12-Month Interim Analysis of APOE4 Carriers for Fixed and Titration Dosing Regimens in PRIME, a Phase 1b study of Aducanumab

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Disclosures

This study is funded by Biogen[a]

- JO, TC, AE, PC, SBH, and AS are employees and shareholders of Biogen
- VV and LW were employees and shareholders of Biogen while this work was completed
- CH and RMN are employees and shareholders of Neurimmune

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

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Introduction

- 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, pharmacokinetics, and pharmacodynamics of aducanumab in patients with prodromal or mild Alzheimer's disease
- Here we present 12-month interim data of ApoE ε4 carriers for both fixed-dose and titrated aducanumab in PRIME

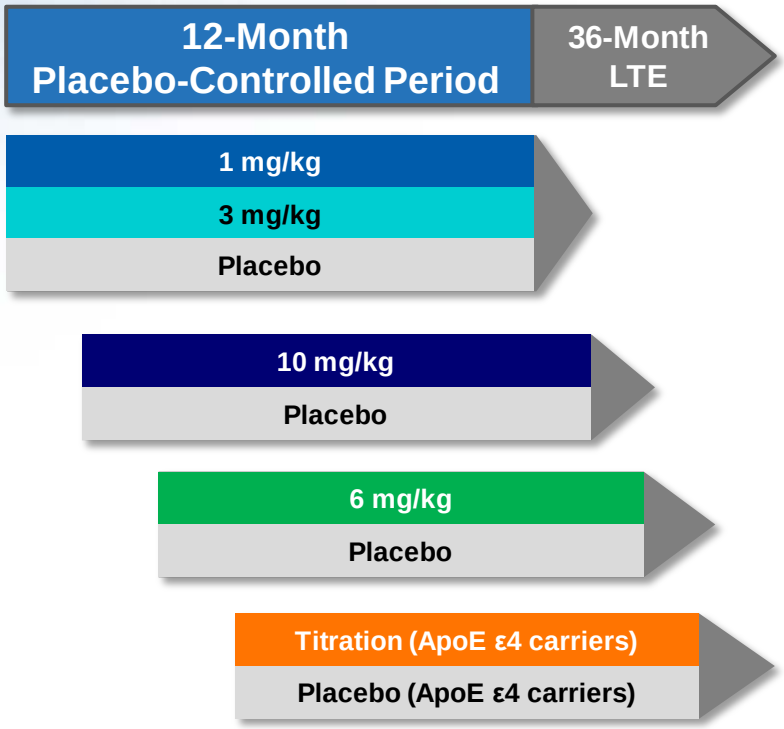
ApoE ε4, Apolipoprotein E ε4

PRIME Study Design: Placebo-Controlled and LTE Periods

Staggered Parallel-Group Design

Population

- Prodromal or mild AD
- MMSE ≥20
- Stable concomitant medications
- Positive amyloid PET scan



