Aducanumab 48-month analyses from PRIME, a Phase 1b study in patients with early Alzheimer's disease

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Conclusions

- Amyloid plaque levels continued to decrease in a dose- and time-dependent manner in patients treated with aducanumab who completed the first three years of the long-term extension (LTE).
  - Mean amyloid plaque levels in the 10 mg/kg fixed-dose cohort reached and remained at a standardized uptake value ratio (SUVR) level below 1.1, which is considered the quantitative cut-point suggested to discriminate between a positive and negative scan.[1]
- Analyses of exploratory clinical endpoints Clinical Dementia Rating Scale–Sum of Boxes (CDR–SB) and Mini Mental State Examination (MMSE) suggest clinical benefit in patients continuing aducanumab over 48 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 Alzheimer's disease (AD) in the ENGAGE and EMERGE Phase 3 trials.

Introduction

- Aducanumab (BIIB037) is a human anti-amyloid beta monoclonal antibody that binds to both soluble and insoluble aggregated forms of amyloid beta, including oligomers, protofibrils, and fibrils.[2,3]
- PRIME is an ongoing Phase 1b study assessing the safety, tolerability, pharmacokinetics, and pharmacodynamics of aducanumab in patients with prodromal or mild AD.[1]
- Here, we report 48-month results from the fixed-dose cohorts of PRIME, including 12 months from the placebo-controlled period and 36 months from the LTE.

Objective

- To report amyloid positron emission tomography (PET) data and clinical data at 48 months follow up, including cumulative safety data for aducanumab as of the cutoff date of the most recent interim analysis.

Methods

- In this randomized, double-blind, placebo-controlled study (NCT01677572), patients (50–90 years old; prodromal/mild AD; positive florbetapir PET read) were randomized 3:1 to cohorts of fixed aducanumab doses or placebo.
- After completion of fixed-dose cohort enrollment, a cohort of ApoE ε4 carriers was added who received either aducanumab titrated to 10 mg/kg or placebo.
  - As patients in the titration cohort have not yet completed the third year of the LTE, only data from patients originally assigned to fixed-dose cohorts during the placebo-controlled period are presented here.
- Patients meeting eligibility criteria at Week 56 could enroll in the LTE, where all patients were assigned to receive aducanumab 3, 6, or 10 mg/kg, fixed or titrated (**Figure 1**).
- The primary endpoint in PRIME is safety/tolerability.
- Exploratory endpoints in the LTE include changes in amyloid PET and measures of clinical decline such as CDR-SB and MMSE.

Results

48-month efficacy data for fixed-dose cohorts

- Of 165 patients randomized and dosed in PRIME within the fixed-dose cohorts, 117 were dosed in the LTE and 59 completed treatment at Month 48.
  - Baseline characteristics are shown in **Table 1**.
- In patients treated up to 48 months, amyloid plaque levels as measured by PET, continued to decrease in a dose- and time-dependent manner (**Figure 2**).
  - Mean amyloid plaque levels in the 10 mg/kg fixed-dose treatment group reached and remained at an SUVR level below 1.1, which is considered a quantitative cut-point suggested to discriminate between a positive and negative scan.[1]
- CDR–SB and MMSE data suggest a clinical benefit in patients continuing aducanumab over 48 months (**Figure 3**).

Cumulative safety data for fixed-dose cohorts

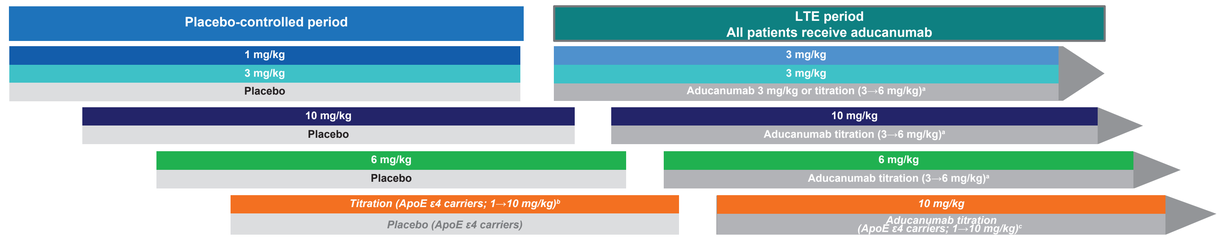
- Cumulative aducanumab safety data for adverse events (AEs) and serious adverse events (SAEs) during the combined placebo-controlled and LTE periods after first exposure to aducanumab are shown in **Table 2**.
  - Based on incidence reporting by preferred term, the most common AEs (incidence ≥ 15%) were amyloid-related imaging abnormalities (ARIA), headache, fall, urinary tract infection, upper respiratory tract infection and diarrhea.
  - The most common SAE (incidence > 5%) was ARIA (n=16 [10%]).
- There were a total of 8 deaths: 2 patients received placebo (1 died after leaving the study) and 6 patients received aducanumab.
- The incidence of ARIA-E (ARIA-vasogenic edema) and ARIA-H (ARIA-microhemorrhages, macrohemorrhages, or superficial siderosis) is listed in **Table 3**.

ARIA characteristics since the start of PRIME in 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 those 46 patients, 61% were asymptomatic and 39% had associated symptoms, which were typically mild
    - ARIA-E tended to occur early in the course of treatment most often within the first 6 months of the first active dose.
    - ARIA events typically resolved or stabilized within 4-12 weeks, with most patients continuing treatment.
  - 8 patients experienced more than one event of ARIA-E.
    - Clinical and imaging characteristics of recurrent ARIA-E were similar to those of ARIA-E previously reported in the PRIME study.

