

# 24-Month Analysis of Change From Baseline In Clinical Dementia Rating Scale Cognitive and Functional Domains in PRIME, A Randomized Phase 1b Study of the Anti-Amyloid Beta Monoclonal Antibody Aducanumab

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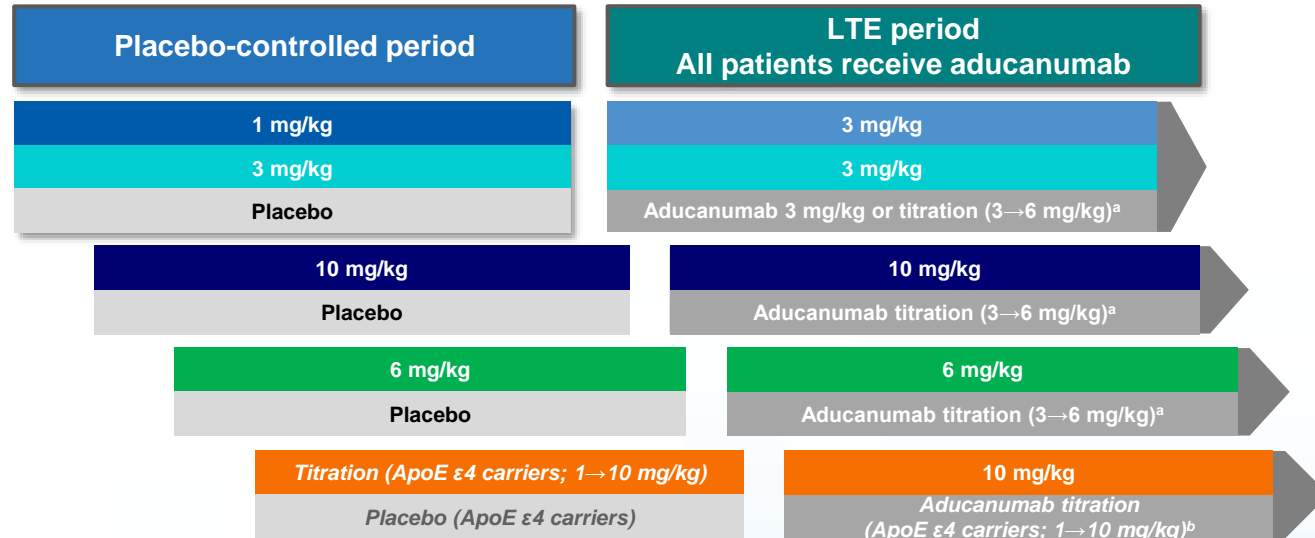
# Disclosures

- This study is funded by Biogen<sup>a</sup>
- SBH, CCV, SG, TC, JO, LS, CvH, PvR, and AS are employees and shareholders of Biogen
- PC was an employee and shareholder of Biogen at the time of this work
- GW is an employee of Cytel
- CH and RMN are employees and shareholders of Neurimmune
- Biogen licensed the worldwide rights to aducanumab from Neurimmune Holding AG in 2007 and is responsible for its development and the commercialization
- As of October 22, 2017, Biogen and Eisai are collaborating on the development and commercialization of aducanumab globally

# Overview

- Aducanumab is a human monoclonal antibody that binds to both soluble and insoluble aggregated forms of A $\beta$ , including oligomers, protofibrils, and fibrils<sup>1</sup>
- PRIME is an ongoing Phase 1b study assessing the safety, tolerability, PK and PD of aducanumab in patients with prodromal or mild Alzheimer's disease
- In PRIME, treatment with aducanumab resulted in a time and dose dependent removal of plaques from the brain as shown by positron emission tomography (PET) standardized uptake value ratio<sup>1</sup>
- Patients with early Alzheimer's disease enrolled in PRIME experienced a sustained delay in the disease progression as measured by exploratory clinical endpoints at 12, 24 and 36 months<sup>1-3</sup>
- The primary endpoint in the PRIME LTE is safety/tolerability
- Exploratory endpoints include:
  - Changes in amyloid PET
  - Measures of clinical decline on the CDR-SB and MMSE
- A post hoc analysis was conducted on the fixed-dose and titration cohorts that assessed cognitive and functional domains of the CDR scale over 24 months, including 12 months from the placebo-controlled period and 12 months from the LTE