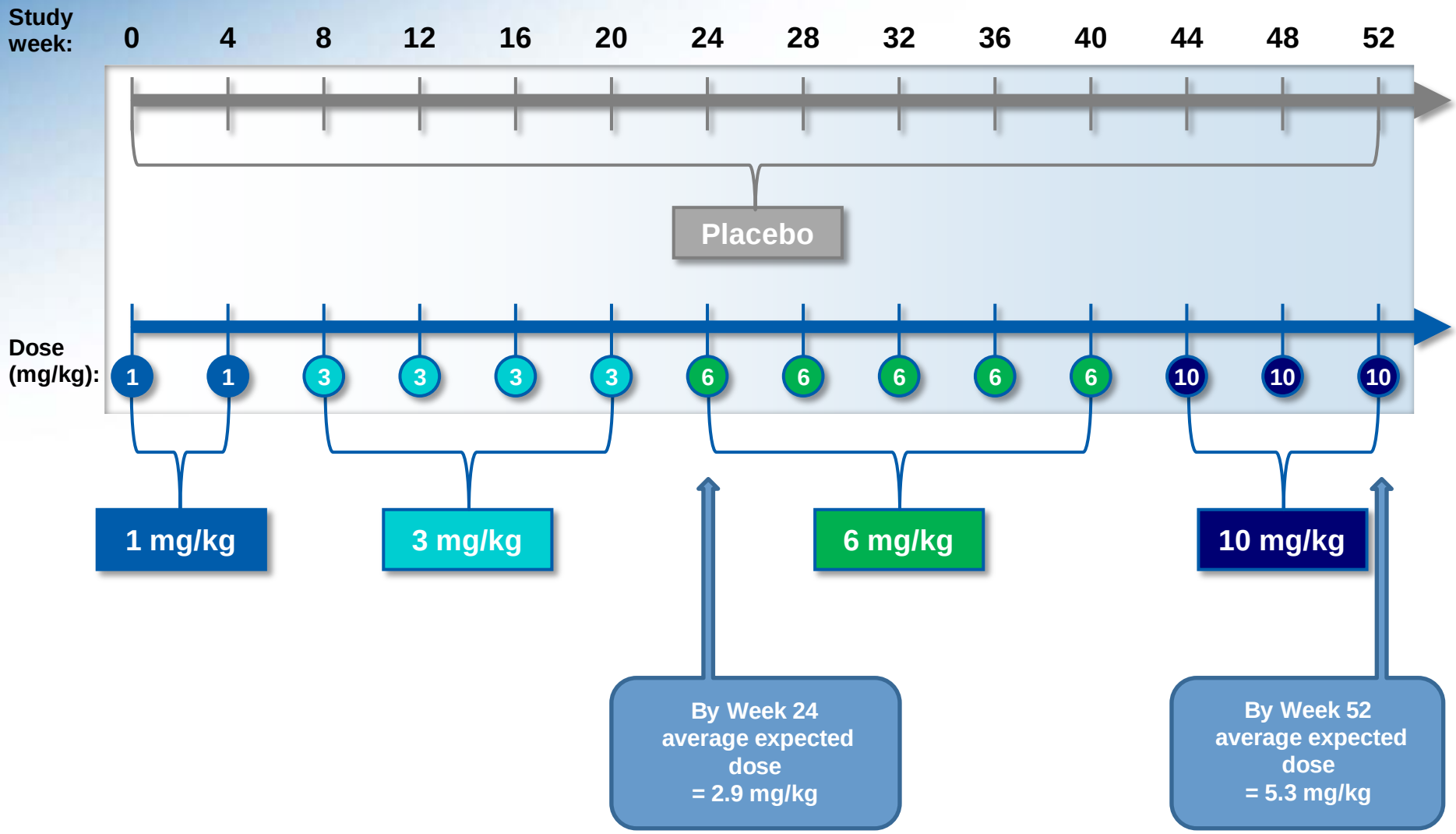
Endpoints

- **Primary**: safety and tolerability
- **Secondary**: serum PK, immunogenicity, change in amyloid PET (Week 26)
- **Exploratory:** included CDR–SB, MMSE, change in amyloid PET (Week 54)

- **Randomization**: 3:1 drug: placebo within cohorts, fixed-dose cohorts stratified by ApoE ε4 status
- **Planned sample size**: 188 patients
- **Titration cohort** of ApoE ε4 carriers added after enrollment into fixed-dose arms was complete (planned sample size: aducanumab, 21: placebo, 7)

ApoE ε4, Apolipoprotein E ε4; CDR–SB, Clinical Dementia Rating–Sum of Boxes; LTE, long-term extension; MMSE, Mini-Mental State Examination; PET, positron emission tomography

