2. STUDY SYNOPSIS

Name of Company: Eisai Inc., Eisai Ltd., Eisai Co., Ltd.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Elenbecestat tablet	Referring to Module 5 of the Dossier	
Name of Active Ingredient: Elenbecestat	Volume: Page:	

Study Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease

Investigators/Sites

E2609-G000-301: Roy William Jones, BSc, MBBS, FRCP, DipPharmMed (principal investigator), et al.

E2609-G000-302: Haruhiko Akiyama, MD (principal investigator), et al.

Multicenter: 426 sites in the following regions: North America (131), Western Europe (including Oceania region and South Africa [107]), Eastern Europe (40), Japan (83), China (20), Other Asian countries (26), and South America (19) (refer to Appendix 16.1.4 for the list of investigators and sites)

Publication (Reference)

None.

Study Period

E2609-G000-301: 20 Oct 2016 to 15 Jan 2020

E2609-G000-302: 29 Dec 2016 to 14 Jan 2020

Phase of Development

Phase 3

Core Study Objectives

Studies E2609-G000-301 and E2609-G000-302 (Studies 301 and 302) were terminated early by the sponsor following the recommendation of an independent Data Safety Monitoring Board (DSMB) who concluded that for those on active drug treatment there was no evidence of potential efficacy, and the adverse event (AE) profile was worse than placebo. As a result of the early termination of the studies, some secondary, biomarker, and exploratory objectives were modified, added, or deleted as specified below.

Primary Objective

- To determine whether elenbecestat is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD) pooled across studies E2609-G000-301 and E2609-G000-302

Key Secondary Objectives

- To determine whether elenbecestat is superior to placebo on the change from baseline in Alzheimer's Disease Composite Score (ADCOMS) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD in each study. Deleted objective: The analyses to support this objective were not conducted

Other Secondary Objectives

- To evaluate the safety and tolerability of elenbecestat in subjects with EAD
- To determine whether elenbecestat is superior to placebo on the change from baseline in the CDR-SB at 24 months for subjects with EAD enriched by baseline PET standardized uptake value ratio (SUVR) pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the change from baseline in ADCOMS at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores by 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302. Modified objective: Instead of evaluating change from baseline at 27 months, analyses were conducted to evaluate the change from baseline in CDR-SB after last dose pooled across studies E2609-G000-301 and E2609-G000-302.
- To determine whether elenbecestat is superior to placebo on the Alzheimer's Disease Assessment Scale - cognitive subscale 14 item (ADAS-cog14), Mini Mental State Examination (MMSE), Functional Assessment Questionnaire (FAQ), and Alzheimer's Disease Assessment Scale - cognitive subscale 11 item (ADAS-cog11; added post hoc) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302. Added to this objective: To evaluate the change from baseline in ADCOMS, ADAS-cog11, ADAS-cog14, and MMSE after last dose pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302. Added to this objective: To evaluate the change from baseline after last dose in ADAS-cog14 Word List pooled across studies E2609-G000-301 and E2609-G000-302
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] amyloid beta [Aβ] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, tau PET, volumetric magnetic resonance imaging [vMRI], functional magnetic resonance imaging [fMRI]) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302. Modified objective: Added ADAS-cog11, and added plasma Aβ(1-x) and neurofilament light (NFL), and removed fMRI.
- To evaluate the population pharmacokinetics (PK) of elenbecestat in subjects with EAD. Deleted objective: Analyses to support this objective were not conducted.

Biomarker Objectives

For each study (E2609-G000-301 and E2609-G000-302) the biomarker objectives were as follows:

- To determine whether elenbecestat is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD. Modified objective: Analyses to support this objective were conducted instead using the data from the tau PET scans performed at the Early Discontinuation (ED) Visit and/or during the Follow-up Period.
- To determine whether elenbecestat is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD. Modified objective: Analyses to support this objective were conducted instead using the data from the CSF samples performed at the Early Discontinuation Visit and/or during the Follow-up Period.

- To determine whether elenbecestat is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD. Deleted objective: Statistical analyses to support this objective were not conducted, but data are summarized using descriptive statistics.
- To determine whether elenbecestat is superior to placebo on plasma amyloid levels (eg, Aβ(1-x)) at 24 months in subjects with EAD
- To explore potential plasma and CSF biomarkers of Alzheimer's disease (AD) (eg, NFL, visinin like protein 1 [VILIP1], human cartilage glycoprotein-39 [YKL-40], and neurogranin [Ng]). Modified objective: Analyses of VILIP1 and YKL-40 were not conducted.
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months. Modified objective: Analyses to support this objective were conducted instead at the Early Discontinuation Visit.
- To determine whether elenbecestat is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI. Deleted objective: Analyses of fMRI are not included in this Clinical Study Report (CSR) and will be reported separately.
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months. Deleted objective: Analyses of fMRI are not included in this CSR and will be reported separately.
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of AD as deemed appropriate. Modified objective: Analyses to support this objective were to be conducted only if a trend with time of treatment was noted with the biomarkers.
- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD. Modified objective: Analyses to support this objective were conducted instead at other visits.

