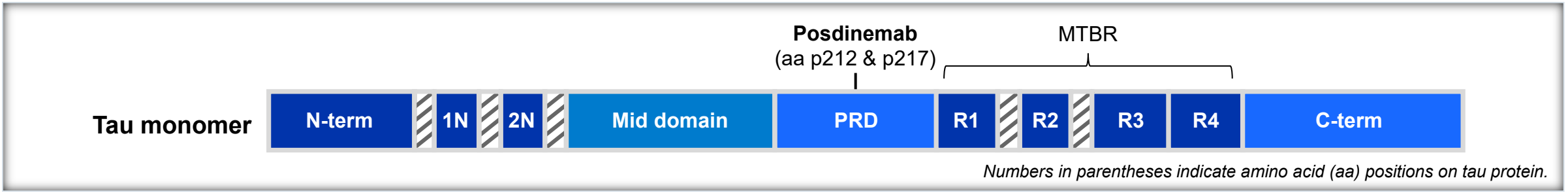
When Target Engagement Is Not Enough:
Lessons from Posdinemab on Bridging Tau Biology to Clinical Outcomes

Ziad S Saad[1], Gallen Triana-Baltzer[1], Gil D Rabinovici[2], Fiona Elwood[3]

[1]Johnson & Johnson - San Diego, [2]UCSF - San Francisco, [3]Johnson & Johnson - Cambridge

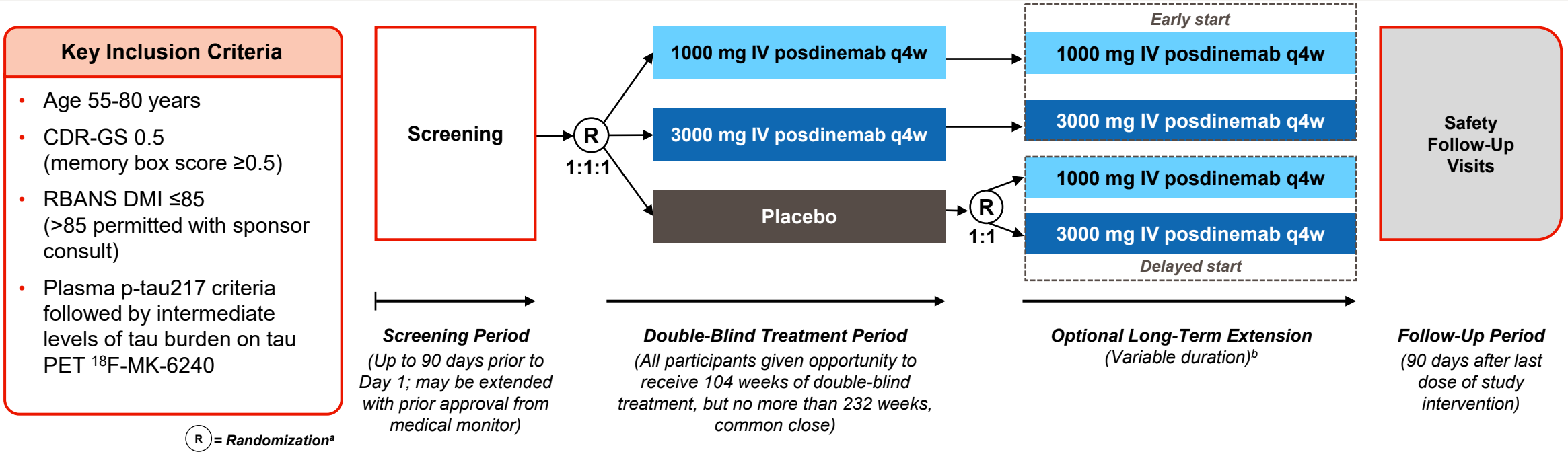


Posdinemab (JNJ-63733657), an anti-tau IgG1 monoclonal antibody, targets extracellular tau in the mid-domain proline-rich domain (PRD), binding with high affinity to phosphorylated tau and weakly to non-phosphorylated tau[1]

1. Galpern WR et al. *J Prev Alzheimers Dis*. 2024;11(6):1592-1603.
aa, Amino acid; C-term, C terminal; IgG: immunoglobulin G; MTBR, microtubule-binding region; N, N-terminal inserts; N-term, N terminal; p-tau217, tau phosphorylated at amino acid residue 217; PRD, proline-rich domain; R, repeat regions.

Presented by Ziad Saad at the Clinical Trials on Alzheimer's Disease (CTAD) Congress; November 16-19, 2026; Boston, MA, USA

Posdinemab was evaluated in early Alzheimer's disease in Autonomy, a global phase 2b proof-of-concept trial (N=521)

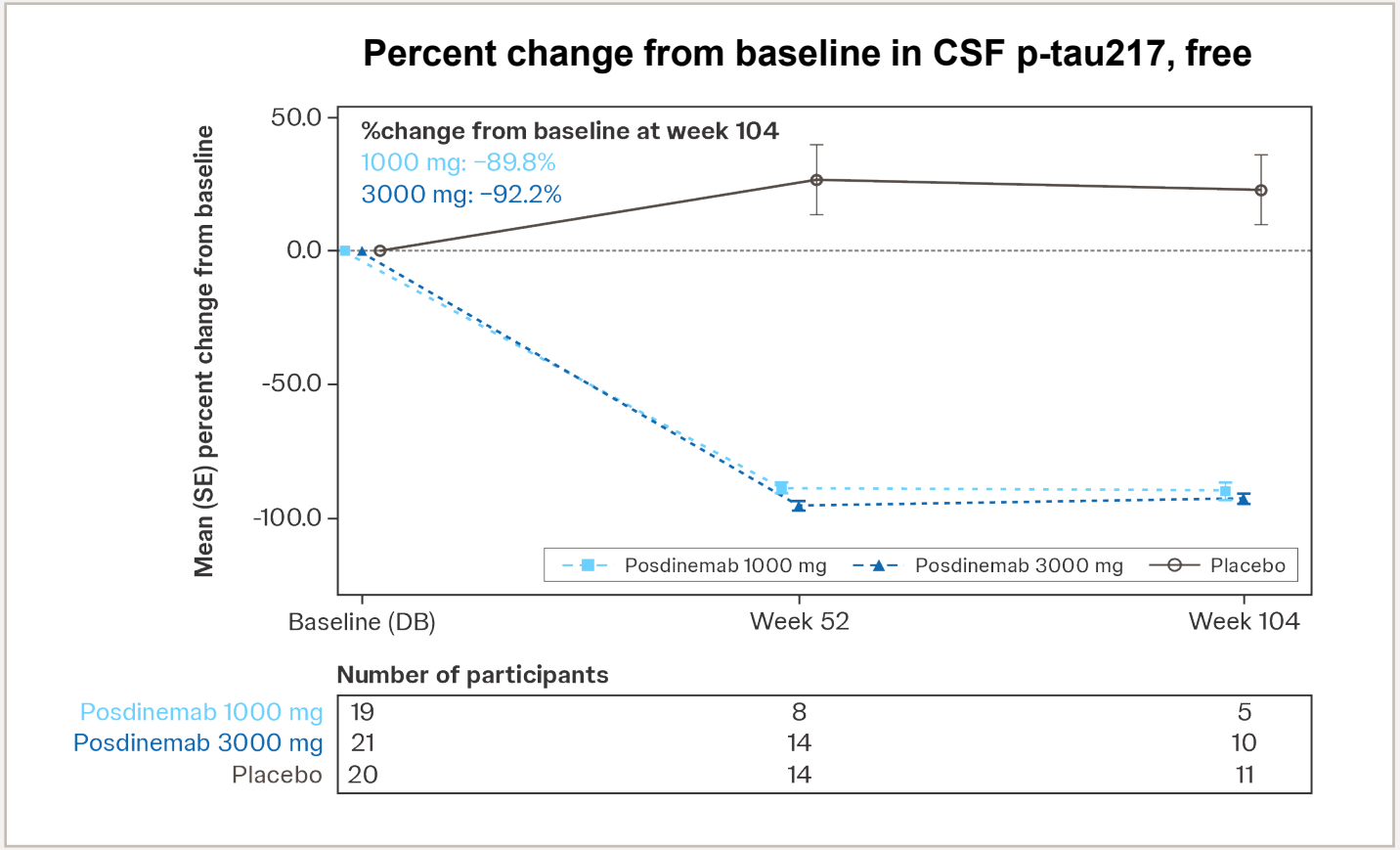


The proof-of-concept, phase 2b Autonomy study (NCT04619420) evaluated the primary hypothesis that posdinemab would decrease tau spread and thereby slow clinical decline as measured by iADRS-MCI, a composite of cognition and function, as compared with placebo

[a]Randomization was stratified by geographic region (North America, Europe, Australia, and Japan) and baseline tau burden on tau PET (Braak 4 ROI z-score ≤ or >4.62). [b]Until 2 years after marketing authorization for the indication in a participant's respective country or until posdinemab becomes commercially available or can be provided via another access mechanism or the participant no longer benefits from further treatment or withdraws consent, or the sponsor terminates clinical development. CDR-GS, Clinical Dementia Rating Global Score; DB, double-blind; DMI, Delayed Memory Index; iADRS-MCI, integrated Alzheimer's Disease Rating Scale for Mild Cognitive Impairment; IV, intravenous; p-tau217, tau phosphorylated at amino acid residue 217; q4w, every 4 weeks; R, randomization; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; ROI, region of interest; tau PET, tau positron emission tomography.

