Aducanumab Titration Dosing Regimen: 24-Month Interim Analysis from PRIME, a Randomized, Double-Blind, Placebo-Controlled Phase 1b Study in Patients With Prodromal or Mild Alzheimer's Disease

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Disclosures

This study is funded by Biogen[a]

- PvR, SG, TC, JO, PC, LS, CvH, SBH, and AS are employees and shareholders of Biogen
- GW is an employee of Cytel
- CH and RMN are employees and shareholders of Neurimmune

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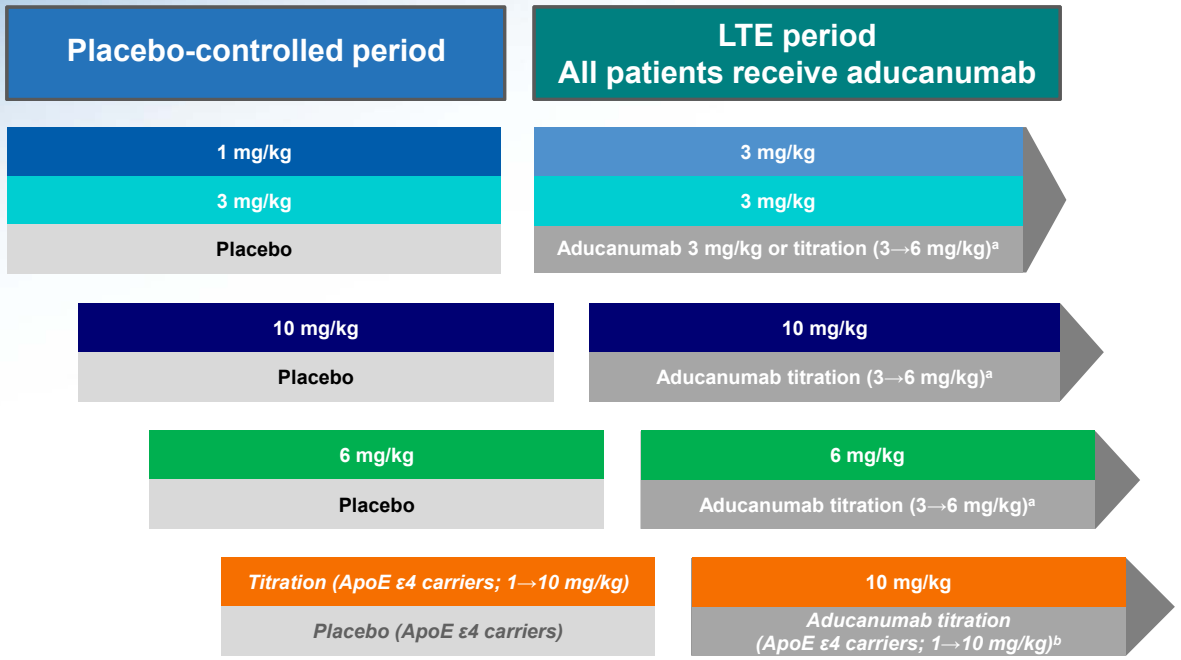
Overview

- Aducanumab is a human monoclonal antibody selective for aggregated forms of Aβ, including soluble oligomers and insoluble fibrils
- 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
- Here, we report 24-month data for both fixed-dose and titration cohorts, including 12 months from the placebo-controlled period and the first 12 months of the PRIME LTE
- The primary endpoint in the LTE was safety/tolerability
- Exploratory endpoints included:
  - Changes in amyloid PET
  - Measures of clinical decline on the CDR-SB and MMSE