Exploratory Objectives

For each study (E2609-G000-301 and E2609-G000-302) the exploratory objectives were as follows:

- To explore the relationship between elenbecestat exposure/pharmacodynamics (PD) (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate
- To evaluate whether elenbecestat is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI)-10 item
- To evaluate whether elenbecestat is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures. Deleted objective: Statistical analyses to support this objective were not conducted, but data are summarized using descriptive statistics.
- EuroQol - 5 Dimensions (EQ-5D) (5 Level version was used)
- Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview. Deleted objective: Statistical analyses to support this objective were not conducted, but data are summarized using descriptive statistics.

Extension Phase Objectives

For the Extension Phase of each study (E2609-G000-301 and E2609-G000-302) the planned objectives were as listed below. At the time of early termination of the study no subjects had yet enrolled in the Extension Phase of Study E2609-G000-302. Because of the small number of subjects enrolled in the Extension Phase of Study E2609-G000-301 the statistical analyses to support each of the planned Extension Phase objectives was not conducted. Instead, Extension Phase data are presented in listings:

Primary Objective

- To evaluate the long-term safety and tolerability of daily dosing with elenbecestat in subjects with EAD

Secondary Objectives

- To evaluate the long-term effects of elenbecestat on CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- To evaluate the time to conversion to dementia, for subjects who were not clinically staged as having dementia at Core Study baseline, based on a clinical diagnosis
- To evaluate whether the treatment benefit of elenbecestat at the end of the Core Study is maintained over time in the Extension Phase

Biomarker Objectives

- To evaluate the long-term effect of elenbecestat on brain amyloid and tau levels as measured by PET (optional substudy)
- To evaluate the long-term effect of elenbecestat on hippocampal atrophy as measured by changes in hippocampal volume using vMRI
- To evaluate the long term-effect of elenbecestat in preserving brain connectivity as measured by task-free fMRI
- To evaluate the long-term effect of elenbecestat on CSF tau, p-tau, and Aβ levels (optional substudy)
- To evaluate the long-term effect of elenbecestat on plasma amyloid (eg, Aβ(1-x)) levels
- To explore the long-term effect of elenbecestat on potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, Ng)

Exploratory Objectives

- To explore the long-term effect of elenbecestat on the initiation or dose increase of other AD pharmacotherapies
- To explore the long-term effect of elenbecestat on the NPI-10 and if available NPI-12

Methodology

Study E2609-G000-301 (Study 301) and Study E2609-G000-302 (Study 302) each consisted of a Core Study followed by an open-label Extension Phase. The Core Studies were multicenter, double-blind, placebo controlled, parallel group studies in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. The Extension Phases were to be available for subjects who completed the Core Studies, including 24 months of treatment and a 3-month posttreatment follow up. The Extension Phase was to provide subjects with open-label treatment with elenbecestat for 24 months, or until commercial availability of elenbecestat or a lack of positive benefit-risk was determined.

In the Core Studies, subjects were randomized in a double blind manner to receive either placebo or elenbecestat 50 mg per day (1:1 randomization ratio) for 24 months. Randomization was stratified according to region (up to 7 levels), clinical disease staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

The studies were designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Three longitudinal biomarker substudies evaluated the effects of study treatment on the underlying pathophysiology of AD using amyloid PET, tau PET and/or CSF biomarkers. Participation in the substudies was optional.

Studies 301 and 302 were terminated early by the sponsor on the recommendation of the E2609 DSMB. The DSMB reviewed data from 2130 subjects in the Full Analysis Set (FAS), of whom 1676 had at least 6 months follow-up, 853 had 12 months, 241 had 18 months, and 43 had 24 months follow up (based on the CDR-SB assessment). The DSMB concluded that for those on active drug treatment there was no evidence of potential efficacy, and the AE profile was worse than placebo. The E2609 DSMB considered that the safety risk outweighed any potential benefit for subjects continuing in the study. Concerning cognitive safety, the DSMB saw evidence of detrimental trends for subjects on active treatment on some cognitive measures by 18 months, and a more consistent negative trend at 24 months.

The end of the Core Studies was predefined as the date of the last study visit (3-month Follow-up Visit) for the last subject in the double-blind Randomization Phase. The end of the Extension Phase was the date of the last study visit for the last subject enrolled in the Extension Phase. The sites were notified on 13 Sep 2019 to immediately discontinue dosing. At that time, 1839 subjects were ongoing in the Core Study and 19 subjects were ongoing in the

Extension Phase (including 1 subject who did not receive any treatment in the Extension Phase). Investigators were instructed to complete the ED Visit as soon as feasible and to complete the 1-month Follow-up Visit (Core Studies and Extension Phase) and 3-month Follow-up Visit (Core Studies only). At the time of study termination, no subjects had yet enrolled in the Extension Phase of Study 302.

Number of Subjects (Planned and Enrolled)

Planned: The planned total for Studies 301 and 302 combined was approximately 1900 randomized subjects (at least 850 subjects randomized in each study).

