# Modeled Impact of APOE4 Genotype on ARIA-E Incidence in Patients Treated With Lecanemab

**Larisa Reyderman,[1] Seiichi Hayato,[2] Harsha Reddy,[1] Osamu Takenaka,[1] Sanae Yasuda,[2] Chad J. Swanson,[1] Brian A. Willis,[1] and Ziad Hussein[3]**

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

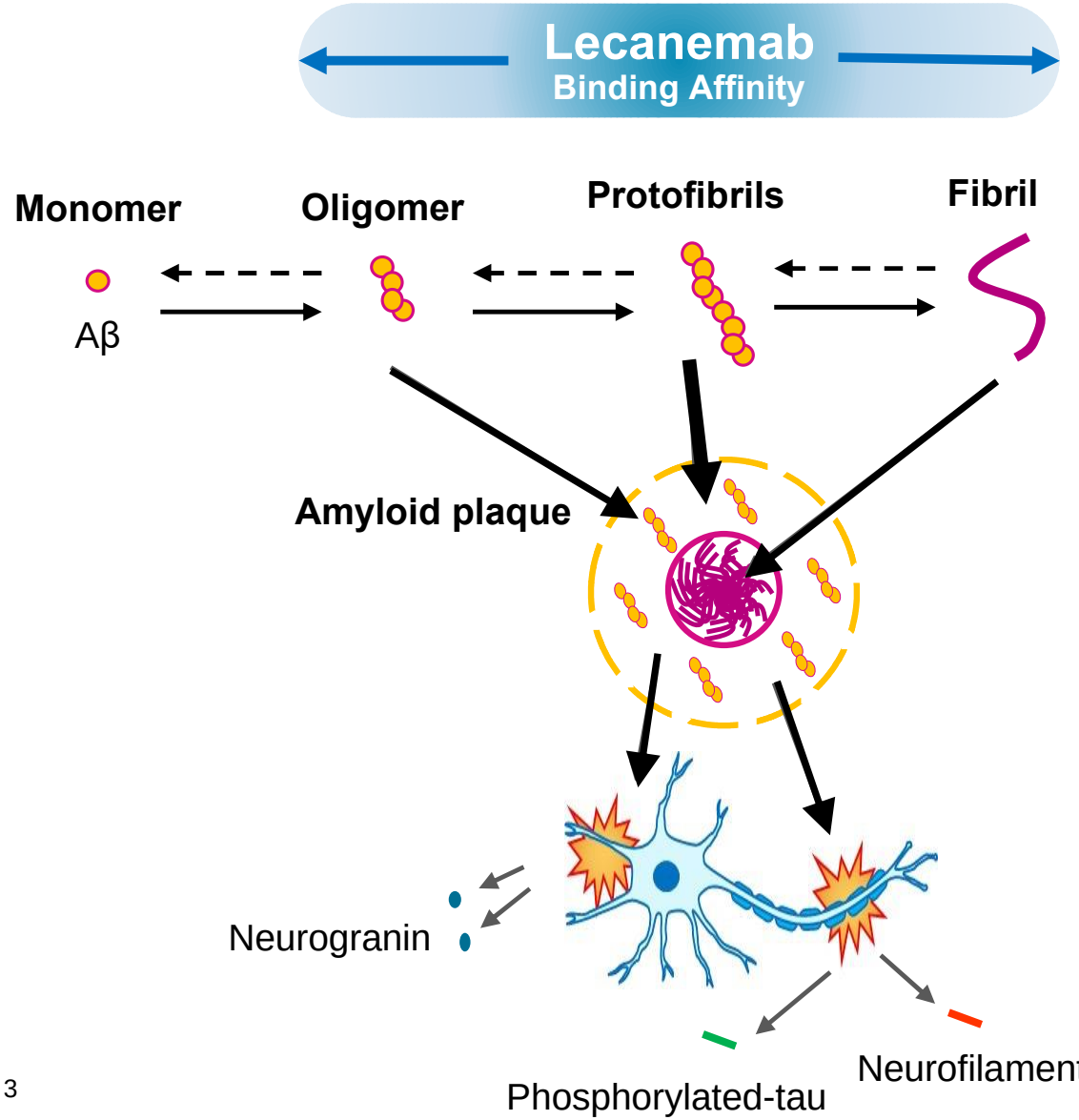
2022 AAIC Annual Meeting | July 31-August 4, 2022 | San Diego