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

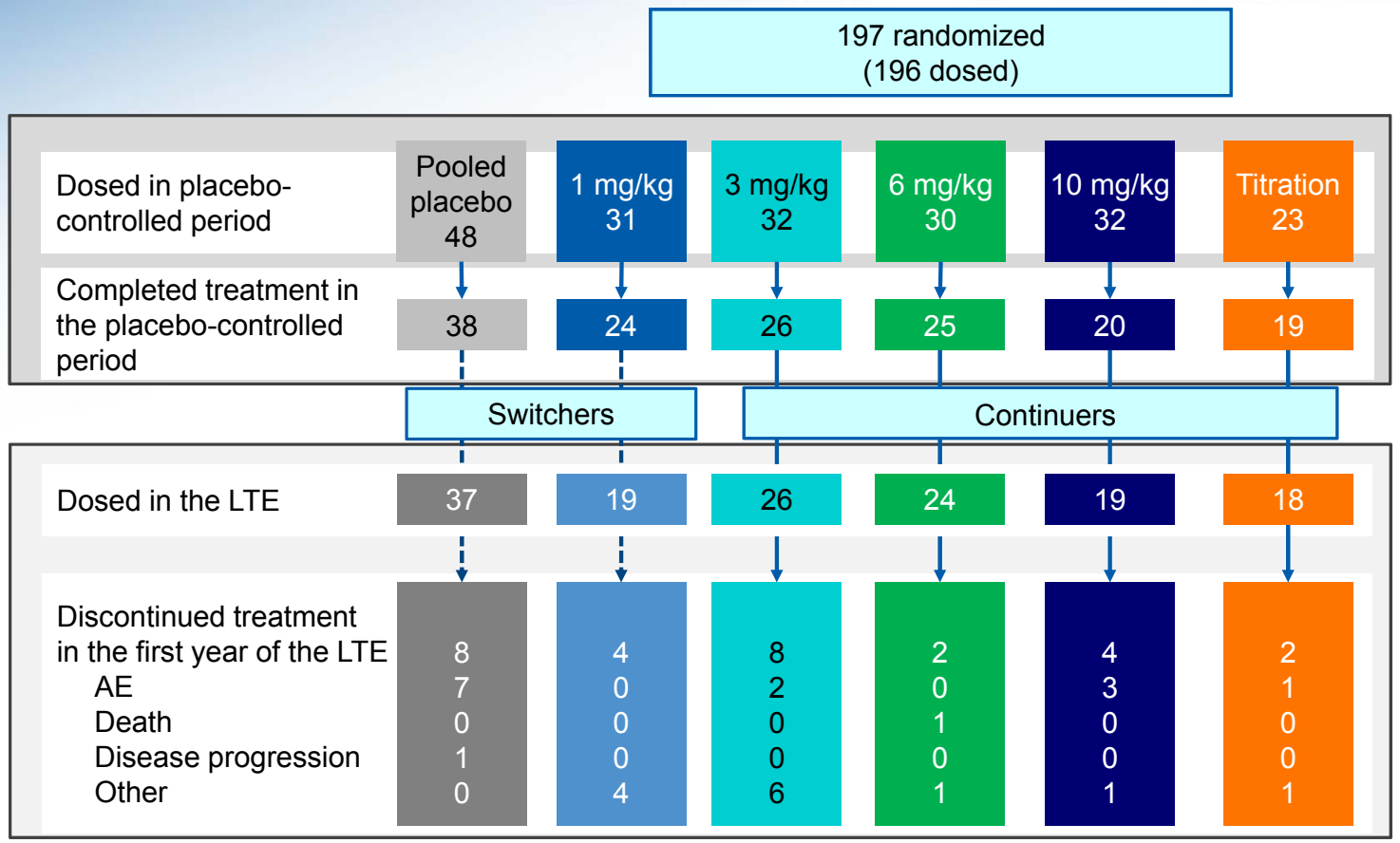
PRIME Study Design: Placebo-Controlled and LTE Periods



- **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.

