GAP- Global Alzheimer's Platform Foundation Webinar

Aducanumab Data Review

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Forward-Looking Statements

- This presentation contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to results from the Phase 3 clinical studies of aducanumab; the potential clinical effects of aducanumab; the potential benefits, safety, and efficacy of aducanumab; potential regulatory discussions, submissions, and approvals and the timing thereof; clinical development programs, clinical trials, data readouts, and presentations related to aducanumab; the treatment of Alzheimer's disease; the potential of Biogen's pipeline programs, including aducanumab; and risks and uncertainties associated with drug development and commercialization. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "intend," "may," "plan," "potential," "possible," "will," "would," and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical trials may not be indicative of full results or results from later-stage or larger-scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.

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Statement on Aducanumab

Aducanumab is an investigational drug that is currently under regulatory review. It is not approved for use in any country at this time.

Thank You to Everyone Who Has Contributed to Alzheimer's Disease Research!

Aducanumab Phase 3 trials included 3285 patients at 348 sites in 20 countries

Countries with active sites included:
Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

Biogen Position on the FDA Advisory Committee

Biogen stands behind the analyses and results of aducanumab:

- The core joint briefing book (FDA & Biogen) is the first ever in the neurology division
- The totality of data provides substantial evidence of clinical effectiveness of aducanumab, as demonstrated by study 302 (EMERGE) and supported by study 103 (PRIME)
- Biogen and the FDA concluded that partially discordant results of study 301 (ENGAGE) do not meaningfully detract from the persuasiveness of study 302

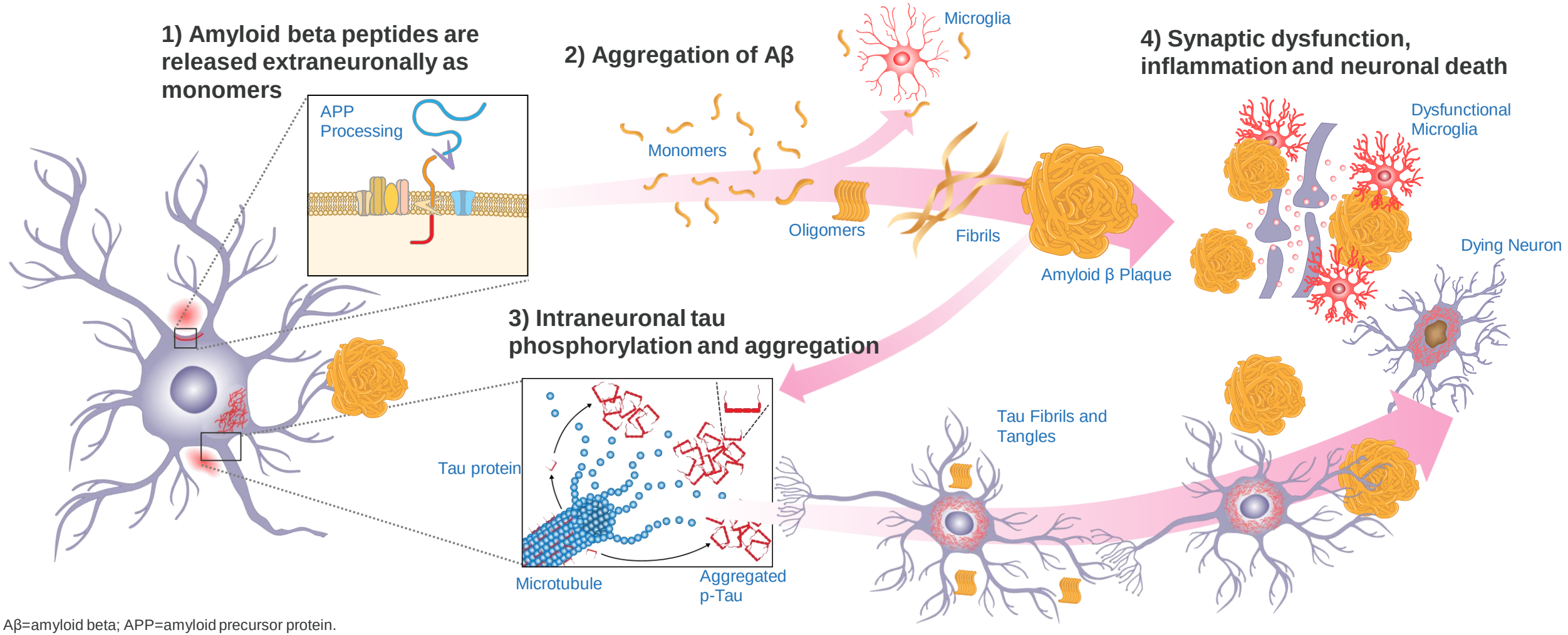
- We have applied the highest scientific rigor and integrity in the analyses submitted
- We recognize the complexity of the dataset and the challenges associated with the first positive Ph3 study in Alzheimer

Alzheimer's Disease Presents a Significant Unmet Medical Need

- As of 2018, there were about 50 million people living with dementia worldwide[a]
- Progressive neurological disorder resulting in memory loss, behavioral symptoms, and loss of ability to perform daily activities
- In advanced stages of dementia patients become completely dependent
- Alzheimer's disease is ultimately fatal
- No available treatment that alters the course of disease

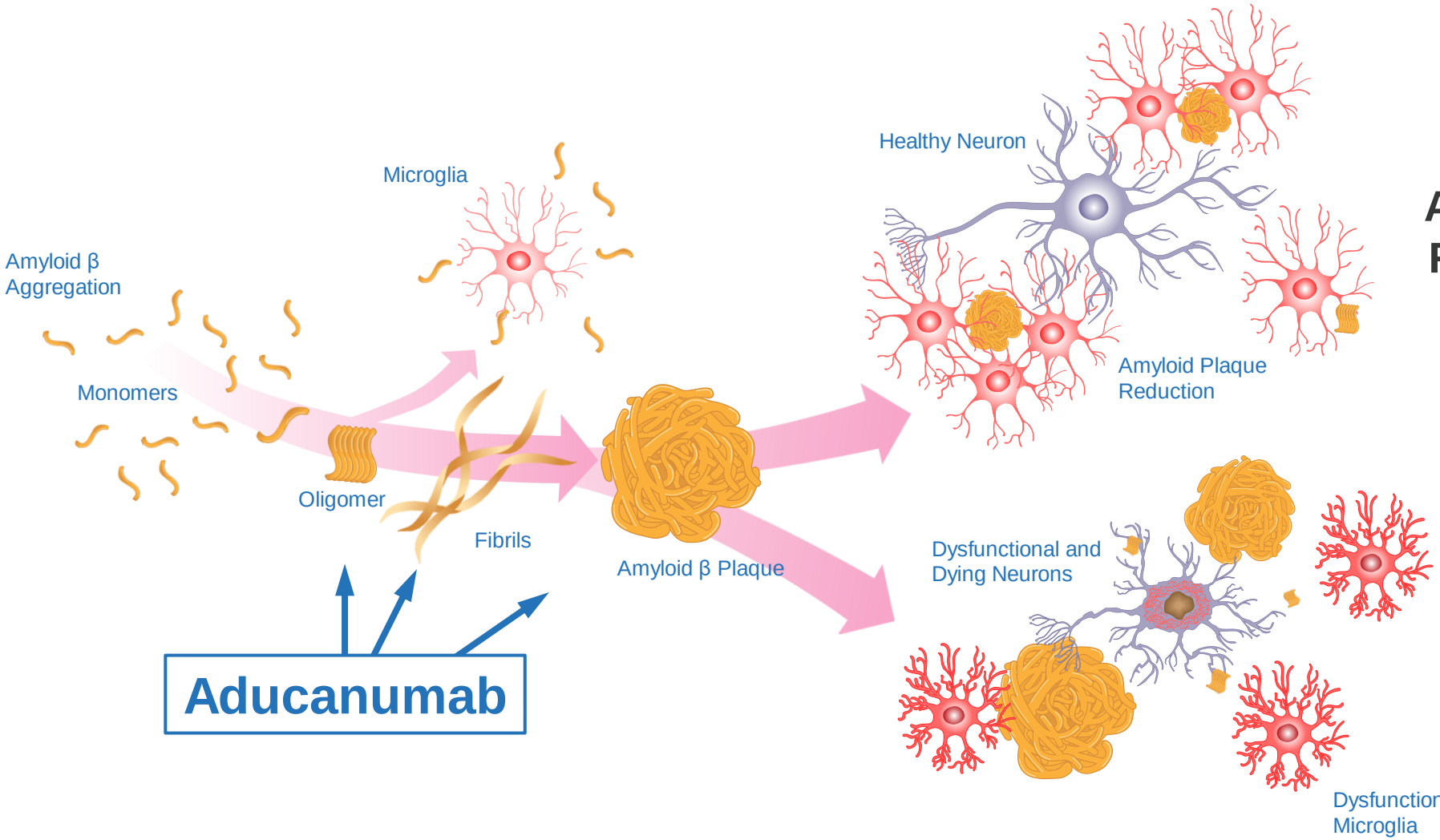
[a] 2018 Alzheimer's Disease International .

The Two Pathological Hallmarks of Alzheimer's Disease in the Brain Are Aβ Plaques and Neurofibrillary Tangles



Aβ=amyloid beta; APP=amyloid precursor protein.
Based on Pospich S, Raunser S. *Science.* 2017;358(6359):45-46.

Aducanumab: Targeting Alzheimer's Disease Pathology



Aducanumab Treatment: Reduced Progression of Alzheimer's Disease

No treatment

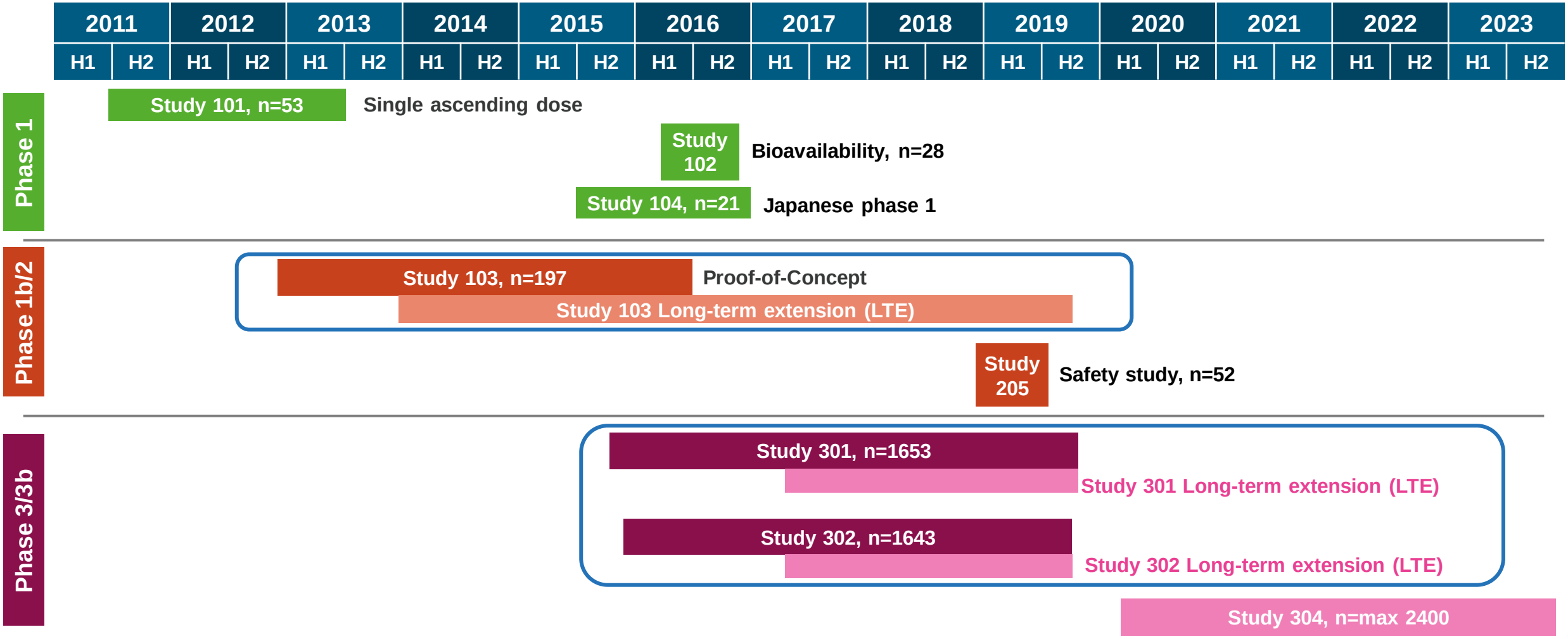
Aducanumab Is Differentiated From the First Generation of Anti-Aβ Antibodies