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Robust target engagement: reduction of CSF p-Tau 217 by up to 92%

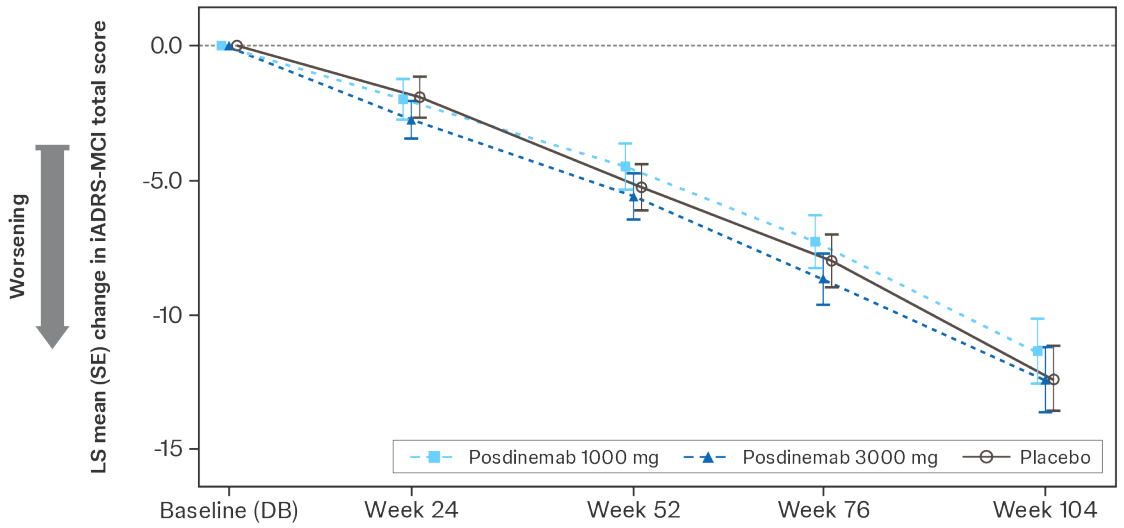


- Robust reductions were observed in free p-tau217 in CSF for both doses of posdinemab

CSF, cerebrospinal fluid; DB, double-blind; p-tau217, tau phosphorylated at amino acid residue 217; SE, standard error.

RESULTS – No significant difference between posdinemab and placebo in the primary endpoint iADRS-MCI total score and secondary endpoint CDR-SB

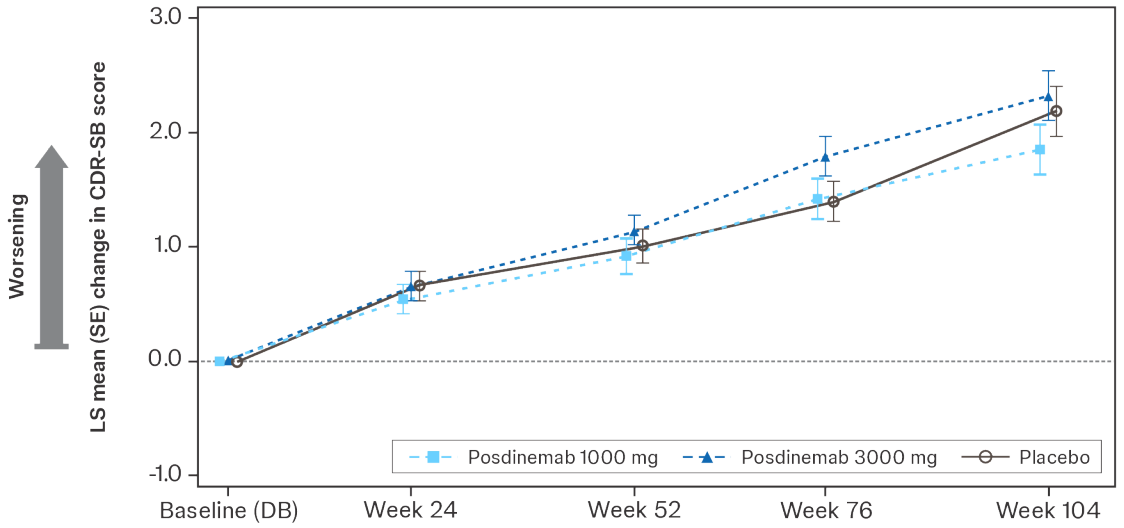
Least squares mean change from baseline in iADRS-MCI total score (full efficacy analysis set)



Number of participants

	Baseline (DB)	Week 24	Week 52	Week 76	Week 104
Posdinemab 1000 mg	170	165	152	144	142
Posdinemab 3000 mg	174	166	151	143	132
Placebo	172	166	153	147	137

Least squares mean change from baseline in CDR-SB score (full efficacy analysis set)



Number of participants

	Baseline (DB)	Week 24	Week 52	Week 76	Week 104
Posdinemab 1000 mg	171	167	153	147	143
Posdinemab 3000 mg	175	165	155	148	137
Placebo	175	170	155	153	144

LS mean change from baseline and SE are derived using MMRM with factors for treatment, visit, treatment-by-visit interaction, geographic region, sex, APOE ε4 carrier status, education level, AChEI and/or memantine use at baseline, and covariates for baseline score, baseline tau burden on tau PET, and age at baseline. Full efficacy analysis set: all randomized participants who receive ≥1 dose of study intervention in the double-blind treatment period. AChEI, acetylcholinesterase inhibitors; APOE ε4, apolipoprotein E ε4; CDR-SB, Clinical Dementia Rating - Sum of Boxes; DB, double-blind; iADRS-MCI, integrated Alzheimer's Disease Rating Scale for Mild Cognitive Impairment; LS, least squares; MMRM, mixed model for repeated measures; SE, standard error; tau PET, tau positron emission tomography

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19th Clinical Trials on Alzheimer's Disease (CTAD 2026)

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Presentation 1

Spatial Determinants of Posdinemab's Effect on Tau PET

Ziad S. Saad

Xingjian Zhang, Ritobrato Datta, Gil D. Rabinovici, Reisa Sperling, Henrik Zetterberg, Maggie Fedgchin, Tricia Thornton-Wells, Jaren Landen, Janice Wong, Gayle Wittenberg, Arthur Simen, Fiona Elwood

Presentation 2

CSF and Plasma Biomarker Changes After Anti-Tau Therapy: Fluid Biomarker Results from the Autonomy Phase 2 Clinical Trial

Gallen Triana-Baltzer

Tina Wang, Reisa Sperling, Gil D. Rabinovici, Henrik Zetterberg, Shannon Leslie, Manja Schoene, Setareh Moughadam, Ziad S. Saad, Janice Wong, Stanley Belkowski, Gayle Wittenberg, Tricia Thornton-Wells, Maggie Fedgchin, Arthur Simen, Fiona Elwood

Presentation 3

Biomarker Associations with Cognition: Results from the Autonomy Phase 2 Clinical Trial

Gil D. Rabinovici

Reisa Sperling, Henrik Zetterberg, Xingjian Zhang, Tina Wang, Ritobrato Datta, Macarena Garcia Valdecasas Colell, Maggie Fedgchin, Tricia Thornton-Wells, Jaren Landen, Janice Wong, Gayle Wittenberg6, Arthur Simen, Fiona Elwood, Gallen Triana-Baltzer, Ziad S. Saad4

Presented by Ziad Saad at the Clinical Trials on Alzheimer's Disease (CTAD) Congress; November 16-19, 2026; Boston, MA, USA

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Spatial Determinants of Posdinemab's Effect on Tau PET

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[1]Johnson & Johnson, San Diego, CA, USA; [2]University of California San Francisco, San Francisco, CA, USA; [3]Harvard Medical School, Boston, MA, USA; [4]University of Gothenberg, Gothenberg, Sweden; [5]Johnson &Johnson, Titusville, NJ, USA; [6]Johnson &Johnson, Cambridge, MA, USA

*Presenting author
[†]Affiliation at the time of the study

Presented by Ziad Saad at the Clinical Trials on Alzheimer's Disease (CTAD) Congress; November 16-19, 2026; Boston, MA, USA
This study was sponsored by Johnson & Johnson

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Disclosures

- **Ziad S. Saad, Xingjian Zhang, Ritobrato Datta, Maggie Fedgchin, Tricia Thornton-Wells, Jaren Landen, Janice Wong, Gayle Wittenberg, Arthur Simen, and Fiona Elwood:** Are or were employees of Johnson & Johnson and may hold stock or stock options in Johnson & Johnson.

- **Gil D. Rabinovici:** receives research support from NIH, Alzheimer's Association, American College of Radiology, Rainwater Charitable Foundation, Eli Lilly, GE Healthcare, Life Molecular Imaging, Genentech. Paid consultant for Bristol Myers Squibb, Eli Lilly, Genentech, Johnson & Johnson, Merck, Novo Nordisk, Roche.

