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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About Aducanumab

- Aducanumab (BIIB037) is an investigational compound being developed for the treatment of early AD. Aducanumab is a human recombinant monoclonal antibody (mAb) derived from a de-identified library of B cells collected from healthy elderly subjects with no signs of cognitive impairment or cognitively impaired elderly subjects with unusually slow cognitive decline using Neurimmune's technology platform called Reverse Translational Medicine (RTM). Biogen licensed aducanumab from Neurimmune under a collaborative development and license agreement. As of October 2017, Biogen and Eisai entered into a global collaboration agreement to jointly develop and commercialize aducanumab.

- In Phase 1b studies, the most frequently reported treatment-related serious adverse event (SAE) and adverse event (AE) was ARIA (amyloid-related imaging abnormalities).

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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

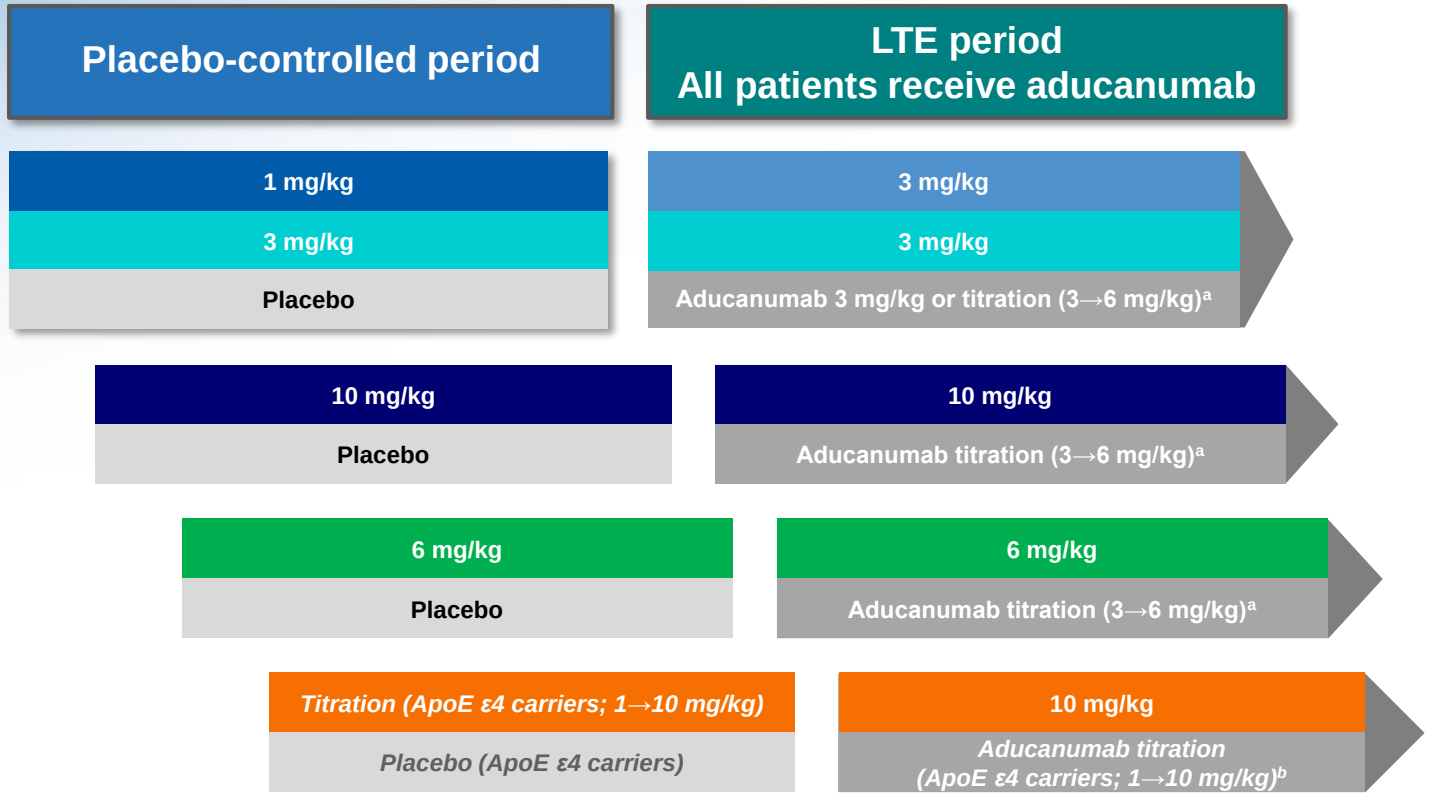
[a]Medical writing support and editing for this presentation was funded by Biogen and was provided by Nucleus Global.