Molecular Characteristics of Aducanumab	Key Clinical Trial Design Elements
• Specificity for neurotoxic aggregated forms of Aβ • Effector-function enabling immune cell-mediated clearance of aggregated Aβ	• Inclusion of patients with biomarker-confirmed early symptomatic Alzheimer's disease • Demonstration of robust reduction in pathology • Appropriate clinical outcome measures

- Aducanumab was the first of this generation of antibodies to demonstrate proof of concept before initiating phase 3 trials
- Aducanumab is the only program at this time to have read out with positive results in phase 3 trials*

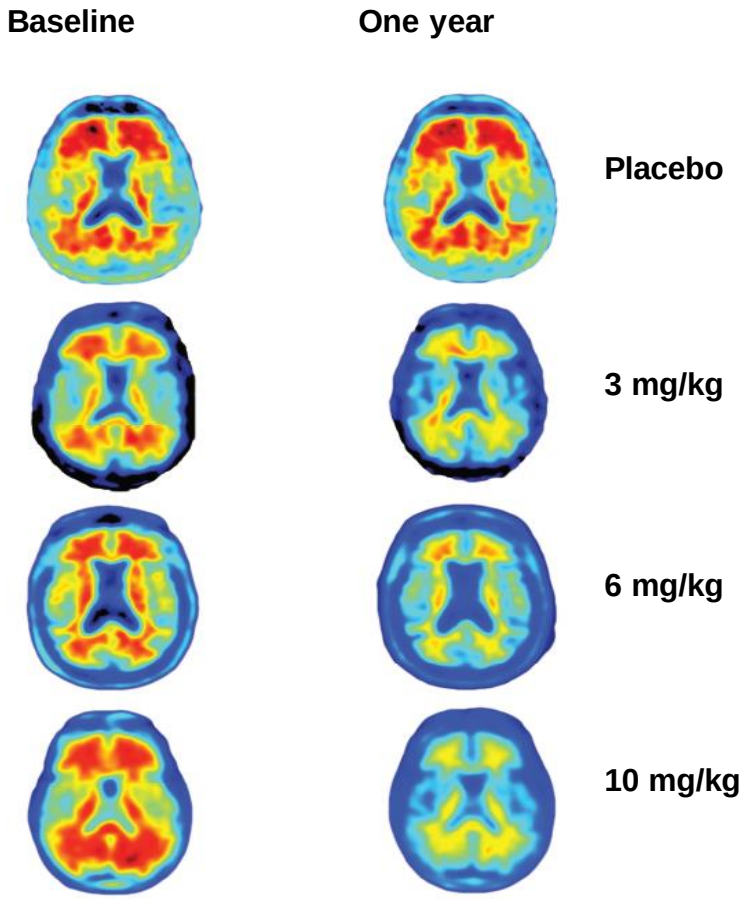
*Primary and secondary endpoints were met in Study 302. In Study 301, patients with the opportunity for full 10mg/kg dosing had results similar to Study 302.

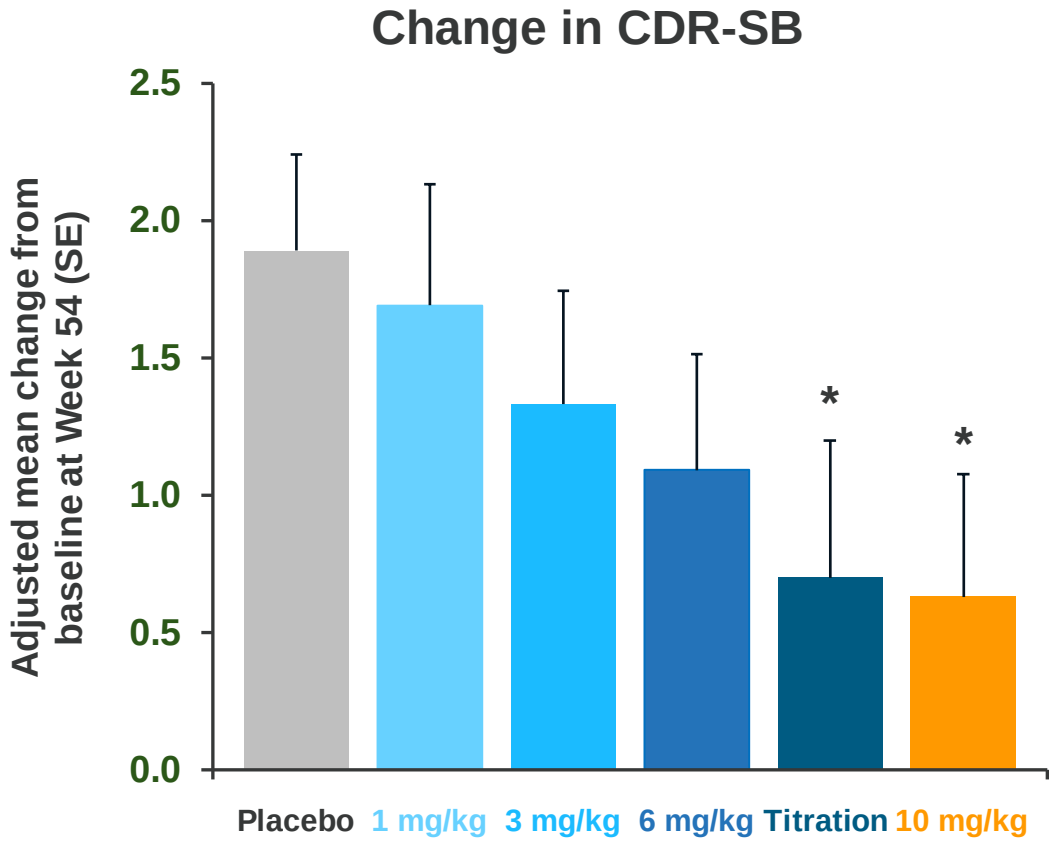
Aducanumab Clinical Development Program



Phase 1b Study 103

Aducanumab Was the First Program Where Proof-of-Concept Was Demonstrated Prior to Phase 3



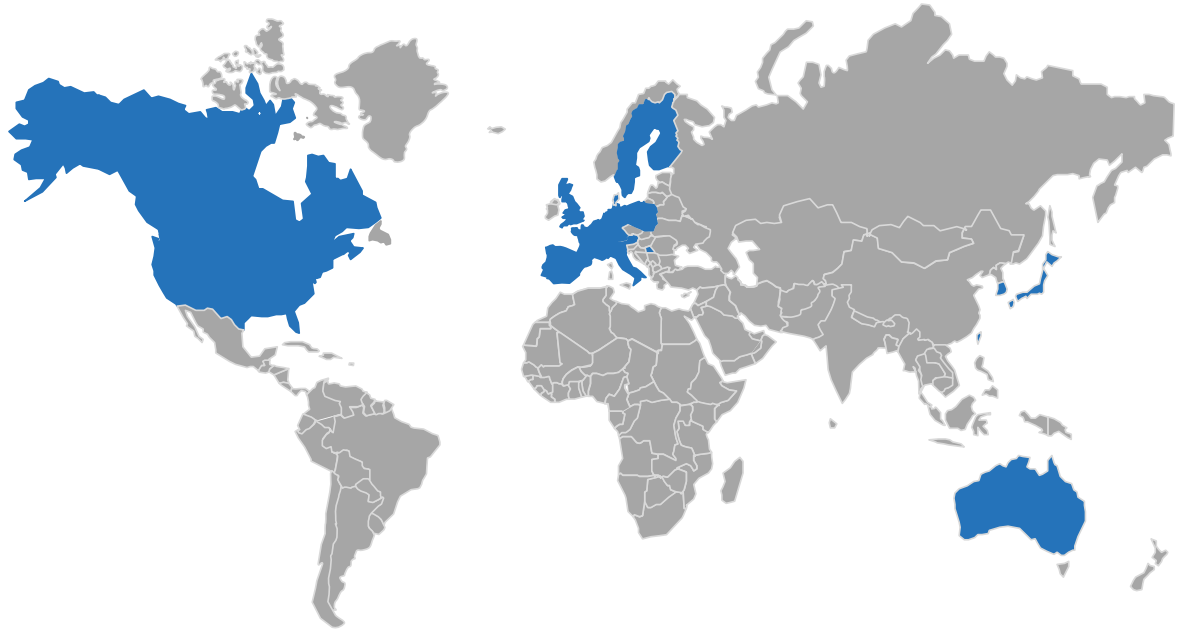


*p<0.05, compared with placebo (nominal)

Phase 3 Studies

Aducanumab Phase 3 Trial Design
Studies 301 and 302

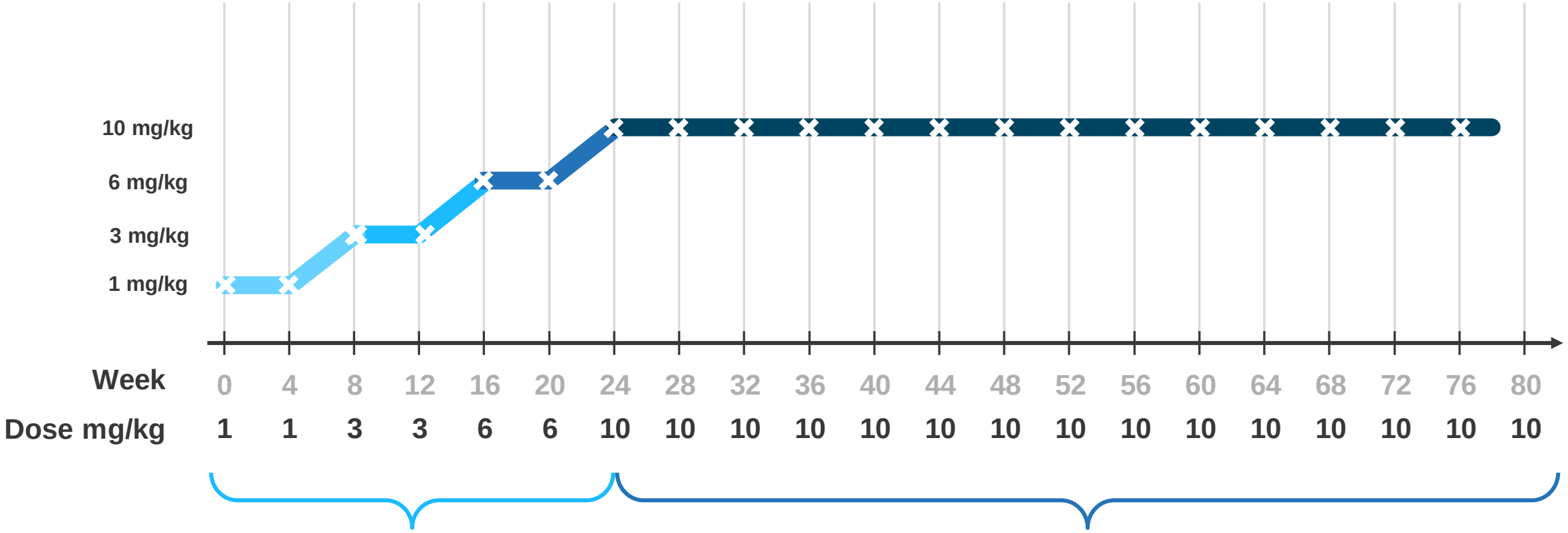
Studies	Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
Geography/ Sample size	3285 patients at 348 sites in 20 countries
Population	• Early Alzheimer's disease (MCI due to Alzheimer's disease + mild Alzheimer's disease dementia) – MMSE 24-30, CDR-G 0.5, RBANS ≤ 85, with confirmed amyloid pathology
Doses	• Two dosing regimens (low and high) and placebo; randomized 1:1:1
Primary endpoint	• CDR-SB at 18 months
Other endpoints	• Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI • Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers



