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[a]
- 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

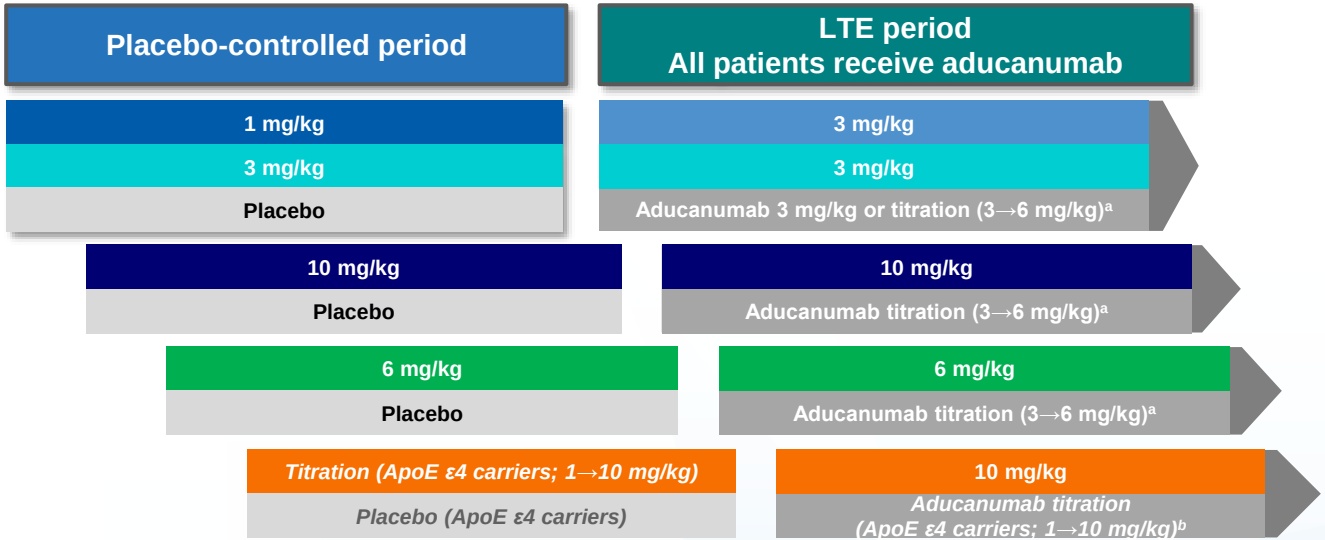
[a]Medical writing support and editing for this presentation was funded by Biogen and was provided by Nucleus Global.

Overview

- Aducanumab is a human monoclonal antibody that binds to both soluble and insoluble aggregated forms of Aβ, including oligomers, protofibrils, and fibrils[1]
- 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[1]
- 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[1-3]
- 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

1. Sevigny et al. Nature. 2016;537:50–56; 2. Viglietta V, et al. J Prev Alz Dis 2016;3:284. Data presented at CTAD 2016; 3. Budd Haeberlein S, et al. J Prev Alz Dis 2017;4:313. Data presented at CTAD 2017. CDR, Clinical Dementia Rating scale; CDR-SB, Clinical Dementia Rating-Sum of Boxes; MMSE, Mini-Mental State Examination; PD, pharmacodynamics; PET, positron emission tomography; PK, pharmacokinetics; LTE, long-term extension.

