Aducanumab 36-Month Data 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 was funded by Biogen[a]

- SBH, SG, TC, JO, PvR, PC, CvH, LS 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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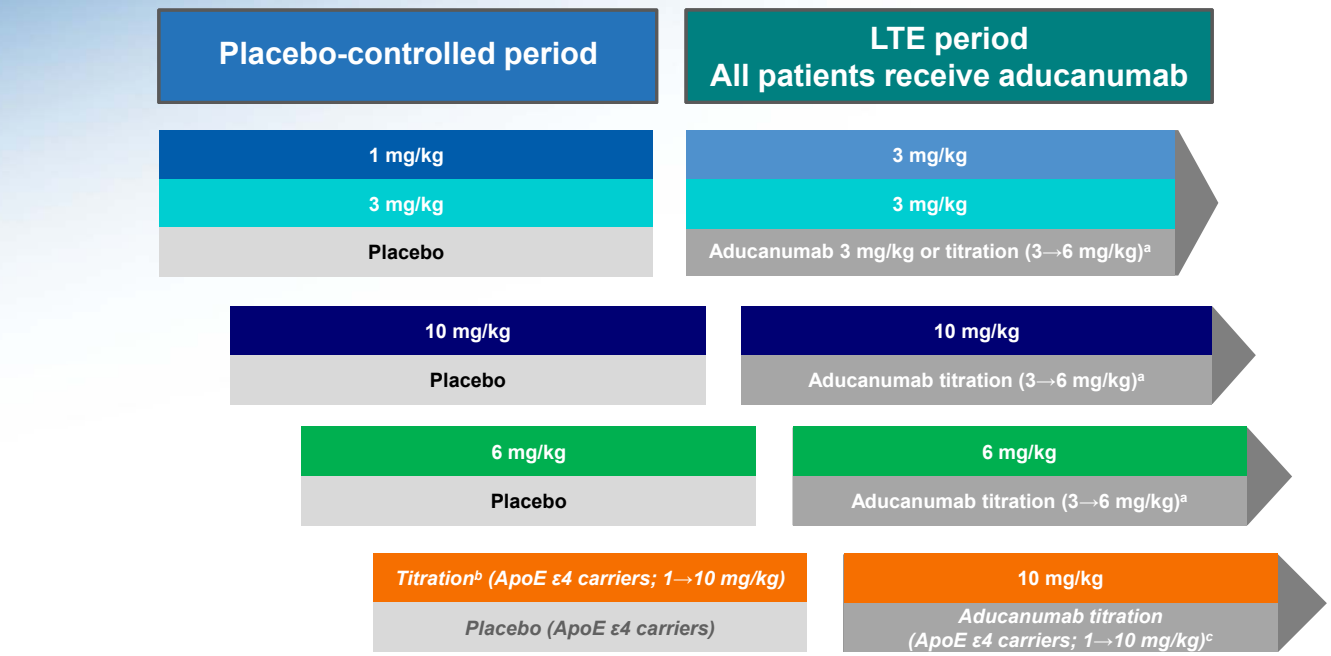
Overview

- 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 present 36-month data for fixed-dose cohorts, including the 12-month placebo-controlled period as well as the first two LTE years of the PRIME study
  - Data from the titration cohort are not reported here because 36-month data are not yet available for this cohort
- 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.