Randomized (Core Studies): Total of 2212 subjects:	Study 301: 1179 subjects (587 elenbecestat, 592 placebo) Study 302: 1033 subjects (517 elenbecestat, 516 placebo)
Enrolled and treated in Extension Phase:	Study 301: 19 enrolled/18 subjects treated Study 302: 0 subjects

Diagnosis and Main Criteria for Inclusion

The diagnosis and criteria for eligibility were identical for Study 301 and Study 302.

Core Study: Key inclusion criteria included the following:

- MCI due to AD or mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and were required to have all of the following at Screening:
  - MMSE score equal to or greater than 24
  - CDR global score of 0.5
  - CDR Memory Box score of 0.5 or greater
- A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening (corroborated by a study partner)
- Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the International Shopping List Task (ISLT)
- Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
  - PET assessment of amyloid imaging agent uptake into brain.
  - CSF AD assessment (eg, tau:Aβ(1-42) ratio)
- Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
- If receiving an acetylcholinesterase inhibitor (AChEI) or memantine or both for AD, required to have been on a stable dose for at least 12 weeks before Randomization. Treatment-naïve subjects with AD were permitted to enter into the study.
- Required to have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks before Randomization, except for medications that are administered as short courses (eg, up to 3 weeks unless discussed and agreed with medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis.
- Required to have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject).

Subjects who met any of the following key exclusion criteria were excluded from the studies:

- Any condition that may have contributed to cognitive impairment above and beyond that caused by the subject's AD
- Any of the following psychiatric symptoms:
  - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could have interfered with study procedures
  - Had a "yes" answer to Columbia Suicide Severity Rating Scale (C-SSRS) suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or was hospitalized or treated for suicidal behavior in the 5 years before Screening

- Had any contraindications to magnetic resonance imaging (MRI) scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
  - Had any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
  - Exhibited other significant pathological findings on central read of the brain MRI at Screening
- Results of laboratory tests conducted during Screening that were outside the following limits:
  - Absolute lymphocyte count (ALC) below the lower limit of normal (LLN) or below 800 per mm^3 (whichever was higher)
  - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range were only exclusionary if they were considered clinically significant by the investigator
  - Abnormally low (below LLN) serum Vitamin B12 levels (if subject was taking Vitamin B12 injections, level was to be at or above the LLN)

Extension Phase: Subjects who completed the 24-month Treatment Period and the 3-month Follow-up Period (Visit 15) of the Core Studies, and whose Visit 15 fell within a 4-week window from the start of the Extension Phase were eligible to enroll. Subjects were to continue to have an identified study partner.

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

Core Study and Extension Phase: Elenbecestat was supplied by the sponsor as tablets of 50-mg dose strength and was administered orally once daily (QD) in the morning with or without food.

Study 301 Core Study batch numbers: P66003ZZ, P66003ZZA, P66003ZZB, P73001ZZA, P7X003ZZ, P7X003ZZA

Study 301 Extension Phase batch number: P85002ZZA

Study 302 Core Study batch numbers: P66003ZZ, P66003ZZA, P66003ZZB, P73001ZZ, P73001ZZA

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

Placebo tablets to match elenbecestat was of identical appearance and was administered orally QD in the morning with or without food.

Study 301 Core Study batch numbers: P66002ZZ, P66002ZZA, P66002ZZB, P72024ZZA, P7X002ZZ, P7X002ZZA

Study 302 Core Study batch numbers: P66002ZZ, P66002ZZA, P66002ZZB, P72024ZZ, P72024ZZA

Duration of Treatment

Core Study: The planned maximum estimated duration for each subject in both Study 301 and Study 302 was approximately 29 months (ie, 2 month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase and a 3 month follow up).

Extension Phase: The planned estimated duration for each subject was 25 months (ie, 24 months of treatment and 1 month follow up).

Assessments

The assessments were identical for Study 301 and Study 302.

Efficacy (both Core Study and Extension Phase)

CDR, MMSE, FAQ, and ADAS-cog14 and the composite clinical score, ADCOMS (Wang, et al., 2016), were used to assess efficacy. Description of these assessments is provided in the study protocols (Protocol 301 Appendix 16.1.1, Section 9.5.1.3 and Protocol 302 Appendix 16.1.1, Section 9.5.1.3).

Pharmacokinetics (Core Study Only)

Blood samples were collected for the determination of the concentrations of elenbecestat in all randomized subjects. For subjects who consented to CSF sample collection, CSF samples were to be collected for the determination of elenbecestat concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments (both Core Study and Extension Phase)

Blood samples were obtained at Screening and were used for assessment of putative AD diagnostics and to determine the apolipoprotein E (*ApoE*) genotype of all subjects. Determination of N-acetyltransferase 2 (*NAT2*) was to be done in a subset of subjects, but was not analyzed due to the early termination of the studies.

Blood was collected to measure PD [Aβ(1-x)] and biomarkers in both the Core Studies and the Extension Phase.

Subjects who consented to participate in the amyloid-PET and tau-PET longitudinal substudies were to have assessments at 12 months (amyloid PET only), 24 months, or at the ED Visit in the Core Studies and at 24 months or at the ED Visit in the Extension Phase.

Subjects who consented to the CSF substudy were to have samples taken at 24 months or at the ED Visit in both the Core Studies and Extension Phase for PD [Aβ(1-x)] and biomarker assessments.

