

Consistent Cognitive and Functional Outcomes Across Prespecified Subgroups in the Phase 2b Autonomy Trial Evaluating Posdinemab in Early Alzheimer’s Disease

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Background

- Posdinemab is an anti-phosphorylated tau monoclonal antibody evaluated in the Phase 2b Autonomy study in participants with early Alzheimer's disease (AD).¹
- Early AD trials require sensitive clinical outcome assessments capable of detecting subtle cognitive and functional decline over time.²
- Autonomy prospectively incorporated complementary cognitive, functional and global/composite endpoints to evaluate disease progression.¹⁻⁴
- Consistency across multiple clinical outcome measures may strengthen interpretation of treatment effects and support endpoint selection for future AD trials.²⁻⁵
- This analysis evaluated the performance of all efficacy assessments across treatment groups and prespecified participant subgroups through Week 104 of the double-blind study period.

Methods

- The proof-of-concept, Phase 2b Autonomy study (NCT04619420) was a randomized, double-blind, placebo-controlled trial evaluating posdinemab in participants with early AD (clinical diagnosis of mild cognitive impairment [MCI] and/or mild dementia due to AD); screening Clinical Dementia Rating [CDR] - Global Score 0.5).
- Participants were randomized 1:1:1 to placebo, posdinemab 1000 mg, or posdinemab 3000 mg, administered IV every 4 weeks, for at least 104 weeks in the double-blind period.
- Clinical outcome assessments were selected to capture complementary domains of cognition, daily function, and global clinical status, enabling evaluation of consistency across six complementary AD instruments.

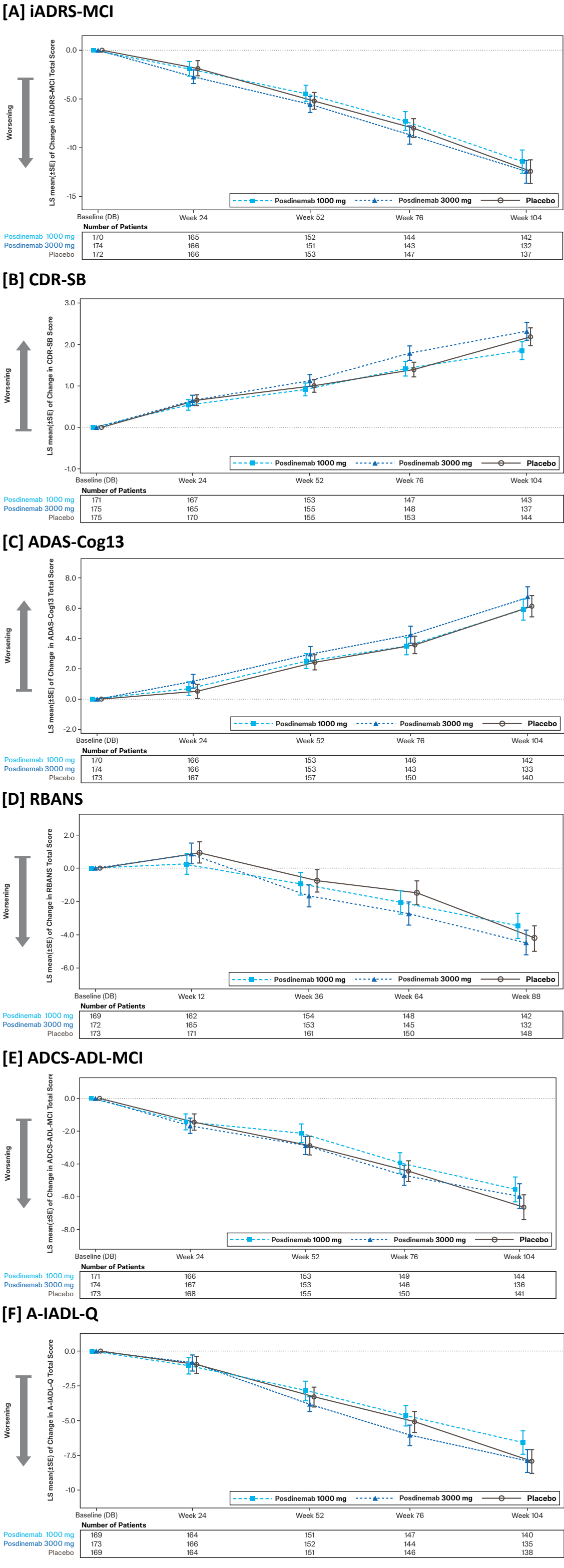
Cognition/ function	- Integrated AD Rating Scale for Mild Cognitive Impairment (iADRS-MCI, primary) - CDR - Sum of Boxes (CDR, secondary)
Cognition	- Alzheimer's Disease Assessment Scale - Cognitive, 13-Item Version (ADAS-Cog13, key secondary) - Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, secondary)
Function	- Alzheimer's Disease Cooperative Study Activities of Daily Living for Mild Cognitive Impairment (ADCS-ADL-MCI, key secondary) - Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q, exploratory)

