Lecanemab for Early Alzheimer's Disease: Effectiveness and Value

Public Meeting — March 17, 2023

Meeting materials available at: https://icer.org/assessment/alzheimers-disease-2022/

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

AN ICER PROGRAM
CTAF
CALIFORNIA TECHNOLOGY ASSESSMENT FORUM

Patient Experts

Doreen Monks, RN, MSN, Advocate

- *No conflicts to disclose*

Russ Paulsen, **MA,** Chief Operating Officer, UsAgainstAlzheimer's

- *UsAgainstAlzheimer's receives funding from companies, including less than 25% from Eisai Co.*

Clinical Experts

Victor Henderson, MD, **MS,** Professor of Epidemiology & Population Health and of Neurology, Stanford University

- *No conflicts to disclose*

Jason Karlawish, MD, Professor of Medicine, University of Pennsylvania

- *Dr. Karlawish has received manufacturer support of research in the clinical area of this meeting.*
- *Dr. Karlawish has served as a site investigator for clinical trails sponsored by Eli Lilly & Co. and Biogen Inc.*

Why are we here today?

“I get frustrated when people question my diagnosis – ‘oh you are fine and are just looking for attention’. I get frustrated when I can’t understand a joke and everyone else is laughing. I get frustrated when I don’t remember somebody, but they remember me – it’s mortifying.... It’s hard when I’m not sharp like I used to be.”

Person living with Alzheimer’s disease

Why Are We Here Today?

- What happens the day these treatments receive FDA approval?
- Questions about:
  - What are the risks and benefits?
  - How do new treatments fit into the evolving landscape?
  - What are reasonable prices and costs to patients, the health system, and the government?
  - What lessons are being learned to guide our actions in the future?

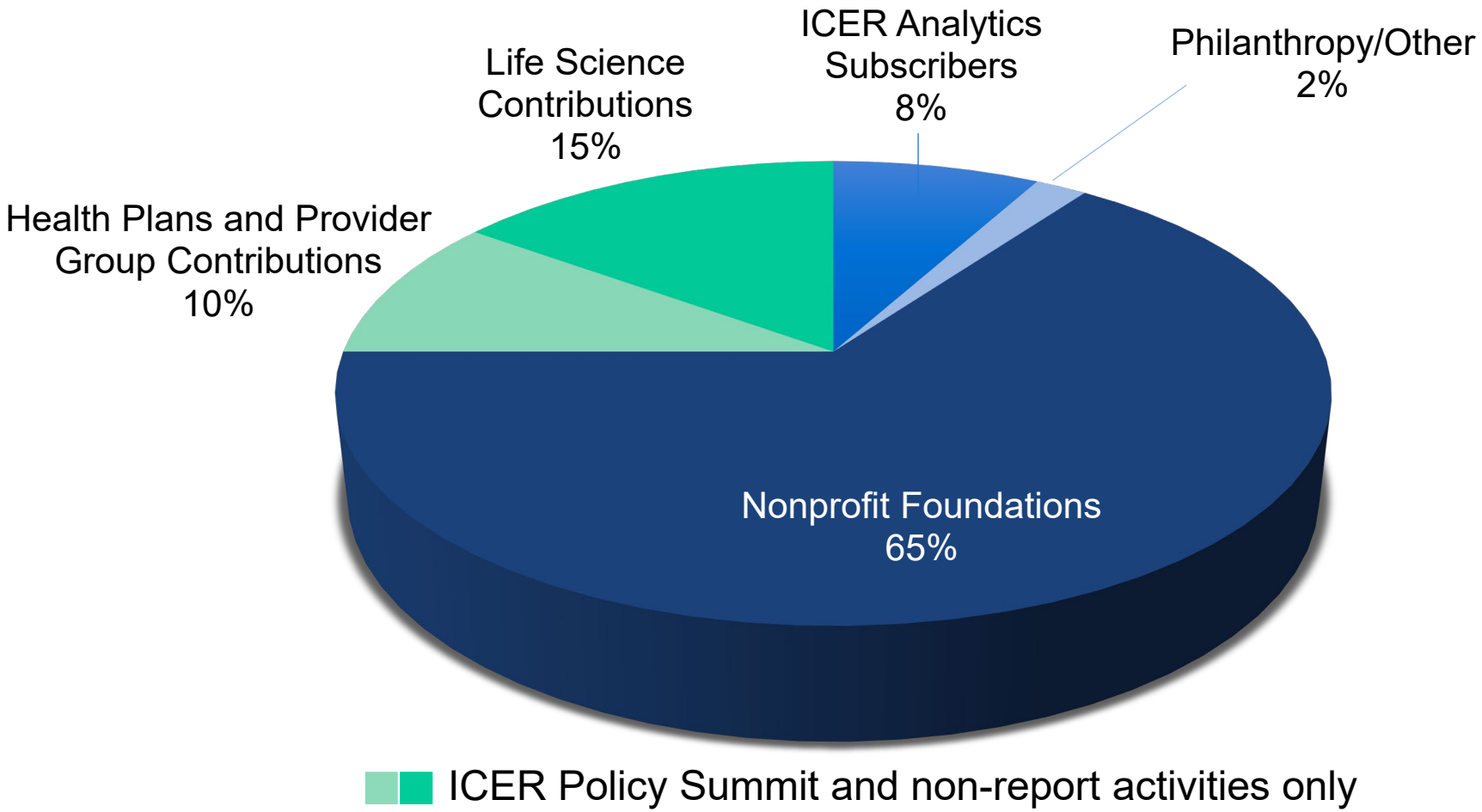
The Impact on Rising Health Care Costs for Everyone

https://khn.org/news/article/diagnosis-debt-investigation-100-million-americans-hidden-medical-debt/

Organizational Overview

- California Technology Assessment Forum (CTAF)
- Institute for Clinical and Economic Review (ICER)

Funding 2023



https://icer.org/who-we-are/independent-funding/

How Was the ICER Report Developed?