Countries with active sites included:
Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

Phase 3 Target Dose: 10 mg/kg With 6-Month Titration

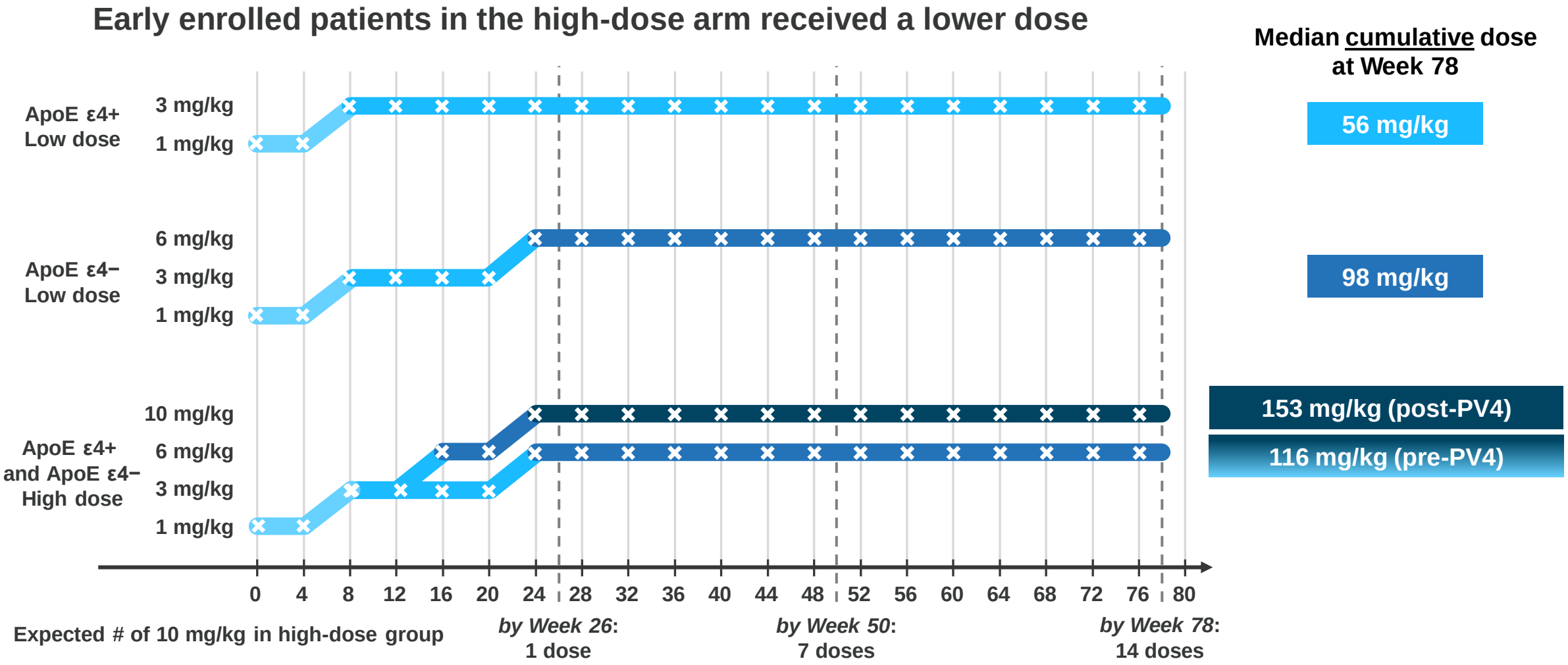
Studies 301 and 302



24-week titration to reduce incidence of ARIA

14 doses of 10 mg/kg as in Study 103

Dose Regimen
Studies 301 and 302



ApoE=apolipoprotein E; PV4=Protocol Version 4.

Phase 3 Studies Were Prematurely Terminated Following What Was Later Determined To be An Inaccurate Futility Prediction

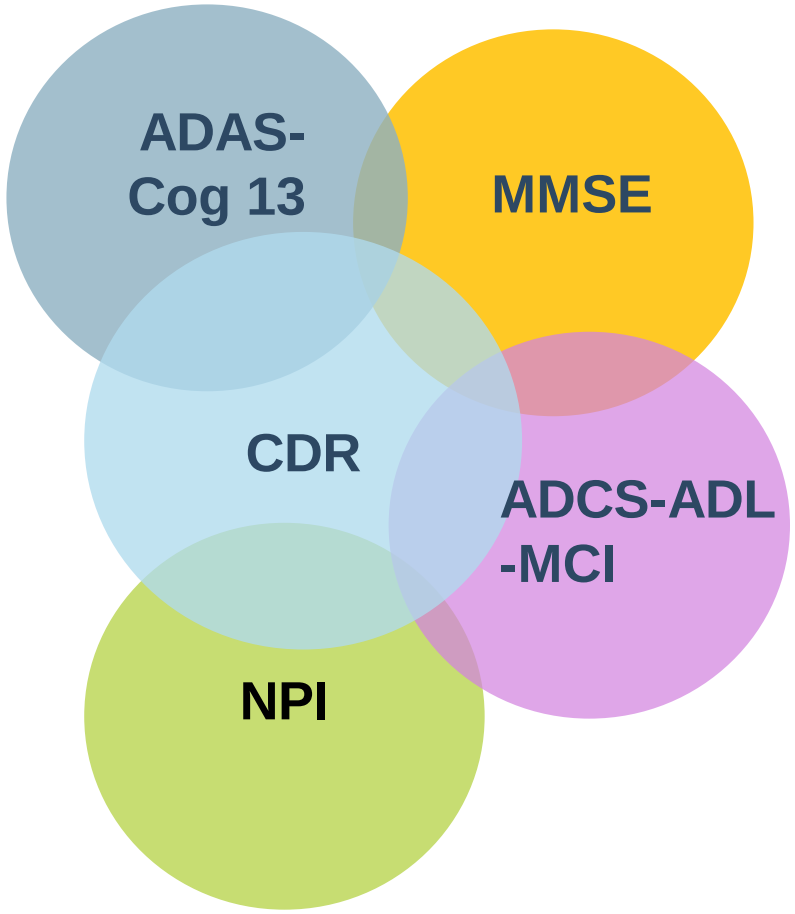
- **Conditional power**: probability that primary efficacy endpoint analysis would be statistically significant at final analysis
- **Two key assumptions did not hold, and futility analysis did not accurately predict the future results**
  - Assumption 1: Identically designed studies would lead to similar study results. Therefore, pooled conditional power is appropriate
  - Assumption 2: Treatment effect will remain consistent over time
- At the time of futility analysis, Study 302 was trending positive, whereas Study 301 was not

Clinical Endpoints Measure Distinct, Important Symptoms of Cognition, Function, and Behavior

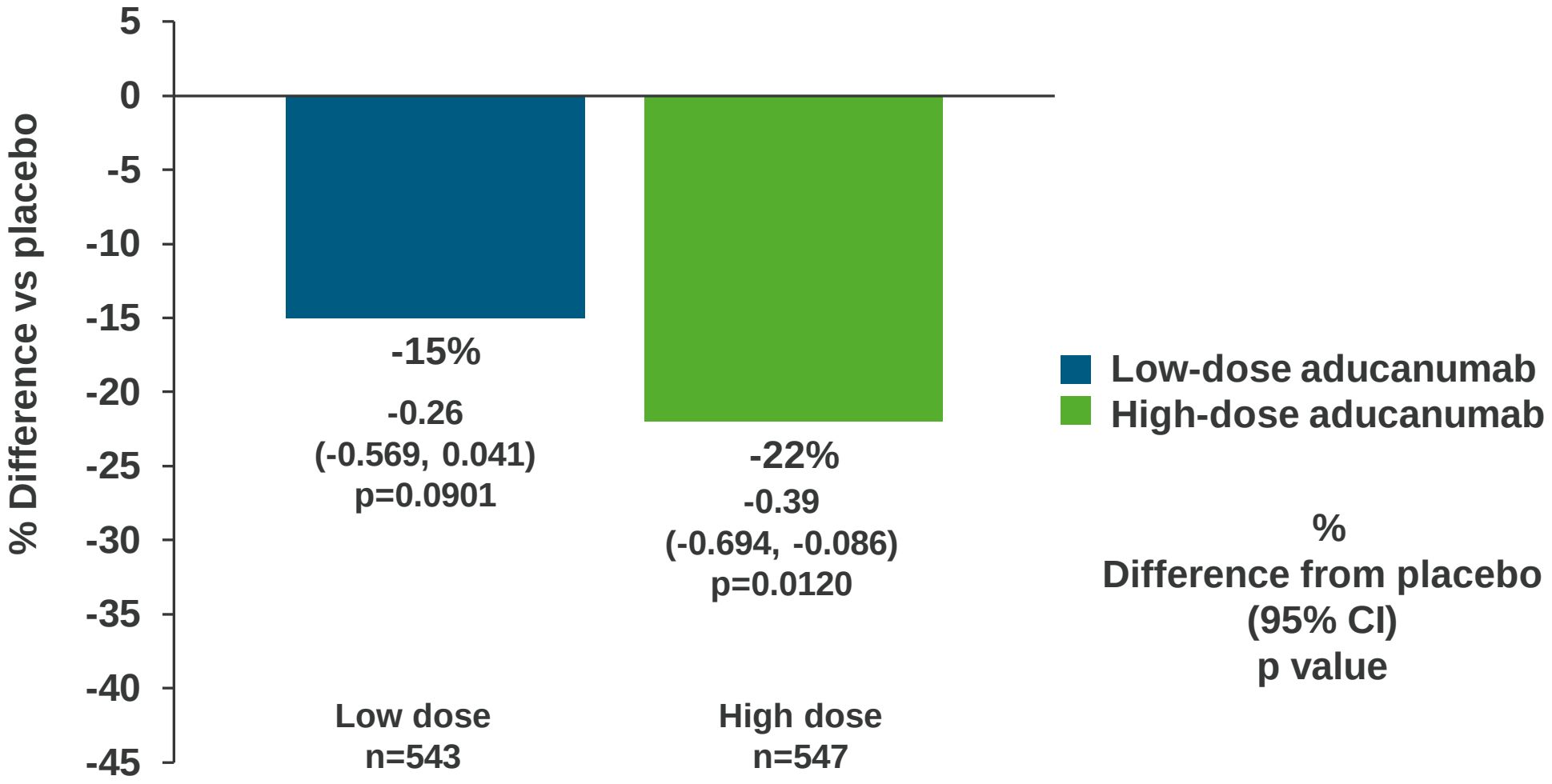
Five clinical rating scales were used in Studies 301 and 302

- Validated and widely used in early Alzheimer's disease
- Covers the full scope of symptoms experienced by patients with Alzheimer's disease
- Include a range of paradigms:
  - Expert clinical judgements based on patient examination and caregiver input
  - Patient and caregiver reports
  - Cognitive performance tests
- Together they cover a range of important and distinct dimensions with minimal overlap