# Presenter Disclosures

- **Dr Reyderman is an employee of Eisai.**

# Lecanemab: Anti-Aβ Protofibril 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]
- Evaluated in an 856-patient placebo-controlled, randomized phase 2 study with an open-label extension (OLE)[6]
  - Reduction in brain amyloid accompanied by a consistent reduction of clinical decline
  - Well-tolerated with 9.9% ARIA-E at 10 mg/kg IV biweekly (~3% symptomatic)
    - Incidence of ARIA-E was lecanemab dose-dependent and greater in APOE4 carriers.

Aβ, amyloid-beta; ARIA-E, amyloid related imaging abnormalities - edema; IV, intravenous; p-tau, phosphorylated tau.

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. 6. Swanson et al. Alzheimers Res Ther. 2021;13(1):80.

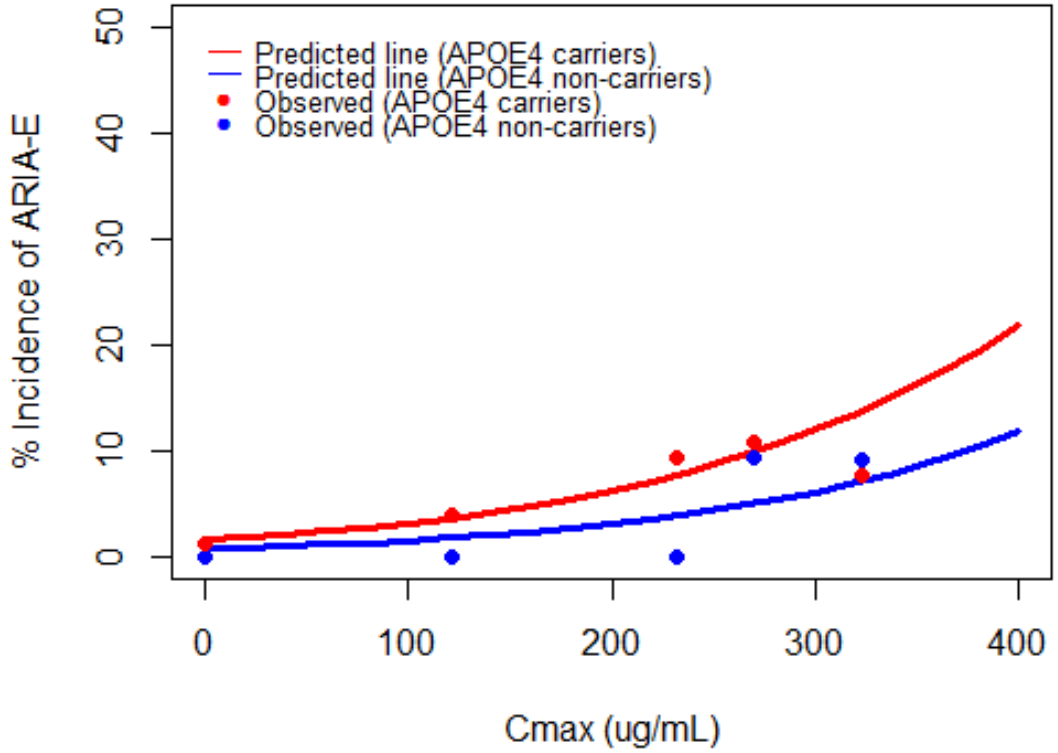
# ARIA-E Exposure-Response Analysis

## *Effect of APOE4 Carrier Status*

- Population PK model was used to derive $C_{max,ss}$ and $C_{ave,ss}$ for sequential Exposure-Response analysis of ARIA-E
- The incidence of ARIA-E as a function of lecanemab exposure was modeled using logit function
  - The exposure parameters, $C_{av,ss}$ and $C_{max,ss}$ were tested as linear function
  - Observed and predicted ARIA-E incidence attenuates over time
  - Log-hazard model was used as a base model