- Longitudinal analyses were performed through Week 104 to characterize trajectories of clinical decline and assess consistency across efficacy outcome measures.
- Prespecified subgroup analyses assessed the consistency of treatment effects across demographic, clinical, biomarker, and genetic subgroups. Baseline tau PET burden, a potential modifier of clinical outcomes, was used to stratify analyses.
- Multivariate O'Brien composite analyses were used to assess multidimensional treatment effects at Week 104 across the full endpoint framework and determine whether observed patterns reflected a coherent clinical signal.

Results

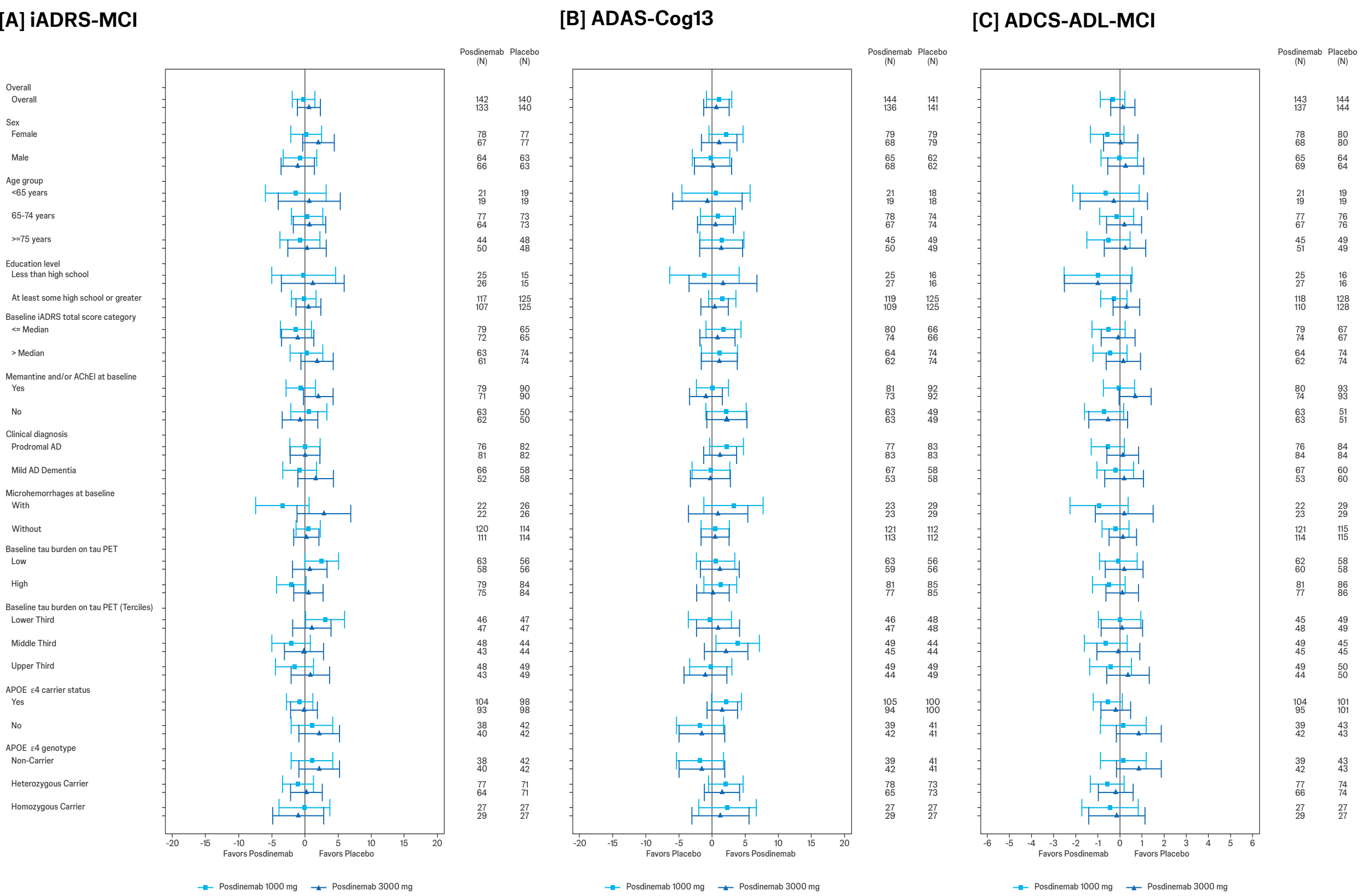
- Clinical outcome assessments demonstrated consistent patterns of disease progression**
- Clinical outcome assessments demonstrated progressive cognitive and functional decline over 104 weeks, consistent with the expected course of early AD.
 - No significant differences were observed between posdinemab and placebo treatment groups across any efficacy endpoint.