Titration Dosing Regimen in the 12-Month Placebo-Controlled Period

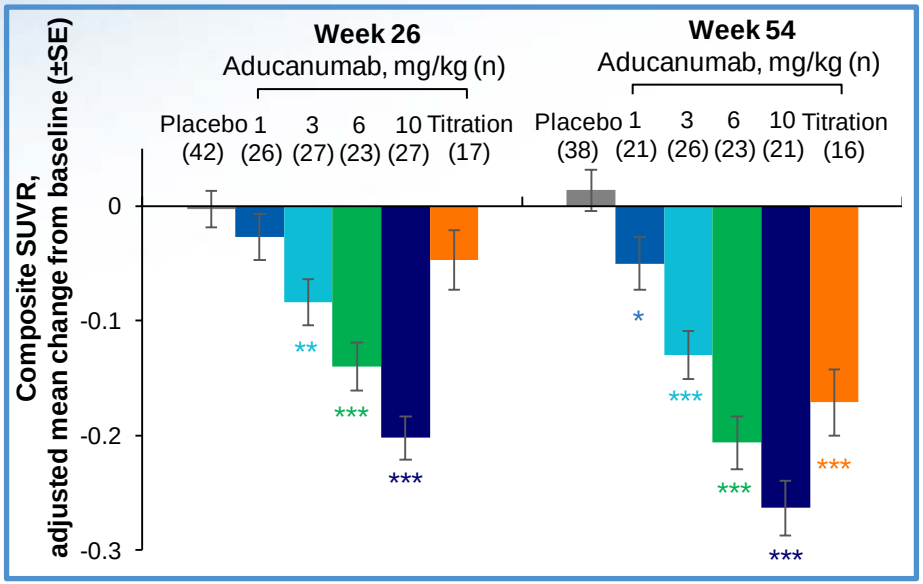


Summary of Previously Presented PRIME 12-Month Interim Results

Safety (primary endpoint)

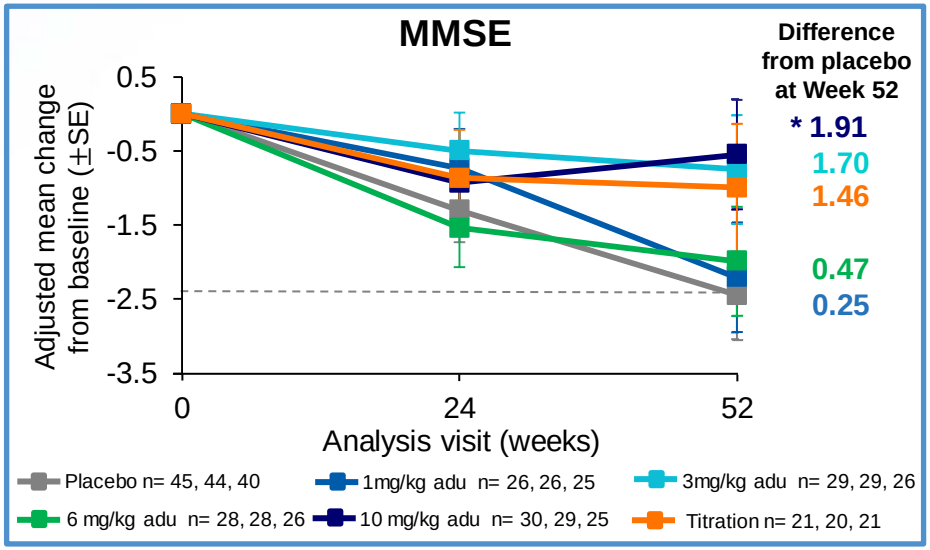
ARIA-E were the main safety and tolerability finding
- Dose- and ApoE ε4-dependent
- Monitorable and manageable

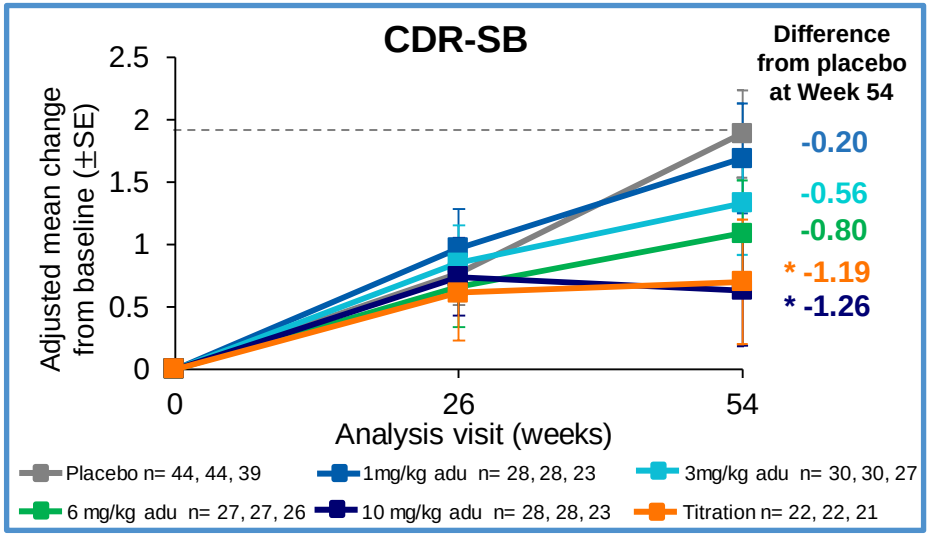
Amyloid plaque reduction with aducanumab (secondary endpoint)



