Aducanumab Titration Dosing Regimen: 36-month Analyses from PRIME, a Phase 1b Study in Patients with Early Alzheimer's Disease

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Disclosures

- This study is funded by Biogen[a]
- SBH, CCV, TC, JO, RR, DP, PvR, SC, LS, CP and AS are employees and shareholders of Biogen
- 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

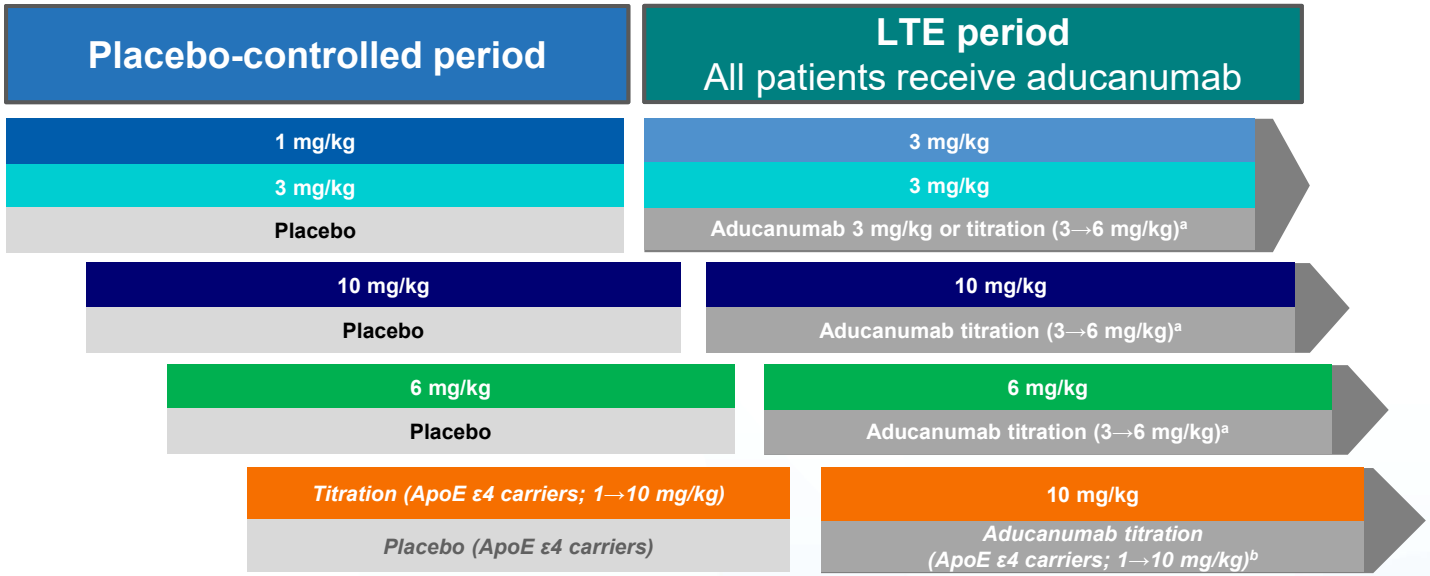
[a]Medical writing support and editing for this presentation was funded by Biogen and was provided by Nucleus Global.

Overview

- Aducanumab is a human monoclonal antibody that binds to both soluble and insoluble aggregated forms of Aβ, including oligomers, protofibrils, and fibrils[1,2]
- PRIME is an ongoing Phase 1b study assessing the safety, tolerability, pharmacokinetics and pharmacodynamics of aducanumab in patients with prodromal or mild Alzheimer's disease[1]
- Here, we report 36-month data for both fixed-dose and titration cohorts
- The primary endpoint in PRIME is safety/tolerability
- Exploratory endpoints in the LTE include:
    - Changes in amyloid PET
    - Measures of clinical decline such as the CDR-SB and MMSE

1. Sevigny et al. Nature. 2016;537:50–56; 2. Biogen data on file.
CDR-SB, Clinical Dementia Rating-Sum of Boxes; MMSE, Mini-Mental State Examination; PET, positron emission tomography; LTE, long-term extension.