- **Reisa Sperling:** has served as a consultant or on scientific advisory boards for AbbVie, AC Immune, Acumen, Alector, Apellis, Biohaven, Bristol Myers Squibb, Immunobrain, Janssen, Novo Nordisk, Oligomerix, Prothena, Roche, Ionis, Therini and Vaxxinity over the past 3 years, all under the NIH guidelines of $5k. She also has institutional consulting contracts with Eli Lilly and Roche. She has received research funding from Eisai and Eli Lilly for public-private partnership clinical trials and receives research grant funding from the National Institute on Aging/National Institutes of Health, GHR Foundation, and the Alzheimer's Association. Her spouse, K. Johnson, reports consulting fees from Bristol-Myers Squibb, Janssen, Merck, Novartis and Voyager Therapeutics over the past 3 years.

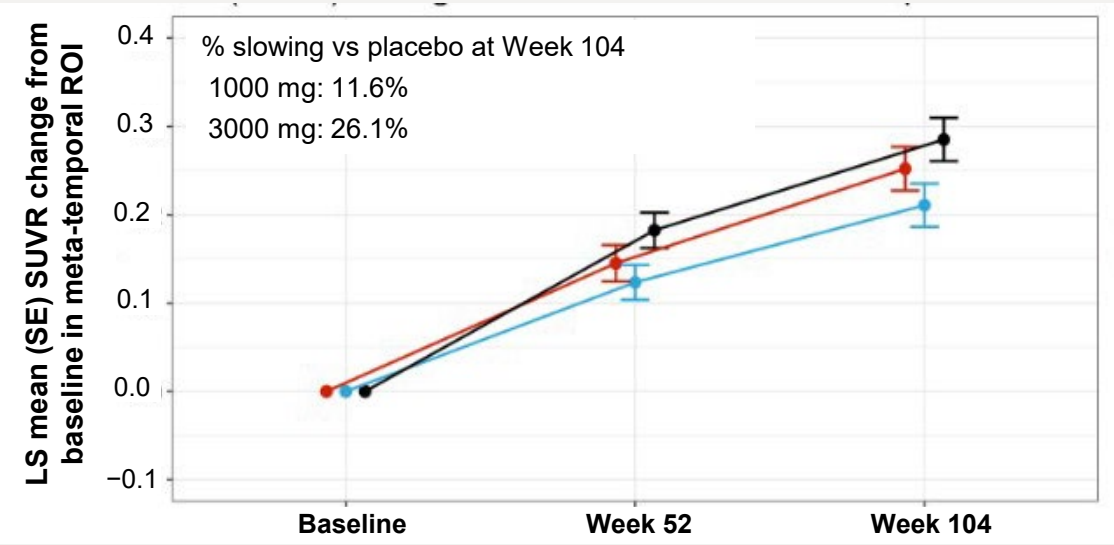
- **Henrik Zetterberg:** has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alamar, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, Johnson & Johnson, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, New Amsterdam, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD, is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, and is a shareholder of CERimmune Therapeutics (outside submitted work).

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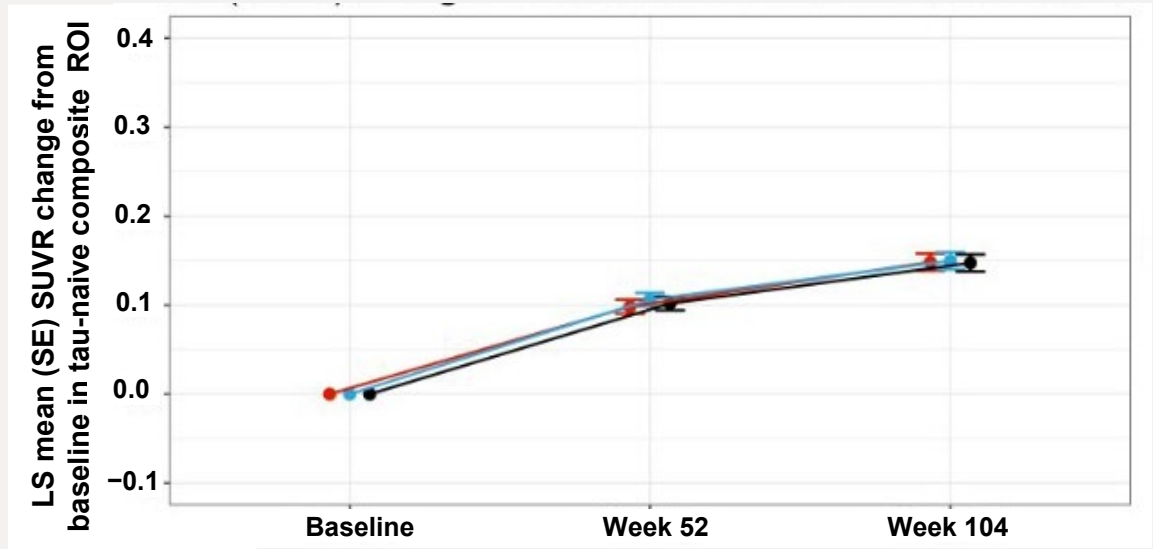
Background: In the Autonomy trial, posdinemab slowed accumulation of neurofibrillary tangles in some brain areas but not others

- The Autonomy phase 2b trial showed that the posdinemab did not slow clinical decline in early Alzheimer's disease[1]
- Posdinemab slowed the rate of Neurofibrillary tangle (NFT) accumulation as measured by MK6240 tau PET, in some brain areas but not others

Meta-temporal



Tau-naïve cortex



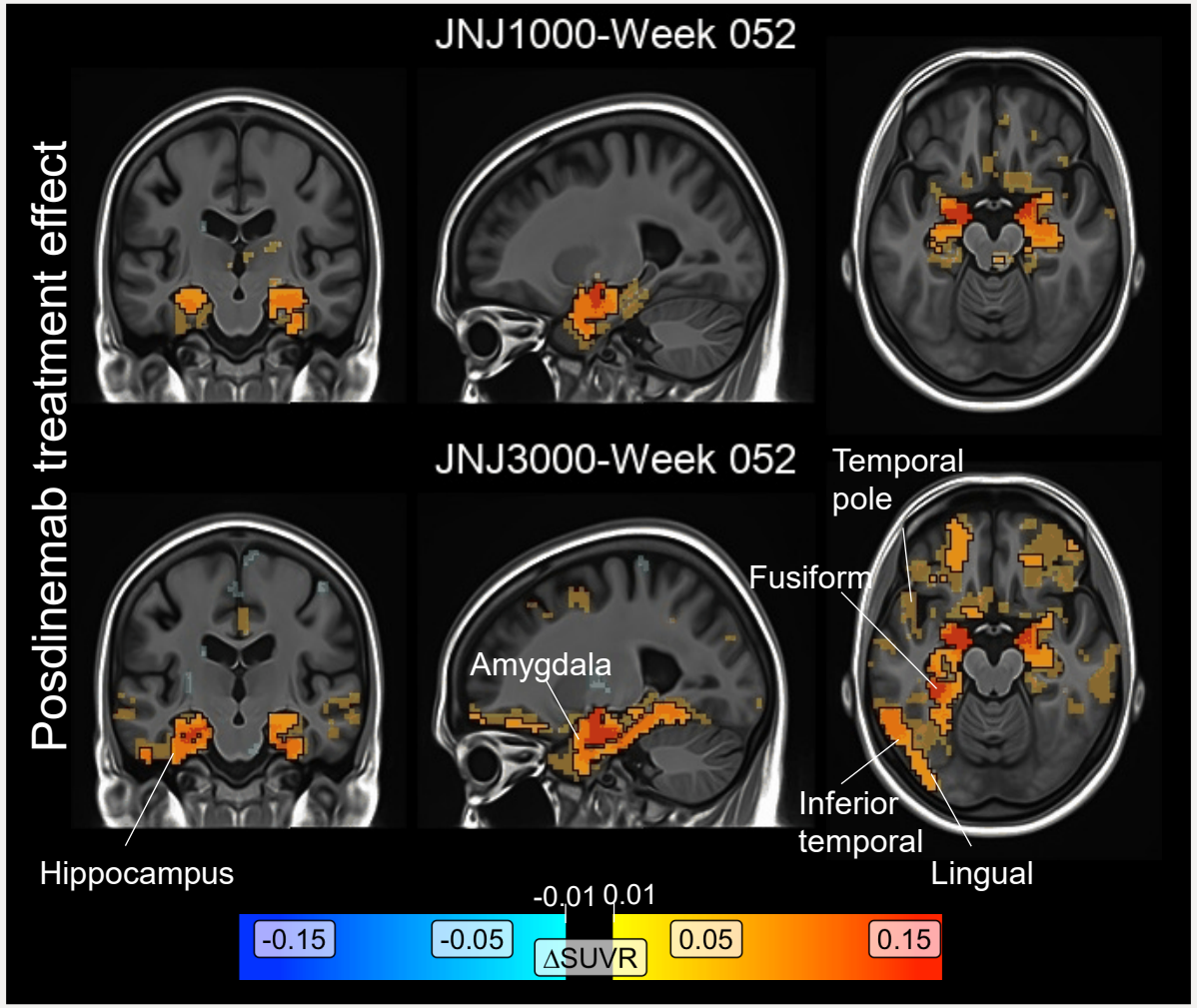
Number of participants			
Posdinemab 1000	170	147	138
Posdinemab 3000	175	154	130
PLA	175	155	137

1. Cohen S, et al. Results from the Phase 2b Autonomy Trial of Anti-p-tau Monoclonal Antibody Posdinemab for Early Alzheimer's Disease. Presented at the 20th International Conference on Alzheimer's and Parkinson's Diseases, Copenhagen, Denmark, 21 March 2026; abstract ID 3062.