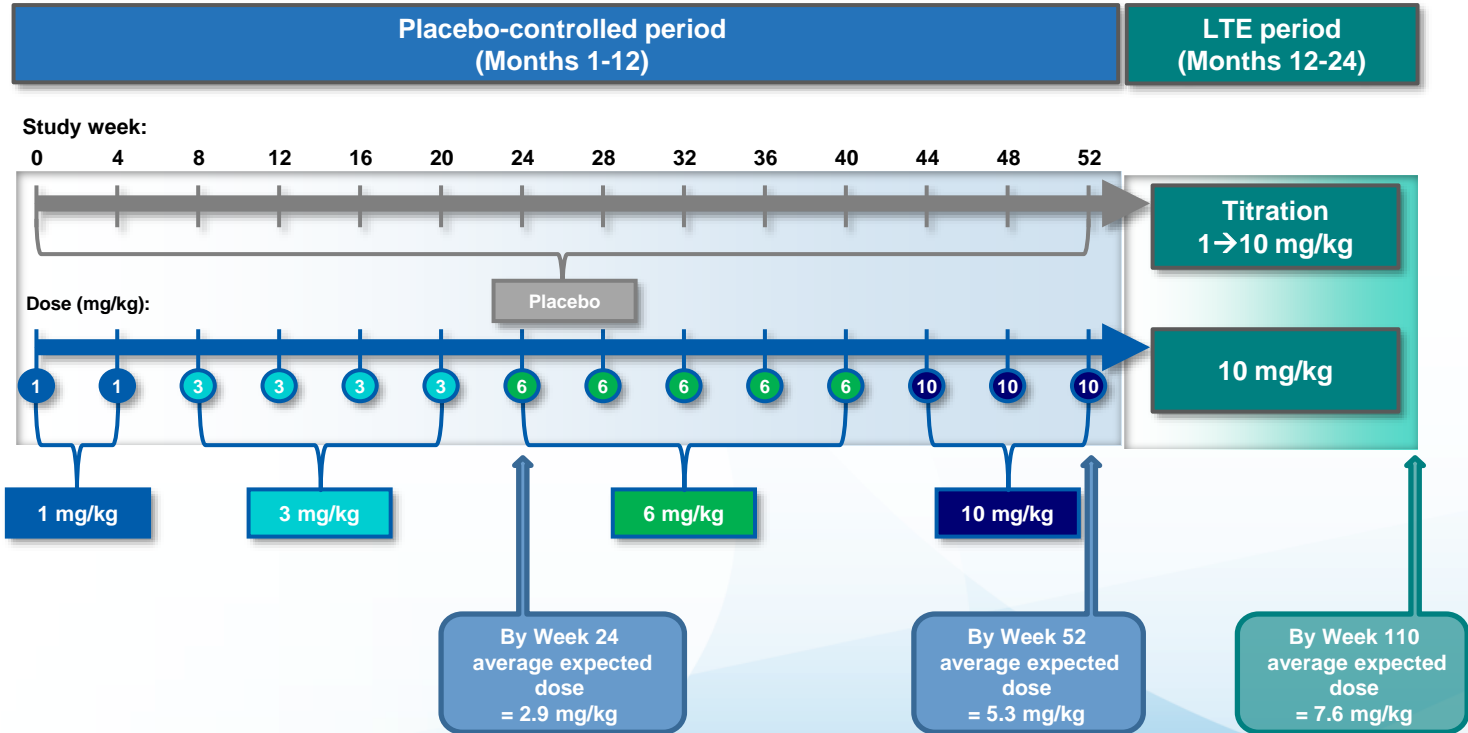
# PRIME Study Design: Placebo-Controlled and LTE Periods



