Introduction

Aducanumab is a human, immunoglobulin gamma 1 monoclonal antibody directed against aggregated soluble and insoluble forms of Aβ.1

Aducanumab is the first FDA-approved Alzheimer’s disease treatment that reduces Aβ plaques, a defining pathophysiological feature of Alzheimer’s disease.2

The efficacy of aducanumab was evaluated in two Phase 3, double-blind, randomized, placebo-controlled, parallel-group studies in patients with Alzheimer’s disease (EMERGE, NCT03405447 and ENGAGE, NCT03471850). EMERGE and ENGAGE were terminated prior to their planned completion; study endpoints were analyzed based on the prespecified statistical analysis plan. The effects of aducanumab were supported by a Phase 1b, double-blind, randomized, placebo-controlled, dose-ranging study (PRIME, NCT03179797).3

EMERGE demonstrated a statistically significant drug-placebo difference in the prespecified primary and secondary clinical endpoints.4

This analysis tested the consistency of aducanumab treatment effects across multiple domains within clinical assessments.

Methods

EMERGE data were analyzed (ENGAGE did not meet the primary endpoint). ENGAGE (N=1643) included participants aged 50-85 years with confirmed presence of amyloid pathology and mild cognitive impairment or mild dementia, consistent with Stage 3 and Stage 4 Alzheimer’s disease.5

Aducanumab or placebo was administered via intravenous infusion every 4 weeks over 76 weeks (20 doses total); details on the trial design, patient population, and full analysis have been described.6

Participants were randomized to receive high-dose aducanumab, low-dose aducanumab, or placebo. Baseline characteristics are shown in Table 1.

The primary endpoint was change from baseline in CDR-SB score at Week 78. Secondary outcome measures were MBI-E, ADAS-Cog13, and ADCS-ADL-MCI scores. NPI was a tertiary clinical outcome measure.

Item-level analyses using mixed model for repeated measures were conducted on these clinical efficacy endpoints using the ITT population. Due to deviation from the normality assumption, this analysis is considered descriptive and, thus, no multiplicity adjustment was considered.

Results

At Week 78, treatment effects were observed across all 6 domains of the CDR (Figure 1).

An aducanumab treatment effect was evident by slowing of decline on the ADAS-Cog13 item that are sensitive to change in early symptomatic Alzheimer’s disease (e.g., word recognition, orientation, word recall [immediate and delayed], and number cancellation) (Figure 2).

The clinical benefit of aducanumab with respect to presenting daily function was observed across a broad range of items on the ADCS-ADL-MCI (Figure 3).

Aducanumab treatment was associated with a reduction in the behavioral and psychiatric symptoms associated with Alzheimer’s disease, as measured by NPI-10 (Figure 4).

CONCLUSIONS

To examine the treatment benefit of high-dose aducanumab across individual items/domains in the primary, secondary, and tertiary clinical endpoints in EMERGE.

The item-level analyses are consistent with the results from the primary analysis of the clinical endpoints.

The aducanumab high-dose group showed a consistent drug-placebo difference across 5 clinical efficacy endpoints, slowing clinical decline over 78 weeks.

The results demonstrate the consistency of the aducanumab treatment effect in slowing decline across cognitive, functional, and behavioral domains in early Alzheimer’s disease.