Overlap of scales is only 5% to 25%

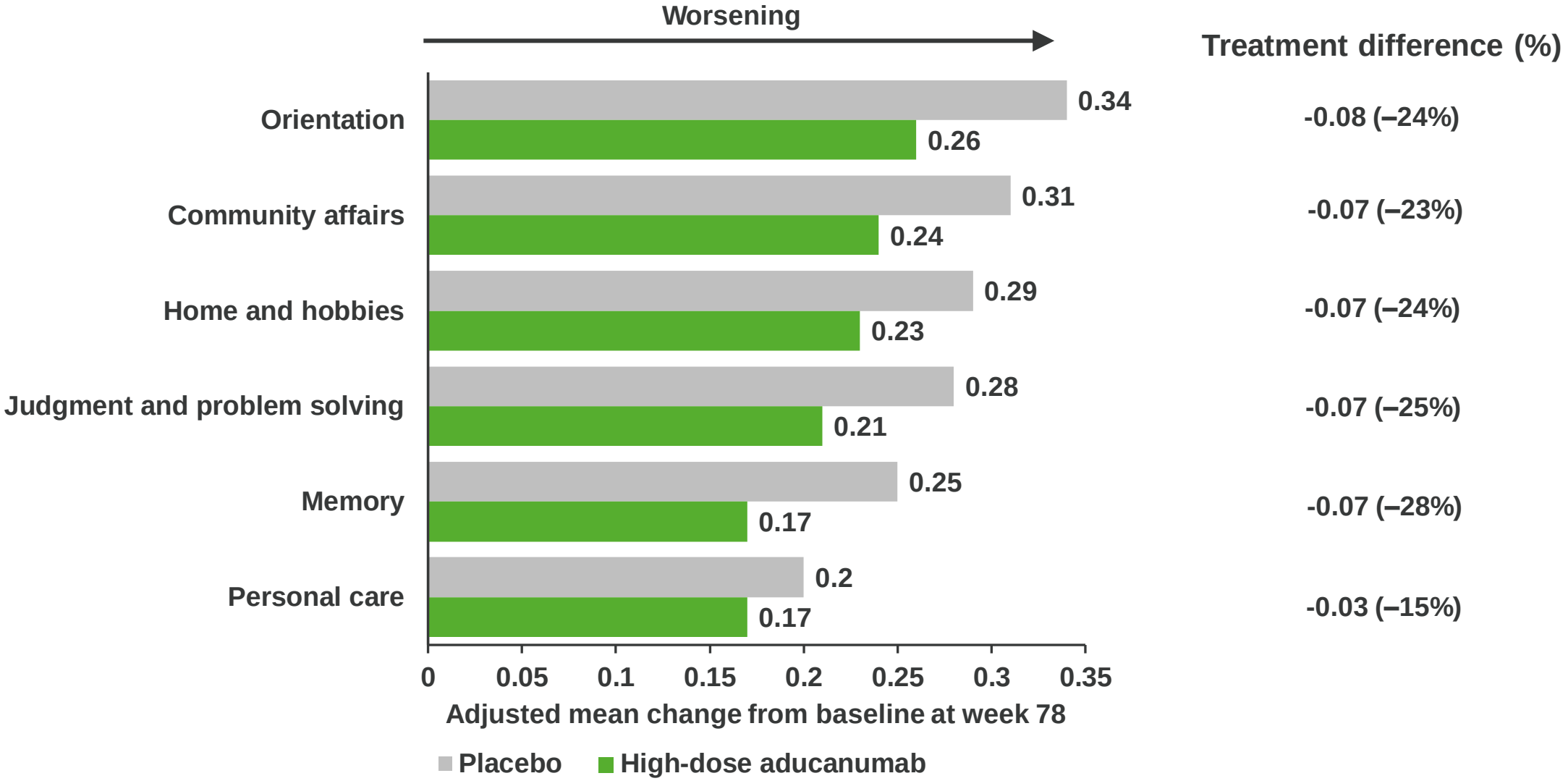


Study 302: High Dose Aducanumab Met Primary Objective of CDR-SB at Week 78

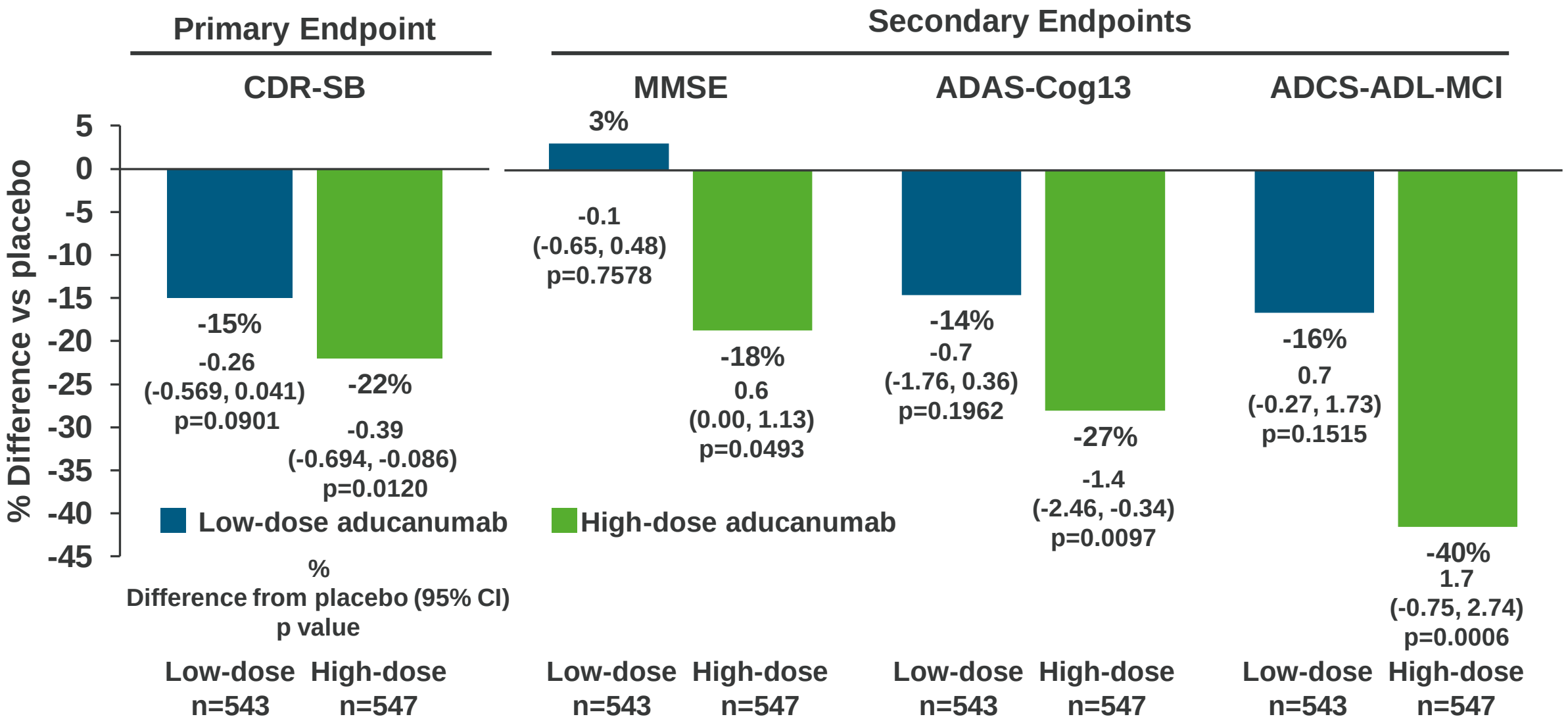


n=numbers of randomized and dosed participants included in the analysis

Study 302: All Items Measured in Primary Endpoint (CDR-SB) Were Improved by High-Dose Aducanumab



Study 302: High-dose Aducanumab Met All Clinical Endpoints Assessing Cognition and Function at Week 78



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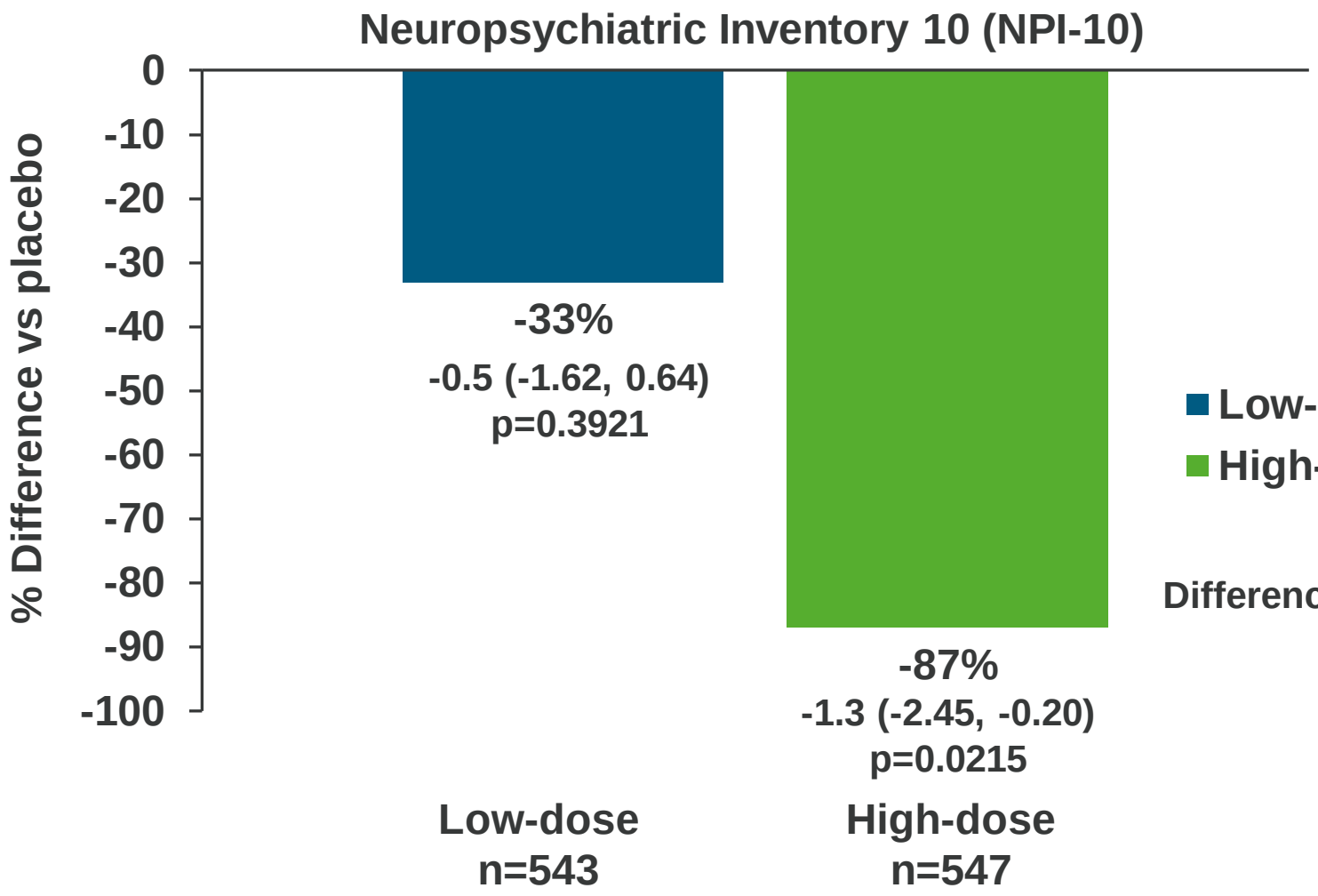
Study 302: Treatment Effect Observed in Exploratory Clinical Endpoint of NPI-10 Assessing Behavior at Week 78



