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: E2609 tablet	Referring to Module 5 of the Dossier	
Name of Active Ingredient: Elenbecestat	Volume: Page:	

Study Title

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study to Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild to Moderate Dementia Due to Alzheimer's Disease

Investigators/Sites

David Watson, Psy.D CCTI (principal investigator), et al.

Multicenter: 30 sites in the United States (refer to Appendix 16.1.4 for the list of investigators and sites)

Publication (Reference)

None

Study Period

26 Nov 2014 to 27 Mar 2018

Phase of Development

Phase 2

Objectives

Primary objective

- To assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with elenbecestat/E2609 (referred to as elenbecestat hereafter) in Mild Cognitive Impairment (MCI) due to Alzheimer's disease (AD)/Prodromal AD (referred to as MCI/prodromal throughout the clinical study report [CSR]) subjects and in subjects with mild to moderate dementia due to Alzheimer's disease (referred to as mild to moderate AD throughout the CSR)

Secondary objectives

- To characterize the plasma and cerebrospinal fluid (CSF) pharmacokinetics (PK) of elenbecestat
- To assess the effects of elenbecestat on amyloid β (Aβ)(1-x) and Aβ(1-42) in CSF from 4 weeks and up to 18 months of treatment

Exploratory objectives

- To explore the effects of elenbecestat dose level on CSF Aβ(1-40) and beta (β)-amyloid converting enzyme 1 (BACE1) measurements from 4 weeks and up to 18 months of treatment
- To explore the effects of elenbecestat compared with placebo on various biomarkers. Biomarkers to be explored included, but were not limited to:
  a. CSF biomarkers of neurodegeneration (eg, total tau [t-tau], phosphorylated-tau [p-tau]) after 18 months of treatment
  b. Plasma and CSF amyloid, and CSF BACE1 measurements from 4 weeks and up to 18 months of treatment
  c. Total hippocampal atrophy at 12 and 18 months of treatment, as measured by volumetric magnetic resonance imaging (vMRI)

d. vMRI measurements including left and right hippocampal volume, whole brain volume, and total ventricular volume at 6, 12, and 18 months of treatment (ie, individual comparisons to their own baseline)

e. Brain amyloid levels at 18 months as measured by amyloid positron emission tomography (PET)

- To explore the effects of elenbecestat compared with placebo on clinical status at various time points during 18 months of treatment, and during posttreatment follow-up by assessment of:
  a. The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog$_{14}$)
  b. The Clinical Dementia Rating (CDR) scale
  c. The Mini-Mental State Examination (MMSE)
  d. The International Shopping List Task (ISLT)
  e. The CogState Brief Battery (CBB)
  f. The Functional Assessment Questionnaire (FAQ; also known as the Functional Activities Questionnaire)
- To explore the relationship between the treatment effects of elenbecestat on measured clinical efficacy scales (eg, MMSE, CDR) and its effects on CSF amyloid, CSF amyloid isoforms, brain amyloid, and vMRI
- To explore relationships between both elenbecestat dose and exposure, with pharmacodynamic (PD) and safety endpoints

Methodology

This study was a multicenter, placebo-controlled, double-blind, parallel-group, randomized, dose-finding study with an Open-Label Extension (OLE) Phase of up to 27 months in subjects with MCI/prodromal AD or mild to moderate AD (mild to moderate AD was added to the study population during the study, Amendment 01, 28 May 2015).

A common set of inclusion criteria, consistent with the National Institute on Aging–Alzheimer's Association (NIA-AA) clinical research criteria for MCI due to AD or mild to moderate AD was required for all subjects. In addition, the MCI due to AD subject population was also consistent with the research criterion for "Prodromal AD" in that episodic memory was impaired on a list learning task (ISLT). As the non-demented subjects were consistent with criteria for both MCI due to AD and Prodromal AD, they are identified as MCI/prodromal subjects in this CSR. The diagnosis of MCI/prodromal AD or mild to moderate AD was based on both clinical and biological (ie, confirmation of amyloid load in the brain) criteria.

The study consisted of 3 phases: Prerandomization, Randomization, and OLE. The Prerandomization and Randomization Phases are referred to as the Core Study and only the results of the Core Study are presented in this CSR.

Core Study

The Core Study was originally designed with 2 stages, Stage A and Stage B. Stage A was to be limited to approximately 60 subjects with MCI/prodromal AD or mild to moderate AD. Once subjects from Stage A completed 12 weeks of treatment (or discontinued from study drug), an interim analysis was to take place to assess the safety and tolerability of elenbecestat prior to expanding the study to Stage B, during which up to 500 MCI/prodromal subjects and 200 subjects with mild to moderate AD were to be randomized using a Bayesian response adaptive randomization. However, during study conduct, Stage B was removed as a part of Amendment 05 (26 Sep 2016).

The Core Study had 2 phases: The Prerandomization Phase (up to 60 days, plus an additional window of up to 30 days if required) which consisted of a Screening Visit and a Baseline Visit. All screening assessments were completed and eligibility to continue to the Baseline Period was confirmed before any baseline assessments commenced. Following successful completion of the Prerandomization Phase, eligible subjects were randomly assigned to treatment and entered the Randomization Phase, which consisted of 2 periods: Treatment (78 weeks) and Follow-Up (post last dose; 12 weeks). Within the 2 clinical cohorts (MCI/prodromal and mild to moderate AD), subjects were stratified at randomization by Apolipoprotein E (ApoE) 4 status (positive or negative) and prior treatment with acetylcholinesterase inhibitors (AChEIs) or memantine or both (yes or no).

This study enrolled at 30 sites in the United States. At Visit 3 (Randomization Visit), 70 eligible subjects were randomly assigned to the 4 planned treatment groups (elenbecestat 5, 15, and 50 mg or placebo) in a ratio of

1:1:1:1. PK/PD modeling predicted that these doses would achieve target reduction in CSF Aβ levels relative to placebo by approximately 25% (5 mg), 50% (15 mg), and 75% (50 mg) from baseline, when administered once daily with food. CSF Aβ levels were evaluated based on the 4 week (or later) assessment of CSF Aβ(1-x) in subjects who provided voluntary consent for CSF measurement.

