Aducanumab for the Treatment of Alzheimer's Disease

U.S. Food & Drug Administration

Peripheral and Central Nervous System Drugs Advisory Committee

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Opening Remarks

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Biogen

Alzheimer’s Disease Presents a Significant Unmet Medical Need

- 5.8 million Americans suffer from Alzheimer’s disease[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] 2020 Alzheimer's Disease Facts and Figures.

Proposed Patient Population and Dosing Recommendation

Proposed Indication	Aducanumab is an amyloid beta targeting antibody indicated to delay clinical decline in patients with Alzheimer’s disease
Dosing and Administration	10 mg/kg administered as an intravenous infusion over approximately one hour every four weeks following titration

Background

- Aducanumab works by targeting underlying pathology of disease and is the first therapeutic to show a reduction in clinical decline in patients with Alzheimer’s disease
- Study 301 and 302 were prematurely terminated following what was later determined to be an inaccurate futility prediction
- Based on prespecified analyses, Study 302 is a robustly positive study, while Study 301 is a failed study
- An earlier clinical trial, Study 103, demonstrated a treatment effect on clinical and biomarker endpoints
- Analyses to understand these results were performed in collaboration with the FDA
- These analyses ultimately led to the FDA advising Biogen that submission of a marketing application for approval of aducanumab was reasonable

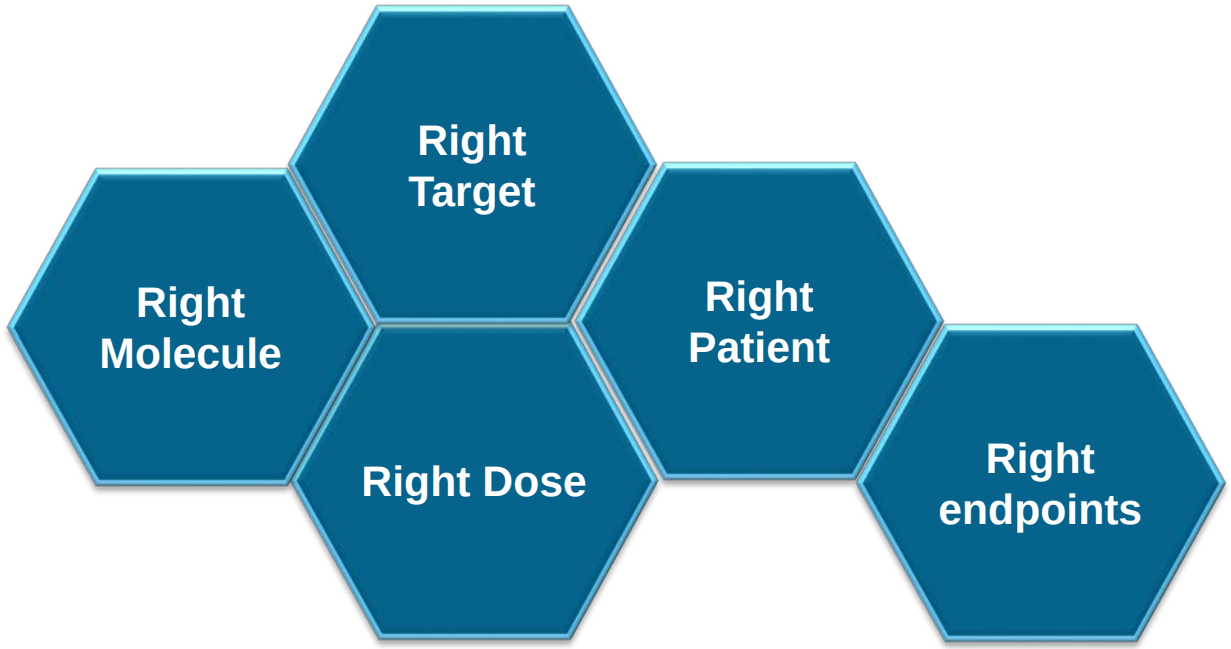
Demonstrating Substantial Evidence of Effectiveness

- FDA Guidance on Substantial Evidence of Effectiveness* allows for flexibility in the evidence needed
- Study 302 is a robust and exceptionally persuasive study and provides the primary evidence of effectiveness
- Study 103 was an adequate and well-controlled study and provides supportive evidence of effectiveness
- Compelling mechanistic evidence, preclinical and clinical dose-dependent reduction of amyloid pathology
- Strong dose-exposure-response for disease specific pathology and clinical outcomes

Study 301 does not detract from the persuasiveness of Study 302

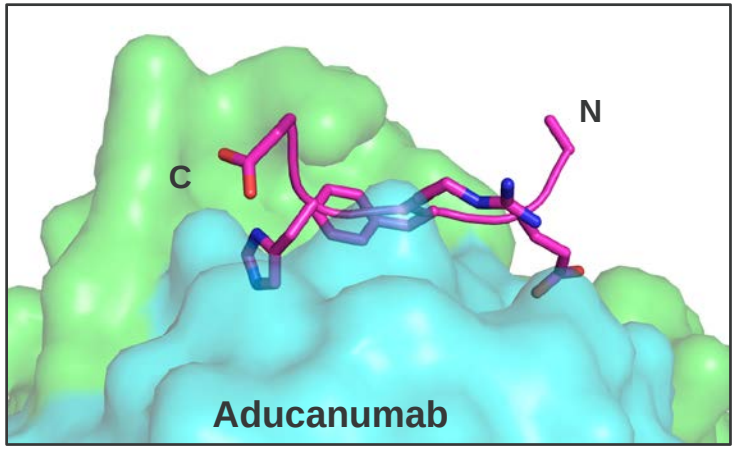
* U.S. Department of Health and Human Services, Food and Drug Administration. (2019). *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for the Industry*, [Draft Guidance].

Clinical Development in Alzheimer's Disease: Critical Elements for Success



- Required advances to better understand disease pathophysiology and new innovations in tools for clinical trials
- Study 103, initiated in 2012, implemented these advances

Aducanumab Disrupts the β-amyloid Aggregation Pathway



Shallow and compact epitope of Aducanumab contributes to its selectivity for Aβ aggregates [Arndt 2018][a]

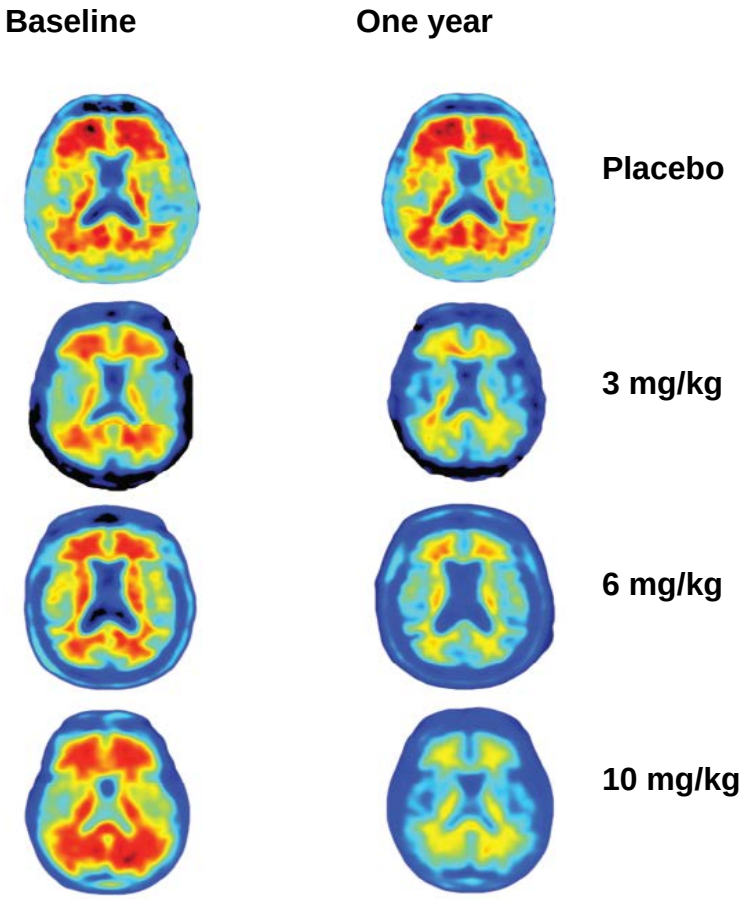
Binding of Aducanumab to fibrils interferes with aggregation process and reduces formation of neurotoxic Aβ oligomers [Linse 2020][b]

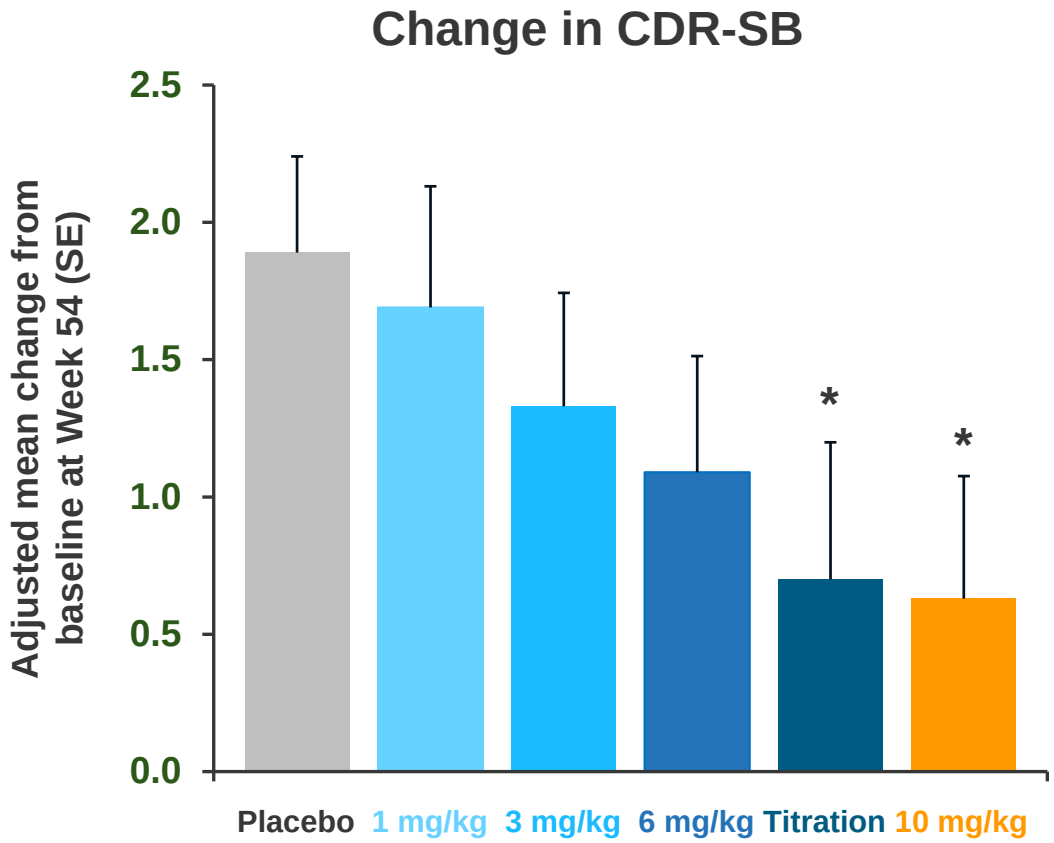
Formation of oligomers on the fibril surface
("Secondary Nucleation")

Beta-Amyloid Aggregation Pathway

[a] Image reprinted with permission from, Arndt J, et al. *Sci. Rep*. 2018 Apr 23;8(1):6412.
[b] Image adpted from, Linse S, et al. *Nat struct Mol Biol*. 2020 Sep 28. online ahead of print.

