A Stepwise Tier-Based Approach for Determining Patient Eligibility in Clarity AD:

A Phase 3 Placebo-Controlled, Double-Blind Study to Confirm the Safety and Efficacy of Lecanemab (BAN2401) 10 mg/kg Biweekly in Patients with Early Alzheimer's Disease

Shau Yu Lynch,[1] **Michelle Gee**,[2] Michio Kanekiyo,[1] June Kaplow,[1] Shobha Dhadda,[1] Michael Irizarry,[1] David Li,[1] Mark Hodgkinson, [1] Thomas Doherty, [2] Masaki Nakagawa,[3] Chad J. Swanson[1]

1. Eisai Inc., Woodcliff Lake, NJ, USA
2. Eisai Ltd., Hatfield, UK
3. Eisai Co., Ltd., Tokyo, Japan

Disclosures

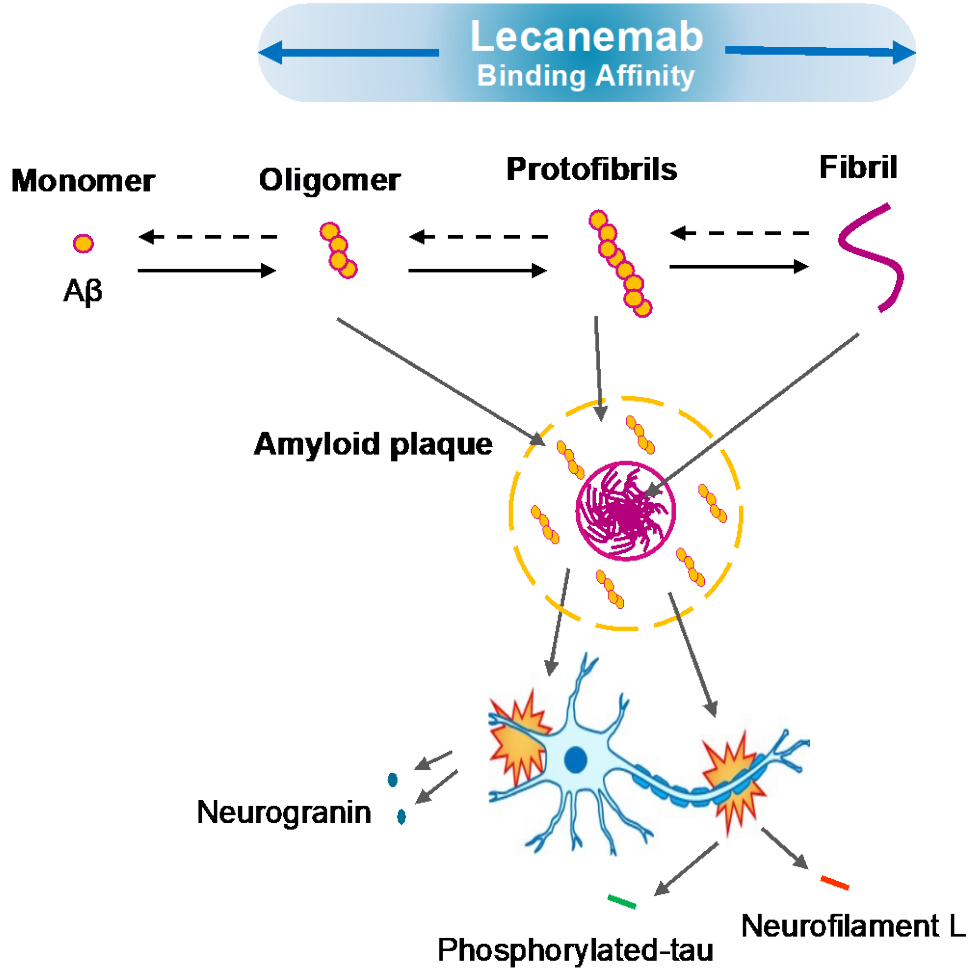
- Dr Gee is an employee of Eisai Ltd.
- All authors are employees or former employees of Eisai Inc., Eisai Ltd., or Eisai Co Ltd.

