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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.
- 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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Change From Baseline in Clinical Dementia Rating Scale Cognitive and Functional Domains in PRIME, a Randomized Phase 1b Study of the Anti-Amyloid Beta Monoclonal Antibody Aducanumab (BIIB037)

P1-053

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Conclusions

- This post hoc analysis suggests slowing of decline, as measured by cognitive and functional Clinical Dementia Rating (CDR) domains, at Week 54 in aducanumab-treated patients with prodromal or mild Alzheimer's disease (AD), compared with those treated with placebo.
- Results from a small subset of participants with early AD were consistent with those from the overall study population.

Introduction

- Aducanumab is a human monoclonal antibody selective for aggregated forms of Aβ, including soluble oligomers and insoluble fibrils.[1]
- PRIME is an ongoing Phase 1b study evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of aducanumab in patients with prodromal or mild AD.[1]
- Results from a 12-month interim analysis of fixed-dose and titrated aducanumab have been presented previously.[2]
  - Slowing of decline as measured by the Clinical Dementia Rating–Sum of Boxes (CDR–SB) and Mini-Mental State Examination (MMSE) was observed in the titration and fixed-dose cohorts.[2]

Objective

- The objective of this post hoc analysis of PRIME interim data was to assess change from baseline to Week 54 in cognitive and functional CDR domains in the overall study population and a subpopulation of patients with early AD.

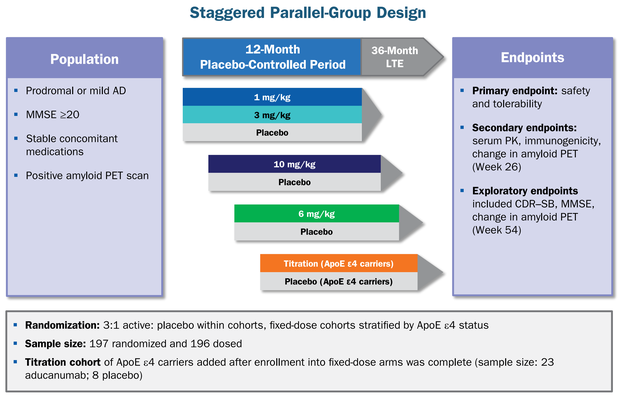
Methods

- This multicenter, randomized, double-blind, placebo-controlled study (PRIME; NCT01677572) enrolled 50- to 90-year-old patients who met clinical criteria for prodromal or mild AD and had a positive florbetapir PET scan.
- During the double-blind, placebo-controlled phase, patients received aducanumab (1, 3, 6, or 10 mg/kg or a titration regimen up to 10 mg/kg [average expected dose: 5.3 mg/kg by 52 weeks]) or placebo once every 4 weeks for 52 weeks in a staggered, parallel-group design, stratified by ApoE ε4 status (**Figure 1**).
- Baseline to Week 54 change in CDR–SB score was an exploratory endpoint.
- Post hoc analysis assessed cognitive and functional domains of the CDR at the Week 54 visit in the overall study population and a subpopulation of patients with early AD, defined as those with CDR global score of 0.5, CDR memory domain score ≥0.5, and MMSE score ≥24.

Results

- A total of 196 patients were randomized and dosed; baseline characteristics are listed in **Table 1.**
- Baseline cognitive and functional CDR domain scores based on the overall study population and a subpopulation of patients with early AD are shown in **Table 2.**
- At Week 54, in the overall population, the adjusted mean changes for the cognitive domain scores were 0.93 (placebo), 0.94 (1 mg/kg), 0.72 (3 mg/kg), 0.49 (6 mg/kg), 0.30 (10 mg/kg), and 0.64 (titration regimen).
- At Week 54, in the overall population, the adjusted mean changes for the functional domain scores were 0.91 (placebo), 0.81 (1mg/kg), 0.67 (3 mg/kg), 0.62 (6 mg/kg), 0.32 (10 mg/kg), and 0.10 (titration regimen).
- Forest plots of adjusted mean change in CDR cognitive and functional domain scores for aducanumab versus placebo in the overall study population and in a subpopulation of patients with early AD are shown in **Figure 2**.