Patient Disposition at 24 Months



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

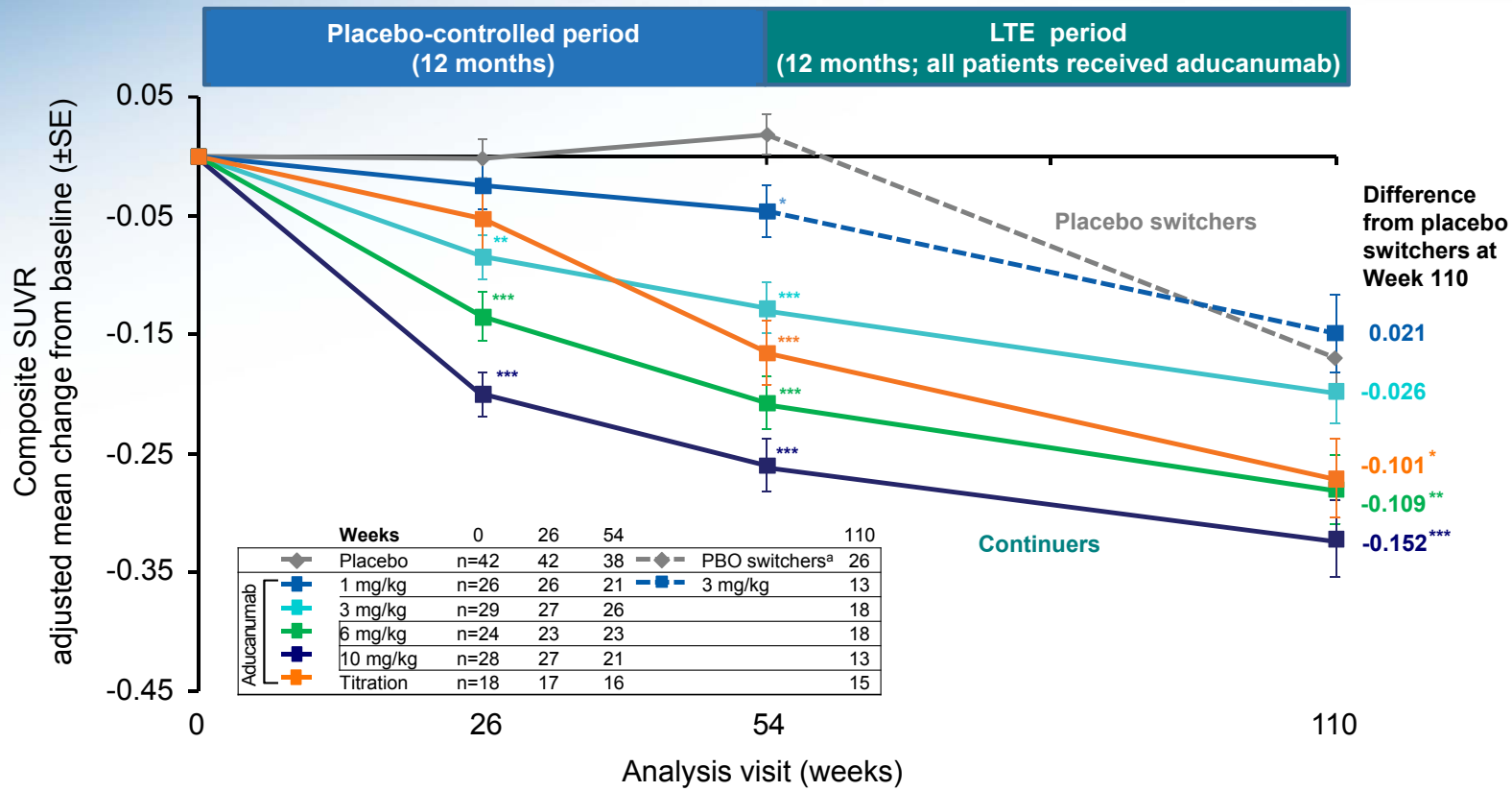
Baseline Disease Characteristics

		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.