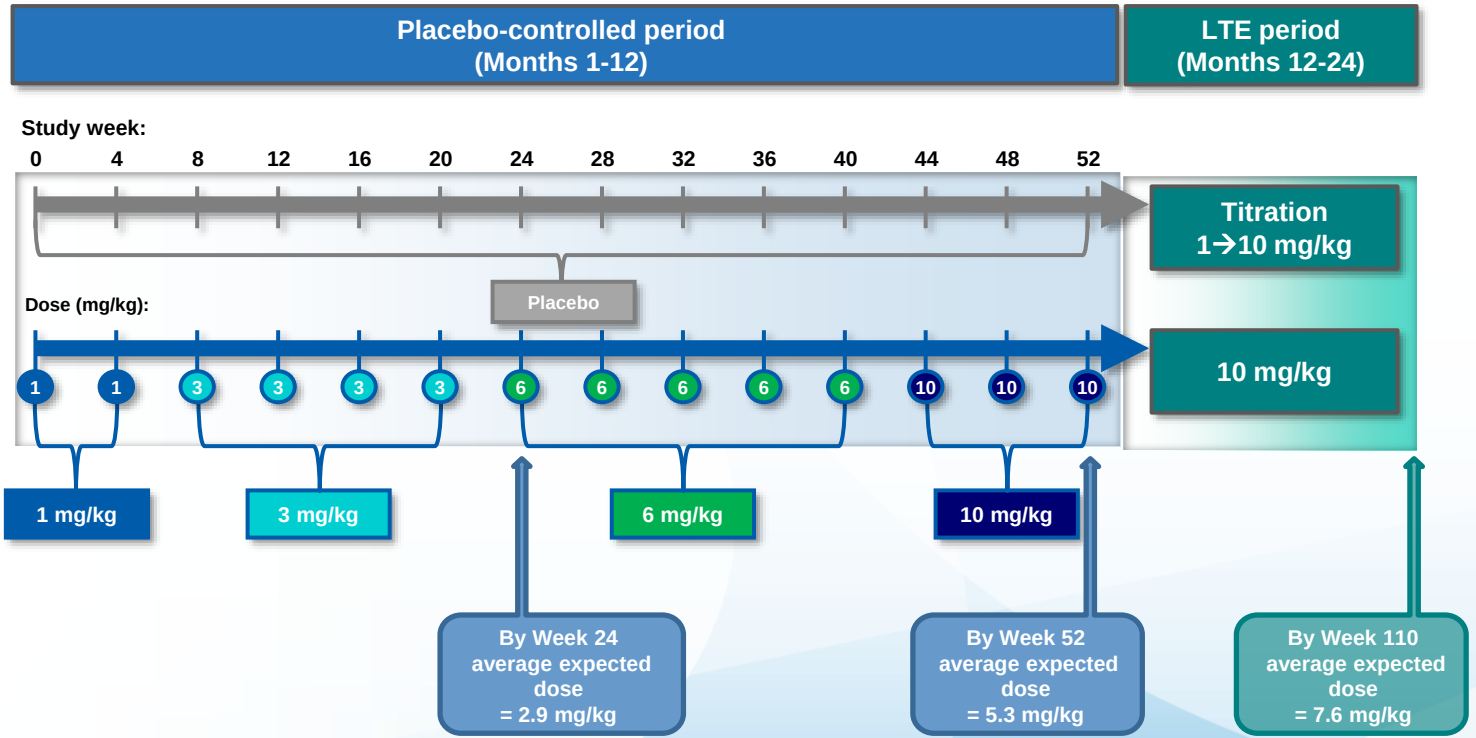
PRIME Study Design: Placebo-Controlled and LTE Periods