Introduction

- Identifying eligible patients is one of the biggest challenges of amyloid-modifying clinical trials in early Alzheimer's disease (EAD)
- Major contributors of low recruitment rates:
  - Access to amyloid PET & LP capabilities, evidence of amyloid burden, clinical disease stage, medical comorbidities, concurrent medications, and study partner availability
- More efficient screening methods are needed
  - Excludes ineligible patients early during the screening process
  - Reduce burden on clinical sites, trial patients and study partners
  - Allow the allocation of trial resources to focus on eligible patients

Lecanemab: Anti-Aβ monoclonal Antibody

Selectively Targets Aβ Protofibrils



- Humanized immunoglobulin G1 (IgG1) monoclonal antibody
- Selectively binds to soluble Aβ aggregate species
  - >1000-fold selectivity for protofibrils over Aβ monomers (low affinity for Aβ monomer[1])
  - Preferential activity for Aβ protofibrils over fibrils (>10x) [2-5]

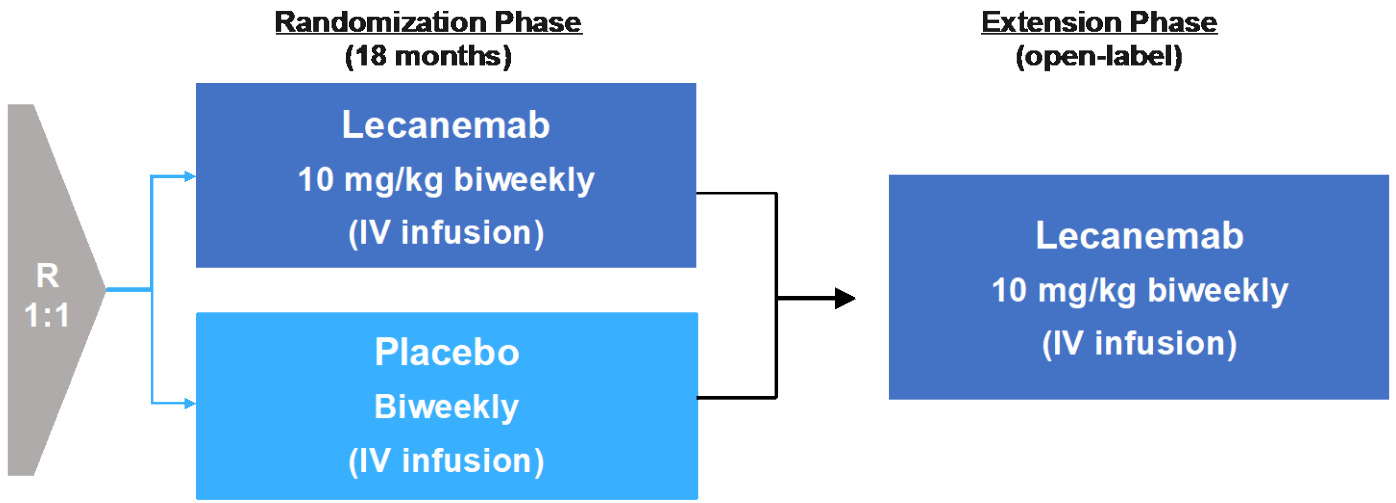
1. Tucker S, et al. J Alzheimers Dis. 2015;43(2):575-88. 2. Lord A, et al. *Neurobiol Dis*. 2009;36:425–34. 3. Sehlin D, et al. *PLoS One*. 2012;7:e32014. 4. Sehlin D, et al. *Neurodegener Dis*. 2011;8:117–23. 5. Logovinsky V, et al. *Alzheimer's Research & Therapy*. 2016;8:14.