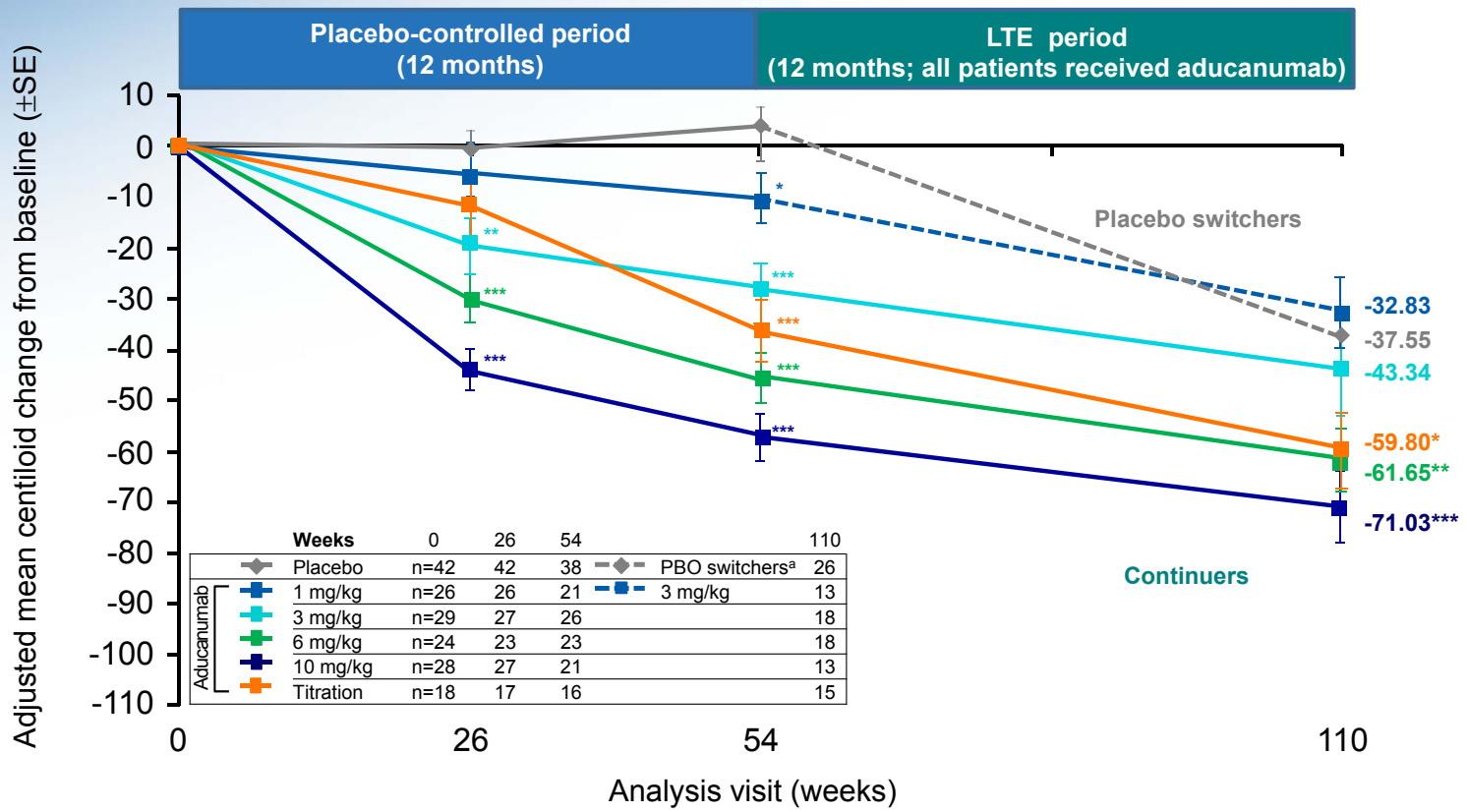
PET AMYLOID IMAGING

Effect of Aducanumab on Amyloid Plaque Levels (Composite SUVR)



[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. 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; SE, standard error.