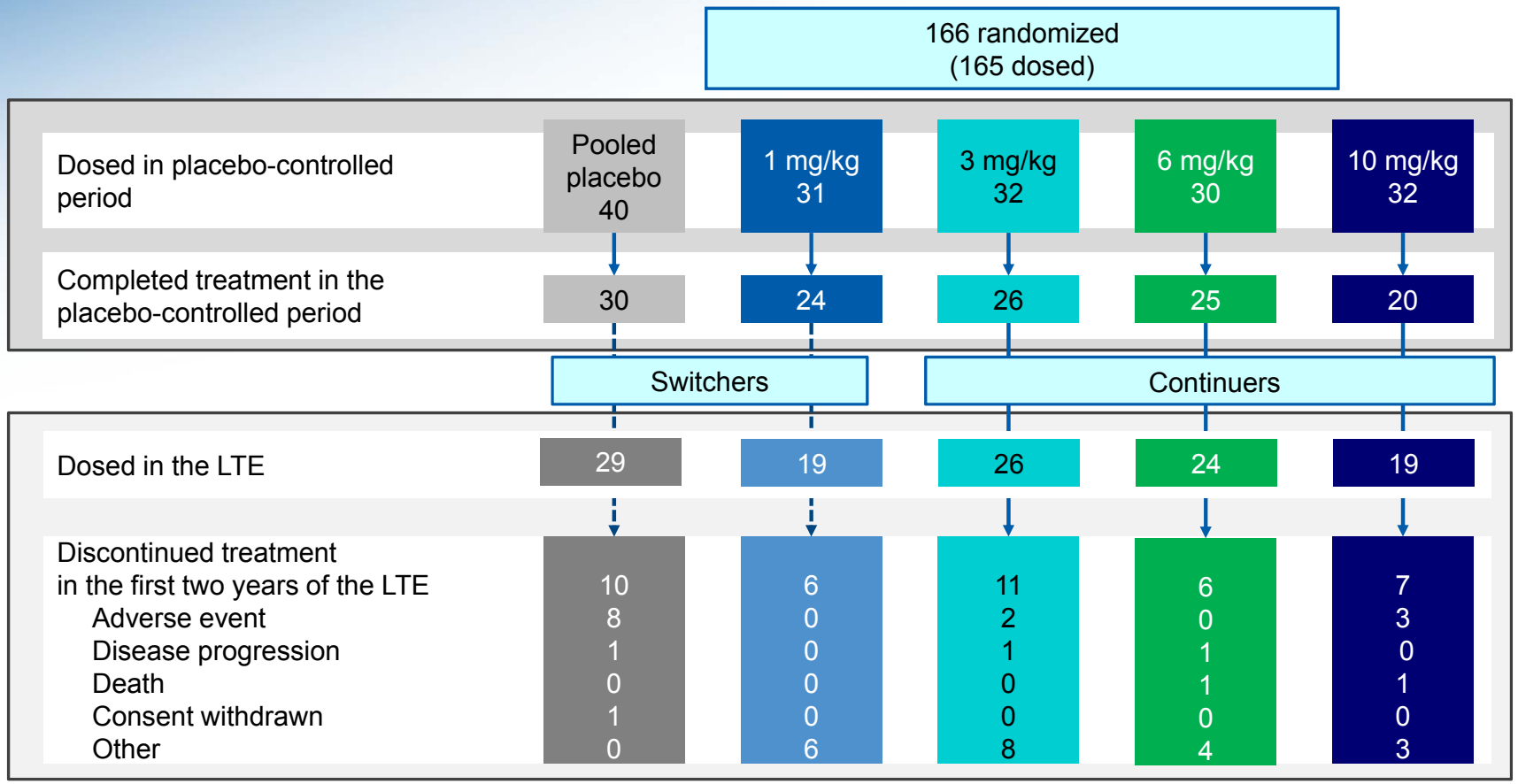
PRIME Study Design: Placebo-Controlled and LTE Periods



- **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]Data from the titration cohort are not included in this analysis as 36-month data from this cohort are not yet available. [c]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 36 Months