Overview

- Aducanumab is a human monoclonal antibody 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
  - 24-month data for fixed-dose cohorts were previously presented[1]
- 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

1. Viglietta V, et al. *J Prev Alz Dis*. 2016;3:284. Data presented at CTAD 2016. 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

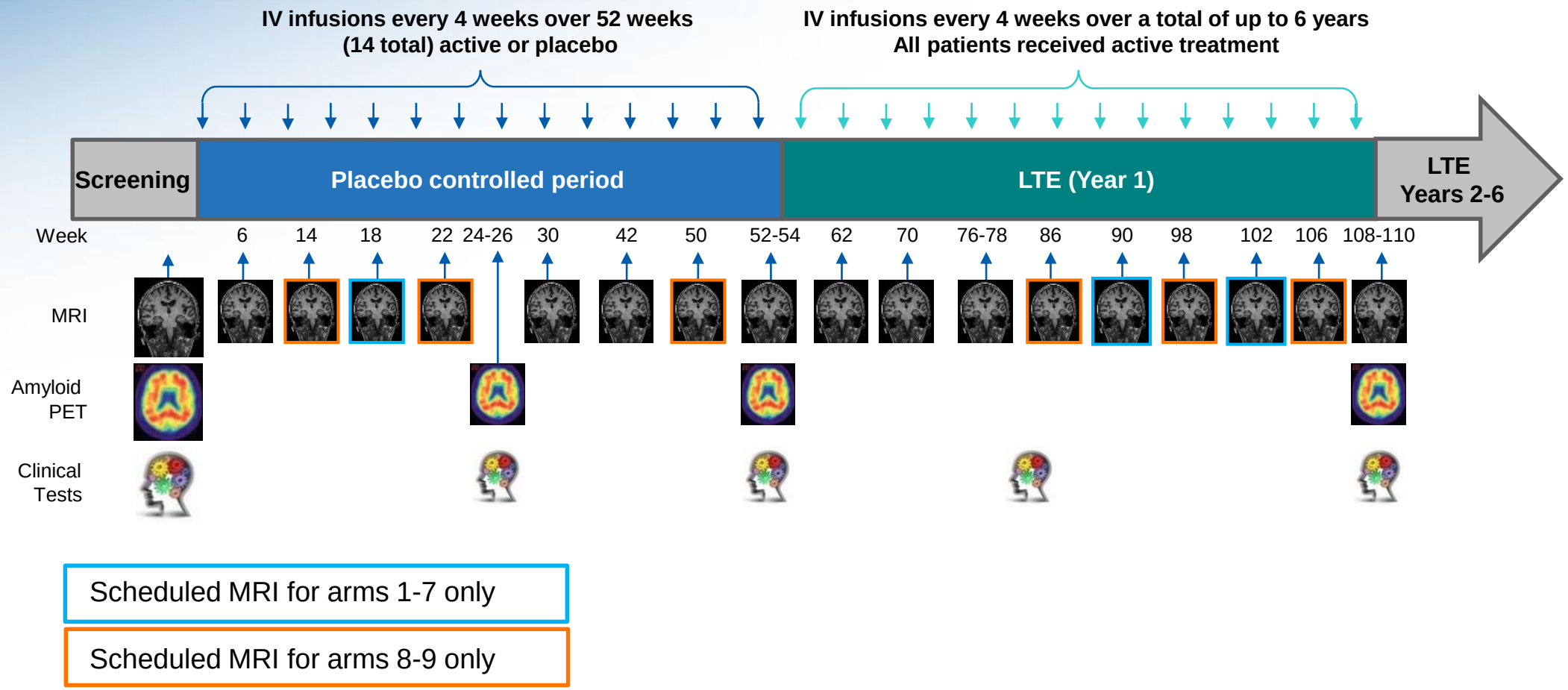
PRIME Study Design: Placebo-Controlled and LTE Periods