Caregivers of patients who received high-dose aducanumab reported **84% less burden** compared with caregivers of patients who received placebo

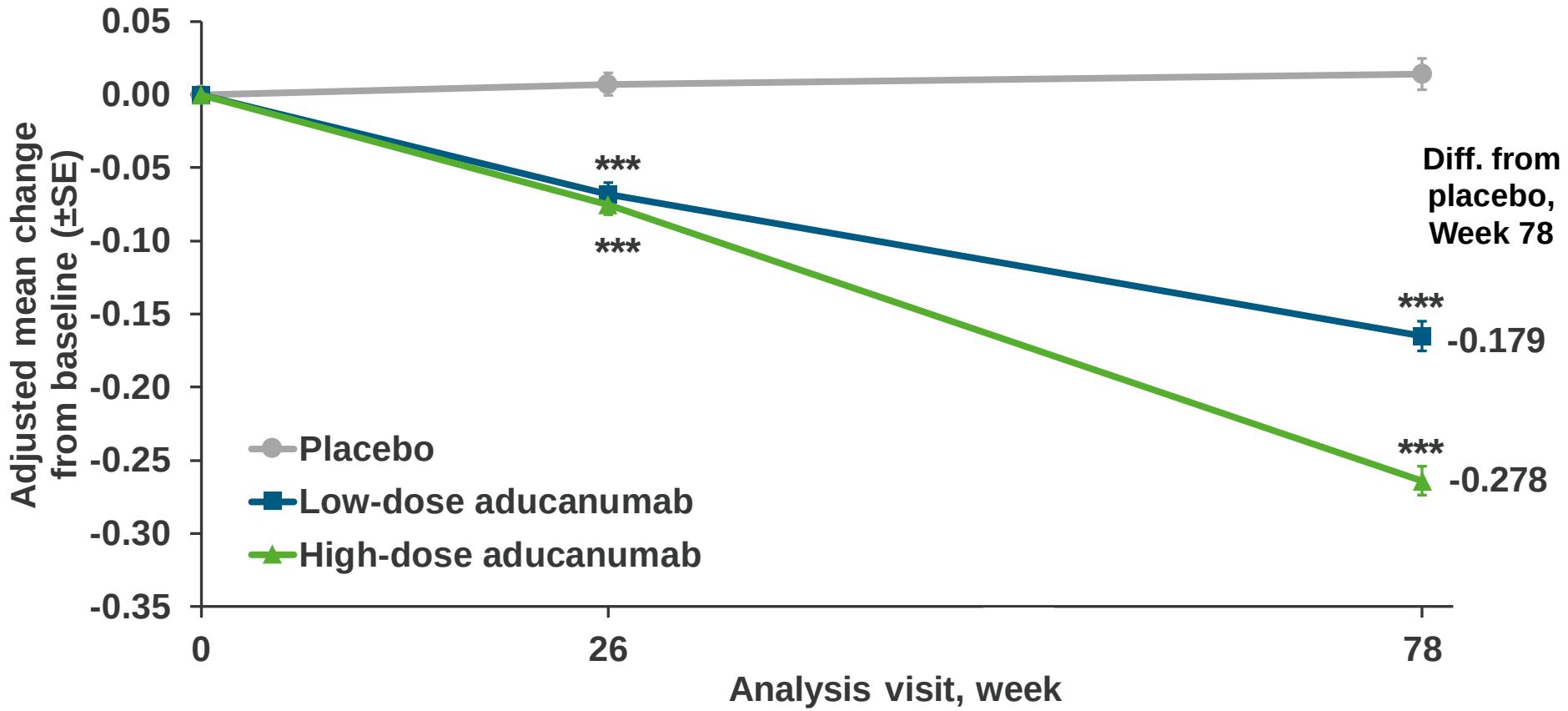
Low-dose aducanumab

High-dose aducanumab

%
Difference from placebo (95% CI)
p value

n=numbers of randomized and dosed participants included in the analysis

Study 302: Amyloid PET Shows Aducanumab Dose-Dependent Reduction in β-Amyloid Pathology

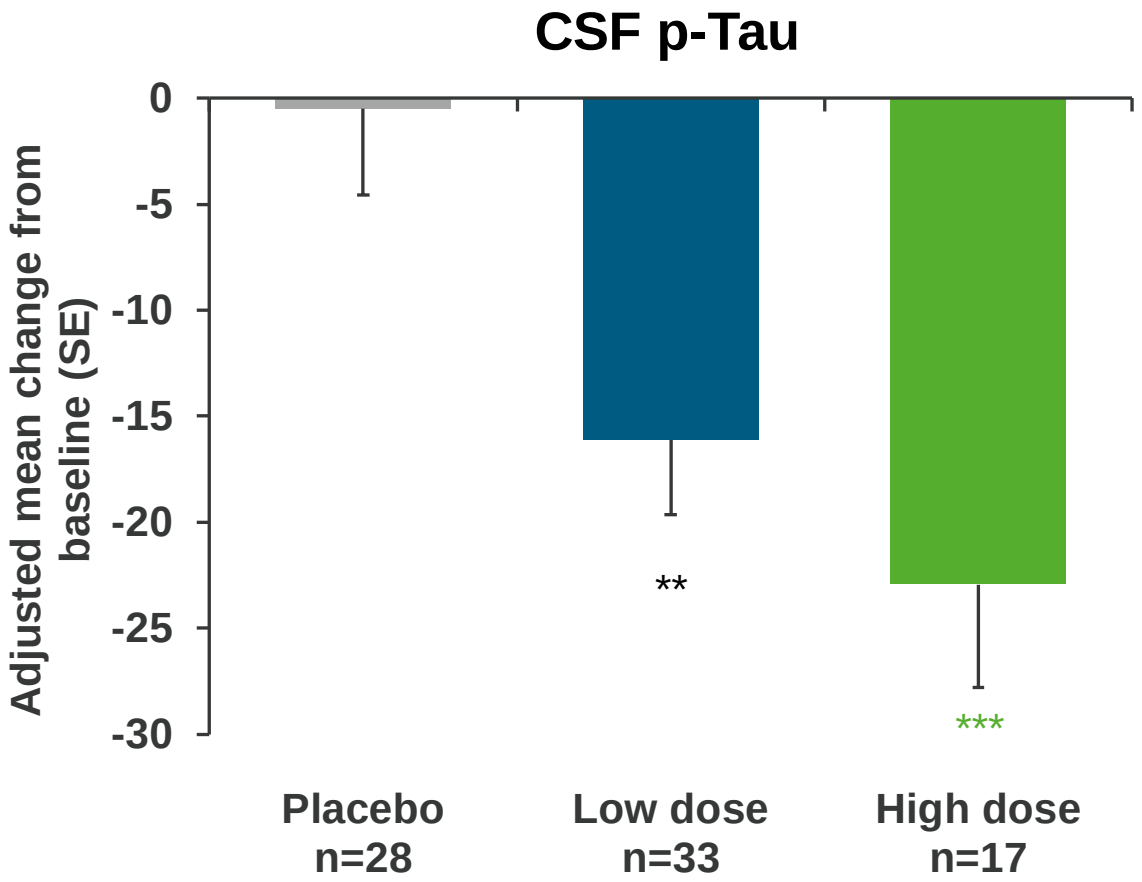


Placebo	159	129	93
Low-dose aducanumab	159	129	100
High-dose aducanumab	170	138	109

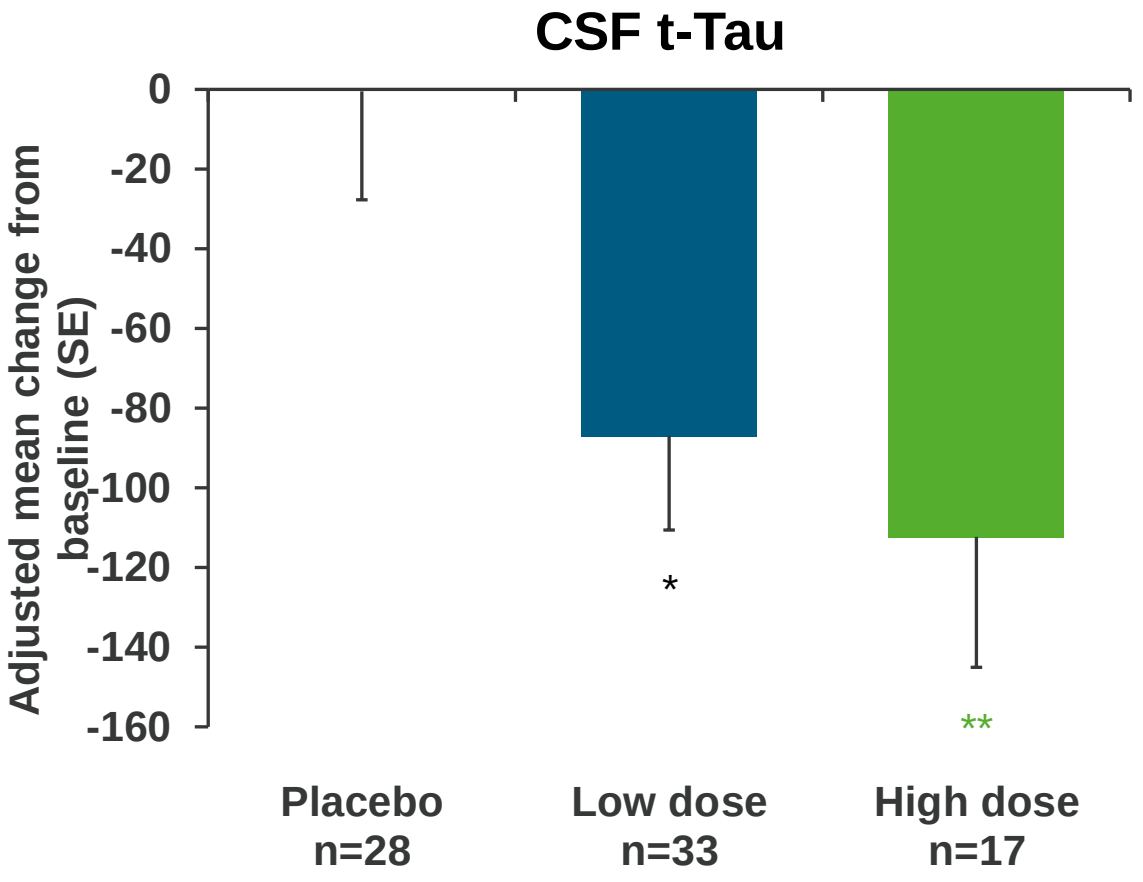
*** p<0.001 (nominal)

Study 302: Aducanumab Reduced Biomarkers of Alzheimer's Disease-specific Tau Pathophysiology and Neurodegeneration