- Scoping with guidance from patients, clinical experts, manufacturers, and other stakeholders
- Internal ICER evidence analysis and cost-effectiveness modeling
- Public comment and revision
- UsAgainstAlzheimer's provided initial feedback on the draft report
- Expert reviewers of the draft report
  - Victor Henderson, MD, MS, Professor, Stanford University
  - Jason Karlawish, MD, Professor, University of Pennsylvania
- How is the evidence report structured to support CTAF voting and policy discussion?

Value Assessment Framework: Long-Term Value for Money

Agenda

Time (PT)	Activity
9:00 am—9:20 am	Meeting Convened and Opening Remarks
9:20 am—10:00 am	Presentation of the Clinical Evidence
10:00 am—10:40 am	Presentation of the Economic Model
10:40 am —11:10 am	Public Comments and Discussion
11:10 am—11:50 am	Lunch Break
11:50 am—12:50 pm	CTAF Vote on Clinical Effectiveness and Value
12:50 pm—1:00 pm	Break
1:00 pm—2:30 pm	Policy Roundtable
2:30 pm—3:00 pm	Reflections from CTAF
3:00 pm	Meeting Adjourned

Presentation of the Clinical Evidence

Grace Lin, MD

Medical Director for Health Technology Assessment, ICER

Professor of Medicine and Health Policy, University of California, San Francisco

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Key Collaborators

- **Abigail Wright, PhD, MSc,** Senior Research Lead, Evidence Synthesis, ICER
- **Serina Herron-Smith, BA,** Associate Research Manager, ICER
- **Foluso Agboola, MBBS, MPH,** Vice President of Research, ICER

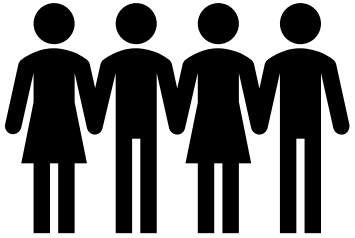
Disclosures:

We have no conflicts of interest relevant to this report.