LS, least squares; NFT, neurofibrillary tangle; PLA, placebo; PET, positron emission tomography; ROI, region of interest; SE, standard error; SUVR, standardized uptake value ratio.

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Objective: Evaluate three spatial factors that may account for observed regional differences in posdinemab treatment effect on tau PET



Spatial determinants for posdinemab treatment effect

- Baseline (BL) tau PET standardized uptake value ratio (SUVR)
- Distance to ventricular cerebrospinal fluid (dCSFv)
- Neurodegeneration (ND) measured by gray matter volume

BL, baseline; CSF, cerebrospinal fluid; dCSFv, distance to ventricular cerebrospinal fluid; ND, neurodegeneration; PET, positron emission tomography; SUVR, standardized uptake value ratio.

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Methods: Tau PET SUVR and Distance to Ventricular CSF

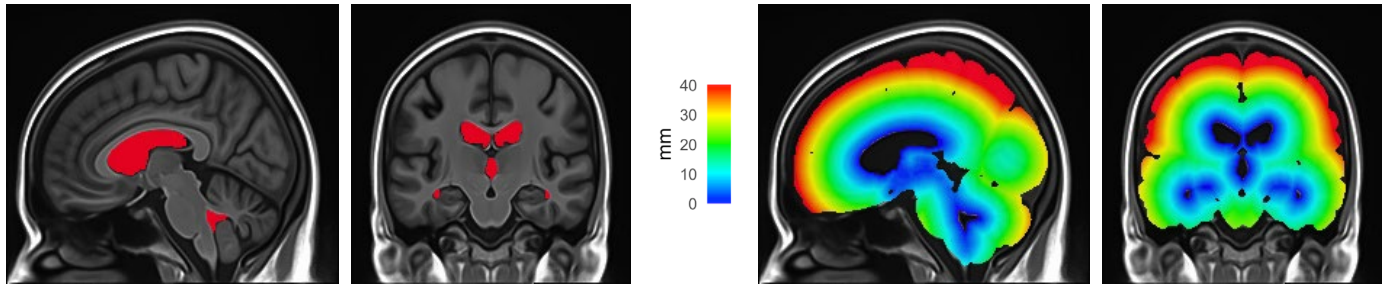
Tau PET SUVR

- SUVR maps were generated within gray matter voxels using the cerebellar gray as a reference region
- Longitudinal PET scans were aligned to the spatial midpoint to avoid longitudinal bias

Distance to ventricular CSF (dCSFv)

- A voxel's distance to CSF was set to its shortest distance to ventricular CSF

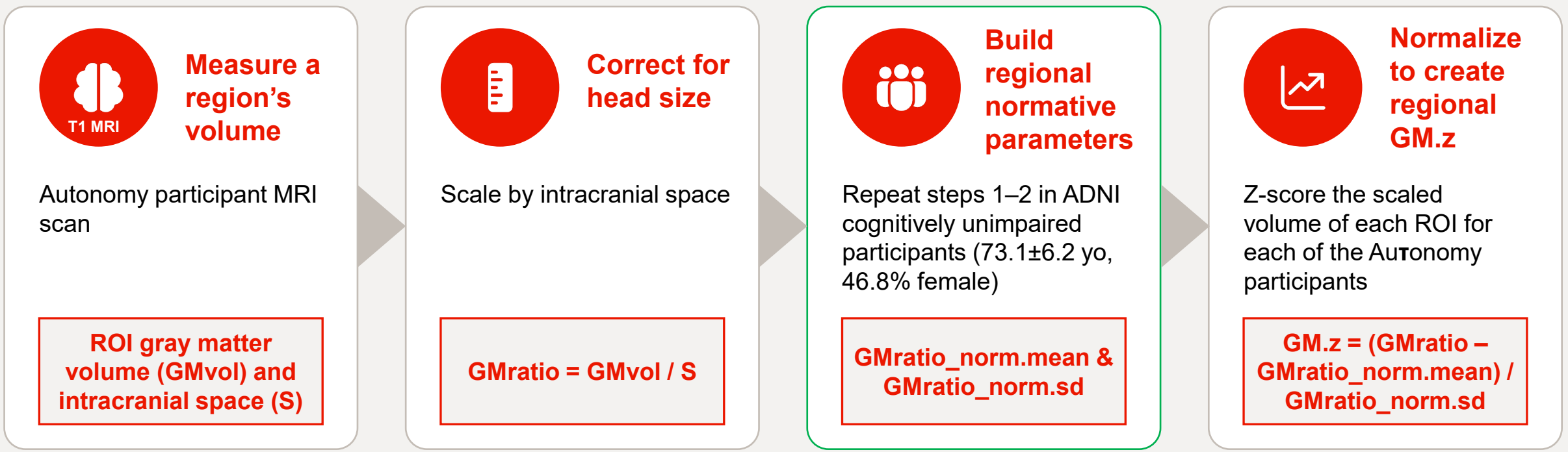
Ventricle mask | **Distance to ventricle**



CSF, cerebrospinal fluid; PET, positron emission tomography; SUVR, standardized uptake value ratio.

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Methods: Neurodegeneration (ND) estimation



- **Neurodegeneration (ND) = −1 * GM volume z score**

ADNI, Alzheimer's Disease Neuroimaging Initiative; GM, gray matter; GMratio, gray matter volume/intracranial space ratio; GMvol, gray matter volume; GM.z, gray matter z-score; MRI, magnetic resonance imaging; ND, neurodegeneration; ROI, region of interest; S, intracranial space; sd, standard deviation.

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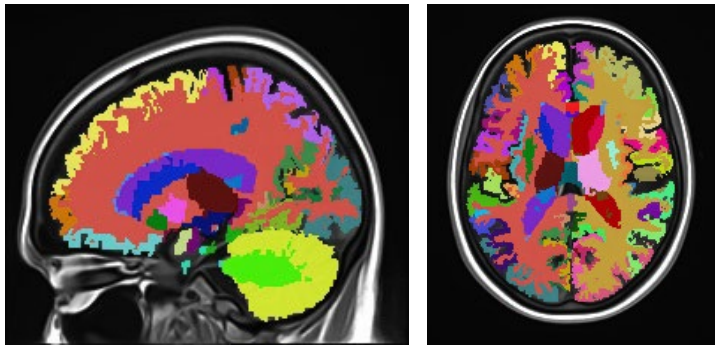
Methods: A common domain for simultaneous modeling of all three factors using the Schaeffer-232 parcellation

- Unlike tau PET SUVR and ventricular CSF distance, Neurodegeneration (ND) is measured at the level of brain segmentations.
- To model all 3 factors together, we map them to the Schaefer-232 parcellation which tiles the cortex with a fine, uniform set of cortical patches

FreeSurfer parcellation

Anatomical segmentation

FreeSurfer draws anatomy-based ROIs that are variable in size and shape

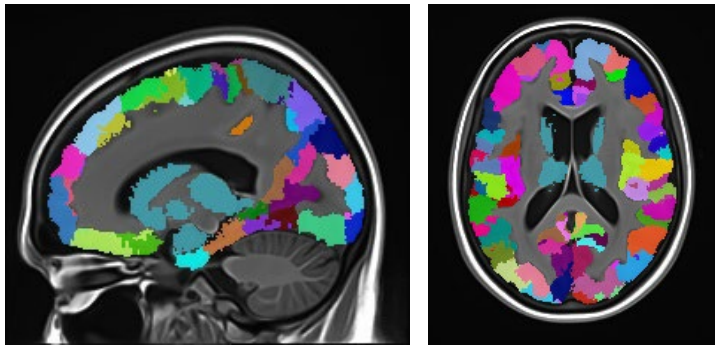


FS segmentation

Schaefer-232 parcellation

Uniform parcellation

Schaefer-232 divides the cortical and subcortical regions into fine, uniform, connectivity-based patches[1—3]

