2022 Clarity AD CTAD Presentations

Clarity AD: A Phase 3 Placebo-Controlled, Double-Blind, Parallel-Group, 18-Month Study Evaluating Lecanemab in Early Alzheimer's Disease

Clinical Trials on Alzheimer's Disease (CTAD)
San Francisco, CA, USA
November 29 – December 2, 2022

Welcome and Introductions

Takeshi Iwatsubo

University of Tokyo

Clarity AD Topline Results Presentations

CTAD 2022 Clarity AD Session Agenda

CTAD 2022 Session Agenda: *Clarity AD: A Phase 3 Placebo-Controlled, Double-Blind, Parallel-Group, 18-Month Study Evaluating Lecanemab in Early Alzheimer's Disease*		
TIME	**SESSION**	**PRESENTERS**
5 min	**Welcome & Introductions** This introduction will highlight the importance of this first large completed positive phase 3 trial to patients and their families living with Alzheimer's disease and scientists in the field. He will introduce the speakers and the materials to be presented.	***Takeshi Iwatsubo*** ***The University of Tokyo***
10 min	***Clarity AD: Clinical Trial Background and Study Design Overview*** This session will highlight relevant Alzheimer's disease background and review the Clarity AD trial study design. The background will include an overview of the varying mechanisms of emerging Aβ immunotherapy in development and what makes lecanemab different than other antibodies.	***Michael Irizarry*** ***Eisai***
15 min	***Lecanemab for the Treatment of Early Alzheimer's Disease: Topline Efficacy Results from Clarity AD*** This session will explore the Clarity AD clinical trial efficacy results: Amyloid PET, Clinical Dementia Rating-Sum-of-Boxes (CDR-SB; primary endpoint), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14), Alzheimer's Disease Composite Score (ADCOMS) and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL).	***Christopher van Dyck*** ***Yale School of Medicine***
10 min	***Safety Profile of Lecanemab in Early Alzheimer's Disease*** This session will review lecanemab safety results from Clarity AD and overall lecanemab safety profile, including an in-depth review of current evidence related to amyloid related imaging abnormalities (ARIA). Safety profiles of emerging anti-amyloid antibody Alzheimer's disease will also be summarized.	***Marwan Sabbagh*** ***Barrow Neurological Institute***
10 min	***Imaging, Plasma, and CSF Biomarkers Assessments from Clarity AD*** This session will highlight the Clarity AD clinical trial biomarker assessment results. Evidence supporting the optimal dosing regimen and timing will also be presented.	***Randall Bateman*** ***Washington University***
10 min	***Context of Clarity AD Results*** This session will place the efficacy and safety results from the Clarity AD study in context of real-world practice, including the lecanemab Phase 2 results.	***Sharon Cohen*** ***Toronto Memory Program***
15 min	***Panel Discussion and Q&A*** Dr. Iwatsubo will moderate this session.	***All***
	Adjourn	

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Lecanemab in Early Alzheimer's Disease

Christopher H. van Dyck, M.D., Chad J. Swanson, Ph.D., Paul Aisen, M.D., Randall Bateman, M.D., Christopher Chen, B.M., B.Ch., Michelle Gee, Ph.D., Michio Kanekiyo, M.S., David Li, Ph.D., Larisa Reyderman, Ph.D., Sharon Cohen, M.D., Lutz Froelich, M.D., Ph.D., Sadao Katayama, M.D., Marwan Sabbagh, M.D., Bruno Vellas, M.D., David Watson, Psy.D., Shobha Dhadda, Ph.D., Michael Irizarry, M.D., Lynn D. Kramer, M.D., and Takeshi Iwatsubo, M.D.

Clarity AD: Clinical Trial Background and Study Design Overview

Michael Irizarry
Eisai Inc.

Acknowledgements

Participants & Their Support

We acknowledge with thanks the individuals who enrolled in lecanemab Clarity AD Trial as well as their family, caregivers, and friends who supported them.

Data Safety Monitoring Board (DSMB), Raters, Investigators, and Study Team Members

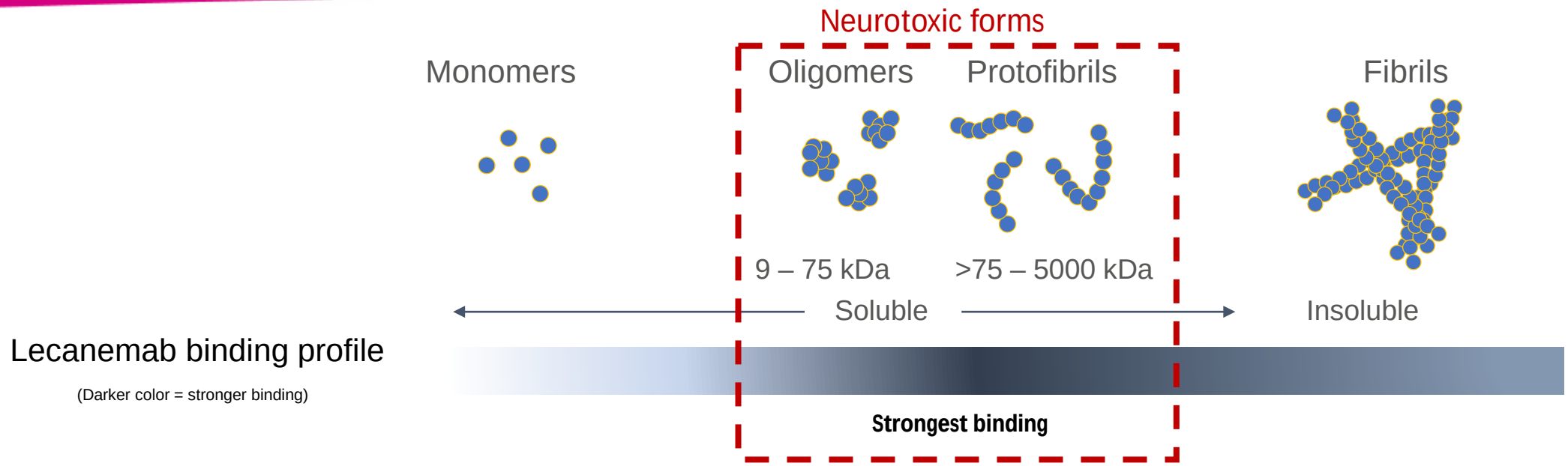
We also acknowledge the DSMB members, Site Investigators, Study Coordinators, Raters, contract research organization (CRO), and other personnel whose dedication and hard work in collecting data and providing care were essential to the completion of this trial.

Disclosure

- Dr. Irizarry is an employee of Eisai Inc.

Lecanemab: Unique Selectivity Towards Toxic Soluble Species of Aβ

Highest Preference for Soluble Protofibrils/Oligomers Versus Monomeric and Fibrillar Forms of Aβ



Ab pathway in Alzheimer's Disease

- Aβ dynamically evolves through different conformational states, including:[1,2]
  - Soluble monomers
  - Soluble aggregates of increasing size (eg, dimers, trimers, oligomers, protofibrils)
  - Protofibrils are defined as large (>75-100kDa), soluble, aggregated Aβ filaments[1]
  - Insoluble fibrils and amyloid plaques
- Recent studies have garnered considerable interest in the role of protofibrils in the pathophysiology of Alzheimer's disease[2-4]

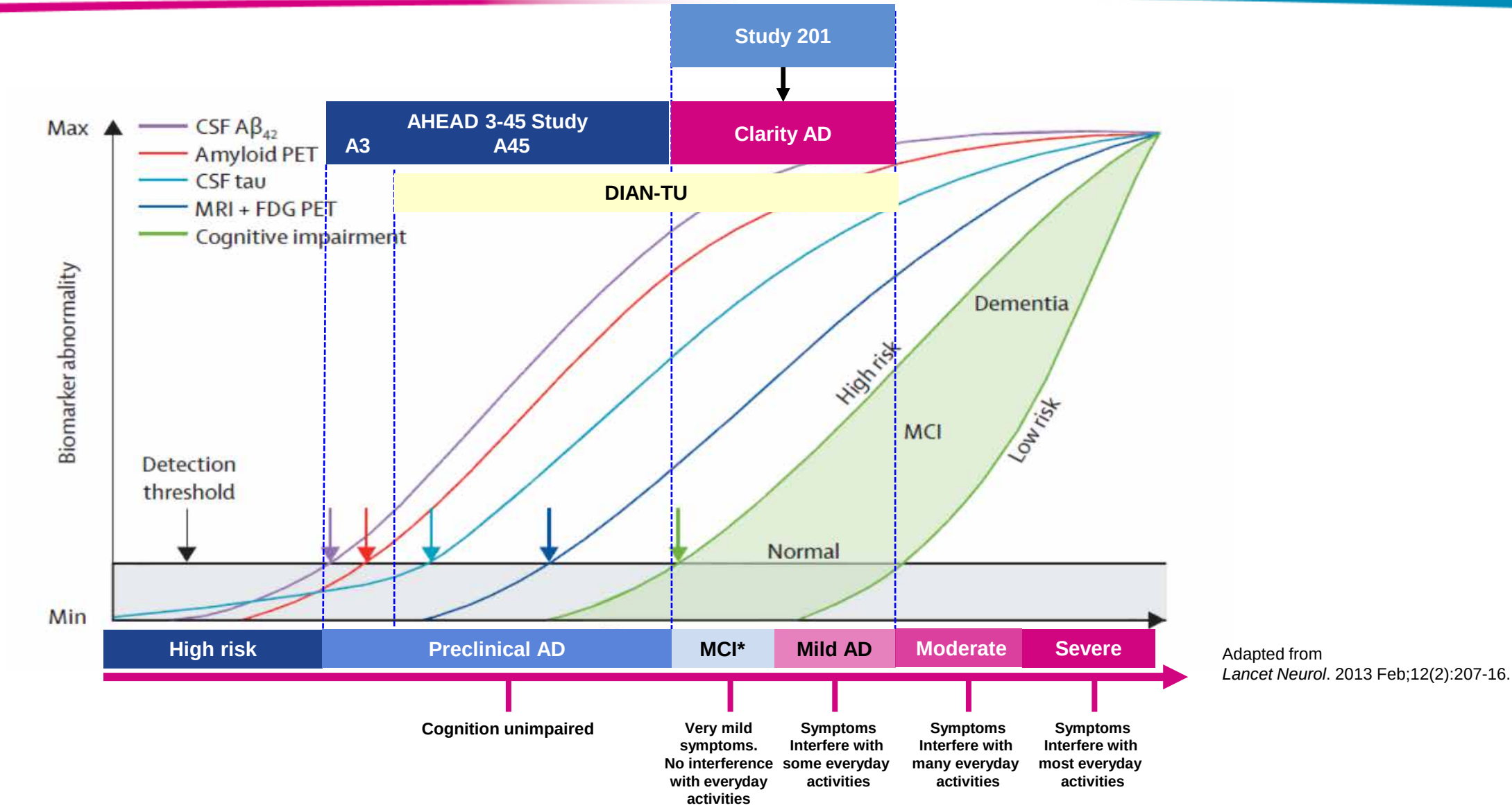
Lecanemab

- Lecanemab is a 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[5])
  - Preferential activity for Aβ protofibrils over fibrils (>10x)[6-10]
- Initiates microglial mediated clearance of protofibrils and plaques

Aβ, amyloid-beta; kDa, kilodaltons. Source: Presented at CTAD 2021. Note: Illustration is based on data from Biacore, inhibition ELISA and immunoprecipitation.

1. Walsh DM, et al. *J Biol Chem.* 1997;272:22364-22372. 2. Paranjape GS, et al. *ACS Chem Neurosci.* 2012;3:302-311. 3. Haass C, Selkoe DJ. Nat Rev Mol Cell Biol. 2007 Feb;8(2):101-12. 4. Stern AM, et al. bioRxiv 2022.10.18.512754. 5. Tucker S, et al. J Alzheimers Dis. 2015;43(2):575-88. 6. Lord A, et al. *Neurobiol Dis.* 2009;36:425–34. 7. Sehlin D, et al. *PLoS One.* 2012;7:e32014. 8. Sehlin D, et al. *Neurodegener Dis.* 2011;8:117–23. 9. Logovinsky V, et al. *Alzheimer's Research & Therapy*. 2016;8:14. Söderberg L, et al. *Neurotherapeutics*. 2022 Oct 17. Epub ahead of print.

Alzheimer's Disease Continuum & Lecanemab Clinical Trials



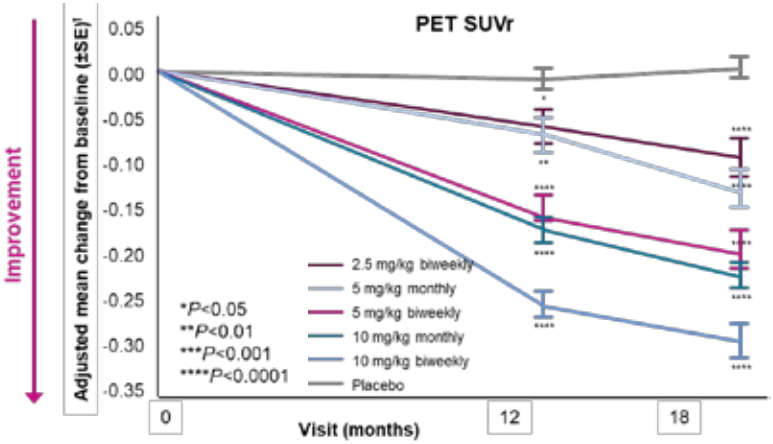
Adapted from
Lancet Neurol. 2013 Feb;12(2):207-16.

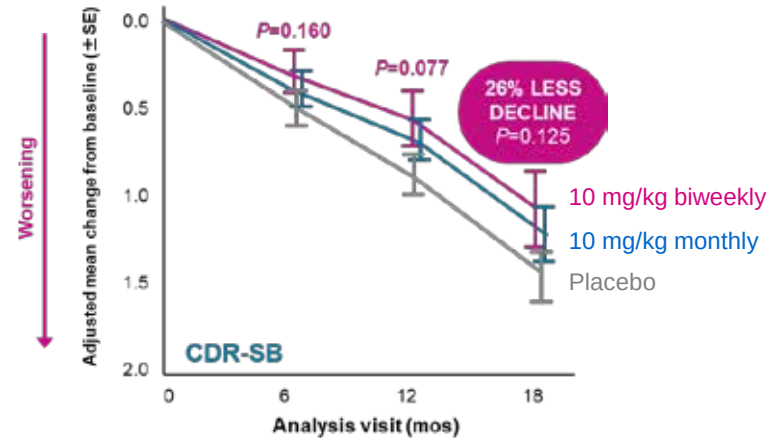
*MCI due to AD.
Aβ, amyloid-beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography.

Lecanemab Phase 2b Study

Results Enabled Optimization of Design of Clarity AD

	Study 201 (Phase 2b)	Clarity AD (Phase 3)
Study Design	**Bayesian Adaptive Randomization Design and Dose Regimen-finding Study with OLE** 854 Randomized	**Global, Placebo-Controlled, Double-blind, Randomized Trial with OLE**
Study Population	**MCI due to AD or mild AD dementia (NIA-AA criteria, CDR 0.5-1)** • Confirmed amyloid pathology (amyloid PET or CSF) • Memory impairment (WMS-IV LMSII ≥1 SD below age-adjusted mean) • MMSE 22-30 **Selected Exclusions:** • Neurological condition that may be contributing to cognitive impairment beyond that caused by AD • Medical conditions which are not adequately controlled, could affect safety or the study assessments	
Dose	• Lecanemab 2.5, 5, or 10 mg/kg IV q2wk • Lecanemab 5 or 10 mg/kg IV q4wk • Placebo	• Lecanemab 10 mg/kg IV q2wk dose selected based on Study 201 clinical and biomarker outcomes
Clinical Outcomes	• Primary outcome (ADCOMS at 12 mo) not met • ADCOMS at 18 months: 30% less decline • ADAS-Cog14 at 18 months: 47% less decline • CDR-SB at 18 months: 26% less decline	• Dose selected had largest treatment effect on ADCOMS • Clarity AD powered on CDR-SB based on Study 201 results
Biomarker Outcomes	• Amyloid PET: Dose & time dependent reduction of amyloid • Amyloid lowering correlated with clinical outcomes	• Dose selected had most rapid and deep amyloid clearance
Safety	• ARIA-E: 9.9% for LEC10BW; 14.3% in ApoE4+ • Treatment discontinued for ARIA-E • Infusion-related reactions: 19.9% Lecanemab 10 mg/kg q2wk, most mild-moderate	• No titration based on ARIA-E rates in study 201 • Dose through mild asymptomatic ARIA-E; otherwise pause dosing until resolution





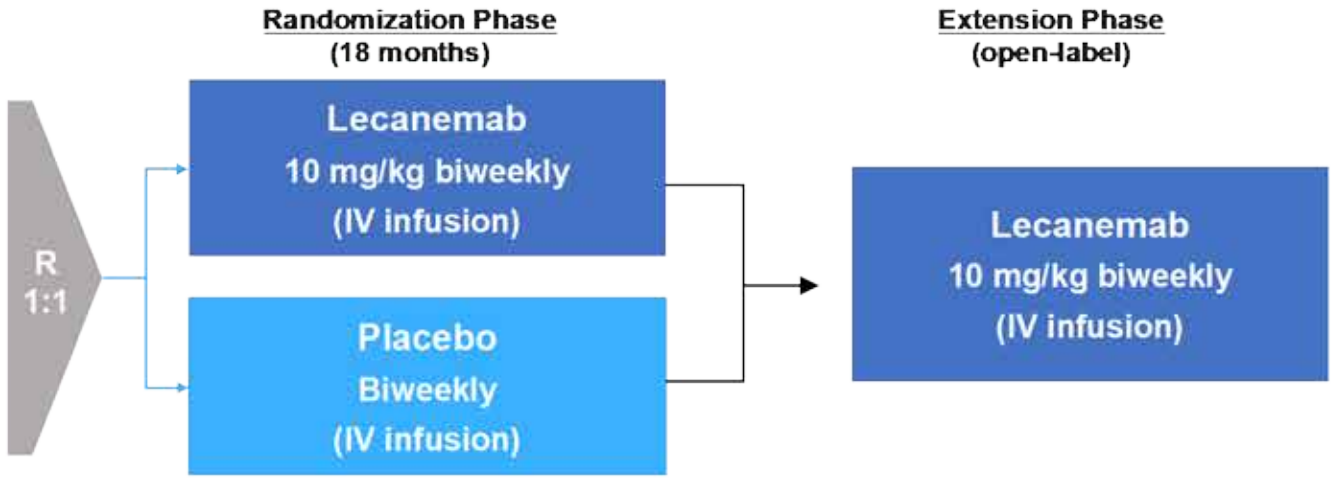
Aβ, amyloid-beta; AD, Alzheimer's disease; ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities - edema; CDR-SB, Clinical Dementia Rating-sum of boxes; CSF, cerebrospinal fluid; IV, intravenous; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging – Alzheimer's Association; OLE, open-label extension; PET, positron emission tomography; q2wk, every 2 weeks; SE, standard error; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II.

Clarity AD Study Design

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

Patient Population

- 1,795 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:

CDR: Change from Baseline at 18 months

Key Secondary Outcome Measures:

Change from Baseline at 18 months:
Amyloid PET
ADAS-Cog14
ADCOMS
ADCS MCI-ADL

Extension Phase Primary Outcome Measures

Number of Participants with TEAEs
Change from Core Study Baseline in CDR-SB

Randomization 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

Diverse patient population

- Eligibility Criteria
- Site selection
- Community outreach
- Decentralized activities

Optional longitudinal sub-studies

- Amyloid burden (amyloid PET; n=716)
- Brain tau pathology (tau PET; n=257)
- CSF biomarkers of neurodegeneration (n=281)
- Subcutaneous formulation (OLE)

AD, Alzheimer's disease; ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; CSF, cerebrospinal fluid; IV, intravenous; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; OLE, open-label extension; PET, positron emission tomography; SD, standard deviation; TEAEs, treatment emergent adverse events; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II.

Sample Size Calculation & Statistical Testing Hierarchy

Sample Size Determination for CDR-SB

- Estimated standard deviation for placebo: 2.031
- Estimated treatment difference: 0.373 in all subjects
  - Assumptions based on effect seen in phase 2
  - Translates to 25% less decline on treatment
- 1795 total sample size planned, assuming:
  - 20% dropout rate
  - 90% power
  - 2-sample t-test using 2-sided alpha = 0.05
  - Accounts for subjects who missed 3 or more consecutive doses due to extenuating circumstances

Statistical Testing Hierarchy

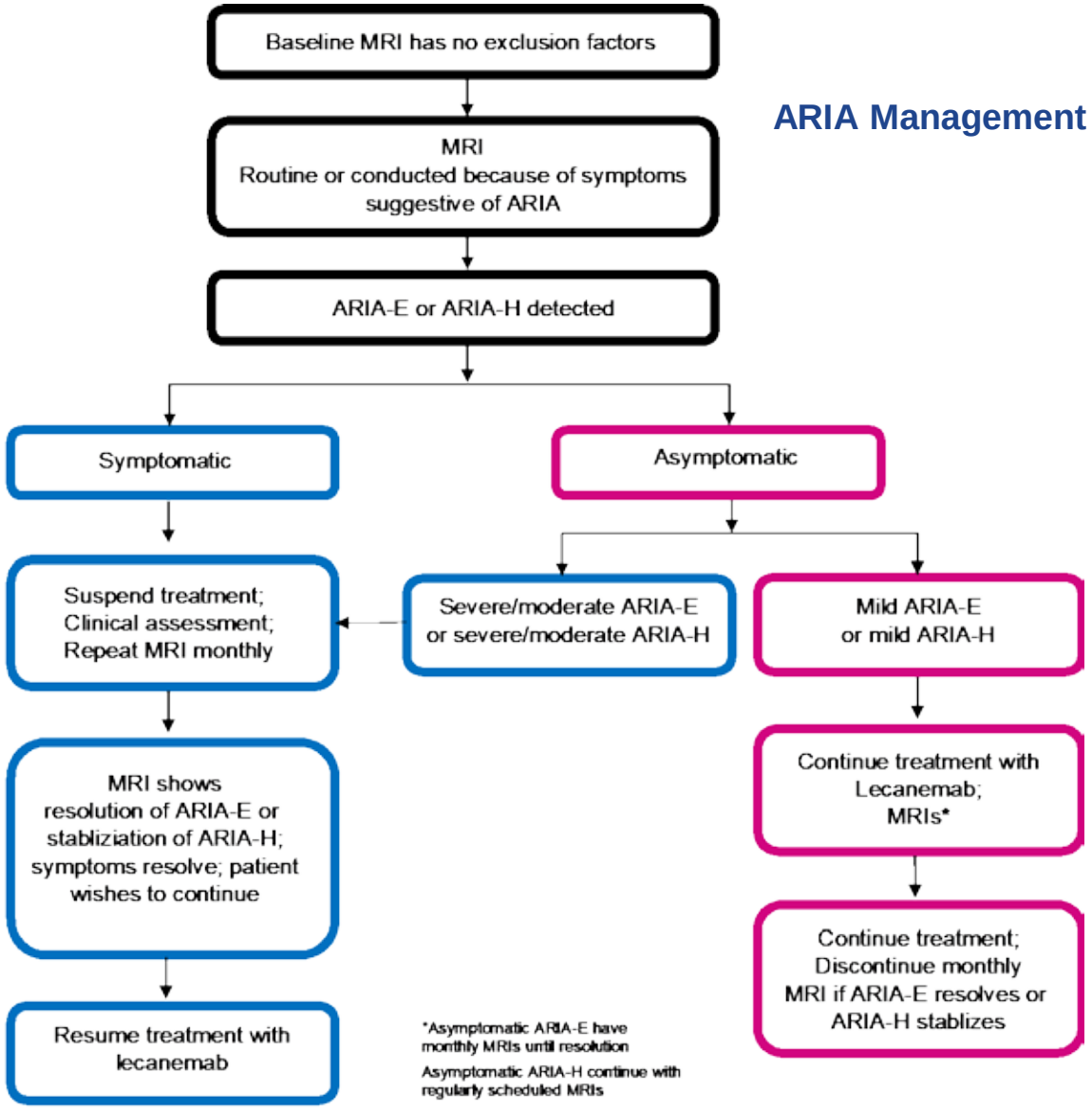
1. **CDR-SB change from baseline at 18 months**
   - Increases across any of the six CDR domains scores (which range from 0, 0.5, 1, 2, 3 for a scale range from 0-18, with early Alzheimer's disease consistent with the 0.5-6 portion of the range) represent a clinically notable decline in a primary domain of Alzheimer's disease symptomatology.
2. **Amyloid PET change from baseline using Centiloids at 18 months for brain amyloid levels**
   - Quantitative measurement of amyloid-beta deposition
3. **ADAS-Cog14 change from baseline at 18 months**
   - Cognitive assessment instrument with a scale of 0-90 points with higher scores indicating increased impairment
4. **ADCOMS change from baseline at 18 months**
   - Developed to measure outcomes among patients with early Alzheimer's disease; scale of 0-1.97, with 1.97 indicating maximum impairment.
5. **ADCS MCI-ADL change from baseline at 18 months**
   - Scale for evaluating activities of daily living, with scale 0-53, where lower score indicates greater level of impairment

ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating-sum of boxes; PET, positron emission tomography.