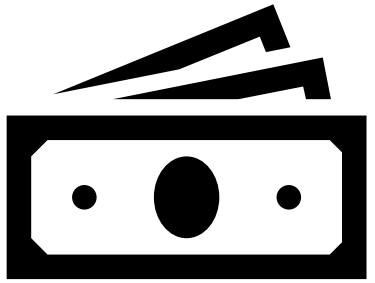
Alzheimer's Disease

Impact of Illness

6.5 million cases in the United States

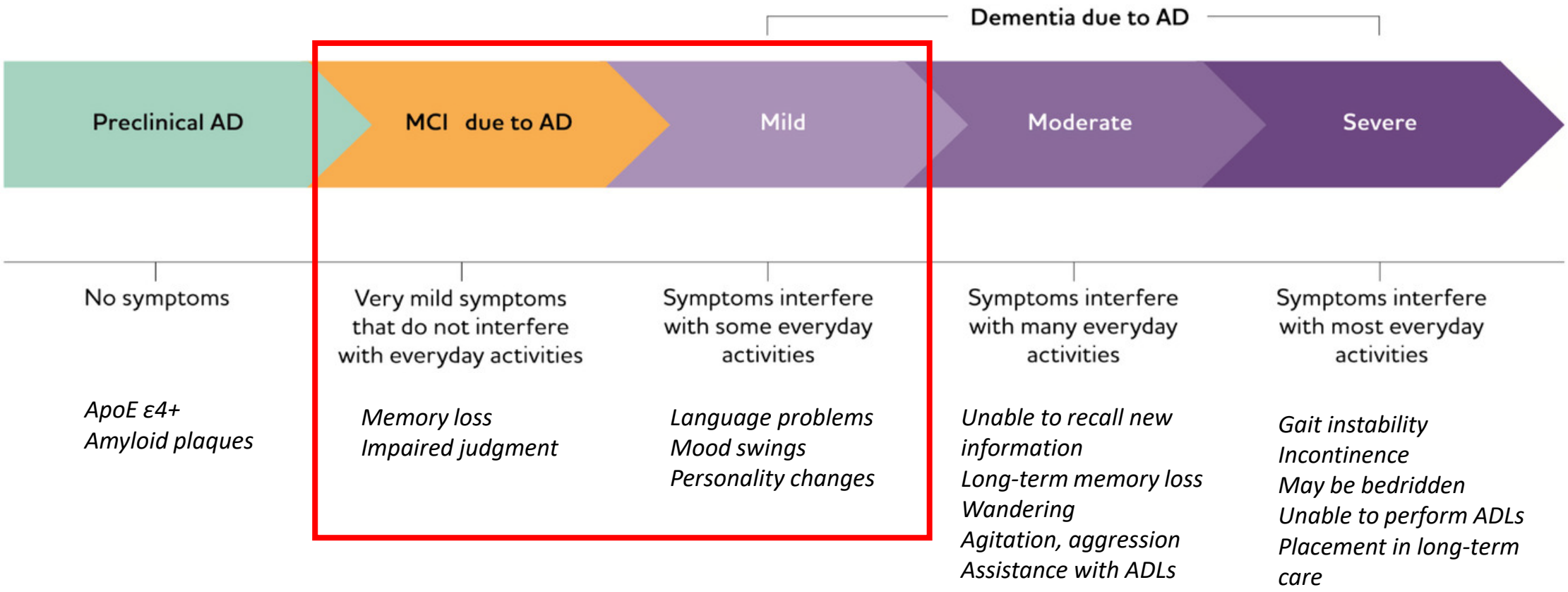


11 million caregivers provide **16 billion hours** of care



Medical costs: **$321 B**
Caregiving costs: **$272 B**

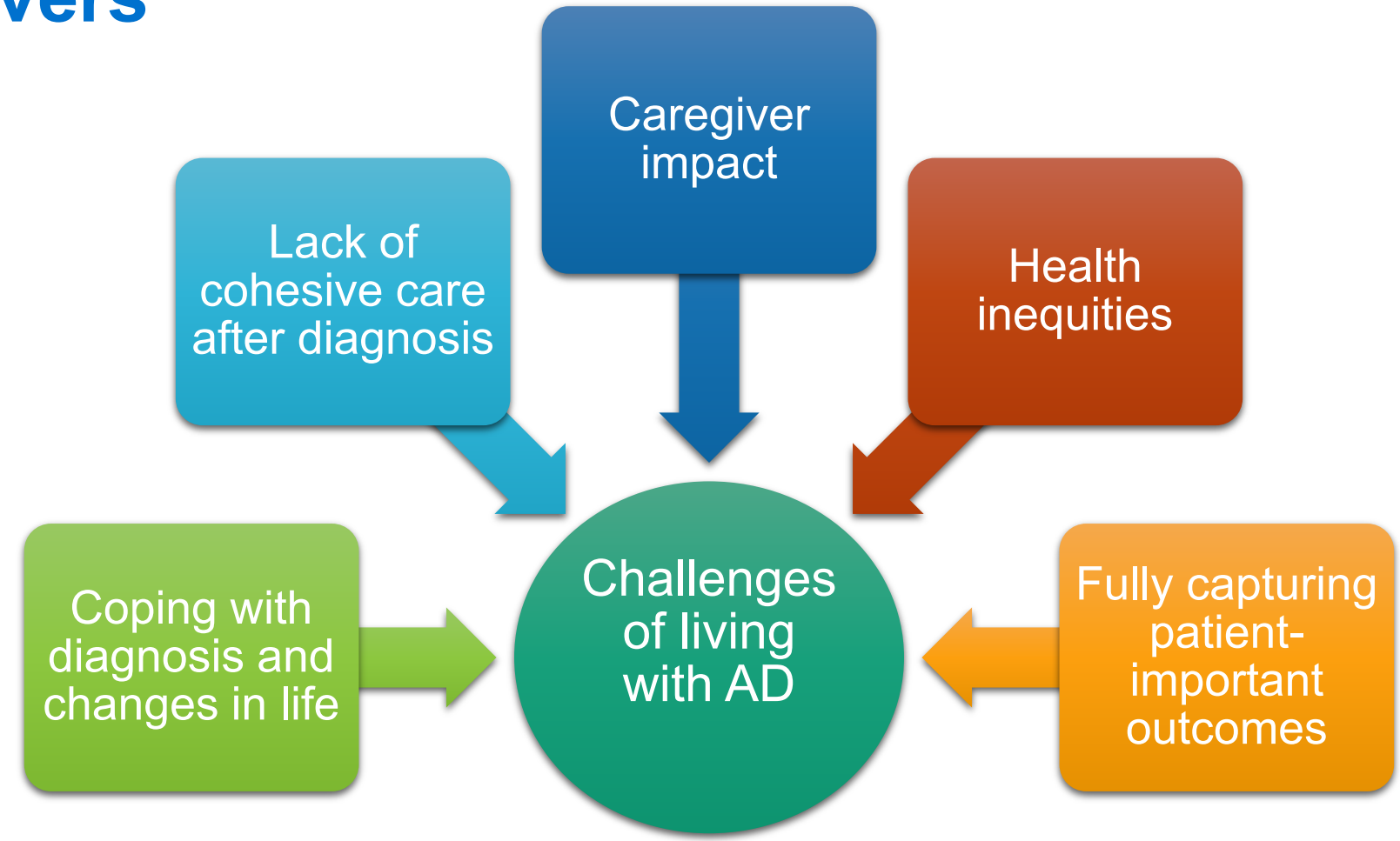
Stages and Symptoms of AD



Adapted from 2020 Alzheimer's Facts and Figures. Alzheimer's Dement.2020;16: 394

AD: Alzheimer's disease, ApoE ε4: Apolipoprotein E, ADLs: activities of daily living, MCI: mild cognitive impairment

Living with Alzheimer's: Insights from Patients and Caregivers



Alzheimer's Disease

Treatment Options

Non-Pharmacologic Treatment

- Environmental manipulation
- Family support
- Prevention of other comorbidities

Symptomatic Treatment

- Cholinesterase inhibitors (e.g., donepezil)
- NMDA Receptor Antagonist (e.g., memantine)
- Antioxidants (e.g., selegiline)