Figure 1. Longitudinal Change Through Week 104 Across Clinical Outcome Assessments



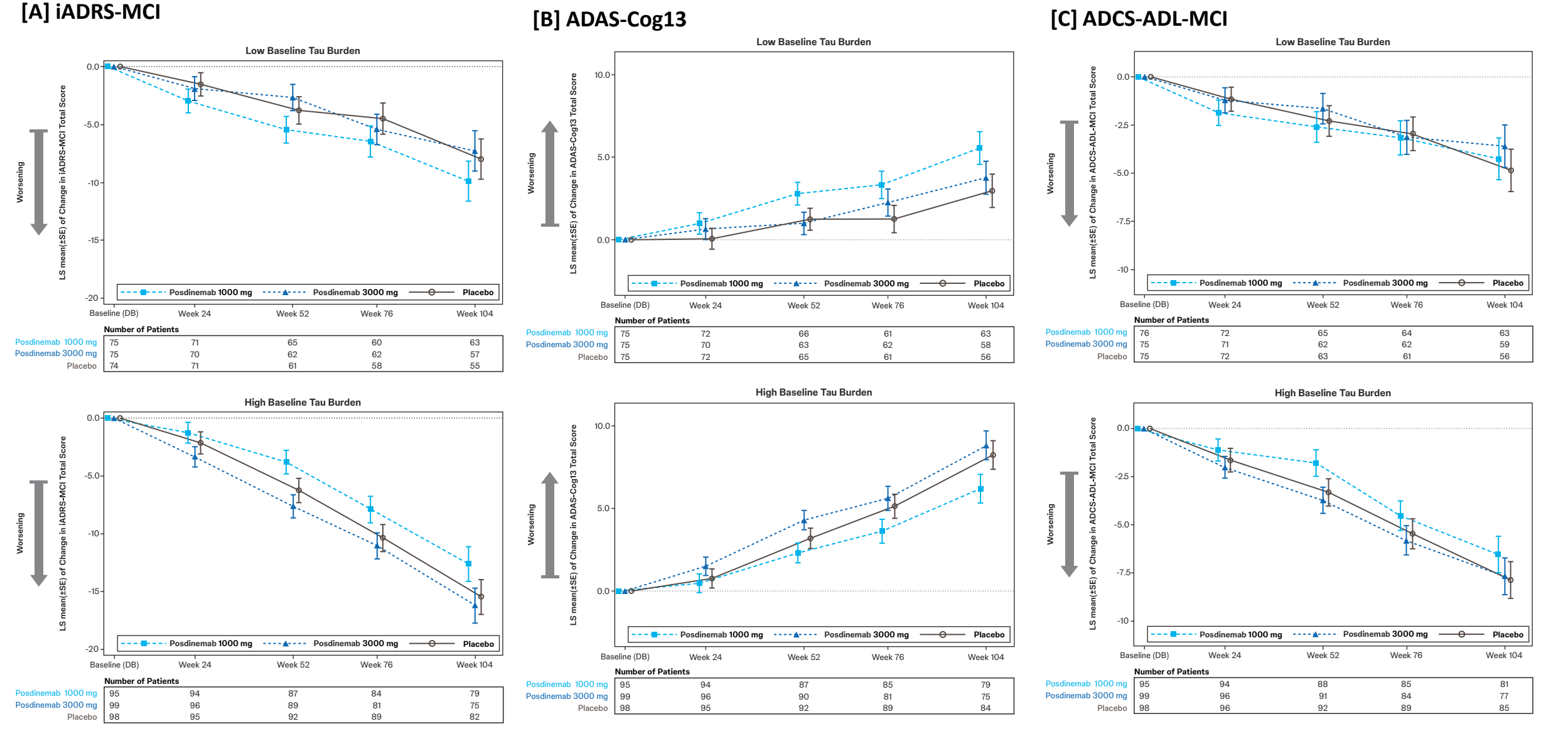
- Treatment effects were consistent across prespecified subgroups**
- Treatment effects were consistently centered near null (zero) across all prespecified subgroup analyses.
 - Confidence intervals overlapped zero for all clinical outcome assessments.
 - The absence of directional separation across demographic, clinical, biomarker, and genetic subgroups suggests that the overall neutral finding was not driven by a specific participant subgroup.

