# Disclaimer

The following materials, which have been posted in the “Medical and Scientific Conferences Presentations” IR section of the Biogen website, are provided for informational purposes to the investor community only and may include information about investigational compounds that have not been approved by the applicable regulatory authorities as safe and effective.

# 24-Month Analysis of ApoE ε4 carriers in PRIME, a Randomized Phase 1b Study of the Anti-Amyloid Beta Monoclonal Antibody Aducanumab

P1-041

Philipp von Rosenstiel, MD[1], Carmen Castrillo-Viguera, MD[1], Sarah Gheuens, MD, PhD[1], Tianle Chen, PhD[1], John O'Gorman, PhD[1], Ping Chiao, PhD[2], Guanfang Wang, PhD[3], Christian von Hehn, MD, PhD[1], LeAnne Skordos, PharmD[1], Christoph Hock, MD[4], Roger M Nitsch, MD[4], Samantha Budd Haeberlein, PhD[1], Alfred Sandrock, MD, PhD[1]

[1]Biogen, Cambridge, MA, USA; [2]Former employee of Biogen, Cambridge, MA, USA; [3]Cytel, Cambridge, MA, USA; [4]Neurimmune, Schlieren-Zurich, and University of Zurich, Switzerland

## Conclusions

- At 24 months, in this subgroup analysis of ApoE ε4 carriers from both fixed-dose and titration cohorts, amyloid plaque levels continued to decrease.
- The clinical endpoints, CDR–SB and MMSE, suggest continued benefit of aducanumab treatment in ApoE ε4 carriers over 24 months.
- No new safety signals were identified in ApoE ε4 carriers.
- 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.

## Introduction

- Aducanumab binds to both soluble and insoluble aggregated forms of Aβ, including oligomers, protofibrils, and fibrils.[1]
- Treatment with aducanumab in the Ph1b study (PRIME) resulted in a time and dose dependent removal of plaques from the brain as shown by positron emission tomography (PET) standardized uptake value ratio.[1]
- Patients with early AD enrolled in PRIME experienced a sustained delay in the disease progression as measured by exploratory clinical endpoints at 12, 24 and 36 months.[1-3]
- Here, we report 24-month results from ApoE ε4 carriers in PRIME, including 12 months from the placebo-controlled period and 12 months from the long-term extension (LTE).

## Objective

- To describe the effect of aducanumab on ApoE ε4 carriers from both fixed-dose and titration cohorts in the PRIME study.

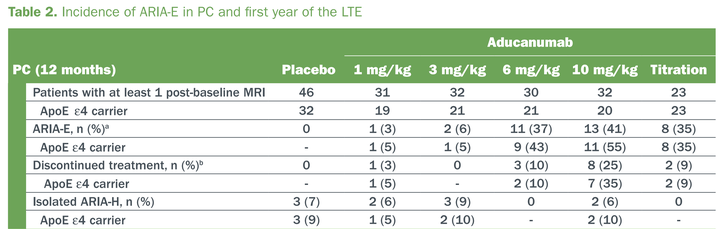
## Methods

- In this randomized, double-blind, placebo-controlled study (NCT01677572), patients (50–90 years; prodromal/mild AD; positive florbetapir positron emission tomography [PET] read) were randomized 3:1 to cohorts of fixed aducanumab doses or placebo every 4 weeks for 52 weeks, stratified by ApoE ε4 status (**Figure 1**).
- After completion of fixed-dose cohort enrollment, a cohort consisting of only ApoE ε4 carriers and a corresponding placebo group was added who received titrated aducanumab (1 mg/kg [2 doses]; 3 mg/kg [4 doses]; 6 mg/kg [5 doses]; 10 mg/kg thereafter) or placebo (**Figure 1**).
  - The average expected dose for patients in the titration cohort was 2.9 mg/kg, 5.3 mg/kg, and 7.6 mg/kg, by Week 24, Week 52, and Week 110, respectively.
- Patients meeting eligibility criteria at Week 56 were enrolled 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 the LTE was safety/tolerability.
- Exploratory endpoints included changes in amyloid PET and measures of clinical decline on the Clinical Dementia Rating–Sum of Boxes (CDR–SB) and Mini-Mental State Examination (MMSE).