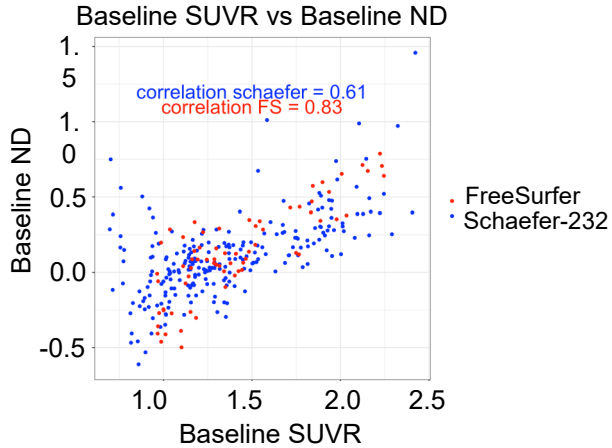


Schaefer-232

BL SUVR vs BL ND

Simultaneous modeling

Baseline SUVR and baseline ND are correlated under both parcellations



ND = −1 * GM volume z score

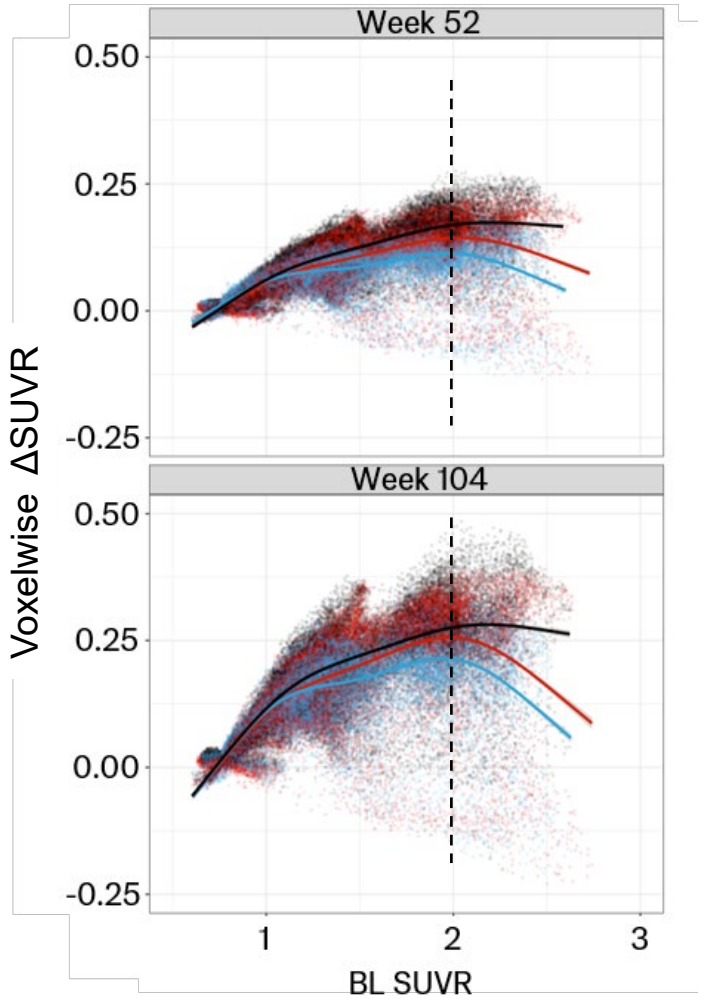
1. Schaefer A, et al. *Cereb Cortex*. 2018:28(9):3095-3114. 2.Tian Y, et al. *Nat. Neurosci.* 2020:23(11):1421-1432. 3.Luppi AI, et al. *Netw Neurosci.* 2021:5(1):96-124.

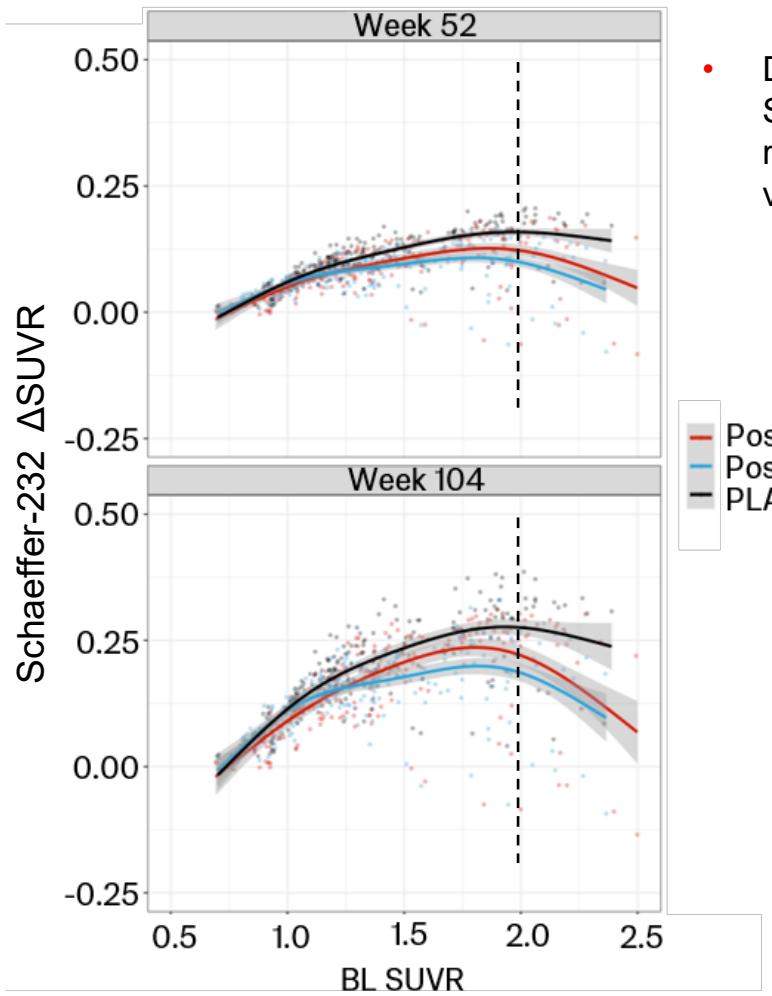
BL, baseline; CSF, cerebrospinal fluid; FS, FreeSurfer; GM, gray matter; ND, neurodegeneration; PET, positron emission tomography; ROI, region of interest; SUVR, standardized uptake value ratio.

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Results: Overall, change of SUVR is positively correlated with baseline tau PET SUVR, however not uniformly

- Average ΔSUVR rises with baseline SUVR until ~2.0 where it plateaus in the placebo arm and begins to drop in the active arms





- Data from the Schaefer-232 ROIs reproduce the voxelwise pattern

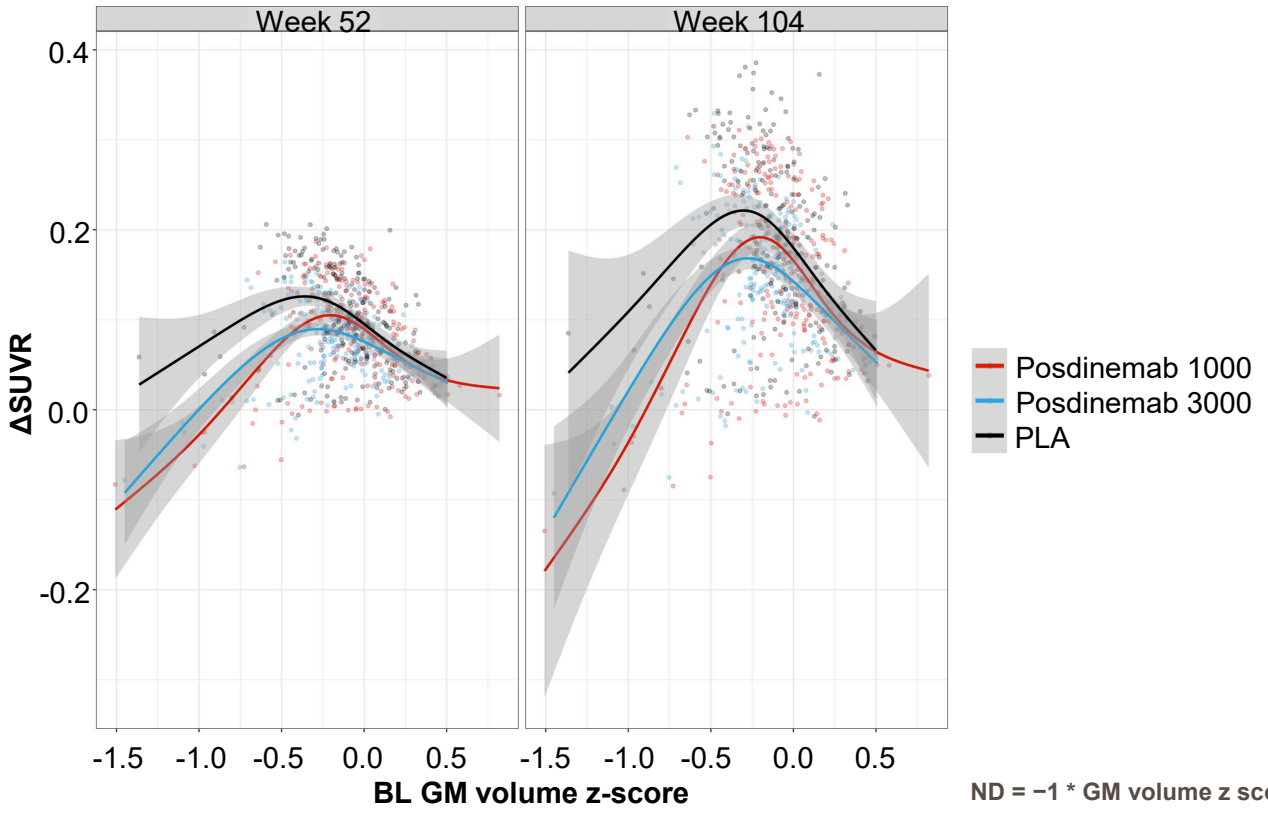
BL, baseline PLA, placebo; PET, positron emission tomography; SUVR, standardized uptake value ratio.