Clarity AD Study Design

Clarity AD is a global, placebo-controlled, double-blind, parallel-group, randomized study

Patient Population

- 1,766 patients with Early AD
- MCI due to AD or mild Alzheimer's dementia
- Amyloid pathology confirmed
- MMSE score between 22 and 30 at screening and baseline
- WMS-IV LMSII ≥1 SD below age-adjusted mean at screening



Randomization Phase Primary Outcome Measure:
Change from Baseline in the CDR-SB
(Time Frame: 18 months)

Extension Phase Primary Outcome Measures
Number of Participants with TEAEs
(Time Frame: up to Month 45)
Change from Core Study Baseline in CDR-SB
(Time Frame: up to Month 45)

Randomization will be stratified according to

- Clinical subgroup (MCI due to AD or mild AD dementia)
- Presence or absence of ongoing approved AD treatment (eg, acetylcholinesterase inhibitors, memantine, or both)
- ApoE4 status (ie, carriers or non-carriers)
- Geographical region

3 optional longitudinal sub-studies

- Amyloid PET
- Tau PET
- CSF biomarkers of neurodegeneration

Clarity AD Core Study Endpoints

Primary Endpoint

- The primary efficacy endpoint in the core study is change in CDR-SB from baseline at 18 months

Secondary & Other Endpoints

Key secondary endpoints include change from baseline at 18 months in:

- Amyloid PET SUVr
- ADCOMS
- ADAS-Cog14

Other objectives include change from baseline at 18 months in :

- ADCS-ADL-MCI
- MMSE, CDR-Global
- Biomarkers*

Safety

- Adverse Events
- Laboratory Abnormalities
- Vital Signs
- Monitored throughout the study by the sponsor and by an independent data safety monitoring committee

CDR-SB: Clinical Dementia Rating, sum of boxes. ADCOMS: Alzheimer's Disease Composite Score. ADAS-cog: Alzheimer's Disease Assessment Scale–cognitive subscale. PET SUVr: positron emission topography standardized uptake value ratio. ADAS-ADL-MCI: Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for mild cognitive impairment (MCI) subjects. * Amyloid PET positive to negative conversion; Tau PET; Blood and CSF biomarkers, including: Aβ[1-42], neurogranin, NFL, t-tau, and p-tau; Morphometric measures in the brain as measured by vMRI; Changes in brain tau pathology (tau PET)

Methods

- During the pre-randomization phase, eligibility assessments are organized into 5 progressive tiers and patients must meet all criteria within each tier before progressing to the following tier
- The early screening tiers (Tiers 1 and 2) consist of psychometric measures (MMSE, WMS-IV LMI and LMII, and CDR) and assessments of past and concurrent medical conditions and medications
- MRI, baseline cognitive and safety measures, and confirmation of amyloid pathology by amyloid PET and/or CSF are placed in later screening and baseline tiers (Tiers 3-5)
- Patients who meet all eligibility criteria in the 5 screening tiers will be randomized in a 1:1 randomization schedule to receive either placebo or lecanemab 10mg/kg biweekly
- Approximately 1766 patients will be randomized

Clarity AD Screening and Baseline Tiers

Screening Tiers (1-3)

Tier 1

- Informed consent, Demographics, Medical history
- GDS
- MMSE, CDR and WMS-IV LMI and LMII

Tier 2

- Physical Exam
- Vital Signs, Height & Weight
- ECG and Labs
- C-SSRS

Tier 3

- MRI (safety and volumetric)

Baseline Tiers (4-5)