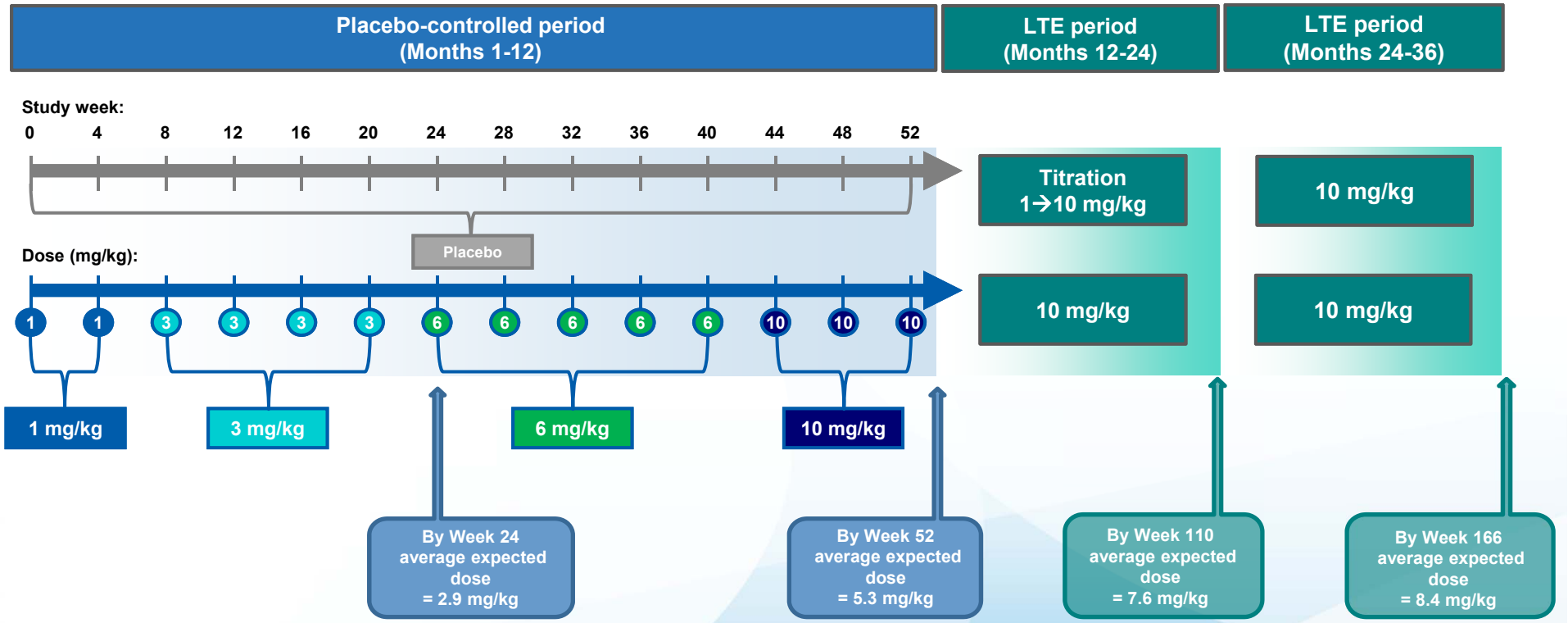
PRIME Study Design



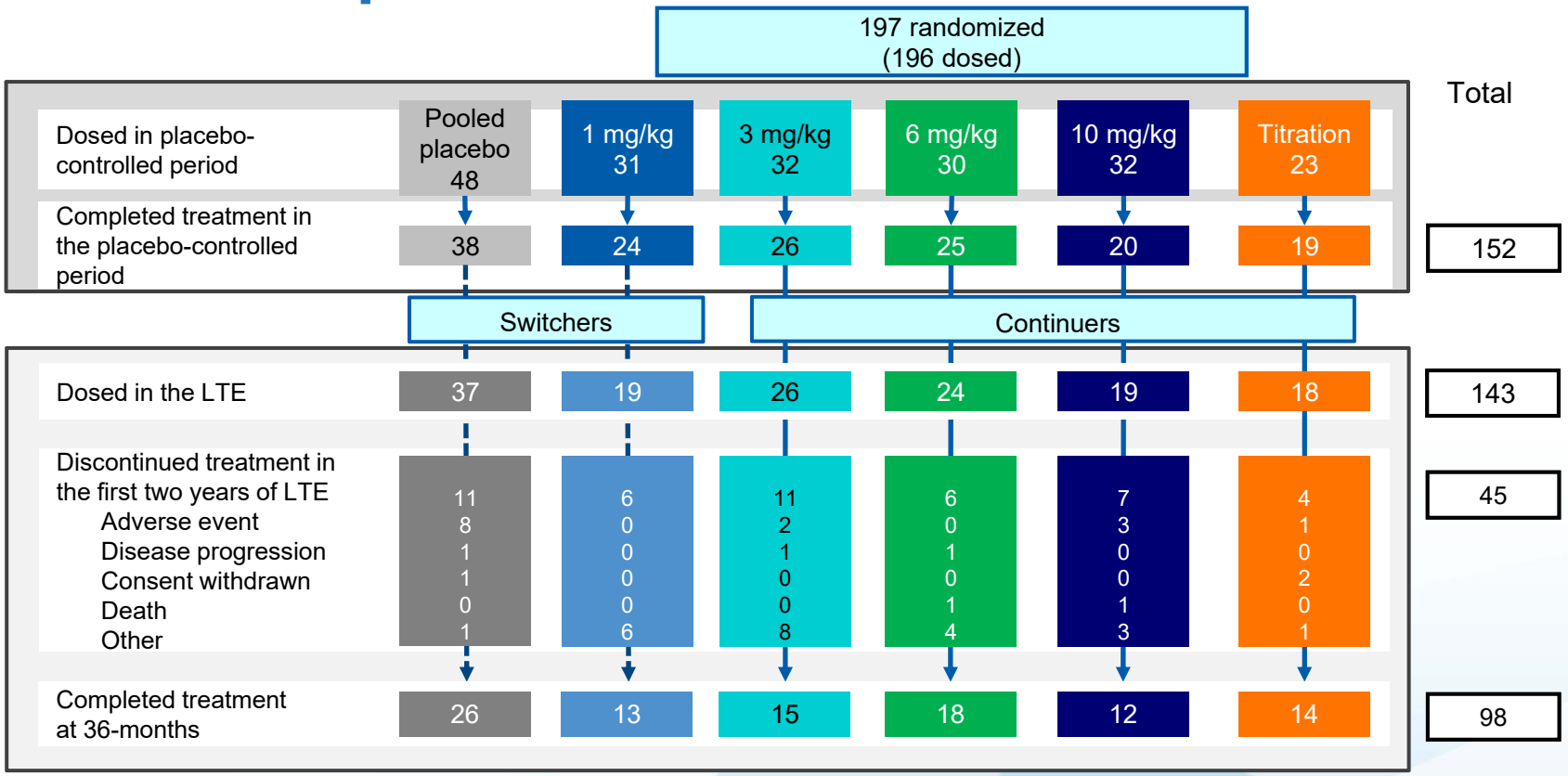
- **Randomization**: 3:1 active: placebo within cohorts, fixed-dose cohorts stratified by ApoE ε4 status
- Patients randomized to placebo in the placebo-controlled period were switched to aducanumab 3 mg/kg or a titration regimen in the LTE ("**placebo switchers**"). Patients randomized to aducanumab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



Patient Disposition at 36 Months