Safety data were monitored in a blinded fashion throughout the Core Study by the Sponsor. In addition, approximately every 3 months from the time the first subject was randomized into the study, an independent data safety monitoring board (DSMB; including at least 1 immunologist) reviewed all safety data in an unblinded manner. The DSMB made recommendations to the Sponsor after each review as to whether any change(s) to the study were necessary.

Once all subjects completed at least 12 weeks of treatment in the Core Study (or discontinued study drug early), an interim safety analysis was conducted by the Sponsor and the DSMB. At the completion of this interim safety review, the frequency of subsequent unblinded safety reviews was reevaluated by the DSMB and the Sponsor, and this information was provided in the DSMB charter. Subjects continued study drug while the DSMB reviewed all the available safety data. At the time of the interim safety analysis, some subjects had more than 12 weeks of safety data.

During the study, unblinded interim analyses of plasma elenbecestat PK for all subjects and CSF elenbecestat PK and PD profiles were performed on baseline data and samples collected after at least 4 weeks of treatment in the Core Study. All unblinded analyses were performed by an independent PK/PD scientist at the Sponsor; all members of the study team remained blinded throughout the study. During these unblinded interim analyses, the CSF PD effects of elenbecestat doses (as measured by reductions from baseline in CSF Aβ(1-x) levels) were evaluated. In addition, exploratory PK/PD modeling was performed. The PK/PD modeling used the observed PK and PD data and related the average steady state plasma elenbecestat concentration to steady state CSF Aβ(1-x) percentage reduction from baseline determined after at least 4 weeks of dosing.

Based on the results of the unblinded interim analyses, the elenbecestat 50 mg dose was chosen as the clinical dose for Phase 3 development. In order to collect additional safety data for elenbecestat 50 mg to support the Phase 3 Program, subjects initially randomly assigned to elenbecestat 5 or 15 mg in the Core Study were reassigned to elenbecestat 50 mg if they had at least 12 weeks of treatment remaining in the Randomization Phase following study drug dose reassignment. As study drug dose reassignment occurred in a blinded manner, a 4-week interim safety assessment following study drug reassignment was required for all subjects.

Early Discontinuation

Subjects who discontinued taking study drug prematurely for any reason underwent an Early Discontinuation Visit within 7 days of their last dose of study drug.

Follow-up Period

All subjects, regardless of whether they completed all 18 months of treatment or discontinued study drug prematurely, completed 4 posttreatment Follow-Up Visits: 2, 4, 8, and 12 weeks after the last dose of study drug. If clinically indicated, more frequent safety assessments could be conducted as part of unscheduled visits during the posttreatment Follow-up Period.

Number of Subjects (Planned and Randomized)

Planned: 60 (±20%) subjects (with a target of approximately 15 subjects per treatment arm). There was no limit to the number of subjects randomized from either clinical cohort.

Randomized: 70 subjects (53 elenbecestat, 17 placebo).

Diagnosis and Main Criteria for Inclusion

Seventy male and female subjects, aged 50 to 85 years, inclusive at time of consent, were enrolled in the study. Key inclusion criteria included the following:

- Met the core clinical research criteria of the NIA-AA for MCI due to AD or AD dementia and was "staged" or classified as either MCI or mild to moderate dementia and also complied with the following:

Required at Screening Visit 1:

a. Subjective Memory Complaint with evidence of concern about a decline in cognition from the subject, informant, or clinician’s observation

b. Cognitive impairment of at least 1 SD from age adjusted norms in delayed recall on the ISLT.

Alternatively, cognitive impairment of at least 0.5 SD from age adjusted norms in delayed recall on the ISLT plus impairment of at least 1 SD from age adjusted norms in at least 1 other computerized learning and memory test (ISLT immediate recall, or 1 of the learning and memory components of the CBB).

c. FAQ ≤24

d. MMSE ≥16

- Amyloid positive PET image based on centralized PET scan reading; an historical amyloid positive PET scan was used if conducted within the previous 12 months and provided that the scan and result were considered acceptable by the central PET reading group.
- Had an identified caregiver or informant who was willing and able to provide follow-up information on the subject throughout the course of the study. This person had to, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that the caregiver or informant could reliably fulfill the study requirements and had to provide separate written consent. The caregiver or informant did not need to be living in the same residence as the subject. If the caregiver or informant was not residing with the subject, the investigator had to be satisfied that the subject could contact the caregiver or informant readily during the times when the caregiver or informant was not with the subject. If in doubt about whether a subject's care arrangements were suitable for inclusion, the investigator discussed this with the Medical Monitor. At visits where the CDR or FAQ were conducted, caregivers or informants needed to either attend the visit in person along with the subject or be able to be contacted by telephone at the time of the visit. The investigator determined whether attendance in person was required or whether telephone contact was suitable and based this determination upon the functional ability of the subject among other factors.
- If receiving AChEIs or memantine, had to be on a stable dose for at least 12 weeks before the Baseline cognitive assessments at Visit 2, with no plans for dose adjustment in the foreseeable future. Treatment naïve subjects were allowed to be entered into the study but there had to be no plans to initiate treatment with AChEIs or memantine at the time of entry into the study.
- Was on stable doses of all other permitted chronically used concomitant medications (ie, not related to their cognitive decline) for at least 4 weeks before randomization.

Test Treatment, Dose, Mode of Administration, and Batch Numbers

E2609 tablets of 5-, 10-, and 25-mg dose strengths were supplied. Each subject received 2 tablets, which combined made up the required doses of elenbecestat 5, 15, 50 mg, or placebo, orally once daily with food. Treatments administered during the Core Study were 5, 15, and 50 mg elenbecestat or placebo prior to the implementation of Amendment 06, and 50 mg elenbecestat or placebo after the implementation of Amendment 06. Study treatment began on Day 1 (at the study site) following Randomization and continued for approximately 78 weeks.