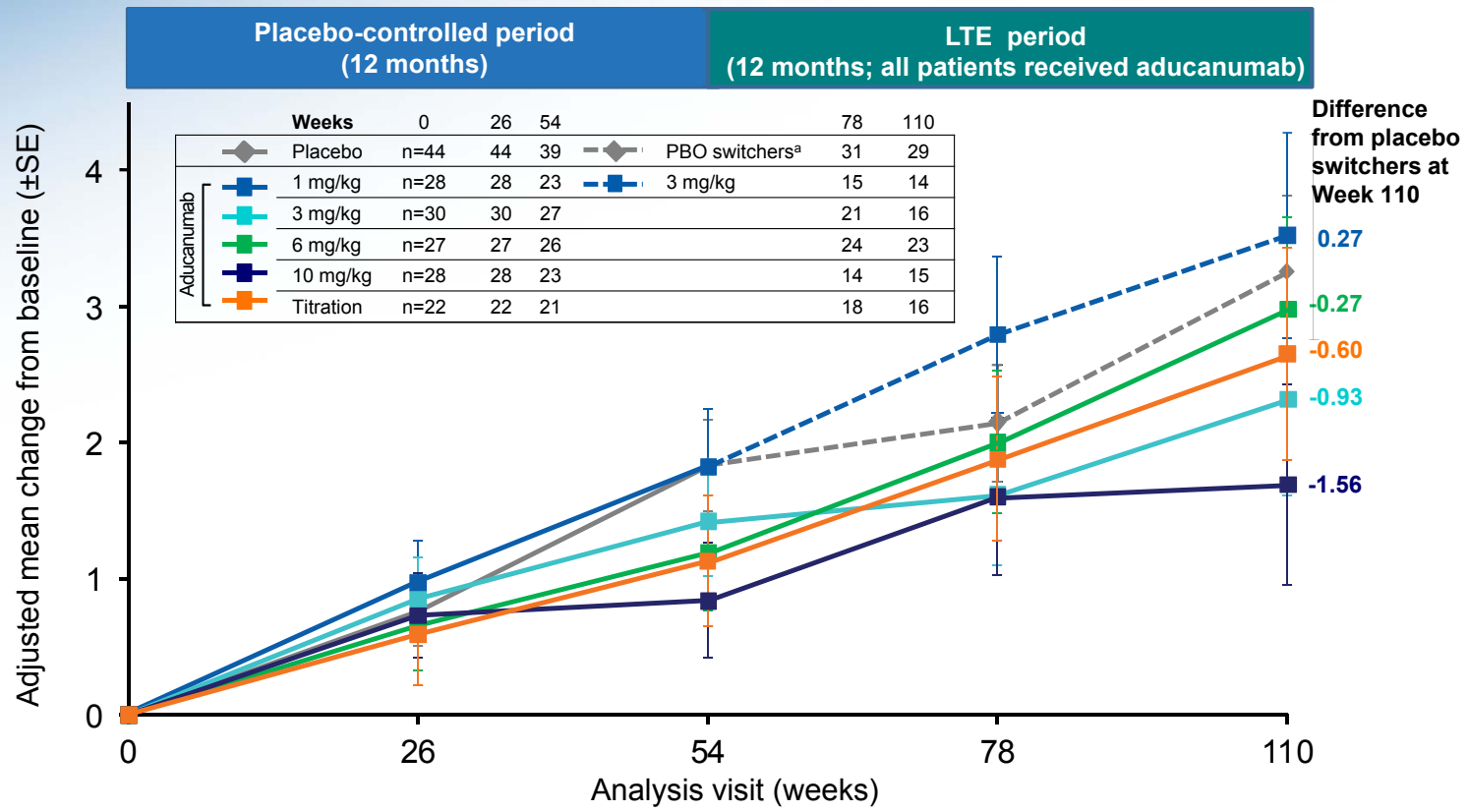
Effect of Aducanumab on Amyloid Plaque Levels (Centiloid Scale)



[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. 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; SE, standard error.