Study Conduct: Safety

- Safety monitored throughout the study in a blinded manner by the sponsor and in an unblinded manner by an independent data safety monitoring committee
  - Safety evaluations included monitoring of vital signs, physical examinations, adverse events, clinical laboratory parameters, 12-lead electrocardiograms
  - ARIA occurrence monitored throughout the study
    - Safety MRI at screening, 9wk, 13wk, 6mo, 12mo, 18mo
    - Investigators responsible for medical management of patients were different from those involved in clinical assessments
    - Independent medical monitoring team managed ARIA and infusion-related related reactions firewalled from clinical team managing the study
    - An independent unblinded DSMB convened at regular intervals to monitor the overall safety of the study and made recommendations to sponsor as needed

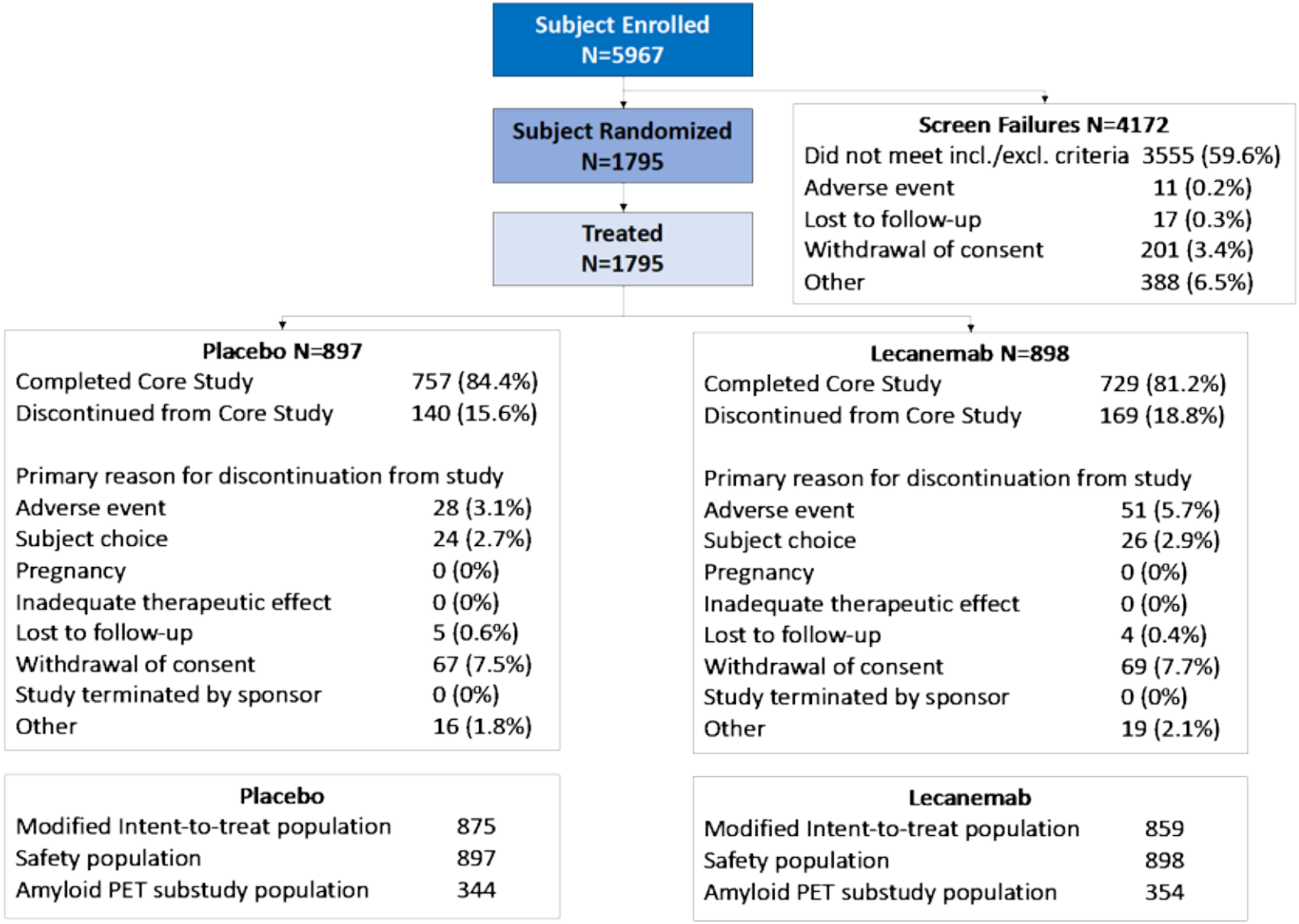
ARIA Management



ARIA-E, amyloid related imaging abnormalities-edema; ARIA-H, ARIA with hemosiderin deposits; DSMB, Data Safety Monitoring Board; mo, month; MRI, magnetic resonance imaging; wk, week.

Clarity AD

Subject Disposition and Analyses Populations



Clarity AD Baseline Characteristics

Demographic Characteristics

Characteristic	Combined Total N=1795	United States N=948
Age, median (range), years	72 (50, 90)	73(50,90)
Age Group, n (%)		
<65 years	353 (19.7)	158 (16.7)
≥65 to <80	1203 (67.0)	637 (67.2)
≥80	239 (13.3)	153 (16.1)
Female , n (%)	938 (52.3)	487 (51.4)
Region, n (%)		
North America	1072 (59.7)	948 (100)
Europe	429 (23.9)	0
Asia-Pacific	294 (16.4)	0
Race, n (%)		
Asian	303 (16.9)	7 (<1)
Black	47 (2.6)	43 (4.5)
Caucasian	1381 (76.9)	896 (94.5)
Native American	2 (<1)	1 (<1)
Native Hawaiian or Other Pacific Islander	1 (<1)	1 (<1)
Other	33 (1.8)	0
Missing	28 (1.6)	0
Ethnicity, n (%)		
Hispanic or Latino	232 (12.9)	213 (22.5)
Not Hispanic or Latino	1527 (85.1)	734 (77.4)
Missing	36 (2.0)	1 (<1)

Clarity AD Baseline Characteristics

Comorbidities and Comedications

Characteristic	Combined Total N=1795	United States N=948
Comorbidities		
Hypertension, n (%)	993 (55.3%)	612 (64.6%)
Hyperlipidemia, n (%)	1085 (60.4%)	674 (71.1%)
Ischemic Heart Disease, n (%)	291 (16.2%)	189 (19.9%)
Diabetes, n (%)	271 (15.1%)	180 (19.0%)
Obesity, n (%)	298 (16.6%)	229 (24.2%)
At least 2 comorbidities above, n (%)	917 (51.1%)	604 (63.7%)
At least 3 comorbidities above, n (%)	441 (24.6%)	319 (33.6%)
At least 4 comorbidities above, n (%)	139 (7.7%)	111 (11.7%)
At least 5 comorbidities above, n (%)	25 (1.4%)	22 (2.3%)
Comedications		
Anticoagulants	80 (4.5%)	54 (5.7%)

Clarity AD Baseline Characteristics

Clinical Characteristics

	Placebo (N=875)	Lecanemab 10 mg/kg biweekly (N=859)
Age, mean (standard deviation), years	71.0 (7.8)	71.4 (7.9)
Female, n (%)	464 (53.0)	443 (51.6)
Caucasian	677 (77.4)	655 (76.3)
Years since diagnosis	1.17 (1.537)	1.25 (1.506)
Years since onset of symptoms	3.98 (2.530)	3.96 (2.349)
CDR Global=0.5	706 (80.7)	694 (80.8)
Mild dementia due to Alzheimer's disease	331 (37.8)	331 (38.5)
ApoE4 Status		
Noncarrier	275 (31.4)	267 (31.1)
Carrier	600 (68.6)	592 (68.9)
Heterozygous	468 (53.5)	456 (53.1)
Homozygous	132 (15.1)	136 (15.8)
On AChEIs and/or memantine	476 (54.4)	454 (52.9)
CDR-SB, mean (SD)	3.22 (1.343)	3.17 (1.340)
PET Centiloids, mean (SD)	75.28 (41.85)	77.94 (44.78)
ADAS-Cog14, mean (SD)	24.37 (7.561)	24.45 (7.082)
ADCOMS, mean (SD)	0.400 (0.15)	0.398 (0.15)
ADCS-ADL-MCI	40.9 (6.89)	41.2 (6.61)
MMSE, mean (SD)	25.6 (2.23)	25.5 (2.19)

AChEIs, acetylcholinesterase inhibitors; ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; MMSE, Mini-Mental State Exam; PET, positron emission tomography; SD, standard deviation.

Summary

- **The lecanemab phase 2b proof-of-concept study provided a robust framework to optimally design the confirmatory phase 3 study Clarity AD**
- **Clarity AD is intended to be a definitive Phase 3 study to confirm efficacy and safety**
  - Simple randomized, double-blind, parallel group design without dose titration
  - CDR-SB, the gold-standard clinical assessment, utilized as the primary endpoint
  - Comprehensive assessment of clinical (cognitive, functional, QoL), biomarker (A/T/N/+), and safety outcomes
  - Efforts to enhance global enrollment of a diverse group of participants (e.g., race, ethnicity, co-morbidities) and mitigate the impact of COVID

A/T/N/+, amyloid/tau/neurodegeneration/other; CDR-SB, Clinical Dementia Rating-sum of boxes; COVID, coronavirus disease; QoL, quality of life.

Acknowledgements

Site Investigators

Australia: Bruce Brew (St Vincent's Hospital - Translational Research Centre); Roger Clarnette (Australian Alzheimer's Research Foundation); Stephen Macfarlane (HammondCare Malvern Clinical Trials Unit); Ranjeev Chrysanth Pulle (The Prince Charles Hospital/Internal Medicine & Dementia Research Unit); Paul Yates (Austin Health - Medical and Cognitive Research Unit); Rosalyn Cora Lai (KaRa Institute of Neurological Diseases); Cathy Short (Central Adelaide Local Health Network, The Queen Elizabeth Hospital and the Royal Adelaide Hospital).

Canada: Jennifer Ingram (Kawartha Centre - Redefining Healthy Aging); Sharon Cohen (Toronto Memory Program (Neurology Research Inc.); Ziad Nasreddine (MoCA Clinic and Institute/NeuroSearch Developpements Inc.); Eugene Okorie (Okanagan Clinical Trials); Richared Bergeron (Recherches Neuro-Hippocampe Inc. d/b/a Clinique de la Mémoire de l'Outaouais); Mark Allan (True North Clinical Research Kentville, Inc.); Paule Royer, (Q&T Research Sherbrooke Inc.); Jennie Wells (St. Joseph's HC- Parkwood Institute); Rodney Brittain (True North Clinical Research Halifax, Inc.); Kevin Kjernisted (Health Research).

France: Clair Paquet (Centre de Neurologie Cognitive du Pr Paquet); Hélène Mollion (Hôpital neurologique Pierre Wertheimer); Mathieu Ceccaldi (Hopital de la Timone); Pierre-Jean Ousset (Centre de Recherche Clinique du Gérontopôle); Claire Boutoleau-Bretonniere (Hopital Guillaume et RenÃ LaÃnnec); Stéphanie Bombois (Groupe Hospitalier Pitie-Salpetriere); Karim Bennys (Hôpital Gui de Chauliac); Frédéric Blanc (Hôpital de Hautepierre).

Germany: Matthias Boehringer (Neurozentrum Bielefeld Schwerpunktpraxis fuer Neurologie, Psychiatrie und Klinische); Richare Dodel (Geriatrie-Zentrum Haus Berge Klinik für Geriatrie - Chefarzt); Matthias Riepe, (Bezirkskrankenhaus Guenzburg); Lutz Frölich, (Central Institute o Mental Health - Department of Psychaitry); Gerd Reifschneider, (Neuro Centrum Science GmbH); Timo Grimmer, (Psychiatry of TU Munich); Oliver Peters, (Klinik und Hochschulambulanz für Psychiatrie und Psychotherapie, Charité Universitätsmedizin Berlin, Gedächtnissprechstunde am ECRC).

Italy: Giancarlo Logroscino, (Ospedale "Card. G. Panico"); Flavio Nobili, (Clinica Neurologica, IRCCS Ospedale Policlinico San Martino, Genova); Gioacchino Tedeschi, (Prima Clinica Neurologica, Primo Policlinico AOU "L. Vanvitelli"); Carlo Ferrarese, (ASST-Monza, Ospedale San Gerardo); Lucilla Parnetti, (Ospedale S. Maria della Misericordia, S. Andrea delle Fratte); Giuseppe Bruno , (Universita` Sapienza di Roma - Dipartimento di Neuroscienze Umane); Roberto Ceravolo, (Azienda Ospedaliero Universitaria Pisana); Elio Scarpini, (Fondazione IRCCS CA' Granda Ospedale Maggiore Policlinico - U.O.S.D. Malattie Neurodegenerative); Camilo Marra, (Fondazione Policlinico Agostino Gemelli - UCSC); Luigi Grimaldi, (Fondazione Istituto G.Giglio di Cefalù); Angelo Mita, (Ospedale "Vito Fazzi"); Marco Salvatore, (IRCCS SDN); Orazio Schillaci, (UOC Medicina Nucleare Fondazione PTV "Policlinico Tor Vergata").

Acknowledgements

Site Investigators

Japan: Sadao Katayama, (Rijikai Medical Corporation Katayama Medical Clinic); Yoshiaki Aihara, (Shinozuka Hospital); Sadahisa Tokuda, (Sapporo Teishinkai Hospital); Akiko Yamazaki, (NIPPON MEDICAL SCHOOL MUSASHI KOSUGI HOSPITAL); Noriko Kawashima, (Kawashima Neurology Clinic); Satoshi Naruse, (General Rehabilitation Center Midori Hospital); Yoshiaki Itoh, (Osaka City University Hospital); Takao Takeshima, (Tominaga Hospital); Kenichi Shimada, (Hyogo Brain and Heart Center); Riki Matsumoto, (Kobe University Hospital); Kazunori Okahara, (Keimei Memorial Hospital); Takashi Asada, ((Memory clinic Ochanomizu); Hamano Tadanori, (University of Fukui Hospital); Yutaka Arahata, (National Center for Geriatrics and Gerontology); Chigusa Watanabe, (National Hospital Organizaton Hiroshima-Nishi Medical Center); Tsutomu Nagamitsu, (Nagamitsu Clinic); Soichiro Shimizu, (Tokyo Medical University Hospital); Haruhiko Akiyama, (Yokohama Brain and Spine Center); Shizuo Hatashita, (Shonan Atsugi Hospital); Hiroyuki Hatsuta, (Hatsuta Neurology Clinic); Masaharu Amagasa, (Yamagata Tokushukai Hospital); Noeru Shiraki, (Memory clinic Toride); Yuichi Maruki, (Saitama Neuropsychiatric Institute); Daisuke Ito, (Keio University Hospital); Tatsushi Toda, (The University of Tokyo Hospital); Tomoyuki Kamata, (Japanese Red Cross Musashino Hospital); Kiyoshi Kanaya, (Tokyo Medical University Hachioji Medeical Center); Sotaro Hieda, (Showa University Hospital East Branch); Osamu Iritani, (Kanazawa Medical University Hospital); Makoto Urushitani, (Shiga University of Medical Science Hospital); Shinji Tagami, (Osaka University Hospital); Tadashi Kanda, (Yamaguchi University Hospital); Koichi Kashiwado, (Kashiwado hospital).

Russia: Vladimir Vladimirovich Zakharov, (First Moscow State Medical University n.a. I.M. Sechenov).

South Korea: Seong Hye Choi, (Inha University Hospital); Jae-Hong Lee, (Asan Medical Center); Jun-Young Lee, (Seoul National University Boramae Medical Center); Dong Young Lee, (Seoul National University Hospital); Kyung Won Park, (Dong-A University Hospital); Hee-Jin Kim, (Hanyang University Seoul Hospital); Sang Won Seo, (Samsung Medical Center); Seol-Heui Han (Konkuk University Medical Center); Dong Won Yang, (The Catholic University of Korea, Seoul ST. Mary's Hospital); Ji Won Han, (Seoul National University Bundang Hospital); Sang Yun Kim, (Seoul National University Bundang Hospital); Byeong-Chae Kim, (Chonnam National University Hospital); Young Ho Sohn, (Severance Hospital, Yonsei University Health System).

Singapore: Christopher Chen, (National University Hospital).

Spain: Félix Viñuela Fernandez, (Hospital Victoria Eugenia - Cruz Roja); Ernest Balaguer Martinez, (Hospital General de Catalunya); Miguel Baquero, (Hospital Universitari i Politècnic La Fe); Gurutz Linazasoro Cristobal, (Policlinica Guipuzkcoa); Eduardo Aguera Morales, (Hospital Universitario Reina Sofía); Manuel Fernandez-Martinez, (Centro CAE Oroitu); Juan Jose Lopez Lozano, (Complejo Hospitalario Ruber Juan Bravo); Pablo Martinez Lage, (Fundación CITA-alzheimer Findazioa); Raquel Sanchez Valle, (Hospital Clinic i Provincial de Barcelona); Mercé Boada Rovira, (Fundacion ACE, Barcelona); Angel Montejo Gonzalez, (Hospital de Salamanca); Albert Lleó, (Servicio de Neurologia. Hospital Santa Cruz y San Pablo Calle Sant Antoni Maria Claret 167);

Sweden: Lena Kilander, (Uppsala University Hospital, Uppsala); Anne Börjesson-Hanson, (Karolinska University Hospital); Michael Jonsson, (Psykiatri kognition och äldrepsykiatri); Henrik Östlund, (Skånes universitetssjukhus).

United Kingdom: Stephen Pearson, (Re:Cognition Health); Petrina Ayertey-Gbeve, (St. Pancras Clinical Research); Brady McFarlane, (Memory Assessment & Research Centre (MARC)); Janet Hutchison, (Sheffield Memory Service); Nicholas Mannering, (Re:Cognition Health Ltd); Emer MacSweeney, (Re:Cognition Health Ltd); Richard Perry, (Charing Cross Hospital).