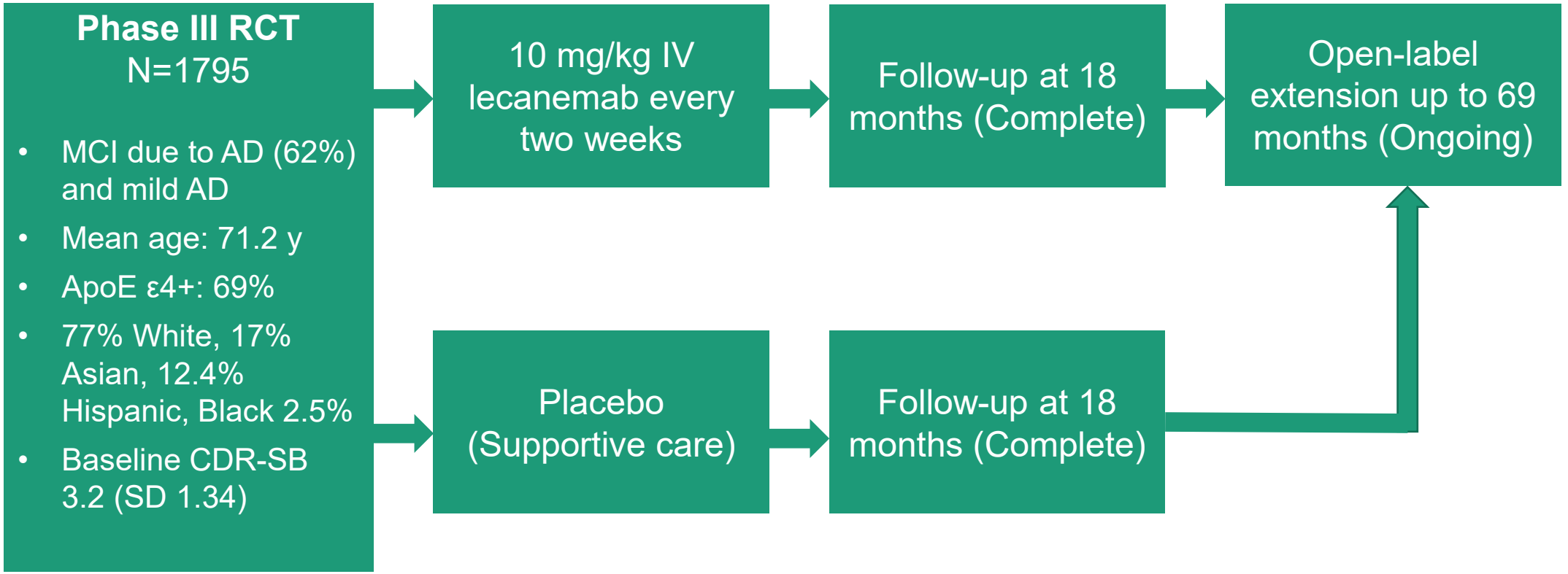
Disease-Modifying Treatment

- Anti-amyloid antibodies

NMDA: N-methyl-D-aspartate

Clinical Evidence

CLARITY AD Design and Baseline Characteristics

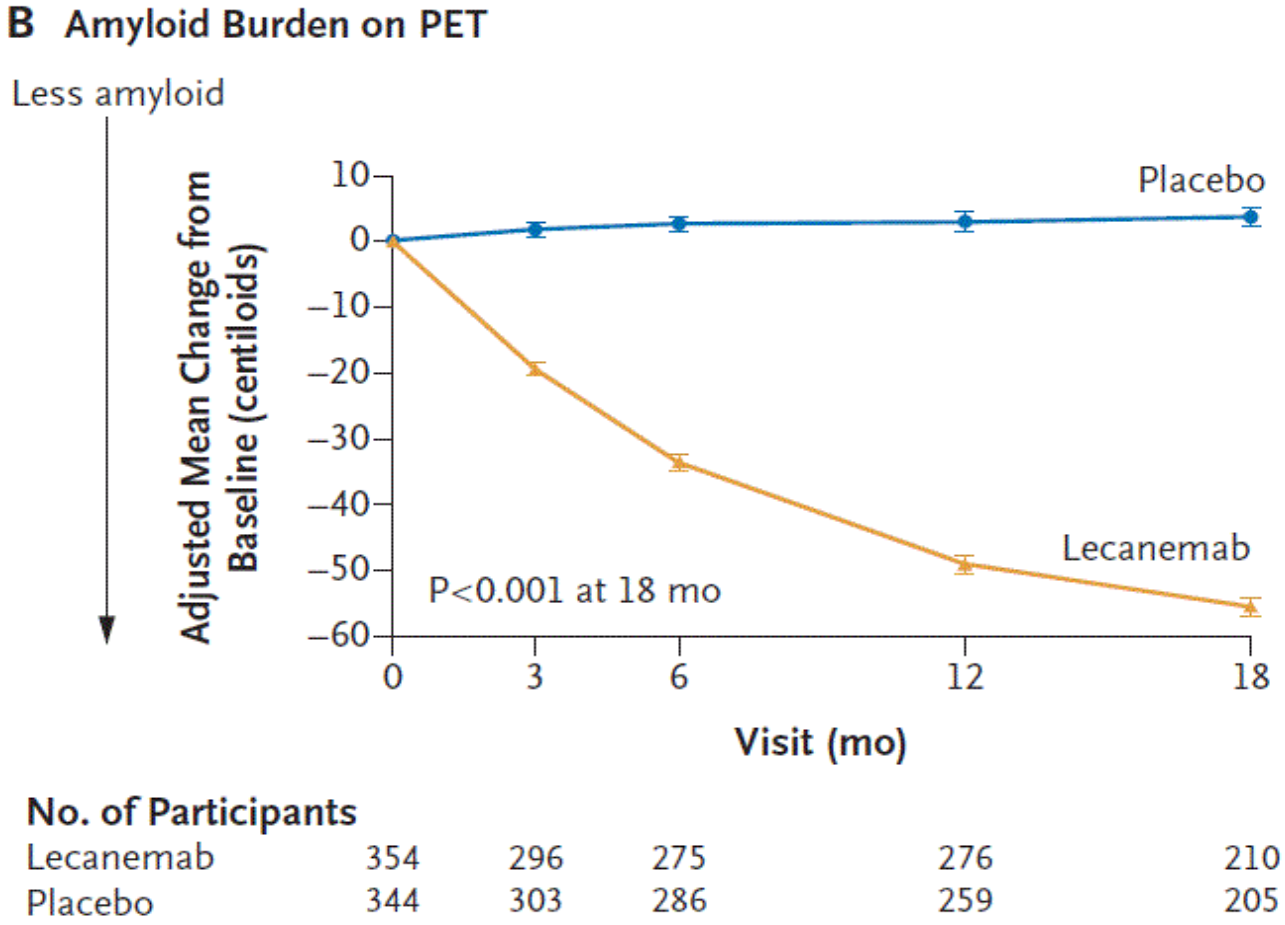


AD: Alzheimer's Disease, ApoE: apolipoprotein E, CDR-SB: Clinical Dementia Rating scale Sum of Boxes, IV: Intravenous, MCI: Mild Cognitive Impairment, RCT: randomized control trial, SD: standard deviation.
van Dyck et al. 2022