Aducanumab was the First Program where Proof-of-Concept was Demonstrated Prior to Phase 3



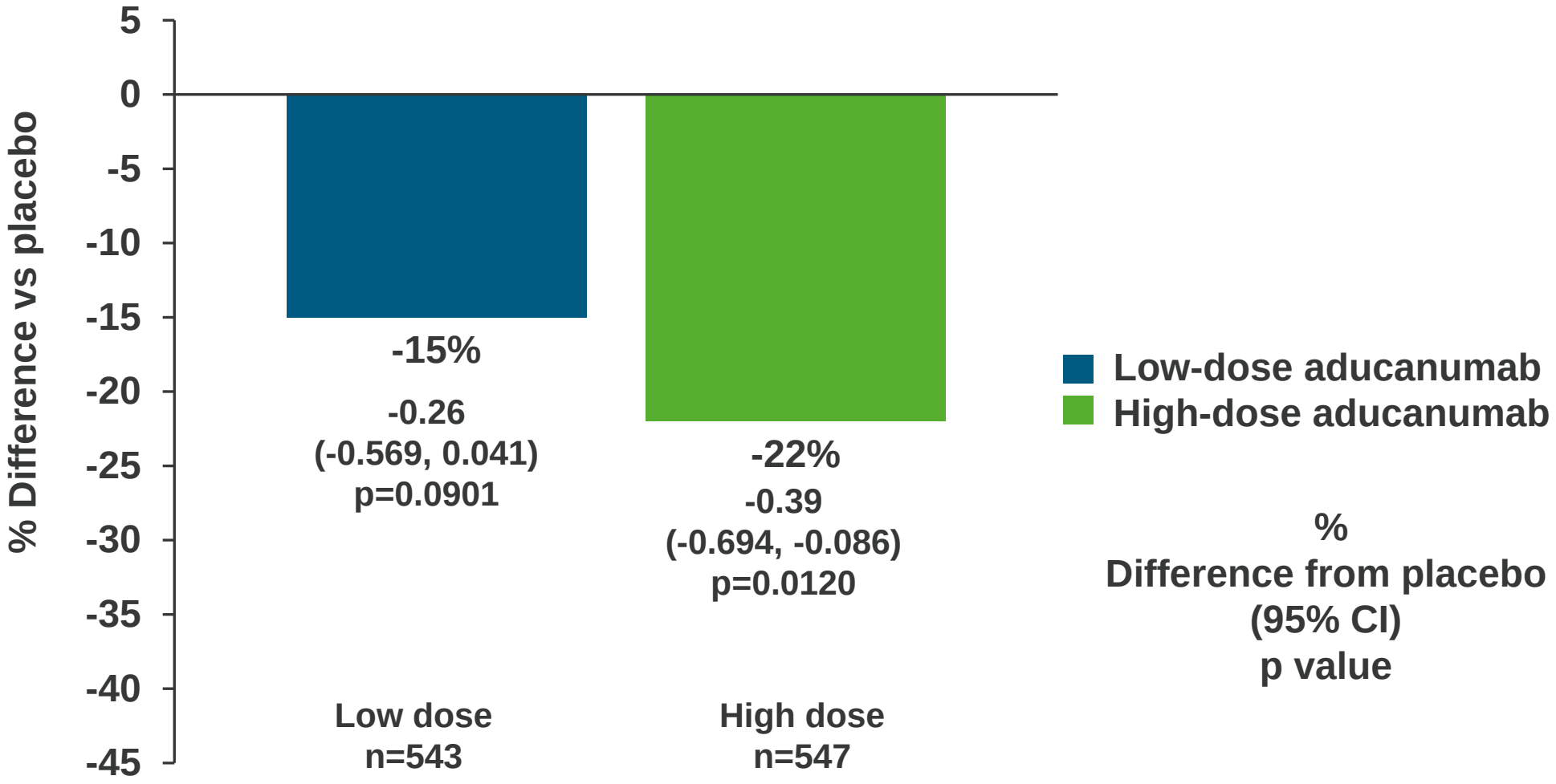


*p<0.05, compared with placebo (nominal)

Design Innovations in Study 103 were Implemented in Phase 3

- Enrolled patients with early symptomatic Alzheimer's disease
- Testing for amyloid pathology improved diagnostic accuracy
- Reduction in β-amyloid pathology was detectable early and before changes in clinical endpoints
- CDR-SB was sensitive to change in this patient population
- ARIA was dose dependent, with incidence higher in ApoE4 carriers and reduced by titration
- 10 mg/kg was selected as the target dose

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

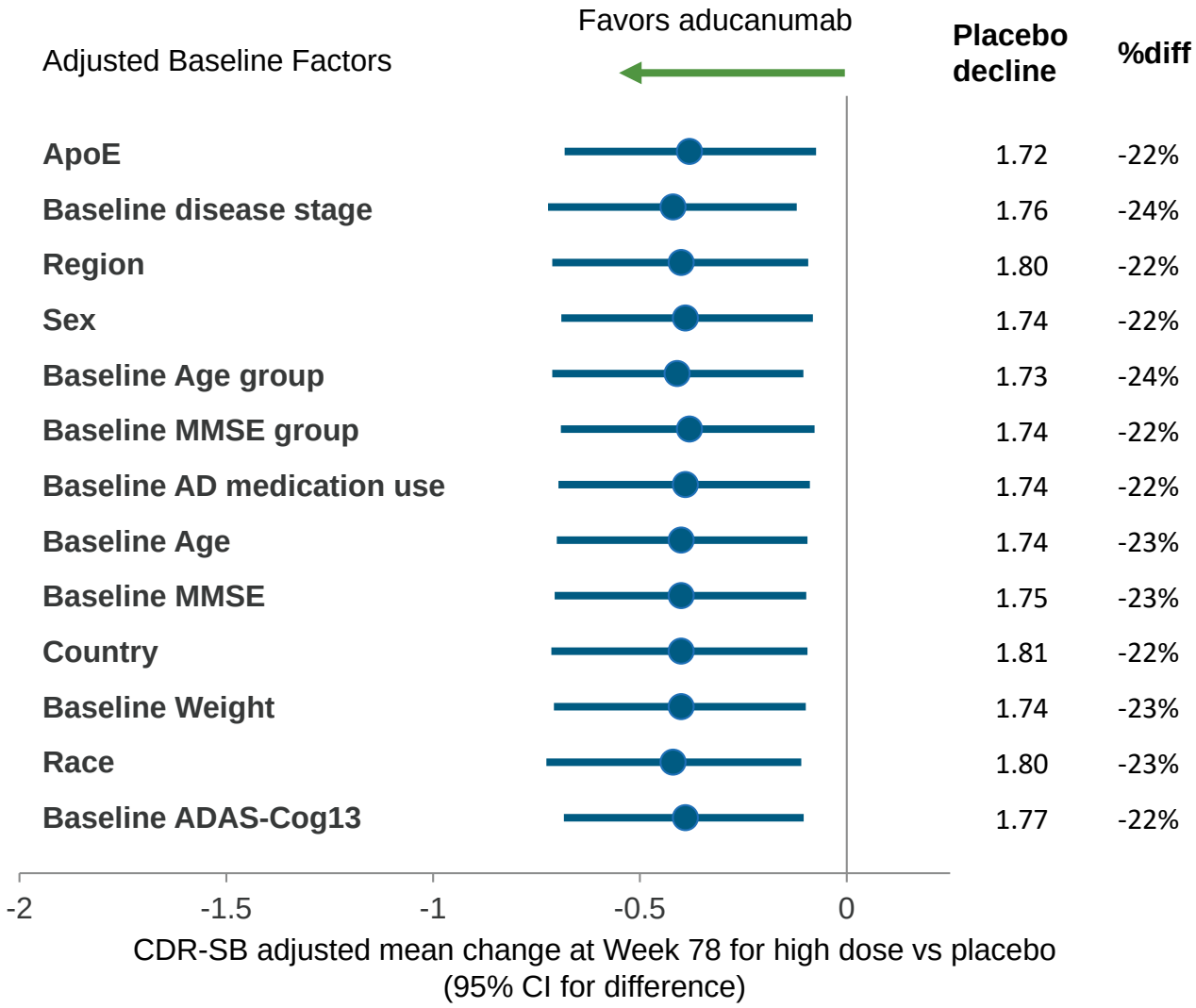


n=numbers of randomized and dosed participants included in the analysis

Study 302: Baseline Factors Had Minimal Impact on Results

MMRM model adjusting for interaction of baseline factor, visit and treatment

- Baseline factors balanced across treatment groups
- Baseline factors had minimal influence on progression
- Baseline factors are not major modifiers of treatment effect

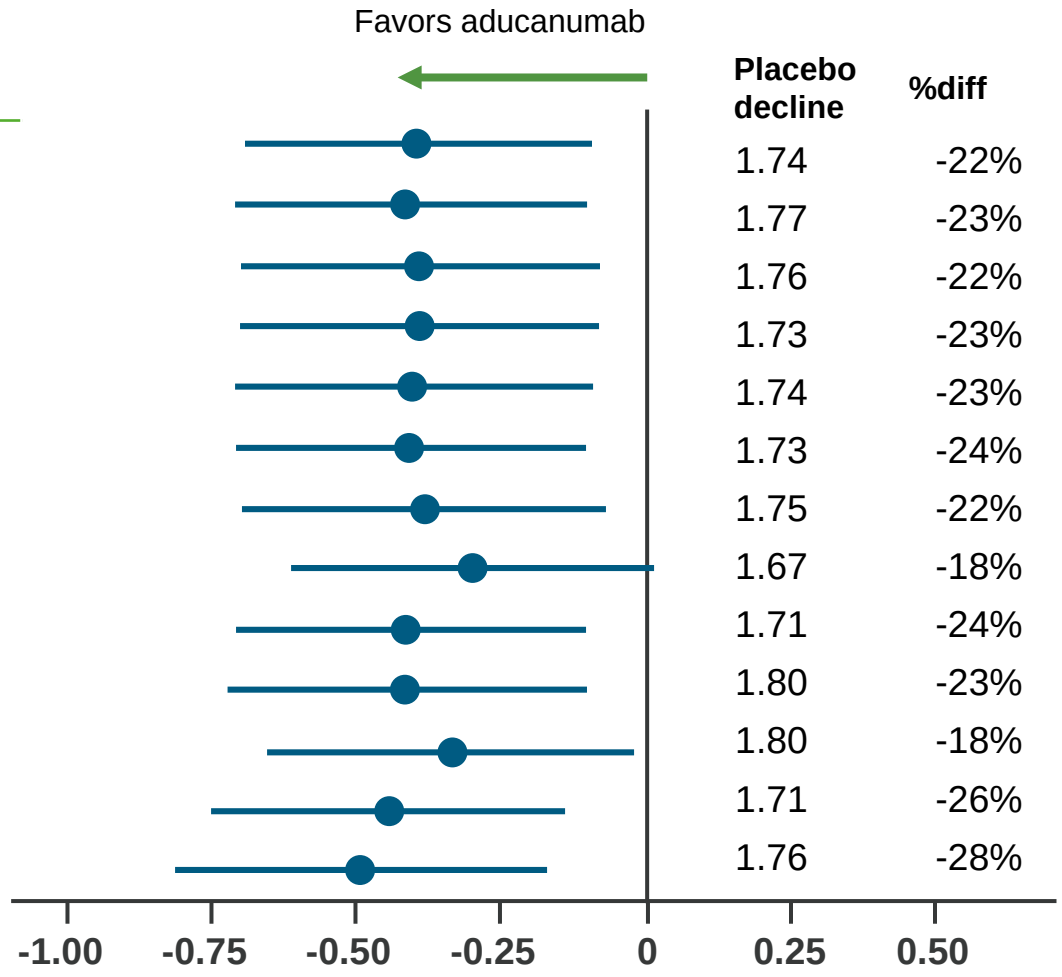


Note: The treatment difference adjusted for sample size in each subgroup category for categorical baseline factors.