- **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**")

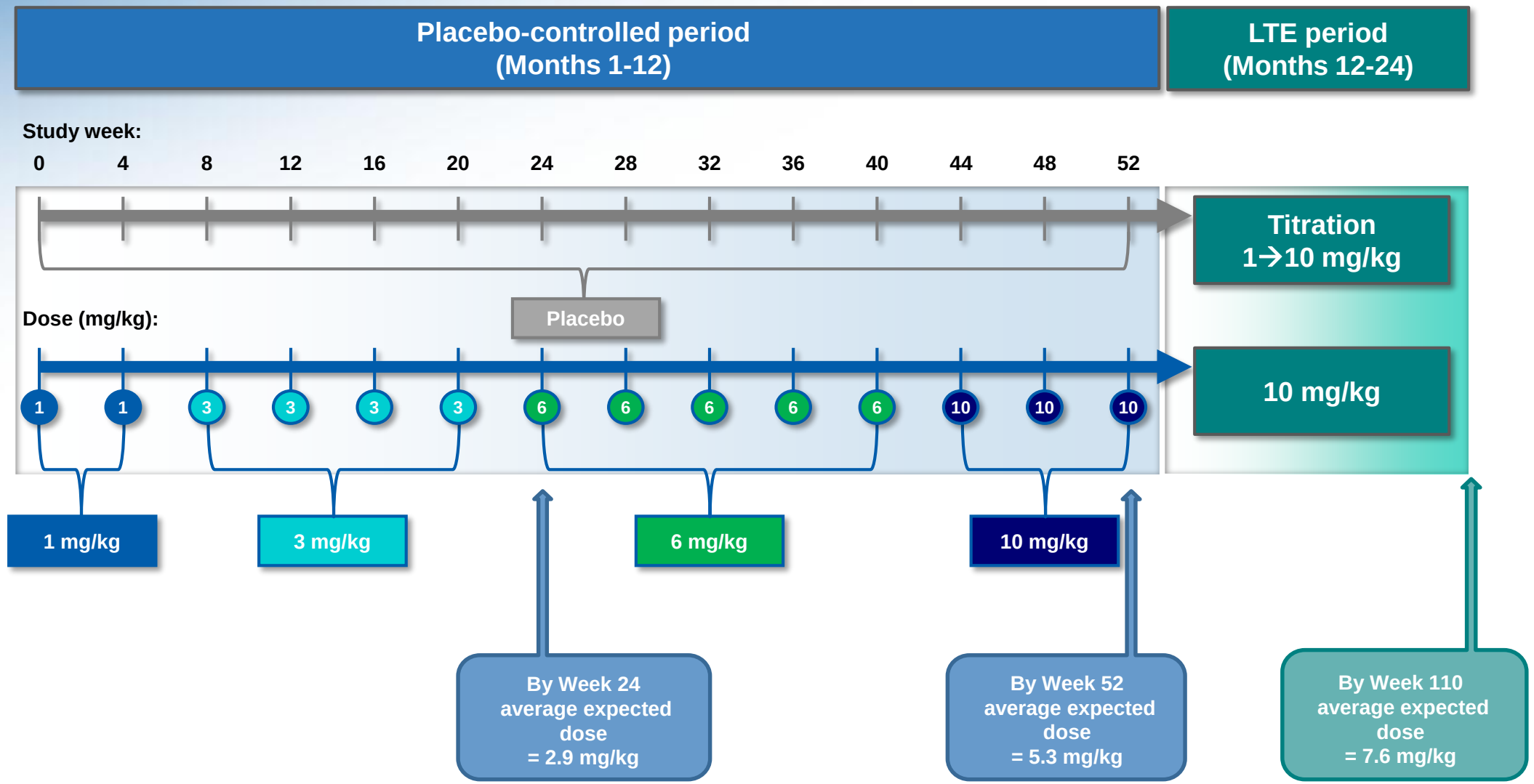
[a]Titration denotes 2 doses of 3 mg/kg followed by subsequent doses of 6 mg/kg. [b]Titration denotes 2 doses of 1mg/kg, 4 doses of 3 mg/kg, 5 doses of 6 mg/kg followed by subsequent doses of 10 mg/kg. ApoE ε4, Apolipoprotein E ε4; LTE, long-term extension.