Amyloid PET imaging or CSF AD assessment (eg, Aβ(1-42) or tau:Aβ(1-42) ratio) or both were used to confirm that all study subjects had amyloid deposition in the brain, which was required for eligibility. Use of a historical amyloid positive PET (conducted within 12 months before the planned randomization date) was acceptable for determination of eligibility (providing that the historical imaging data was made available to the sponsor), but did not suffice for baseline assessment if the subject wished to consent to the amyloid PET longitudinal substudy.

Due to the early termination of the study by the sponsor, the number of subjects for whom ED biomarker assessment were conducted was limited.

Safety Assessments (both Core Study and Extension Phase)

Safety was assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings (evaluated by a central reader in the Core Studies); physical, dermatologic, and neurologic examinations; assessment of suicidality, events of possible signals of drug abuse potential, and MRIs during the Treatment Period.

Absolute lymphocyte count from the hematology and differential panel was monitored during the study.

Subjects were monitored for hypersensitivity reactions and infections by AEs, physical examinations, and laboratory tests.

Dermatologic review was conducted as part of the physical examination. These assessments specifically included evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects were also questioned by the investigator at each visit to identify any changes that might represent a drug induced rash/reaction or infection. Subjects and their study partners were instructed to contact the investigator if they saw any lesions or other symptoms that might have been associated with a drug induced rash/reaction or infection, so that such AEs could be reviewed promptly.

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality was performed at every visit.

AEs that may have signaled drug abuse potential during the Treatment Period or withdrawal effects (during the first 4 weeks of the Follow-up Period) in the Core Studies and during the Extension Phase required a detailed follow up.

Following early termination of the study all subjects were to return to the study site as soon as feasible for their ED Visit and to return for their 1-month and 3-month Follow-up Visits.

Other Assessments (Core Study Only)

The NPI-10 item was conducted at Visit 2 and then every 6 months. Health related quality of life (HRQoL) was measured using the EQ-5D and QOL-AD assessments at Screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner served as the subject's proxy and completed the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. Additionally, the primary study partner burden was measured using Zarit's Burden Interview every 6 months. Due to the early termination of the studies and the resulting small sample size, statistical analyses of the EQ-5D, QoL-AD, and Zarit's Burden Interview was not conducted.

Other Assessments (Extension Phase Only)

The NPI-10 or if available NPI-12 was conducted at Day 1, Month 4, Month 12, and then every 12 months. If the NPI-12 questionnaire was used, both NPI-10 and NPI-12 scores were generated.

Bioanalytical Methods

CSF assessments were performed for eligibility and treatment response in consenting subjects using validated, commercially available kits. Exploratory CSF biomarkers (eg, Ng) were also to be measured using validated assays.

The *ApoE* genotype for all subjects was determined from blood specimens using validated assays.

Plasma concentrations of elenbecestat that may extend to the key metabolites M1, M2, and M5 was measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Plasma Aβ(1-x) and other relevant plasma biomarkers were measured in the blood samples collected at times that match the PK draws and during the Follow-up Period.

Statistical Methods

Due to the termination of the studies by the sponsor and the resulting reduction in sample size, certain analyses that were originally planned to support key secondary, other secondary, and exploratory objectives were not conducted and are not included in this CSR. The changes to the original statistical analysis plan are described in Section 9.8.3. Below is a description of the final analyses planned and conducted.

All statistical analyses were performed by the sponsor or designee after the studies were terminated by the sponsor and the databases were locked and released for unblinding. Statistical analyses were performed based on the pooled data from 2 studies (301 and 302). The analyses were also performed within each study for study disposition, demographic and baseline characteristics, primary endpoint, secondary endpoints, extent of exposure and key AE tables.

Core Study

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months in the combined studies

Key Secondary Endpoints

- Change from baseline in ADCOMS at 24 months in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the combined studies

Other Secondary Endpoints

- Change from baseline in the CDR-SB at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- Change from baseline in the ADCOMS at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- The rate of change over time (mean slope) based on CDR-SB score over 24 months in the combined studies
- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken) in the combined studies
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis in the combined studies
- Change from baseline in ADAS-cog14, MMSE, FAQ, and ADAS-cog11 at 24 months in the combined studies
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in the combined studies
- Change from last dose to follow-up in CDR-SB, ADCOMS, ADAS-cog11, ADAS-cog14, MMSE, and ADAS-cog14 Word List in the combined studies

Biomarker Endpoints

- Change from baseline in tau PET signal
- Change from baseline in CSF biomarkers t-tau and p-tau
- Change from baseline in CSF amyloid biomarkers Aβ(1-x), Aβ(1-42), and Aβ(1-40)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x))
- Change from baseline in plasma NFL and CSF NFL and Ng
- Change from baseline in vMRI parameters (eg, total hippocampal volume etc.) at 24 months using vMRI

Analysis of the change from baseline in the preservation of connectivity on fMRI at 24 months will be presented in a separate report

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AchEI or memantine after randomization) by 24 months in the combined studies
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization in the combined studies
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months in the combined studies
- Change from baseline in NPI-10 item at 24 months in the combined studies
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months in the combined studies

Core Study

Analysis Sets

- The Randomized Set was the group of subjects who were randomized to study drug.
- The Safety Analysis Set was the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.
- The FAS was the group of randomized subjects who received at least 1 dose of study drug and had baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) was the subset of subjects in the FAS who sufficiently complied with the protocol. Criteria for exclusion from the PPS are provided in the Statistical Analysis Plan (SAP) (Appendix 16.1.9).
- The PK Analysis Set was the group of subjects with at least 1 quantifiable elenbecestat plasma concentration with a documented dosing history.
- The PD Analysis Set was the group of subjects who had sufficient PD data to derive at least 1 PD parameter.