Study 302: No (ex-US) Country Had Major Impact on Results

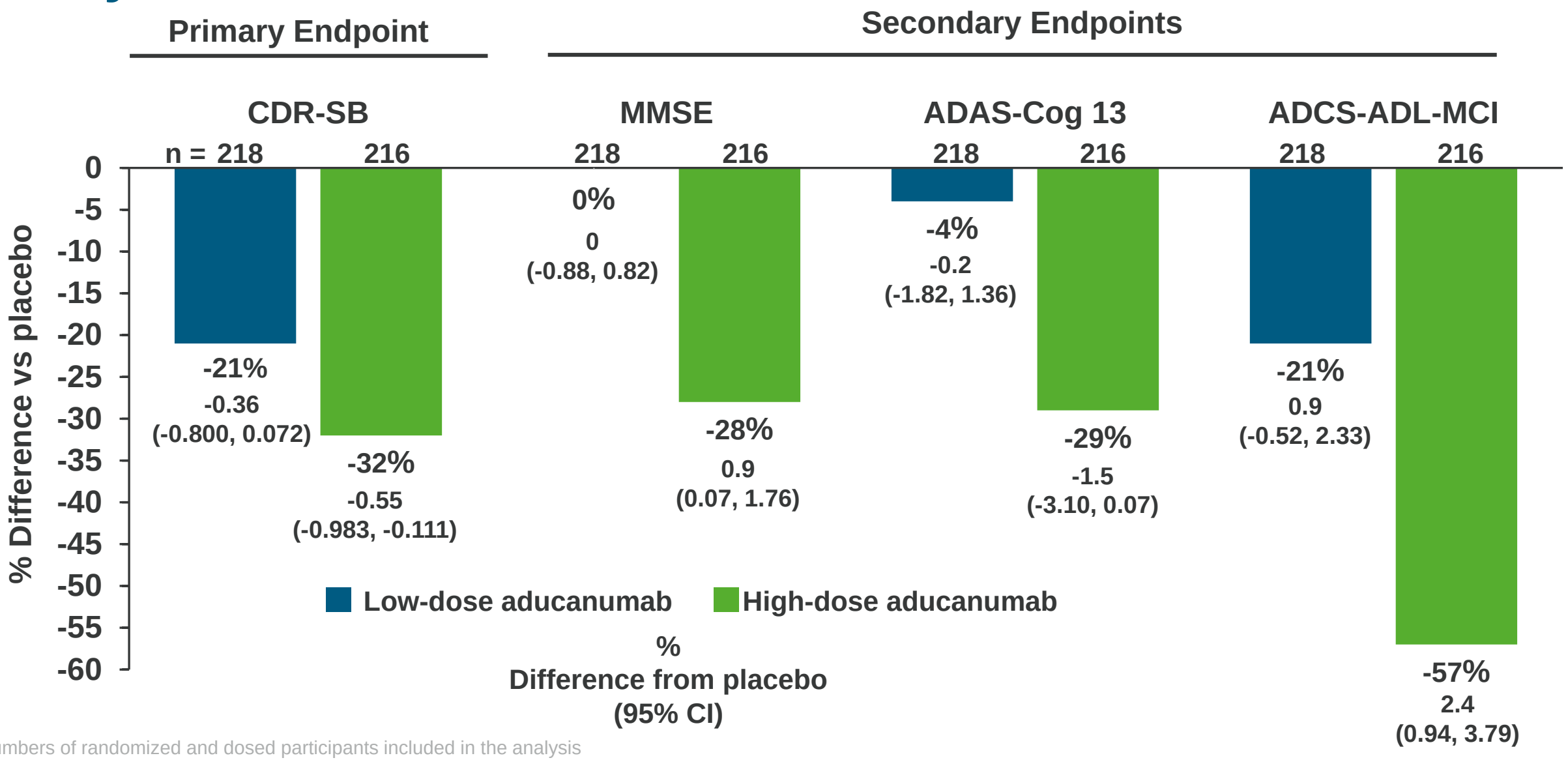
Including country interaction in the model, the treatment effect remains significant

Analysis Population	N	Placebo decline	%diff
ITT	1,638	1.74	-22%
Excluding Finland	1,605	1.77	-23%
Excluding Sweden	1,601	1.76	-22%
Excluding Netherlands	1,591	1.73	-23%
Excluding Belgium	1,589	1.74	-23%
Excluding Switzerland	1,587	1.73	-24%
Excluding France	1,560	1.75	-22%
Excluding Spain	1,560	1.67	-18%
Excluding Italy	1,557	1.71	-24%
Excluding Canada	1,542	1.80	-23%
Excluding Japan	1,517	1.80	-18%
Excluding Germany	1,516	1.71	-26%
Excluding Poland	1,445	1.76	-28%



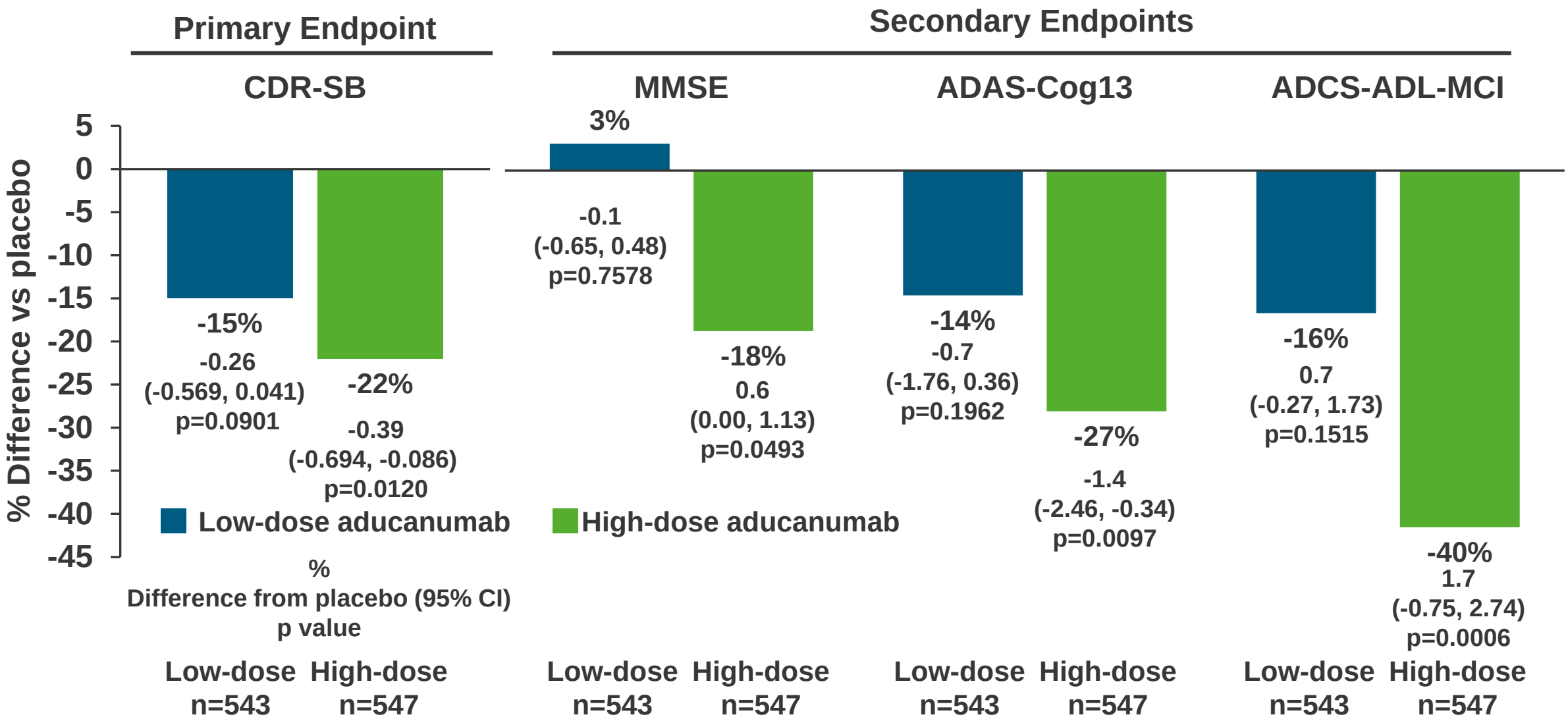
CDR-SB adjusted mean change at Week 78 for high dose vs placebo
(95% CI for difference)

