Introduction

Aducanumab (BIIB035) 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.3

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.4

Amyloid-related imaging abnormalities (ARIAs), 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 strategies for 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 (NCT03677772), patients (50-90 years old; prodromal/mild AD; positive florbetapir PET read) were randomized 3:1 to cohorts of fixed aducanumab doses or placebo.

As of the conclusion of the overall study, 37% of patients in the PRIME study received placebo, 50% received aducanumab 3 mg/kg or titration (3 mg/kg → 6 mg/kg), and 13% received aducanumab 6 mg/kg. Patients randomized to receive 3, 6, and 10 mg/kg were scheduled to receive the same dose throughout the LTE. Patients who received aducanumab as part of the LTE were scheduled to receive 3 mg/kg for 10 months or titration (3 mg/kg → 6 mg/kg or 6 mg/kg → 10 mg/kg) until study completion. Patients who received placebo as part of the LTE were scheduled to receive placebo for 10 months.

Results

Of the 526 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.

- 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 2.

- Based on incidence reporting by preferred term, the most common AE (incidence ≥ 15%) was 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 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 26% 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.

- Of the 40 patients with ARIA-E, 28 (61%) were asymptomatic and 13 (31%) had associated symptoms, which were typically mild with the most common symptoms being headache, dizziness and confusion/nasal stuffiness.

- 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.


- 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.