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

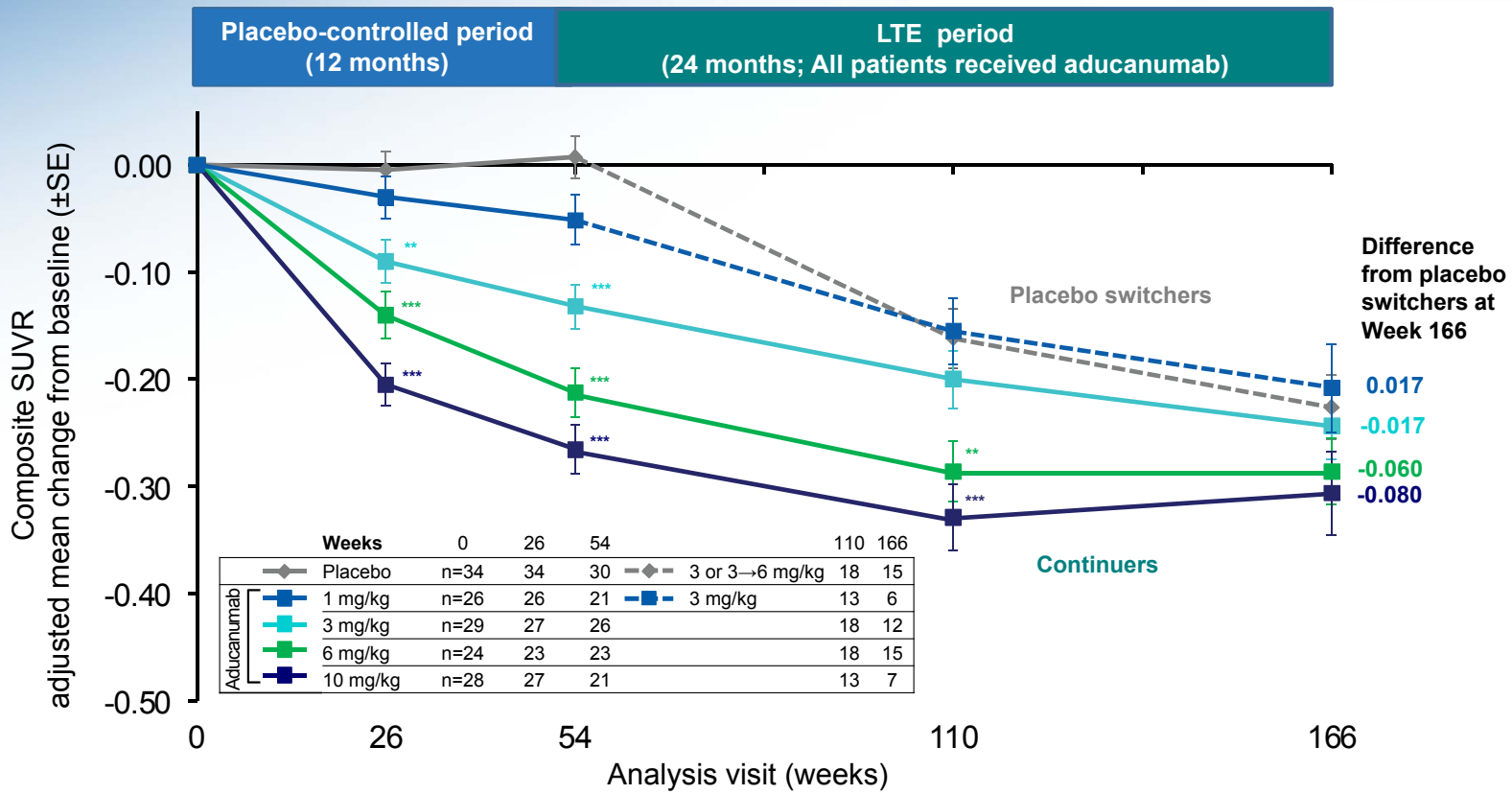
Baseline Disease Characteristics

	Placebo (n=40)	Aducanumab 1 mg/kg (n=31)	Aducanumab 3 mg/kg (n=32)	Aducanumab 6 mg/kg (n=30)	Aducanumab 10 mg/kg (n=19)
Age in years, mean ± SD	72.8 ± 7.2	72.6 ± 7.8	70.5 ± 8.2	73.3 ± 9.3	73.7 ± 8.3
ApoE ε4, n (%)					
Carriers	26 (65)	19 (61)	21 (66)	21 (70)	20 (63)
Non-carriers	14 (35)	12 (39)	11 (34)	9 (30)	12 (38)
Clinical stage, n (%)					
Prodromal	19 (48)	10 (32)	14 (44)	12 (40)	13 (41)
Mild	21 (53)	21 (68)	18 (56)	18 (60)	19 (59)
MMSE, mean ± SD	24.7 ± 3.6	23.6 ± 3.3	23.2 ± 4.2	24.4 ± 2.9	24.8 ± 3.1
CDR Global Score, n (%)					
0.5	34 (85)	22 (71)	22 (69)	25 (83)	24 (75)
1	6 (15)	9 (29)	10 (31)	5 (17)	8 (25)
CDR-SB, mean ± SD	2.66 ± 1.50	3.40 ± 1.76	3.50 ± 2.06	3.32 ± 1.54	3.14 ± 1.71
PET SUVR, mean composite	1.441	1.441	1.464	1.429	1.441
AD medications used,[a] n (%)	25 (63)	21 (68)	28 (88)	20 (67)	17 (53)

[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.