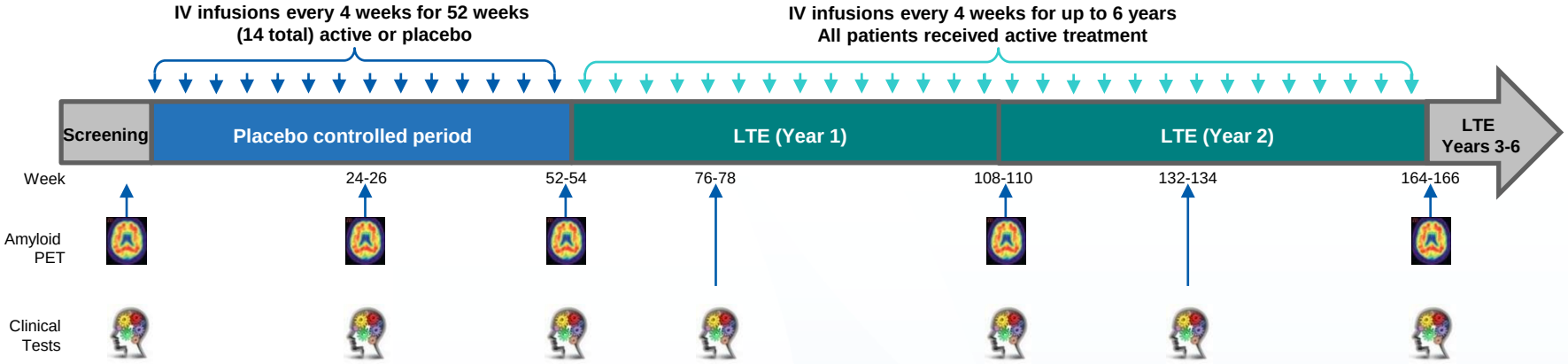
- **Randomization**: 3:1 active: placebo within cohorts, fixed-dose cohorts stratified by ApoE ε4 status
- Patients randomized to placebo in the placebo-controlled period were switched to aducanumab 3 mg/kg or a titration regimen in the LTE ("**placebo switchers**"). Patients randomized to aducanumab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

[a]Titration denotes 2 doses of 3 mg/kg followed by subsequent doses of 6 mg/kg. [b]Titration denotes 2 doses of 1mg/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