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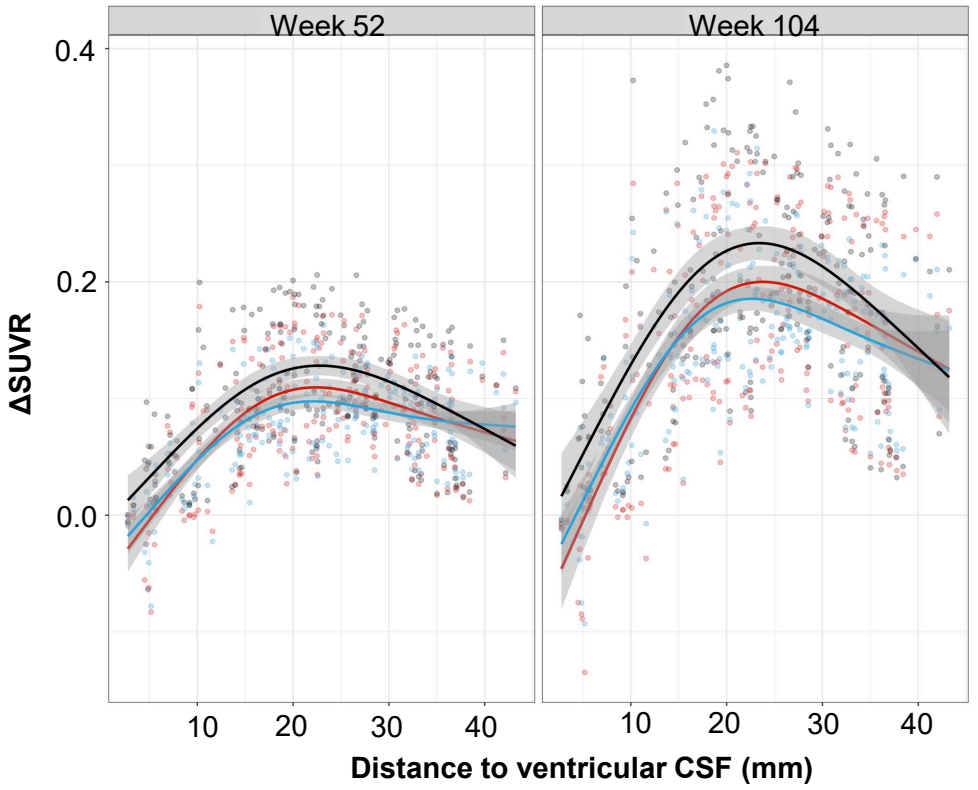
Results: Non-monotonic relationships between change in SUVR and each of BL GM volume and dCSFv

- ΔSUVR peaks at intermediate BL GM volume, both doses below placebo

ΔSUVR vs BL GM Volume Schaeffer-232



ΔSUVR vs dCSFv Schaeffer-232

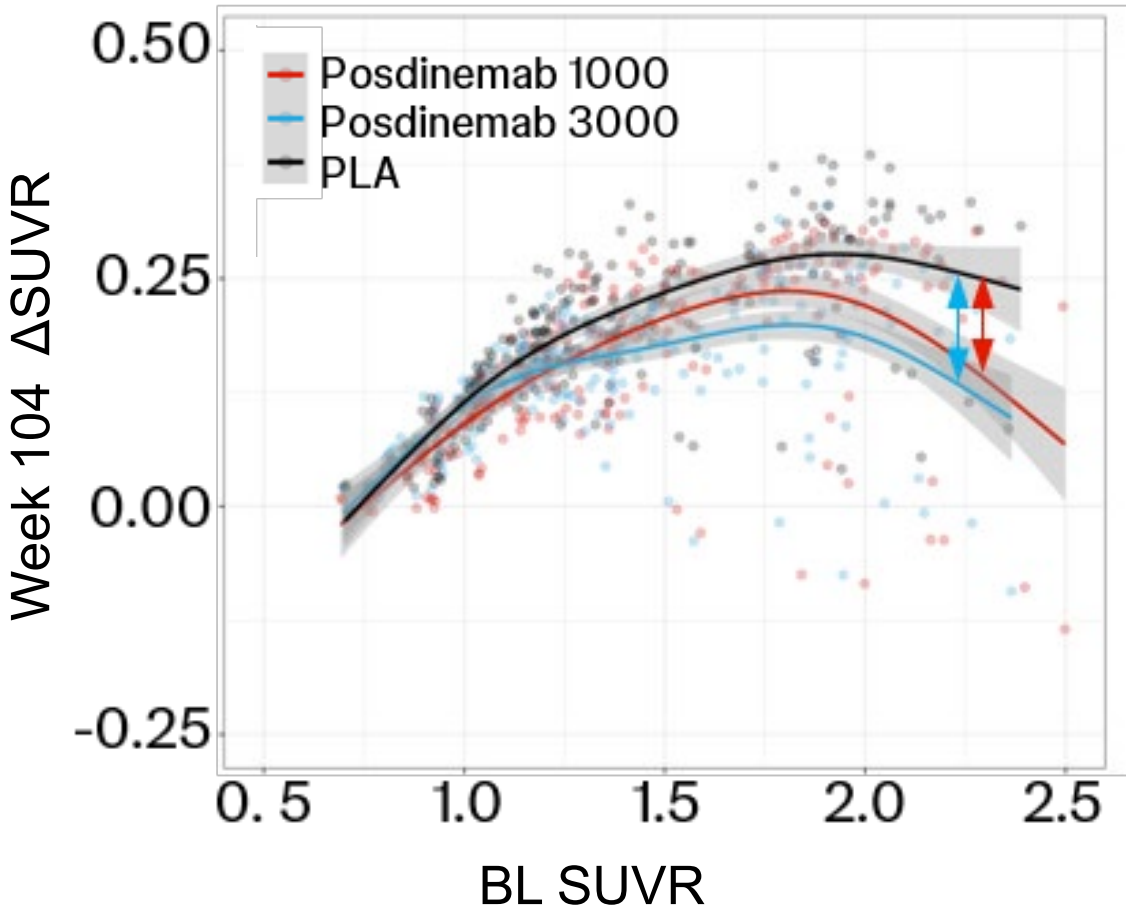


BL, baseline; CSF, cerebrospinal fluid; dCSFv, distance to ventricular CSF; GM, grey matter; PET, positron emission tomography; PLA, placebo; SUVR, standardized uptake value ratio.
Data over Shaeffer-232 ROIs

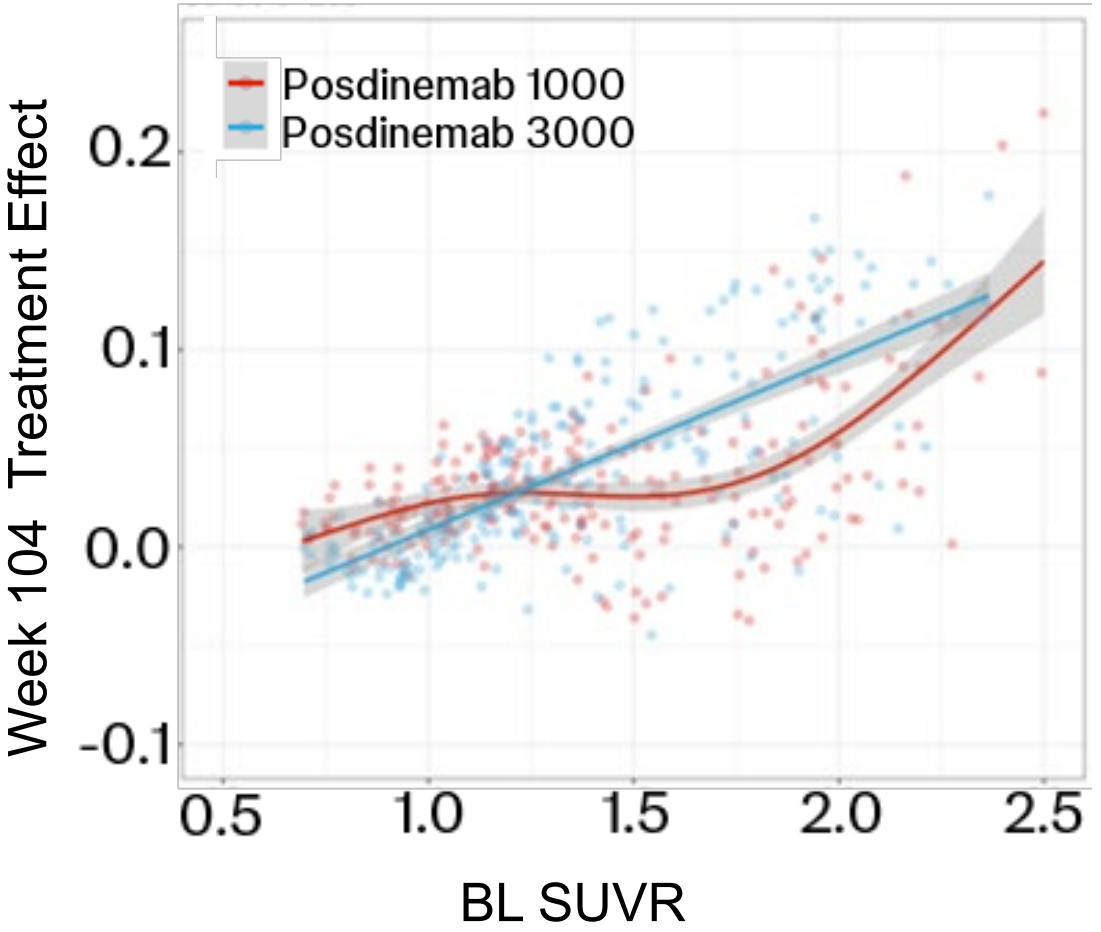
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In the following we examine the spatial factors' contributions to the treatment effects of posdinemab on tau PET