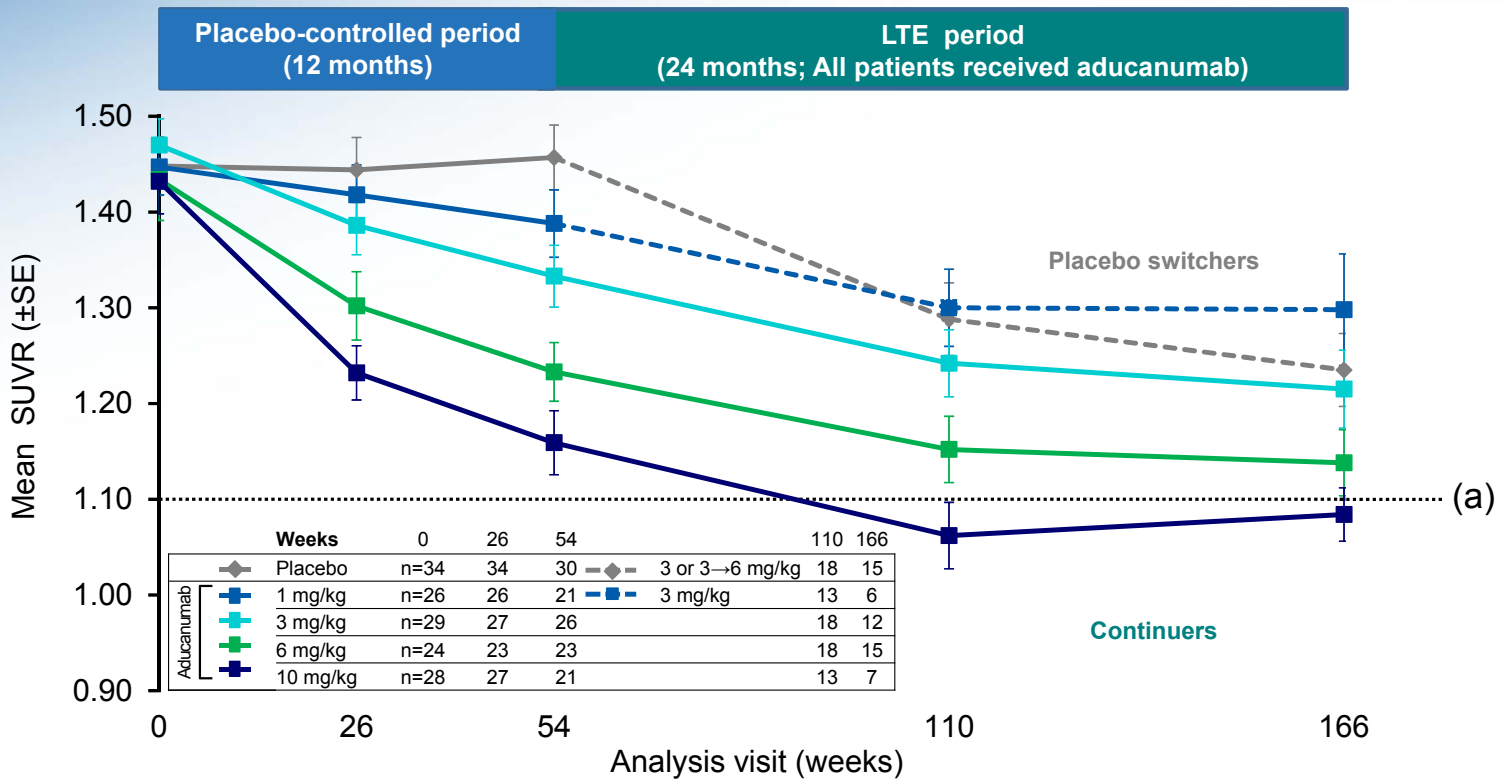
PET AMYLOID IMAGING

Effect of Aducanumab on Amyloid Plaque Levels (Composite SUVR)