Acknowledgements

Site Investigators

United States: David Watson, (Alzheimer's Research and Treatment Center); Orlando Maldonado-Robles, (Bradenton Research Center, Inc.); Jonathan Liss, (Columbus Memory Center); Marshall Nash, (NeuroStudies.net, LLC); Marc Agronin, (Miami Jewish Health Systems); Gregory Jicha, (University of Kentucky Medical Center); John Nardandrea, (Renstar Medical Research); Michael Plopper, (Sharp Mesa Vista Hospital); Anton Porsteinsson, (AD-CARE, URMC); Sanjiv Sharma, (Advanced Memory Research Institute of NJ, PC); Mary Stedman, (Stedman Clinical Trials, LLC); Michael Badruddoja, (Neurological Associates of Tucson dba Center for Neurosciences); John Stoukides, (Rhode Island Mood & Memory Research Institute); Victor Faradji, (Visionary Investigators Network); Richard Holub, (Neurological Associates of Albany, PC); Lee Stein, (Neurology Clinic, P.C.); Cherian Verghese, (Keystone Clinical Studies, LLC); Julie Schwartzbard, (Visionary Investigators Network); Allan Bernstein, (North Bay Neuroscience); Mark Goldstein, (JEM Research Institute); Michael Tuchman, (Advanced Research Consultants, Inc.); David Hart, (Albany Medical College); Scott Losk, (Summit Research Network (OR) Inc.); William Smith, (Alliance for Multispecialty Research LLC, New Orleans Center for Clinical Research / Volunteer Research Group, an AMR company); John Scott, (National Clinical Research Inc.-Richmond); Cynthia Murphy, (DBA The Memory Clinic); Raymond Turner, (Georgetown University Hospital); Seth Gale, (Brigham and Women's Hospital); Mohammad Bolouri, (ANI Neurology, PLLC d/b/a Alzheimer's Memory Center); Babak Tousi, (Cleveland Clinic); Wendy Bond, (Neuropsychiatric Research Center of Southwest FL); Jose De La Gandara, (Quantum Laboratories Inc.); Allan Levey, (Emory University Cognitive Neurology Clinic & ADRC); Tiffany Schwasinger-Schmidt, (KU Wichita Center for Clinical Research); Anthony Ciabarra, (Neurology Center of North Orange County); Stephen Thein, (Pacific Research Network, Inc.); Jared Brosch, (Indiana University School of Medicine); Stephen Salloway, (Butler Hospital - Memory and Aging Program); Paul Mazzeo, (Coastal Neurology, P.A.); Maryam Beigi , (University of California - Los Angeles); Paul Solomon, (Boston Center for Memory); Donald Marks, (Donald S. Marks, MD. P.C.); Barbara Joy Snider, (Knight ADRC Clinical Trials Unit Clinic - Washington University School of Medicine); Jonathan Drake, (Rhode Island Hospital); Christopher van Dyck, (Yale University School Of Medicine); Adam Boxer, (UCSF Memory and Aging Center); Sharon Sha, (Stanford University Medical Center); Gil Fernandez-Yera, (Advanced Clinical Research Network); Michael Pfeffer, (Allied Biomedical Research (Clinical Trial)); Jose Gamez, (Galiz Research); Yaneicy Gonzalez Rojas, (Gonzalez MD & Aswad MD Health Services); Darren Gitelman, (Advocate Lutheran General Hospital); Martin Sadowski, (New York University Medical Center PRIME); Aimee Pierce, (Oregon Health & Science University); Melissa Yu, (Baylor College of Medicine AD and Memory Disorders Center); Guido Perez, (BioMed Research Institute); Kimball Johnson, (iResearch Atlanta, LLC); Noah Gilson, (Neurology Specialists of Monmouth County, PA); Mercedes Ponce De Leon, (Vitae Research Center); Jaron Winston, (Senior Adult Specialty Research); Alex White, (Progressive Medical Research); Lawrence Honig, (Neurological Institute of New York); Ramon Leon, (IMIC, Inc.); David Greeley, (Kingfisher Cooperative LLC); Ira Goodman, (Synexus Clinical Research US, Inc.); Ayesha Lall, (Synexus Clinical Research); Richard Singer, (Infinity Clinical Research, LLC); Murray Grossman, (University of Pennsylvania); Bart Sloan, (Research Center for Clinical Studies, Inc.); Lilia Ables, (Finlay Medical Research); Srinath Kadimi, (Yale University, School of Medicine, Department of Neurology); Danielle Goldfarb, (Banner Sun Health Research); David Weidman, (Banner Alzheimer’s Institute- Clinical Trials Department); Amanda Smith, (USF Suncoast Gerontology Center); Paul Winner, (Premiere Research Institute, West Palm); Allan Bernstein, (St Joseph Heritage Healthcare); Aaron Ritter, (Cleveland Clinic Lou Ruvo Center for Brain Health); Alexander Smirnoff, (Charter Research); Diana Kerwin, (Kerwin Research Center); Elly Lee, (Irvine Clinical Research); David Russell, (Institute for Neurodegenerative Disorders); Mitchell Isaac, (PMG Research of Winston Salem); John Duffy, (Apex Research Institute); Michael McCartney, (ActivMed Practices & Research); Bharat Mocherla, (Las Vegas Medical Research); Douglas Scharre, (Ohio State University); Harvey Schwartz, (Infinity Clinical Research); James Stevens, (Fort Wayne Neurological Center); Brent Forester, (McLean Hospital); Gincy Samuel, (Texas Neurology, PA); Bradley Robottom, (Raleigh Neurology Associates, P.A. - Research Department); Mark Brody, (Brain Matters Research); Deren Huang, (MDH Research, LLC.); Michael Mega, (Neural Net Research, LLC); Francisco Ricart, (CCM Clinical Research Group); Jacobo Mintzer, (Ralph H. Johnson VAMC); Ronald Schwartz, (Hattiesburg Clinic); Ana Acosta, (Advance Medical Research Center); Jeffrey Burns, (University of Kansas Medical Center Research Institute); Ernesto Diaz, (Linfritz Research Institute, Inc.); Ryan Drake, (NeuroScience Research Center LLC); Jack Klapper, (Mile High Research Center); Djamchid Lotfi, (Clinical Trial Network); Jeffrey Ross, (Great Lakes Clinical Trials); Ashok Patel, (Bio Behavioral Health); Cynthea Blake, (ImmunoE Research Center); Lourdes Bosch, (Pharmax Research of South Florida, Inc); Carl Griffin, (Lynn Health Science Institute); Esteban Olivera, (ClinCloud, LLC); Kore Kai Liow, (Hawaii Pacific Neuroscience); David McDonald, (Neurology Associates of Ormond Beach); Liliana Montoya, (Neurostudies, Inc.); Franco Sicuro, (Millenium Psychiatric Associates, LLC); James Sutton, (Pacific Neuroscience Medical Group).

Lecanemab for the Treatment of Early Alzheimer's Disease: Topline Efficacy Results from Clarity AD

Christopher van Dyck

Yale School of Medicine

Christopher van Dyck - Disclosures

Advisor/Consultant for:

Roche Pharmaceuticals
Eisai, Inc
Ono Pharmaceuticals
Cerevel

Yale University and Dr. van Dyck receive grant support from:

Eli Lilly
Biogen Idec
Roche Pharmaceuticals
Biohaven Pharmaceuticals
UCB

Janssen Pharmaceuticals
Eisai, Inc
Genentech, Inc
Cerevel Therapeutics

Clarity AD: Topline Efficacy Endpoints

Primary Endpoint

- Change from baseline at 18 months in CDR-SB

Key Secondary Endpoints

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

- Amyloid PET
- ADAS-Cog14
- ADCOMS
- ADCS MCI-ADL

ADAS-Cog14, Alzheimer's Disease Assessment Scale–cognitive subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS ADL-MCI: Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for mild cognitive impairment (MCI) subjects; CDR-SB, Clinical Dementia Rating, sum of boxes; PET: positron emission tomography.

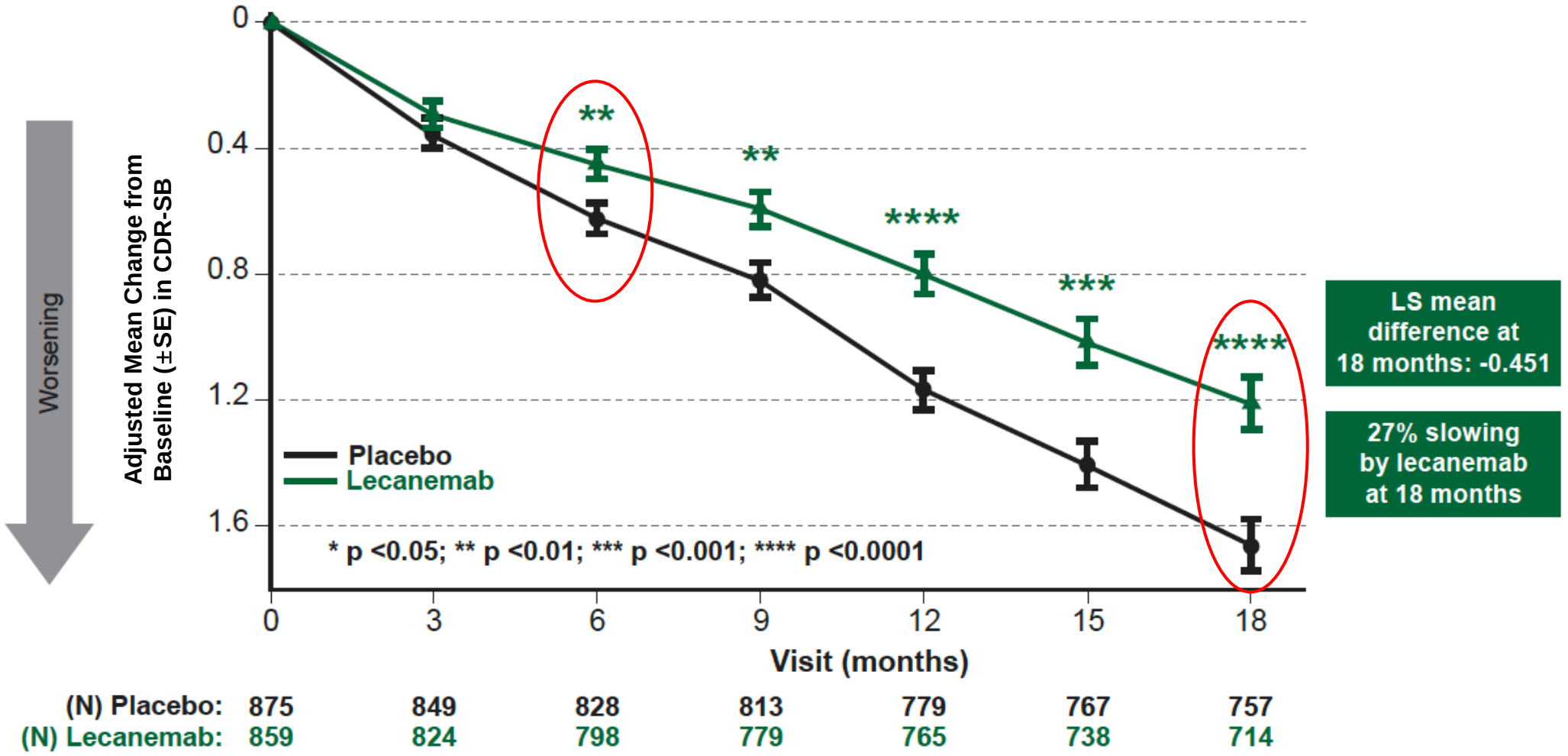
Statistically Significant Results for Primary & Key Secondary Endpoints

	Lecanemab vs Placebo
Primary efficacy endpoint	
CDR-SB Change from baseline to 18 months	
Difference in least square mean	-0.451
95% CI of the least square mean	-0.669, -0.233
P value vs placebo	0.00005
Key secondary efficacy endpoints	
Amyloid PET Centiloids Change from baseline to 18 months	
Difference in least square mean	-59.12
95% CI of the least square mean	-62.64, -55.60
P value vs placebo	<0.00001
ADAS-Cog14 Change from baseline to 18 months	
Difference in least square mean	-1.442
95% CI of the least square mean	-2.270, -0.613
P value vs placebo	0.00065
ADCOMS Change from baseline to 18 months	
Difference in least square mean	-0.050
95% CI of the least square mean	-0.074, -0.027
P value vs placebo	0.00002
ADCS MCI-ADL Change from baseline to 18 months	
Difference in least square mean	2.016
95% CI of the least square mean	1.208, 2.823
P value vs placebo	<0.00001

ADAS-Cog14, Alzheimer's Disease Assessment Scale–cognitive subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS ADL-MCI: Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for mild cognitive impairment (MCI) subjects; CDR-SB, Clinical Dementia Rating, sum of boxes; CI, confidence intervals; PET: positron emission tomography.

Clarity AD Primary Endpoint: CDR-SB

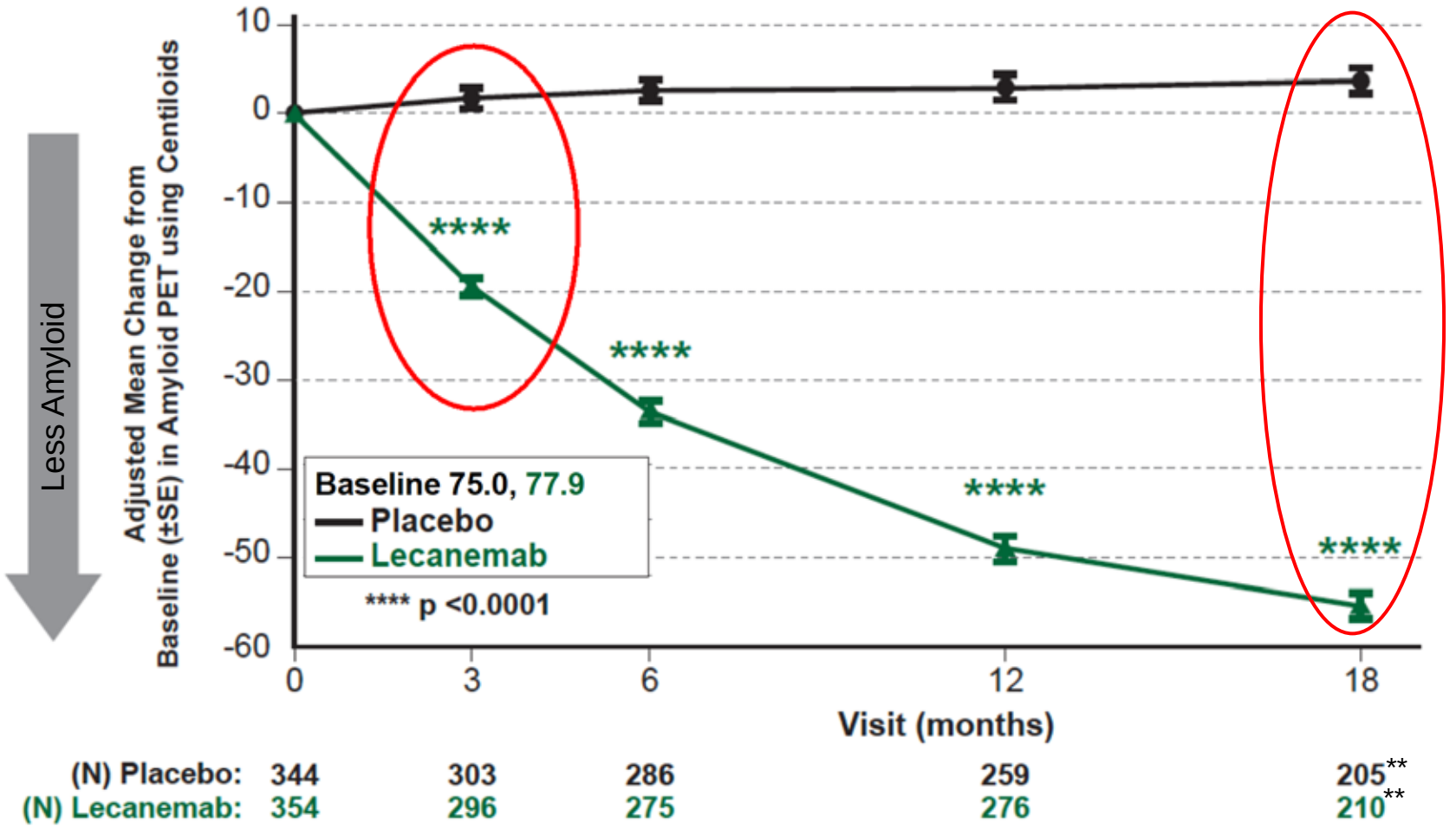
Lecanemab Significantly Slowed Disease Progression on CDR-SB by 27% at 18 Months and at All Time Points Beginning at 6 Months



Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.
CDR-SB, Clinical Dementia Rating, sum of boxes; LS, least squares; SE, standard error.

Amyloid PET:

Lecanemab Significantly Reduced Fibrillar Amyloid Burden at All Time Points Beginning at 3 Months



Mean <30 Centiloids for lecanemab at 18 months*

Difference of -59.1 Centiloids at 18 months

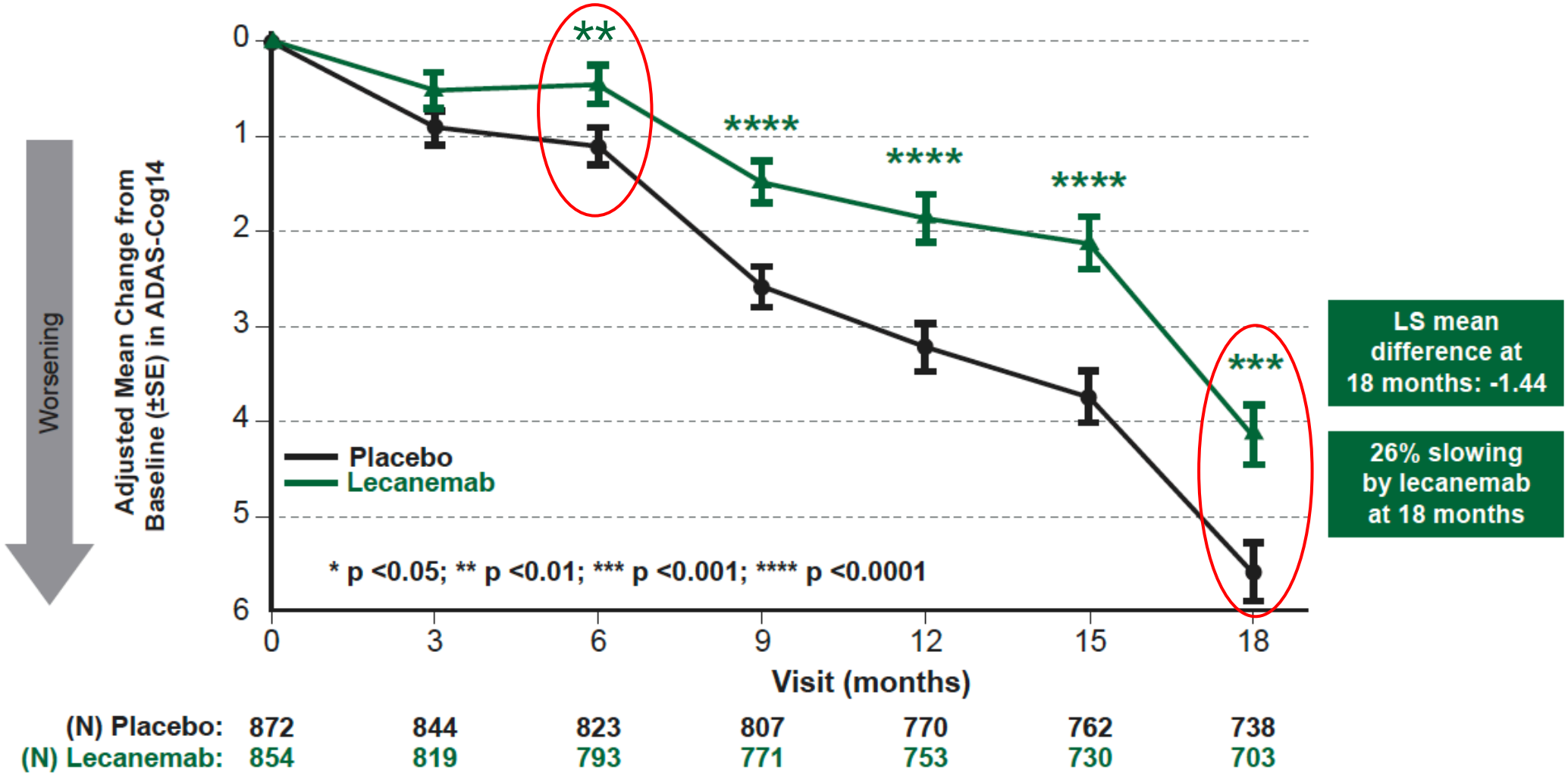
*After 18 months of treatment, the average amyloid level was 23 Centiloids in the lecanemab treatment group in the amyloid PET substudy, which is below the threshold for amyloid positivity of approximately 30 Centiloids above which participants are considered to have elevated brain amyloid.

** 73 subjects were not included at 18 months (per Statistical analysis plan) since their PET assessments were performed after receiving lecanemab in the extension phase.

Note: Based on pharmacodynamic analysis population (amyloid PET substudy population). Adjusted mean change from baseline, standard error (SE) and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.
PET: positron emission tomography. SE, standard error.

ADAS-Cog14:

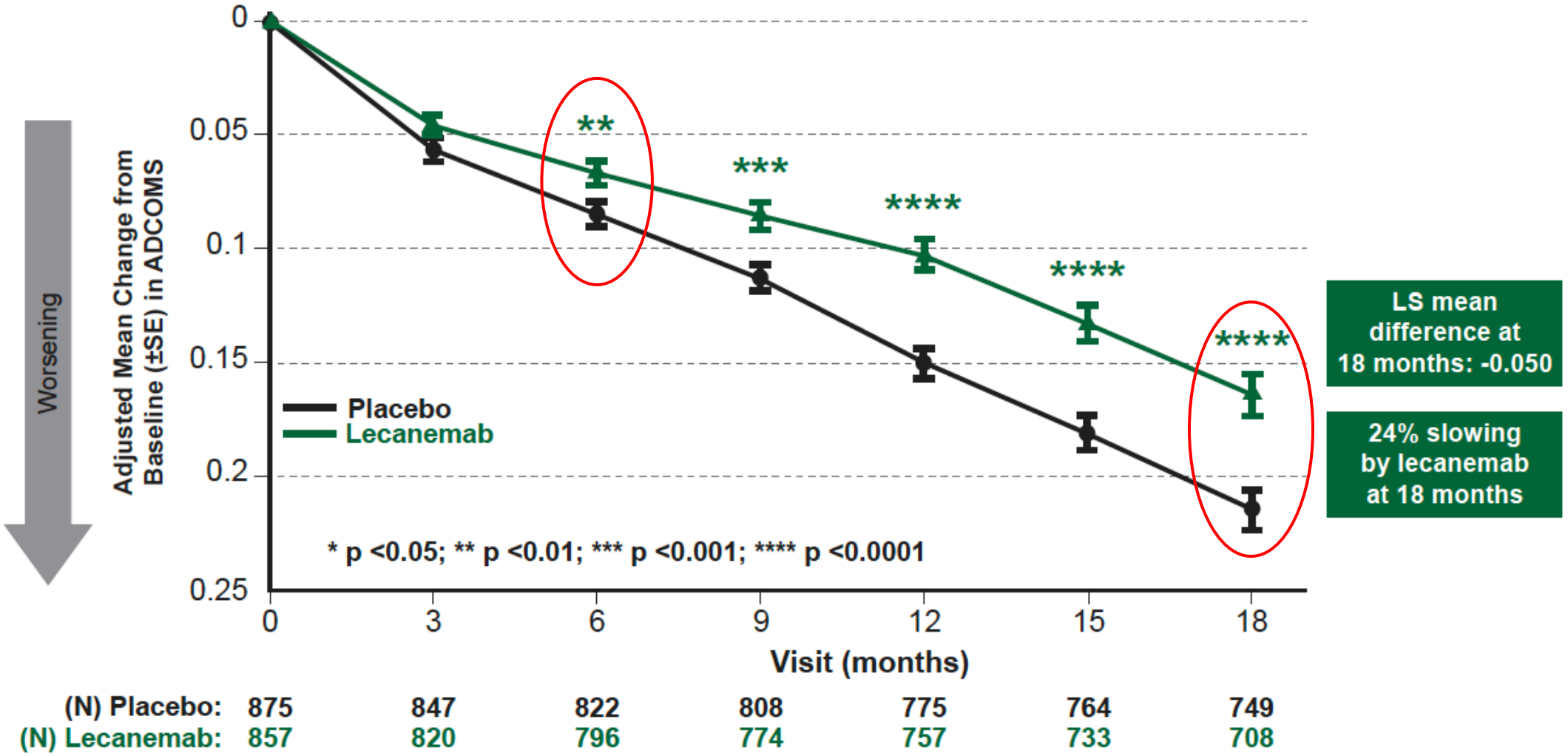
Lecanemab Significantly Slowed Disease Progression on ADAS-Cog14 by 26% at 18 Months and at All Time Points Beginning at 6 Months



Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.
ADAS-Cog14, Alzheimer's Disease Assessment Scale–cognitive subscale; LS, least squares; SE, standard error.