Study 302: Treatment Effect at Week 78 for US Patients Only



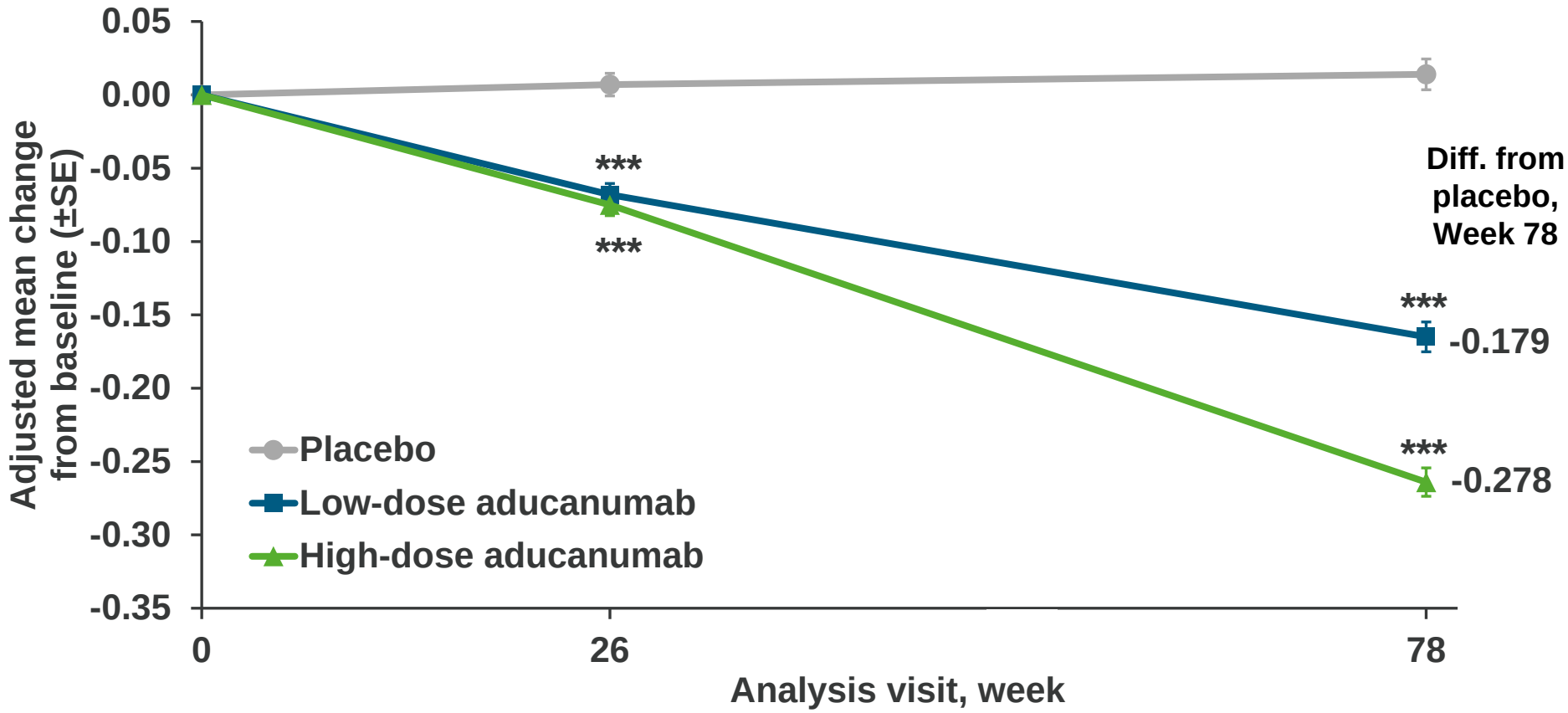
n=numbers of randomized and dosed participants included in the analysis

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



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

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

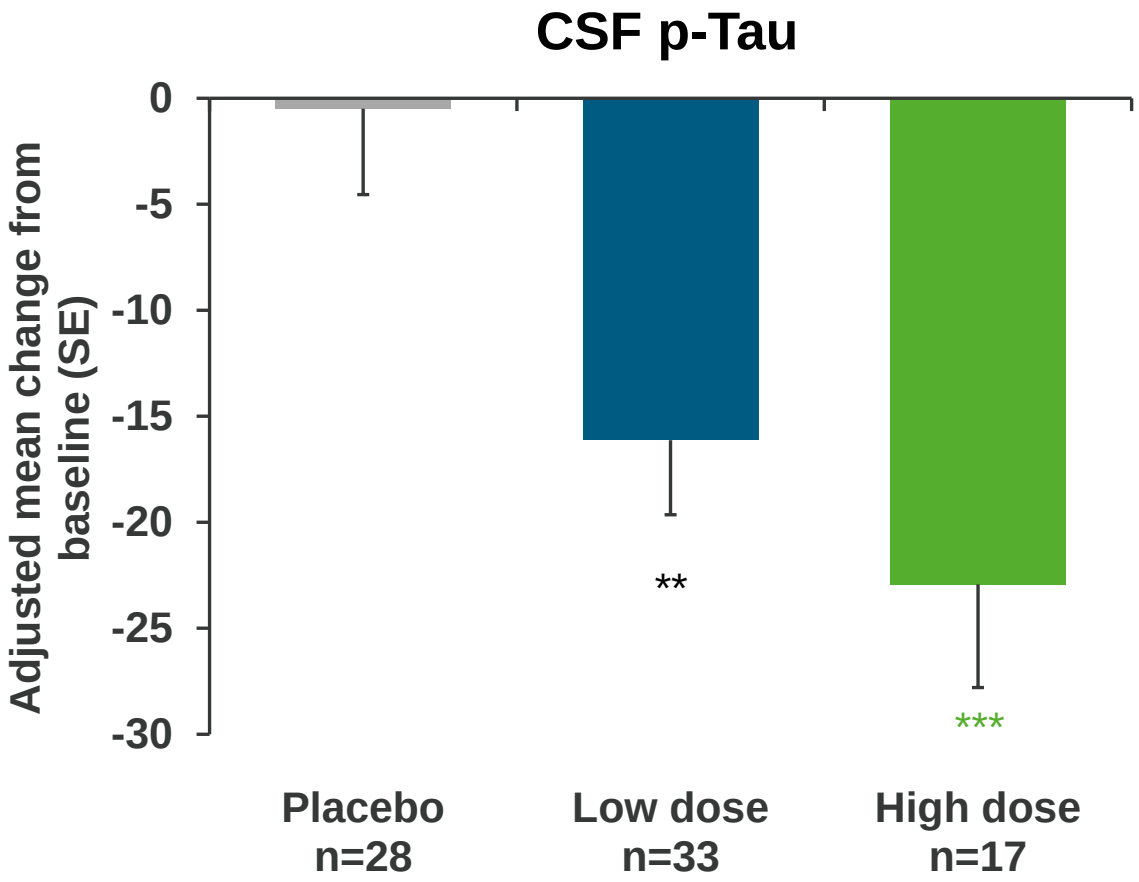


Placebo	159	129	93
Low-dose aducanumab	159	129	100
High-dose aducanumab	170	138	109

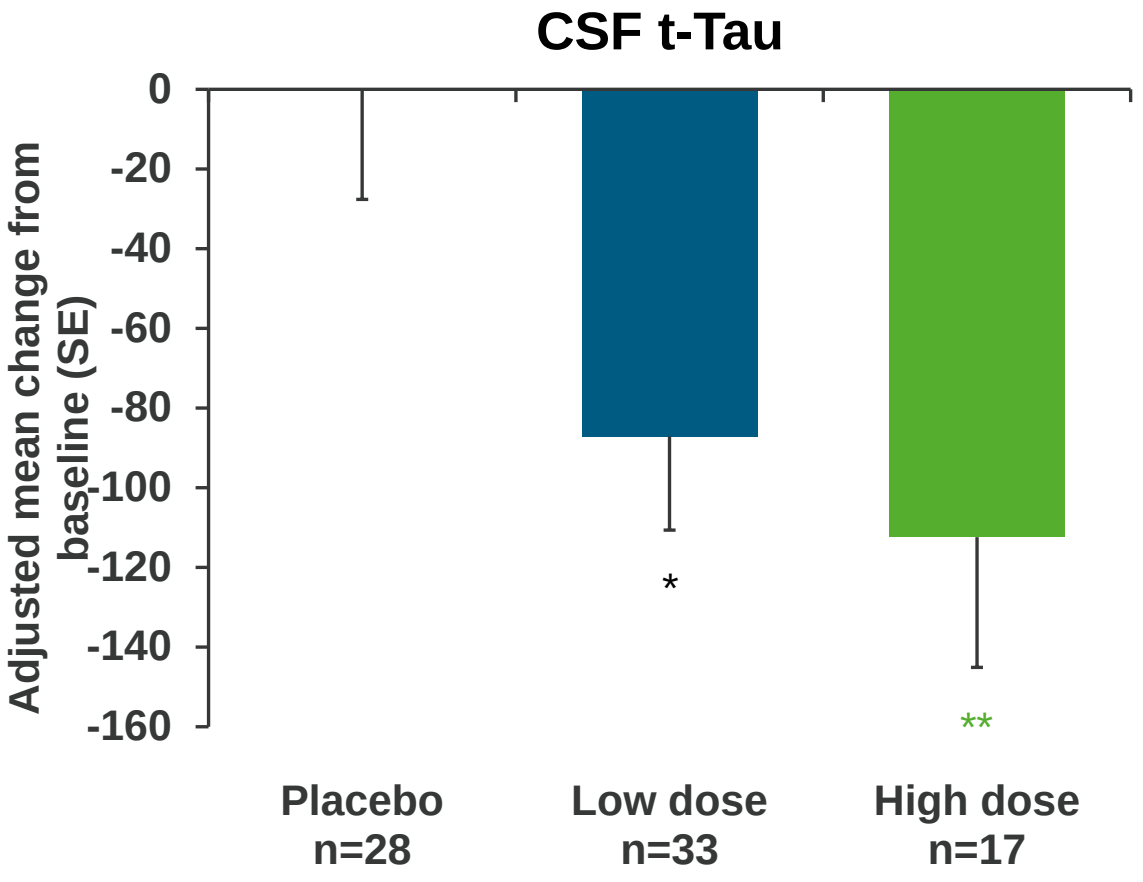
*** p<0.001 (nominal)