Analysis of data up to Month 36. AE, adverse event; LTE, long-term extension.

Baseline Disease Characteristics

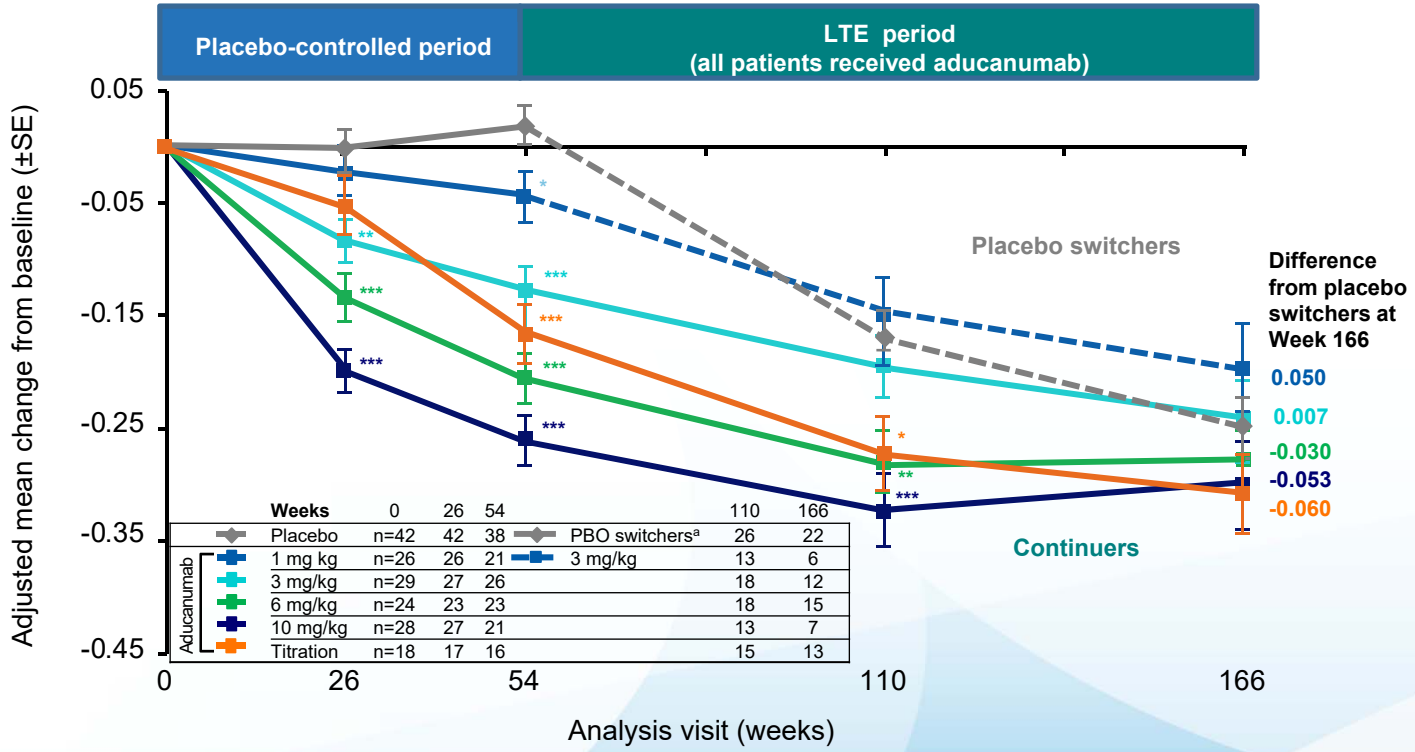
		Aducanumab				
	Placebo (n=48)	1 mg/kg (n=31)	3 mg/kg (n=32)	6 mg/kg (n=30)	10 mg/kg (n=32)	Titration (n=23)
Age in years, mean ± SD	73.3 ± 6.8	72.6 ± 7.8	70.5 ± 8.2	73.3 ± 9.3	73.7 ± 8.3	73.1 ± 7.8
ApoE ε4, n (%)						
Carriers	34 (71)	19 (61)	21 (66)	21 (70)	20 (63)	23 (100)
Non-carriers	14 (29)	12 (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.