Batch numbers: E2609 5 mg (P3X006ZZA, P3X006ZZZA, P3Z004ZZA, P3Z005ZZA), E2609 10 mg (P3X007ZZA, P3Z006ZZA), E2609 25 mg (P3X008ZZA, P3Z007ZZA, P3Z008ZZA)

Reference Therapy, Dose, Mode of Administration, and Batch Numbers

E2609-matched placebo tablets were supplied.

Batch numbers: P3X004ZZA, P3X005ZZA, P3Z001ZZA, P3Z002ZZA

Duration of Treatment

The maximum duration of a subject's participation in the study was approximately 2 years, comprising the following:

- Screening and Baseline Periods (Prerandomization Phase): up to 60 days, plus an additional window of up to 30 days if required

  (In subjects who had an active infection within 4 weeks of the planned randomization date, the duration of the Prerandomization Phase was extended by up to 4 weeks to allow additional time for resolution of the infection.)
- Treatment Period (Randomization Phase): up to 78 weeks
- Follow-up Period (Randomization Phase): 12 weeks (post last dose)

Assessments

Efficacy

Alzheimer's Disease Assessment Scale - cognitive subscale: The 14-item version was used since it was considered more sensitive for subjects with MCI/prodromal AD or mild AD.

Clinical Dementia Rating: Assesses 6 domains of subject function; memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

Mini-Mental State Examination: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing.

International Shopping List Task: The ISLT was a verbal learning and episodic memory test assessing both immediate and delayed recall.

CogState Brief Battery: A computer-based battery comprising 4 cognitive tests:

- Detection – a simple reaction time test. Speed of response is the measure.
- Identification – a simple choice reaction time test. Speed of response is the measure.
- One Card Back – a simple working memory test. Accuracy of response is the measure.
- One Card Learning – a visual learning and memory test. Accuracy of response is the measure.

Functional Assessment Questionnaire: The FAQ had 10 items concerned with performing daily tasks necessary for independent living. The caregiver or informant provided performance ratings on 10 complex activities of daily living performed within the preceding 4 weeks.

Volumetric Magnetic Resonance Imaging: vMRI was used to evaluate disease modification, including the change from baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated magnetic resonance imagings (MRIs).

Pharmacokinetics

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

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Brain atrophy was measured by vMRI: see Efficacy Assessments (above).

The soluble biomarkers Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, and p-tau were measured in subjects who consented to CSF sample collection. Aβ(1-x) and Aβ(1-42) in CSF were measured at Visit 7 (Week 5) and Visit 18 (Week 79). Aβ(1-40) in CSF were measured at Visit 7 and t-tau and p-tau in CSF were measured at Visit 18. BACE1 levels and activity in CSF were also measured in subjects who consented to CSF sample collection. Other exploratory biomarkers and amyloid isoforms (eg, Aβ[1-40]) were also evaluated in plasma or CSF. Subjects who initially consented to CSF collection and provided a baseline CSF sample but did not provide a postrandomization sample were approached to consider reconsenting to postrandomization CSF sample collection even if they were beyond Week 5 (Visit 7); however, reconsent to this procedure was optional for these subjects.

Amyloid PET imaging was used to confirm that all subjects eligible for progression to the Baseline Period had amyloid deposition in the brain. An historical amyloid positive PET scan was accepted, if conducted within the previous 12 months and provided that the scan and result were considered acceptable by the central PET reading group. Longitudinal amyloid PET imaging was also conducted after 18 months of treatment (or at Early Discontinuation, providing the subject received at least 39 weeks of study drug). Longitudinal amyloid PET imaging was only conducted on subjects with Screening PET scans performed for this study (ie, historical scans were not used for the longitudinal analyses).

ApoE and N-acetyltransferase 2 (NAT2) genotyping/phenotyping was conducted. A blood sample was obtained at Baseline and was used to determine the ApoE genotype (homozygous or heterozygous E4 versus non-E4) and the NAT2 phenotype of subjects enrolled in this study. The findings may be used in the statistical analysis to determine the effects on treatment response, safety, or PK of elenbecestat.

The genomic DNA samples were stored to examine the role of genetic variability in subjects' absorption,

distribution, metabolism, and excretion, the development of adverse events (AEs), or underlying AD. Variations in elenbecestat exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Safety

Routine safety assessments included the monitoring and recording of all AEs and serious adverse events (SAEs), monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs, regular electrocardiograms (ECGs), physical and neurological examinations, and centralized dermatological assessments (via photography) at regular intervals. AEs that might have indicated signals of possible drug abuse potential required a more detailed follow-up. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror were questioned on the frequency and impact of these events.

Complete blood counts and lymphocyte subsets absolute counts and percentages were measured (by a centralized laboratory) every week for the first month, every 2 weeks for the next 2 months (Months 2 and 3) and monthly for the next 3 months (Months 4, 5, and 6). Thereafter, they were monitored every 3 months until the end of the Treatment Period and at all 4 Follow-Up Visits at 2, 4, 8, and 12 weeks after the last dose of study drug. Serum immunoglobulin (Ig) G, IgA, and IgM were monitored monthly for the first 3 months, at 6, 12, and 18 months, and at the Follow-Up Visits that occurred 4, 8, and 12 weeks after the last dose of study drug.

Peripheral blood mononuclear cells (PBMCs) were collected at Baseline, during treatment, and posttreatment for exploratory immunomodulatory and immune-based analyses as needed. Baseline and on-study blood and DNA samples were taken and stored for all subjects, and CSF samples were taken and stored for all subjects from whom CSF samples were collected. Blood samples were collected and stored for determination of a subject's previous exposure to infective pathogens in the event of AEs that warranted further investigation occurring at a later point in the study.

Centralized skin assessments, using standardized photography, were conducted by a reviewing dermatologist at baseline and at 3-month intervals during the Treatment Period. These assessments specifically included evaluation of any areas of depigmentation or rash. Subjects were also questioned by the investigator at each visit to identify any changes that might have represented a drug induced rash/reaction or infection. Subjects and their caregivers/informants were instructed to contact the investigator when they saw any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so such AEs were reviewed promptly.