Timeline of Dose Administration and Key Assessments in PRIME

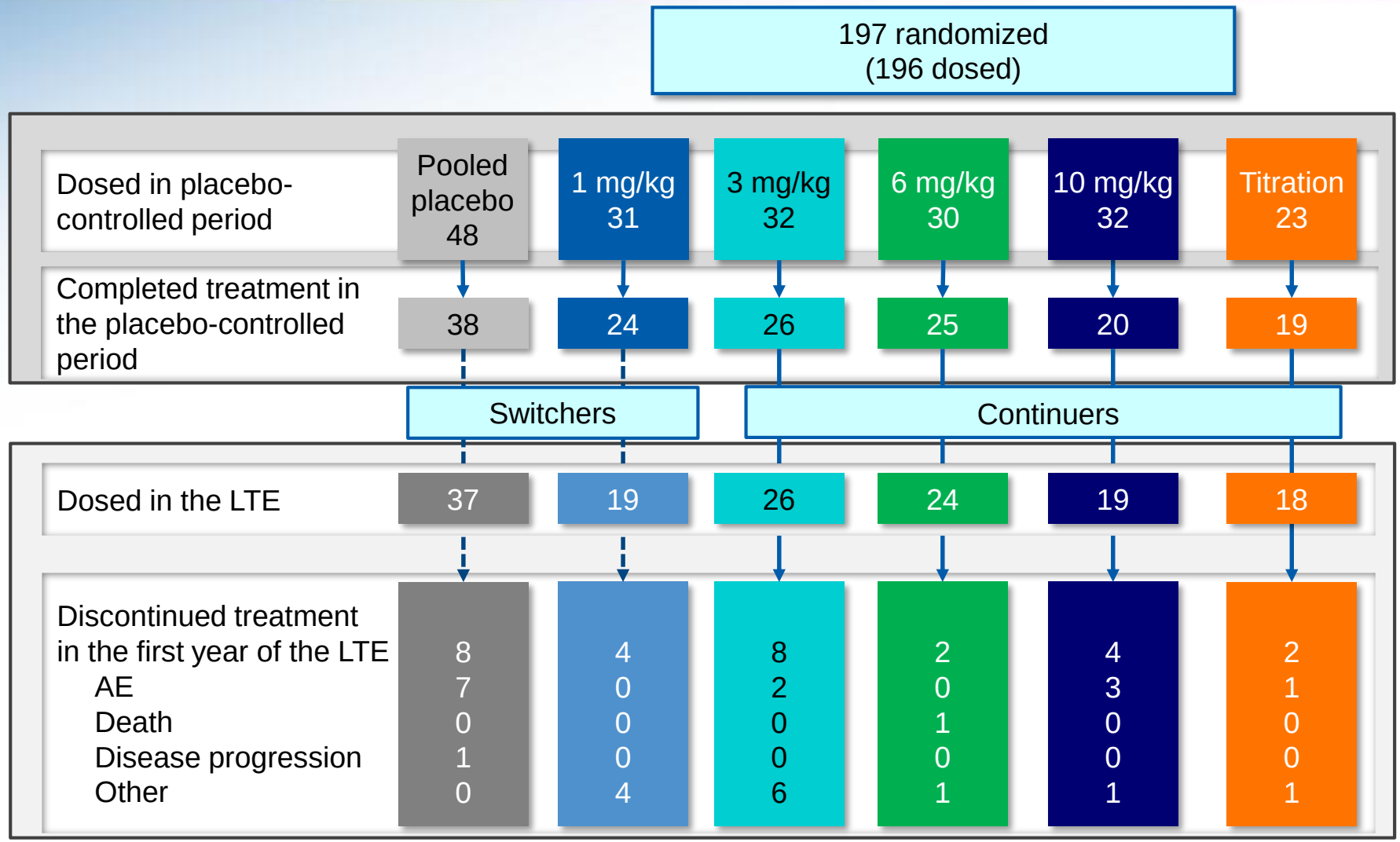


MRI, magnetic resonance imaging.