Tau pathophysiology



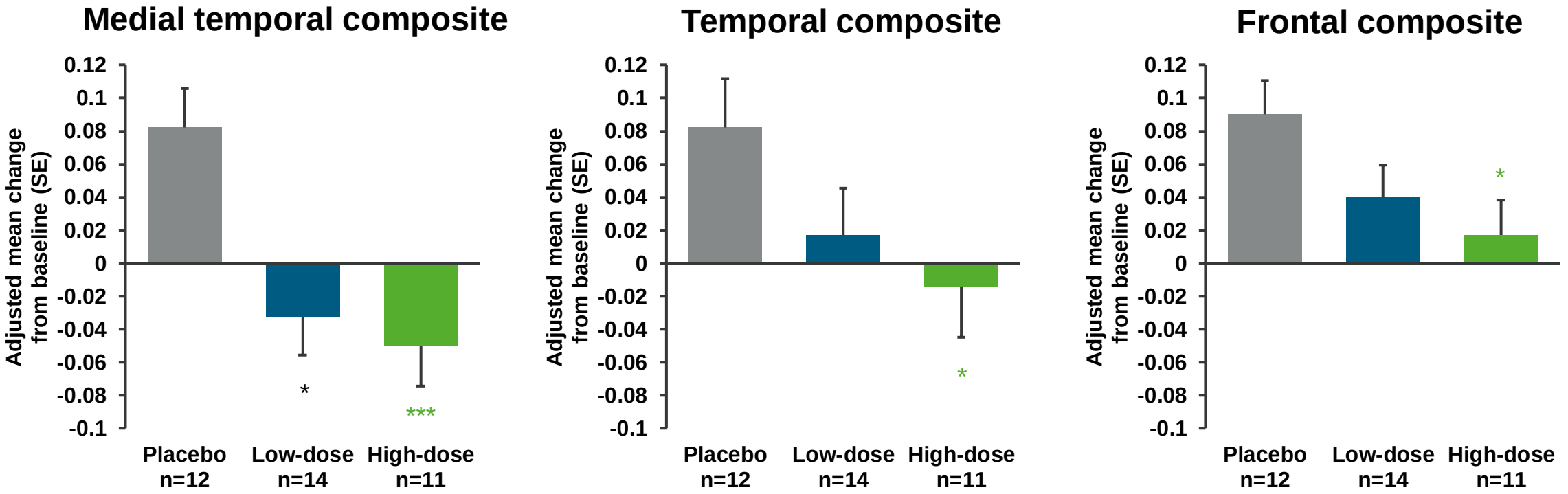
Neurodegeneration



*p<0.05, ** p<0.01 , *** p<0.001 (nominal)
n=numbers of randomized and dosed participants included in the analysis

Aducanumab Reduced Biomarkers of Tau Neurofibrillary Tangles in the Brain

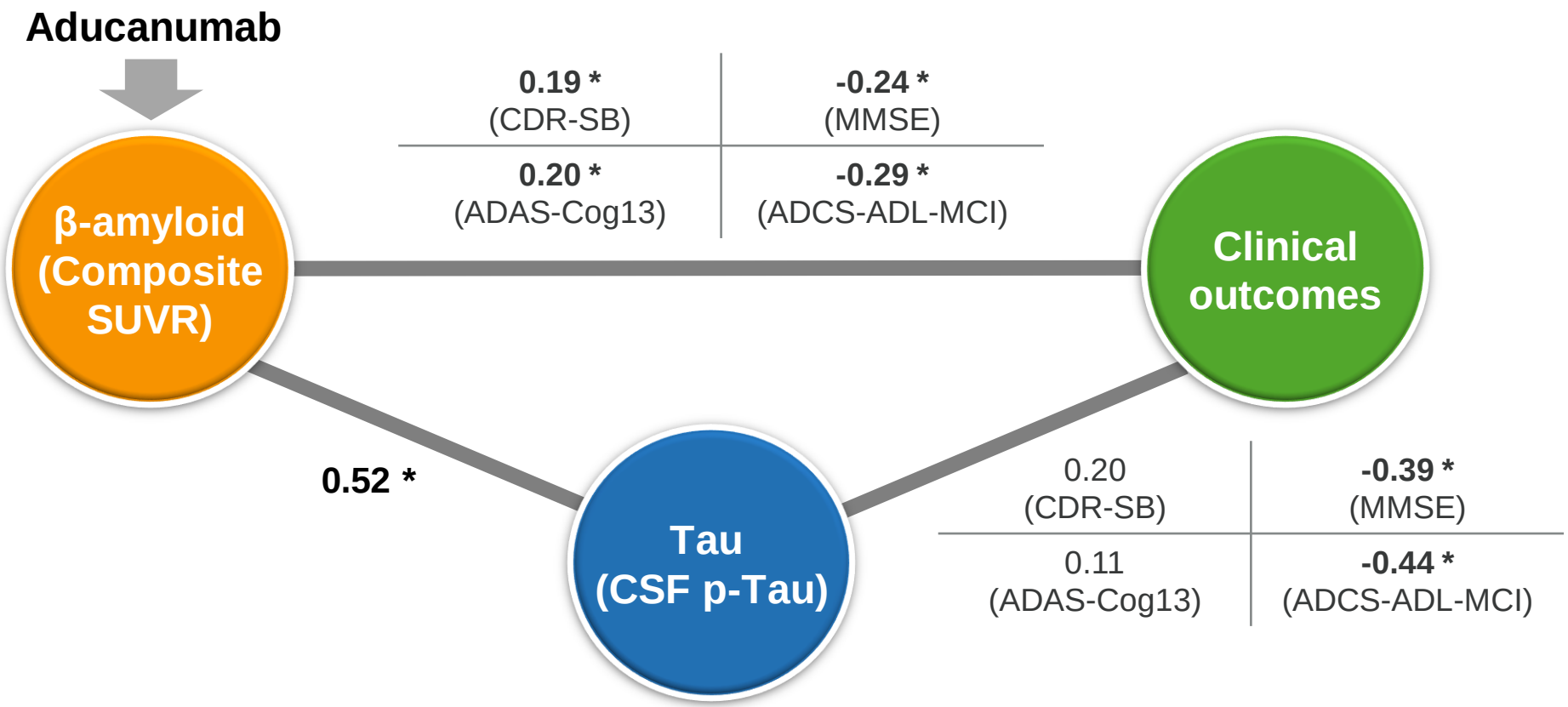
Pooled Data, Studies 301 and 302



* p<0.05, *** p<0.001 (nominal).

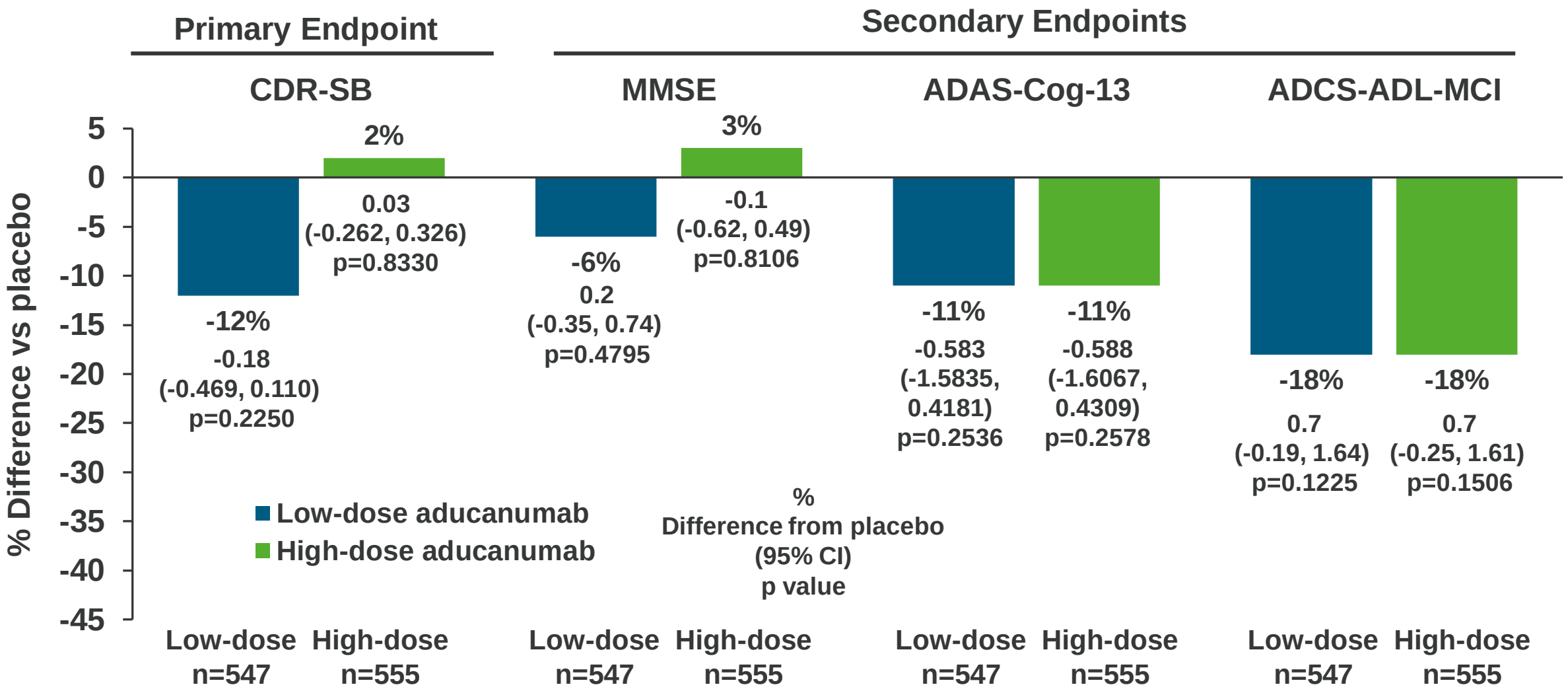
n=numbers of randomized and dosed participants included in the analysis

Study 302: Aducanumab-related Biomarker Changes Are Associated With Slowing in Clinical Decline



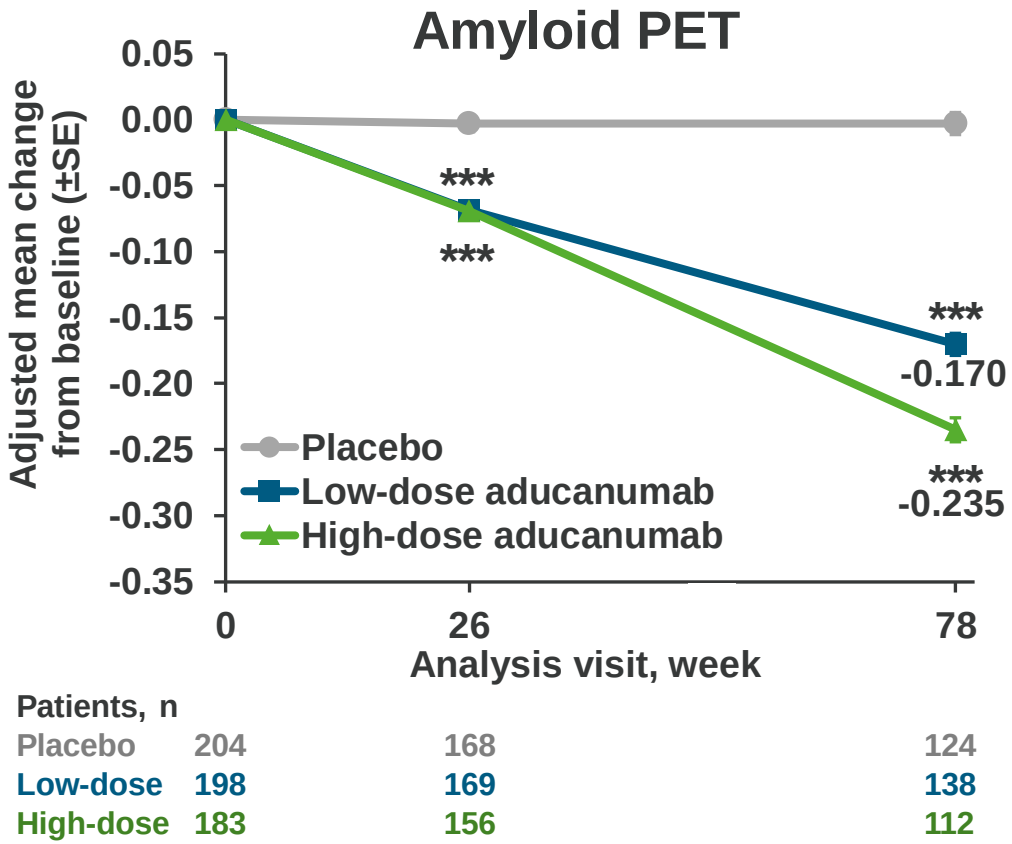
* p<0.05 (nominal)
All associations are partial Spearman correlation of change from baseline to Week 78 between each variable