Figure 2. Forest Plot Analyses Across Clinical Outcome Assessments



- Baseline tau burden was associated with differences in rate of clinical decline but not differential treatment response**
- Participants with high baseline tau burden experienced greater cognitive and functional decline than those with low tau burden across all evaluated outcome measures.
 - The prognostic effect of tau burden was directionally consistent across evaluated endpoints.
 - No significant differences between posdinemab and placebo were observed within either tau burden subgroup.
 - These findings suggest that baseline tau burden was prognostic of disease progression but not predictive of treatment response.

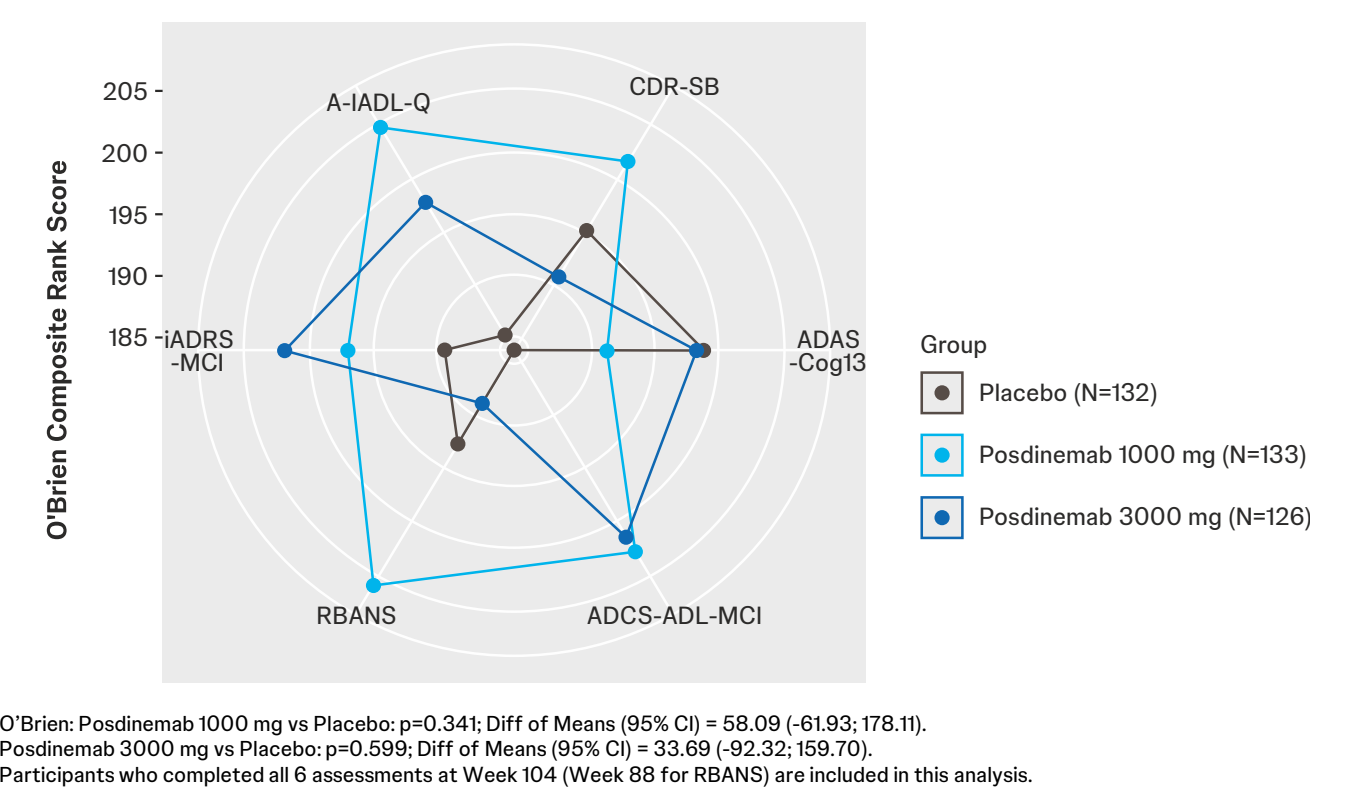
Figure 3. Longitudinal Outcomes by Baseline Tau Burden [iADRS-MCI, ADAS-Cog13, ADCS-ADL-MCI]