Titration Dosing Regimen



Patient Disposition at 24 Months



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

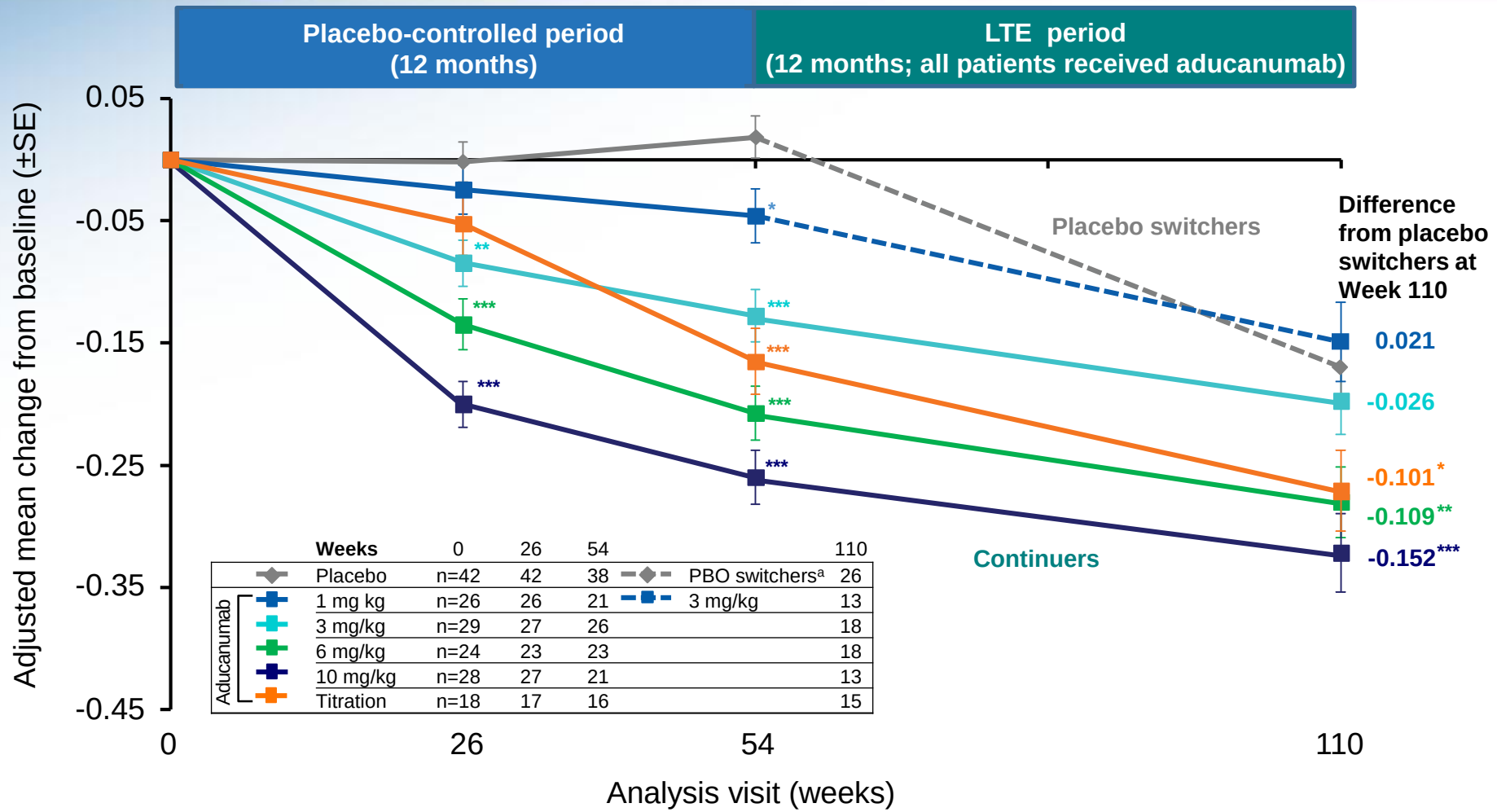
Baseline Disease Characteristics