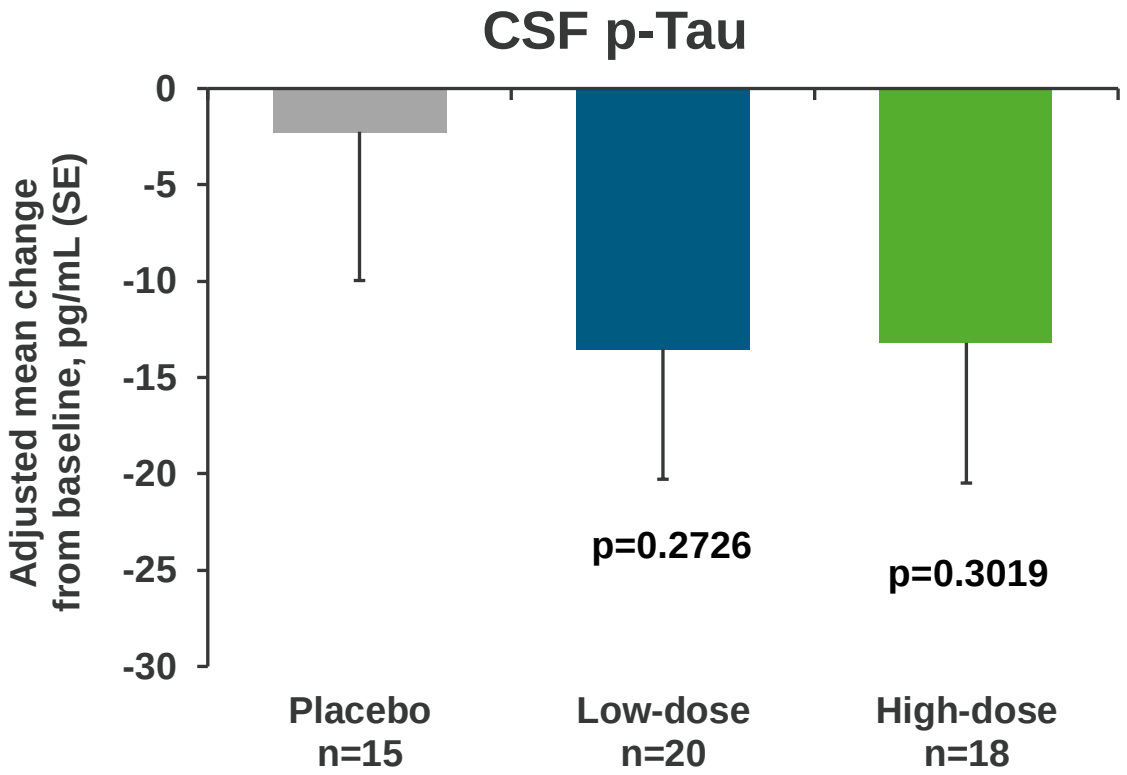
Results of Study 301 Were Partially Discordant



n=numbers of randomized and dosed participants included in the analysis

Biomarker Response in High Dose Aducanumab is Lower in Study 301 than in Study 302





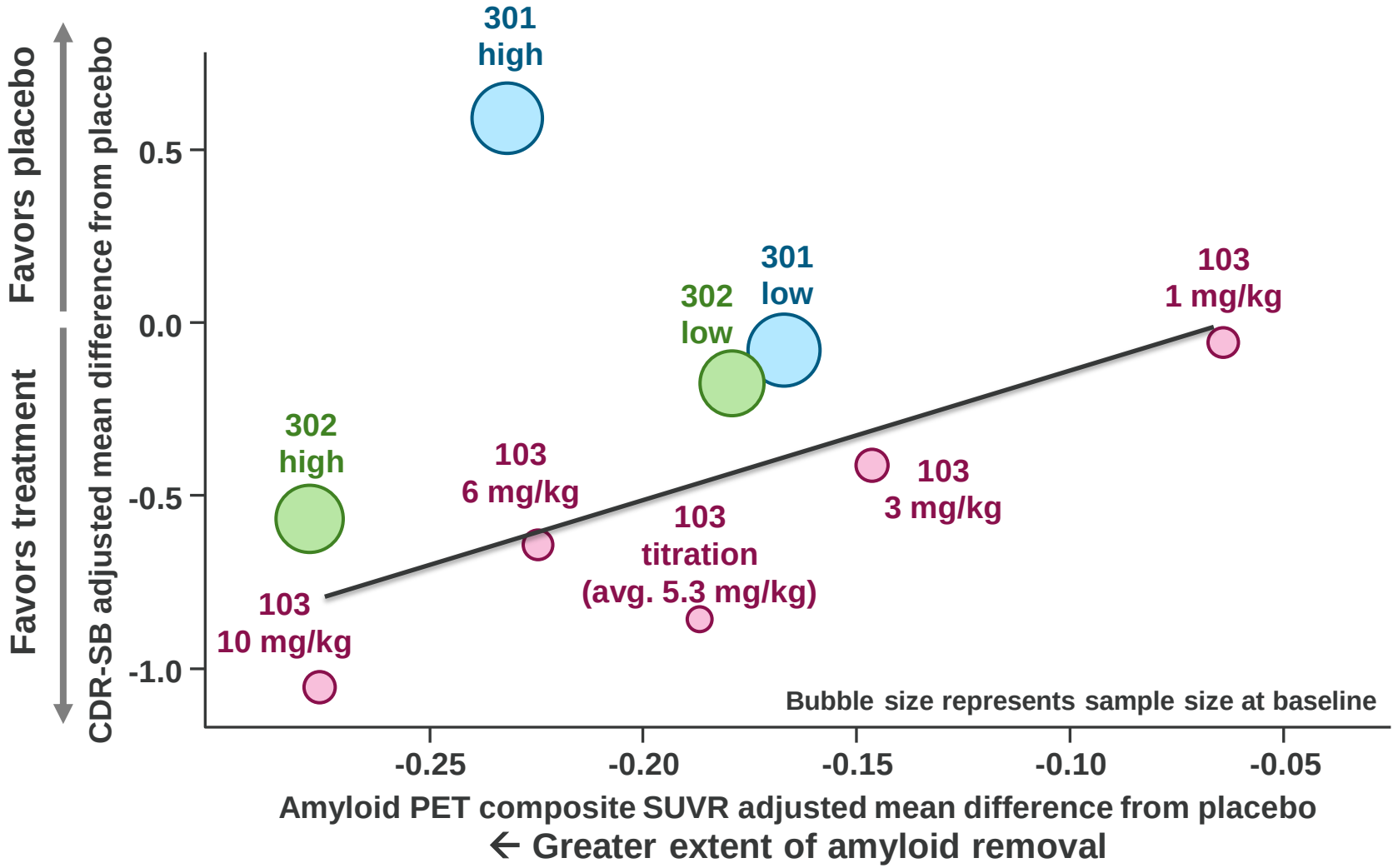
- Treatment effect 16.5% smaller
- Cumulative dose 10.4% smaller

- Treatment effect 51.2% smaller
- Cumulative dose 20.3% smaller

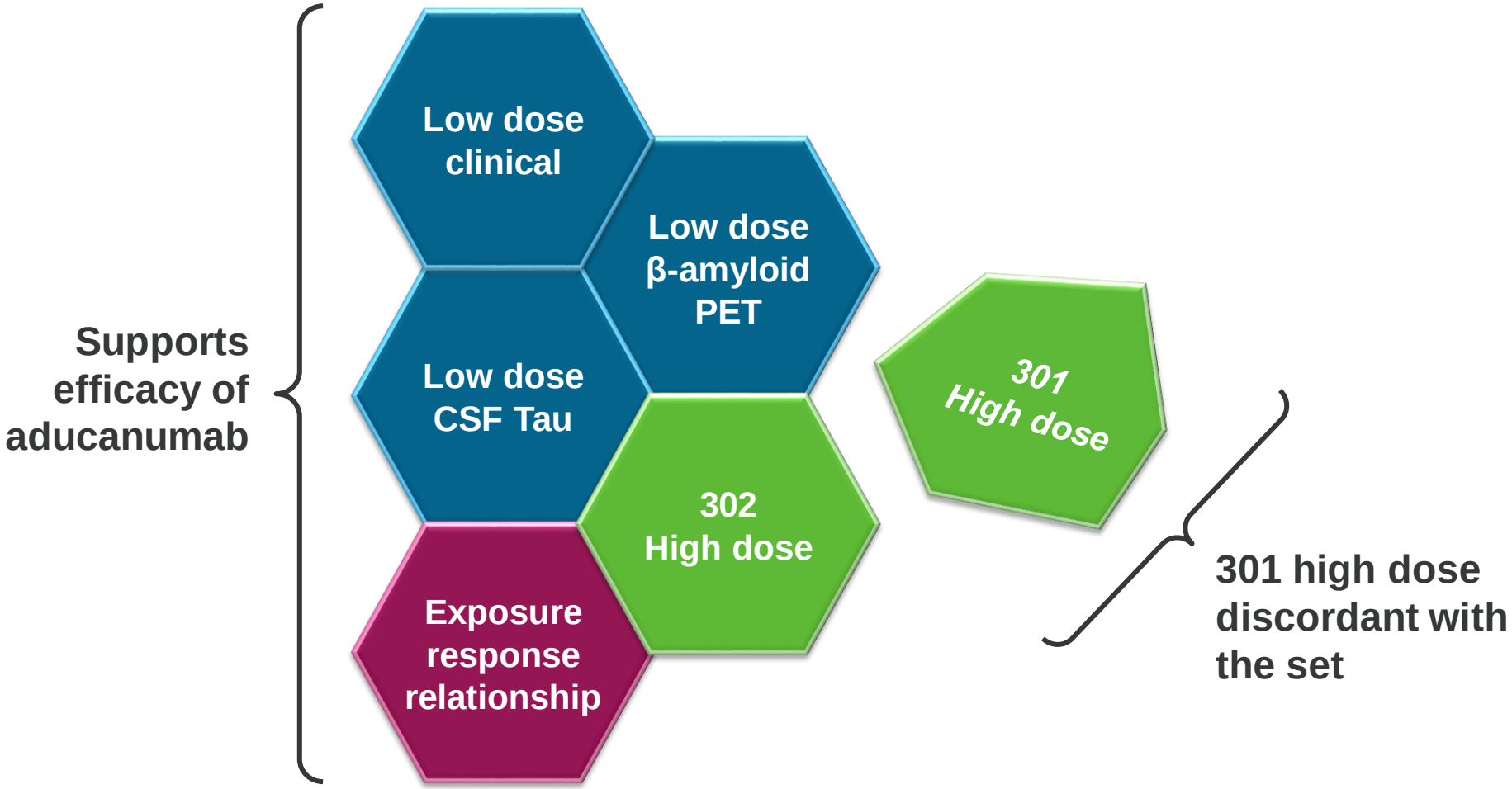
*** p<0.001 (nominal)

Study 301 High-Dose Group Diverged From an Otherwise Consistent Association Between Aβ Reduction and Slowing of Clinical Decline

Studies 301, 302, and 103



Results in Study 301 and 302 Were Partially Discordant



Summary of Efficacy and Biomarker Results

Studies 301, 302, and 103

Diff vs Placebo (%)	Study 301		Study 302		Study 103
	Low dose N=547	High dose N=545	Low dose N=543	High dose N=547	10 mg/kg N=32
CDR-SB	-0.18 (-12%)	0.03 (2%)	-0.26 (-15%)	**-0.39 (-22%)**	**-1.26 (-67%)**
MMSE	0.2 (-6%)	-0.1 (3%)	-0.1 (3%)	**0.6 (-18%)**	**1.9 (-76%)**
ADAS-Cog13	-0.583 (-11%)	-0.588 (-11%)	-0.70 (-14%)	**-1.40 (-27%)**	
ADCS-ADL-MCI	0.7 (-18%)	0.7 (-18%)	0.7 (-16%)	**1.7 (-40%)**	
Amyloid-PET* **SUVR** (centiloid)	**-0.167 (-38.476)**	**-0.232 (-53.472)**	**-0.179 (-41.250)**	**-0.278 (-64.182)**	**-0.277 (-61.363)**