ADCOMS:

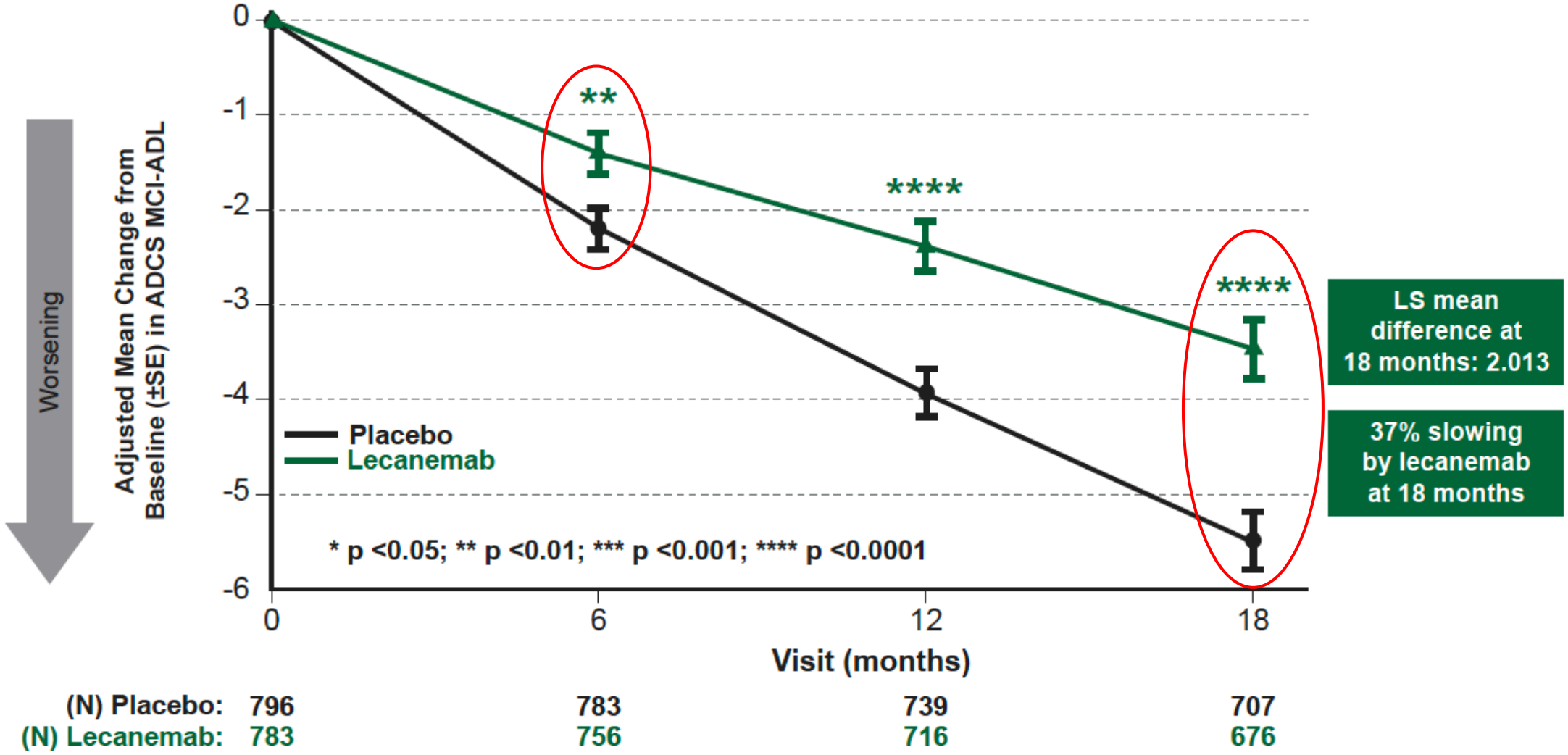
Lecanemab Significantly Slowed Disease Progression on ADCOMS by 24% at 18 Months and at All Time Points Beginning at 6 Months



Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.
ADCOMS, Alzheimer's Disease Composite Score; LS, least squares; SE, standard error.

ADCS MCI-ADL:

Lecanemab Significantly Slowed Disease Progression on ADCS MCI-ADL by 37% at 18 Months and at All Time Points Beginning at 6 Months



Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.
ADCS ADL-MCI: Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for mild cognitive impairment (MCI) subjects; LS, least squares; SE, standard error.

Results of CDR-SB Sensitivity Analyses

Results are Robust Across Pre-Specified Sensitivity Analyses

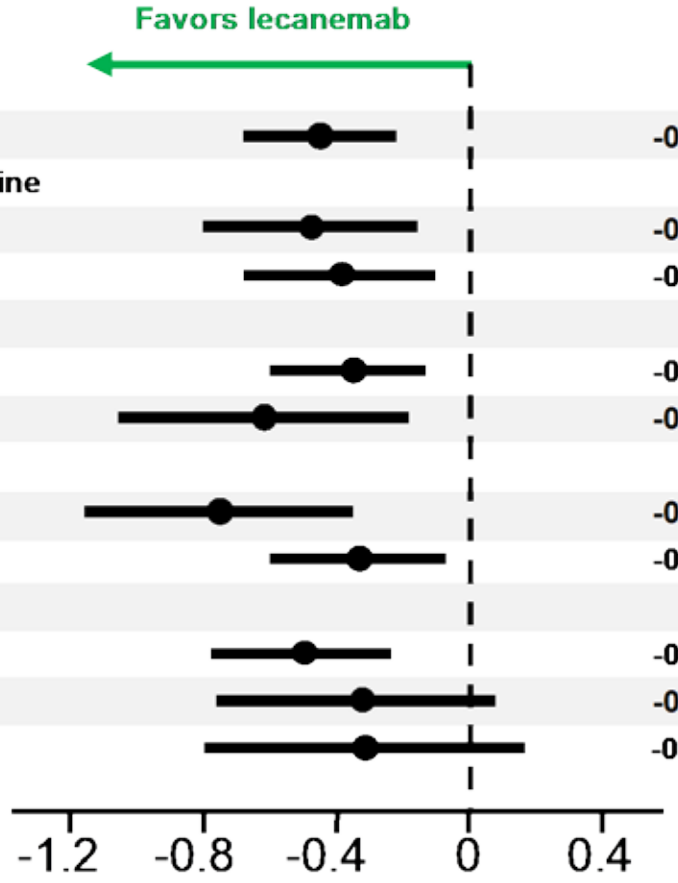
Type of Sensitivity Analysis	Adjusted mean change from baseline at 18 months for placebo group	Adjusted mean change from baseline at 18 months for lecanemab group	Treatment difference at 18 months	% Slowing	P-value
Primary MMRM results (modified ITT)	1.663	1.213	-0.451	27	<0.001
Rank ANCOVA with missing data imputed via multiple imputation approach.	NA	NA	-0.456*	NA	<0.001
MMRM repeated on all randomized subjects (ITT)‡	1.659	1.225	-0.434	26	<0.001
Primary MMRM repeated censoring assessments after occurrence of ARIA-E	1.672	1.169	-0.503	30	<0.001
Primary MMRM repeated to evaluate impact of COVID	1.603	1.208	-0.394	25	<0.001

*Hodges-Lehmann non-parametric estimate of median difference. †Hodges-Lehmann estimate of median difference and asymptotic standard error are calculated and then combined using Rubin's rules to compute the CI.
‡Missing values for randomized subjects who are not in ITT analysis set are imputed using placebo mean at each visit.
ANCOVA, Analysis of covariance; ARIA-E, amyloid related imaging abnormalities-edema; CI, Confidence interval; COVID, coronavirus disease; ITT, intention-to-treat; mITT; modified ITT. MMRM, Mixed model for repeated measures; NA, Not applicable.

Clarity AD Subgroup Analyses: CDR-SB

Consistent Results Across Randomization Strata

	No. of Participants (placebo, lecanemab)	Adjusted Mean Difference	Percent Slowing of Decline (%)
Overall	875, 859	-0.45	27
Use of Symptomatic AD Medication at Baseline			
Yes	468, 447	-0.48	25
No	407, 412	-0.39	28
Clinical Subgroup			
MCI	544, 528	-0.35	28
Mild AD	331, 331	-0.62	27
ApoE4 Status			
Noncarrier	275, 267	-0.75	41
Carrier	600, 592	-0.33	21
Region			
North America	516, 514	-0.52	34
Asia	146, 141	-0.33	25
Europe	213, 204	-0.33	14



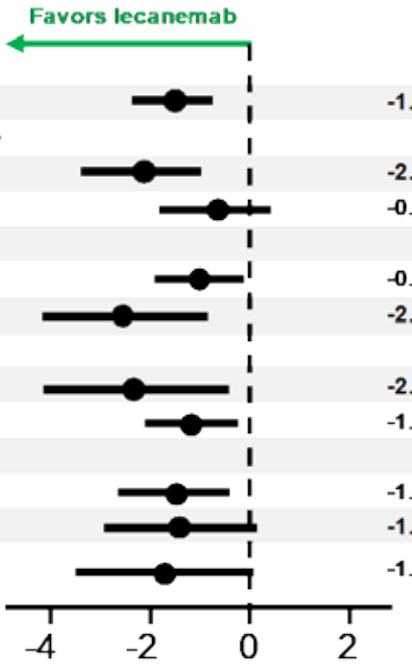
AD, Alzheimer's disease; ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; CI, confidence interval; MCI, mild cognitive impairment.

Clarity AD Subgroup Analyses: ADAS-Cog14 & ADCS MCI-ADL

Consistent Results Across Randomization Strata

ADAS-Cog14

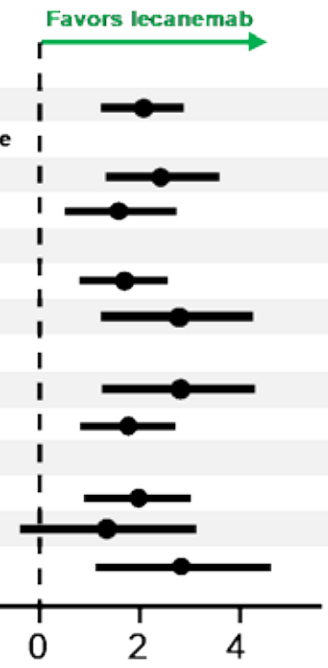
	No. of Participants (placebo, lecanemab)	Adjusted Mean Difference	Percent Slowing of Decline (%)
Overall	872, 854	-1.44	26
Use of Symptomatic AD Medication at Baseline			
Yes	466, 445	-2.06	29
No	406, 409	-0.64	16
Clinical Subgroup			
MCI	542, 525	-0.93	23
Mild AD	330, 329	-2.46	30
ApoE4 Status			
Noncarrier	273, 266	-2.19	35
Carrier	599, 588	-1.11	21
Region			
North America	514, 512	-1.43	31
Asia	146, 140	-1.38	25
Europe	212, 202	-1.71	22



Adjusted Mean Difference in ADAS-Cog14 versus Placebo (95% CI)

ADCS MCI-ADL

	No. of Participants (placebo, lecanemab)	Adjusted Mean Difference	Percent Slowing of Decline (%)
Overall	796, 783	2.02	37
Use of Symptomatic AD Medication at Baseline			
Yes	423, 404	2.39	37
No	373, 379	1.53	33
Clinical Subgroup			
MCI	499, 492	1.64	38
Mild AD	297, 291	2.71	38
ApoE4 Status			
Noncarrier	245, 234	2.73	47
Carrier	551, 549	1.72	33
Region			
North America	473, 473	1.9	42
Asia	130, 121	1.31	23
Europe	193, 189	2.76	41

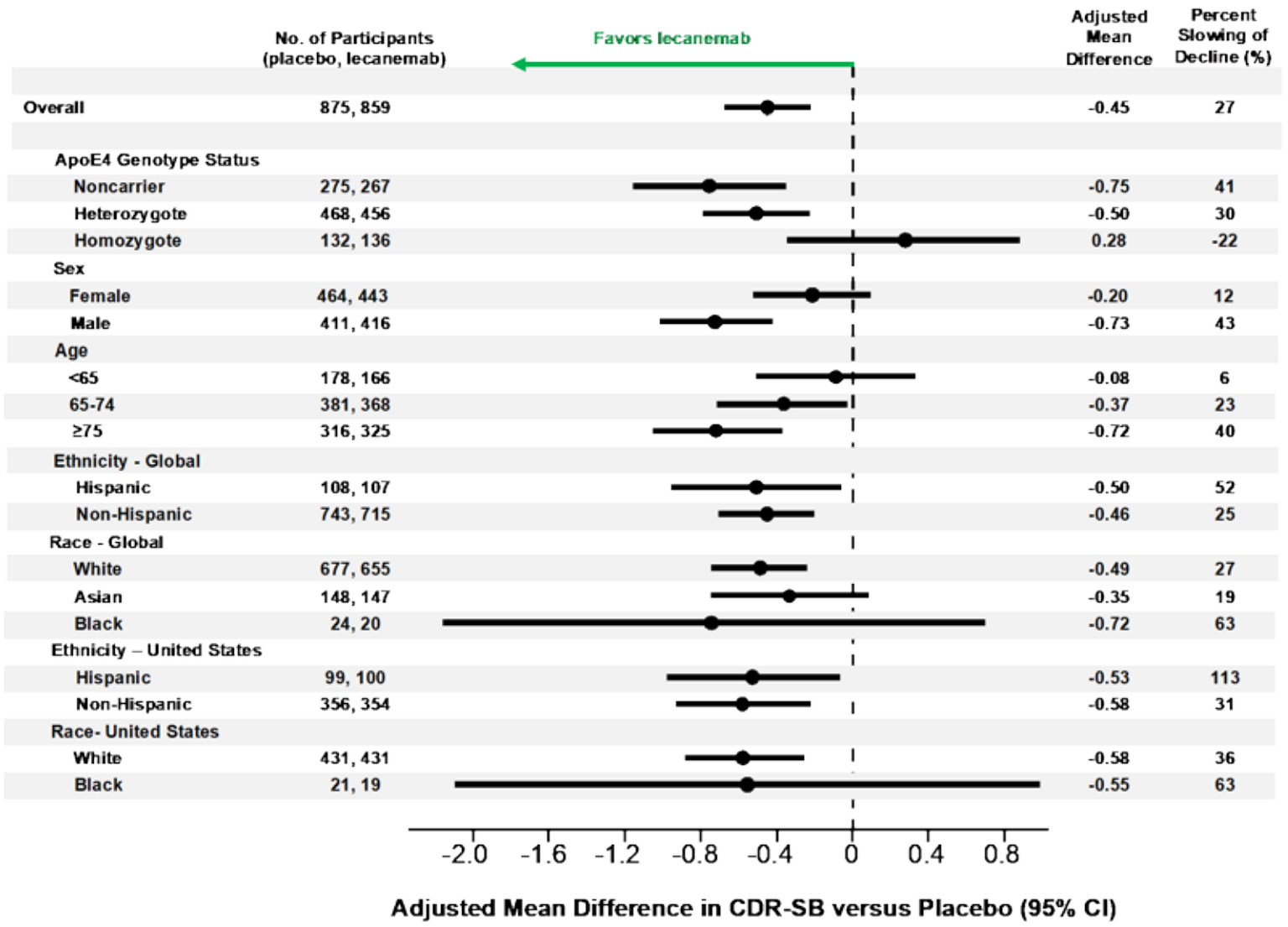


Adjusted Mean Difference in ADCS MCI-ADL versus Placebo (95% CI)

AD, Alzheimer's disease; ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE4, apolipoprotein E4; CI, confidence interval; MCI, mild cognitive impairment.

Clarity AD Subgroup Analyses: CDR-SB

Consistent Results Across Other Subgroups of Interest



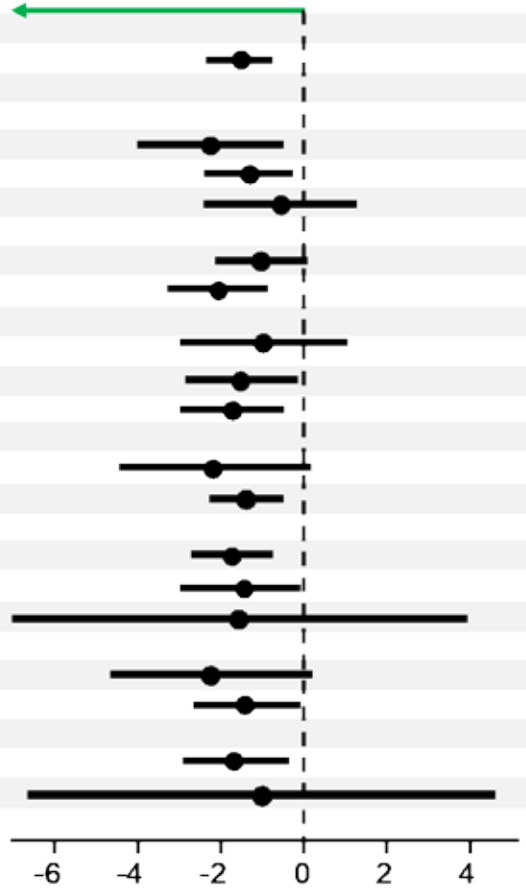
ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; CI, confidence interval.

Clarity AD Subgroup Analyses: ADAS-Cog14 & ADCS MCI-ADL

Consistent Results Across Other Subgroups of Interest

ADAS-Cog14

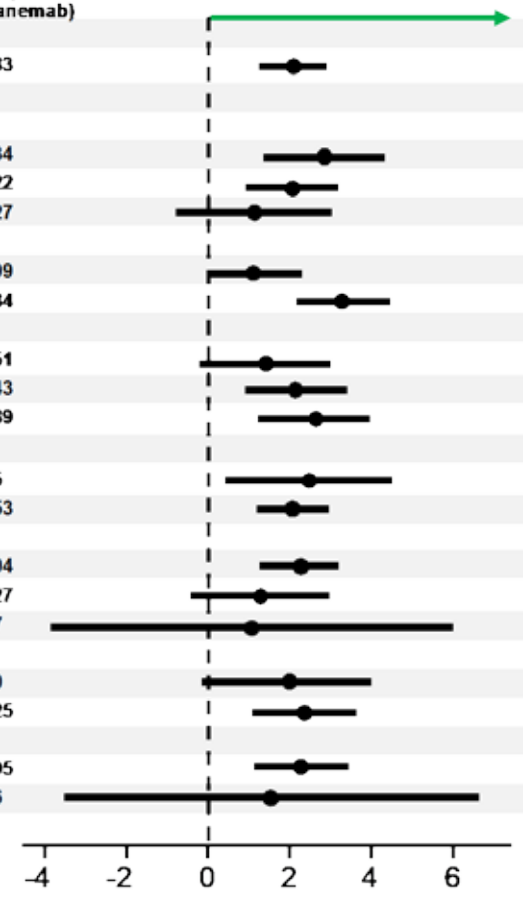
	No. of Participants (placebo, lecanemab)	Adjusted Mean Difference	Percent Slowing of Decline (%)
Overall	872, 854	-1.44	26
ApoE4 Genotype Status			
Noncarrier	273, 266	-2.19	35
Heterozygote	467, 453	-1.28	23
Homozygote	132, 135	-0.53	13
Sex			
Female	462, 441	-0.98	18
Male	410, 413	-1.97	34
Age			
<65	177, 165	-0.92	14
65-74	380, 365	-1.47	29
≥75	315, 324	-1.67	30
Ethnicity - Global			
Hispanic	108, 107	-2.06	387
Non-Hispanic	740, 711	-1.37	21
Race - Global			
White	674, 652	-1.65	28
Asian	148, 146	-1.46	25
Black	24, 20	-1.59	280
Ethnicity – United States			
Hispanic	99, 100	-2.18	-222
Non-Hispanic	354, 353	-1.34	21
Race- United States			
White	429, 430	-1.65	33
Black	21, 19	-1.00	209



Adjusted Mean Difference in ADAS-Cog14 versus Placebo (95% CI)

ADCS MCI-ADL

	No. of Participants (placebo, lecanemab)	Adjusted Mean Difference	Percent Slowing of Decline (%)
Overall	796, 783	2.02	37
ApoE4 Genotype Status			
Noncarrier	245, 234	2.73	47
Heterozygote	430, 422	1.97	36
Homozygote	121, 127	1.03	25
Sex			
Female	416, 399	1.01	19
Male	380, 384	3.17	54
Age			
<65	166, 151	1.28	26
65-74	356, 343	2.02	38
≥75	274, 289	2.48	40
Ethnicity - Global			
Hispanic	95, 95	2.22	92
Non-Hispanic	677, 653	1.98	33
Race - Global			
White	616, 604	2.20	40
Asian	132, 127	1.26	23
Black	22, 17	1.08	184
Ethnicity – United States			
Hispanic	86, 90	1.92	318
Non-Hispanic	329, 325	2.29	40
Race- United States			
White	392, 395	2.23	45
Black	20, 16	1.5	-221



Adjusted Mean Difference in ADCS MCI-ADL versus Placebo (95% CI)

ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE4, apolipoprotein E4; CI, confidence interval.

Summary

Clarity AD Met All Primary and Key Secondary Endpoints

- Lecanemab treatment met the primary and secondary end points vs placebo at 18-months, with highly significant differences starting at six months (all P<0.001):
  - CDR-SB: reduced clinical decline by 27% (difference: -0.45; P value = 0.00005),
  - Reduced brain amyloid starting at 3 months (difference: -59.1 Centiloids)
  - Slowed cognition loss by 26% (ADAS-Cog14)
  - Slowed disease progression by 24% (ADCOMS)
  - Slowed functional decline by 37% (ADCS MCI-ADL)
- Results were consistent across broad range of endpoints and subgroups

Lecanemab reduced markers of amyloid in early AD and resulted in less decline than placebo on all measures of cognition and function at 18 months. These differences were observed as early as 6 months. These findings encompassed a broad range of endpoints and subgroups.

AD, Alzheimer's disease; ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating-sum of boxes.

Safety Profile of Lecanemab in Clarity AD

Marwan Sabbagh

Barrow Neurological Institute

Disclosures

- Dr Sabbagh has the following disclosures:
  - Ownership interest (Stock or stock options): NeuroTau, Optimal Cognitive Health Company, uMethod Health, Versanum, Athira, TransDermix, Seq BioMarque, NeuroReserve, Cortexyme/Quince Therapeutics, Lighthouse Pharmaceuticals, Alzheon
  - Consulting: Roche-Genentech, Eisai, Lilly, Synaptogenix, NeuroTherapia, T3D, Signant Health, Novo Nordisk, Corium, Prothena
  - Royalties: Humanix
  - Board of Director: EIP Pharma

Clarity AD: Safety Topline Endpoints

- Adverse Events
- Laboratory Abnormalities
- Vital Signs
- ARIA-E and H
- Infusion-related reactions

- Safety was monitored throughout study by the data safety monitoring board (DSMB) and by an independent medical monitoring team

ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA-H, ARIA with hemosiderin deposits; DSMB, Data Safety Monitoring Board.

Overall Adverse Event (AE) Summary

Core Study

	Placebo (n=897) n (%)	Lecanemab (n=898) n (%)
Deaths*	7 (0.8)	6 (0.7)
Serious adverse event (SAE)	101 (11.3)	126 (14.0)
SAE with ARIA-E	0	7 (0.8)
SAE with ARIA-H	1 (0.1)	5 (0.6)
SAE with infusion-related reactions	0	11 (1.2)
SAE without ARIA or infusion-related reactions	101 (11.3)	111 (12.4)
Treatment-emergent AE (TEAE)**	735 (81.9)	798 (88.9)
TEAE without ARIA or infusion-related reactions	719 (80.2)	746 (83.1)
TEAE leading to drug withdrawal	26 (2.9)	62 (6.9)
TEAE leading to drug withdrawal excluding AESI	24 (2.7)	28 (3.1)

*Cause of deaths in placebo group: death, acute respiratory failure, myocardial infarction, metastases to bone, hemorrhage intracranial, COVID-19, pancreatic cancer.
Cause of death in lecanemab group: death, cerebrovascular accident, myocardial infarction, respiratory failure, metastases to meninges, COVID-19. No participants died with or from ARIA in Core study.
**AE rates are similar between placebo and lecanemab when ARIA and infusion-related reactions are excluded.
AESI, adverse event of special interest; ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA-H, ARIA with hemosiderin deposits.