		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

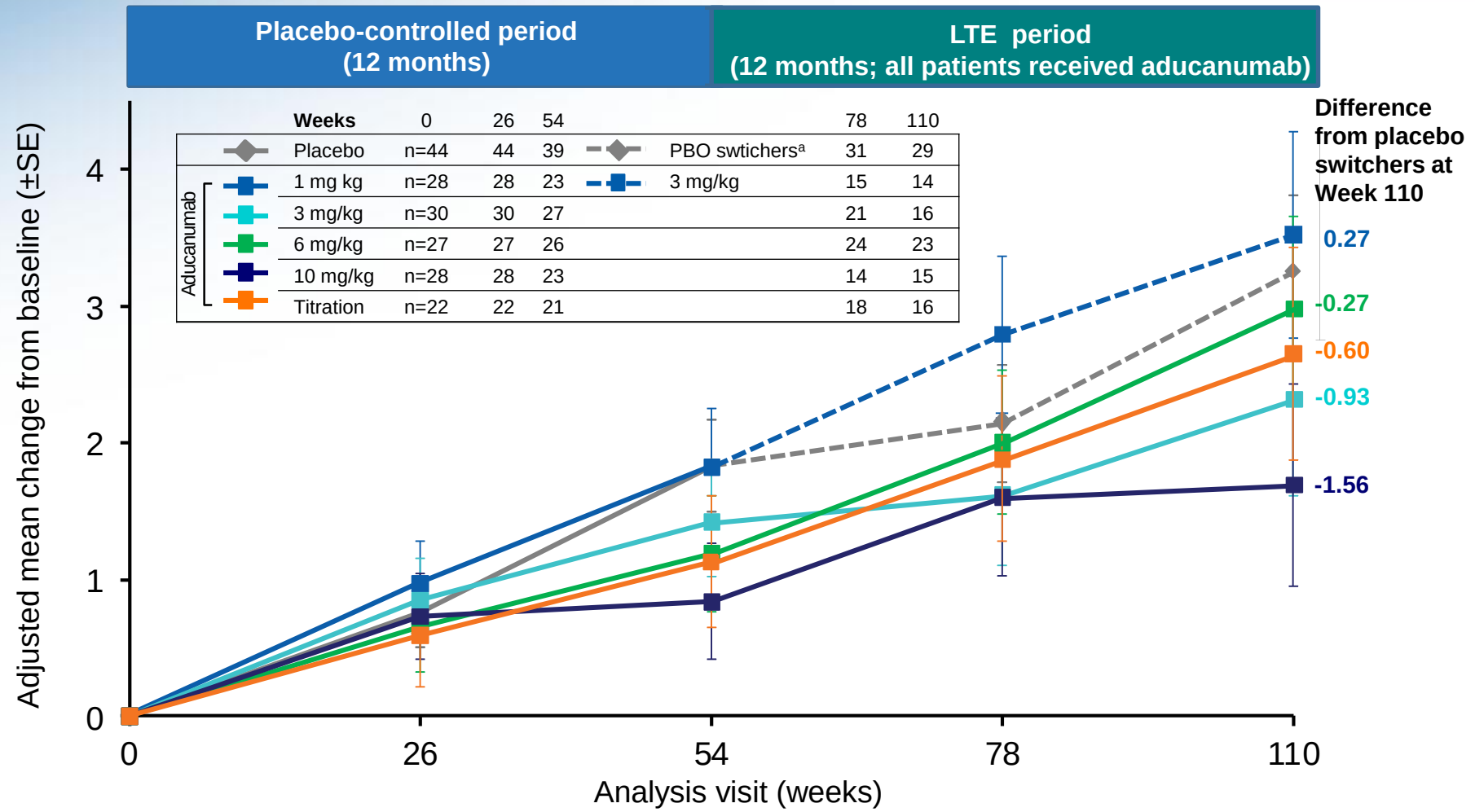
Effect of Aducanumab on Amyloid Plaque Levels



[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; PBO, placebo; SE, standard error.