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

Tau pathophysiology

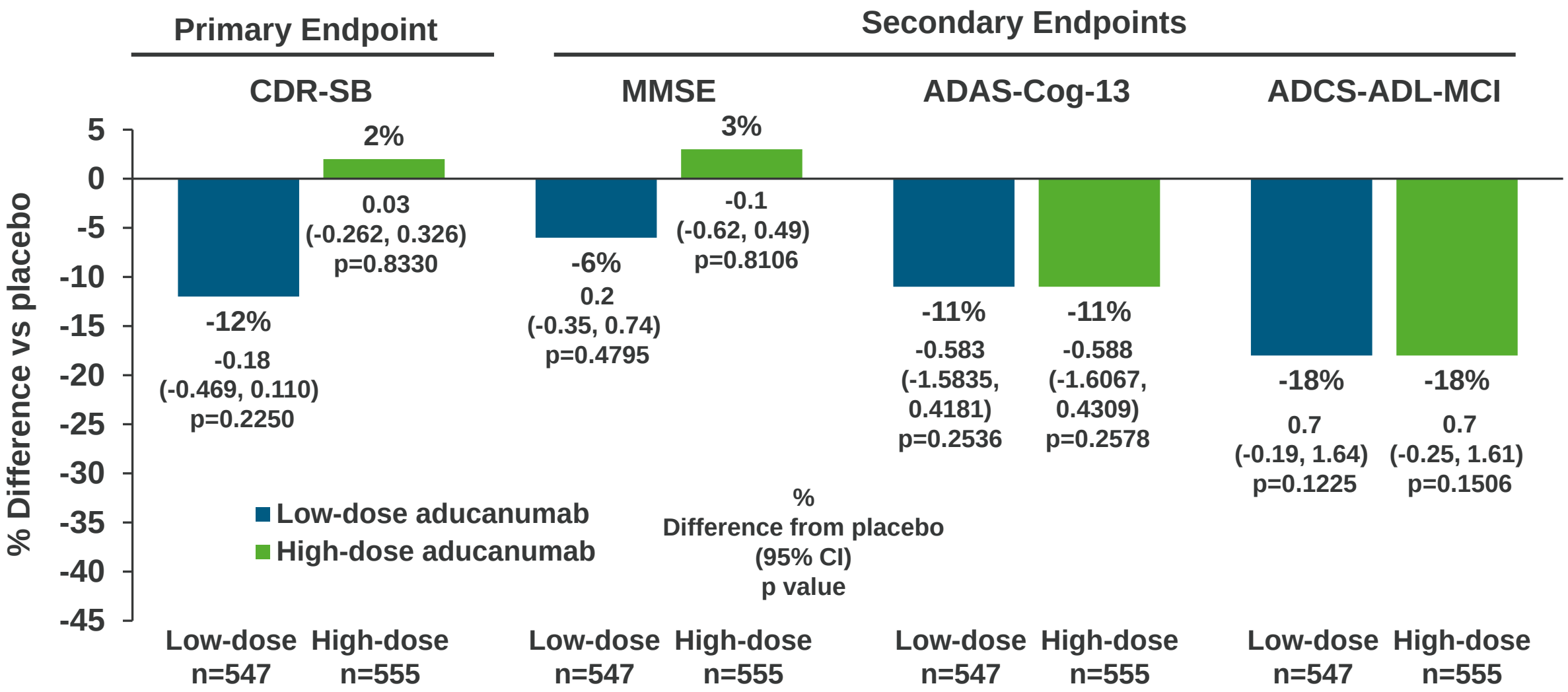


Neurodegeneration



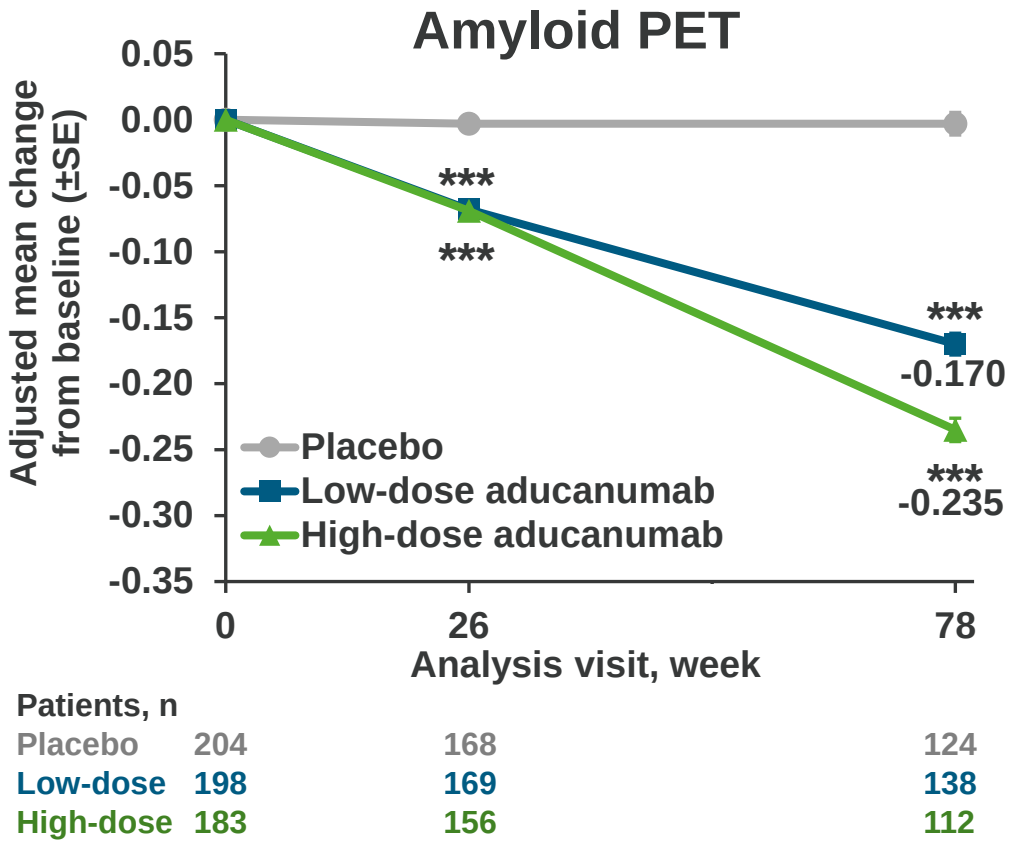
*p<0.05, ** p<0.01 , *** p<0.001 (nominal)
n=numbers of randomized and dosed participants included in the analysis

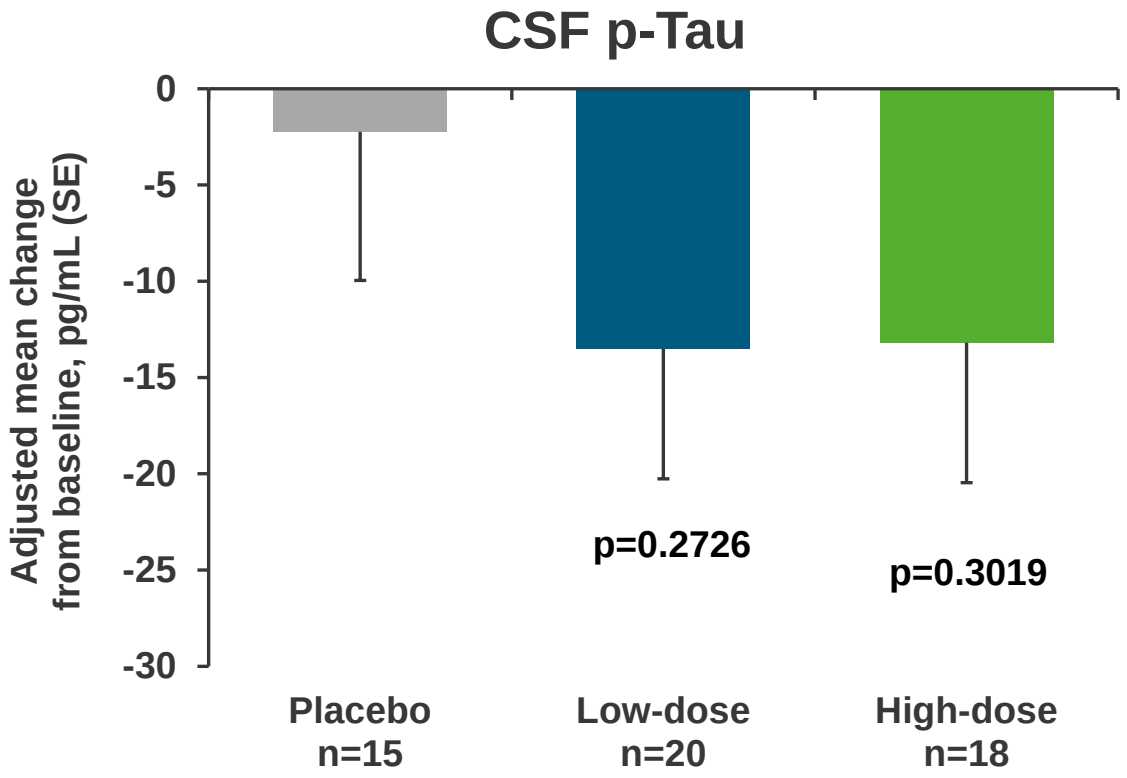
Results of Study 301 were Partially Discordant