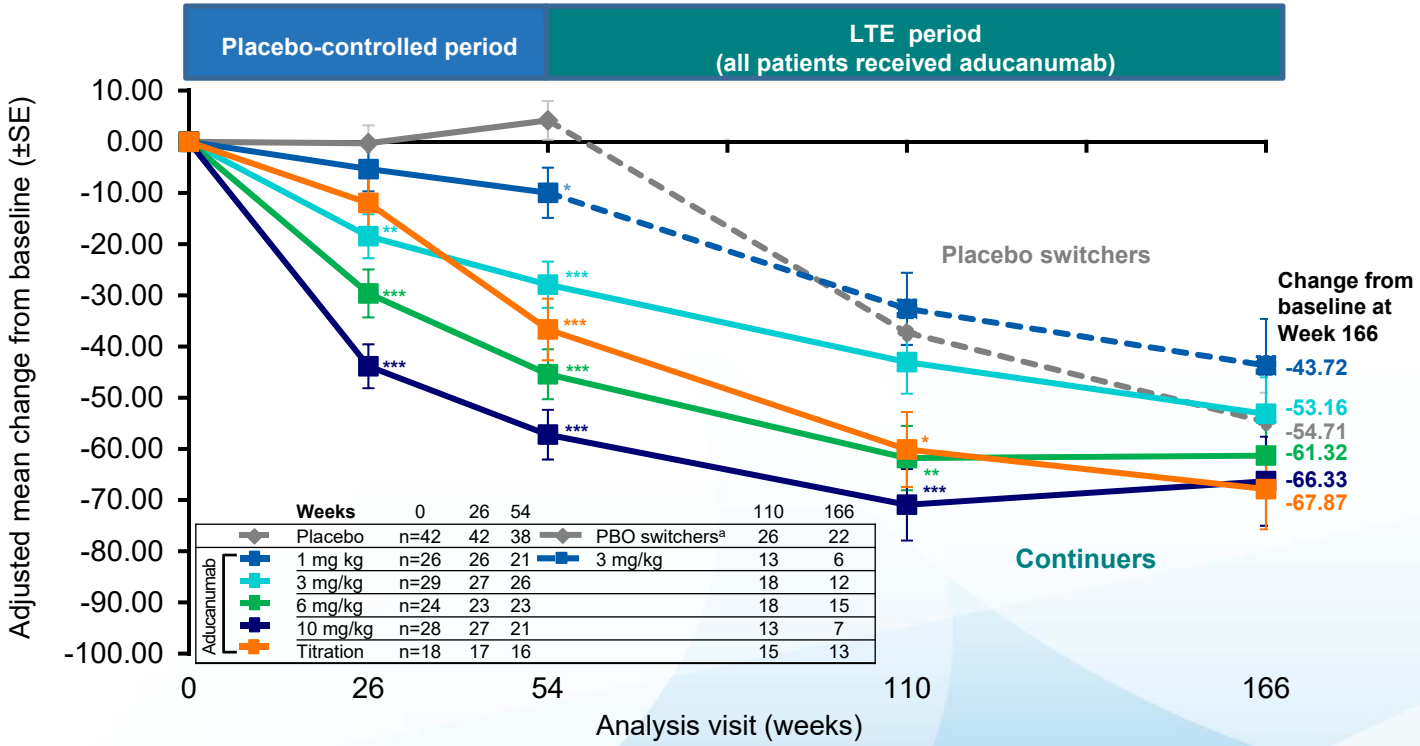
PET Amyloid Imaging

Effect of Aducanumab on Amyloid Plaque Levels (Composite SUVR)



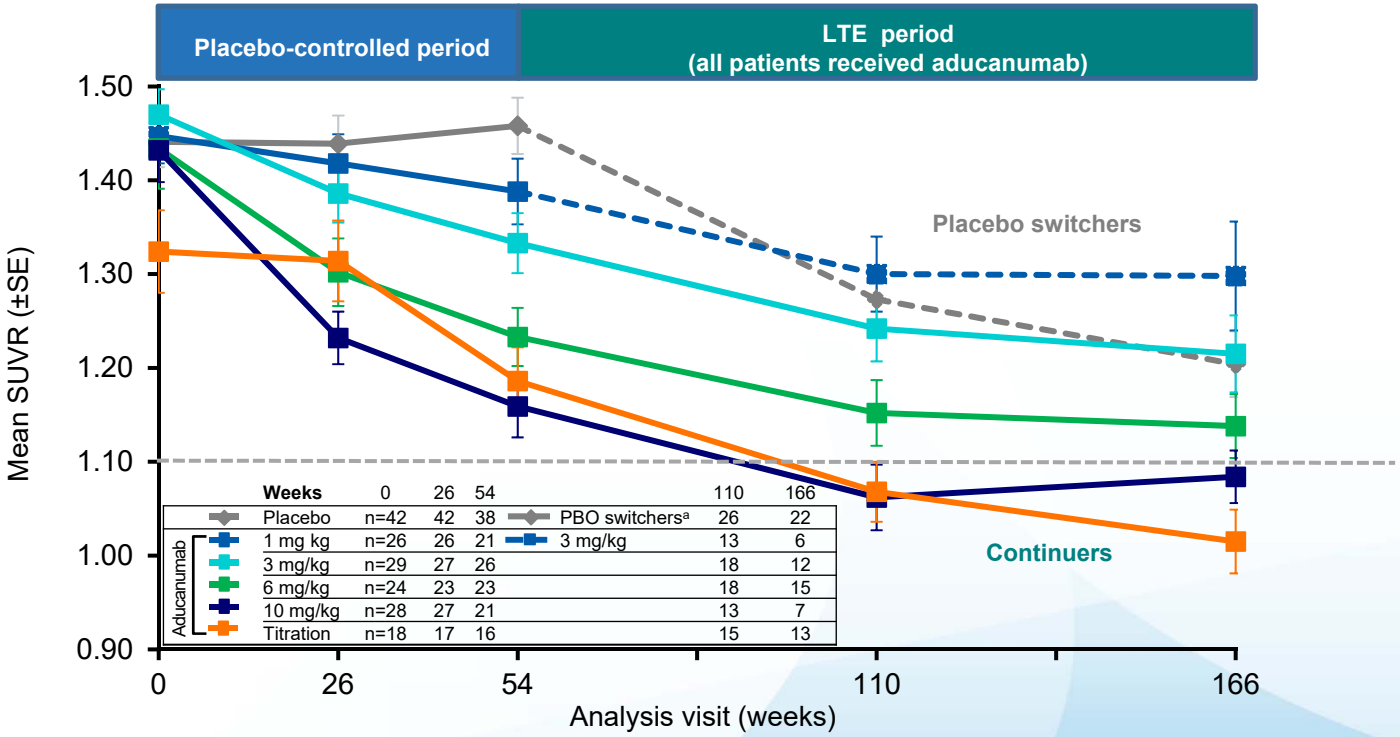
* P<0.05; ** P<0.01; *** P<0.001 vs PBO in the placebo-controlled period and vs PBO switchers in the LTE period. [a]Placebo switchers received aducanumab 3 mg/kg or titration (3 mg/kg → 6 mg/kg or 1 mg/kg →10 mg/kg) in the LTE. Results based on MMRM, fitted with change from baseline as a dependent variable, 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). LTE, long-term extension; MMRM, mixed model for repeated measures; PBO, placebo; SE, standard error.