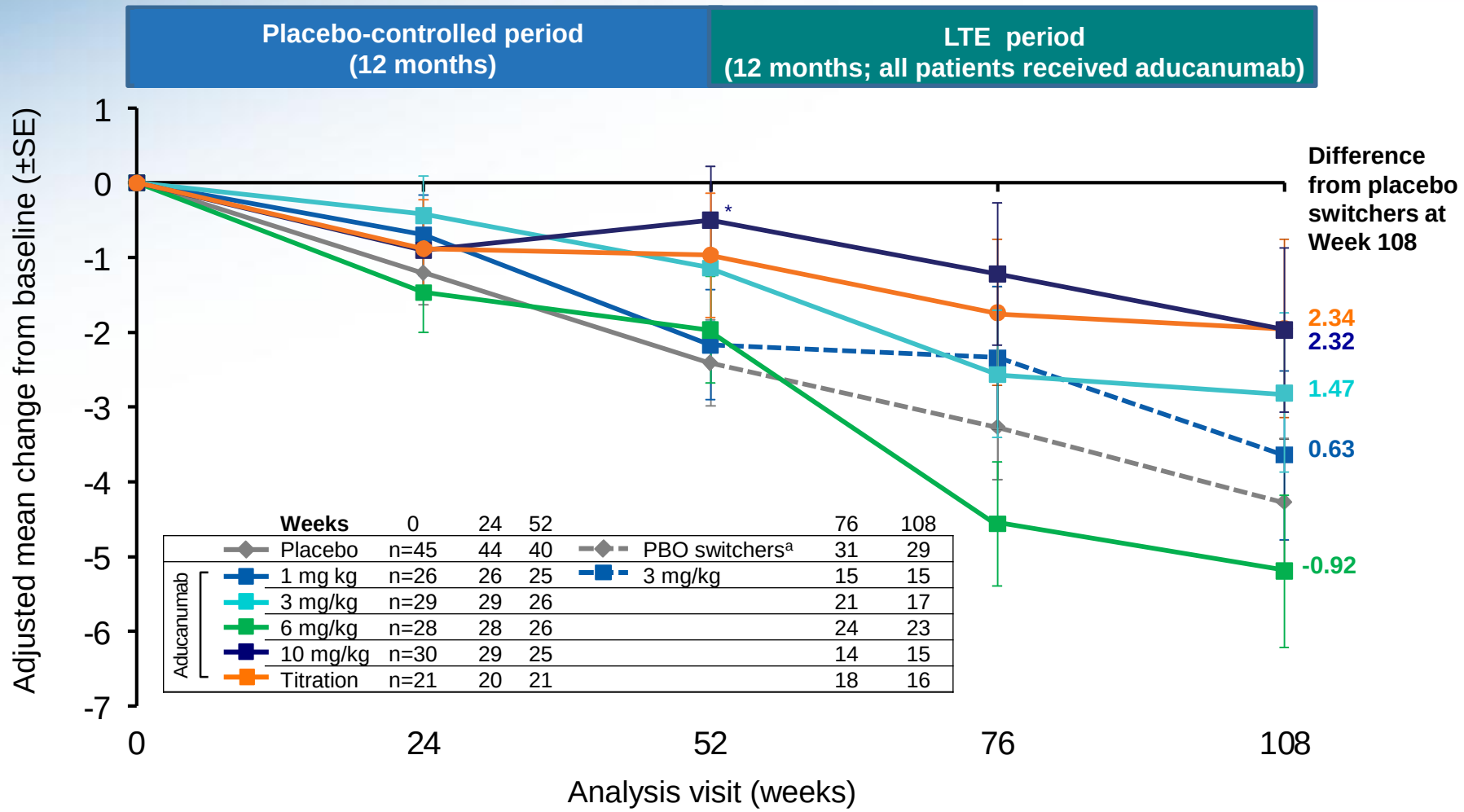
CLINICAL ENDPOINTS

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; PBO, placebo; 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; PBO, placebo; 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 occurred 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

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.