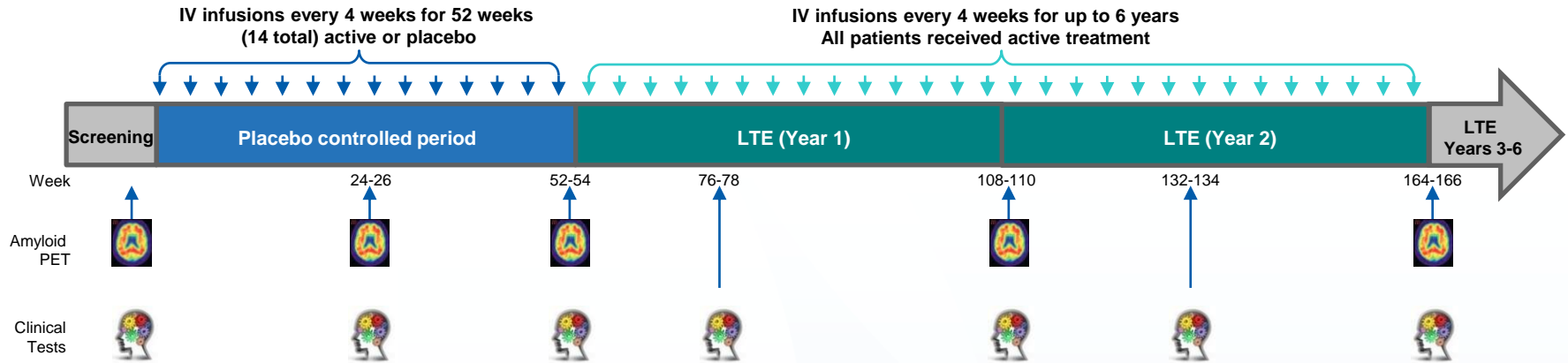
- **Randomization:** 3:1 active: placebo within cohorts, fixed-dose cohorts stratified by ApoE ε4 status
- Patients randomized to placebo in the placebo-controlled period were switched to aducanumab 3 mg/kg or a titration regimen in the LTE (“**placebo switchers**”). Patients randomized to aducanumab 3, 6, or 10 mg/kg or titration in the placebo-controlled period were assigned to continue in the same dose group in the LTE (“**continuers**”)

<sup>a</sup>Titration denotes 2 doses of 3 mg/kg followed by subsequent doses of 6 mg/kg. <sup>b</sup>Titration denotes 2 doses of 1 mg/kg, 4 doses of 3 mg/kg, 5 doses of 6 mg/kg followed by subsequent doses of 10 mg/kg. ApoE ε4, Apolipoprotein E ε4; LTE, long-term extension.