Week 104 change in SUVR vs BL SUVR



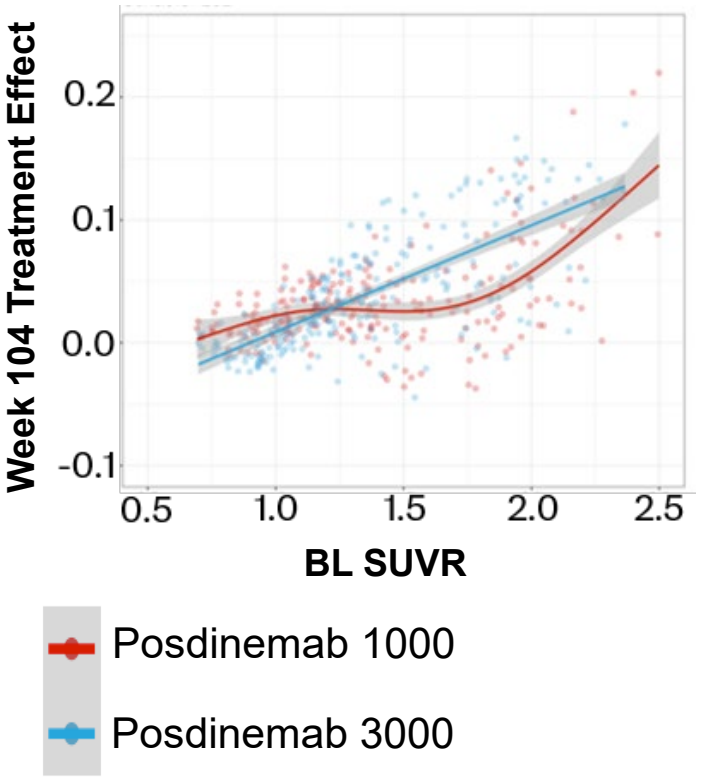
Week 104 tau PET treatment effect vs BL SUVR



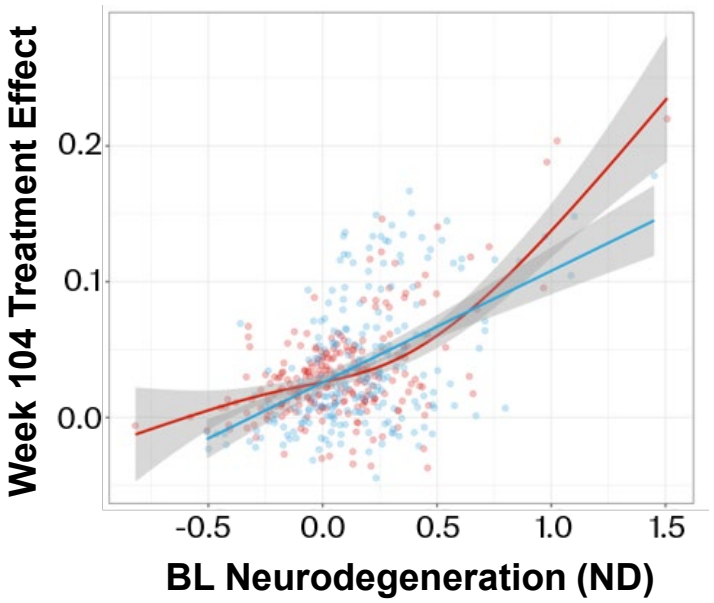
Data over Shaeffer-232 ROIs

Results: Posdinemab treatment effect increased with baseline tau PET SUVR, neurodegeneration; decreased with distance to ventricular CSF at the low dose

Baseline tau PET SUVR

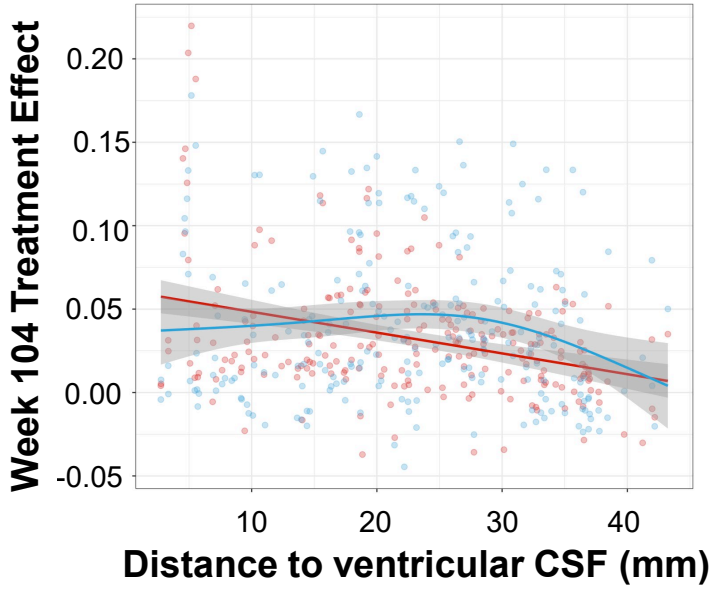


Neurodegeneration



ND = -1 * GM volume z score

Distance to ventricular CSF



CSF, cerebrospinal fluid; GM, gray matter; ND, neurodegeneration; PET, positron emission tomography; SUVR, standardized uptake value ratio.
Data over Shaeffer-232 ROIs

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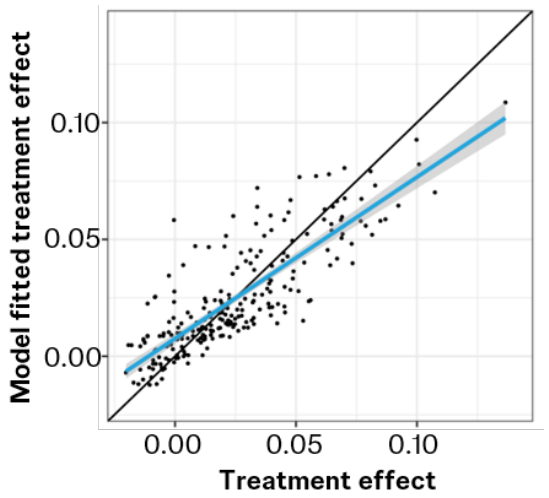
Results: At the low dose, all three spatial factors contribute to treatment effects on tau PET; at the high dose, only baseline tau SUVR contributes

- At the low dose, at Week 52 and 104, a stronger treatment effect on NFTs was observed in regions with:
  - Higher BL SUVR
  - Higher BL ND
  - Combined elevation in BL SUVR & ND (interaction)
  - proximity to ventricular CSF
- At the higher dose, only BL SUVR was associated with a stronger treatment effect on NFTs at Week 52 and 104
  - BL ND and dCSFv were nominally significant at Week 52 only

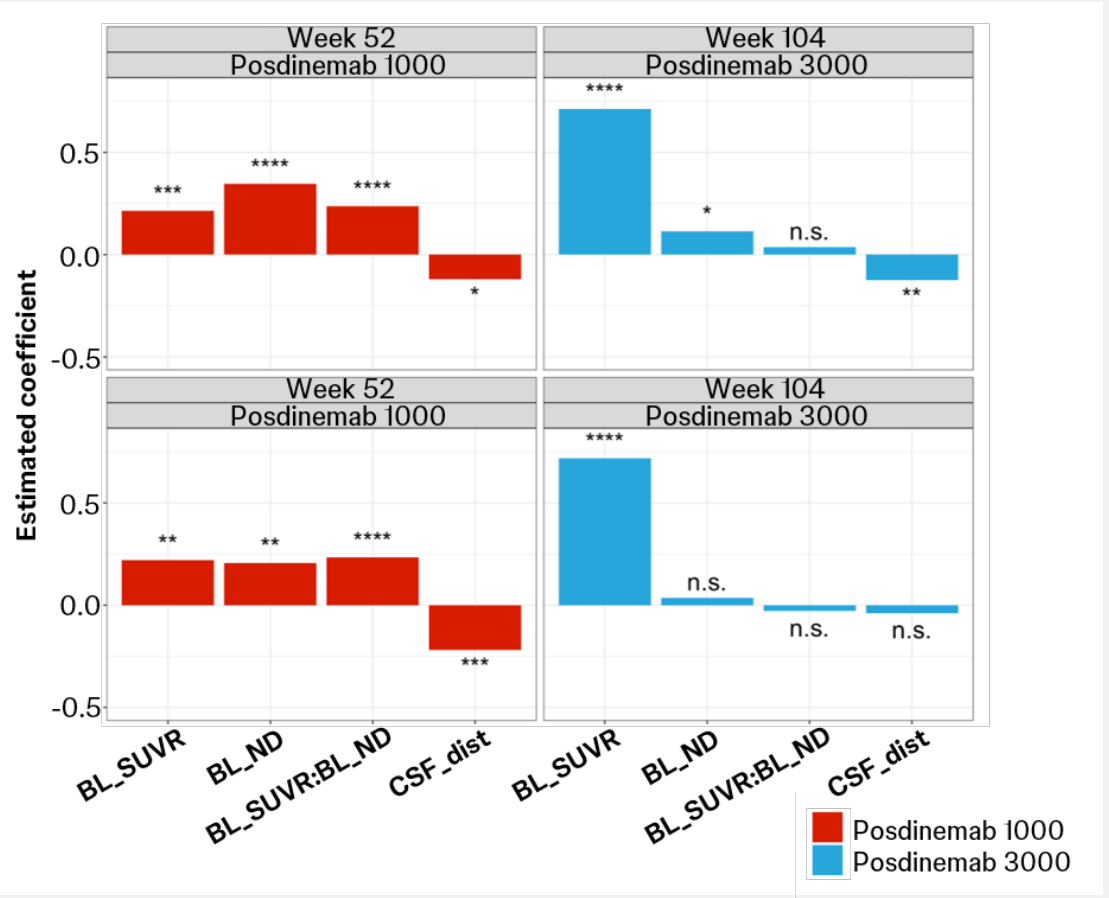
$Effect_{NFTs}$ ~ BL SUVR * BL ND + CSF_{dist}