Key Outcomes

- Primary outcome: Clinical Dementia Rating-Sum of Boxes (CDR-SB)
  - Measures 6 domains of cognition and function
  - Score 0-18, higher scores = more severe disease
- Secondary outcomes:
  - Cognitive and Functional Scales (e.g., ADAS-Cog14, ADCS-MCI-ADL, ADCOMS)
  - Health-Related Quality of Life (e.g., EQ-5D-5L, QOL-AD, and Zarit Burden Interview)
  - Biomarkers including amyloid, p-tau, t-tau (PET and CSF)

Beta-amyloid Levels by PET at 18 Months

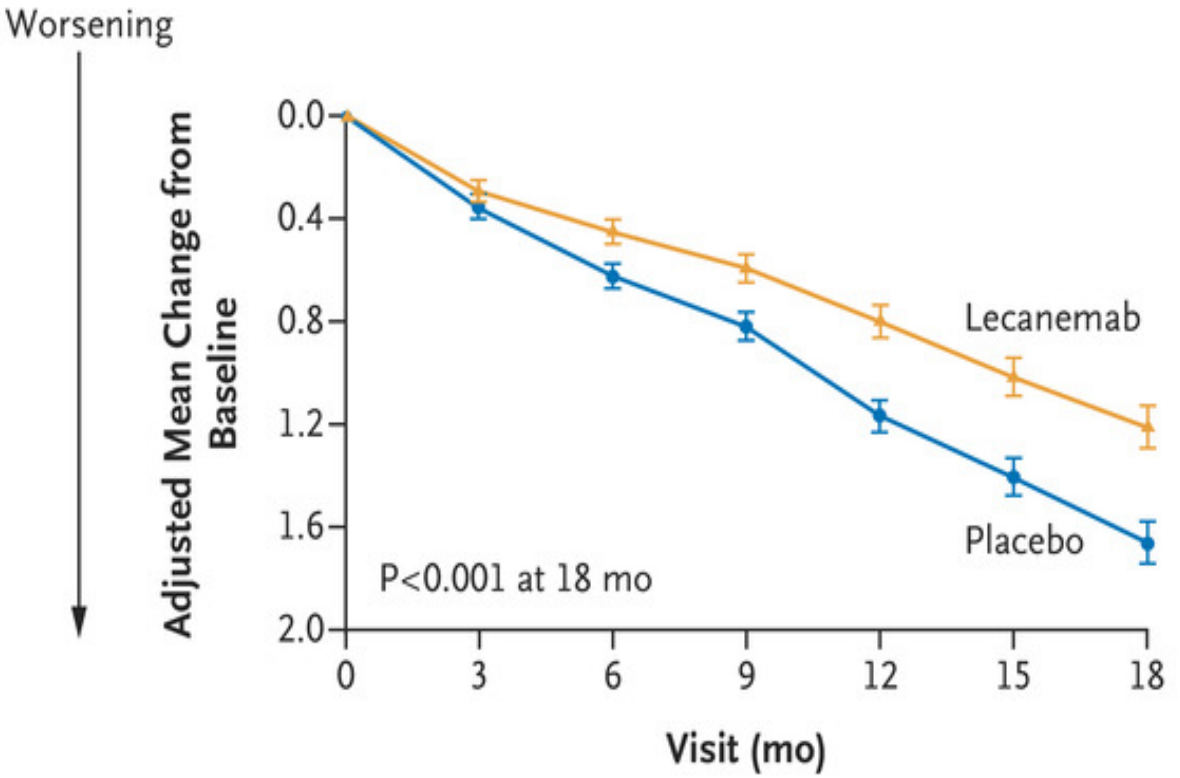


Amyloid-negative (<30 CL) patients at 18 months:

Lecanemab: 32.4%
Placebo: 7.8%

van Dyck et al. N Engl J Med 2023;388(1):14

CDR-SB at 18 Months



No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

% Slowing of Decline	Mean Difference vs. Placebo
27%	-0.45 (95% CI: -0.67 to -0.23)

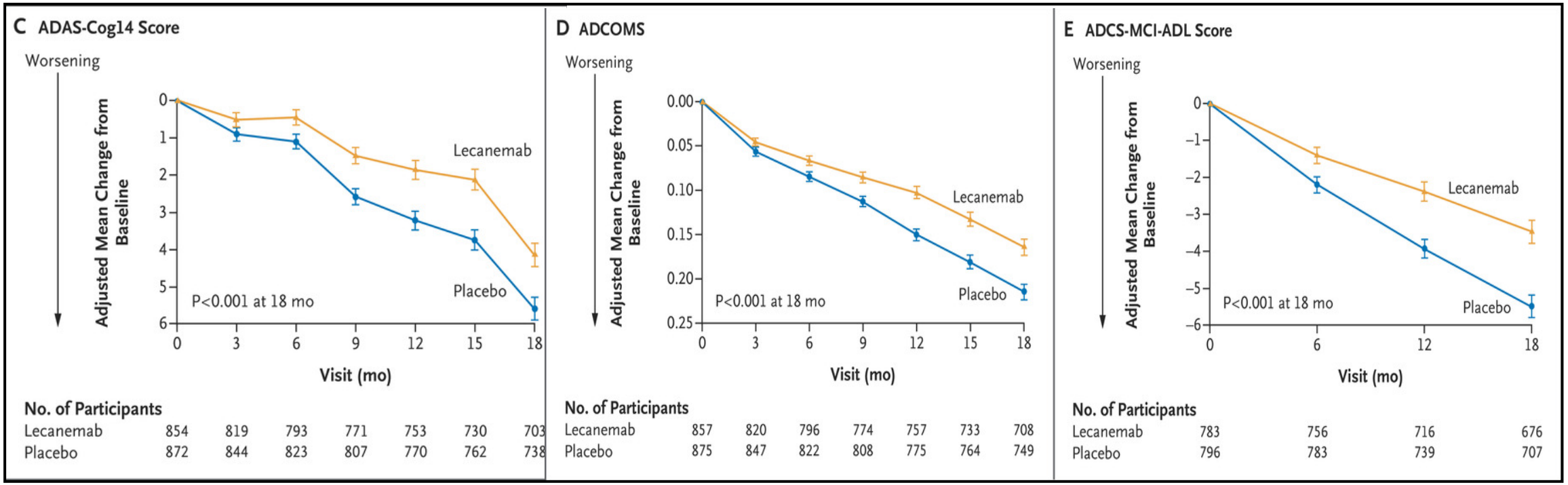
van Dyck et al. N Engl J Med 2023;388(1):14