# Titration Dosing Regimen

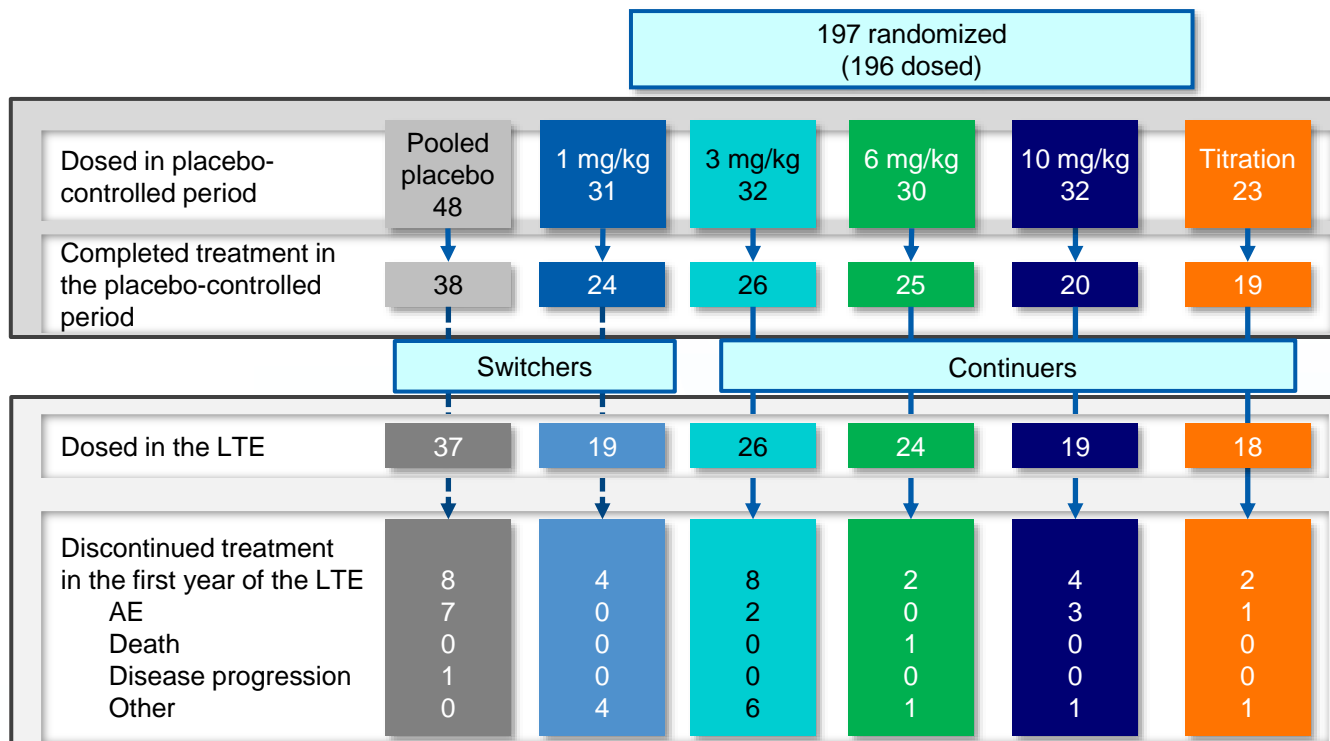


# Timeline of PET and Clinical Assessments in PRIME





# Patient Disposition at 24 Months



# Baseline Disease Characteristics

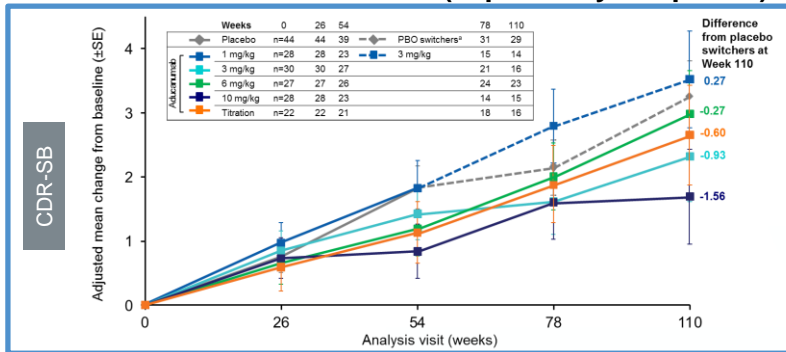
	Placebo (n=48)	Aducanumab				
		1 mg/kg (n=31)	3 mg/kg (n=32)	6 mg/kg (n=30)	10 mg/kg (n=32)	Titration (n=23)
Age in years, mean ± SD	73.3 ± 6.8	72.6 ± 7.8	70.5 ± 8.2	73.3 ± 9.3	73.7 ± 8.3	73.1 ± 7.8
ApoE ε4, n (%)						
Carriers	34 (71)	19 (61)	21 (66)	21 (70)	20 (63)	23 (100)
Non-carriers	14 (29)	12 (39)	11 (34)	9 (30)	12 (38)	0
Clinical stage, n (%)						
Prodromal	22 (46)	10 (32)	14 (44)	12 (40)	13 (41)	13 (57)
Mild	26 (54)	21 (68)	18 (56)	18 (60)	19 (59)	10 (43)
MMSE, mean ± SD	24.7 ± 3.6	23.6 ± 3.3	23.2 ± 4.2	24.4 ± 2.9	24.8 ± 3.1	24.7 ± 3.0
CDR Global Score, n (%)						
0.5	40 (83)	22 (71)	22 (69)	25 (83)	24 (75)	18 (78)
1	8 (17)	9 (29)	10 (31)	5 (17)	8 (25)	5 (22)
CDR-SB, mean ± SD	2.69 ± 1.54	3.40 ± 1.76	3.50 ± 2.06	3.32 ± 1.54	3.14 ± 1.71	3.24 ± 1.84
PET SUVR, mean composite	1.435	1.441	1.464	1.429	1.441	1.325
AD medications used, <sup>a</sup> n (%)	32 (67)	21 (68)	28 (88)	20 (67)	17 (53)	12 (52)