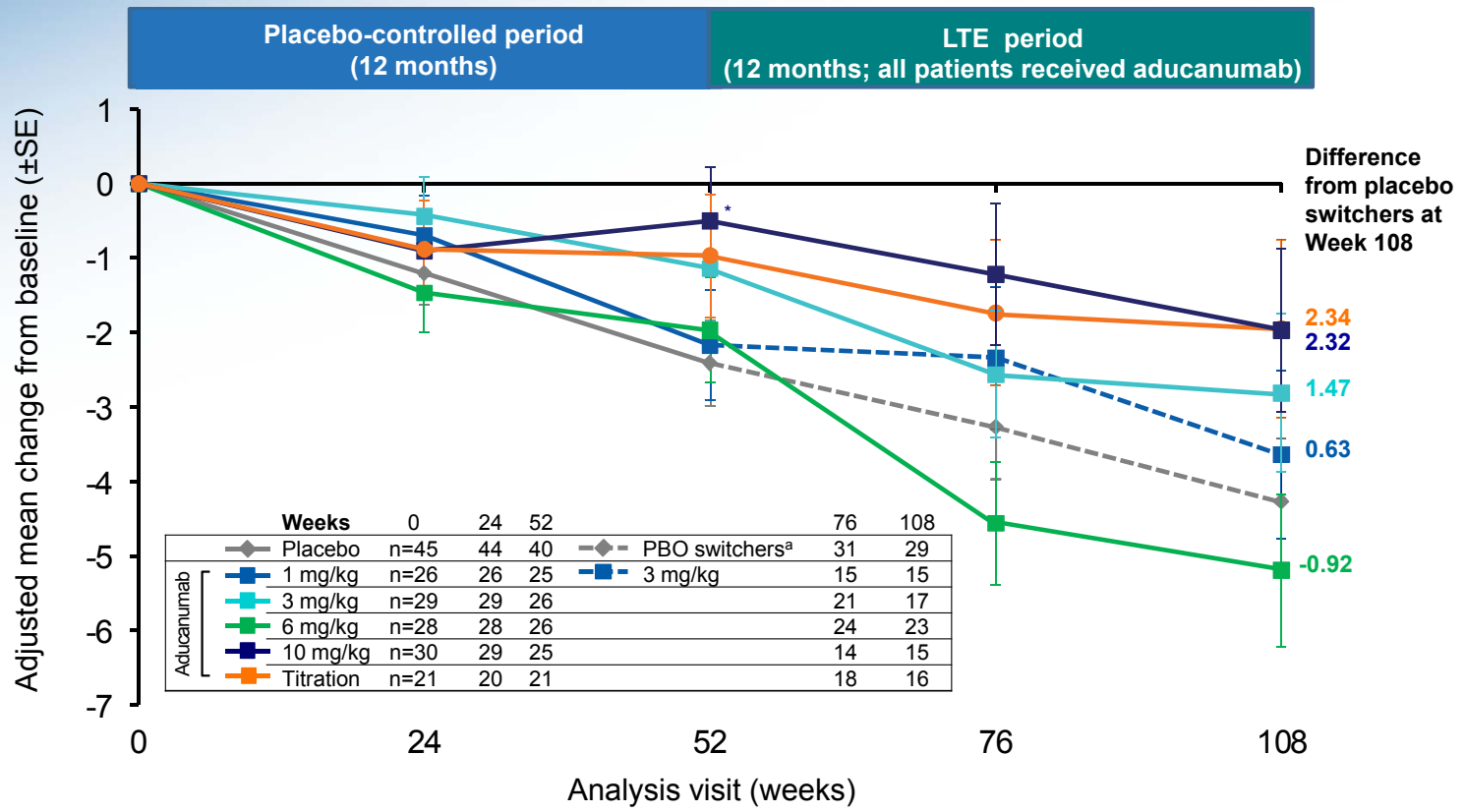
CLINICAL ENDPOINTS

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; SE, standard error.

Effect of Aducanumab on Clinical Decline as Measured by MMSE (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. Nominal *P<0.05 vs placebo in the placebo-controlled period and vs placebo switchers in the LTE period. 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; SE, standard error.

SAFETY AND TOLERABILITY

Safety of Aducanumab Between Months 12 and 24 (First Year of the LTE)

	Placebo Switchers[a] (n=37)	1 mg/kg → 3 mg/kg (n=19)	Continuers[b]			
			3 mg/kg (n=26)	6 mg/kg (n=24)	10 mg/kg (n=19)	Titration (n=18)
Number with an AE (%)	35 (95)	15 (79)	18 (69)	22 (92)	15 (79)	17 (94)
Number with an SAE (%)	14 (38)	2 (11)	2 (8)	6 (25)	3 (16)	4 (22)
Number discontinuing treatment due to AE (%)	7 (19)	0	2 (8)	0	3 (16)	1(6)

- The most common AEs (incidence ≥ 15%) were fall, headache, and ARIA[c]
- The most common SAE was ARIA (n=5 [3%])
- One death due to cardiac event occurred in the 6 mg/kg arm during the first year of the LTE
- No significant changes in chemistry, hematology, urinalysis, ECGs, or vital signs

[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.

Incidence of ARIA-E Between Months 12 and 24 (First Year of the LTE)

	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	17	23	24	19	18
ARIA-E[a], n/total (%)	7/37 (19)	3/17 (18)	0/23 (0)	0/24 (0)	0/19 (0)	2/18 (11)
ApoE ε4 carriers	6/25 (24)	3/11 (27)	-	-	-	2/18 (11)
ApoE ε4 non-carriers	1/12 (8)	0/6 (0)	-	-	-	-
Discontinued treatment,[b] n (%)	4 (11)	0 (0)	-	-	-	1 (6)
Isolated ARIA-H, n (%)	2 (5)	0 (0)	3 (13)	2 (8)	1 (5)	0 (0)

- The incidence of ARIA-E in patients switching from placebo to aducanumab was consistent with that reported in the placebo-controlled portion of the study

[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

Summary

- Amyloid plaque levels continued to decrease in a dose- and time- dependent manner in patients from the titration and fixed-dose cohorts who completed the first year of the LTE
- Analyses of exploratory clinical endpoints CDR-SB and MMSE suggest a continued benefit on the rate of clinical decline over 24 months
  - Clinical effects with titrated aducanumab were generally consistent with findings in the fixed-dose cohorts
- 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
- 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

ARIA-E, amyloid-related imaging abnormalities - vasogenic edema; CDR-SB, Clinical Dementia Rating–Sum of Boxes; LTE, long-term extension; MMSE, Mini-Mental State Examination.

Acknowledgments

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