Nominal p values: * $P<0.05$; ** $P<0.01$; *** $P<0.001$ vs placebo. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-SB. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment. PD analysis population is defined as all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter. ANCOVA, analysis of covariance; ApoE ε4, Apolipoprotein E ε4; ARIA-E, amyloid-related imaging abnormalities - vasogenic edema; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; SE, standard error; SUVR, standardized uptake value ratio.

Clinical effect of aducanumab (exploratory endpoints)





Baseline Disease Characteristics for ApoE ε4 Carriers

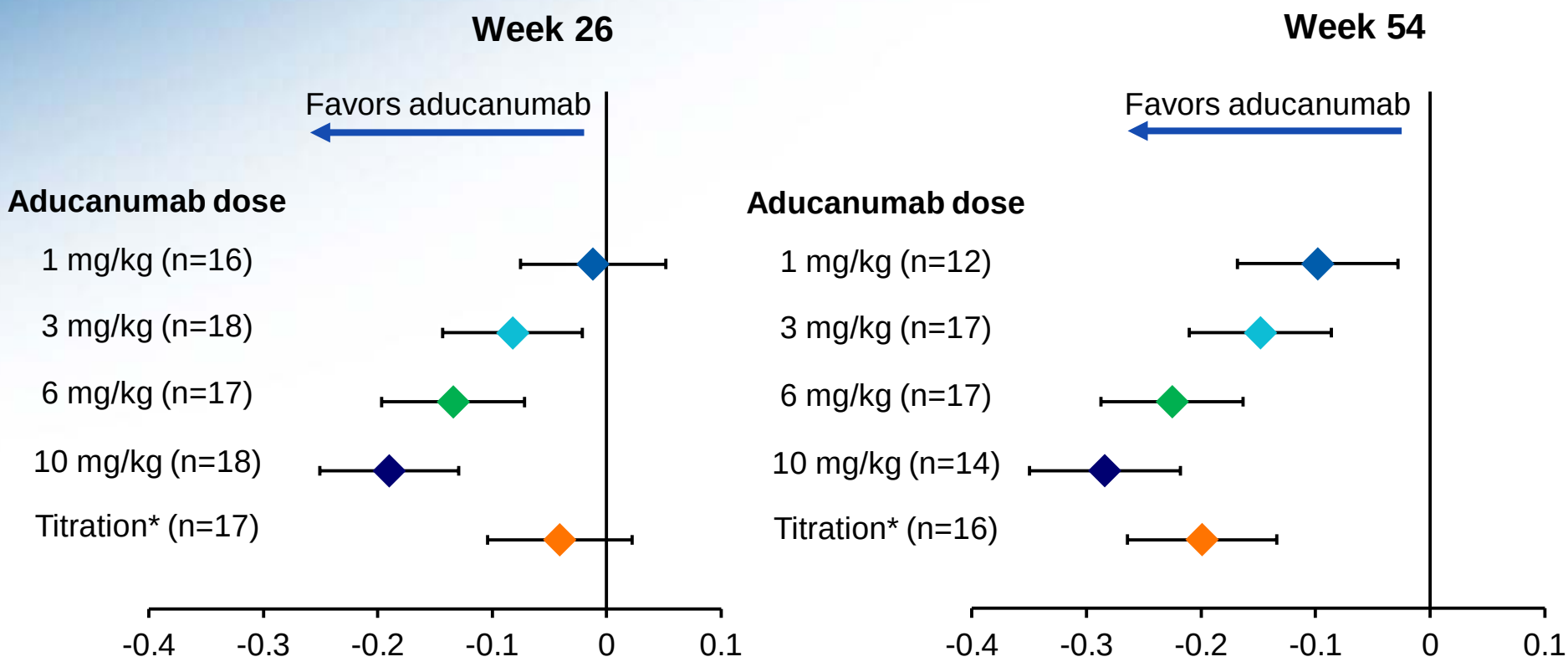
		Aducanumab				
	Placebo (n=34)	1 mg/kg (n=19)	3 mg/kg (n=21)	6 mg/kg (n=21)	10 mg/kg (n=20)	Titration (n=23)
Age, years, mean ± SD	72.9 ± 6.6	71.6 ± 7.1	70.4 ± 7.0	72.1 ± 8.7	71.9 ± 6.8	73.1 ± 7.8
Clinical stage, n (%)						
Prodromal	14 (41)	7 (37)	11 (52)	8 (38)	8 (40)	13 (57)
Mild	20 (59)	12 (63)	10 (48)	13 (62)	12 (60)	10 (43)
MMSE, mean ± SD	24.7 ± 3.2	23.1 ± 3.8	24.1 ± 4.1	24.6 ± 2.8	25.0 ± 2.9	24.7 ± 3.0
CDR Global Score, n (%)						
0.5	28 (82)	15 (79)	15 (71)	17 (81)	16 (80)	18 (78)
1	6 (18)	4 (21)	6 (29)	4 (19)	4 (20)	5 (22)
CDR-SB, mean ± SD	2.66 ± 1.44	2.95 ± 1.41	3.29 ± 2.06	3.62 ± 1.68	2.93 ± 1.45	3.24 ± 1.84
PET SUVR, mean composite	1.438	1.483	1.468	1.432	1.426	1.325
AD medications used,[a] n (%)	20 (59)	15 (79)	18 (86)	14 (67)	10 (50)	12 (52)