Effect of Aducanumab on Amyloid Plaque Levels (Centiloid Scale)



* P<0.05; ** P<0.01; *** P<0.001 vs PBO in the placebo-controlled period and vs PBO switchers in the LTE period. [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). The centiloid conversion equation for amyloid PET SUVR composite score (RR = whole cerebellum) is 100*(SUVR-1.0034)/0.4536. LTE, long-term extension; MMRM, mixed model for repeated measures; PBO, placebo; SE, standard error.

Effect of Aducanumab on Amyloid Plaque Levels (Mean SUVR)



The value of 1.10 has been proposed as a quantitative cut-point suggested to discriminate between a positive and negative scan[1]

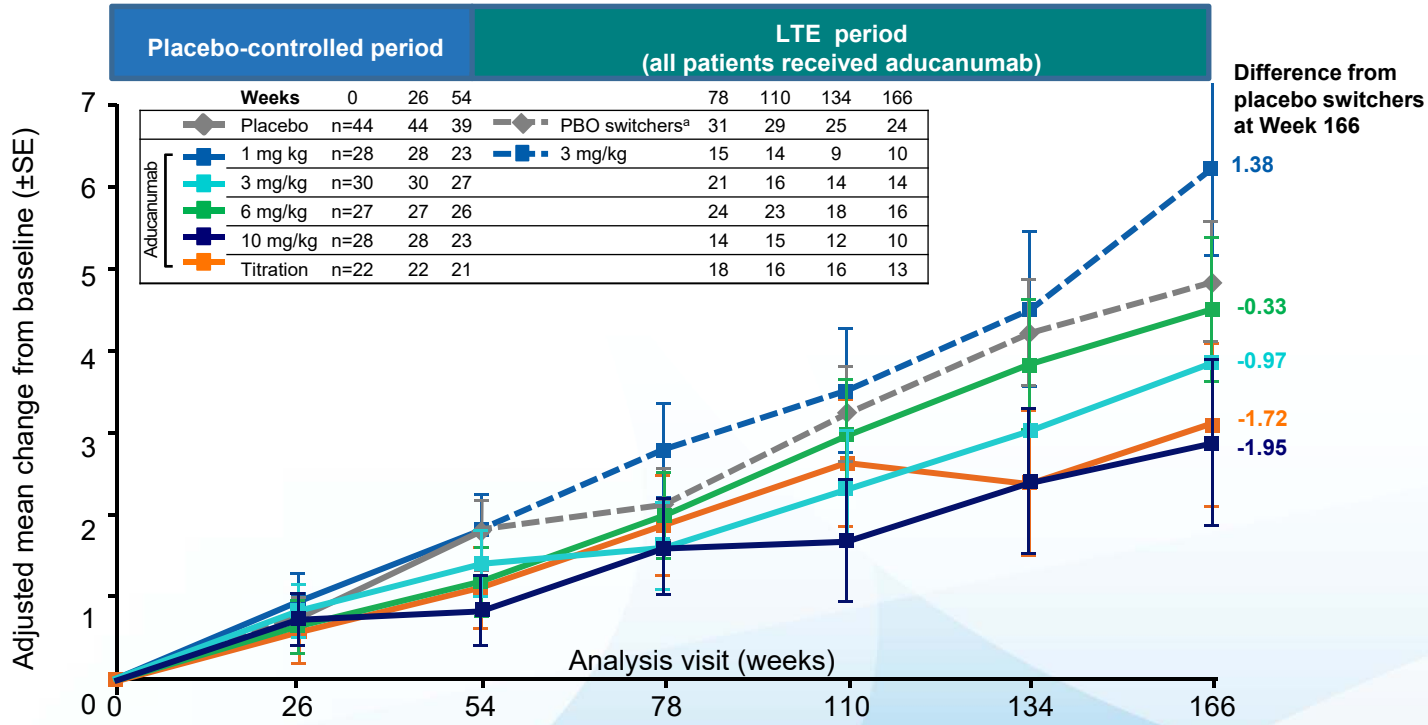
[a]Placebo switchers received aducanumab 3 mg/kg or titration (3 mg/kg → 6 mg/kg or 1 mg/kg →10 mg/kg) in the LTE.

1. Joshi AD, et al. *J Nucl Med*. 2015;56:1736-1741.

LTE, long-term extension; PBO, placebo; SUVR, standardized uptake value ratio.