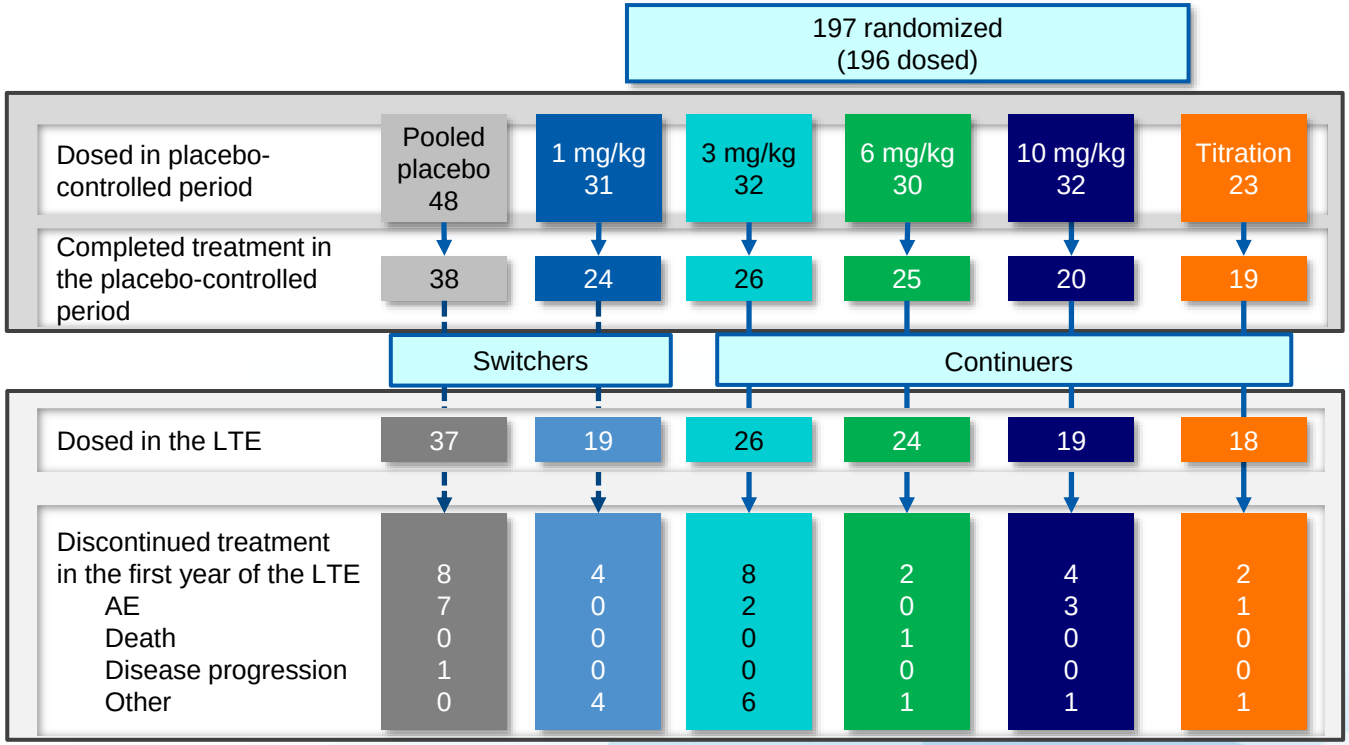


Timeline of PET and Clinical Assessments in PRIME



PET, positron emission tomography.

Patient Disposition at 24 Months



Analysis of data up to Month 24. AE, adverse event; LTE, long-term extension.

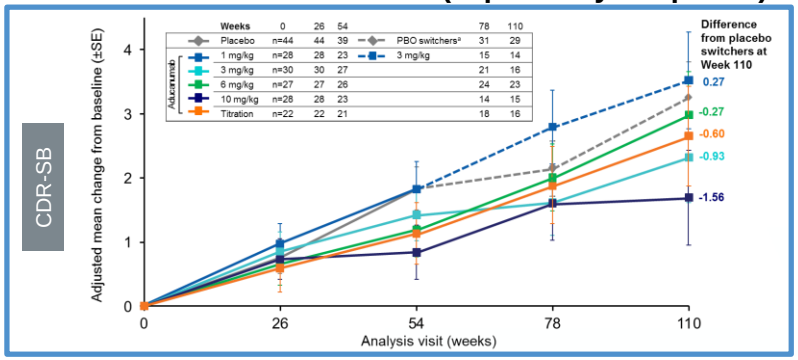
Baseline Disease Characteristics

		Aducanumab				
	Placebo (n=48)	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,[a] n (%)	32 (67)	21 (68)	28 (88)	20 (67)	17 (53)	12 (52)

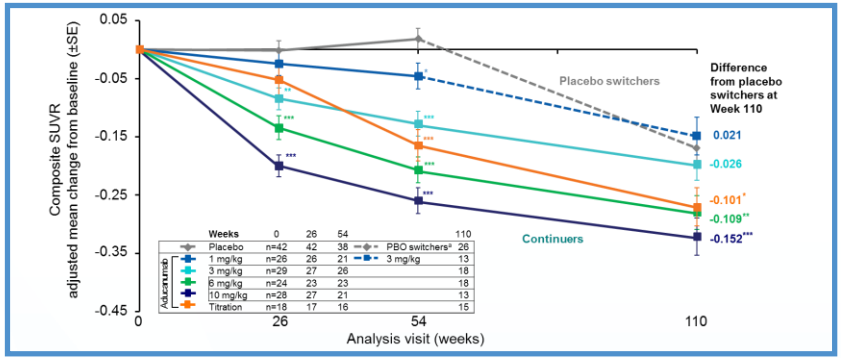
[a]Cholinesterase inhibitors and/or memantine.
AD, Alzheimer's disease; ApoE ε4, Apolipoprotein E ε4; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SD, standard deviation; SUVR, standardized uptake value ratio.

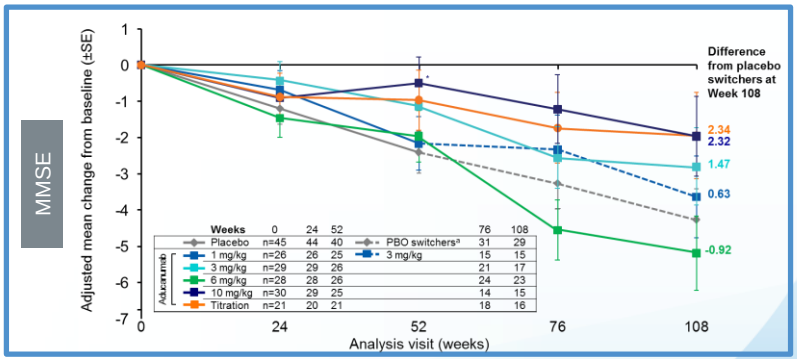
Summary of Previously Presented PRIME 24-Month Interim Results