- **Estimated baseline hazard was 26% lower for APOE4 non-carriers than carriers**
- **ARIA-E best correlated with $C_{max}$ at steady-state**

**Model-Predicted % Incidence of ARIA-E vs. Lecanemab $C_{ss,max}$[2]**




Filled circles represent the observed proportion of subject with ARIA-E for each $C_{ss,max}$ quartile (1Q-4Q), plotted at the median $C_{ss,max}$ of each group. Solid line represents the model predicted line.



1. Swanson et al. Alzheimers Res Ther. 2021;13(1):80. 2. Hussein, et al., International Conference on Alzheimer's & Parkinson's Diseases (AD/PD), 2019.

# Analysis Objectives

- To evaluate APOE4 genotype defined as APOE4 homozygous carrier, heterozygous carrier, and APOE4 non-carrier as a covariate in the exposure-ARIA-E model
- To evaluate lecanemab exposure parameter ($C_{ss,max}$ or $C_{ss,ave}$) that is best predictor of ARIA-E incidence
- To test hypothesis that ARIA-E incidence in APOE4 heterozygous carriers and APOE4 noncarriers is similar



1. Swanson et al. Alzheimers Res Ther. 2021;13(1):80.

# ARIA-E Exposure-Response Model :

## *Exposure Parameters and APOE4 Genotype Covariate Evaluation*

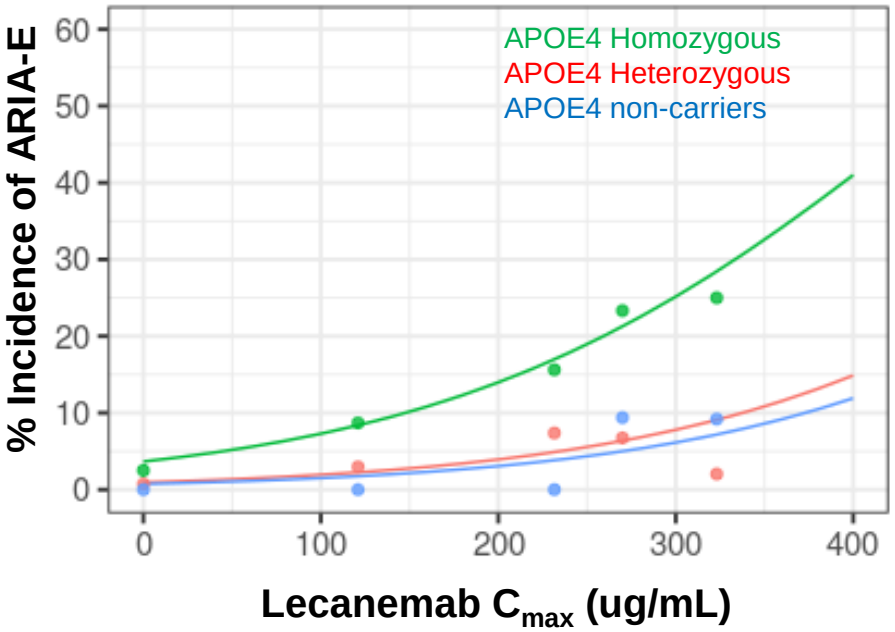
- Inclusion of APOE4 genotype as a covariate in the model with 3 categories led to a statistically significant decrease in model objective function (OFV) (P <0.001)
- Inclusion $C_{ss,ave}$ as a measure of lecanemab exposure resulted in larger OFV
  - $C_{ss,max}$ is a better predictor of ARIA-E compared to $C_{ss,ave}$
- Incidence of ARIA-E is similar in APOE4 heterozygous carriers and APOE4 noncarriers and distinct in APOE4 homozygous carriers