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



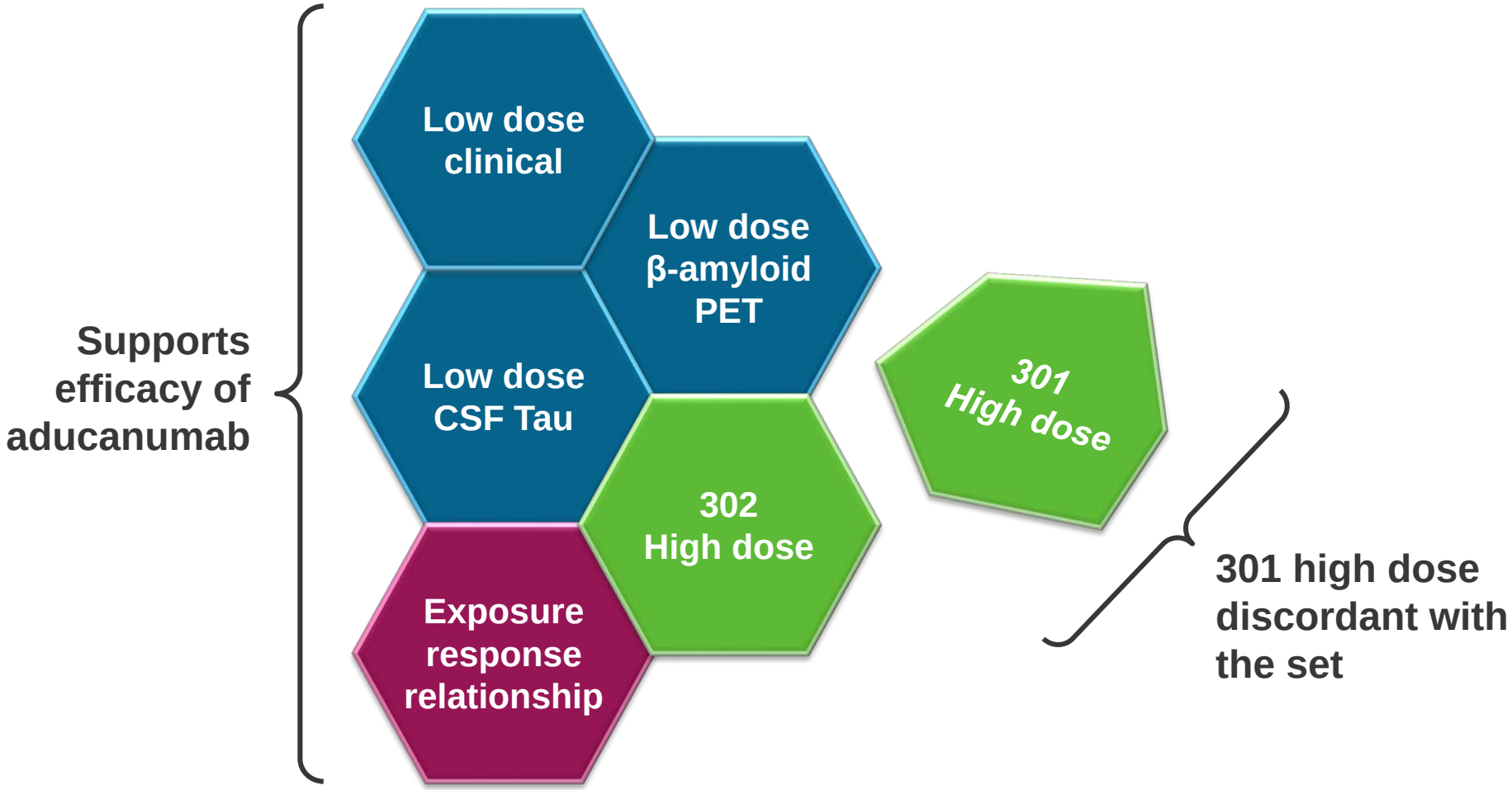


- Treatment effect 16.5% smaller
- Cumulative dose 10.4% smaller

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

*** p<0.001 (nominal)

Results in Study 301 and 302 Were Partially Discordant

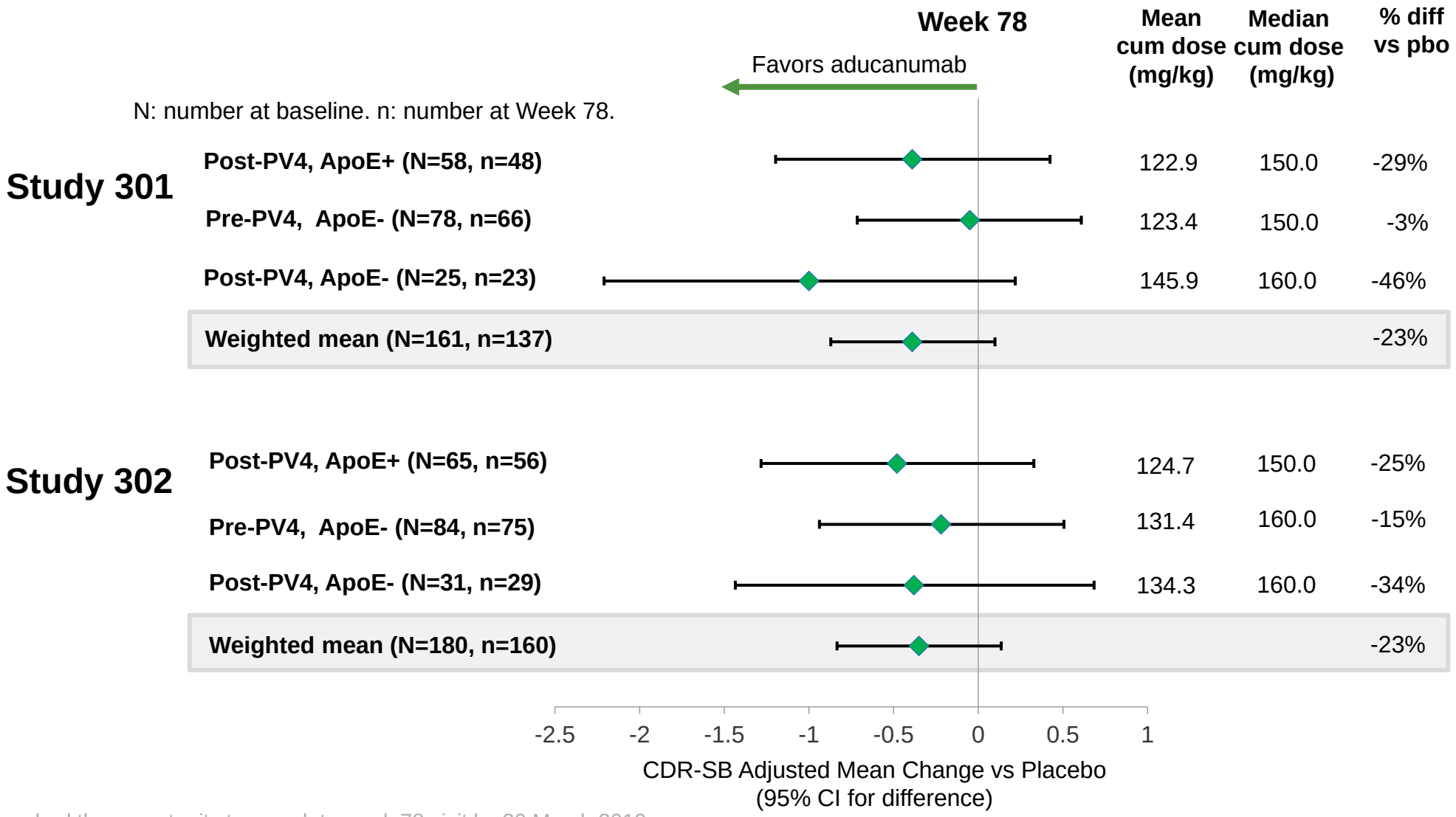


Differences in Study 301 Are Sufficiently Understood so as Not to Detract From Study 302

- 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.

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.

Safety Data Collection and Risk Evaluation Will Continue in Post-marketing Setting

Safety Data Collection

- Safety surveillance
- Ongoing long-term clinical study

ARIA Risk Minimization and Management

- Dose titration
- MRI monitoring
- Dose suspension
- Education of prescribers, radiologists, patients and caregivers

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

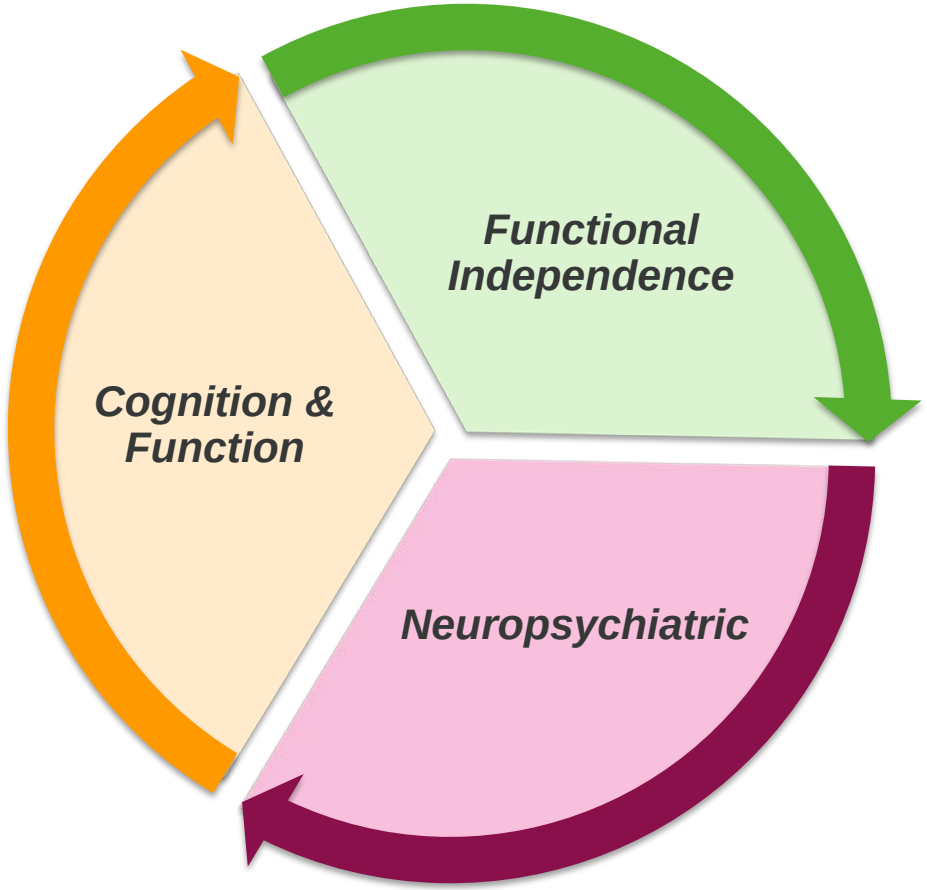
High dose outcomes at week 78 versus placebo

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 Substantial Effectiveness 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

Aducanumab Sponsor Team

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Back-up Slides

Datasets Used at Different Stages of the Phase 3 Analyses

Studies 302 and 301

Data set	Population	Study 302 n (%)	Study 301 n (%)
Dec data set	**Opportunity to complete (OTC)** Patients who have had the opportunity to complete Week 78 visit by Dec 26, 2018	803 (49%)	945 (57%)
Mar data set	**Opportunity to complete (OTC)** Patients who have had the opportunity to complete Week 78 visit by March 20, 2019	982 (60%)	1084 (66%)
	Intent to treat (ITT) All patient data (data after March 20 are censored for efficacy analyses)	1638 (100%)	1647 (100%)
Final data set	**Primary Analysis** Intent-to-treat (ITT) population, excluding data collected after 20 March 2019. MMRM model is pre-specified in SAP.	1638 (100%)	1647 (100%)
	OTC Analysis Primary analysis (by MMRM) is repeated in OTC population, defined as population who have opportunity to complete Week 78 by 20 March 2019.	982 (60%)	1084 (66%)
	Uncensored Analysis MMRM model in primary analysis was repeated in ITT population with all data collected during studies (without excluding data after March 20)	1638 (100%)	1647 (100%)
Sub-studies	**Amyloid PET (florbetapir or flutemetamol)**	515 (31%)	585 (36%)
	CSF	78 (5%)	53 (3%)
	Tau PET	6 (<1%)	31 (2%)

CSF=cerebrospinal fluid; ITT=intent to treat; OTC=opportunity to complete; PET=positron emission tomography.

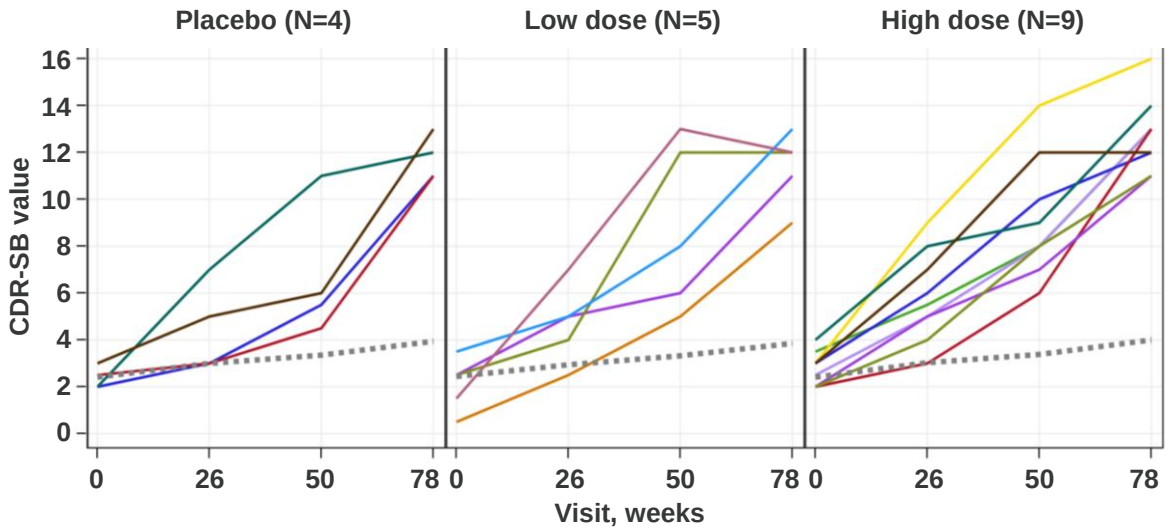
Inference Based on Pre-specified Analysis on Final Data

- The study could not be stopped for positive efficacy at the futility, hence no alpha spent.
- No conclusion on efficacy inference was drawn from the March data, hence no alpha spent.
  - March data “interpretable and suitable for further consideration”
  - Exploratory analysis for initial insight into the divergent results between studies.
- Using the March data allowed us to learn about what was going on sooner.
  - Since efficacy data were censored after 20Mar2019, minimal differences were anticipated between efficacy results on March data and the final data
  - Confirmed in the final data efficacy analysis.