Safety brain MRI assessments were performed at Screening, at 6, 12, and 18 months during the Treatment Period and at the final Follow-Up Visit. Additional safety MRI scans were performed as clinically necessary. MRI acquisition and interpretation were organized centrally to ensure reproducibility and consistency between units involved.

Full neurologic examinations were performed at Baseline, at 6, 12, and 18 months, and at the 4 and 12-week Follow-Up Visits, by either a neurologist or a physician with comparable training and experience in undertaking neurologic examinations. The neurologic examinations included muscle strength testing and assessment of cranial nerves including olfaction, with the use of the Brief Smell Identification Test, as well as other parts of the central nervous system.

Cognitive decline was assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments included the ADAS-cog$_{14}$, MMSE, and CBB.

An assessment of suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS) was performed at Screening and Baseline and at regular intervals throughout the Treatment and Follow-up Periods.

An ophthalmic examination (including retinal examination) was conducted at Baseline. An additional examination was conducted if the subject experienced visual disturbances during the course of the study.

Bioanalytical Methods

Plasma and CSF elenbecestat concentrations were measured by a validated liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) in both CSF and plasma was measured using a commercially based enzyme-linked immunosorbent assay (ELISA). The pre- and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau was performed using commercially available ELISAs.

BACE1 levels and activity were measured using a customized assay (BIOMT-2015-013, BIOMT-2015-014).

Substrates of BACE1 inhibition could be explored using Western blots or other amenable methodology if clinical observations warranted and if analytes could be reliably tested in samples collected.

Statistical Methods

All statistical tests were based on the 5% (2-sided) level of significance. Upon implementation of protocol Amendment 06, subjects receiving elenbecestat 5 or 15 mg who had not yet completed Visit 17 (Week 66) were reassigned to 50 mg at the next regularly scheduled visit for the remainder of the Treatment Period. The time of dose reassignment varied among subjects and therefore the treatment duration of 5 or 15 mg among subjects varied. In order to evaluate safety and efficacy of all dosing groups (5, 15 and 50 mg) of elenbecestat, and understand the effects of dose change and treatment duration while maintaining a certain level of unbiased comparison and interpretation, 3 sets of analyses were performed in different baseline or treatment group settings. Additional post hoc analyses were also performed. The details were described in the statistical analysis plan (SAP) and in text in the CSR.

Study Endpoints

Primary Endpoint

- Safety and tolerability, which included incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECG parameters

Secondary Endpoints

- Percentage change of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline after from 4 weeks and up to 18 months of treatment
- The population PK parameters of elenbecestat in CSF and plasma, including the effect of intrinsic and extrinsic factors

Exploratory Endpoints

Change from baseline in:

- CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment
- CSF biomarkers of neurodegeneration (eg, t-tau, p-tau, neurofilament light chain [NFL], visinin-like protein 1 [VILIP1], and neurogranin [Ng]) at 18 months of treatment
- Plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- Total hippocampal volume at 12 and 18 months of treatment as measured by vMRI
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months of treatment as measured by vMRI
- Amyloid PET standardized uptake value ratio (SUVR) composite at 18 months for brain amyloid levels as measured
- The following clinical assessments at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ

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. Safety analyses were conducted using the Safety Analysis Set on a treatment-emergent basis.
- **The Full Analysis Set** (FAS) was the group of randomized subjects who received at least 1 dose of study

drug and had baseline and at least 1 postdose exploratory efficacy measurement. FAS was used for the analyses of amyloid PET and clinical endpoints.

- **The PK Analysis Set** was the group of subjects with at least 1 quantifiable elenbecestat plasma concentration accompanied by a documented dosing history.
- **The PD Analysis Set** was the group of subjects who had a baseline PD measurement and at least 1 postdose PD measurement. PD Analysis Set was used for the analyses of CSF and plasma biomarkers and vMRI endpoints.

Efficacy and Biomarker Analyses

Primary Efficacy Analyses

There was no primary efficacy endpoint.

Secondary Biomarker Analyses

A mixed-effects model with repeated measures (MMRM) model was used to analyze the following secondary endpoint:

- Percentage change of Aβ(1-x) and Aβ(1-42) in CSF relative to baseline from 4 weeks and up to 18 months of treatment

In addition, absolute change from baseline in Aβ(1-x) and Aβ(1-42) was also analyzed similarly.

Exploratory Efficacy and Biomarker Analyses

An MMRM was used to analyze the following exploratory endpoints. The exploratory endpoints were the change (absolute and percentage) from baseline in:

- CSF Aβ(1-40) and BACE1 variables (eg, activity and protein levels) from 4 weeks and up to 18 months of treatment
- CSF biomarkers of neurodegeneration (eg, t-tau, p-tau, NFL, VILIP1, and Ng) at 18 months of treatment
- Plasma amyloid measurements from 4 weeks and up to 18 months of treatment, and during posttreatment follow-up
- Total hippocampal volume at 12 and 18 months of treatment as measured by vMRI
- Left and right hippocampal, whole brain, and total ventricular volume at 6, 12, and 18 months as measured by vMRI
- Amyloid PET SUVR composite at 18 months for brain amyloid levels measured by an appropriate method based on PET tracers.

The following efficacy endpoints were summarized using descriptive statistics:

- Change from baseline in the clinical assessments: ADAS-cog$_{14}$, CDR, MMSE, ISLT, CBB, and FAQ at 12 weeks and at 6, 9, 12, 15, 18, 19, and 21 months

The MMRM model was used to analyze the above endpoints similarly as in the secondary biomarker analysis.

The change (absolute and percentage) from baseline in all nonclinical endpoints were summarized using descriptive statistics. The clinical endpoints were only summarized with the absolute change from baseline.

The relationship between efficacy endpoints and biomarker endpoints were explored.