<sup>a</sup>Cholinesterase inhibitors and/or memantine.

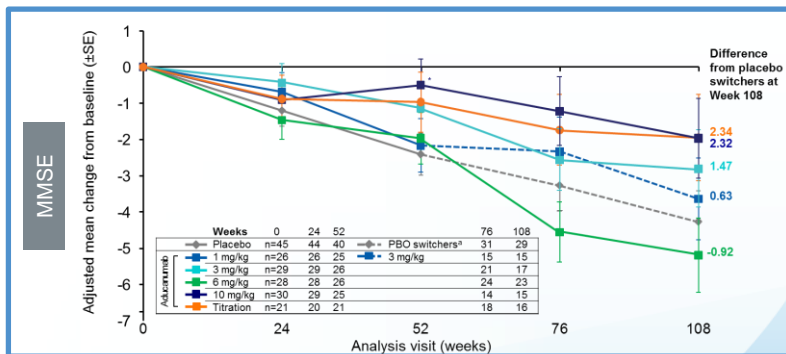
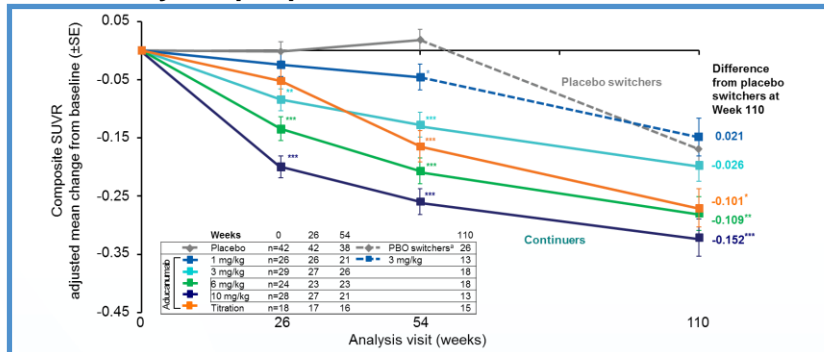
AD, Alzheimer's disease; ApoE ε4, Apolipoprotein E ε4; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SD, standard deviation; SUVR, standardized uptake value ratio.

# Summary of Previously Presented PRIME 24-Month Interim Results

## Clinical effect of aducanumab (exploratory endpoints)



## Amyloid plaque reduction with aducanumab



## Safety (primary endpoint)

- Of the 185 patients dosed with aducanumab since the start of the PRIME study, 46 patients experienced ARIA-E
- Of the 46 patients who experienced ARIA-E, 65% were asymptomatic and 35% were symptomatic; the majority of symptomatic cases experienced symptoms that were mild to moderate in severity
- 6 patients experienced more than one episode of ARIA
- The majority of ARIA events occurred early in the course of treatment; they were typically mild, asymptomatic, and resolved or stabilized within 4-12 weeks, with most patients continuing treatment