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

[a]Cholinesterase inhibitors and/or memantine.

PET AMYLOID IMAGING

Aducanumab Reduces Amyloid Plaques in ApoE ε4 Carriers

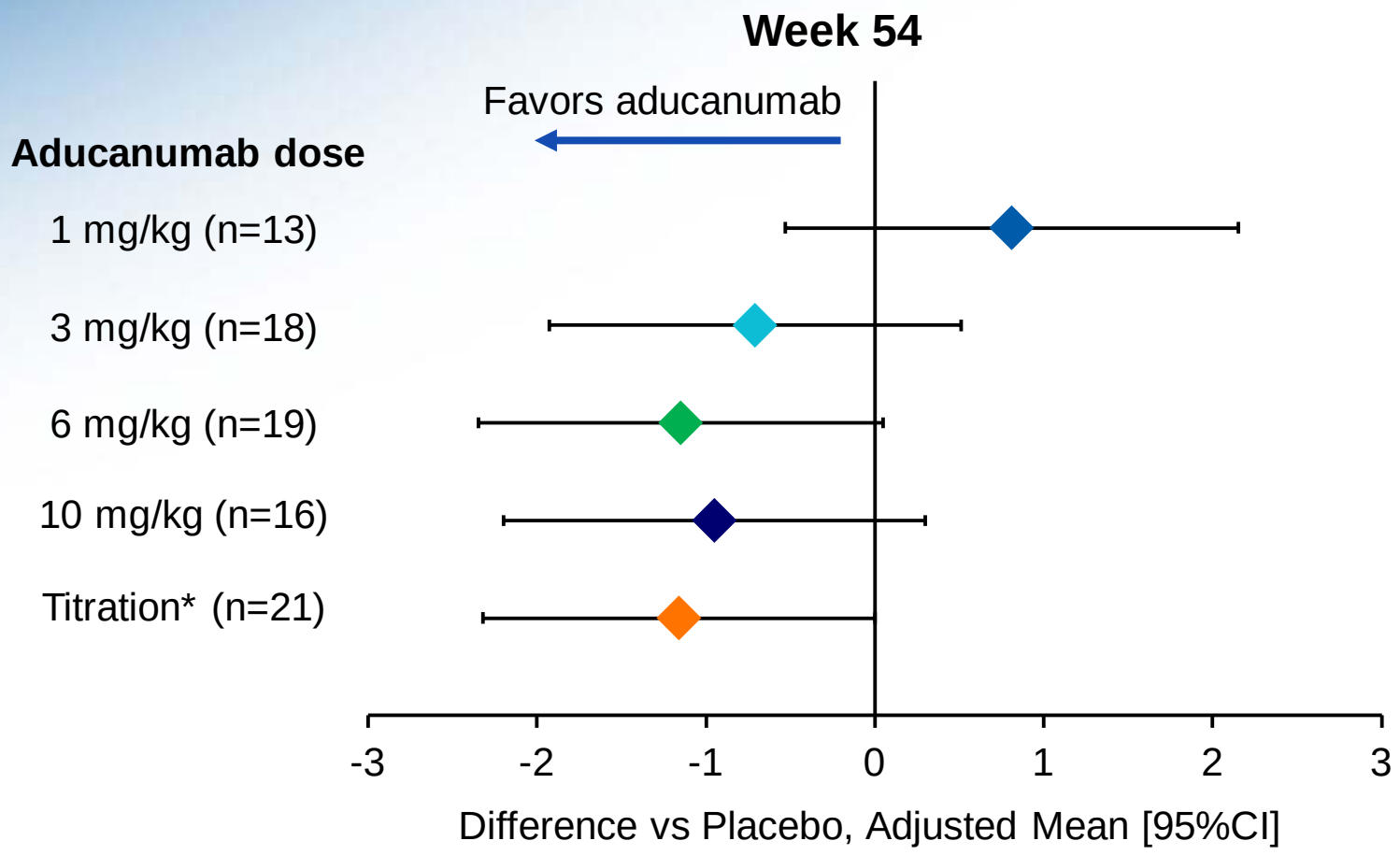


Amyloid PET SUVR[1]
Difference vs Placebo, Adjusted Mean [95%CI]

*For titration cohort: average expected dose 2.9 mg/kg by week 24 and 5.3 mg/kg by week 52. Analyses based on observed data. Difference with placebo and 95% CI based on ANCOVA model. ANCOVA for change from baseline with factors of treatment and baseline composite SUVR. ApoE ε4, Apolipoprotein E ε4; CI, confidence interval; PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.