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.

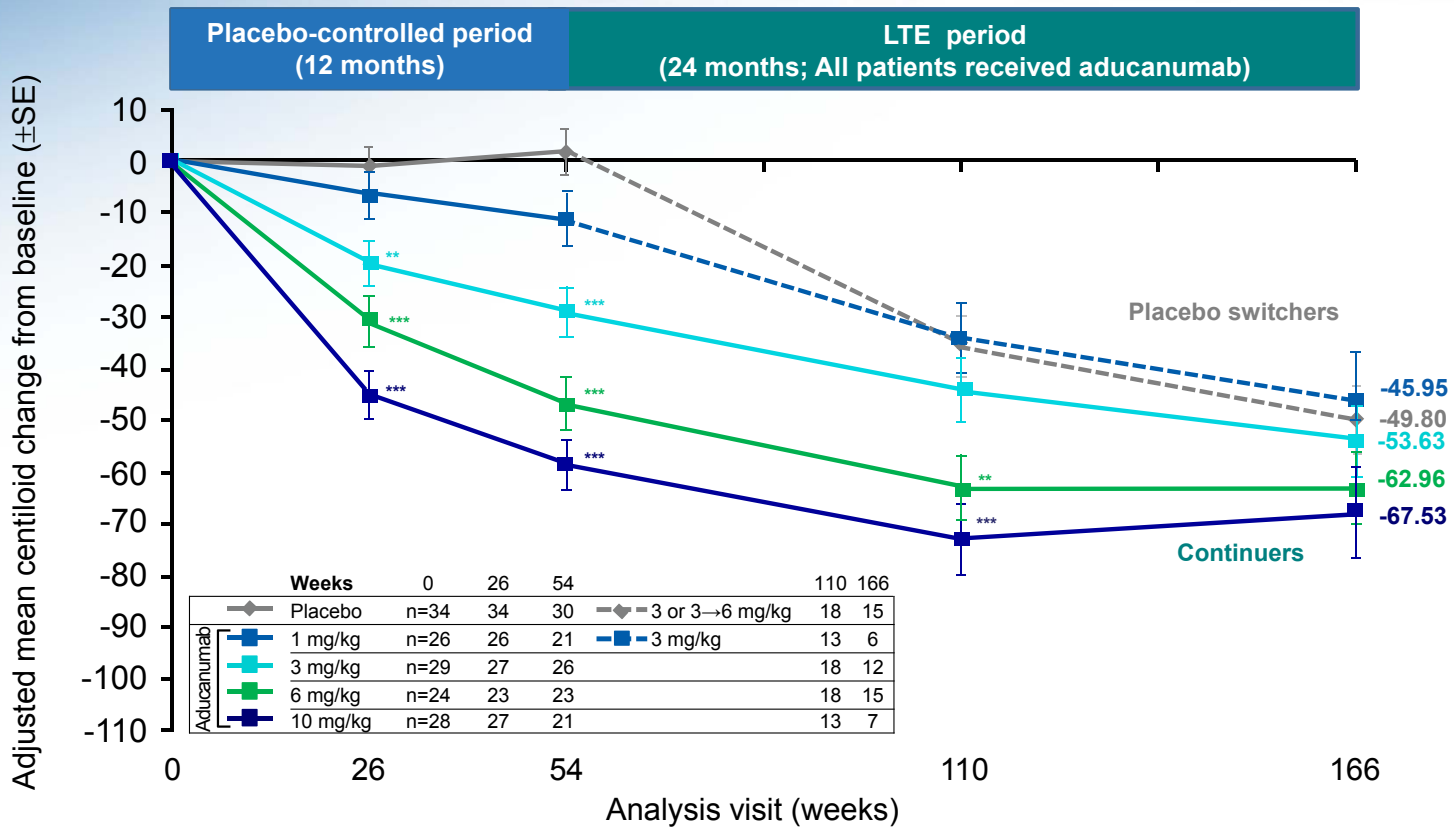
Effect of Aducanumab on Amyloid Plaque Levels