The subjects who enrolled into the Extension Phase and received at least 1 dose of Extension Phase study drug were considered as "All Safety Subjects" and used for Extension Phase tables and listings.

Efficacy Analyses

The FAS was used as the primary population for all efficacy analyses, while the PPS was used as the supportive population.

Analyses for Primary Efficacy Endpoints

The estimand of the primary analysis is the mean difference of the change from baseline in CDR-SB at 24 months between treatment groups on the FAS. The primary analysis was based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months was performed to compare elenbecestat 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model included baseline CDR-SB and baseline CDR-SB by visit interaction as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical disease staging [MCI due to AD, early stage of mild AD], and concurrent AD medication use at randomization (Visit 2, [yes, no]), *ApoE4* status, and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix was employed to model the covariance of within subject effect, and the Kenward-Roger approximation was used to estimate the denominator degrees of freedom; if MMRM failed to converge, then a covariance structure with fewer parameters from the following list was employed according to the prespecified order in the list until the MMRM converged. The list of covariance structure included Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. If a structured covariance is used, then the sandwich estimator is used to estimate variance of the treatment effect estimator. This primary analysis included all observed postbaseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat versus placebo was compared at 24 months based on MMRM model. The least squares (LS) means and difference in LS means between elenbecestat treatment group and placebo, and corresponding 95% CI was presented.

The null hypothesis was that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo. The corresponding alternative hypothesis was that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo.

To minimize the impact of intercurrent events (ie, treatment discontinuation or change in concomitant AD medications), an MMRM analysis was conducted, by censoring the data after intercurrent events (ie, treatment discontinuation, initiation of new AD medications [AChEI or memantine] and/or change in dose of current AD medications).

The following sensitivity analysis were conducted to evaluate the impact of missing data: The primary endpoint was analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model included baseline CDR-SB as a covariate, with treatment group, randomization stratification variables, and *ApoE4* status as factors.

Subgroup analysis (eg, stratification factors and *ApoE4* status) and additional sensitivity analysis for the primary endpoint were performed as appropriate.

Analyses for Key Secondary Efficacy Endpoints

The key secondary analyses were to be performed only if the primary analysis was significant. The treatment effect for elenbecestat 50 mg per day versus placebo, for each key secondary efficacy endpoint, was tested using a sequential testing procedure at a significance level of 2-sided alpha=0.05, ie, any test started only if the test with higher hierarchical order was significant.

The change from baseline in ADCOMS at 24 months was analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline ADCOMS in the model. For ADCOMS, the MMRM analysis was conducted on the FAS, by censoring the data after intercurrent events as sensitivity analyses.

The change from baseline in amyloid PET SUVR at 24 months was analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline amyloid PET SUVR in the model. Analysis of change from baseline in amyloid PET SUVR at 24 months in the individual studies was planned, but was not conducted due to reduced sample size following the early termination of the study. The amyloid PET SUVR from 3 tracers (florbetapir, florbetaben, and flutemetamol) was standardized using the Centiloid scale (Adamczuk, et al., 2019) and combined for the key secondary endpoint. Other amyloid PET SUVR parameters (ie, mean composite SUVR using whole cerebellum, cerebellar grey matter, or subcortical white matter as reference region for florbetapir and flutemetamol and mean composite SUVR including occipital rollups using whole cerebellum, cerebellar grey matter, or subcortical white matter as reference region for florbetaben) were summarized by tracer as biomarker endpoints using the same statistical method.

Analyses for Other Secondary Endpoints

The change from baseline in CDR-SB and ADCOMS at 24 months was analyzed using the same MMRM model as the primary analysis for subjects enriched by baseline PET SUVR between eg, 1.2 and 1.6 on the FAS.

Time to worsening of CDR scores by 24 months was analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors, and *ApoE4* status. Time to worsening of a CDR score was defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of the Treatment Period of the Core Studies, the time to worsening of the CDR score was censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis was analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors, and *ApoE4* status. Proportion of subjects with dementia diagnosis at 24 months was estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis was censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB was analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis),

where the mean slope in each group depends on a continuous assessment time. The LME model included assessment time, and treatment group-by-assessment time as well as random intercept and slope.

The other continuous secondary efficacy endpoints as defined above were analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model. For ADAS-cog11, ADAS-cog14, and MMSE, the MMRM analysis were conducted on the FAS, by censoring the data after intercurrent events as sensitivity analyses.