Most Common Adverse Events

Adverse Events Of Special Interest (Pooled preferred terms [PTs])	Placebo (n=897) %	Lecanemab (n=898) %
Infusion-related reaction	7.4	26.4
ARIA-E	1.7	12.6
ARIA-H (pooled PTs)	9.0	17.3
Isolated ARIA-H (pooled PTs)	7.8	8.9

Other Adverse Events >5%	Placebo (n=897) %	Lecanemab (n=898) %
Headache	8.1	11.1
Fall	9.6	10.4
Urinary tract infection	9.1	8.7
COVID-19	6.7	7.1
Back pain	5.8	6.7
Arthralgia	6.9	5.9
Dizziness	5.1	5.5
Diarrhea	6.5	5.3
Anxiety	4.2	5.0

- There were no significant trends in mean changes over time or shifts from baseline for any of the laboratory, ECG or vital sign parameters and no notable differences between groups

ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA-H, ARIA with hemosiderin deposits; COVID-19, coronavirus disease of 2019, ECG, electrocardiogram.

Infusion-Related Reactions and Immunogenicity

Infusion-Related Reactions

Infusion-related reactions are limited in impact and do not recur in most subjects regardless of prophylaxis

- Infusion-related reactions were largely mild-to-moderate (grade 1-2: 96%) and occurred on the first dose (75%)
  - Most subjects (65%) only had 1 infusion-related reaction
- ~40% of subjects received preventative medications (e.g. acetaminophen, antihistamine, hydrocortisone) for an infusion after experiencing the first infusion-related reaction
  - Recurrence rate ~35% of infusion-related reaction was the same regardless of receiving preventative medication
- 6 of the 7 severe infusion-related reactions (grade 3-4) occurred with first dose

	Placebo (n=897) n (%)	Lecanemab (n=898) n (%)
Infusion-related reactions	66 (7.4)	237 (26.4)
Mild	57 (6.4)	163 (18.2)
Moderate	9 (1.0)	67 (7.5)
Severe	0	7 (0.8)

Mild (grade 1): Discomfort noticed, but no disruption of normal daily activity
Moderate (grade 2): Discomfort sufficient to reduce or affect normal daily activity
Severe (grade 3-4): Incapacitating, with inability to work or to perform normal daily activity

Immunogenicity

- Incidence of treatment-emergent positive anti-drug antibody (ADA) was 10.3%, with low titers*
- Incidence of treatment-emergent neutralizing antibody (Nab) positivity was 4.1%, with low titers (≤10)
- There was no impact of immunogenicity on efficacy and safety endpoints or pharmacokinetics

* Q1-Q3: 16 and 400, with 3 subjects having a titer ≥2000.

ARIA-E

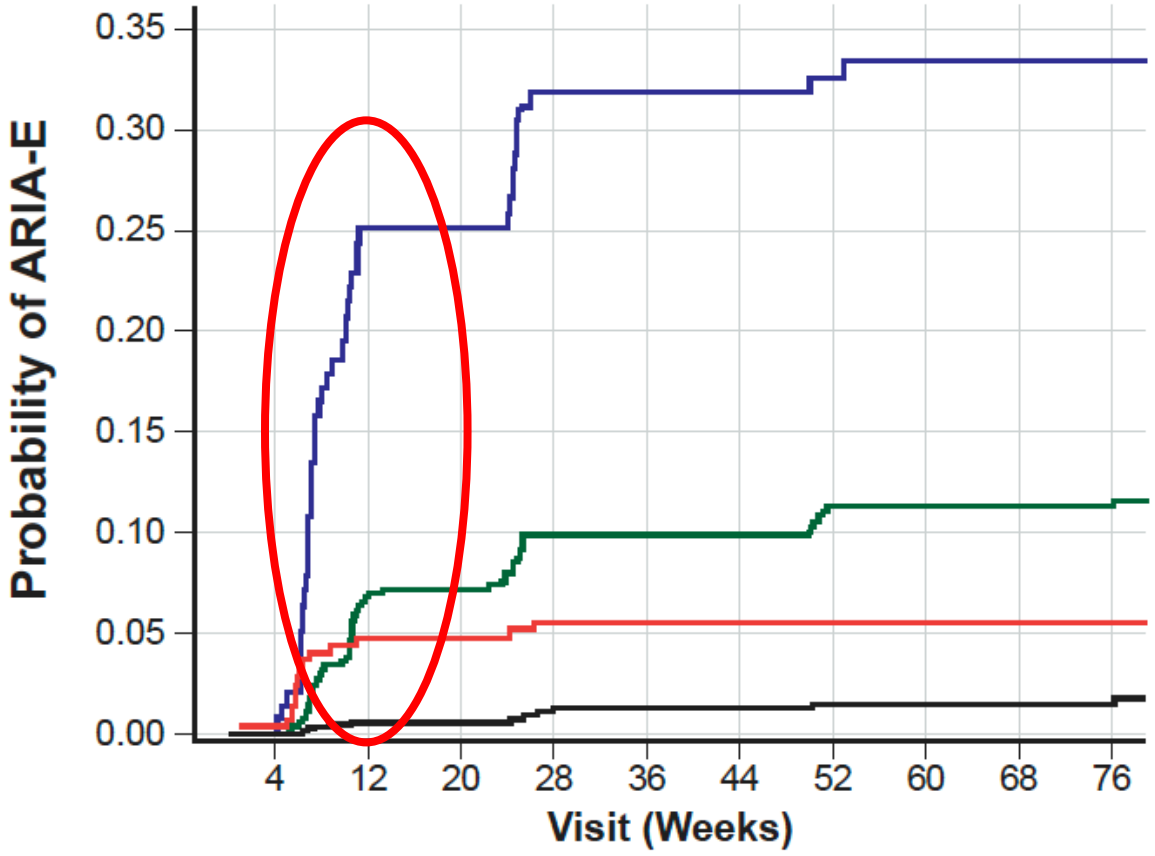
	Placebo (N=897) n/N (%)	Lecanemab (N=898) n/N (%)
ARIA-E	15/897 (1.7)	113/898 (12.6)
ARIA-E by ApoE4 genotype		
ApoE4 noncarrier	1/286 (0.3)	15/278 (5.4)
ApoE4 carrier	14/611 (2.3)	98/620 (15.8)
ApoE4 heterozygote	9/478 (1.9)	52/479 (10.9)
ApoE4 homozygote	5/133 (3.8)	46/141 (32.6)
Symptomatic ARIA-E*	0	25/898 (2.8)
ApoE4 noncarrier	0	4/278 (1.4)
ApoE4 carrier	0	21/620 (3.4)
ApoE4 heterozygote	0	8/479 (1.7)
ApoE4 homozygote	0	13/141 (9.2)

*Symptomatic concurrent ARIA-E and ARIA-H were included under ARIA-E.

- ARIA-E events were largely mild-to-moderate radiographically (91%) and asymptomatic (78%)
- In the 2.8% of subjects with symptomatic ARIA-E, commonly reported symptoms were headache, visual disturbance, and confusion
- Recurrent ARIA-E
  - Placebo: 1 (0.1%)
  - Lecanemab: 28 (3.1%)

ApoE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA-H, ARIA with hemosiderin deposits.

Time to ARIA-E Events



Heterozygous for LEC10-BW	479	423	410	395	387	381	374	367	362	343
Homozygous for LEC10-BW	141	101	100	91	89	89	88	86	85	83
Noncarrier for LEC10-BW	277	255	247	239	231	221	216	211	205	204
Overall Placebo	897	879	863	850	822	800	792	777	762	731

- ARIA-E with lecanemab generally occurred within the first 3 months of treatment (71%) and by 6 months (92%)
- ARIA-E resolved within 4 months of detection (81%), regardless of ApoE4 carrier status
  - 60/111 (54%) resolved by 90 days
  - 90/111 (81%) resolved by 120 days

ApoE4, apolipoprotein E4. ARIA-E, amyloid related imaging abnormalities - edema; LEC10-BW, lecanemab 10 mg/kg biweekly.

Lecanemab ARIA-E Events:

Radiographic and Clinical Severity Overall and by APOE4 Genotype

- ARIA-E more common in ApoE4+ on treatment and placebo, with highest frequency in homozygotes
- Mostly mild to moderate in radiographic and clinical severity, including homozygotes
- Most subjects with mild radiographic ARIA-E did not worsen and could continue dosing without drug interruption
- Subjects with mild radiographic ARIA-E who continued dosing resolved (3 months) in similar time frame to those who discontinued dosing (3 months)

			Radiographic severity (mild/moderate/severe)		Symptomatic ARIA-E (no symptomatic in placebo)	Symptomatic - Clinical Severity (mild/moderate/ severe)
	Placebo (N=897)	Lecanemab (N=898)	Placebo (N=897)	Lecanemab (N=898)	Lecanemab (N=898)	Lecanemab (N=898)
ARIA-E	15/897 (1.7%)	113/898 (12.6%)	9 / 6 / 0	37 / 66 / 9	25 (2.8%)	10/12/3
ApoE4+	14/611 (2.3%)	98/620 (15.8%)	9 / 5 / 0	31 / 57 / 9	21 (3.4%)	9/9/3
Homozygote	5/133 (3.8%)	46/141 (32.6%)	2 / 3 / 0	6 / 33 / 7	13 (9.2%)	5/7/1
Heterozygote	9/478 (1.9%)	52/479 (10.9%)	7 / 2 / 0	25 / 24 / 2	8 (1.7%)	4/2/2
ApoE4-	1/286 (0.3%)	15/278 (5.4%)	0 / 1 / 0	6 / 9 / 0	4 (1.4%)	1/3/0

ApoE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities – edema.

ARIA-H

- Isolated ARIA-H was similar between lecanemab (8.9%) and placebo (7.8%) with low rates of clinically symptomatic ARIA-H
- Timing of isolated ARIA-H occurs randomly during treatment course, while ARIA-H that occurs with ARIA-E tended to occur early in the course of lecanemab treatment

	Total		Isolated ARIA-H (no ARIA-E)	
	Placebo (N=897) n (%)	Lecanemab (N=898) n (%)	Placebo (N=897) n (%)	Lecanemab (N=898) n (%)
ARIA-H (micro, macro, superficial)	81 (9.0)	155 (17.3)	70 (7.8)	80 (8.9)
Microhemorrhage	68 (7.6)	126 (14.0)	63 (7.0)	60 (6.7)
Superficial siderosis	21 (2.3)	50 (5.6)	13 (1.4)	23 (2.6)
Cerebral macrohemorrhage	1 (0.1)	5 (0.6)	1 (0.1)	4 (0.4)
Symptomatic ARIA-H	2 (0.2)	13 (1.4)	2 (0.2)	4 (0.4)
ARIA-H by ApoE4 genotype				
ApoE4 noncarrier, n/N (%)	12/286 (4.2)	33/278 (11.9)	11/286 (3.8)	23/278 (8.3)
ApoE4 carrier, n/N (%)	69/611 (11.3)	122/620 (19.7)	59/611 (9.7)	57/620 (9.2)
ApoE4 heterozygote, n/N (%)	41/478 (8.6)	67/479 (14.0)	35/478 (7.3)	40/479 (8.4)
ApoE4 homozygote, n/N (%)	28/133 (21.1)	55/141 (39.0)	24/133 (18.0)	17/141 (12.1)

ApoE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA-H, ARIA with hemosiderin deposits.

Cerebral Macrohemorrhage in Lecanemab Studies

Data Cutoff October 22, 2022 for Open-Label Extension (OLE; Ongoing)

Study	Total		Anticoagulant Use	
	Placebo n/N (%)	Lecanemab 10 mg/kg q2wk n/N (%)	Placebo n/N (%)	Lecanemab 10 mg/kg q2wk n/N (%)
201 Core Phase	0/245 (0%)	1/161 (0.6%)	0/20 (0%)	0/11 (0%)
201 OLE	N/A	1/180 (0.6%)	N/A	0/18 (0%)
301 Core Phase	2/897 (0.2%) [1]	6/898 (0.7%) [2]	0/74 (0%)	2/83 (2.4%) [2]
301 Core + OLE (includes cases in 301 Core above)	N/A	10/1608 (0.6%) [2, 3]	N/A	5/140 (3.6%) [2, 3]
301 Core & OLE Deaths with concurrent macrohemorrhage	1/897 (0.1%) [4]	2/1608 (0.1%) [3]	0/74 (0%)	2/140 (1.4%) [3]

[1] Includes one non-treatment emergent case in placebo (event > 30 days after discontinuing study medication)
[2] Includes one non-treatment emergent case on anticoagulation (event > 30 days after discontinuing study medication)
[3] 1 case of macrohemorrhage in 65F E4 homozygous after tPA for left MCA occlusion (OLE) and 1 case in 87M E4 non-carrier on apixaban (stopped) then received heparin for MI (OLE, cause of death cardiopulmonary)
[4] In core phase

AD, Alzheimer's disease; ApoE4, apolipoprotein E4; MRI, magnetic resonance imaging; NA, Not applicable; q2wk, every 2 weeks.

Cerebral Macrohemorrhage in AD

- Lobar macrohemorrhage in AD in the absence of arteriovenous malformation, hemorrhagic cerebral infarction, or tumor is usually caused by cerebral amyloid angiopathy (CAA)
- Risk factors for lobar macrohemorrhage include ApoE4 genotype, presence of microhemorrhages (which is evidence of CAA), and anticoagulant medications
- Background rates of macrohemorrhage in placebo arms of prior AD clinical trials is 0.4% (*JAMA Neurol*. 2022;79:13-21)

Safety Assessment

- There is a low rate of macrohemorrhage with lecanemab therapy (0.6-0.7%), which is higher than placebo (0.2%)
- Rate of macrohemorrhage for subjects on both anticoagulants and lecanemab was 2.4-3.6%. Background rate of macrohemorrhage in AD patients on anticoagulation is not known but is expected to be higher than in non-AD patients due to CAA; therefore, comparative risk is difficult to assess.
- No clear relationship of macrohemorrhage to ApoE4 status, baseline MRI, or timing of treatment
- Subjects allowed to continue on anticoagulation in OLE with informed consent language regarding increased risk of cerebral hemorrhage with concomitant anticoagulant use

Summary

Clarity AD Safety

- Lecanemab was generally well-tolerated
  - Most common adverse events were infusion-related reactions, ARIA-H, ARIA-E, and headache
- ARIA incidence profile was within expectations, and the symptomatic ARIA rate was low
  - Incidence of ARIA-E: 12.6% for lecanemab and 1.7% placebo
  - Symptomatic ARIA-E: lecanemab: 2.8%; placebo: 0.0%
  - ARIA-E most commonly occurred within the first 3 months of treatment (71%) and resolved within 4 months of detection (81%)
- The ARIA-H (ARIA cerebral microhemorrhages, cerebral macrohemorrhages, and superficial siderosis) rate was 17.3% in the lecanemab group and 9.0% in the placebo group
  - Symptomatic ARIA-H: lecanemab: 0.7% and placebo: 0.2%
  - There was no imbalance in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) between lecanemab (8.9%) and placebo (7.8%)
- ARIA-E and ARIA-H were less common in ApoE4 non-carriers versus carriers, with higher frequency in ApoE4 homozygous carriers vs ApoE4 heterozygous carriers

Infusion-related reaction, ARIA-E, and rare macrohemorrhage are important adverse events that can be seen with lecanemab treatment. If approved, clinicians, patients, and caregivers will need to understand the incidence, monitoring, and management of these events

ApoE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA-H, ARIA with hemosiderin deposits.

Imaging, Plasma, and CSF Biomarkers Assessments from Clarity AD

Randall J. Bateman

Washington University School of Medicine

Disclosures

- Dr Bateman is the Director of DIAN–TU and Principal Investigator of DIAN–TU-001
- He receives research support from the NIA of the NIH, DIAN–TU trial pharmaceutical partners (Eli Lilly and Company, F. Hoffman-La Roche Ltd and Avid Radiopharmaceuticals), Alzheimer's Association, GHR Foundation, Anonymous Organization, DIAN–TU Pharma Consortium (active: Biogen, Eisai, Eli Lilly and Company, Janssen, F. Hoffmann-La Roche Ltd/Genentech; previous: AbbVie, Amgen, AstraZeneca, Forum, Mithridion, Novartis, Pfizer, Sanofi, United Neuroscience)
- He has been an invited speaker and consultant for AC Immune, F. Hoffman-La Roche Ltd and Janssen and a consultant for Amgen and Eisai
- Dr. Bateman is a co-founder of C2N Diagnostics. Washington University has equity ownership interest in C2N Diagnostics. Dr. Bateman is a co-inventor of assay technologies licensed by Washington University to C2N Diagnostics. Dr. Bateman receives income from C2N Diagnostics for serving on the scientific advisory board

Biomarker Objectives in Lecanemab Development

Biomarkers hierarchy	Assessment	Purpose	Hypothesis
Patient Selection	Amyloid PET CSF Ab42/40 plasma Ab42/40 (AHEAD 3-45)	Ø Confirm diagnosis in early AD Ø Select preclinical AD population (AHEAD 3-45)	l Treatment of early AD prior to advanced irreversible neurodegeneration l Preclinical population responsive to tailored dose of lecanemab
Target Engagement/ Pharmacodynamic	CSF protofibril* Amyloid PET CSF or plasma Ab42/40	Ø Activity against protofibrils Ø Activity against amyloid plaques	l Reduction of free CNS protofibrils l Reduction of amyloid plaques l Reduction of amyloid aggregation process
Pathophysiological and Clinically Predictive (including a panel of amyloid, tau and pathophysiologic related biomarkers)	Amyloid PET CSF and plasma Aβ[42], Aβ42/40 ratio, p-tau181 and NfL CSF t-tau, neurogranin and GFAP Tau PET MRI regional volumes	Ø Predict clinical benefit for accelerated approval Ø Activity against downstream process in AD (disease modification)	l Correlation of soluble and aggregated measures of amyloid and tau with clinical effects l Delay in progression of AD pathophysiological biomarkers
Clinical Consequence	Early AD: CDR-SB, ADCS MCI-ADL, ADAS-Cog14, ADCOMS	Ø Confirm efficacy	l Slowing of cognitive and functional decline

*Assay in development

Ab, amyloid beta; AD, Alzheimer's disease; ADAS-Cog14, Alzheimer's disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's disease COMposite Score; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating-Sum-of-Boxes; CSF, cerebrospinal fluid, GFAP: glial fibrillary acidic protein; NfL, neurofilament light chain, MRI, magnetic resonance imaging; PET, positron emission tomography; p-tau, phosphorylated tau; t-tau, total tau.

Clarity AD: Biomarker Assessments

All Prospectively Pre-specified in Statistical Analysis Plan

CSF

- Aβ[1-40][1]
- Aβ[1-42][1]
- t-tau[1]
- p-tau181[1]
- Neurogranin[2]
- Neurofilament light chain (NfL)[3]

Plasma

- Aβ 42/40 ratio[4]
- p-tau181[3]
- Glial fibrillary acidic protein (GFAP)[3]
- NfL[3]

Imaging

- Amyloid PET[5]
- Tau PET (MK-6240)
- Volumetric MRI (vMRI; Whole brain volume, cortical thickness, and total hippocampal volume)

[1] Fujirebio Lumipulse. [2] Euroimmune ELISA. [3] Quanterix Simoa. [4] C2N Precivity AD-Ab. [5] florbetaben, florbetapir or flutemetamol tracers

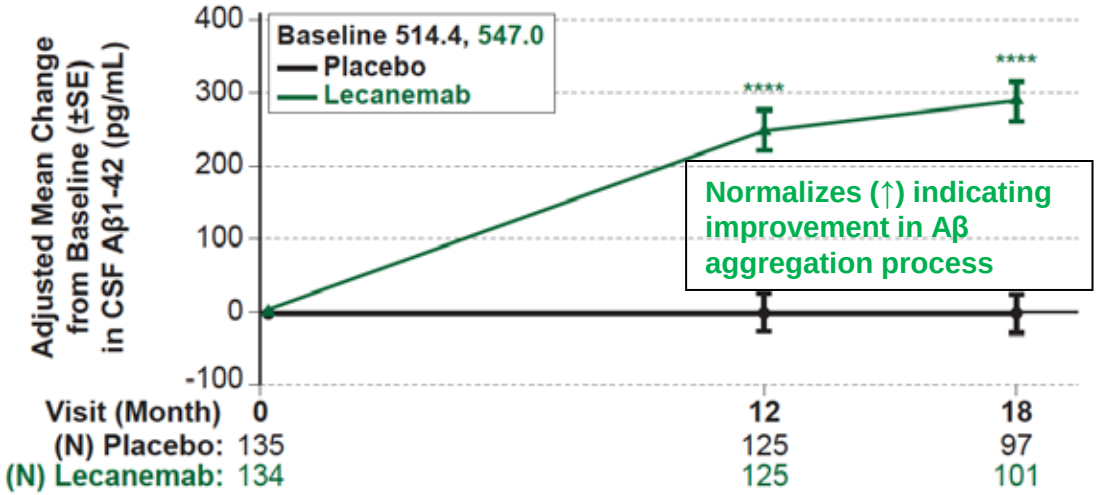
All analyses of biomarkers report pre-specified nominal p-values without multiple comparison corrections

Ab, amyloid beta; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography; p-tau, phosphorylated tau; t-tau, total tau.