Health-Related Quality of Life Outcomes

Quality of Life Measure	% Less Decline vs. Placebo
EQ-5D-5L (Participant)	49%
QOL-AD (Participant)	56%
QOL-AD (Caregiver)	23%
Zarit Burden Interview (Caregiver)	38%

EQ-5D-5L: European Quality of Life – 5 dimensions (5 level version), QOL-AD: Quality of Life in Alzheimer's Disease
Note: All were significant at $p<0.05$.

Key Secondary Cognitive Outcomes at 18 Months



All differences were statistically significant compared with placebo

Biomarker Outcomes at 18 Months (Preliminary)

- Statistically significant reductions in CSF t-tau, CSF and plasma p-tau in lecanemab group versus placebo.
- MRI Outcomes:
  - Less atrophy in hippocampal volume
  - Greater decrease in whole brain volume and greater increase in ventricular volume

Harms

- Amyloid-related imaging abnormalities (ARIA)
  - ARIA-E: 12.6% in lecanemab, 1.7% in placebo
    - Symptomatic ARIA-E: 2.8% in lecanemab, 0% in placebo
    - Mostly mild-moderate in severity, occurred early and resolved within 4 months
  - ARIA-H: 17.3% in lecanemab, 9% in placebo
    - Few symptomatic cases
    - More likely to co-occur with ARIA-E in lecanemab
  - More common in ApoE ε4, especially homozygotes
- Three reported deaths in OLE related to hemorrhage, potentially ARIA
- Discontinuation due to AEs: 6.9% in lecanemab and 2.9% in placebo

AE: adverse event, ARIA-E: amyloid related imaging abnormalities – edema/effusion, ARIA-H: amyloid related imaging abnormalities - hemorrhage, OLE: open label extension

Controversies and Uncertainties

Correlation Between Amyloid Clearance and Cognition	• Inconsistent benefit across drugs • Lack of data at the individual patient level • 7% of placebo group were amyloid “negative” at end of trial
Clinical Significance of Results	• Changes may not reach minimum clinically important difference for cognitive measures • Differences in outcomes by subgroup
Generalizability	• Clinical trial population younger, less diverse, fewer comorbidities than U.S. AD population
Safety	• Real-world monitoring of ARIA • Risk of cerebral hemorrhage with use of anticoagulants

Potential Other Benefits and Contextual Considerations

- Delay in progression impacts both patient and caregiver abilities to achieve major life goals - e.g., work, education, family
- Complexity of treatment (biweekly IV infusions + potential monitoring for ARIA) may be significant burden
- Effective treatment could potentially decrease health inequities
  - African American and Hispanic patients tend to be underdiagnosed and diagnosed later

Public Comments Received

- Minimum clinically important difference for CDR-SB is debatable and applies to individual changes, not aggregate changes
- Risk of ARIA is overstated
- Disproportionate impact of disease on both persons with dementia and their caregivers in African American community
  - Later diagnosis, more severe symptoms
  - Greater caregiving burden
  - Underrepresentation in clinical trials

Summary

- Lecanemab shows statistically significant slowing of cognitive decline over 18 months of treatment, but questions about clinical significance remain
- ARIA remains a concern
  - 3 deaths in OLE potentially related to anticoagulation, ARIA
- Clinical trial results may not be generalizable to some populations
  - Underrepresentation of African Americans, older patients (>85) in trial

ICER Evidence Rating for Lecanemab

Treatment	Comparator	Evidence Rating
Lecanemab	Supportive care	P/I

Questions?

Presentation of the Economic Model

Melanie D. Whittington, PhD, MS

Director of Health Economics

Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

Disclosures

No conflicts to disclose defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.