References 1. Joshi AD, et al. J Nucl Med. 2015;56:1736-1741. **2.** Sevigny et al. Nature. 2016;537:50–56. **3.** Data on file. **Disclosures** PvR, SBH, CCV, TC, JO, RR, DP, GW, SC, LS, CP, and AS are employees and shareholders of Biogen. GW is an employee of Cytel. CH and RMN are employees and shareholders of Neurimmune. **Acknowledgments** This study was sponsored by Biogen (Cambridge, MA, USA). Writing and editorial support for the preparation of this poster was provided by Nucleus Global and was funded by Biogen. 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.

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
- 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**")

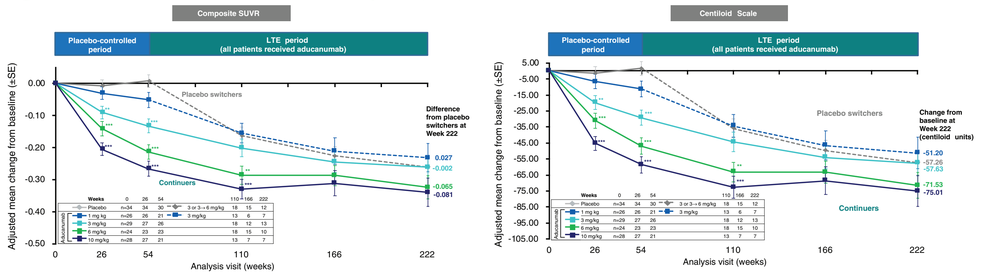
[a]Titration denotes 2 doses of 3 mg/kg followed by subsequent doses of 6 mg/kg. [b]Data from the titration cohort are not included in this analysis as 48-month data from this cohort are not yet available. [c]Titration denotes 2 doses of 1 mg/kg, 4 doses of 3 mg/kg, 5 doses of 6 mg/kg followed by subsequent doses of 10 mg/kg.
ApoE ε4, Apolipoprotein E ε4; LTE, long-term extension.

Table 1. Baseline disease characteristics

		Aducanumab			
	Placebo (n=40)	1 mg/kg (n=31)	3 mg/kg (n=32)	6 mg/kg (n=30)	10 mg/kg (n=32)
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)

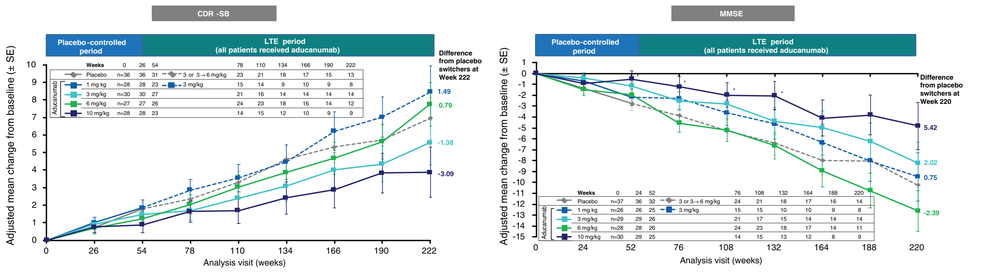
[a]Cholinesterase inhibitors and/or memantine.
AD, Alzheimer's disease; ApoE ε4, Apolipoprotein E ε4; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SD, standard deviation; SUVR, standardized uptake value ratio.

Figure 2. Effect of aducanumab on amyloid plaque levels



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; PBO, placebo.

Figure 3. Effect of aducanumab on clinical decline (exploratory endpoints)



Nominal *P<0.05 vs placebo in the placebo-controlled period and vs placebo switchers in the LTE period. CDR-SB and MMSE are exploratory endpoints. 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; MMSE, Mini-Mental State Exam; PBO, placebo; SE, standard error.

Table 2. Cumulative safety of aducanumab

	Placebo Switchers[a] (n=29)	1 mg/kg → 3 mg/kg (n=31)	Continuers[b] 3 mg/kg (n=32)	Continuers[b] 6 mg/kg (n=30)	Continuers[b] 10 mg/kg (n=32)
Number with an AE (%)	29 (100)	29 (94)	29 (91)	30 (100)	29 (91)
Number with an SAE (%)	19 (66)	11 (35)	10 (31)	14 (47)	16 (50)
Number discontinuing treatment due to AE (%)	11 (38)	4 (13)	4 (13)	4 (13)	16 (50)

[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.
AE, adverse event; ARIA, amyloid-related imaging abnormality; LTE, long-term extension; SAE, serious AE.

Table 3. Cumulative ARIA-E incidence for aducanumab

	Placebo Switchers[c]	1 mg/kg → 3 mg/kg	Continuers[d] 3 mg/kg	Continuers[d] 6 mg/kg	Continuers[d] 10 mg/kg
Patients with at least 1 post-baseline MRI	29	31	32	30	32
ARIA-E[a], n/total (%)	6/29 (21)	4/31 (13)	2/32 (6)	11/30 (37)	13/32 (41)
ApoE ε4 carriers	5/17 (29)	4/19 (21)	1/21 (5)	9/21 (43)	11/20 (55)
ApoE ε4 non-carriers	1/12 (8)	0/12	1/11 (9)	2/9 (22)	2/12 (17)
Discontinued treatment,[b] n (%)	5 (17)	1 (3)	0 (0)	3 (10)	9 (28)
Isolated ARIA-H, n (%)	2 (7)	1 (3)	7 (22)	2 (7)	2 (6)

[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.