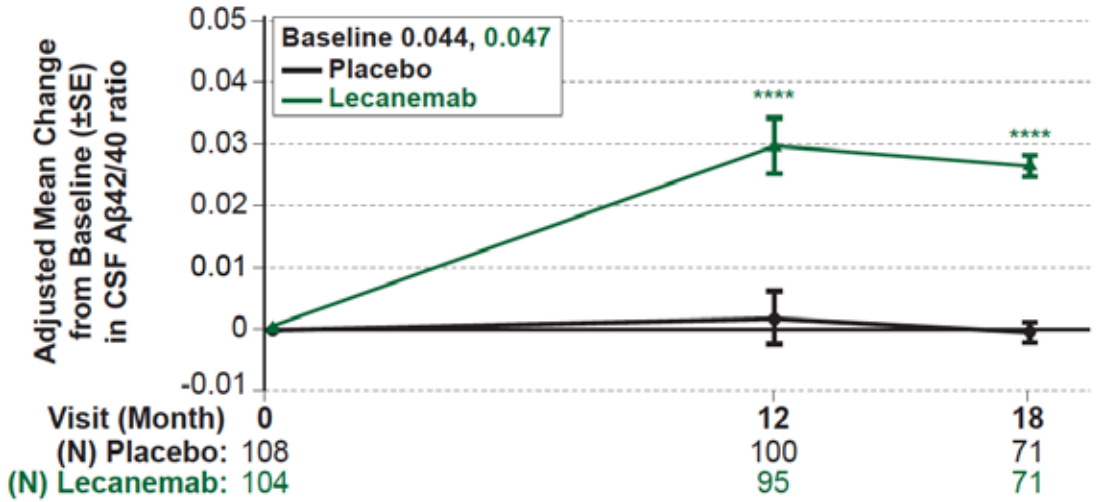
Amyloid Biomarkers

CSF and Plasma Aβ42/40 Improves Indicating Early/Sustained Amyloid Reversal Effects

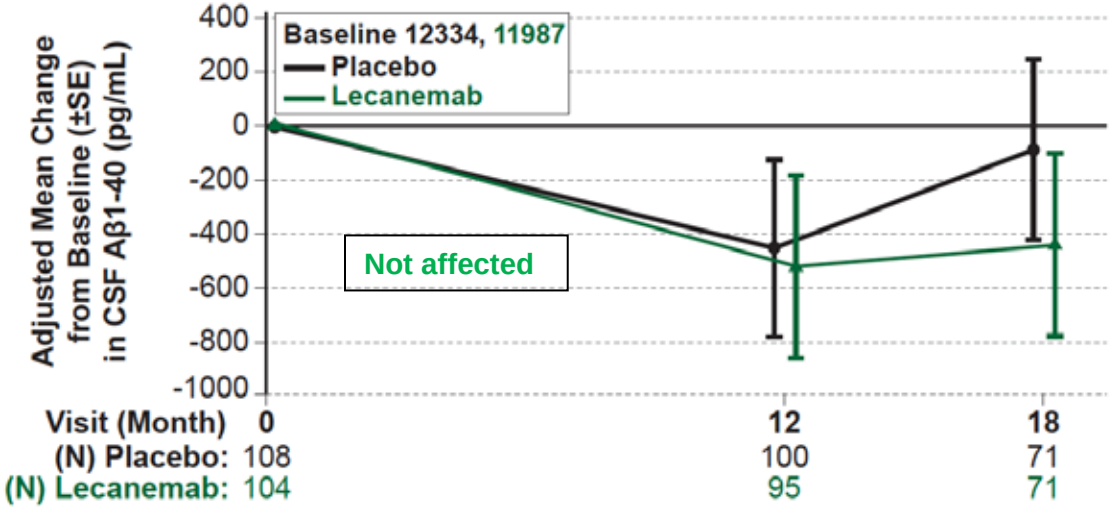
CSF Aβ1-42



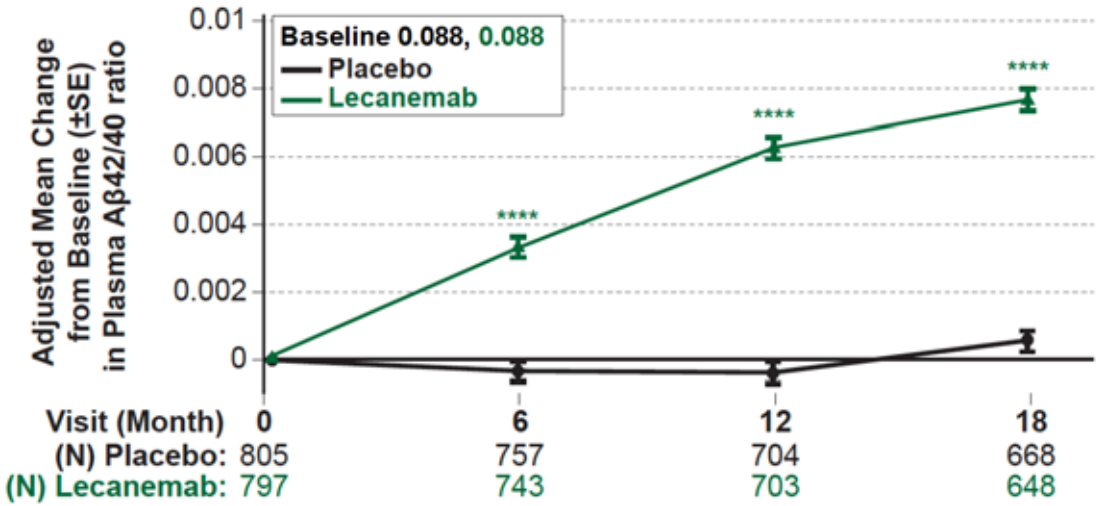
CSF Ab42/40



CSF Aβ1-40



Plasma Ab42/40

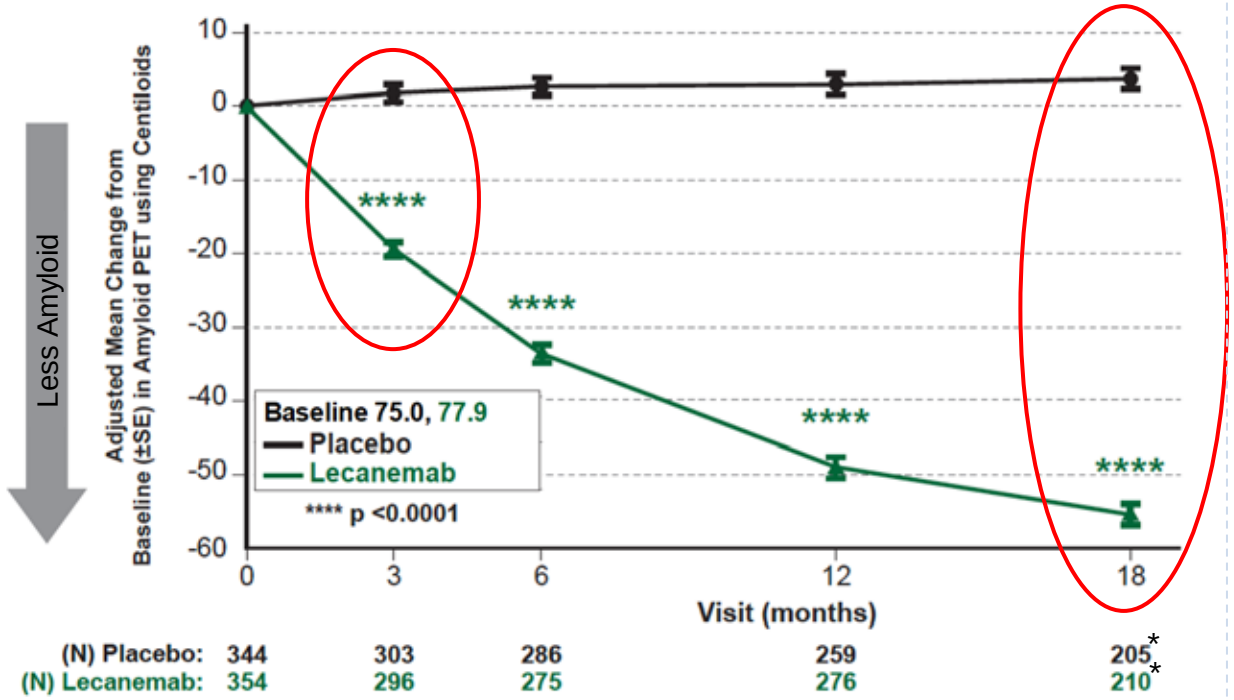


**** P<0.0001

Ab, amyloid beta; CSF, cerebrospinal fluid, SE, standard error.

PET Centiloids and Amyloid PET SUVr Images at Baseline and 18 Months

Highly Significantly Reduced Amyloid Plaque (Centiloids) at All Time Points; Mean at 18 Months of 23 Centiloids (Below 30 Centiloid Threshold of Positivity)



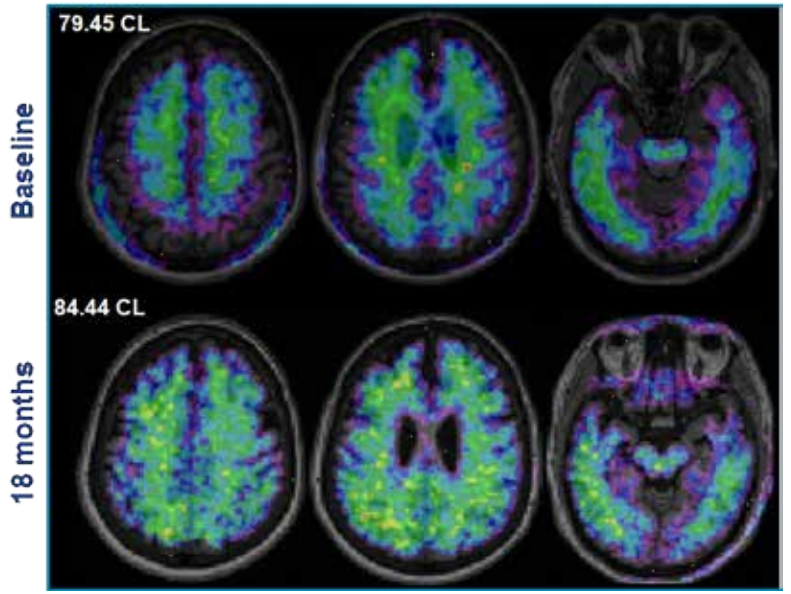
(N) Placebo:	344	303	286	259	205*
(N) Lecanemab:	354	296	275	276	210*

% Amyloid Negative (<30 CL)				
Placebo	15	14	15	16
Lecanemab	24	36	54	68

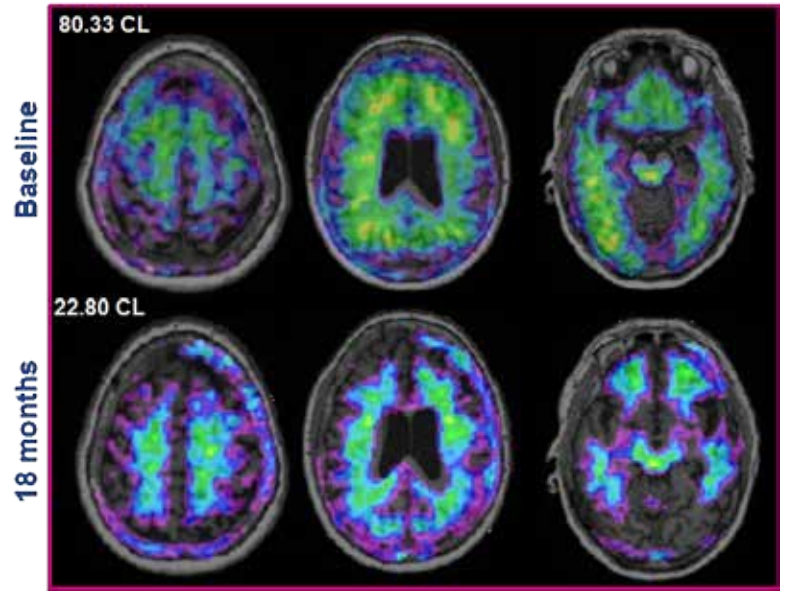
* 73 subjects were not included at 18 months (per SAP) since their PET assessments were performed after receiving lecanemab in the extension phase.

Note: Based on PD analysis population (PET substudy population). Adjusted mean change from baseline, SE and p-value are derived using MMRM with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, *ApoE4* carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

Placebo



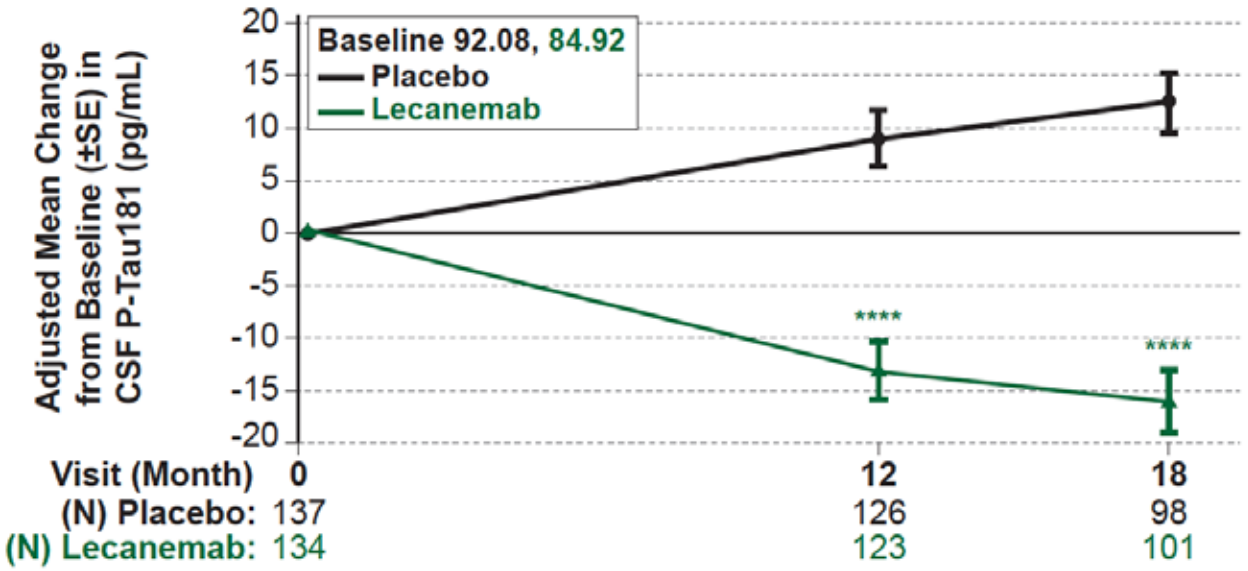
Lecanemab



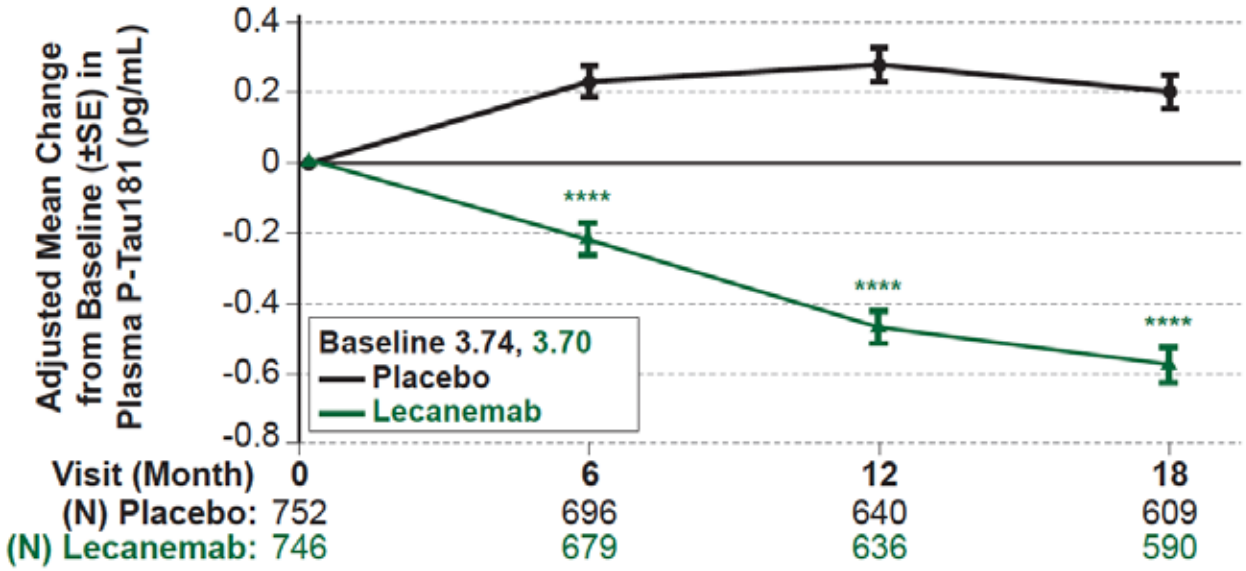
Tau Biomarkers

- CSF and plasma p-tau181 continued to increase in placebo group
- CSF and plasma p-tau181 decreased in lecanemab group towards normal at all times measured
- Indicates removing amyloid improves downstream tau phosphorylation at amyloid responsive 181 site

CSF P-Tau181



Plasma P-Tau181



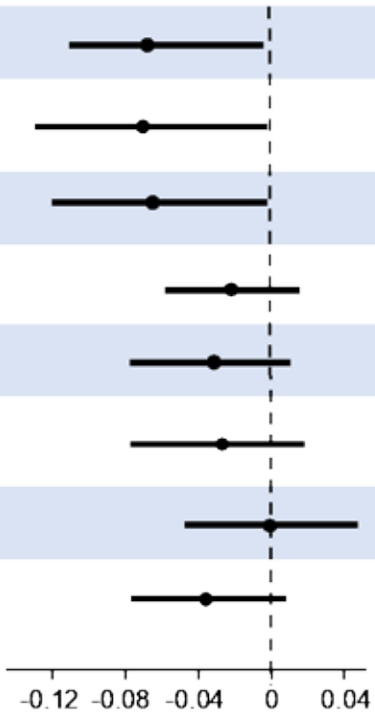
CSF, cerebrospinal fluid, p-tau, phosphorylated tau; SE, standard error.

**** P<0.0001

Tau PET

*Lecanemab Slows Tau Pathology in Temporal Lobe (Early Braak Regions)**

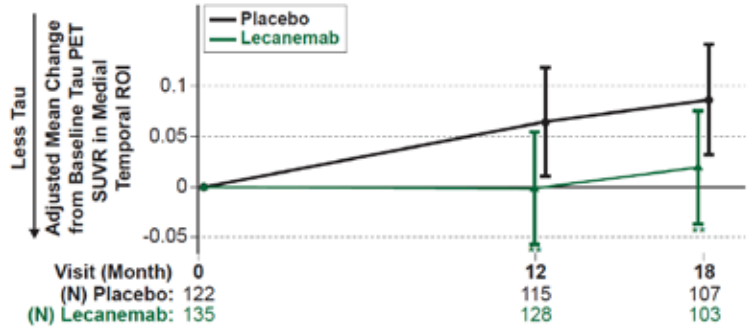
	No. of Participants (placebo, lecanemab)	Adjusted Mean Difference	P Value
	Favors lecanemab		
Medial temporal	122, 135	-0.068	0.0024
Meta temporal	122, 135	-0.071	0.012
Temporal	132, 136	-0.065	0.016
Frontal	122, 135	-0.023	0.22
Cingulate	132, 135	-0.034	0.13
Parietal	122, 135	-0.029	0.25
Occipital	132, 135	-0.003	0.91
Whole cortical gray matter	122, 443	-0.035	0.10



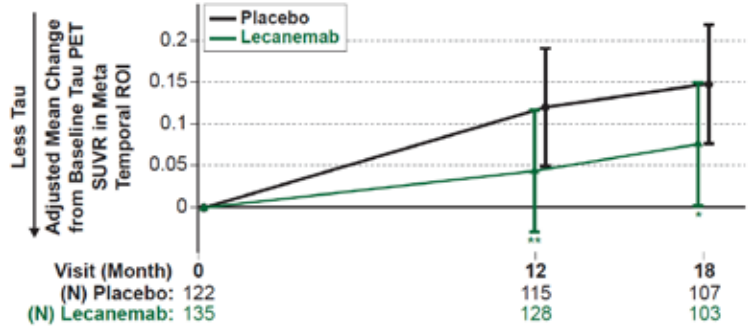
Adjusted Mean Difference versus Placebo (95% CI)

*Other regions favored lecanemab but were p > 0.05

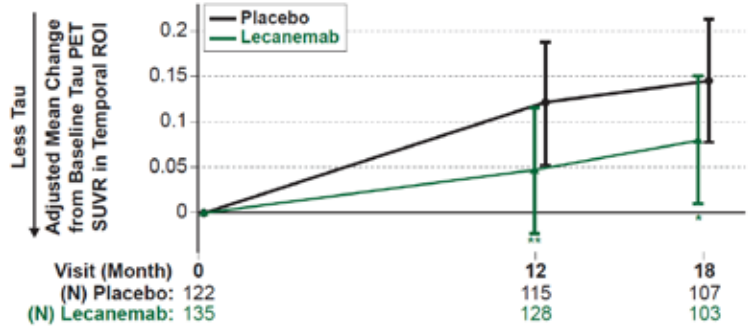
Medial Temporal



Meta Temporal



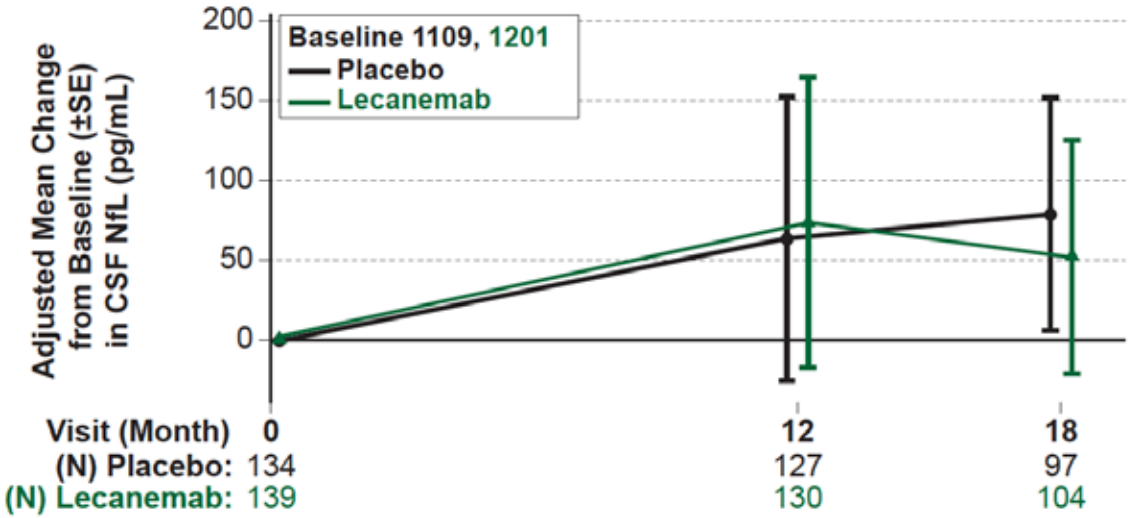
Temporal



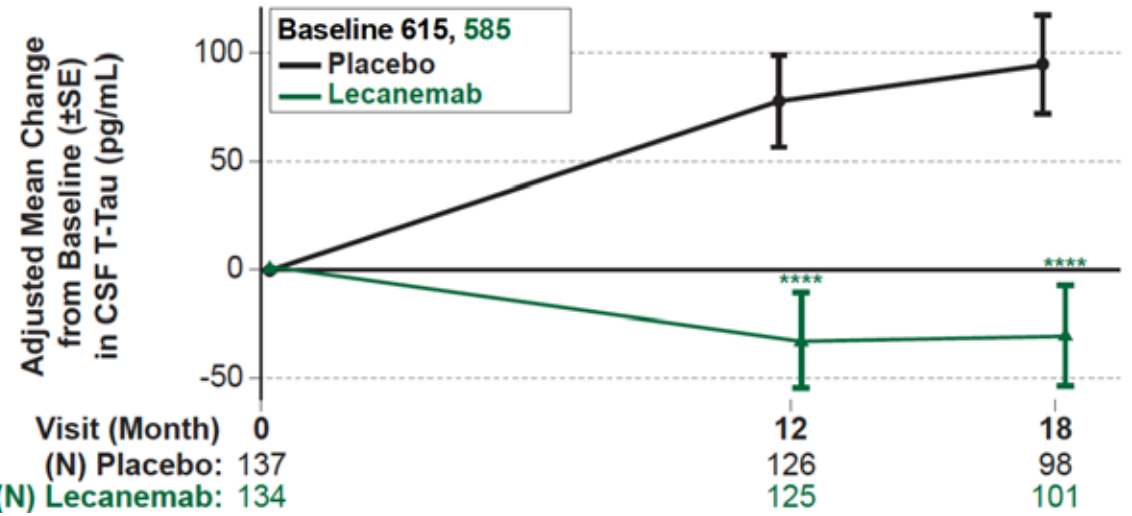
CI, confidence interval; PET, positron emission tomography; ROI, regions of interest.