## Results

- 138 (70%) of 196 patients randomized and dosed in PRIME and 100 (70%) of the 143 patients dosed in the LTE were ApoE ε4 carriers.
  - Baseline characteristics of ApoE ε4 carriers are shown in **Table 1**.
- ARIA occurred more frequently in ApoE ε4 carriers (n=17 [17%]) as compared with noncarriers (n=3 [7%]) in the LTE; the most common serious adverse event in ApoE ε4 carriers in the LTE was ARIA (n=4 [4%]).
- Incidence of ARIA-E in ApoE ε4 carriers switching from placebo to aducanumab in the LTE was consistent with that reported in the placebo-controlled portion of the study (**Table 2**).
- ApoE ε4 carriers who continued aducanumab treatment up to 24 months experienced continued reductions in brain amyloid plaque levels, as measured by PET (**Figure 2**).
- CDR-SB and MMSE data suggest clinical benefit on the rate of clinical decline in ApoE ε4 carriers continuing aducanumab over 24 months (**Figure 3**).

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




ApoE ε4, Apolipoprotein E ε4; LTE, long-term extension.
[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.

**Table 1.** Baseline disease characteristics in 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, n (%)[a] | 22 (65) | 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.

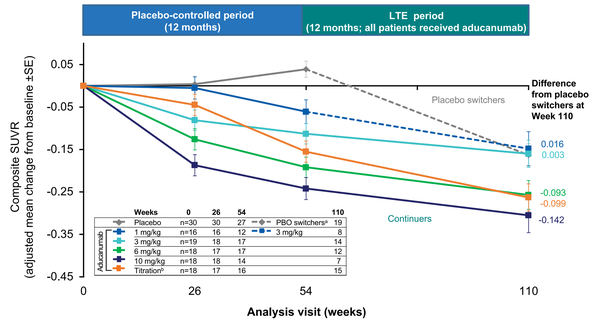
**Table 2.** Incidence of ARIA-E in PC and first year of the LTE

| | | Aducanumab | | | |
|---|---|---|---|---|---|
| **PC (12 months)** | **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 |
| ApoE ε4 carrier | 32 | 19 | 21 | 21 | 20 | 23 |
| ARIA-E, n (%)[a] | 0 | 1 (3) | 2 (6) | 11 (37) | 13 (41) | 8 (35) |
| ApoE ε4 carrier | - | 1 (5) | 1 (5) | 9 (43) | 11 (55) | 8 (35) |
| Discontinued treatment, n (%)[b] | 0 | 1 (3) | 0 | 3 (10) | 8 (25) | 2 (9) |
| ApoE ε4 carrier | - | 1 (5) | - | 2 (10) | 7 (35) | 2 (9) |
| Isolated ARIA-H, n (%) | 3 (7) | 2 (6) | 3 (9) | 0 | 2 (6) | 0 |
| ApoE ε4 carrier | 3 (9) | 1 (5) | 2 (10) | - | 2 (10) | - |

| | | | Continuers[c] | | | |
|---|---|---|---|---|---|---|
| **LTE (12 months)** | **Placebo Switchers[d]** | **1 mg/kg → 3 mg/kg** | **3 mg/kg** | **6 mg/kg** | **10 mg/kg** | **Titration** |
| Patients with at least 1 MRI in the LTE | 37 | 17 | 23 | 24 | 19 | 18 |
| ApoE ε4 carrier | 25 | 11 | 16 | 17 | 12 | 18 |
| ARIA-E, n (%)[a] | 7 (19) | 3 (18) | 0 | 0 | 0 | 2 (11) |
| ApoE ε4 carrier | 6 (24) | 3 (27) | - | - | - | 2 (11) |
| Discontinued treatment, n (%)[b] | 4 (11) | 0 | - | - | - | 1 (6) |
| ApoE ε4 carrier | 3 (12) | - | - | - | - | 1 (6) |
| Isolated ARIA-H, n (%) | 2 (5) | 0 | 3 (13) | 2 (8) | 1 (5) | 0 |
| ApoE ε4 carrier | 1 (4) | - | 2 (13) | 2 (12) | 1 (8) | - |