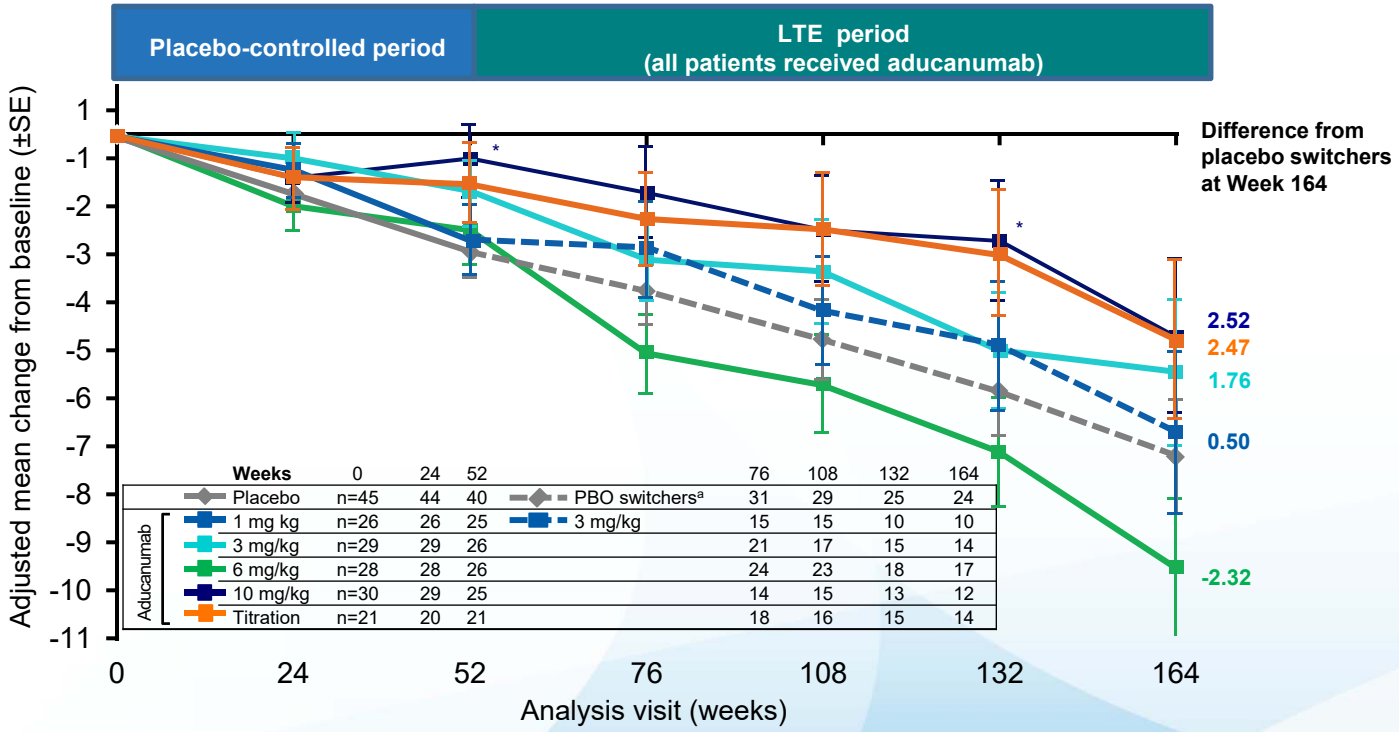
Clinical Endpoints

Effect of Aducanumab on Clinical Decline as Measured by CDR-SB (Exploratory Endpoint)



[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. CDR-SB is an exploratory endpoint. 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-SB, Clinical Dementia Rating–Sum of Boxes; LTE, long-term extension; MMRM, mixed model for repeated measures; PBO, placebo; SE, standard error.

Effect of Aducanumab on Clinical Decline as Measured by MMSE (Exploratory Endpoint)



*P<0.05 vs placebo in the placebo-controlled period and vs placebo switchers in the LTE period. [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 MMSE is an exploratory endpoint. 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). LTE, long-term extension; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; PBO, placebo; SE, standard error.