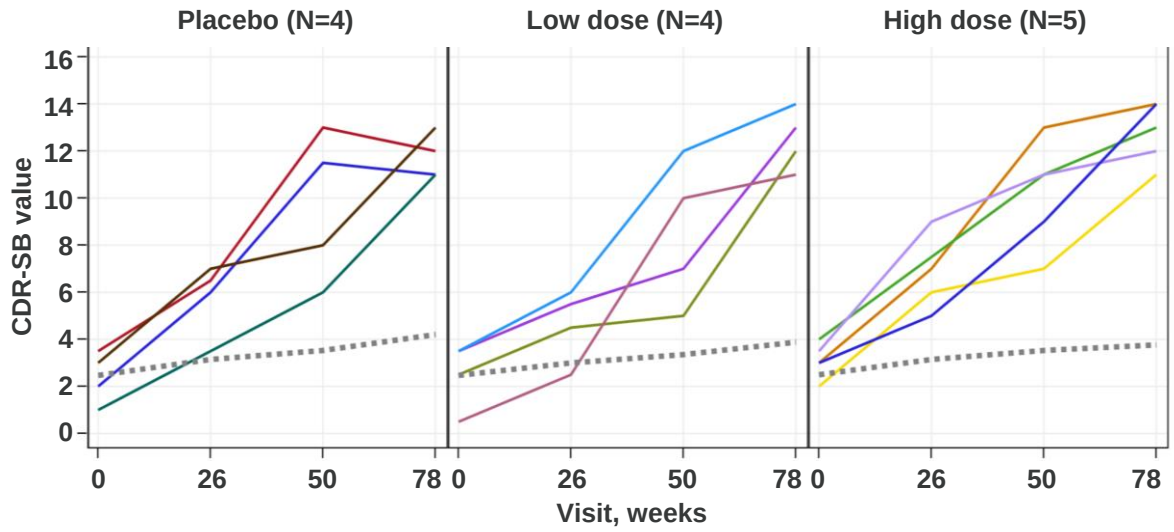
CDR-SB Over Time for Rapid Progressors

Studies 301 and 302

Study 301



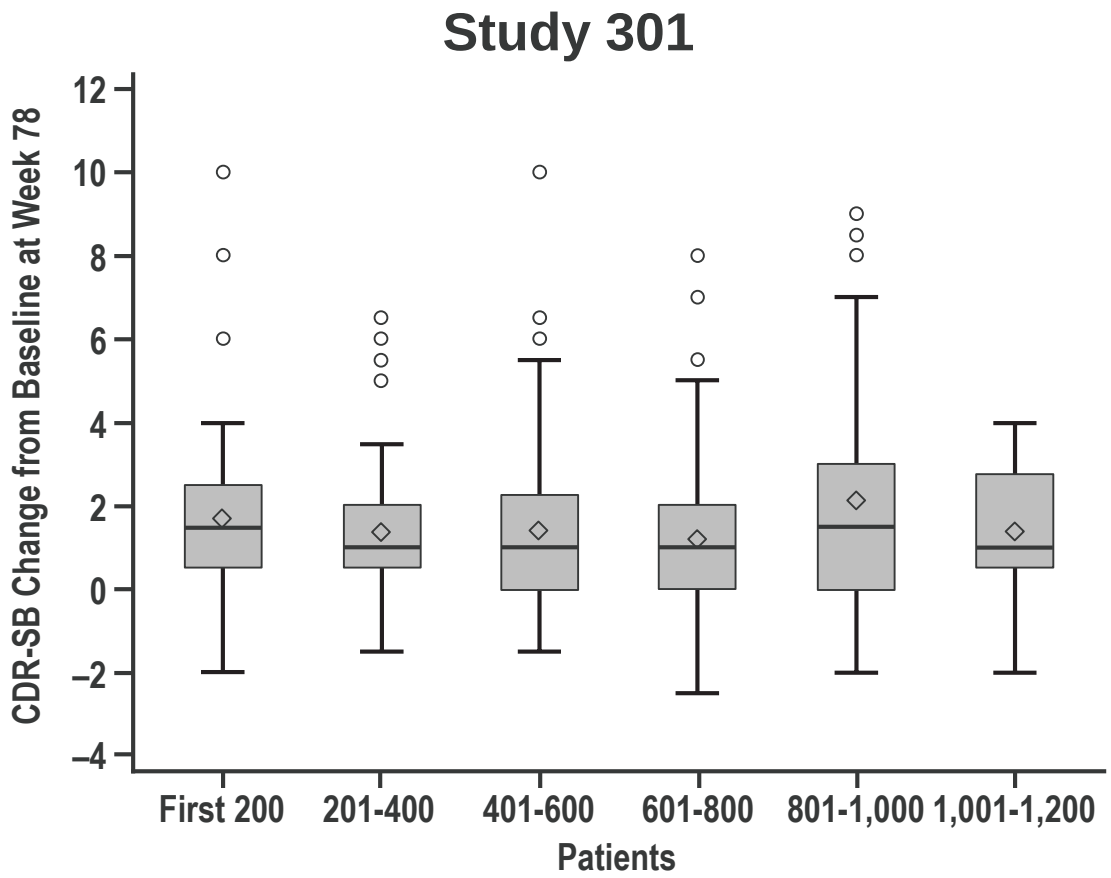
Study 302



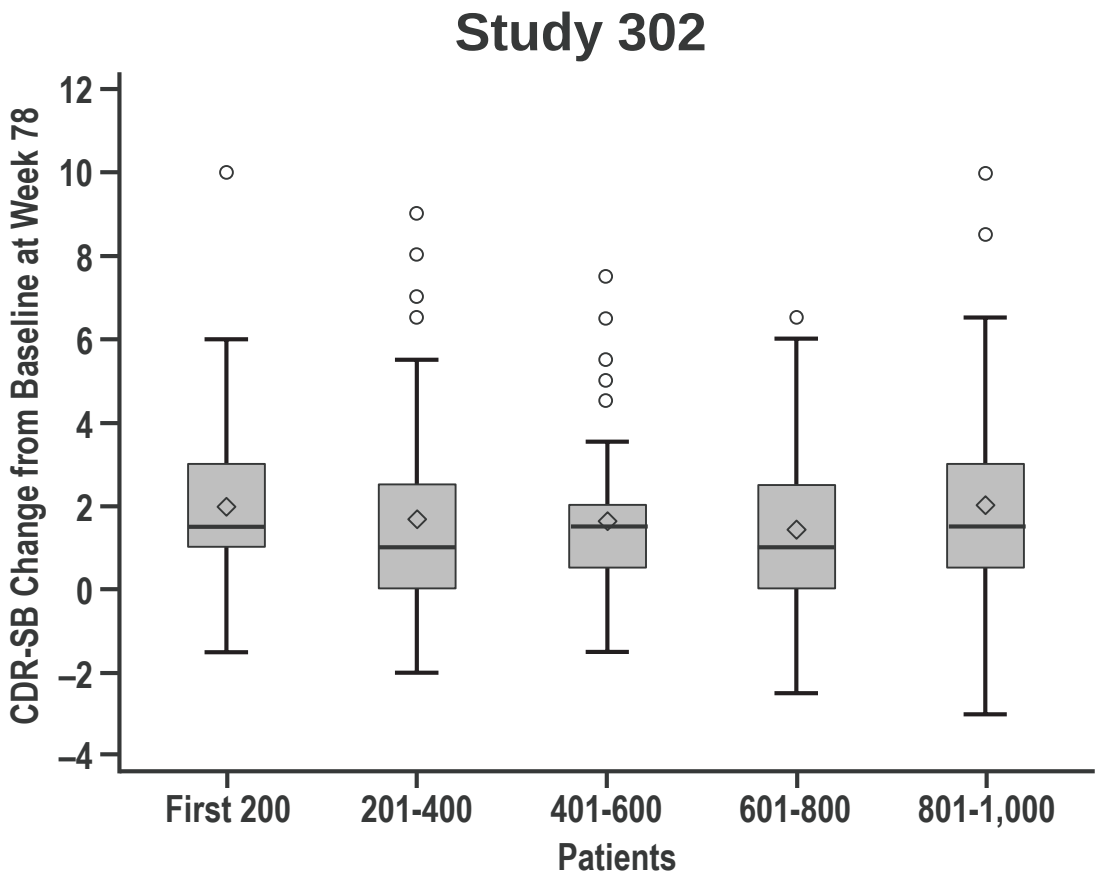
NOTE 1: Rapid progressor is defined as any patient with >8 change from baseline in CDR sum of boxes at Week 78.
NOTE 2: The grey dashed line represents the mean value over time in the ITT population per treatment group.

No Trend in Placebo Decline Over Enrollment Time

Study 301 and 302



	First 200	201-400	401-600	601-800	801-1,000	1,001-1,200
N	58	67	64	65	59	20
Mean	1.67	1.36	1.41	1.19	2.14	1.38
Median	1.5	1.0	1.0	1.0	1.5	1.0



	First 200	201-400	401-600	601-800	801-1,000
N	55	60	57	66	50
Mean	1.97	1.68	1.63	1.39	2.03
Median	1.5	1.0	1.5	1.0	1.5

Placebo Decline Did Not Influence 301 / 302

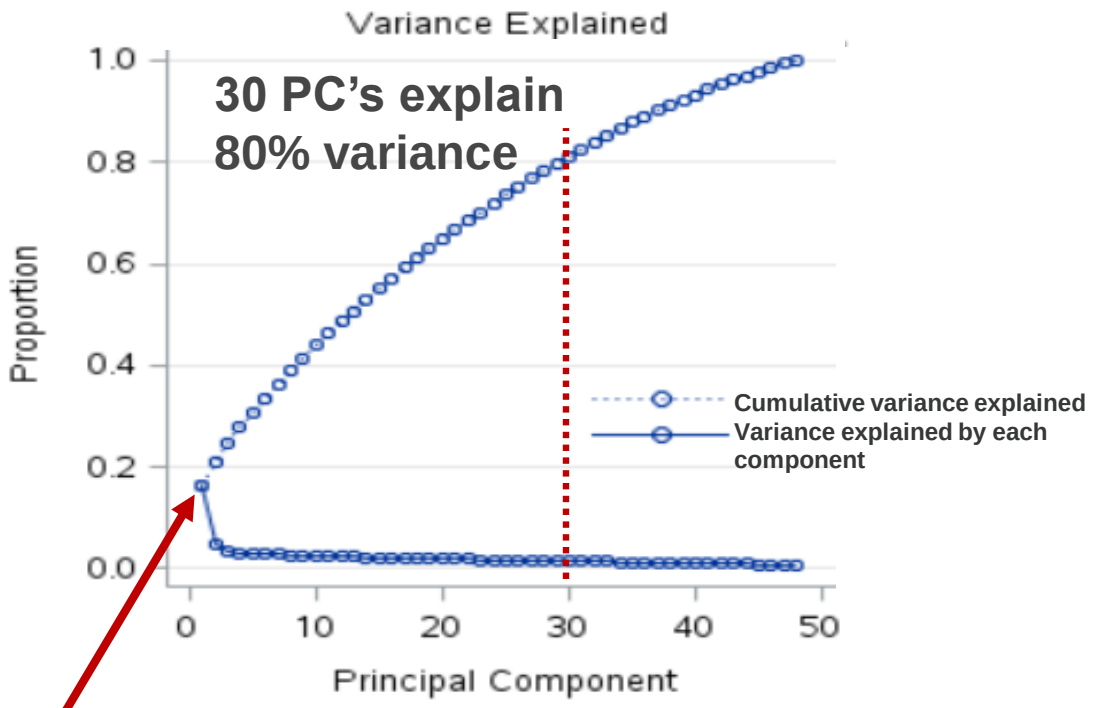
- Baseline demographic and disease characteristics were consistent across studies
- Placebo decline was within the range of recent trials, but slightly less than the specific value assumed in study development
- Placebo decline at Week 78 varied by endpoint
  - More decline in 302 on CDR-SB (1.56 vs. 1.74) and ADCS-ADL-MCI (-3.8 vs. -4.3)
  - Less decline in 302 on MMSE (-3.5 vs. -3.3)
  - Similar decline on ADAS-Cog13 (5.14 vs. 5.16)
- Treatment effect in low dose consistent between 301 and 302, suggesting differences between studies in placebo decline was unlikely to have large effect on high dose