The MMRM using the change from baseline at last on treatment visit and 12-week Follow-up Visit was conducted based on the subjects in FAS who had the assessments at both visits to evaluate the change after last dose in CDR-SB, ADCOMS, ADAS-cog11, ADAS-cog14, MMSE, and ADAS-cog14 Word List. The same MMRM as the primary efficacy analysis (except excluding baseline by visit interaction) was used with appropriate contrast to evaluate the difference between last on treatment visit and 12-week Follow-up Visit by each treatment group.

The relationship between clinical changes (CDR-SB, ADCOMS, ADAS-cog11, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, tau PET, plasma PD/biomarker, CSF biomarker, and vMRI) were evaluated using correlational analysis. In the presence of strong or moderate correlation, a linear model was fitted to further characterize the relationship between the changes in clinical endpoints and changes in biomarkers. For tau PET and CSF biomarkers, the clinical assessments closest to the assessment date for tau PET or CSF biomarkers were used.

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below was performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses were conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo was tested at a significance level of 2-sided alpha = 0.05. As tau PET and CSF biomarkers were collected once per subject at different analysis visits, the ANCOVA model with factors of treatment group, visit, treatment group-by-visit interaction, randomization stratification variables (ie, region, clinical disease staging [MCI due to AD, early stage of mild AD], and concurrent AD medication used at randomization (Visit 2, [yes, no]), *ApoE4* status, and baseline value as a covariate were applied.

The relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of AD as deemed appropriate were evaluated graphically only if a trend in biomarkers with time of treatment was noted.

Only summary statistics were prepared for CSF Aβ(1-x), CSF Aβ(1-42), and CSF Aβ(1-40) because of the limitation of available data for the analysis.

The relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of AD as deemed appropriate was evaluated graphically only if a trend in biomarkers with time of treatment is noted.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment was analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment was defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment was censored at the date of last assessment of concomitant medication on or before the 24 months visit.

The proportion of subjects with any change of concomitant AD treatment at 24 months was analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item was analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints was performed to compare elenbecestat versus placebo by using MMRM or ANCOVA model. For each of them, the treatment effect of elenbecestat 50 mg per day versus placebo was tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

The PK Analysis Set was used for the summaries of elenbecestat plasma and CSF concentrations.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters was explored graphically if a trend in biomarkers with time of treatment was noted.

Additionally, the relationship between various PK parameters (eg, C_{max}) and CDR scores (CDR-SB, CDR global score, and CDR Memory Box score) at 24 months (including both absolute score and the change from baseline), and the relationship between various PK exposure parameters and the change from baseline for 24 months in ADAS-cog14, and the MMSE, was explored graphically if deemed necessary and only in case of a trend with time of treatment.

Safety Analyses

Evaluations of safety were performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, safety MRI findings, suicidality, results of the sleep questionnaire, ADAS-cog Reliable Change Index (RCI) Alert triggered, dermatology finding, and neurological examination, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements were summarized by treatment group.

Results

Subject Disposition/Analysis Sets

Analyses were performed based on the pooled data from 2 studies (301 and 302). A total of 9758 subjects were screened in these studies. Of these, 7546 were screening failures, and 2212 were randomized into the studies (1104 in the elenbecestat group and 1108 in the placebo group). A total of 2204 randomized subjects were included in the Safety Analysis Set, and 2146 subjects were included in the FAS (the analysis set for the clinical efficacy endpoints).

Only 61 subjects completed the Core Studies. The main reason for study withdrawal was termination of the study by the sponsor: 1736 subjects (848 [77.0%] in the elenbecestat group and 888 [80.1%] subjects in the placebo group). Of the 61 subjects who completed the Core Studies, 19 were enrolled and 18 were treated in the open-label Extension Phase.

Efficacy

Due to the early termination of the studies by the sponsor, the number of subjects evaluable for the primary and secondary efficacy endpoints was insufficient for a meaningful evaluation of the efficacy of elenbecestat. Of the 2212 randomized subjects, only 189 subjects had the primary efficacy assessment (CDR-SB), and 243 subjects had the key secondary efficacy assessment (ADCOMS) at 24 months before the study was terminated. Nonetheless, planned analyses on the primary, secondary, and exploratory endpoints were conducted for descriptive purposes.

Overall, the results of the primary efficacy analysis showed that elenbecestat was nearly identical to placebo in the measure of mean change from baseline to 24 months in CDR-SB. The LS mean (SE) change from baseline was 1.99 (0.146) for the elenbecestat group and 2.17 (0.142) for the placebo group (higher scores indicating greater clinical deficit). The LS mean differences (95% CI) between the elenbecestat and placebo groups was -0.17 (-0.57, 0.22). Similar results were observed across all time points.

In general, no differences between the elenbecestat and placebo groups were observed for any efficacy endpoints. Subgroup analyses based on *ApoE4* carrier versus noncarrier or based on clinical disease stage at baseline (MCI due to AD versus early stage of mild AD) similarly showed no difference in any efficacy endpoint between the elenbecestat and placebo group.