| Model # | Model Description | OFV* |
|---|---|---|
| **1** | $C_{ss,max}$ without covariates | 345.597 |
| **2** | $C_{ss,max}$ with APOE4 genotype as 3 categories (APOE4 noncarrier vs. hetero vs. homo) | 326.584 (*P* < 0.001) |
| **3** | $C_{ss,ave}$ with APOE4 genotype as 3 categories (APOE4 noncarrier vs. hetero vs. homo) | 341.897 |
| **4** | $C_{ss,max}$ with APOE4 genotype as 2 categories (APOE4 homo vs others) | 326.979 P = 0.5297 (vs. Model #2) |

OFV = objective function value.
*defined as 2 categories, APOE4 homozygous carriers and other (APOE4 heterozygous carriers and APOE4 noncarriers)

# ARIA-E Exposure-Response Model Predictions

## Model Predicted and Observed ARIA-E vs. $C_{max}$




Filled circles represent the CORE observed proportion of subject with ARIA-E for each $C_{max}$ quartile (1Q-4Q) and placebo, plotted at the median $C_{max}$ of each group. Solid line represents the model predicted line.

- Model-predicted ARIA-E rates for APOE4 homozygous carriers treated with lecanemab 10 mg/kg biweekly were 22.5% (versus 6.8% in heterozygous or 5.4% in noncarriers)
  - Comparable to the observed 25% incidence in newly-treated homozygous carriers (1/4) in the OLE study
  - < 50% incidence in homozygous carriers (5/10) in the Core

### Study 201 Core
**Model Predicted ARIA-E by $C_{max}$**

| Category | 10 mg/kg Monthly ($C_{max}$=239 ug/mL) | 10 mg/kg Biweekly ($C_{max}$=280 ug/mL) |
|---|---|---|
| APOE4+ | | |
| Homo | **17.7%** | **22.5%** |
| Hetero | **5.1%** | **6.8%** |
| APOE4- | **4.0%** | **5.4%** |

### Study 201 OLE
**Observed ARIA-E**

| Category | Newly Treated Core placebo* (N=45) |
|---|---|
| APOE4+ | |
| Homo | 1/4 (**25.0%**) |
| Hetero | 3/27 (**11.1%**) |
| APOE4- | 0/14 (**0%**) |

*10mg/kg bi-weekly



APOE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities – edema; $C_{max}$, maximum serum concentration; OLE, open label extension.

# Summary and Conclusions

- APOE4 genotype is a significant covariate in the exposure-ARIA-E model
- The probability of ARIA-E was best correlated with lecanemab maximum concentration at steady-state ($C_{ss,max}$)
- ARIA-E incidence is higher in APOE4 homozygous carriers and lower and similar in APOE4 noncarriers and APOE4 heterozygous carriers
- No statistically significant difference in ARIA-E incidence was found between non-carriers and heterozygous carriers
- Model-predicted ARIA-E rates for APOE4 homozygous carriers after lecanemab 10 mg/kg biweekly were 22.5% and comparable to observed 25% (1/4) ARIA-E incidence in newly-treated Core placebo APOE4 homozygous carriers in the OLE phase but lower than the 50% rate (5/10 observed in the Core phase
- Limitation: under representation of APOE4 carriers in Core phase in 10 mg/kg biweekly dosing group. However:
  - The 10 mg/kg monthly has 90% APOE4 carriers (and similar $C_{max}$ as 10 mg/kg biweekly)
  - 70% APOE4 carriers in OLE where rates are consistent, and all received 10 mg/kg IV biweekly
  - Kaplan-Meier estimates (not shown) take into account administrative terminations in estimating rate
  - DSMB reviews in Clarity AD and would require informing sponsor/FDA if greater risk
- Data from the larger Clarity AD study will be used to confirm these findings

# Acknowledgments

We thank the participants, their families and study partners, and the sites and staff participating in this study for their significant contributions

Funding for the studies and analyses was provided by Eisai Inc. and Biogen Inc.

Editorial support, funded by Eisai Inc, was provided by Mayville Medical Communications