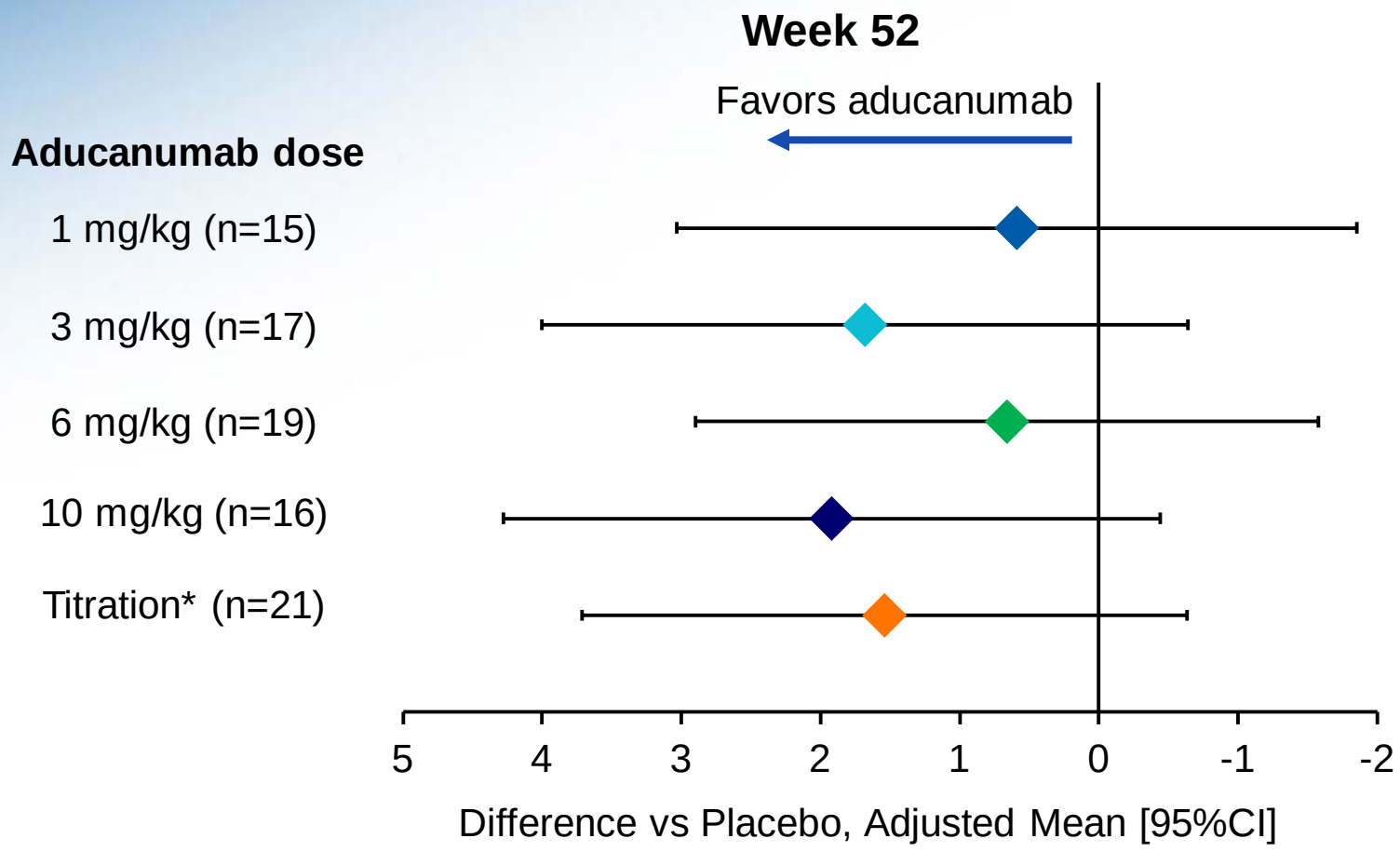
CLINICAL ENDPOINTS

Effect of Aducanumab on CDR–SB in ApoE ε4 Carriers



*For titration cohort: average expected dose by week 52 was 5.3 mg/kg
CDR-SB is an exploratory endpoint. Analyses based on observed data. Difference with placebo and 95% CI based on ANCOVA model. ANCOVA for change from baseline with factors of treatment and baseline CDR-SB. ApoE ε4, Apolipoprotein E ε4; CI, confidence interval; CDR-SB, Clinical Dementia Rating–Sum of Boxes.

Effect of Aducanumab on MMSE in ApoE ε4 Carriers



*For titration cohort: average expected dose by week 52 was 5.3 mg/kg
MMSE is an exploratory endpoint. Analyses based on observed data. Difference with placebo and 95% CI based on ANCOVA model. ANCOVA for change from baseline with factors of treatment and baseline MMSE. ApoE ε4, Apolipoprotein E ε4; CI, confidence interval; MMSE, Mini-Mental State Examination.

SAFETY AND TOLERABILITY

No New Safety Signals were Identified in the ApoE ε4 Carrier Subgroup

			Aducanumab				
Overall	**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)**
Number with an AE (%)	47 (98)	28 (90)	27 (84)	28 (93)	29 (91)	21 (91)
Number with an SAE (%)	16 (33)	4 (13)	4 (13)	4 (13)	12 (38)	5 (22)
Number discontinuing treatment due to AE (%)	4 (8)	3 (10)	2 (6)	3 (10)	10 (31)	2 (9)
ApoE ε4 Carriers	**Placebo (n=34)**	**1 mg/kg (n=19)**	**3 mg/kg (n=21)**	**6 mg/kg (n=21)**	**10 mg/kg (n=20)**	**Titration (n=23)**
Number with an AE (%)	33 (97)	17 (89)	17 (81)	20 (95)	19 (95)	21 (91)
Number with an SAE (%)	11 (32)	3 (16)	2 (10)	3 (14)	8 (40)	5 (22)
Number discontinuing treatment due to AE (%)	3 (9)	1 (5)	2 (10)	2 (10)	7 (35)	2 (9)