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

[a]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

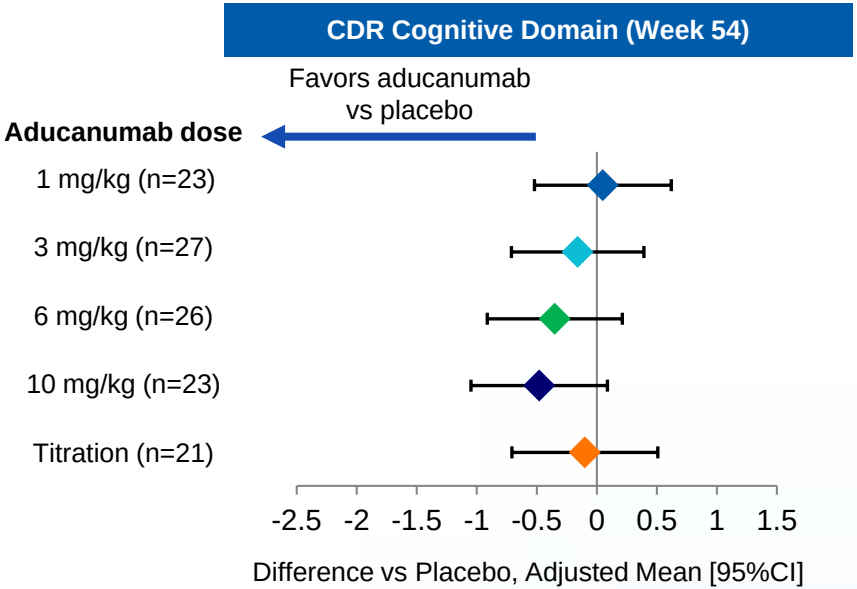
Morris JC, et al. Neurology. 1997;48:1508-10.

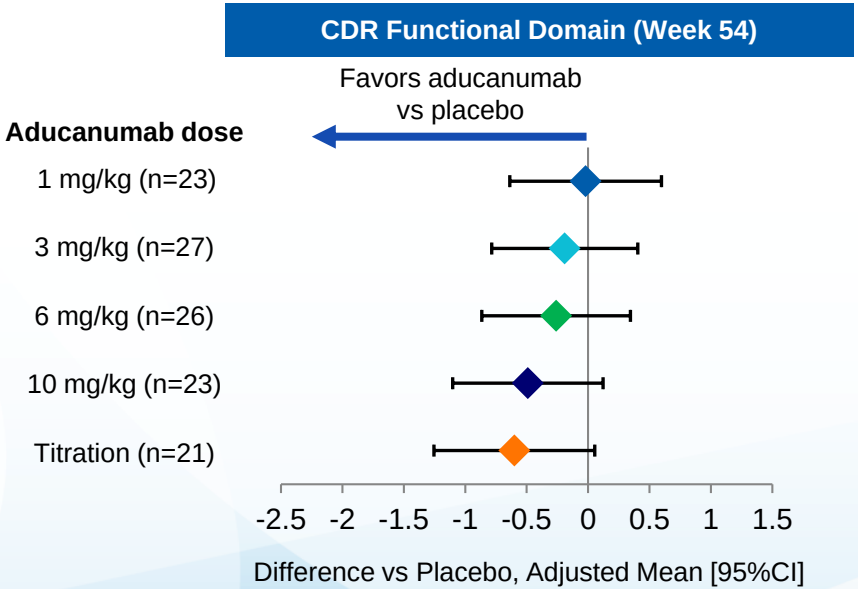
Baseline CDR Global and Domain Scores

	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

CDR-SB, Clinical Dementia Rating–Sum of Boxes; SD, standard deviation.