Due to no convergence in running MMRM, all MMRM tests were replaced with analysis of covariance (ANCOVA) model with baseline value of the response variable as a covariate after treatment unblinding. The least squreas (LS) means and difference in LS means between each elenbecestat treatment group and placebo, and corresponding 95% CI were presented.

Pharmacokinetic Analyses

The PK Analysis Set was used for elenbecestat concentration listings.

For Population PK analysis, the details were described in the separate report, and the results were not included

in this CSR.

Pharmacokinetic and Pharmacodynamic Analyses

The relationships between PK and PD including CSF biomarker levels, amyloid load on PET, and vMRI were investigated. For the PK/PD analysis, the details were described in the separate report, and the results were not included in this CSR.

Pharmacogenomic Analyses

The ApoE genotype and the NAT2 phenotype may be used in the statistical analysis to determine the effects on treatment response, safety, or PK of elenbecestat. Further pharmacogenomic (PGx) analyses may be performed and reported separately.

Safety Analyses

Evaluations of safety were performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out of-range vital signs, suicidality (C-SSRS), and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements, and cognitive decline assessment such as CBB were summarized by treatment group using descriptive statistics.

Lymphocyte Subsets

Lymphocyte subset parameters (ie, CD4 [T helper cells], CD8 [cytotoxic T cells], and CD19 [B cells]) were summarized in the same manner as other laboratory parameters. Mean lymphocyte subsets and the mean change from baseline in lymphocyte subsets were also displayed graphically over time by dose.

Results

In the results section of this CSR, the "R" designation refers to the treatment group to which the subjects were initially randomized, and the groups that include subjects who were randomized to the 5 mg or 15 mg groups and later reassigned to 50 mg are referred as the elenbecestat 5/50 mg or 15/50 mg group, respectively. The elenbecestat 50 mg Total group included subjects in the 50 mg R group and subjects who were reassigned to elenbecestat 50 mg. The extent of exposure was summarized by randomized treatment group and by duration of exposure to each dose. The safety of elenbecestat was summarized by randomized treatment group and by dose at onset, and dose at measurement compared to the pre-treatment baseline and the post-dose baseline (ie, measurement obtained prior to dose re-assignment for subjects who were reassigned from the 5 and 15 mg dose groups to the 50 mg dose group). To put the results in context, subject-months of exposure were used for safety data interpretation, when needed.

Subject Disposition/Analysis Sets

Four hundred forty-four subjects were screened in the study. Of these 444 subjects, 374 were screening failures and 70 (17 in the placebo group, 17 in the elenbecestat 5 mg R group, 19 in the elenbecestat 15 mg R group, 17 in the elenbecestat 50 mg R group) were randomized into the study. Twelve of the 17 subjects randomized to the elenbecestat 5 mg group and 9 of the 19 subjects randomized to the elenbecestat 15 mg group were reassigned to the elenbecestat 50 mg group. A total of 38 subjects were included in the elenbecestat 50 mg Total group.

All 70 randomized subjects were included in the Safety Analysis Set and PK Analysis Set. The FAS, the analysis set for amyloid PET and clinical endpoints, included 68 subjects. The PD Analysis Set, the analysis set for the analyses of CSF and plasma biomarkers and vMRI endpoints, included 69 subjects.

Efficacy

There was no primary efficacy endpoint for this study.

Exploratory efficacy analyses performed for Clinical Dementia Rating Sum of Boxes (CDR-SB), ADAS-cog$_{14}$, MMSE, ISLT, CBB, and FAQ showed the following results at 18 months:

- Overall, the results of the CDR-SB showed 31% less clinical (ie, cognitive and functional) decline in the elenbecestat 50 mg Total group compared with the placebo group. The LS mean (SE) change from baseline was 1.1 (0.43) for the elenbecestat 50 mg Total group, and 1.6 (0.67) for the placebo group (higher scores indicate a greater clinical decline). The LS mean differences (95% CI) between the elenbecestat

50 mg Total and placebo groups was –0.5 (–2.09, 1.12). This finding, however, was not statistically significant possibly due to the small sample size of this study. Results from subgroup analyses varied:

- Less clinical decline was observed in the elenbecestat 50 mg Total group compared with the placebo group for the following subgroups: mild to moderate AD subjects, subjects >65 years old, ApoE4 negative subjects, and subjects not receiving concomitant AD medication(s) at baseline.
- Similar clinical decline was observed between the elenbecestat 50 mg Total and placebo groups for the MCI/prodromal AD subgroup.
- Greater clinical decline was observed in the elenbecestat 50 mg Total group compared with the placebo group in the following subgroups: subjects ≤65 years old, ApoE4 positive subjects, and subjects receiving concomitant AD medication(s) at baseline.