There was a signal of potential cognitive worsening in the elenbecestat group compared with the placebo at the 6 month time point in the clinical endpoints ADAS-cog11 (LS mean differences [95% CI]: 0.40 [0.06, 0.74], nominal P=0.022) and ADAS-cog14 Word List (LS mean differences [95% CI]: 0.24 [0.05, 0.44], nominal P=0.016). This apparent worsening in the elenbecestat group was not seen at subsequent time points.

Analysis of the change in clinical efficacy endpoints from the last on-treatment assessment to the 12-week follow-up assessment showed less cognitive decline in subjects discontinued from elenbecestat relative to those discontinued from placebo as measured by ADAS-cog14 and ADAS-cog14 Word List.

Pharmacokinetics

Due to the early termination of the study, only summary statistics and listings were prepared for elenbecestat concentrations in plasma and CSF for the Core Study.

Pharmacodynamics and Biomarkers

Pharmacodynamics and biomarkers in CSF

Because very few samples were drawn within the 5-day allowance period after last dose (N=0 to 1 for elenbecestat and N=2 to 3 for placebo), no statistical analyses were conducted for change from baseline in CSF Aβ(1-x), Aβ(1-40), and Aβ(1-42), and no conclusions can be drawn from these longitudinal samples.

Over the course of treatment, CSF biomarkers of neurodegeneration (ie, t-tau, p-tau, NFL, and Ng) tended to increase in the placebo group; whereas, the elenbecestat group tended to show either a decrease (Ng), a lesser increase compared with placebo (t-tau), or no consistent pattern of change over time (p-tau and NFL). However, due to the small sample sizes, high degree of variability, and the fact that the time between the last dose and the CSF collection was not restricted for CSF t-tau, p-tau, NFL, and Ng, interpretability of the biomarker longitudinal data are limited.

Pharmacodynamics and biomarkers in plasma

A large mean percent reduction from baseline plasma Aβ(1-x) was observed in the elenbecestat group compared with a mean percent increase in the placebo group, across all time points. A difference between elenbecestat and placebo was evident at the first assessment at 3 months and persisted for the treatment period. The LS mean (SE) percent change from baseline at 3 months was -65.71% (1.475) in the elenbecestat group and +2.58% (1.450) in the placebo group, with an LS mean percent difference (95% CI) of -68.29% (-71.19, -65.38) (nominal $P<0.001$). At 24 months, the LS mean (SE) percent change from baseline was -67.40% (3.2.3.1) in the elenbecestat group and +10.95% (6.2.1.6) in the placebo group, with an LS mean percent difference (95% CI) of -78.36% (-92.21, -64.50) (nominal $P<0.001$).

Plasma NFL showed a greater increase from baseline to 6 months in the elenbecestat group compared with the placebo group. The LS mean (SE) percent change from baseline to Month 6 (Week 27) was +11.36% (2.054) in the elenbecestat group and +2.95% (2.003) in the placebo group, with an LS mean difference (95% CI) of 8.41% (3.93, 12.90), nominal $P<0.001$. No difference between treatment groups was observed at any subsequent time point.

Imaging biomarkers

Change from baseline brain amyloid load (using PET SUVR from 3 tracers [florbetapir, florbetaben, and flutemetamol] standardized using the Centiloid scale) showed a decrease in the LS mean (SE) change from baseline to 24 months in the elenbecestat group (-5.02 [2.046]) compared with an increase in the placebo group (+7.81 [2.500]), resulting in an LS mean treatment difference (95% CI) at 24 months of -12.83 (-18.79, -6.88), nominal $P<0.001$. The difference between the elenbecestat and placebo group was also observed at the earlier assessment at 12 months (LS mean [SE] change from baseline of -3.34 [1.114] in the elenbecestat group compared with +7.55 [1.065] in the placebo group, resulting in an LS mean treatment difference (95% CI) at 12 months of -10.90 [-12.91, -8.88], nominal $P<0.001$). Irrespective of amyloid PET tracers, brain amyloid load decreased for the elenbecestat group and increased for the placebo group.

Change from baseline to Month 12 in tau PET signal showed no difference between the elenbecestat group and the placebo group, but the analysis was based a sample size of 15 subjects per treatment group. Interpretability of these results may be limited due to subject-to-subject variability, small sample size, and the short duration of follow up (12 months) for tau progression.

A greater mean percent decrease from baseline to Month 12 was observed with vMRI in the elenbecestat group compared with placebo in total hippocampal volume (LS mean differences [95% CI]: -0.36% [-0.54, -0.19]), whole brain volume (LS mean differences [95% CI]: -0.31% [-0.40, -0.22]), and cortical thickness Mayo index (LS mean differences [95% CI]: -0.49% [-0.68, -0.31]) and an increase in ventricular volume in the elenbecestat group compared with the placebo group (LS mean differences [95% CI]: 1.45% [0.88, 2.01]), all with nominal $P<0.001$.

Safety

- The incidence of treatment-emergent adverse events (TEAEs) during the Core Study was similar between the elenbecestat group (77.6%) and placebo group (73.0%). TEAEs that occurred in ≥5% of subjects in the elenbecestat group and more frequently than the placebo group were lymphopenia, rash, dizziness, and abnormal dreams.