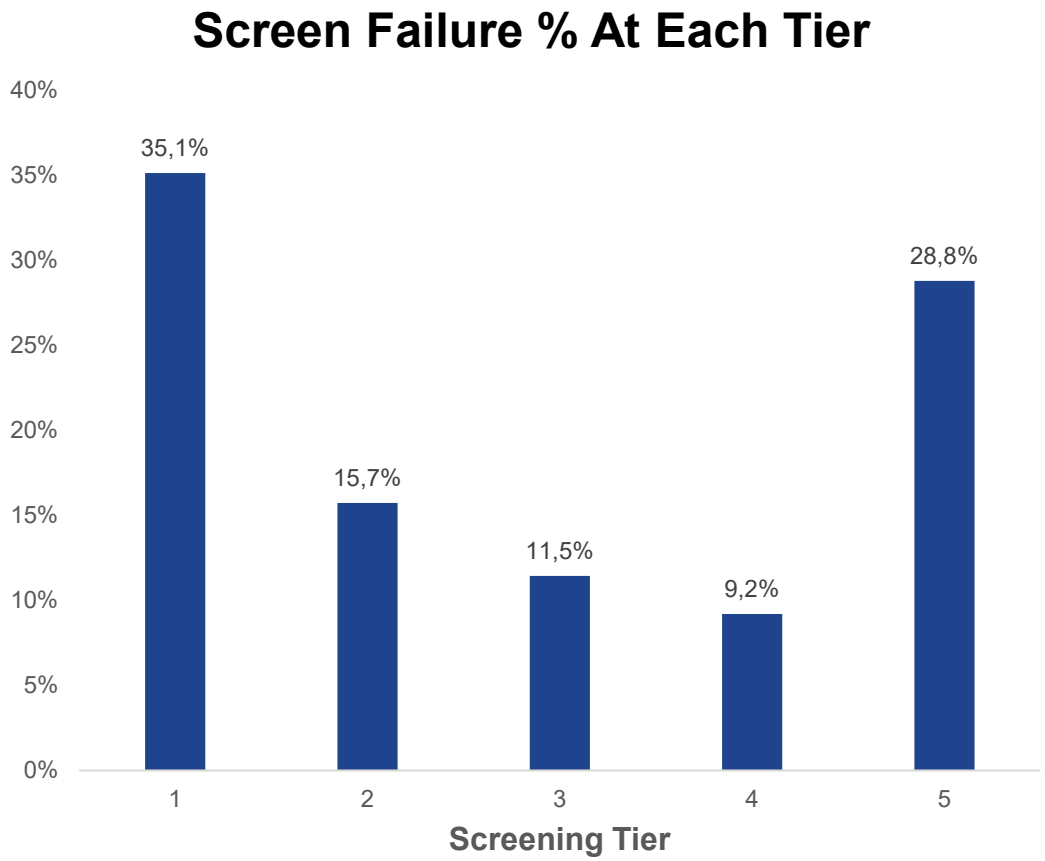
Tier 4

- Physical Exam, Vital Signs, Labs
- MMSE, CDR, ADAS-Cog
- EQ-5D-5L, QoL-AD, ADCS MCL-ADL, ZBI
- C-SSRS

Tier 5

- Amyloid PET (for eligibility and baseline for longitudinal substudy)
- CSF sampling (for eligibility and baseline for longitudinal substudy)
- Tau PET (for baseline for longitudinal substudy)

Results



- 5972 patients were screened, and 1795 patients were randomized. Data cleaning is currently ongoing
- Highest failure reason in Tier 1-2: WMS-IV LMII (>20%)
- Highest failure reason in Tier 3-5: amyloid pathology
  - 28.8% amyloid negative (~10% of screening population)
  - A higher proportion of ApoE4 carriers (86.6%) were amyloid positive compared with ApoE4 noncarriers (56%)
- Results consistent with those observed in the lecanemab phase 2 study

*Data of October 21, 2021

Conclusions

- The stepwise tier-based approach utilized in the Clarity AD study reduced trial burden on clinical sites, patients and study partners by disqualifying approximately 70% of non-eligible patients early in the screening process
- This approach eliminates unnecessary, time-consuming, and invasive procedures in these patients, allowing for sites to focus their resources and attention on potentially qualified patients for the trials
- Such an approach reduces overall recruitment time and costs

Acknowledgments

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