[a]The value of 1.10 has been used as a quantitative cut-point that discriminates between positive and negative scans[1,2]

1. Landau SM, et al. Ann Neurol. 2012;72:578–586; 2. Joshi A et al. J Nucl Med. 2012; 53:378–384. LTE, long-term extension; SUVR, standardized uptake value ratio.

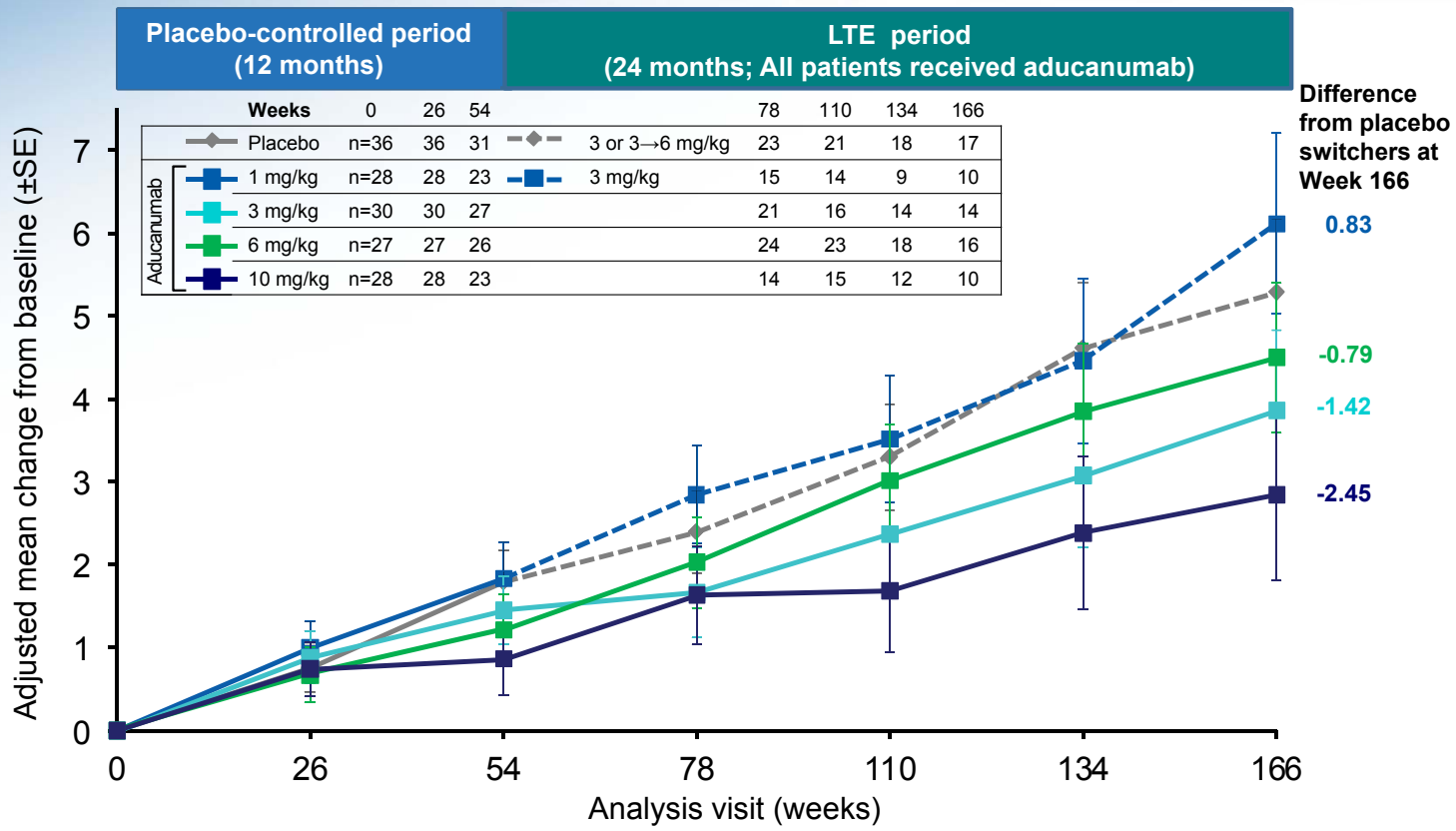
Effect of Aducanumab on Amyloid Plaque Levels (Centiloid scale)