\*Placebo switchers received aducanumab 3 mg/kg or titration (3 mg/kg → 6 mg/kg or 1 mg/kg → 10 mg/kg) in the LTE. Nominal \*  $P < 0.05$ ; Nominal \*\*  $P < 0.01$ ; Nominal \*\*\*  $P < 0.001$  vs placebo in the placebo-controlled period and vs placebo switchers in the LTE period. MMSE and CDR-SB are exploratory endpoints. Results based on MMRM, fitted with change from baseline as a dependent variable, and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction, continuous baseline value, and laboratory ApoE ε4 status (carrier and non-carrier). ARIA-E, amyloid-related imaging abnormalities - vasogenic edema; CDR-SB, Clinical Dementia Rating-Sum of Boxes; LTE, long-term extension; MMRM, mixed model for repeated measures; MMSE, Mini Mental State Exam; SE, standard error.

# Clinical Dementia Rating (CDR) Scale Domains

- The CDR-SB is a validated global assessment of Alzheimer's disease disability that is capable of tracking the progression of Alzheimer's disease in the MCI and mild Alzheimer's disease population
- It assesses a patient's level of impairment on 6 domains using semi-structured interviews by a trained clinician/rater with the patient and an informant

## Functional domains

- Community Affairs
- Home and Hobbies
- Personal Care

## Cognitive domains

- Memory
- Orientation
- Judgement and Problem Solving

- Each impairment level of the cognitive and functional domains (except for Personal Care) is rated on a continuum of five levels, with a scale of 0 to 3
  - The five levels of impairment are 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe)
  - Personal Care uses only 4 levels: 0, 1, 2, and 3

# Baseline CDR Global and Domain Scores

	Placebo (n=48)	Aducanumab				
		1 mg/kg (n=31)	3 mg/kg (n=32)	6 mg/kg (n=30)	10 mg/kg (n=32)	Titration (n=23)
CDR-SB, mean ± SD	2.69 ± 1.54	3.40 ± 1.76	3.50 ± 2.06	3.32 ± 1.54	3.14 ± 1.71	3.24 ± 1.84
CDR cognitive domain score, mean ± SD	1.79 ± 0.87	2.00 ± 0.94	2.20 ± 1.02	2.03 ± 0.67	2.03 ± 1.03	2.04 ± 0.94
CDR functional domain score, mean ± SD	0.90 ± 0.83	1.40 ± 1.09	1.30 ± 1.20	1.28 ± 1.06	1.11 ± 0.90	1.20 ± 1.15

# Week 54: Effect of Aducanumab on Both CDR Cognitive and Functional Domains

## CDR Cognitive Domain (Week 54)

Favors aducanumab  
vs placebo

Aducanumab dose

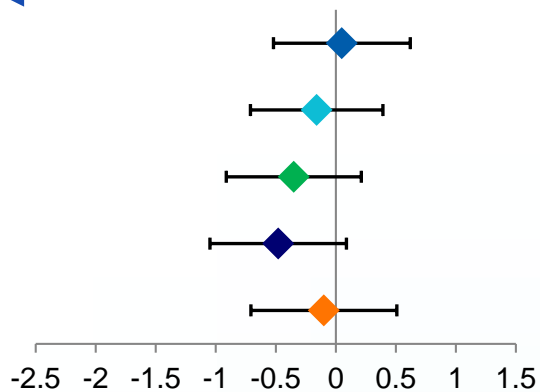
1 mg/kg (n=23)

3 mg/kg (n=27)

6 mg/kg (n=26)

10 mg/kg (n=23)

Titration (n=21)



Difference vs Placebo, Adjusted Mean [95%CI]

