Cumulative aducanumab safety data from PRIME: a randomized, double-blind, placebo-controlled, Phase 1b study

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Conclusions

- In the PRIME study, incident ARIA-E appeared to be dose-dependent.
- ARIA-E was observed more frequently in ApoE ε4 carriers.
  - However, incidence of ARIA-E (± ARIA-H), appeared lower in ApoE ε4 carriers receiving titration to 10 mg/kg compared with carriers receiving fixed-dose regimens of 6 mg/kg or 10 mg/kg.
- ARIA-E tended to occur early in the course of treatment.
- Recurrent ARIA events were consistent with other ARIA events reported to date in the PRIME study.
- The majority of ARIA events occurred early in the course of treatment; they were typically asymptomatic, and resolved or stabilized within 4-12 weeks, with most patients continuing treatment.

Introduction

- Aducanumab (BIIB037) is a human anti-amyloid beta (Aβ) monoclonal antibody that binds to both soluble and insoluble aggregated forms of amyloid beta, including oligomers, protofibrils, and fibrils.[1,2]
- PRIME is an ongoing Phase 1b study investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of aducanumab in patients with prodromal or mild Alzheimer's disease.[1]
- In previously presented interim analyses of PRIME, patients treated with aducanumab experienced dose- and time- dependent decreases in amyloid plaque levels accompanied by slowed clinical decline in patients from titration and fixed-dose cohorts.[3,4]
- Amyloid related imaging abnormalities (ARIA), are imaging findings measured by magnetic resonance imaging (MRI) that have been associated with Aβ-lowering therapies, and in PRIME, are reported as adverse events.
  - ARIA include ARIA-E (ARIA with vasogenic edema) and ARIA-H (ARIA with microhemorrhage, macrohemorrhage, or superficial siderosis).
  - Management of ARIA-E and ARIA-H has evolved during the PRIME study with current management allowing patients with asymptomatic mild ARIA (ARIA-E or ARIA-H) to continue treatment and patients with moderate to severe or symptomatic ARIA (ARIA-E or ARIA-H) to suspend or discontinue treatment.

Objective

- To report cumulative aducanumab safety data from PRIME, including data from the 12-month placebo-controlled period and long-term extension (LTE) as of the last interim analysis after first exposure to aducanumab.

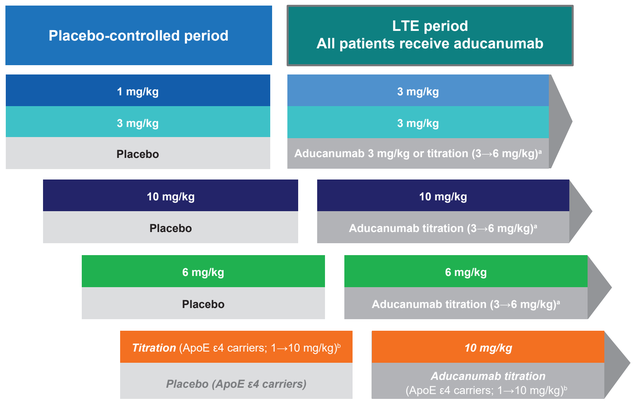
Methods

- 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.
- 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