Multidimensional treatment effects did not demonstrate coherent clinical signal

- O'Brien composite analyses demonstrated substantial overlap across treatment groups.
- No consistent or reproducible dose-response pattern was observed.
- Variability observed within individual endpoints did not translate into a coherent multidimensional treatment effect.
- Integrated assessment across the full endpoint framework supported the interpretation that observed differences were not clinically meaningful.

Figure 4. O'Brien Multivariate Composite Radar Plot



Key Takeaways

- Clinical outcome assessments demonstrated coherent and consistent patterns of disease progression across treatment groups, participant subgroups, and analytical approaches through Week 104.
- No clinically meaningful treatment effect of posdinemab was observed, supporting the robustness and interpretability of the Autonomy endpoint framework in early AD.

Conclusions

- Participants with early AD demonstrated consistent cognitive and functional decline across clinical outcome assessments with no evidence of clinical efficacy for posdinemab across predefined subgroups or dose levels.
- Clinical outcome assessments showed consistent trajectories of decline and concordant findings across prespecified subgroup, biomarker, and multivariate analyses.
- Consistent findings across composite, cognitive, and functional assessments support the robustness, coherence, and interpretability of the endpoint framework used in the Autonomy trial.

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Disclosures

MG-VC, JB, PCC, MF, P-JB, HX, ZSS, FE, AS, and JW: Are employees of Johnson & Johnson and may hold stock and stock options. AV: Was a paid consultant in Johnson & Johnson during the study period. DH: Was an employee of Johnson & Johnson at the time of the study and may hold stock or stock options of Johnson & Johnson.

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List of Abbreviations

ADAS-Cog13=Alzheimer's Disease Assessment Scale - Cognitive Subscale 13-item version; ADCS-ADL-MCI=Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory for Mild Cognitive Impairment; A-IADL-Q=Amsterdam Instrumental Activities of Daily Living Questionnaire; CDR-SB=Clinical Dementia Rating - Sum of Boxes; iADRS-MCI=integrated Alzheimer's Disease Rating Scale - Mild Cognitive Impairment version; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status.

Alzheimer’s Disease



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1. ClinicalTrials.gov. NCT04619420. Available at: <https://clinicaltrials.gov/study/NCT04619420>. 2. U.S. Food and Drug Administration. February 2018. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/early-alzheimers-disease-developing-drugs-treatment-guidance-industry>. 3. Wessels et al., *Alzheimers Dement* (N Y). 2022 Jun 8(11):e12312. 4. Rosen et al., *Am J Psychiatry*. 1984 Nov;141(11):1358-64. 5. O'Bryant et al., *Arch Neurol*. 2008 Aug;65(8):1091-5.