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.

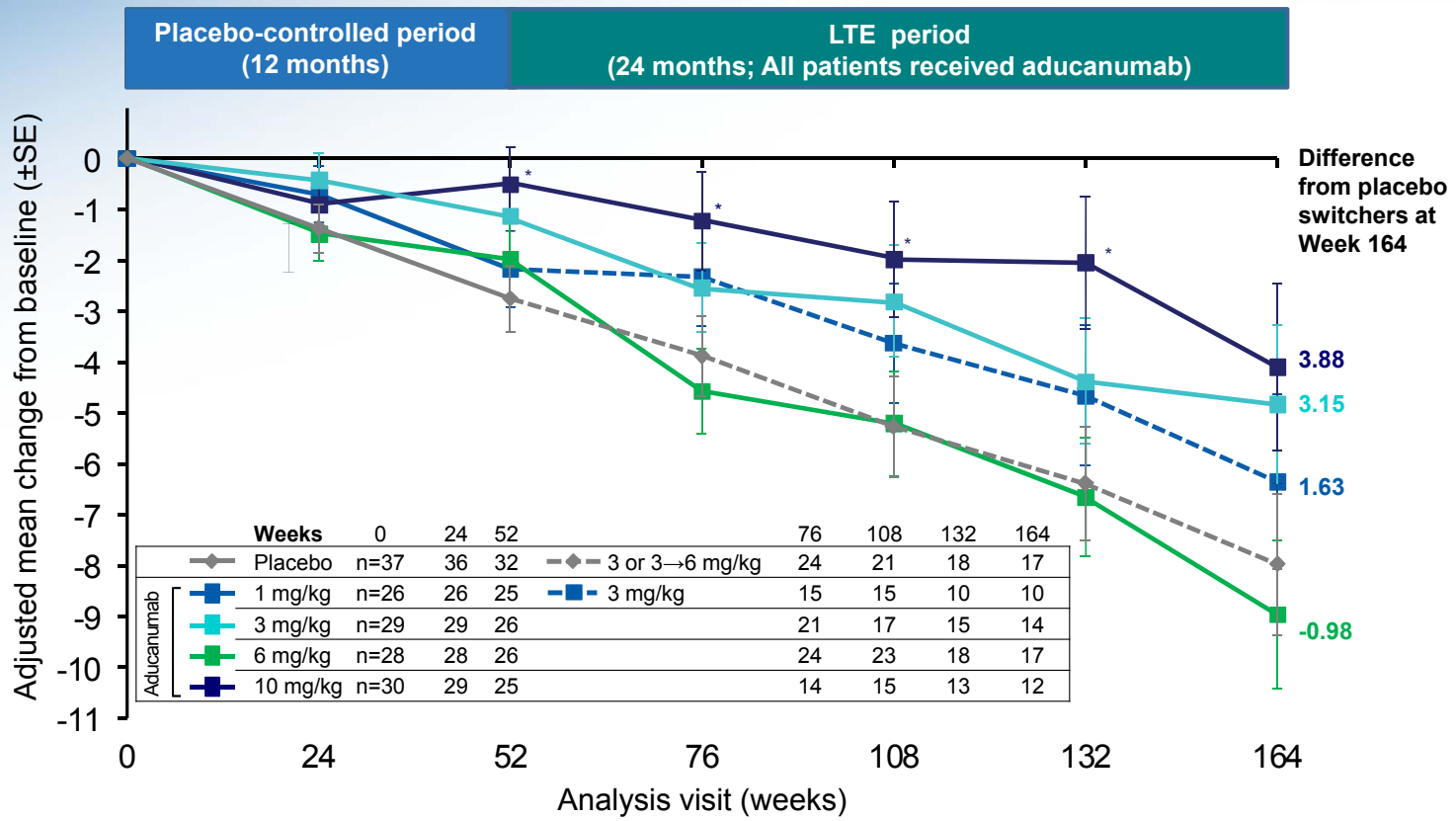
CLINICAL ENDPOINTS

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



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)



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 Exam; SE, standard error.

SAFETY AND TOLERABILITY

Safety of Aducanumab Between Months 12 and 36 (First Two Years of the LTE)

	Placebo Switchers[a] (n=29)	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)
Number with an AE (%)	28 (97)	15 (79)	20 (77)	23 (96)	15 (79)
Number with an SAE (%)	14 (48)	4 (21)	3 (12)	8 (33)	3 (16)
Number discontinuing treatment due to AE (%)	8 (28)	0	2 (8)	0	4 (21)

- The most common AEs in the LTE (incidence ≥ 15%) were fall, headache, and ARIA[c]
- The most common SAE was ARIA (n=5 [4%])
- There were two deaths due to cardiac events— one in the 6 mg/kg arm during the first year of the LTE and one in the 10 mg/kg arm during the second 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 (2 doses of 3 mg/kg followed by subsequent doses of 6 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 36 (First Two Years of the LTE)

	Placebo Switchers[c]	1 mg/kg → 3 mg/kg	Continuers[d]		
			3 mg/kg	6 mg/kg	10 mg/kg
Patients with at least 1 post-baseline MRI	29	17	23	24	19
ARIA-E[a], n/total (%)	5/29 (17)	3/17 (18)	0/23 (0)	0/24 (0)	0/19 (0)
ApoE ε4 carriers	4/17 (24)	3/11 (27)	-	-	-
ApoE ε4 non-carriers	1/12 (8)	0/6 (0)	-	-	-
Discontinued treatment,[b] n (%)	4 (14)	0 (0)	-	-	-
Isolated ARIA-H, n (%)	2 (7)	0 (0)	5 (22)	2 (8)	1 (5)

- There were no new cases of ARIA-E in patients who continued on the same dose of aducanumab during the first two years of the LTE
- 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) 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; LTE, long-term extension; MRI, magnetic resonance imaging

ARIA Characteristics in PRIME Fixed-dose and Titration Cohorts

Since the start of the PRIME study:

- Of the 185 patients dosed with aducanumab, 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

ARIA-E, ARIA–vasogenic edema.

Summary

- Amyloid plaque levels continued to decrease in a dose- and time-dependent manner in patients treated with aducanumab who completed the first two years of the LTE
- Analyses of exploratory clinical endpoints CDR-SB and MMSE suggest clinical benefit in patients continuing aducanumab over 36 months
- 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

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.

Acknowledgements

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