- Of the 196 patients who were randomized and dosed in PRIME, 185 patients have been dosed with aducanumab and had at least 1 post-baseline MRI.
  - Baseline characteristics are shown in **Table 1**.
- Aducanumab safety data for adverse events (AEs) and serious adverse events (SAEs) during the 12-month placebo-controlled period is shown in **Table 2**.
- Cumulative aducanumab safety data for AEs and SAEs during the combined placebo-controlled period and LTE after first exposure to aducanumab are shown in **Table 3.**
  - Based on incidence reporting by preferred term, the most common AEs (incidence ≥ 15%) were ARIA, headache, fall, urinary tract infection, diarrhea, nasopharyngitis and upper respiratory tract infection.
  - The most common AE that led to treatment discontinuation was ARIA.
- Incidence of ARIA during the 12-month placebo-controlled period is shown in **Table 4**.
  - The incidence of ARIA-E in fixed-dose cohorts was dose-dependent and was higher in ApoE ε4 carriers.
  - Incidence of ARIA-E was lower in ApoE ε4 carriers receiving aducanumab titrated to 10 mg/kg (35%) than in ApoE ε4 carriers receiving higher fixed-doses of 6 mg/kg (43%) or 10 mg/kg (55%) aducanumab.
  - Incidence of ARIA-H not accompanied by ARIA-E was low and similar across dose groups, including placebo, and likely indicates a background rate of ARIA-H in this population.
- Cumulative incidence of ARIA during the combined placebo-controlled period and LTE after first exposure to aducanumab is shown in **Table 5.**
  - Since the start of the PRIME study, ARIA-E has been observed in 46 of the 185 patients dosed with aducanumab, with a cumulative incidence of 25% over the course of the study.
  - ARIA-E tended to occur early in the course of treatment.
    - ARIA-E most often occurred within the first 6 months of the first active dose of aducanumab.
    - First-onset ARIA-E typically occurred between the 1st and 5th doses of active aducanumab treatment (n=31 for between doses 1-5, n=8 between doses 6-10, n=5 between doses 11-20, n=1 between doses 21-30, and n=1 for >30 doses).
  - Of the 46 patients with ARIA-E (± ARIA-H), 28 (61%) were asymptomatic and 18 (39%) had associated symptoms, which were typically mild with the most common symptoms being headache, dizziness and confusional state.
  - ARIA-E (± ARIA-H) resolved on MRI in 44 of 46 patients and was ongoing in 2 patients at the time of study withdrawal.
    - In most cases, ARIA-E (± ARIA-H) resolved 4 to 12 weeks after onset, as assessed by MRI.
  - Most patients with ARIA-E (± ARIA-H) continued treatment.
  - 8 patients experienced more than one event of ARIA-E, termed recurrent ARIA-E (± ARIA-H).
    - Clinical and imaging characteristics of recurrent ARIA-E were similar to those of ARIA-E previously reported in the PRIME study.

Figure 1. PRIME study design



- **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.

Table 1. Baseline disease characteristics

	Placebo (n=48)	Aducanumab 1 mg/kg (n=31)	Aducanumab 3 mg/kg (n=32)	Aducanumab 6 mg/kg (n=30)	Aducanumab 10 mg/kg (n=32)	Aducanumab 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.

Table 2: Summary of adverse events during the placebo-controlled period

	Placebo (n=48)	Aducanumab 1 mg/kg (n=31)	Aducanumab 3 mg/kg (n=32)	Aducanumab 6 mg/kg (n=30)	Aducanumab 10 mg/kg (n=32)	Aducanumab 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)	4 (17)
Common adverse events, n (%)[a]						
Amyloid-related imaging abnormalities (ARIA)	3 (6)	2 (6)	4 (13)	11 (37)	15 (47)	8 (35)
Headache	4 (8)	5 (16)	4 (13)	8 (27)	9 (28)	6 (26)

[a]Common adverse events are those with an incidence of ≥15% in the total aducanumab treatment group.
AE, adverse event; SAE, serious adverse event.

Table 3. Cumulative safety of aducanumab

	Placebo Switchers[c] (n=37)	1 mg/kg → 3 mg/kg (n=31)	Continuers[d] 3 mg/kg (n=32)	Continuers[d] 6 mg/kg (n=30)	Continuers[d] 10 mg/kg (n=32)	Continuers[d] Titration to 10 mg/kg (n=23)
Adverse event, n (%)	37 (100)	29 (94)	29 (91)	30 (100)	29 (91)	23 (100)
Serious adverse event, n (%)	21 (57)	11 (35)	10 (31)	14 (47)	16 (50)	9 (39)
Death[a], n (%)	1 (3)	1 (3)	1 (3)	1 (3)	2 (6)	0 (0)
Common adverse events n (%)[b]						
Amyloid-related imaging abnormalities	10 (27)	5 (16)	8 (25)	13 (43)	15 (47)	8 (35)
Headache	10 (27)	7 (23)	8 (25)	9 (30)	13 (41)	6 (26)
Fall	9 (24)	9 (29)	9 (28)	9 (30)	6 (19)	6 (26)
Urinary tract infection	7 (19)	6 (19)	3 (9)	7 (23)	7 (22)	6 (26)
Diarrhea	3 (8)	1 (3)	10 (31)	5 (17)	5 (16)	5 (22)
Nasopharyngitis	6 (16)	3 (10)	7 (22)	3 (10)	4 (13)	6 (26)
Upper respiratory tract infection	5 (14)	3 (10)	4 (13)	7 (23)	6 (19)	3 (13)
Adverse events leading to discontinuation of treatment, n (%)	11 (30)	4 (13)	4 (13)	4 (13)	16 (50)	3 (13)