Neurodegeneration Biomarkers

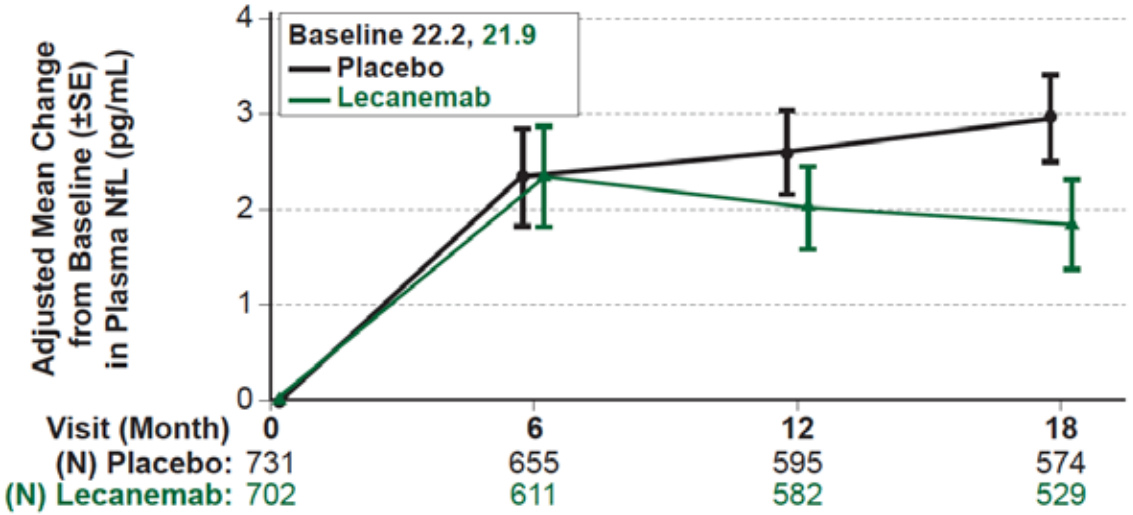
CSF NfL



CSF T-Tau



Plasma NfL



- No difference in CSF NfL which had large variability
- Plasma NfL, with larger sample size, trends towards difference (P=0.06) at 18 months
- CSF-total tau increase in placebo and decreased in lecanemab treated group

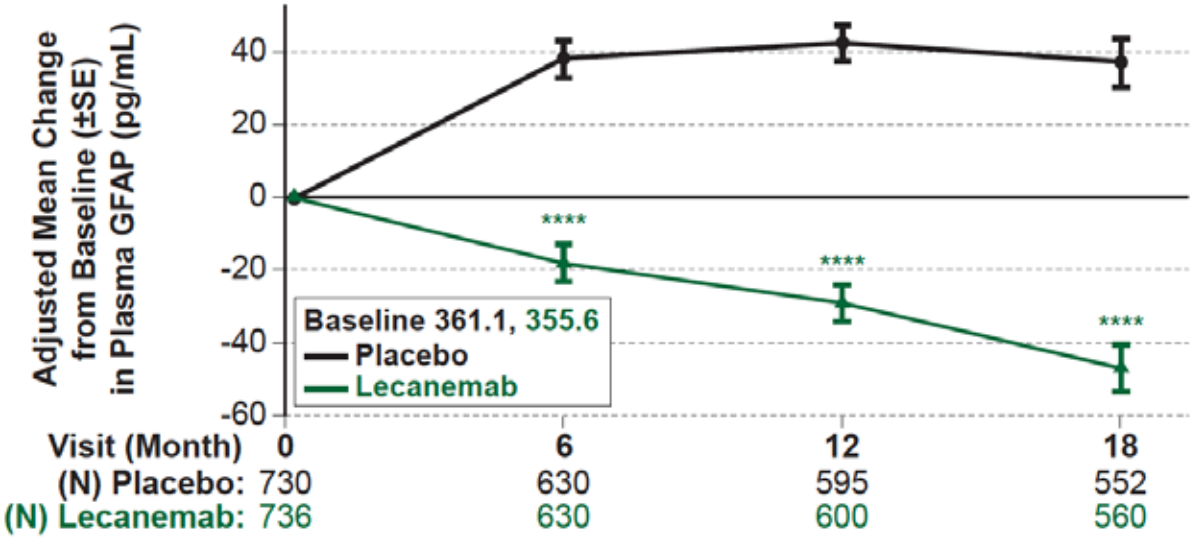
**** P<0.0001

CSF, cerebrospinal fluid, NfL, neurofilament light chain. SE, standard error; p-tau, phosphorylated tau; t-tau, total tau.

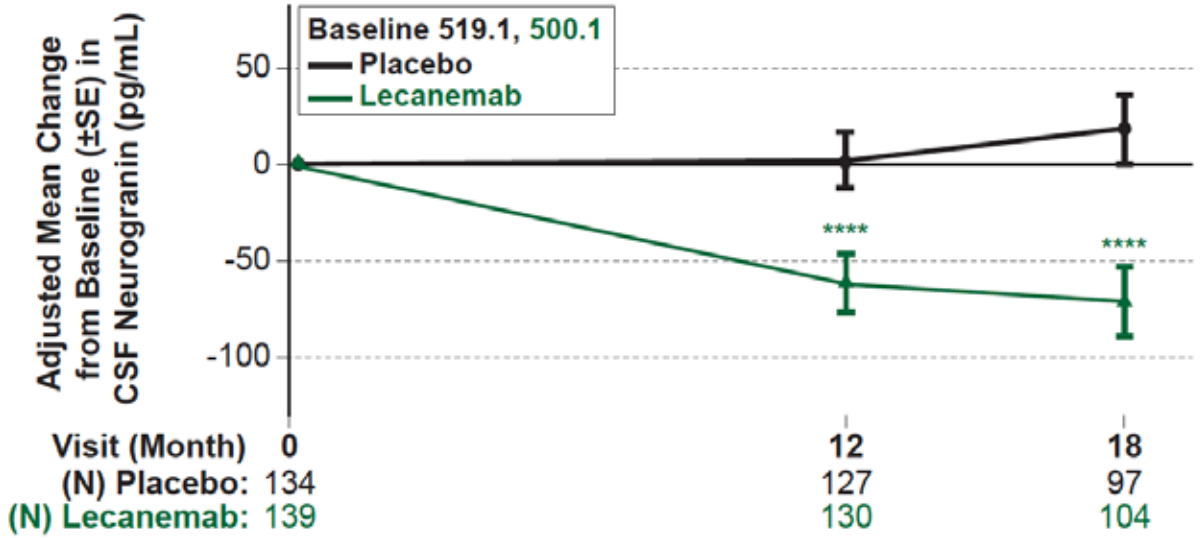
Astrocytic and Synaptic Biomarkers

- GFAP, a marker of astrocyte activation and neurogranin and marker of synaptic dysfunction, both improved towards normal

Plasma GFAP



CSF Neurogranin

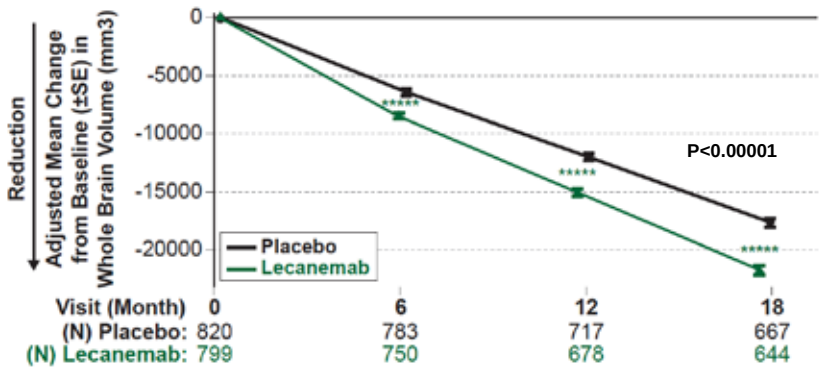


CSF, cerebrospinal fluid, GFAP: glial fibrillary acidic protein; SE, standard error.

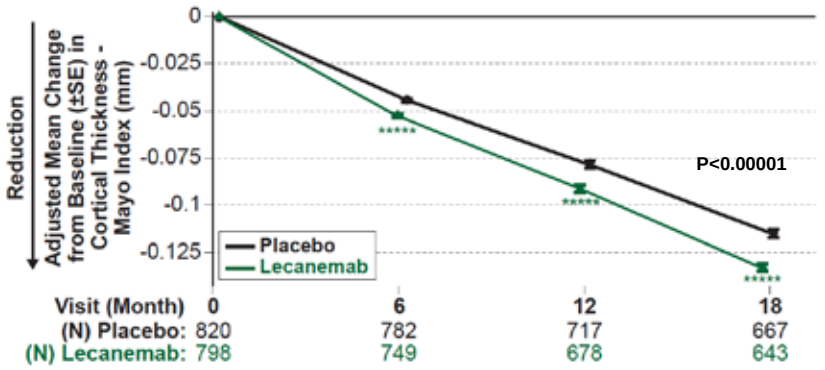
**** P<0.0001

Volumetric MRI: Increased Atrophy in Whole Brain and Cortical Thickness, with Decreased Atrophy in Hippocampi

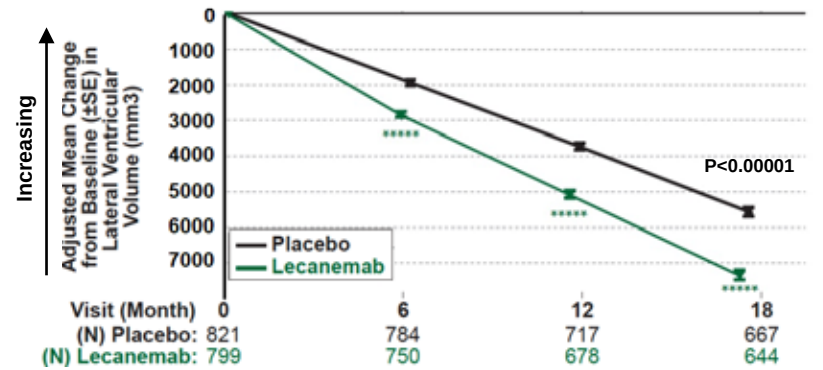
Whole brain volume



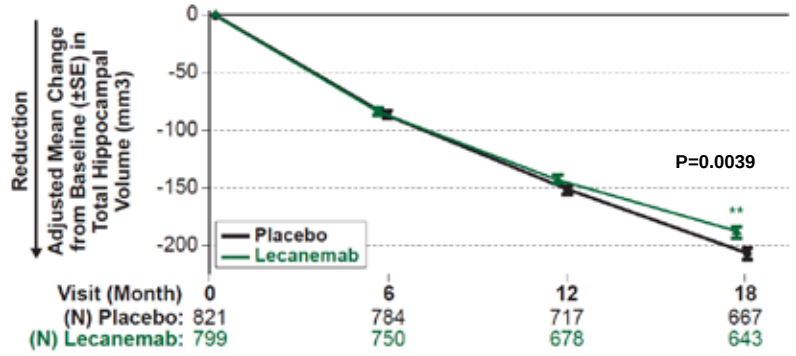
Cortical thickness



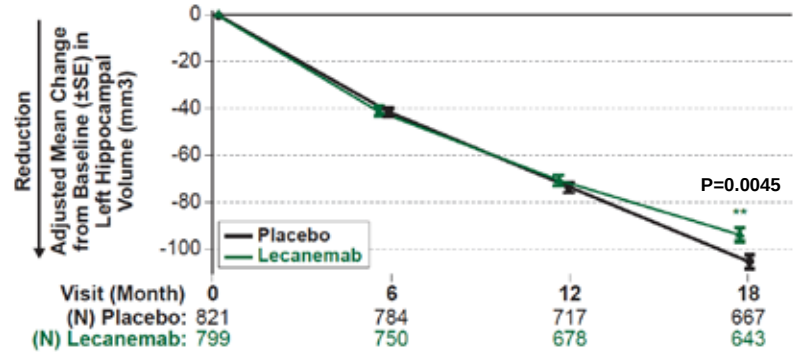
Lateral ventricular volume



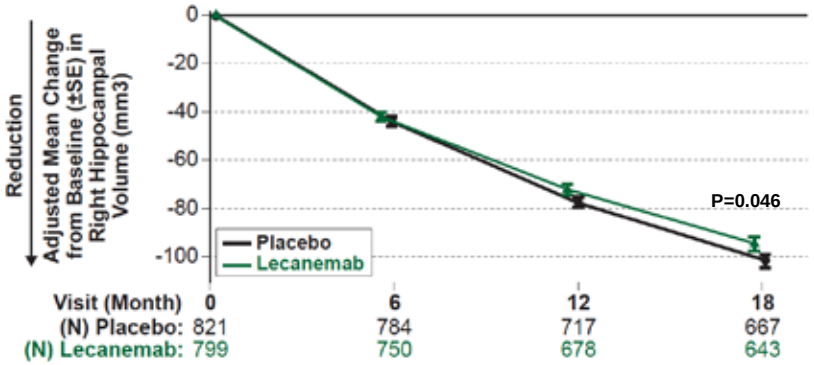
Total hippocampal volume



Left hippocampal volume



Right hippocampal volume



* P<0.05; ** P<0.01; *** P<0.001; **** P<0.0001

CI, confidence interval; SE, standard error; vMRI, volumetric magnetic resonance imaging.

Interpretation

Lecanemab treatment impacted CSF, plasma, and imaging biomarkers across measures of amyloid, tau, neurodegeneration, astrocyte and synaptic pathophysiological measures.

- Lecanemab had beneficial effects on biomarkers of amyloid, tau, and other pathophysiology measures
- The neurodegeneration markers gave a mixed picture, potentially because these measures may take time to respond, and will be followed in ongoing studies
- The drug directly removed amyloid plaques as measured by soluble & PET measures, and also had downstream effects on tau pathology by PET, soluble measures of tau, synaptic dysfunction, and astrocyte activation
- These findings indicate biological disease modification, by improving the amount of amyloid and tau pathology of the disease, while also impacting the pathophysiology of Alzheimer's disease[1,2]
- Disease modification is further supported by clinical benefit, with phase 2 data of durable effect off dosing, and will be further evaluated in the OLE period

1. FDA Draft Guidance for Industry. Early Alzheimer's Disease: Developing Drugs for Treatment (2018). 2. CHMP Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease. Available online at: CPMP/EWP/553/95 Rev.2 (2018).

Clarity AD: Results in Context

Sharon Cohen, MD FRCPC

Toronto Memory Program

Disclosures

- Consultant (no personal fees)
  - Alnyalm, Biogen, Cogstate, Cognivue, Cassava Sciences, Eisai, Eli Lilly, INmuneBio, Novo Nordisk, ProMIS Neuroscience, RetiSpec, Roche

- Research Grants (paid to institution only)
  - Agene Bio, Alector, Alnylam, Alzheon, Anavex, Biogen, Cassava Sciences, Eisai, Eli Lilly, Janssen, Novo Nordisk, RetiSpec, Roche, UCB Biopharma, Vielight

Alzheimer’s Disease – A Major Unmet Need of Our Time

- A chronic, progressive, disabling, and fatal disease[1-7]
- 6th leading cause of death in seniors[3]
- Accounts for 60-80% of cases of dementia[3]
- 55 million – rising to 75 million by 2030, and 150 million by 2050[3]
- Alzheimer’s disease causes a significant economic burden globally[3-4]
- Severe impact on patients, families, and healthcare systems[3-4]
- Established treatments are insufficient[4]

1. Dubois B, et al. Lancet Neurol 2010;9:1118–1127. 2. Masters C, et al. Nature Reviews 2015;1:15056. 3. Alzheimer’s Disease International. World Alzheimer Report 2022. 4. Scheltens P, et al. Alzheimer's disease. Lancet 2021;397:1577-1590. 5. Hampel H, et al. Mol Psychiatry 2021;26:5481-5503. 6. Albert MS, et al. Alzheimers Dement 2011;7(3):270-9. 7. Jack Jr. CA, et al. Alzheimer’s & Dementia 2011;7;257-62.

Important Treatment Goals in Alzheimer's Disease

- Impact on symptoms
  - Greater magnitude of improvement
  - More sustained improvement duration
- Slowing of disease
  - Maintaining or stabilizing abilities for longer periods
  - Delaying or preventing onset of more disabling and costly stages of disease
- Maintaining/Improving quality of life for patients and families

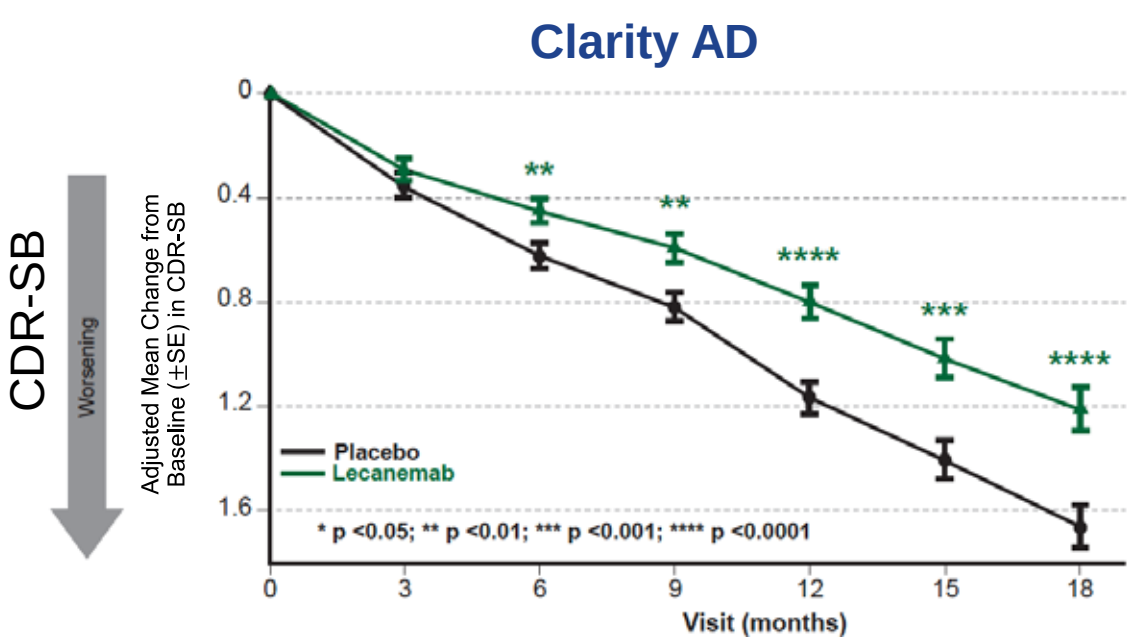
Disease Modification in Alzheimer’s Disease

- FDA definition
  - Persistent effect on disease course
  - Direct effect on the underlying disease pathophysiology
- EMA (CHMP) definition
  - Persistent delay in the underlying neuropathological process
  - Delay of clinical decline

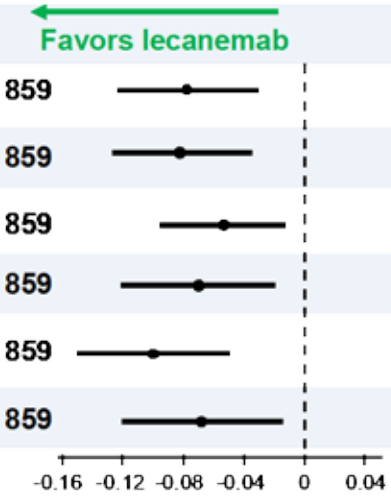
FDA Draft Guidance for Industry. Early Alzheimer's Disease: Developing Drugs for Treatment (2018).
CHMP Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease. Available online at: CPMP/EWP/553/95 Rev.2 (2018).

Clarity AD Treatment Effect: CDR-SB

Global Measure of Cognition and Function



CDR-SB Domains	No. of Participants (placebo, lecanemab)	Adjusted Mean Difference	% Slowing	P Value
Memory	875, 859	-0.077	27.5	0.00117
Orientation	875, 859	-0.081	28.1	0.00044
Judgement/Problem Solving	875, 859	-0.053	23.6	0.01008
Community Affairs	875, 859	-0.070	21.2	0.00524
Home and Hobbies	875, 859	-0.098	28.8	0.00018
Personal Care	875, 859	-0.067	29.9	0.01325



Lecanemab Effect

- 27% slowing on CDR-SB
- Increased magnitude of separation over time (0.45 at 18 months)
- Effect seen across all CDR-SB domains

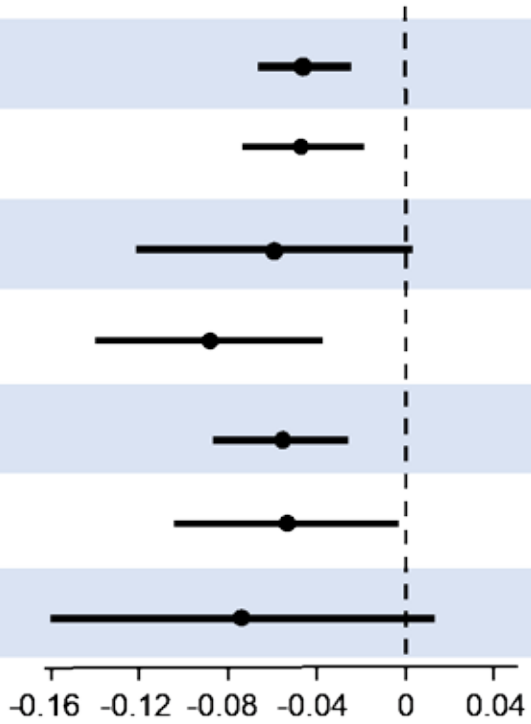
CDR-SB Scale

- Patient and caregiver interview
- Rates 6 cognitive and functional domains
- Each domain scored from 0, 0.5, 1, 2 for range of 0-18
- Mild cognitive impairment and mild AD dementia tend to score 0.5 or 1 in each domain
- Baseline CDR-SB was 3.2

AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating-Sum-of-Boxes; CI, confidence interval; SE, standard error.