- Overall
  - The most common AE/SAE was ARIA
  - Other AEs/SAEs were consistent with the patient population
    - Three deaths; none considered treatment-related; two in placebo and one in 10 mg/kg arm (two occurred after study discontinuation)
  - No significant changes in chemistry, hematology, urinalysis, ECGs, or vital signs
- No new safety signals were identified in ApoE ε4 carriers

ApoE ε4, Apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; ECG, electrocardiogram; SAE, serious adverse event

Dose Titration Slightly Attenuated Incidence of ARIA-E versus Higher Fixed Doses

		Aducanumab				
	Placebo	1 mg/kg	3 mg/kg	6 mg/kg	10 mg/kg	Titration
Patients with at least 1 post-baseline MRI	46	31	32	30	32	23
ARIA-E,[a] n (%)	0/46	1/31 (3)	2/32 (6)	11/30 (37)	13/32 (41)	8/23 (35)
ApoE ε4 carrier	0/32	1/19 (5)	1/21 (5)	9/21 (43)	11/20 (55)	8/23 (35)
ApoE ε4 non-carrier	0/14	0/12	1/11 (9)	2/9 (22)	2/12 (17)	--
Isolated ARIA-H, n (%)	3/46 (7)	2/31 (6)	3/32 (9)	0/30	2/32 (6)	0/23

[a]ARIA-E with or without ARIA-H.

Incidence of ARIA based on MRI.
ApoE ε4, Apolipoprotein E ε4; ARIA-E, ARIA–vasogenic edema; ARIA-H, ARIA–microhemorrhages, macrohemorrhages, or superficial siderosis; MRI, magnetic resonance imaging

The Majority of ApoE ε4 Carriers Experiencing ARIA-E Continued Treatment

Among ApoE ε4 carriers with ARIA-E,

- 4/11 (36%) in the 10 mg/kg group continued treatment
- 7/9 (78%) in the 6 mg/kg group continued treatment
- 6/8 (75%) in the titration group continued treatment

	Aducanumab				
	1 mg/kg	3 mg/kg	6 mg/kg	10 mg/kg	Titration
ApoE ε4 carriers with at least 1 post-baseline MRI	19	21	21	20	23
ARIA-E, n (%)	1 (5)	1 (5)	9 (43)	11 (55)	8 (35)
Continued treatment, n (%)	0	1 (5)	7 (33)	4 (20)	6 (26)
Same dose	0	0	1	0	0
Reduced dose	0	1	6	4	6
Discontinued treatment, n (%)	1 (5)	0	2 (10)	7 (35)	2 (9)

ApoE ε4, Apolipoprotein E ε4; ARIA-E, ARIA–vasogenic edema; MRI, magnetic resonance imaging

ARIA-E Characteristics in ApoE ε4 Carriers

- Majority of cases occurred within the first 5 months of treatment
- 70% of events were asymptomatic
- MRI findings typically resolved within 4–12 weeks

ApoE ε4, Apolipoprotein E ε4; ARIA-E, ARIA–vasogenic edema; MRI, magnetic resonance imaging

Summary

- In subgroup analyses of ApoE ε4 carriers, both titration and fixed doses of aducanumab reduced amyloid plaque burden following 12 months of treatment versus placebo
- Clinical effects in ApoE ε4 carriers were generally consistent with findings in the fixed-dose cohorts
  - Slowing of decline as measured using the CDR–SB and MMSE was observed in ApoE ε4 carriers
- Titration up to 10 mg/kg may reduce incidence of ARIA-E compared with higher fixed dosing, based on the ApoE ε4 sub-population studied
- PRIME results support the study design of the ENGAGE and EMERGE Phase 3 trials, which are investigating the clinical efficacy and safety of aducanumab in patients with early AD

ApoE ε4, Apolipoprotein E ε4; ARIA-E, amyloid-related imaging abnormalities - vasogenic edema; CDR-SB, Clinical Dementia Rating–Sum of Boxes; 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.