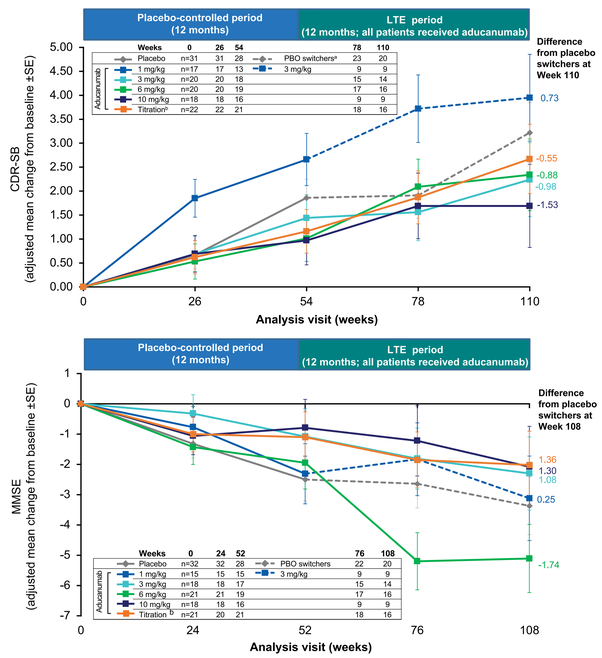
ApoE ε4, Apolipoprotein E ε4; ARIA-E, ARIA–vasogenic edema; ARIA-H, ARIA–microhemorrhages, macrohemorrhages, or superficial siderosis; MRI, magnetic resonance imaging; PC, placebo-controlled period.
[a]ARIA-E with or without ARIA-H. [b]ARIA-E and either 1) no doses after onset of ARIA-E or 2) have subsequent discontinuation due to ARIA. [c]Patients who were randomized to receive 3, 6, and 10 mg/kg were scheduled to receive the same dose throughout the LTE. [d]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. Incidence of ARIA based on MRI. 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.

**Figure 2.** Effect of aducanumab on amyloid plaques levels in ApoE ε4 carriers




ApoE ε4, Apolipoprotein E ε4; LTE, long-term extension period; MMRM, mixed model for repeated measures; PBO, placebo; SE, standard error; SUVR, standardized uptake value ratio.
[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]For titration cohort: average expected dose 5.3 mg/kg by week 52 and 7.6 mg/kg by week 110. Results based on MMRM model, fitted with change from baseline as dependent variable and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction and continuous baseline value.

**Figure 3.** Effect of aducanumab on exploratory clinical endpoints in ApoE ε4 carriers




ApoE ε4, Apolipoprotein E ε4; CDR-SB, Clinical Dementia Rating–Sum of Boxes; LTE, long-term extension period; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; PBO, placebo; SE, standard error.
[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]For titration cohort: average expected dose 5.3 mg/kg by week 52 and 7.6 mg/kg by week 110. CDR-SB and MMSE are exploratory endpoints. Results based on MMRM model, fitted with change from baseline as dependent variable and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction and continuous baseline value.

**References 1.** Sevigny et al. *Nature*. 2016;537:50–56. **2.** Viglietta V, et al. *J Prev Alz Dis* 2016;3:284. Data presented at CTAD 2016. **3.** Budd Haeberlein S, et al. *J Prev Alz Dis* 2017;4:313. Data presented at CTAD 2017. **Disclosures** PvR, CC, SG, TC, JO, CvH, LS, SBH, and AS are employees and shareholders of Biogen. PC is a former employee of Biogen. GW is an employee of Cytel. CH and RMN are employees and shareholders of Neurimmune. Biogen licensed the worldwide rights to aducanumab from Neurimmune Holding AG in 2007 and is responsible for its development and the commercialization. As of October 22, 2017, Biogen and Eisai are collaborating on the development and commercialization of aducanumab globally. **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.