Safety and Tolerability

Cumulative Aducanumab Safety

(Events After First Aducanumab Exposure)

			Continuers[b]			
	Placebo Switchers[a] (n=37)	1 mg/kg → 3 mg/kg (n=31)	3 mg/kg (n=32)	6 mg/kg (n=30)	10 mg/kg (n=32)	Titration (n=23)
Number with an AE (%)	37 (100)	29 (94)	29 (91)	30 (100)	29 (91)	23 (100)
Number with an SAE (%)	21 (57)	11 (35)	10 (31)	14 (47)	16 (50)	9 (39)
Number discontinuing treatment due to AE (%)	11 (30)	4 (13)	4 (13)	4 (13)	16 (50)	3 (13)

[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. [b]Patients who were randomized to receive 3, 6, and 10 mg/kg were scheduled to receive the same dose throughout the LTE. Patients who received a dose reduction during the placebo-controlled period due to ARIA were able to titrate up to the planned dose at study start after consenting to the protocol amendment. [c]Based on incidence reporting by preferred term. AE, adverse event; ARIA, amyloid-related imaging abnormality; LTE, long-term extension; SAE, serious AE.

- The most common AEs (incidence ≥ 15%) by preferred term were ARIA, headache, fall, urinary tract infection, diarrhea, nasopharyngitis, and upper respiratory tract infection
- The most common SAE (incidence ≥ 5%) by preferred term was ARIA (n=17 [9%])

There were a total of 6 deaths reported in patients who were treated with aducanumab; an additional 2 deaths occurred in patients receiving placebo (1 patient died after leaving the study)

AE, adverse event; ARIA, amyloid-related imaging abnormality; LTE, long-term extension; SAE, serious AE.

Cumulative Incidence of ARIA

(Events After First Aducanumab Exposure)

	Placebo Switchers[c]	1 mg/kg → 3 mg/kg	Continuers[d]			
			3 mg/kg	6 mg/kg	10 mg/kg	Titration
Patients with at least 1 post-baseline MRI	37	31	32	30	32	23
ARIA-E[a], n/total (%)	8/37 (22)	4/31 (13)	2/32 (6)	11/30 (37)	13/32 (41)	8/23 (35)
ApoE ε4 carriers	7/25 (28)	4/19 (21)	1/21 (5)	9/21 (43)	11/20 (55)	8/23 (35)
ApoE ε4 non-carriers	1/12 (8)	0/12 (0)	1/11 (9)	2/9 (22)	2/12 (17)	-
Discontinued treatment,[b] n (%)	5 (14)	1 (3)	-	3 (10)	9 (28)	2 (9)
Isolated ARIA-H, n (%)	2 (5)	1 (3)	7 (22)	2 (7)	2 (6)	-

[a]ARIA-E with or without ARIA-H. [b]ARIA-E and either 1) no doses after onset of ARIA-E or 2) have subsequent discontinuation due to ARIA. [c]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. [d]Patients who were randomized to receive 3, 6, and 10 mg/kg were scheduled to receive the same dose throughout the LTE. Patients who received a dose reduction during the placebo-controlled period due to ARIA were able to titrate up to the planned dose at study start after consenting to the protocol amendment.

ARIA-E, ARIA–vasogenic edema; ARIA-H, ARIA–microhemorrhages, macrohemorrhages, or superficial siderosis; MRI, magnetic resonance imaging

Overall ARIA Characteristics (All Cohorts)

- Since the start of the PRIME study:
  - Of the 185 patients dosed with aducanumab, 46 patients experienced ARIA-E with a cumulative incidence of 25% over the course of the study
    - Of the 46 patients with ARIA-E, 61% were asymptomatic and 39% had associated symptoms, which were typically mild
    - ARIA-E tended to occur early in the course of treatment most often within the first 6 months of the first active dose
    - ARIA events typically resolved or stabilized within 4-12 weeks, with most patients continuing treatment
  - 8 patients experienced more than one event of ARIA-E
    - Clinical and imaging characteristics of recurrent ARIA-E were similar to those of ARIA-E previously reported in the PRIME study

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA–vasogenic edema.

Summary

- Amyloid plaque levels continued to decrease in a dose- and time- dependent manner in patients treated with aducanumab from the titration and fixed-dose cohorts who completed the second year of the LTE
    - Mean amyloid plaque levels in both the 10 mg/kg fixed-dose and titration cohorts reached and remained at an SUVR level below 1.1, which has been proposed as a quantitative cut-point suggested to discriminate between a positive and negative scan[1]
- Analyses of exploratory clinical endpoints CDR-SB and MMSE suggest a continued benefit on the rate of clinical decline over 36 months
    - Clinical effects with titrated aducanumab in the second year of the LTE were generally consistent with findings in the 10 mg/kg fixed-dose treatment group
- The safety profile of aducanumab remains unchanged
- These data continue to support further investigation of the clinical efficacy and safety of aducanumab in patients with early AD in the ENGAGE and EMERGE Phase 3 trials

1. Joshi AD, et al. *J Nucl Med*. 2015;56:1736-1741.
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.