Figure 1. PRIME study design: Placebo-controlled and LTE periods



- **Randomization:** 3:1 active: placebo within cohorts, fixed-dose cohorts stratified by ApoE ε4 status
- **Sample size:** 197 randomized and 196 dosed
- **Titration cohort** of ApoE ε4 carriers added after enrollment into fixed-dose arms was complete (sample size: 23 aducanumab; 8 placebo)

Table 1. 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, 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–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 (%)	30 (63)	21 (68)	28 (88)	20 (67)	17 (53)	12 (52)

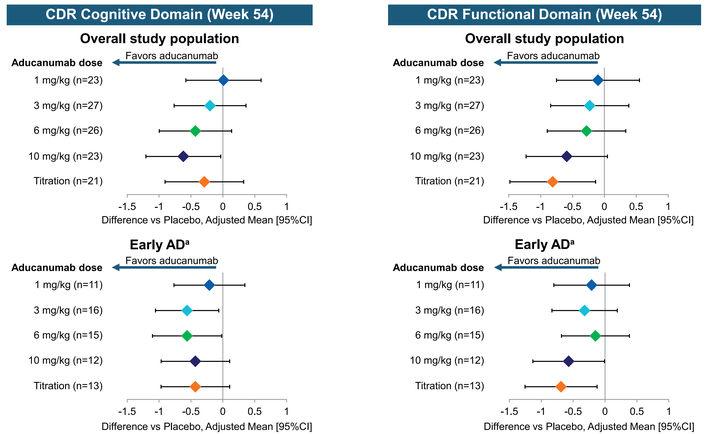
[a]Cholinesterase inhibitors and/or memantine.
ApoE ε4, apolipoprotein E ε4; CDR–SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SD, standard deviation; SUVR, standardized uptake value ratio.

Table 2. CDR cognitive and functional domains, scores at baseline

	Aducanumab					
Overall population (n=196)	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)
CDR cognitive domain score, mean ± SD	1.79 ± 0.87	2.00 ± 0.94	2.20 ± 1.02	2.03 ± 0.67	2.03 ± 1.03	2.04 ± 0.94
CDR functional domain score, mean ± SD	0.90 ± 0.83	1.40 ± 1.09	1.30 ± 1.20	1.28 ± 1.06	1.11 ± 0.90	1.20 ± 1.15
	Aducanumab					
Early AD sub-population[a] (n=110)	Placebo (n=29)	1 mg/kg (n=14)	3 mg/kg (n=18)	6 mg/kg (n=17)	10 mg/kg (n=18)	Titration (n=14)
CDR cognitive domain score, mean ± SD	1.31 ± 0.47	1.36 ± 0.57	1.58 ± 0.60	1.97 ± 0.60	1.47 ± 0.74	1.64 ± 0.86
CDR functional domain score, mean ± SD	0.53 ± 0.57	0.96 ± 0.91	0.58 ± 0.60	0.88 ± 0.52	0.69 ± 0.46	0.86 ± 0.46

[a]Defined as those with CDR global score of 0.5, CDR memory domain score ≥0.5, and MMSE score ≥24.
CDR, Clinical Dementia Rating; SD, standard deviation.

Figure 2. Changes in CDR cognitive and functional domain scores at Week 54



[a]Defined as those with CDR global score of 0.5, CDR memory domain score ≥0.5, and MMSE score ≥24. CDR, Clinical Dementia Rating; CI, confidence interval. Adjusted mean changes and 95% confidence intervals are based on an ANCOVA model for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR domain score.

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This poster reflects a new analysis of previously reported data.

References 1. Sevigny et al. *Nature.* 2016;537:50–5. 2. Viglietta V, et al. *J Prev Alz Dis.* 2016;3:278. Data presented at CTAD 2016. **Disclosures** This study is funded by Biogen. Medical writing support and editing for this presentation was funded by Biogen and was provided by Nucleus Global. JO, TC, SBH, and AS are employees and/or shareholders of Biogen. VV, LW and AE were employees and shareholders of Biogen while this work was completed. AE and VV are employees of Amgen. LW is an employee at SAGE Therapeutics. CH and RMN are employees and shareholders of Neurimmune. **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.