Fraction of variance explained (R^2)

	Posdinemab 1000	Posdinemab 3000
Week 52	0.56	0.69
Week 104	0.46	0.53



Linear model estimated coefficients



BL, baseline; CSF, cerebrospinal fluid; CSFdist, distance to ventricular CSF (dCSFv); FU, follow-up; ND, neurodegeneration; NFT, neurofibrillary tangle; SUVR, standardized uptake value ratio.
Data over Shaeffer-232 ROIs. Significance levels: P < 0.05, *; P < 0.01, **; P < 0.001, ***; P < 0.0001, ****; n.s. not significant.

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Conclusions: More NFT pathology → More slowing of NFT accumulation

- In Autonomy, posdinemab slowed NFT accumulation only modestly, with no measurable effect on the spatial spread of tau pathology
- At the low dose, regional effects on NFTs were greater where baseline NFT burden and baseline ND were higher and with proximity to ventricular CSF
- At the higher dose, baseline NFT burden remained the only significant spatial factor at both week 52 and week 104
- Diminished contributions of baseline ND and distance to ventricular CSF at 3000mg are consistent with dose saturation
  - The 1000 mg dose did not show a saturation of effect, despite 90% target engagement in CSF at trough
- Current data support either a mass-action model of tau clearance across the cell membrane, or a clearance mechanism from engagement of posdinemab with NFTs inside the neuron. More research is required to elucidate the mechanism of NFT slowing

BL, baseline; CSF, cerebrospinal fluid; mAb, monoclonal antibody; ND, neurodegeneration; NFT, neurofibrillary tangle.

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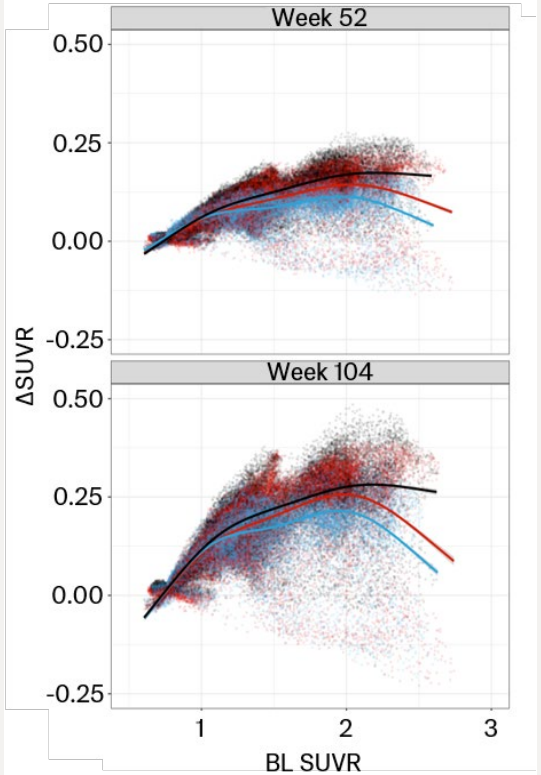
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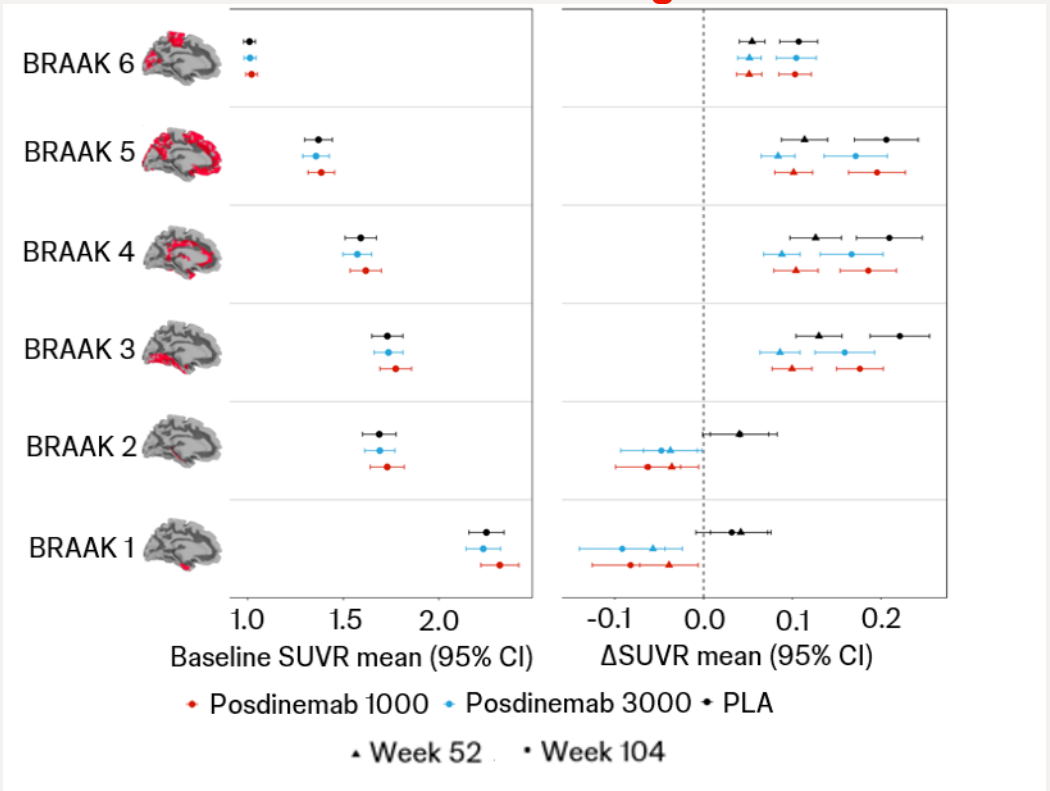
Results: Overall, change of SUVR is positively correlated with baseline tau PET SUVR, however not uniformly

- ΔSUVR rises with baseline SUVR and plateaus near 2.0
- Change of SUVR vs baseline tau at Braak regions:
  - Braak 1&2: high BL SUVR, little SUVR growth
  - Braak 3-6: SUVR growth scales with BL SUVR
- Schaefer-232 reproduces the voxelwise pattern

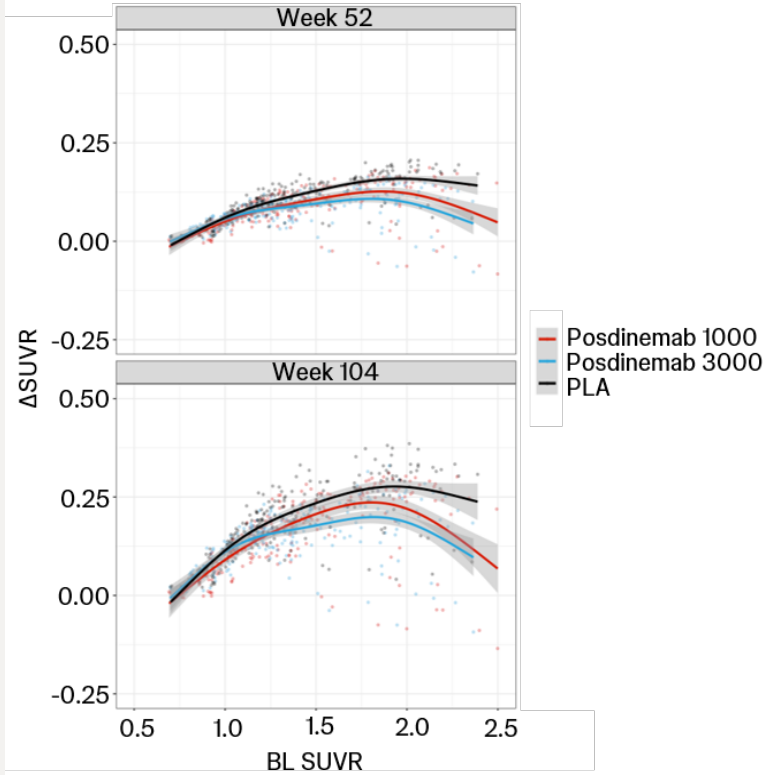
Voxelwise



BL Tau PET **Change of Tau PET**



Schaeffer-232



BL, baseline PLA, placebo; PET, positron emission tomography; SUVR, standardized uptake value ratio.

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