## CDR Functional Domain (Week 54)

Favors aducanumab  
vs placebo

Aducanumab dose

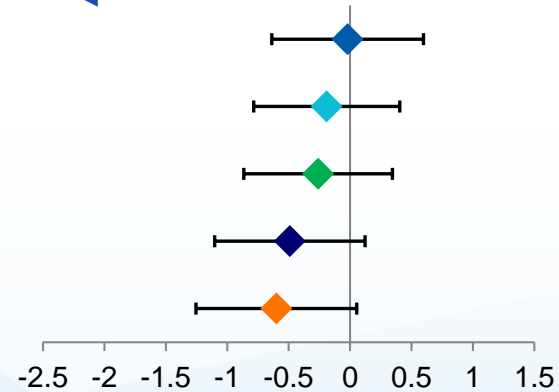
1 mg/kg (n=23)

3 mg/kg (n=27)

6 mg/kg (n=26)

10 mg/kg (n=23)

Titration (n=21)



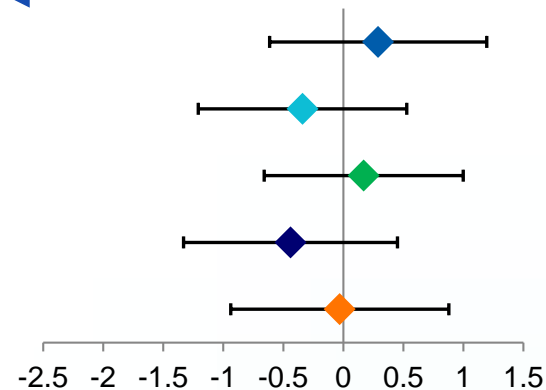
Difference vs Placebo, Adjusted Mean [95%CI]

# Week 110: Effect of Aducanumab on Both CDR Cognitive and Functional Domains

**CDR Cognitive Domain (Week 110)**

Favors aducanumab  
vs placebo switchers

Aducanumab dose

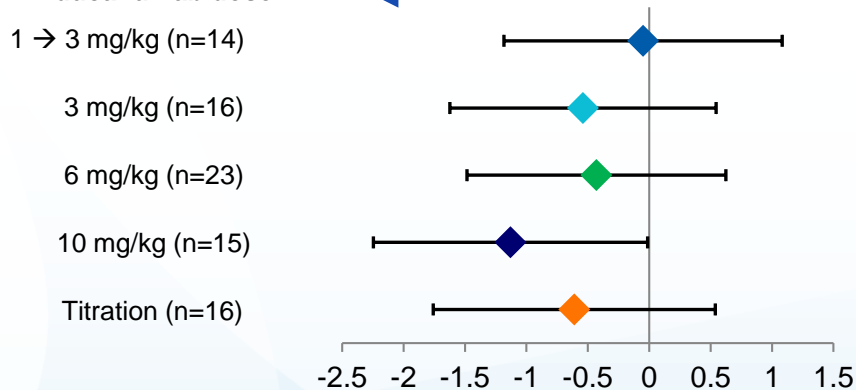


Difference vs Placebo Switchers<sup>a</sup>, Adjusted Mean [95%CI]

**CDR Functional Domain (Week 110)**

Favors aducanumab  
vs placebo switchers

Aducanumab dose



Difference vs Placebo Switchers<sup>a</sup>, Adjusted Mean [95%CI]

<sup>a</sup>Placebo switchers received aducanumab 3 mg/kg or titration (3 mg/kg → 6 mg/kg or 1 mg/kg → 10 mg/kg) in the LTE. Results based on MMRM, fitted with change from baseline as a dependent variable, and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction, continuous baseline value, and laboratory ApoE ε4 status (carrier and non-carrier). CDR, Clinical Dementia Rating; CI, confidence interval; MMRM, mixed model for repeated measures.

# Summary

- Analyses of exploratory clinical endpoint CDR-SB suggest a continued benefit on the rate of clinical decline over 24 months
- Post hoc analysis suggests a beneficial effect of aducanumab on progression of both cognitive and functional CDR domain scores over 24 months
- These data continue to support further investigation of the clinical efficacy and safety of aducanumab in patients with early Alzheimer's disease in the ENGAGE and EMERGE Phase 3 trials



# Acknowledgments

We thank all the patients and their family members participating in the aducanumab studies, as well as the investigators and their staff conducting these studies.