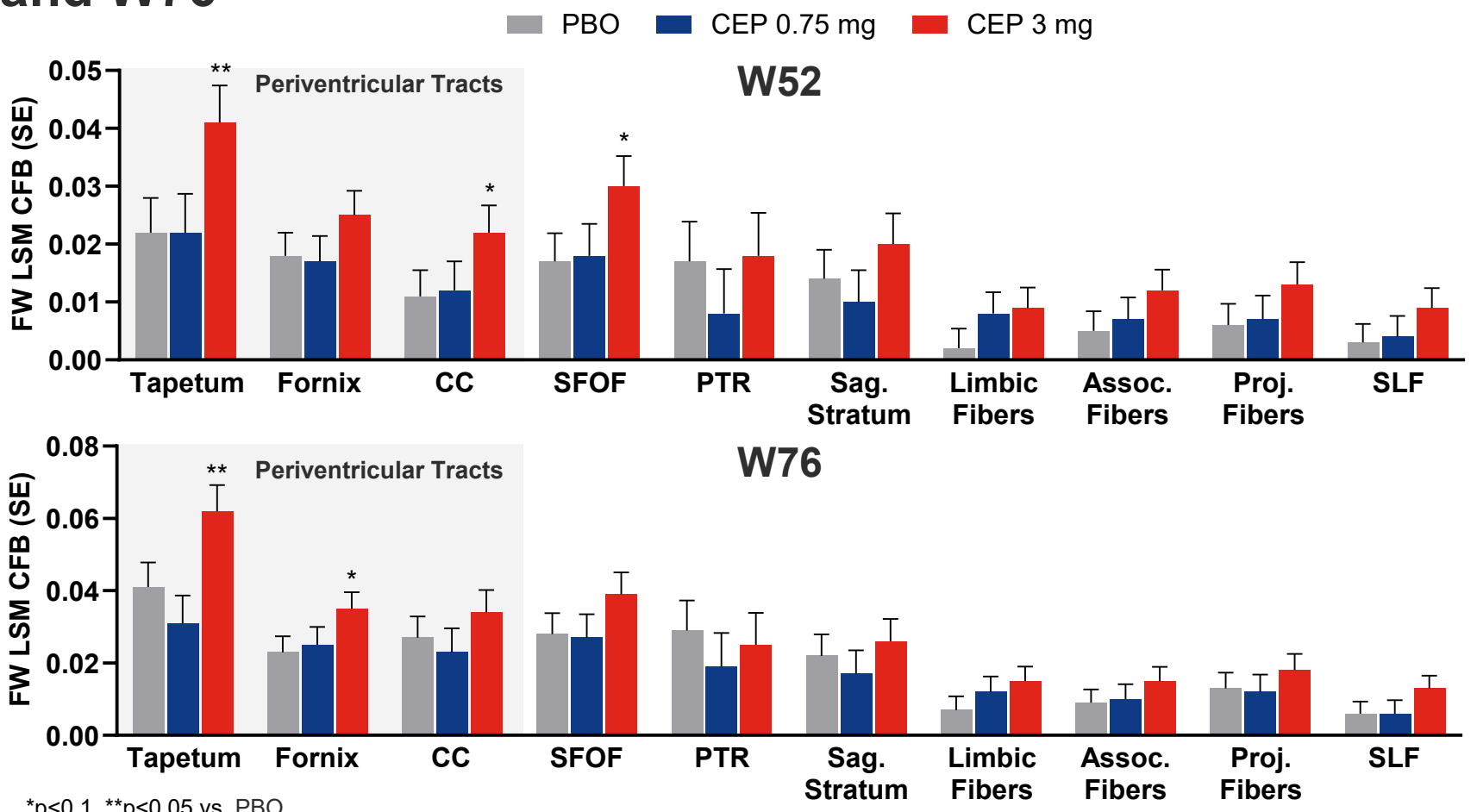
White Matter

- In the tau-vulnerable PTR¹⁶ (Braak III-IV), ceperognastat 3 mg attenuated MD_T and AD_T decline vs. placebo at W52, consistent with **on-target O-GlcNAc-tau mediated maintenance of axonal microstructure** in a tract with direct connectivity to the enrolled disease-stage GM regions
- At W76, in deep WM (projection fibers, association fibers, and superior longitudinal fasciculus [SLF]), ceperognastat 3 mg elevated MD_T vs. placebo with no significant changes in RD_T and FA_T, consistent with **off-target disruption of non-tau OGA substrates** (eg, neurofilament, axonal transport machinery)
- In periventricular tracts, ceperognastat 3 mg elevated FW vs. placebo, most notably in the tapetum, consistent with **disruption of perivascular fluid dynamics** through effects on non-tau OGA substrate

Hypothesized Ceperognastat Mechanism of Action: Somatodendritic O-GlcNAc-Tau Accumulation in Disease-Affected GM



WM: Ceperognastat 3 mg Increased FW Change From Baseline vs. Placebo in Periventricular Tracts¹⁵ at W52 and W76



*p<0.1, **p<0.05 vs. PBO. Note: LSM CFB, SE, 95% CI, and p-value are derived using MMRM with fixed factors for treatment, visit, treatment-by-visit interaction, baseline measure, age at baseline, baseline tau-PET category.