- Results of the ADAS-cog$_{14}$ showed 16% greater cognitive decline in the elenbecestat 50 mg Total group compared with the placebo group. The LS mean (SE) change from baseline was 4.3 (1.05) for the elenbecestat 50 mg Total group and 3.7 (1.69) for the placebo group (higher scores indicate a greater cognitive decline). Overall the LS mean differences (95% CI) between the elenbecestat 50 mg Total and placebo groups for the ADAS-cog$_{14}$ was 0.6 (–3.44, 4.70). This finding was not statistically significant. Results from the subgroup analyses varied:
  - Less cognitive decline was observed in the elenbecestat 50 mg Total group compared to the placebo group for the following subgroups: mild to moderate AD subjects, ApoE4 negative subjects, and subjects receiving concomitant AD medication(s) at baseline.
  - Greater cognitive decline was observed in the elenbecestat 50 mg Total group compared with the placebo group in the following subgroups: MCI/prodromal AD subjects, subjects >65 years old, ApoE4 positive subjects, and subjects not receiving concomitant AD medication(s) at baseline.
- Results of the MMSE showed 28% greater cognitive decline in the elenbecestat 50 mg Total group compared with the placebo group. The LS mean (SE) change from baseline was –2.3 (0.59) for the elenbecestat 50 mg Total group and –1.8 (0.91) for the placebo group (lower scores indicate a greater cognitive decline). The LS mean differences (95% CI) between the elenbecestat 50 mg Total and placebo groups was –0.5 (–2.65, 1.74). This finding was not statistically significant. Results from the subgroup analyses varied.
  - Less cognitive decline was observed in the elenbecestat 50 mg Total group compared with the placebo group in the following subgroups: mild to moderate AD subjects, ApoE4 negative subjects, and subjects receiving concomitant AD medication(s) at baseline.
  - Greater cognitive decline was shown in the elenbecestat 50 mg Total group compared with the placebo group in the following subgroups: MCI/prodromal AD subjects, subjects ≤65 years old, subjects >65 years old, ApoE4 positive subjects, and subjects not receiving concomitant AD medication(s) at baseline.
- Results of the ISLT (Delayed Recall) showed 16% less cognitive decline in the elenbecestat 50 mg Total group compared with the placebo group. The LS mean (SE) change from baseline was –0.783 (0.2955) for the elenbecestat 50 mg Total group and –0.936 (0.4799) for the placebo group (lower scores indicate a greater memory impairment). The LS mean differences (95% CI) between the elenbecestat 50 mg Total and placebo groups was 0.153 (–0.989, 1.295). This finding was not statistically significant.
  - Except for ApoE4 negative subjects, the elenbecestat 50 mg Total group showed less cognitive decline in all subgroups compared with placebo.
- Results of the ISLT (Total Recall) showed 3% less cognitive decline in the elenbecestat 50 mg Total group compared with the placebo group. The LS mean (SE) change from baseline was –3.145 (0.7875) for the elenbecestat 50 mg Total group and –3.234 (1.2243) for the placebo group (lower scores indicate a greater memory impairment). The LS mean differences (95% CI) between the elenbecestat 50 mg Total and placebo groups was 0.089 (–2.858, 3.036). This finding was not statistically significant. Results from the subgroup analyses varied:
  - Less cognitive decline was observed in the elenbecestat 50 mg Total group compared with the placebo group for the following subgroups: ApoE4 positive subjects and subjects not receiving concomitant AD medication(s) at baseline.
  - Greater cognitive decline was observed in the elenbecestat 50 mg Total group compared with the

placebo group in the following subgroups: MCI/prodromal AD subjects, mild to moderate AD subjects, subjects ≤65 years old, subjects >65 years old, ApoE4 negative subjects, and subjects receiving concomitant AD medication(s) at baseline.

- Results of the CBB demonstrated greater decline in the elenbecestat 50 mg Total group compared with the placebo group in the following measures:
  - One-back memory (working memory): the LS mean (SE) changes from baseline for speed and accuracy, respectively, were 0.034 (0.0167) and –0.986 (0.1902) in the elenbecestat 50 mg Total group vs –0.023 (0.0272) and –0.362 (0.3121) for speed of and accuracy, respectively, in the placebo group. Higher scores in speed of performance and lower scores in accuracy indicate a greater decline in performance. The LS mean differences (95% CI) between the elenbecestat 50 mg Total and placebo groups were 0.057 (–0.008, 0.122) and –0.624 (–1.371, 0.123) for speed and accuracy, respectively.
  - Detection (psychomotor processing): the LS mean (SE) change from baseline was 0.056 (0.0185) for the elenbecestat 50 mg Total group vs 0.010 (0.0287) for the placebo group (higher scores indicate a greater decline in performance). The LS mean differences (95% CI) between the elenbecestat 50 mg Total and placebo groups was 0.046 (–0.023, 0.115). This finding was not statistically significant.
  - Identification (attention): the LS mean (SE) change from baseline was 0.022 (0.0130) for the elenbecestat 50 mg Total group vs –0.019 (0.0204) for the placebo group (higher scores indicate a greater decline in performance). The LS mean differences (95% CI) between the elenbecestat 50 mg Total and placebo groups was 0.041 (–0.008, 0.090). This finding was not statistically significant.
  - One-card learning (visual learning): the LS mean (SE) change from baseline was –0.121 (0.1615) for the elenbecestat 50 mg Total group vs –0.035 (0.2663) for the placebo group (lower scores indicate a greater decline in performance). The LS mean differences (95% CI) between the elenbecestat 50 mg Total and placebo groups was –0.085 (–0.725, 0.554). This finding was not statistically significant.
  - CBB memory composite (one-card learning/one-back memory): the LS mean (SE) change from baseline was –0.196 (0.1239) for the elenbecestat 50 mg Total group vs 0.021 (0.2053) for the placebo group (lower scores indicate a greater decline in performance). The LS mean differences (95% CI) between the elenbecestat 50 mg Total and placebo groups was –0.217 (–0.712, 0.277). This finding was not statistically significant.
  - Psychomotor/attention composite: the LS mean (SE) change from baseline was –0.382 (0.1527) for the elenbecestat 50 mg Total group vs 0.163 (0.2382) for the placebo group (lower scores indicate a greater decline in performance). The LS mean differences (95% CI) between the elenbecestat 50 mg Total and placebo groups was –0.544 (–1.119, 0.030). This finding was not statistically significant.
  - Similar results were observed in all subgroups with the following exceptions:
    - Compared with the placebo group, ApoE4 negative subjects in the elenbecestat 50 mg Total group showed less decline in detection (psychomotor processing), and one-card learning (accuracy).
    - Compared with the placebo group, subjects not receiving concomitant AD medication(s) at baseline in the elenbecestat 50 mg Total group showed less decline in one-card learning (accuracy) and CBB memory composite.
- Results of the FAQ showed 25% less functional decline in the elenbecestat 50 mg Total group compared with the placebo group. The LS mean (SE) change from baseline was 4.8 (1.00) for the elenbecestat 50 mg Total group and 6.3 (1.56) for the placebo group (higher scores indicate a greater functional decline). The LS mean differences (95% CI) between the elenbecestat 50 mg Total and placebo groups was –1.6 (–5.34, 2.20). This finding was not statistically significant.
  - Except for subjects ≤65 years old, the elenbecestat 50 mg Total group showed less functional decline in all subgroups compared with placebo.
- Results for all efficacy analyses in this study must be interpreted with caution as the sample sizes in this study are small and the study was not powered to detect statistically significant difference between the elenbecestat 50 mg Total group and the placebo group. Additionally, the small sample size may result in an imbalance across treatment groups at baseline.