Treatment Effect: Consistent Across Comorbidities and Anticoagulant Use

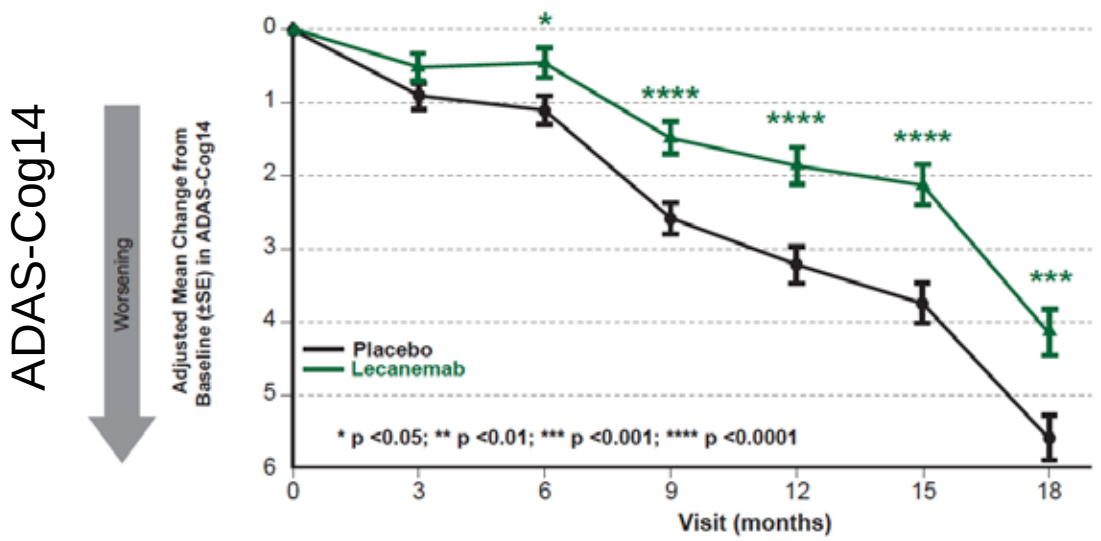
CDR-SB

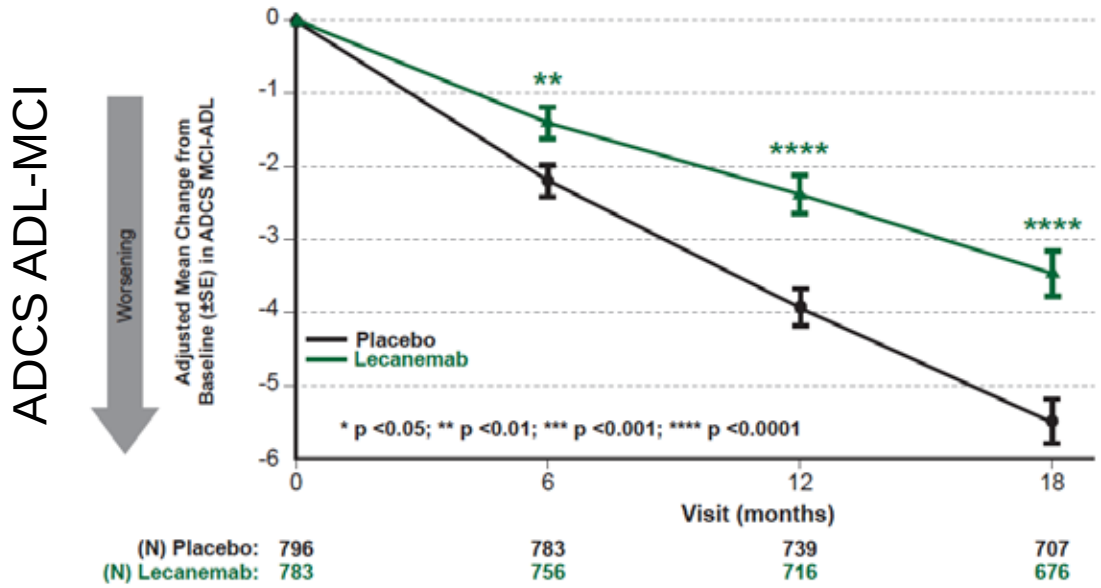


	No. of Participants (placebo, lecanemab)	Placebo Decline	Difference Vs Placebo	% Slowing
Overall	875, 859	1.66	-0.45	27
Hypertension	486, 471	1.56	-0.47	30
Diabetes	130, 130	1.75	-0.58	33
Heart disease	131, 142	1.7	-0.88	52
Hypercholesterolemia	518, 533	1.75	-0.55	32
Obesity	136, 145	1.38	-0.53	38
Anticoagulants	72, 80	2.07	-0.74	36

CDR-SB, Clinical Dementia Rating-Sum-of-Boxes ; CI, confidence interval.

Treatment Effect: Specific Scales of Cognition and Function





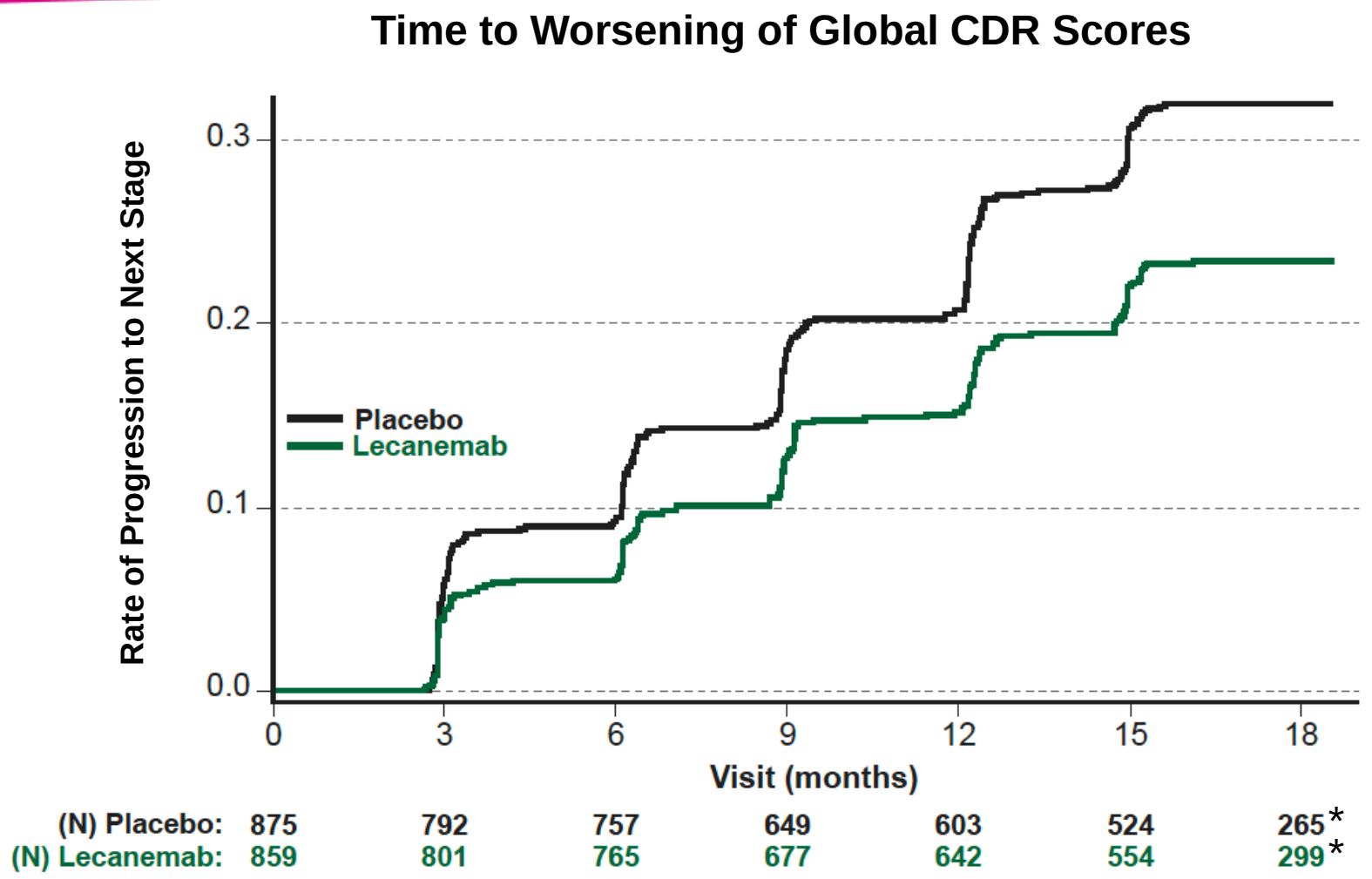
- 26% slowing on ADAS-Cog14 at 18 months
- 37% slowing on ADCS ADL-MCI at 18 months
- Increases in magnitude of separation over time

ADAS-Cog14
- Administered to patient
- Rates 14 domains with score ranging from 0-90 (higher score is worse)
- Baseline ADAS-Cog14 was 24

ADCS ADL-MCI
- Rated by family or caregiver
- 24 items assessing a range of daily activities with score ranging from 0-53 (lower score is worse)
- Baseline ADCS ADL-MCI was 41

ADAS-Cog14, Alzheimer's disease Assessment Scale-Cognitive Subscale; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; SE, standard error.

Time to Worsening of Global CDR Scores



- Hazard ratio 0.69
- 31% lower risk of converting to next stage of disease by global CDR
- Individuals remain in earlier stages of Alzheimer's disease for a longer period of time, even within the 18-month course of the study

Progression was defined as global CDR score progressing from 0.5 [MCI] to 1[mild AD dementia] or 1 [mild dementia] to 2 [moderate dementia])

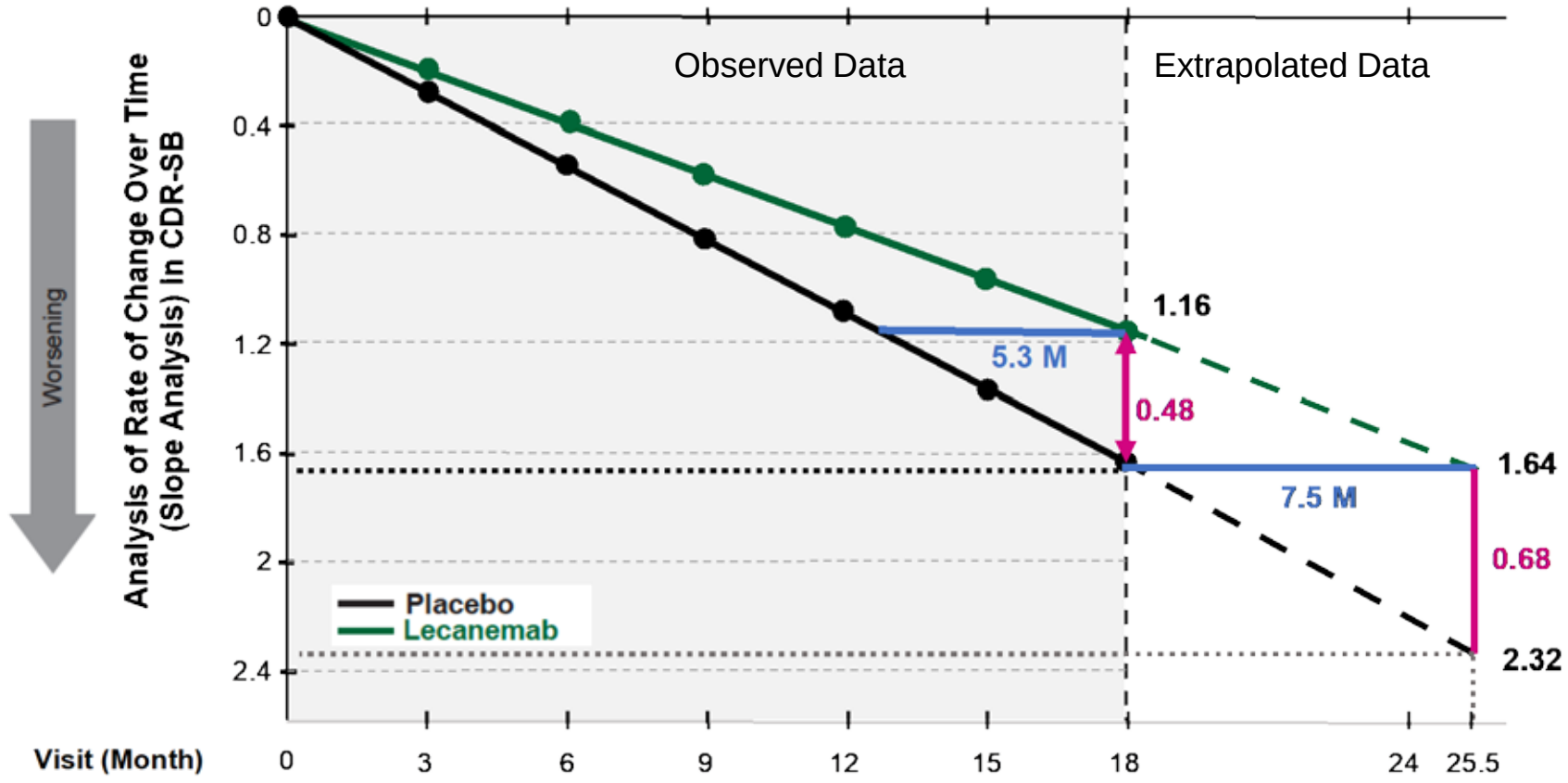
*KM plot uses actual duration for time to event. Including the number at risk within a 2 week window, N at 18 months is 497 in placebo and 527 in LEC10-BW

CDR, Clinical Dementia Rating.

Slope Analysis Using CDR-SB

Observed Data and Extrapolation to 2 Years

- 32% slowing of slope annually [(95%CI: 18% to 46%), p=0.00001] on lecanemab vs. placebo
  - Projected treatment difference at 25.5 months based on slope showed -0.68 treatment difference
- Increasing separation over time between lecanemab & placebo



- Lecanemab takes 25.5 months to reach same level as placebo at 18 months

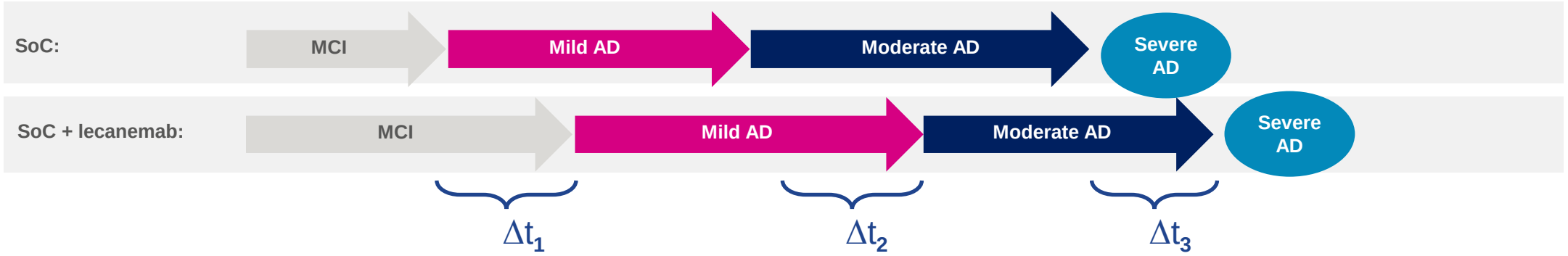
Note: Rate of change over time (mean slope) based on change from baseline in the CDR-SB was analyzed using linear mixed effects (LME) model. LME model included time, treatment by assessment time as covariate with random intercept and slope. CDR-SB, Clinical Dementia Rating-Sum-of-Boxes.

Lifetime Health Outcomes: Trial Data Modeling Simulation

Lecanemab Could Delay AD Progression by Several Years

Modeled early AD patient population[1] based on lecanemab Study 201 and ADNI data[3]

Time to Advance to Mild, Moderate, and Severe AD Longer for Lecanemab



Lecanemab treatment predicted:

- **Slower rate of disease progression with extended duration of MCI and mild AD stages and shortened duration of moderate and severe stages**
- **Mean time to mild, moderate, and severe dementia in lecanemab+SoC vs SoC was 2.51, 3.13, and 2.34 years respectively**
- **Lower lifetime probability of institutionalization (25% vs. 31%)**
- **This model will be updated with Clarity AD data which we anticipate consistent results**

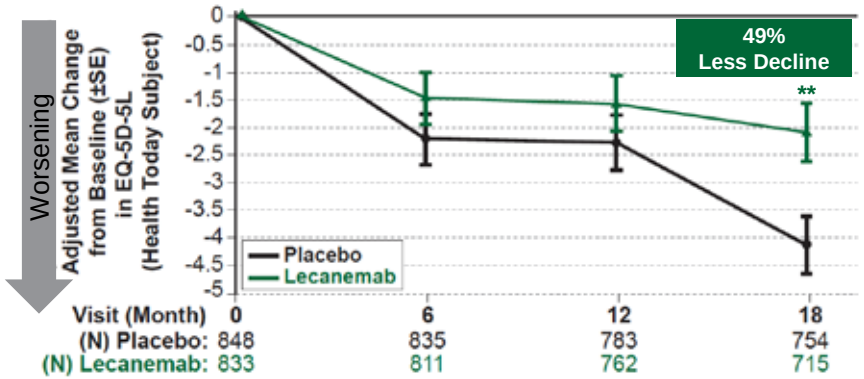
AD, Alzheimer's disease; MCI, mild cognitive impairment; SoC, standard of care; t, time.

1. *Tahami Monfared AA et al. "Long-Term Health Outcomes of Lecanemab in Patients with Early Alzheimer's Disease Using Simulation Modeling". Neurol Ther. 2022.*
2. *Swanson et al. " A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody". Alzheimer's Res Ther. 2021*
3. *ADNI (Alzheimer's Disease Neuroimaging Initiative) study*

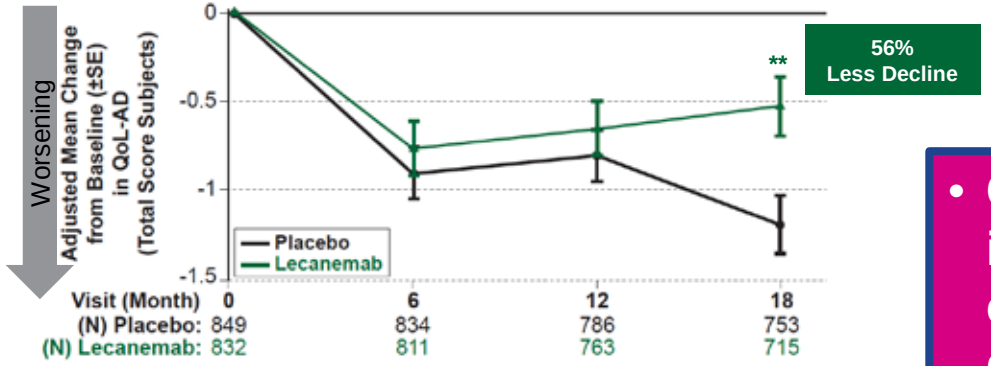
Health-Related Quality of Life Measures

Slowing of Health Decline with Lecanemab on Subject and Study Partner Burden

EQ-5D-5L (Subject)



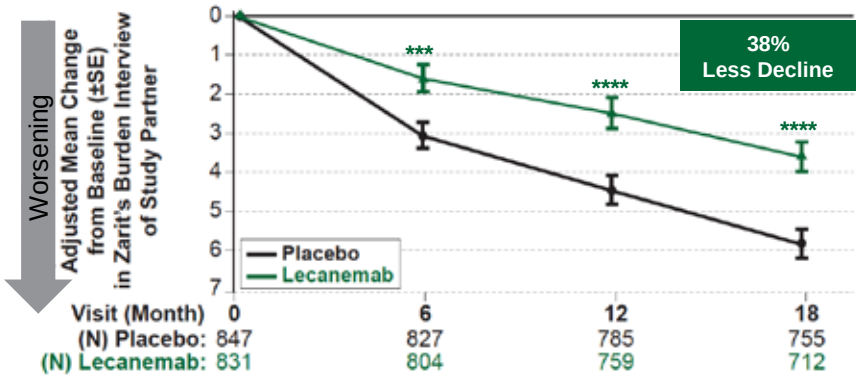
QOL-AD (Subject)



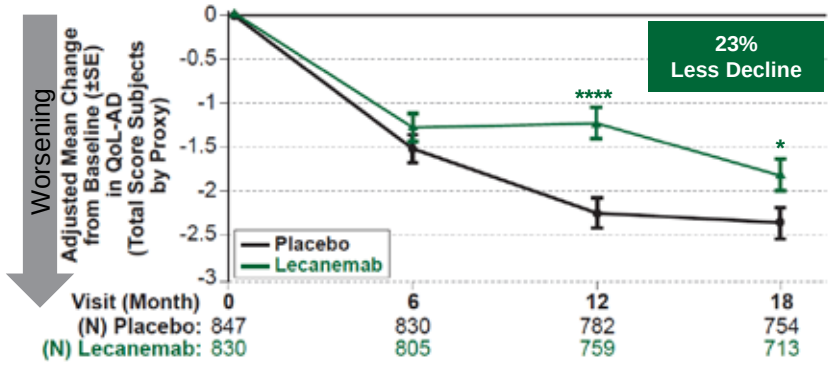
- **Consistent benefits seen in quality of life and caregiver burden across different scales**

Zarit Burden Interview

Study Partner Burden (total score)



QOL-AD (Subject by Proxy)



- **EQ-5D-5L:** European Quality of Life–5 Dimensions (5 Level version): The descriptive system covers 5 dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with 5 levels of severity in each dimension (no problems, slight problems, moderate problems, severe problems, and unable to perform or extreme problems). The score being presented is the VAS: Health Today (Visual Analog Scale subtotal).
- **QOL-AD:** Quality of Life in Alzheimer's Disease: A 13-item questionnaire designed to provide both a patient and a caregiver report of the quality of life (QOL) for patients who have been diagnosed with Alzheimer Disease
- **Zarit Burden Interview:** The 22-item instrument used in dementia caregiving research used to assess the stresses experienced by study partners of subjects with dementia.

SE, standard error.

* P<0.05; ** P<0.01; *** P<0.001; **** P<0.0001

Summary

- **The convergence of evidence across multiple measures of cognition, function, disease progression, health-related quality of life, caregiver burden, and biomarkers, demonstrate that lecanemab treatment may offer meaningful benefits to patients, care partners, and society**
  - Impact across cognition and function (27-37% slowing) and subgroups (race, ethnicity, comorbidities)
  - Delay in progression to later stages of disease (HR=0.69)
    - Slope analysis suggests continued improvement with longer treatment
    - Modeling indicates lecanemab could potentially delay progression by 2.5-3.1 years
  - Relative preservation of health-related quality of life and caregiver burden (23-56% slowing of decline)
  - Impact on multiple A/T/N biomarkers demonstrating target engagement and downstream biological impact
  - Well characterized safety profile with low rates of symptomatic ARIA

The results of Clarity AD:

- **Support the role for amyloid protofibril-targeted therapy in early AD**
- **Are consistent with FDA and EMA terminology for disease modification**
- **Provide momentum to the broader field of AD drug development**
- **Prompt a paradigm shift towards early diagnosis to achieve disease slowing and to extend milder stages of disease**

AD, Alzheimer's disease; ARIA, amyloid related imaging abnormalities; A/T/N/+, amyloid/tau/neurodegeneration/other; EMA, European Medicines Agency; FDA, Food & Drug Administration; HR, hazard ratio.

Panel Discussion and Q&A

Clarity AD

Thank you

Clarity AD