[a]There were 2 deaths in patients who received only placebo treatment (one patient died after leaving the study). [b]Common adverse events are those with an incidence of ≥15% in the total aducanumab treatment group. [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. Preferred terms are presented by decreasing incidence in the total aducanumab treatment group (not shown).

Table 4. Incidence of ARIA during the placebo-controlled period

	Placebo	Aducanumab 1 mg/kg	Aducanumab 3 mg/kg	Aducanumab 6 mg/kg	Aducanumab 10 mg/kg	Aducanumab Titration
Patients with at least 1 post-baseline MRI	46	31	32	30	32	23
ARIA-E[a], n/total (%)	0/46	1/31 (3)	2/32 (6)	11/30 (37)	13/32 (41)	8/23 (35)
ApoE ε4 carriers	0/32	1/19 (5)	1/21 (5)	9/21 (43)	11/20 (55)	8/23 (35)
ApoE ε4 non-carriers	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
Isolated ARIA-E, n (%)	0/46 (0)	0/31 (0)	1/32 (3)	6/30 (20)	5/32 (16)	2/23 (9)

Incidence of ARIA based on MRI. [a]ARIA-E with or without ARIA-H.
ARIA-E, ARIA–vasogenic edema; ARIA-H, ARIA–microhemorrhages, macrohemorrhages, or superficial siderosis; MRI, magnetic resonance imaging.

Table 5. 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	Continuers[d] Titration to 10 mg/kg
Patients with at least 1 post-baseline MRI	37	31	32	30	32	23
ARIA-E[a], n/total (%)	8/37 (22)	4/31 (13)	2/32 (6)	11/30 (37)	13/32 (41)	8/23 (35)
ApoE ε4 carriers	7/25 (28)	4/19 (21)	1/21 (5)	9/21 (43)	11/20 (55)	8/23 (35)
ApoE ε4 non-carriers	1/12 (8)	0/12 (0)	1/11 (9)	2/9 (22)	2/12 (17)	-
ARIA-E categorization, n/patients with ARIA-E (%)						
Asymptomatic	3/8 (38)	2/4 (50)	1/2 (50)	7/11 (64)	8/13 (62)	7/8 (88)
Symptomatic	5/8 (63)	2/4 (50)	1/2 (50)	4/11 (36)	5/13 (38)	1/8 (13)
Discontinued treatment,[b] n/total (%)	5/37 (14)	1/31 (3)	0/32 (0)	3/30 (10)	9/32 (28)	2/23 (9)
ApoE ε4 carriers	4/25 (16)	1/19 (5)	-	2/21 (10)	8/20 (40)	2/23 (9)
ApoE ε4 non-carriers	1/12 (8)	0/12 (0)	-	1/9 (11)	1/12 (8)	-
Isolated ARIA-H, n/total (%)	2/37 (5)	1/31 (3)	7/32 (22)	2/30 (7)	2/32 (6)	0/23 (0)
ApoE ε4 carriers	1/25 (4)	0/19 (0)	5/21 (24)	2/21 (10)	2/20 (10)	-
ApoE ε4 non-carriers	1/12 (8)	1/12 (8)	2/11 (18)	0/9 (0)	0/12	-
Isolated ARIA-E, n/total (%)	3/37 (8)	2/31 (6)	1/32 (3)	5/30 (17)	5/32 (16)	2/23 (9)
ApoE ε4 carriers	3/25 (12)	2/19 (11)	0/21 (0)	3/21 (14)	4/20 (20)	2/23 (9)
ApoE ε4 non-carriers	0/12 (0)	0/12 (0)	1/11 (9)	2/9 (22)	1/12 (8)	-

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

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