Exploratory analyses of the effect of elenbecestat on brain amyloid levels (as measured by amyloid PET SUVR) and vMRI parameters showed the following results:

- After 18 months of treatment, measures of brain amyloid load (using PET SUVR) in the elenbecestat 50 mg Total group and placebo group showed a statistically significant treatment difference of –6.2% (95% CI: –10.54%, –1.83%) for the florbetaben amyloid PET tracer and –13.6% (95% CI: –22.62%, –4.48%) for the florbetapir amyloid PET tracer. Irrespective of amyloid PET tracers, brain amyloid load increased for the placebo group while decreased it for the elenbecestat 50 mg Total group.
    - For the florbetaben amyloid PET tracer, a statistically significant treatment difference between the elenbecestat 50 mg Total and placebo groups was observed for the following subgroups: mild to moderate AD subjects, subjects >65 years old, ApoE4 negative subjects, subjects who took AD medications at baseline, and subjects who did not take AD medications at baseline.
- Analysis of vMRI parameters (left and right hippocampal volume, total hippocampal volume, whole brain volume, and ventricular volume) at 18 months showed a greater decrease in hippocampal and whole brain volumes and a greater increase in ventricular volume in the elenbecestat 50 mg Total group compared with placebo. These differences were not statistically significant.
    - Due to limitations in sample size, results should be interpreted with caution.

Exploratory analyses of relationships between clinical efficacy measures vs brain amyloid levels and vMRI parameters showed the following results:

- No notable correlation was observed between any of the clinical endpoints and PET SUVR composite scores.
- Analysis of the relationship between vMRI parameters vs clinical efficacy measures by pooling subjects from all treatment groups and disease stages showed statistically significant correlations for the following measures:
    - Changes in ventricular volume positively correlated with changes in ADAS-cog$_{14}$, CDR-SB, and FAQ, and negatively correlated with changes in MMSE (higher scores in ADAS-cog$_{14}$, CDR-SB, and FAQ indicate, respectively, a greater cognitive, clinical, and functional impairment. Lower scores in MMSE indicate greater cognitive impairment).
    - Changes in whole brain volume negatively correlated with changes in ADAS-cog$_{14}$, CDR-SB, and FAQ, and positively correlated with changes in MMSE and CBB One Back Memory (accuracy) (higher scores in ADAS-cog$_{14}$, CDR-SB, and FAQ indicate a greater clinical, cognitive, and functional impairment respectively. Lower scores in MMSE and CBB One Back Memory [accuracy] indicate greater cognitive impairment).
    - Changes in total hippocampal volume negatively correlated with changes in CBB Identification (speed of performance). Higher scores in CBB Identification (speed of performance) indicates a greater decline in attention. Additionally, changes in left hippocampus negatively correlated with ADAS-cog$_{14}$ and changes in right hippocampus positively correlated with ISLT Total Recall scores (higher scores in ADAS-cog$_{14}$, and lower scores in ISLT Total Recall indicate a greater impairment).
    - Overall, these results suggest increases in ventricular volume and decreases in whole brain and hippocampal volume are associated with greater cognitive, clinical, and functional decline.
- A statistically significant negative correlation was observed between changes in florbetaben PET SUVR mean composite and ventricular volume and a statistically significant positive correlation between changes in florbetaben PET and whole brain volumes. No significant correlation was observed between changes in florbetaben PET SUVR mean composite and hippocampal volume.

Pharmacokinetics

- Elenbecestat concentrations in plasma and CSF are summarized by dose and day.

Pharmacodynamics

- Analyses of CSF biomarkers showed the following results:
- At weeks 5 and 79, a larger reduction in Aβ(1-x), Aβ(1-40), Aβ(1-42), and soluble amyloid precursor protein beta (sAPPb) and a larger increase in soluble amyloid precursor protein alpha (sAPPa) were observed for the elenbecestat 50 mg R and 50 mg Total groups compared with the placebo group.

- At week 79, a larger reduction in the neurodegenerative markers, t-tau, p-tau, NFL, Ng, VILIP1, was observed in the elenbecestat 50 mg R and 50 mg Total groups compared with the placebo group.
- Due to limitations in sample size, results should be interpreted with caution.

- Analysis of the relationship between CSF biomarkers vs clinical efficacy measures by pooling subjects from all treatment groups and disease stages showed statistically significant correlations for the following measures:
  - Changes in CSF Aβ(1-42) negatively correlated with changes in ADAS-cog$_{14}$ (where higher scores are indicative of poorer cognition) and positively correlated with MMSE (where lower values are indicative of poorer cognition).
  - Changes in CSF p-tau and CSF t-tau positively correlated with changes in ISLT Total recall scores (where higher scores indicate better episodic memory).
  - No notable relationship was found between other clinical cognitive measures and the measured CSF biomarkers.
  - As the sample size for CSF biomarkers are limited, no meaningful conclusion can be drawn.

Pharmacogenomics

- The majority of the subjects (58.8% for the placebo group and 62.3% for the Total elenbecestat group) were ApoE4 positive, and most of them were ApoE4 heterozygous (52.9% for the placebo group and 49.1% for the Total elenbecestat group). The majority of the subjects in both the placebo and elenbecestat groups were NAT2 slow acetylators; only 2 subjects (1 in each of the placebo and elenbecestat 15 mg R groups) were rapid acetylators.