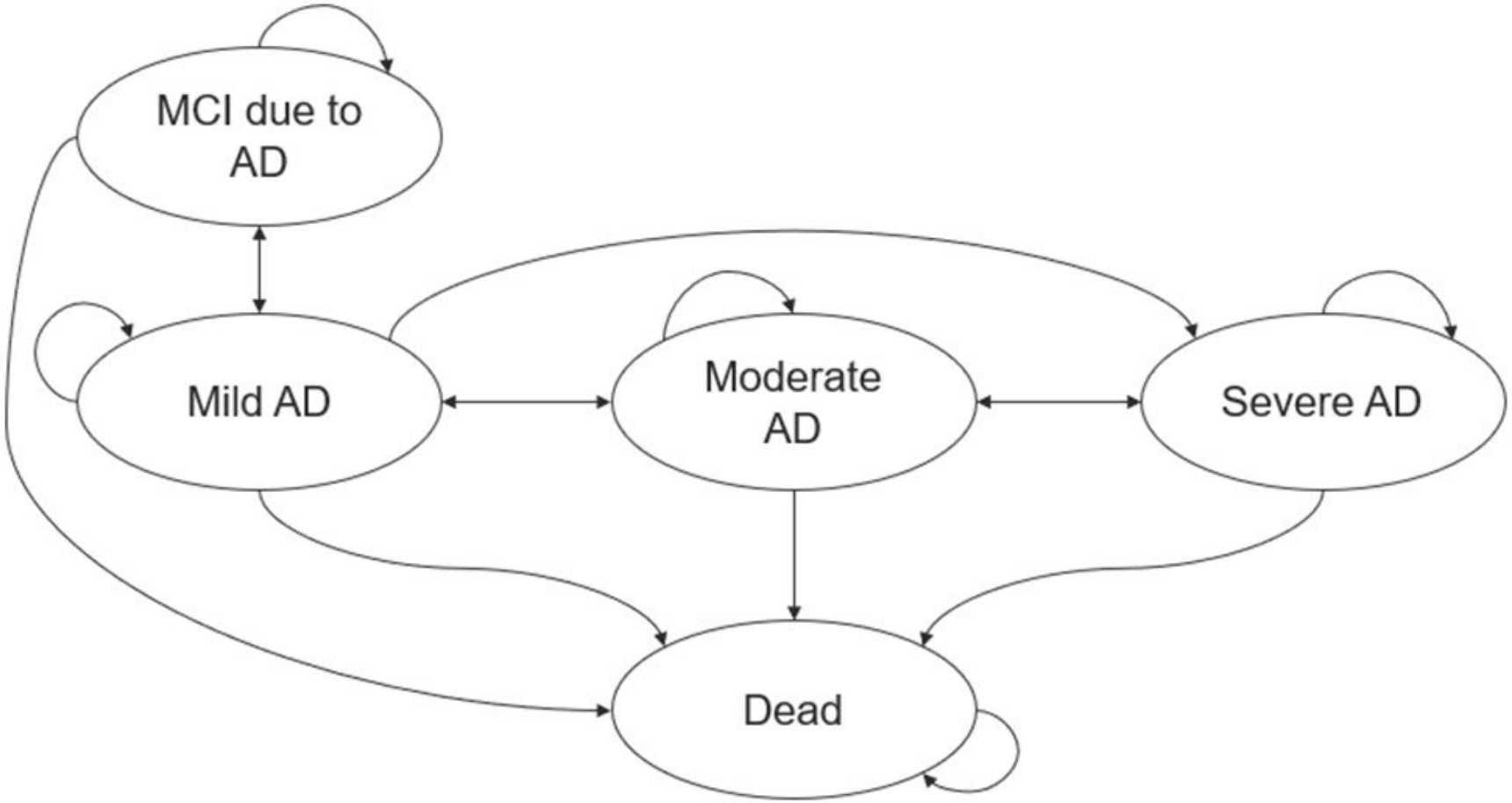
Objective

Estimate the lifetime cost effectiveness of lecanemab in addition to supportive care as compared to supportive care alone for the treatment of early Alzheimer's disease.

Methods Overview

- **Model**: Markov Model
- **Setting**: United States
- **Perspective**: Health Care Sector and Modified Societal Perspective
- **Time Horizon**: Lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: 1 year
- **Primary Outcomes**: cost; quality-adjusted life years (QALYs); equal value life years (evLYs); life years (LYs); years in the community setting

Model Schematic



Population

- The starting population for the economic evaluation included adults with early AD, defined as MCI due to AD or mild AD

Baseline Characteristic	Value
Mean Age, years	71 years
Percent Female, %	52%
Clinical Stage, %	
MCI Due to AD	55%
Mild AD	45%
Setting of Care, %	
Community	92%
Long-Term Care	8%

AD: Alzheimer's disease, MCI: mild cognitive impairment

Key Model Assumptions

- Lecanemab was effective at slowing the progression of disease while a patient had MCI due to AD or mild AD.
- Patients stopped receiving lecanemab treatment once they reached moderate AD.
- No clinical benefit was assumed after a patient stopped treatment.
- All occurrences of ARIA and its associated consequences were modeled in the first year of treatment.

Key Model Inputs: Effectiveness on Disease Progression

Health State	Lecanemab
MCI due to AD	0.69
Mild AD	0.69
Moderate AD	1.00
Severe AD	1.00

AD: Alzheimer's disease, MCI: mild cognitive impairment

Key Model Inputs: Adverse Events

Adverse Event	Lecanemab
Probability of any ARIA	21.5%
Probability of symptomatic ARIA	3.5%
Probability of AE-related discontinuation	6.9%

AE: adverse event, ARIA: amyloid-related imaging abnormalities

Key Model Inputs: Health State Disutilities

Health State	Patient		Caregiver
	Community	LTC	Community or LTC
MCI due to AD	-0.17	-0.17	-0.03
Mild AD	-0.22	-0.19	-0.05
Moderate AD	-0.36	-0.42	-0.08
Severe AD	-0.53	-0.59	-0.10

AD: Alzheimer's disease; LTC: long-term care

Key Model Inputs: Cost Inputs

Cost Input	Cost
Annual Wholesale Acquisition Cost	$26,500
MRI Unit Cost	$261
IV Administration Unit Cost	$78

IV: intravenous; MRI: magnetic resonance imaging

Results

Base-Case Results: Lifetime Model Outcomes

Health Care Sector Perspective						
Treatment	**Intervention Cost***	**Total Cost**	**Life Years**	**QALYs**	**evLYs**	**Years in the Community**
Lecanemab	$109,000	$489,000	6.23	3.84	3.96	4.20
Supportive Care	$0	$363,000	5.77	3.34	3.34	3.69

QALYs: quality-adjusted life years, evLYs: equal value of life years
*Doesn't include provider-administered mark-up, monitoring costs, or administration costs.

Base-Case Results: Lifetime Model Outcomes

Health Care Sector Perspective						
Treatment	**Intervention Cost***	**Total Cost**	**Life Years**	**QALYs**	**evLYs**	**Years in the Community**
Lecanemab	$109,000	$489,000	6.23	3.84	3.96	4.20
Supportive Care	$0	$363,000	5.77	3.34	3.34	3.69
Modified Societal Perspective						
Treatment	**Intervention Cost***	**Total Cost**	**Life Years**	**QALYs**	**evLYs**	**Years in the Community**
Lecanemab	$109,000	$790,000	6.23	3.49	3.64	4.20
Supportive Care	$0	$670,000	5.77	2.98	2.98	3.69

QALYs: quality-adjusted life years, evLYs: equal value of life years
*Doesn't include provider-administered mark-up, monitoring costs, or administration costs.

