PERFORMANCE ON THE INTERNATIONAL SHOPPING LIST TEST AND SUBSEQUENT AMYLOID PET POSITIVITY RATES IN THE ELENBECERAT MissionAD PHASE 3 PROGRAM

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Introduction

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat inhibits the production of Aβ40 and Aβ42 in the brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose and multiple (14 days) ascending dose studies. A phase 2 study (E2609-G000-202; Study 202) has yielded data in subjects with MCI due to Alzheimer’s Disease (AD)/Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat: there were measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-40, 42) after daily administration for 4 weeks. This data along with additional safety and cognitive data from the 18-month long double-blind study provided support and guided the dose selection for the elenbecestat phase 3 studies. The MissionAD global phase 3 elenbecestat program (E2609-G000-301; Study 301 and E2609-G000-302; Study 302) is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat in subjects with Early AD (EAD) who also meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. Eligibility for the MissionAD studies require an MMSE score between 24 and 30 inclusive, a CDR Global score of 0.5, a CDR Memory Box score 20.5, impairment of at least -1.00 z-score on the total recall (TR) and/or delayed recall (DR) components of the International Shopping List Test (ISLT), as well as confirmation of brain amyloid pathology by either amyloid PET or CSF assessment or both.

In the analysis presented herein, the relationship between ISLT performance and amyloid PET positivity rates in these global Phase 3 studies is reported.

Methods

The MissionAD studies are 24-month treatment, global, 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. (Figure 1)

Figure 1: Design of the MissionAD Studies

International Shopping List Test (ISLT)

• The ISLT, a verbal learning and episodic memory test from CogState Ltd, was used to assess both immediate and delayed recall.
• Validated over 90 countries with new cultures and language groups continually added
• Subjects were read a list of 12 items that can be obtained at the local shopping center and then asked to recall as many as possible (ie, immediate recall )
• After a delay of approximately 20 to 30 minutes, in which time the Cogstate Brief Battery was performed as a distractor task, subjects were again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

Amyloid PET Positivity

• Positive biomarker for brain amyloid pathology as indicated.
• Use of 3 amyloid PET tracers approved in the US and other countries were permitted (flutemetamol, florbetaben, and flortiapir).
• Amyloid PET positivity was determined by central visual reads by certified trained experts, according to the approved labels.
• z-scores for the ISLT were calculated based on normative data for age and gender.

Eligible Subjects for Analysis

• In the dataset used for this analysis, 2746 subjects had a centrally-read amyloid PET scan as part of their screening for MissionAD.
• 1475 (54%) out of 2746 subjects were confirmed as being amyloid positive by PET assessment and 1271 subjects (46%) were confirmed to be negative for amyloid.
• Four subgroups were created based on ISLT z-scores: > -1.00, -1.00 to -1.50, -1.50 to -2.00 and ≤ -2.00 on TR and DR respectively.

ISLT – Amyloid PET Positivity Relationship

A summary of results from the ISLT performance and amyloid PET positivity analysis is shown in Figure 2.

Figure 2: Amyloid PET positivity by ISLT Total Recall and Delayed Recall z-scores in Eisai’s MissionAD Phase 3 Studies in Early AD.

Results

• Amyloid PET positivity rates for each subgroup were calculated. Results show the amyloid positive ratios by each ISLT subgroup as well as overall. The “> 2.00 and less” subgroup has a higher amyloid PET positive ratio than all of the other subgroups and the overall group.
• Results indicate that subjects with ISLT scores of >2.00 or less predict a higher amyloid PET positive ratio than the other subgroups and than the overall group.

Figure 3: Amyloid Positive Ratios By The Combination Subgroups Using Each ISLT Score (Total Recall [TR], Delayed Recall [DR]).

Note: number on the bar shows the ratio (amyloid positive subjects / all subjects); Some subjects with missing ISLT z-scores are not categorized, but included in overall

Conclusions

• The amyloid positive ratios by the combination subgroups using each ISLT score (total recall [TR], delayed recall [DR]) are shown in Figure 3.
• Subjects with >2.00 or less of ISLT on DR were especially predictive relative to other categories and subgroups.

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Disclosures

All authors are current employees of Eisai Co, Limited, Eisai Inc or Cogstate Ltd.