Safety

- The incidence of TEAEs during the Treatment Period was similar across the placebo (88.2%, 15/17 subjects), elenbecestat 50 mg R (88.2%, 15/17 subjects), the elenbecestat 50 mg Total (81.6%, 31/38 subjects), and the Total elenbecestat groups (90.6%, 48/53 subjects). TEAEs that occurred in ≥10% of subjects in the Total elenbecestat group and more frequently than the placebo group were contact dermatitis, headache, abnormal dreams, diarrhea, and fall.
- The incidence of severe TEAEs was similar across the placebo (11.8%, 2/17 subjects), elenbecestat 50 mg R (11.8%, 2/17 subjects), the elenbecestat 50 mg Total (10.5%, 4/38 subjects), and the Total elenbecestat groups (13.2%, 7/53 subjects).
- The incidence of treatment-related TEAEs was similar across the placebo (29.4%, 5/17 subjects), elenbecestat 50 mg R (35.3%, 6/17 subjects), and elenbecestat 50 mg Total groups (26.3%, 10/38 subjects); however, the incidence of the events was higher in the Total elenbecestat group (47.2%, 25/53 subjects) than the placebo group. No apparent dose response relationship was observed between elenbecestat dose and the incidence of treatment-related TEAEs.
- TEAEs occurred at similar frequencies during the first 6 months, 6 to 12 months, and after 12 months of treatment. Among TEAEs that occurred in ≥10%, majority of upper respiratory tract infection, abnormal dreams, headache occurred within the first 6 months. The incidence of diarrhea, contact dermatitis, and fall did not show time dependency during the Treatment Period.
- No deaths occurred during the Core Study.
- The incidence of SAEs was similar between the placebo group (5.9%, 1/17 subjects) and elenbecestat 50 mg R group (5.9%, 1/17 subjects); however, the incidence of SAEs was higher in the Total elenbecestat group (15.1%, 8/53 subjects) and elenbecestat 50 mg Total group (13.2%, 5/38 subjects) than the placebo group. No apparent dose response relationship was observed between elenbecestat dose and the incidence of SAEs.
- The incidence of TEAEs leading to study drug discontinuation was higher in the Total elenbecestat group (22.6%, 12/53 subjects) than the placebo group (11.8%, 2/17 subjects); however, no apparent dose response relationship was observed between elenbecestat dose and the incidence of TEAEs. The incidence of elenbecestat 50 mg R group (11.8%, 2/17 subjects), 50 mg Total group (13.2%, 5/38 subjects) and placebo group was similar.

- The TEAEs most commonly resulting in study drug discontinuation in the Total elenbecestat group were B-lymphocyte count (CD19) decreased (5.7%, 3/53 subjects), followed by CD8 lymphocytes decreased (3.8%, 2/53 subjects).
- Elenbecestat did not appear to have higher risk of suicidal ideation, events of abuse potential or amyloid-related imaging abnormalities (ARIA) compared to placebo.
- Higher incidence of AEs of interest relating to skin rash was observed in the elenbecestat 50 mg R group (29.4%, 5/17 subjects) and 50 mg Total group (15.8%, 6/38 subjects) compared with the placebo group (5.9%, 1/17 subjects).
- There were no changes of clinical importance in mean hematology, chemistry including liver function tests, and urinalysis values over time and no shifts of clinical concern. The incidence of markedly abnormal laboratory values was low and generally comparable across the treatment groups.
- There were slight reductions in mean counts of CD4 T helper lymphocytes, CD8 cytotoxic T lymphocytes, and CD19 B lymphocytes in the elenbecestat 50 mg R group compared with the placebo group. These effects were transient. The lymphocyte subset counts subsequently tended to return to baseline levels as treatment was continued. No notable changes were observed for subjects reassigned from elenbecestat 5 mg or 15 mg to 50 mg.
- The incidence of abnormal lymphocyte subset counts results falling below the protocol-specified discontinuation threshold was low and comparable between the elenbecestat dose groups and the placebo group.
- No subject had AEs of infection reported around the time of abnormal lymphocyte values were observed.
- There were no changes of clinical importance in systolic and diastolic blood pressure, pulse rate, respiratory rate, weight, and temperature.
- There were no changes of clinical importance in ECG parameters. No QTc interval calculated using Fridericia's formula (QTcF) prolongation signal of clinical significance was observed in the Core Study.

Conclusions

- Elenbecestat at a dose of 5, 15, and 50 mg once daily was well tolerated in subjects with MCI/prodromal AD and mild to moderate dementia due to AD.
- The biomarker results including CSF Aβ(1-42) and CSF Aβ(1-x) demonstrated a consistent, drug-related PD effect of elenbecestat.
- Results of amyloid PET assessment showed a statistically significant decrease in Aβ levels for elenbecestat 50 mg Total compared with placebo.
- Exploratory efficacy analyses using the CDR-SB, ADAS-cog$_{14}$, MMSE, ISLT, CBB, and FAQ showed varied results. Results from the ADAS-cog$_{14}$, MMSE, CBB and ISLT Total Recall did not demonstrate any treatment benefits for subjects in the elencebecstat 50 mg Total group compared with placebo. However, results from the CDR-SB, a widely accepted global measure of disease progression and clinical course in AD trials, showed that subjects in the elenbecestat 50 mg Total group had 31% less clinical decline compared with subjects in the placebo group after 18 months of treatment. Results from the ISLT Delay Recall and the functional assessment with the beneficial FAQ further support this finding.
- Overall, treatment with elenbecestat 50 mg resulted in a significant decrease in brain amyloid which was associated with less, though not statistically significant, clinical decline (31%) compared with the placebo group in the CDR-SB. These results combined with the decreases in the CSF Aβ isoforms, CSF Aβ(1-x), Aβ(1-40), and Aβ(1-42), in the elenbecestat 50 Total group, suggest that elenbecestat 50 mg may have an attenuating effect on cognitive decline by directly decreasing Aβ production and lowering accumulation in the brain. However, as the sample sizes in this study are small and relatively heterogenous (study included subjects with MCI/prodromal AD as well as subjects with mild to moderate AD), results from the currently ongoing Phase 3 studies will be needed to validate the findings in this study.
- Findings from this study support clinical investigation of elenbecestat 50 mg in global Phase 3 studies in early AD, which are currently being conducted.

Date of Report

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