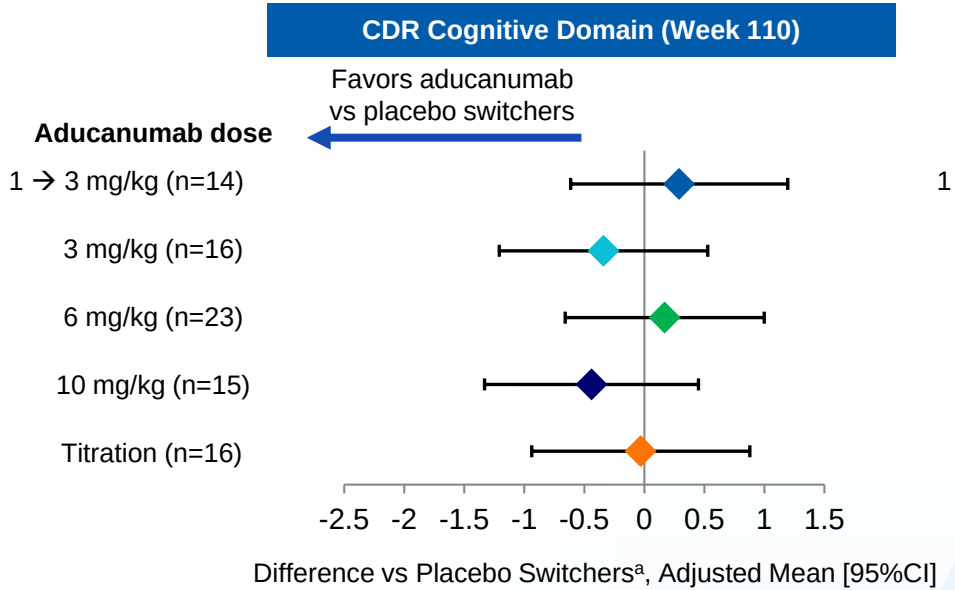
Week 54: Effect of Aducanumab on Both CDR Cognitive and Functional Domains

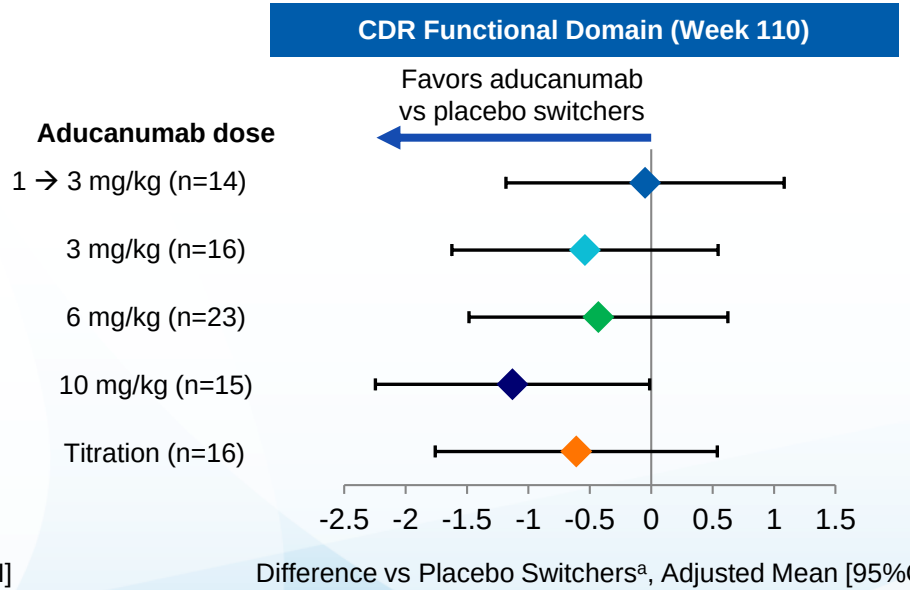




Results based on MMRM, fitted with change from baseline as a dependent variable, and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction, continuous baseline value, and laboratory ApoE ε4 status (carrier and non-carrier). CDR, Clinical Dementia Rating; CI, confidence interval; MMRM, mixed model for repeated measures.

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





[a]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

CDR-SB, Clinical Dementia Rating–Sum of Boxes; LTE, long-term extension; MMSE, Mini-Mental State Examination.

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.