Dark green = p<0.05 favoring aducanumab

Light green = numeric advantage favoring aducanumab

N=numbers of randomized and dosed participants

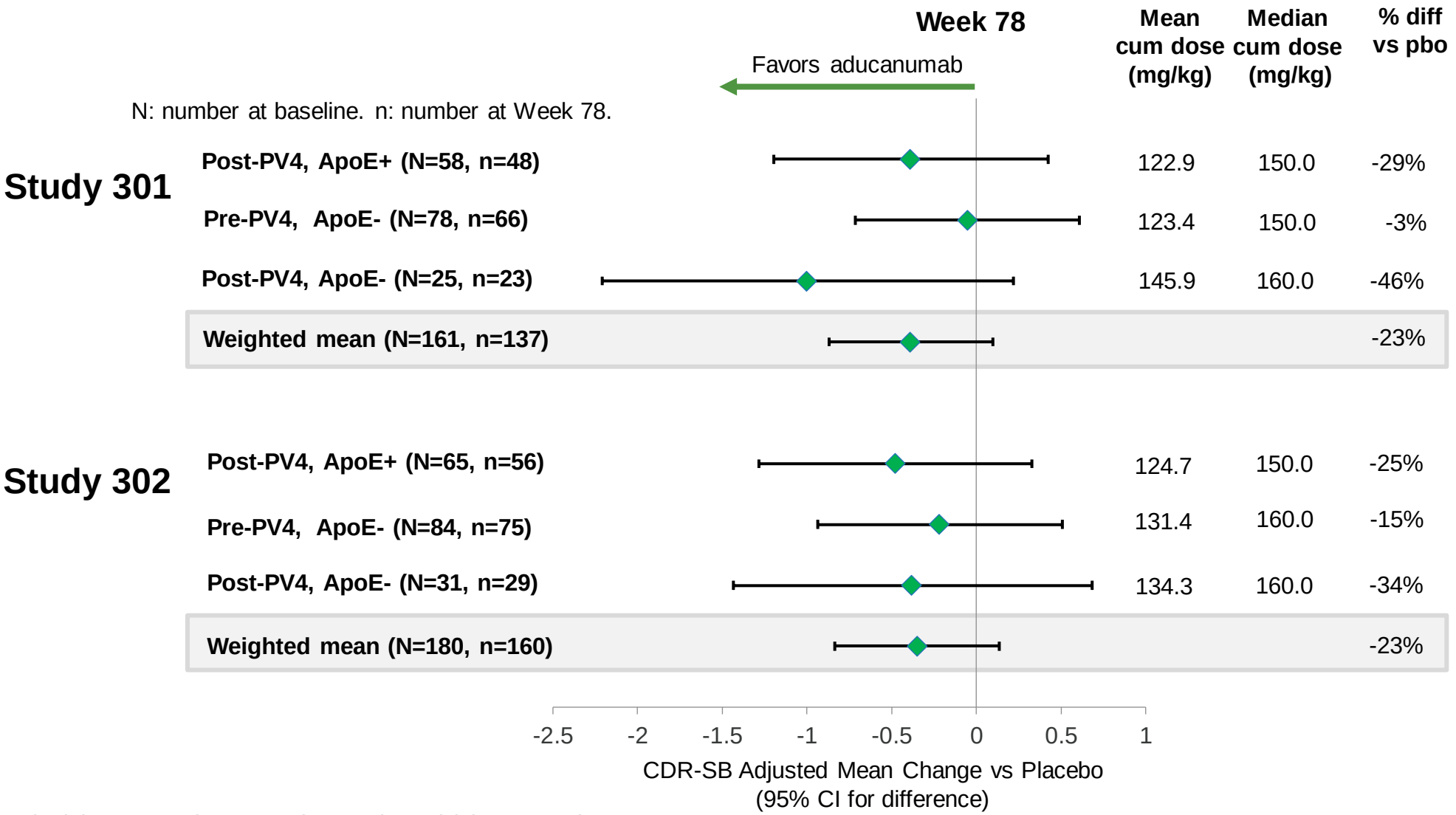
(*) Number of participants in 301 PET substudy = 585 and 302 substudy = 488

Differences in Study 301 Are Sufficiently Understood so as Not to Detract From Study 302

- Demographics, disease characteristics, frequency, severity and management of ARIA were all similar between studies
- Underlying pharmacology of aducanumab is similar in Studies 301 and 302
- Differences between studies were largely driven by:
  - Lower exposure to 10 mg/kg dosing in Study 301
  - Imbalance in number and distribution of rapid progressing Alzheimer's disease patients

In Study 301, patients randomized to groups with the opportunity for full 10mg/kg dosing had results similar to Study 302

Patients Who Had the Opportunity for 14 Doses of 10 mg/kg Had Similar Benefit in Both Studies



Patients who have had the opportunity to complete week 78 visit by 20 March 2019.

Safety

Amyloid-Related Imaging Abnormalities (ARIA)

ARIA refers to radiographic abnormalities observed with anti-Aβ antibodies

- ARIA-Edema (ARIA-E): vasogenic edema or sulcal effusion
- ARIA-Hemorrhage (ARIA-H): brain microhemorrhages or localized superficial siderosis
- May result from increased cerebrovascular permeability as a consequence of antibody binding to deposited amyloid-beta

Greenberg SM, et al. *Nature Rev Neurol*. 2020;16(1):30-42.

Most Common Adverse Events with Aducanumab

Studies 301 and 302 Placebo-Controlled Period

	Patients, n (%)	
	Placebo N=1087	Aducanumab 10 mg/kg N=1033
Adverse events	**945 (86.9)**	**946 (91.6)**
ARIA-E	29 (2.7)	362 (35.0)
Headache	165 (15.2)	212 (20.5)
ARIA-H Brain microhemorrhage	71 (6.5)	197 (19.1)
Fall	128 (11.8)	155 (15.0)
ARIA-H Superficial siderosis	24 (2.2)	151 (14.6)
Diarrhea	74 (6.8)	92 (8.9)

- Serious hypersensitivity reactions to aducanumab had an incidence of <0.1%
- Compared to placebo, aducanumab treatment was not associated with abnormalities in vital signs, clinical labs, or ECGs

Clinical and MRI Characteristics of ARIA-E

Studies 301 and 302 Placebo-Controlled Period

	Patients, n (%)	
	Placebo N=1076	Aducanumab 10 mg/kg N=1029
Patients with ARIA-E	29	362
Asymptomatic	26 (89.7)	268 (74.0)
Symptomatic	3 (10.3)	94 (26.0)

- The most common symptoms were headache, confusion, dizziness, and nausea
- Most symptoms were mild (68%) or moderate (28%) in clinical severity
- MRI findings of ARIA-E were typically mild (30%) or moderate (58%) in severity and transient (98% resolved)

Each participant counted once, at maximum symptomatic status and severity.

Study 302: Aducanumab Impacts Multiple Clinically Meaningful Dimensions of Alzheimer's Disease

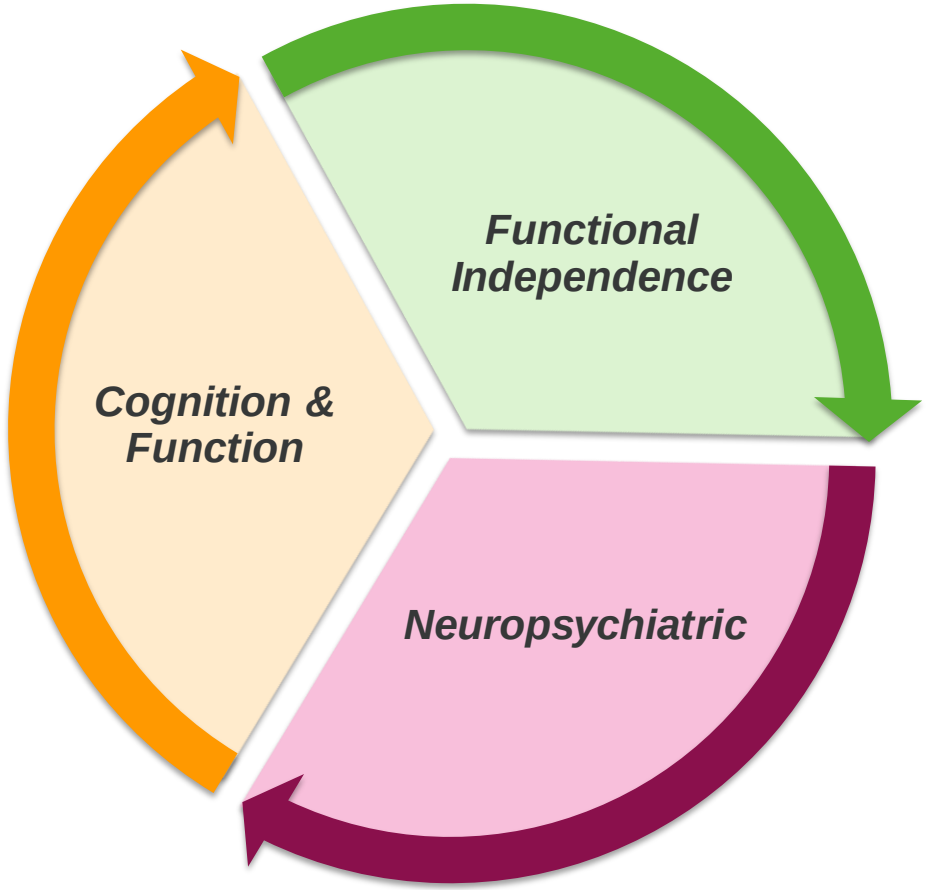
High dose outcomes at week 78 versus placebo

CDR-SB

Primary Endpoint

22% relative reduction in decline from baseline in the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB)

Secondary Endpoints (Cognition)
MMSE: **18%** relative reduction
ADAS Cog: **27%** relative reduction



ADCS-ADL-MCI

Secondary Endpoint

40% relative reduction in decline in AD Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version (ADCS-ADL-MCI)

NPI-10

Exploratory Endpoint
87% relative reduction in decline the Neuropsychiatric Inventory-10 (NPI-10)

Establishing the Safety and Efficacy of Aducanumab

Study 302	A positive study with robust and internally consistent results
Study 103	An independent, second study providing supportive evidence
Study 301	A failed study with reasons for difference between studies in results understood and post hoc subgroups supportive of Study 302 and 103

Consistent exposure to 10 mg/kg aducanumab is effective at reducing the clinical decline in patients with early symptomatic Alzheimer's disease and has a favorable benefit/risk profile

Conclusion

- Aducanumab targets underlying pathology of disease and is the first investigational drug to show a reduction in clinical decline in patients with Alzheimer's disease

- Based on prespecified analyses, Study 302 is a robustly positive study, while Study 301 is a failed study

- Differences between Study 301 and 302 were largely driven by:
    - Lower exposure to 10 mg/kg dosing in Study 301
    - Imbalance in number and distribution of rapid progressing Alzheimer's disease patients

- In Study 301, patients with the opportunity for full 10mg/kg dosing had results similar to Study 302

- A small earlier clinical trial, Study 103, demonstrated a treatment effect on clinical and biomarker endpoints

- Consistent exposure to 10 mg/kg aducanumab is effective at reducing the clinical decline in patients with early symptomatic Alzheimer's disease and has a favorable benefit/risk profile