- The incidence of severe TEAEs was higher in the elenbecestat group (6.4%) than the placebo group (4.6%).
- The incidence of treatment-related TEAEs was higher in the elenbecestat group (33.8%) than the placebo group (20.2%). The most frequently reported treatment-related TEAEs (>2%) were lymphopenia, abnormal dreams, rash, nightmare, and lymphocyte count decreased.
- 2 subjects in the elenbecestat group had a TEAE resulting in death (brain injury/cardiac arrest/aspiration pneumonia and completed suicide), and 3 subjects in the placebo group had a TEAE resulting in death (lung neoplasm, myocardial infarction, and Alzheimer's type dementia). Only lung neoplasm (placebo subjects) was considered by the investigator to be related to the study drug.
- The incidence of other (non-fatal) SAEs was similar between the elenbecestat group (12.0%) and the placebo group (10.3%).
- The incidence of TEAEs leading to study drug discontinuation was higher in the elenbecestat group (11.7%) compared with the placebo group (6.2%). The TEAEs most commonly resulting in study drug discontinuation in the elenbecestat group were lymphopenia, rash, drug eruption, alanine aminotransferase increased, dizziness, hepatic function abnormal, and lymphocyte count decreased. Discontinuation from study drug related to lymphocyte decrease, hepatic impairment, and skin rash were stipulated in the protocol.
- A higher incidence of TEAEs of interest relating to cognition was observed in the elenbecestat group (4.5%) compared with the placebo group (2.7%).
- A higher incidence of TEAEs of interest relating to weight decrease was observed in the elenbecestat group (2.0%) compared with the placebo group (0.5%). A higher percentage of subjects had ≥7% decrease in body weight (11.8% versus 6.4%), and mean body weight decreased from baseline to the last on-treatment assessment to a larger extent in the elenbecestat group (-1.37 kg) compared with the placebo group (-0.16 kg).
- Other TEAEs of interest that occurred with a higher incidence in elenbecestat group compared with the placebo group included abnormal dreams, nightmares, or sleep terror (8.7% versus 5.9%), TEAEs signaling drug abuse potential (15.1% versus 11.9%), skin-related events (16.7% versus 11.2%).
- Elenbecestat did not appear to have higher risk of seizure, herpes zoster, severe infection, amyloid-related imaging abnormalities (ARIA), or suicidal ideation compared with placebo.
- There were slight reductions in ALC in the elenbecestat group compared with the placebo group. The incidence of subjects with a treatment-emergent markedly abnormal value (TEMAV) in lymphocytes was higher in the elenbecestat group compared with placebo (15.4% and 7.1%). The incidence of lymphocyte-related TEAEs was higher in the elenbecestat group compared with the placebo group (10.0% versus 3.1%).
- A higher percentage of subjects in the elenbecestat group had a shift in liver function tests from normal at baseline to high postbaseline. The incidence of liver function test TEMAVs was higher in the elenbecestat group compared with the placebo group (alanine aminotransferase [ALT]: 3.9% versus 0.6%, aspartate aminotransferase [AST]: 2.4% versus 0.6%, and gamma-glutamyltransferase [GGT]: 3.5% versus 1.1%). The incidence of TEAEs related to liver function was higher in the elenbecestat group compared with the placebo group.
- There were no other changes of clinical importance in mean hematology, chemistry, and urinalysis values over time and no shifts of clinical concern. The incidence of TEMAVs was low and generally comparable between the treatment groups.
- There were no changes of clinical importance in blood pressure, heart rate, or ECG parameters.

Conclusions

- Studies 301 and 302 were terminated early by the sponsor based on the recommendation of the E2609 DSMB who concluded that the safety risks outweighed any potential benefit.
- In subjects with MCI and early stages of AD, elenbecestat 50 mg did not show efficacy as measured by any clinical endpoints in this study.
- Elenbecestat was worse than placebo at 6 months for ADAS-cog11 and ADAS-cog14 Word List, but similar to placebo in these scales/scale items at all subsequent time points.
- Brain amyloid levels decreased in the elenbecestat group and increased in the placebo group across all time points.

- Plasma Aβ(1-x) levels in the elenbecestat group demonstrated an expected reduction over the entire study treatment.
- Hippocampal volume, whole brain volume, and cortical thickness decreased in the elenbecestat group to greater extent than placebo. Ventricular volume increased to a greater extent on elenbecestat.
- Elenbecestat was generally well tolerated by the subjects in this study.
- The incidence of TEAEs and SAEs were similar between the elenbecestat and placebo groups. Common TEAEs that occurred more frequently in the elenbecestat group than the placebo group were lymphopenia, rash, dizziness, and abnormal dreams.
- More subjects in the elenbecestat group had TEAEs leading to study drug discontinuation compared with the placebo group.
- The incidence of TEAEs of interest relating to cognition, weight decrease, abnormal dreams/nightmares/sleep terrors, signals of drug abuse potential, and skin-related events were higher in the elenbecestat group compared with the placebo group.
- Elenbecestat treatment resulted in a higher incidence of TEMAVs of elevated ALT, AST, and GGT compared with placebo and a higher incidence of TEMAVs of decreased lymphocytes compared with placebo.

Date of Report

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