Principal Component Analysis - Change From Baseline to Week 78

Study 301 and 302 Placebo Group

PC	Origin Scale	Item name
1	CDR	• Judgment problem solving • Home and hobbies • Personal care • Community affairs • Memory
2	ADAS-Cog 13	• Orientation
	CDR	• Orientation
	MMSE	• Orientation to time
3	ADAS-Cog 13	• Word finding • Spoken language • Comprehension
4	ADCS-ADL-MCI	• Make a meal • Use household appliance
5	MMSE	• Naming
	ADAS-Cog 13	• Registration • Naming
6	ADAS-Cog 13	• Total list recalled • Word recall total
7	ADCS-ADL-MCI	• Usual dressing • Select first clothes
8	ADCS-ADL-MCI	• Travel • Go shopping
9	MMSE	• Reading
10	MMSE	• Recall • Attention and calculation
11	ADAS-Cog 13	• Construction • Recall instructions
12	ADCS-ADL-MCI	• Keep appointments • Use a telephone

PC	Origin Scale	Item name
13	ADAS-Cog 13	• Word recognition
14	ADCS-ADL-MCI	• Clean laundry
15	MMSE	• Comprehension
16	ADAS-Cog 13	• Ideational praxis
17	MMSE	• Repetition
18	ADCS-ADL-MCI	• Watch television
19	ADCS-ADL-MCI	• Read more than 5 minutes
20	ADCS-ADL-MCI	• Balance banking
21	ADCS-ADL-MCI	• Left on his/her own
22	ADAS-Cog 13	• Commands
23	ADCS-ADL-MCI	• Write things down
24	ADCS-ADL-MCI	• Clean room
25	MMSE	• Writing
26	MMSE	• Drawing
27	ADCS-ADL-MCI	• Perform pastime
28	ADCS-ADL-MCI	• Talk about current events
29	ADCS-ADL-MCI	• Find personal belongings
30	MMSE	• Orientation to place
	ADAS-Cog 13	• Number cancellation

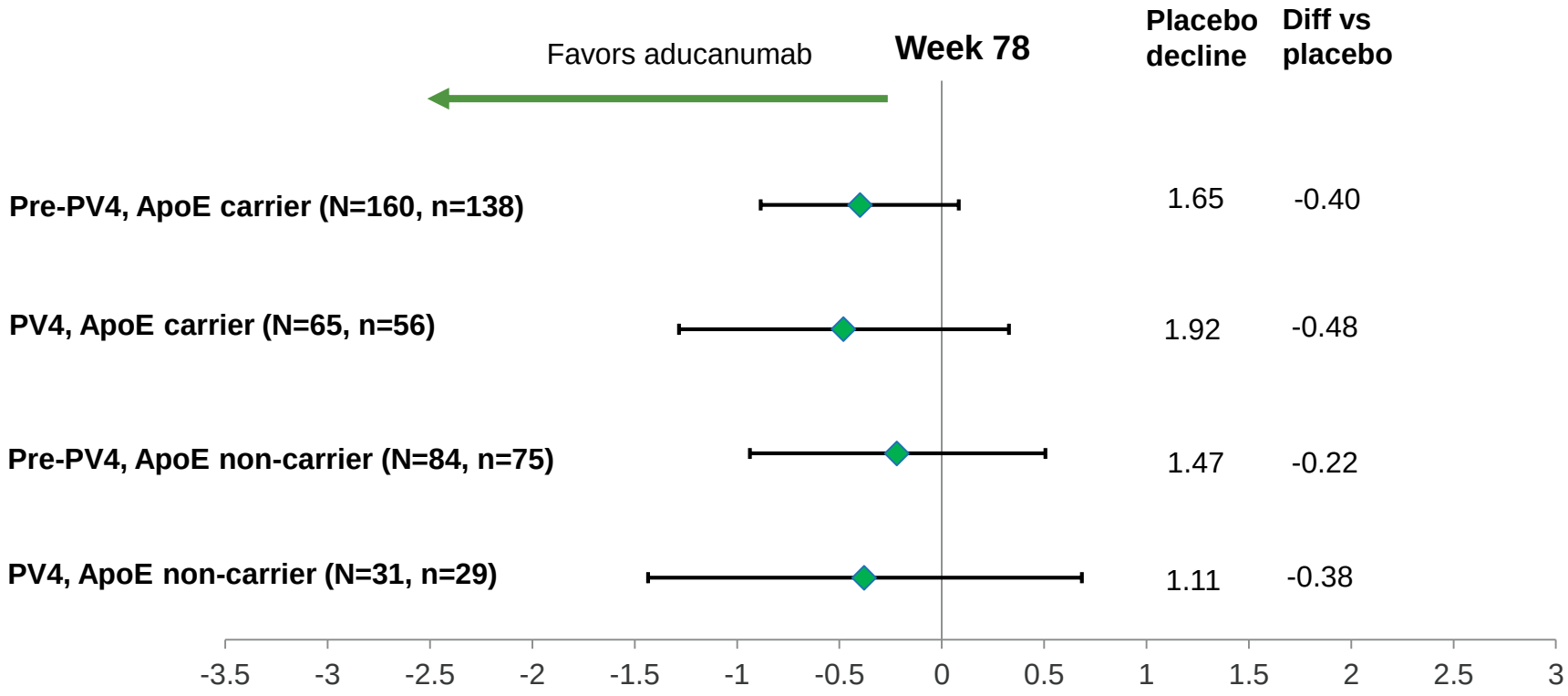


First principal component explains < 20% variance

CDR-SB Results Not Driven by Placebo Decline

CDR-SB by PV4 subset and APOE status

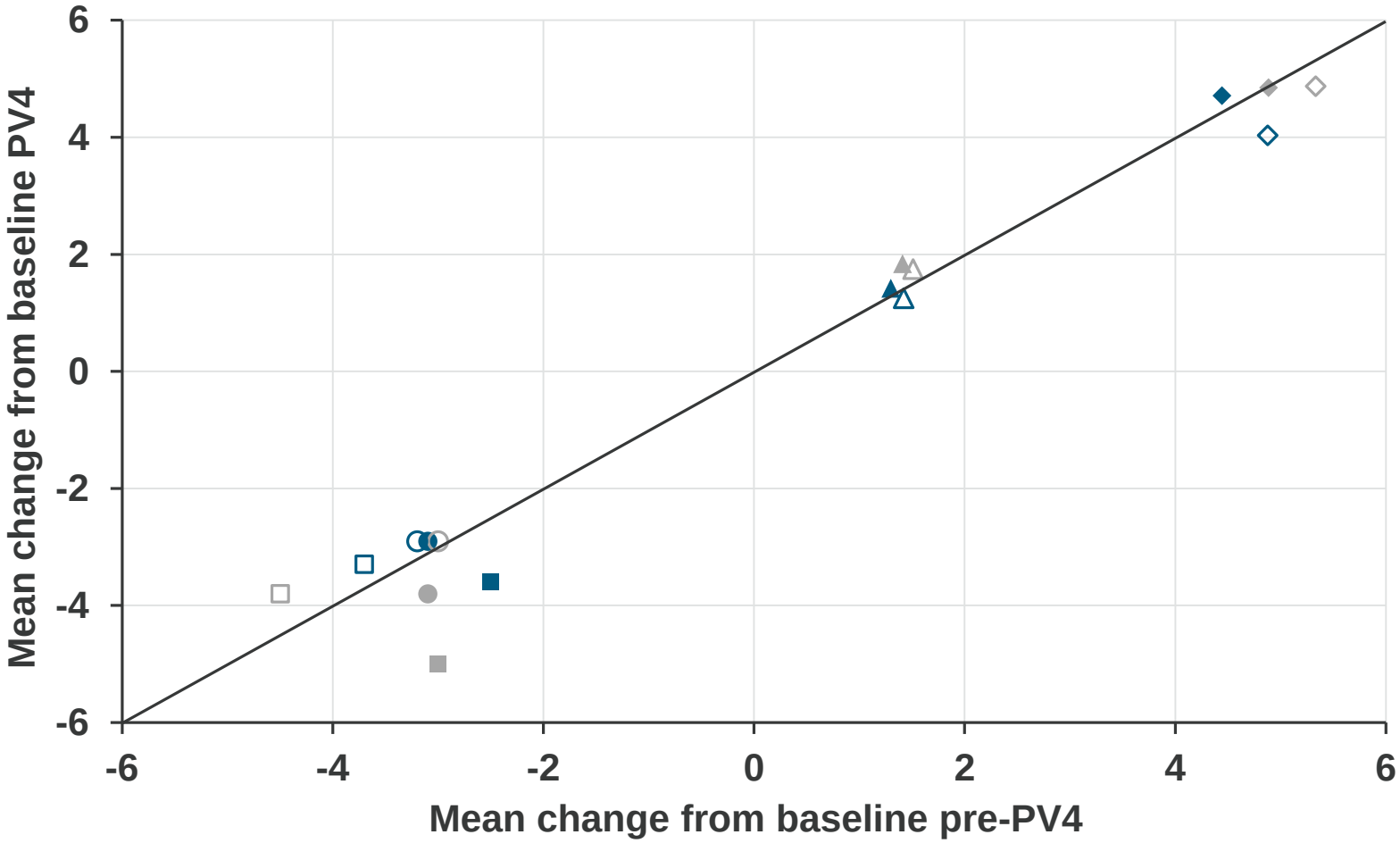
Study 302 High dose, OTC population



N=number of patients at baseline. n=number of patients at Week 78.

No Systematic Effect of PV4 in Treatment Arms That Did Not Have a Dose Change

Study 301 and 302



	Study 301		Study 302	
	PBO	Low dose	PBO	Low dose
CDR-SB	▲	▲	△	△
MMSE	●	●	○	○
ADAS-Cog 13	◆	◆	◇	◇
ADCS-ADL-MCI	■	■	□	□

Pre-PV4: patients who did not have opportunity to receive 14 doses of 10 mg/kg
PV4: patients who had opportunity to receive 14 doses of 10 mg/kg