Base-Case Incremental Results

Perspective	Cost per QALY Gained	Cost per evLY Gained
Health Care Sector	$254,000	$204,000
Modified Societal	$236,000	$183,000

QALYs: quality-adjusted life years, evLYs: equal value of life years

Sensitivity Analyses

- One-way sensitivity analyses
  - Main driver: Hazard ratio on slowing progression of disease
- Probabilistic sensitivity analyses

Perspective	$50,000 per evLYG	$100,000 per evLYG	$150,000 per evLYG	$200,000 per evLYG
Health Care Sector	0%	0%	11%	50%
Modified Societal	0%	1%	25%	63%

evLYG: equal value life years gained

Scenario Analyses

Perspective	Base Case ($/evLYG)	Treatment Stop at Severe ($/evLYG)
Health Care Sector	$204,000	$226,000
Modified Societal	$183,000	$211,000

evLYG: equal value life years gained

Limitations

- Confidence interval for the hazard ratio on the progression to the next stage of dementia was not available.
- Utility evidence is from a study published more than 20 years ago.

Comments Received

- Use a patient-level simulation model like AD ACE
- Use a threshold above common thresholds
- Patients with Alzheimer's disease have more than one caregiver

Conclusions

- At the current wholesale acquisition cost, lecanemab exceeds commonly cited cost-effectiveness thresholds.
- The cost-effectiveness findings are primarily driven by the effectiveness of lecanemab at slowing the progression of disease.

Questions?

Public Comment and Discussion

Manufacturer Public Commenters

Speaker	Title	Affiliation
Michael Irizarry, MD, MPH	Senior Vice President, Clinical Research, Alzheimer's Disease and Brain Health	Eisai Co., Ltd
Katie Herren, PharmD, MS	Senior Director, US Customer Engagement	Eli Lilly & Co.

Michael Irizarry, MD, MPH
Senior Vice President, Clinical Research, Alzheimer's Disease and Brain Health, Eisai Co., Ltd

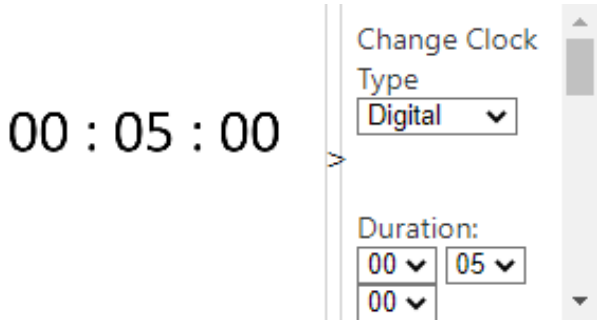
Conflicts of Interest:

- *Dr. Irizarry is a full-time employee of Eisai Co., Ltd*

Katie Herren, PharmD, MS
Senior Director, US Customer Engagement, Eli Lilly & Co.

Conflicts of Interest:

- *Dr. Herren is a full-time employee of Eli Lilly & Co.*



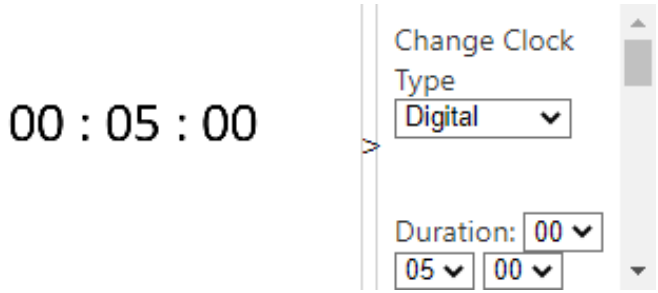
Patient Public Commenters

Speaker	Title	Affiliation
Russ Paulsen, MA	Chief Operating Officer	UsAgainstAlzheimer's
Susan Peschin, MHS	President & CEO	Alliance for Aging Research
James Taylor, MBA	President & CEO	Voices of Alzheimer's

Russ Paulsen, MA
Chief Operating Officer, UsAgainstAlzheimer's

Conflicts of Interest:

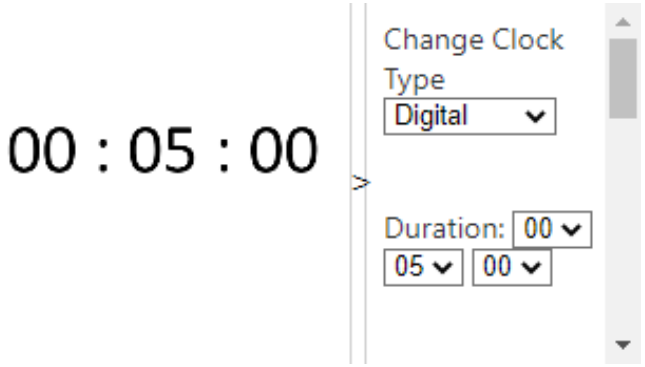
- *UsAgainstAlzheimer's receives funding from companies, including less than 25% from Eisai Co.*



Susan Peschin, MHS
President & CEO, Alliance for Aging Research

Conflicts of Interest:

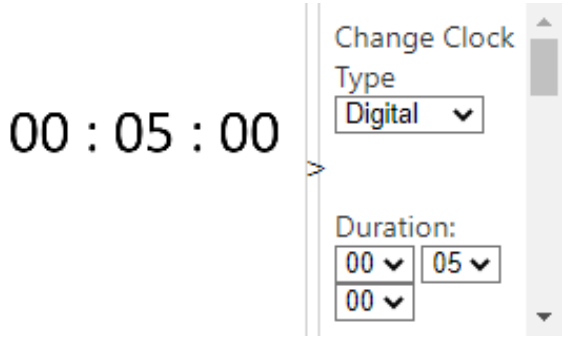
- *The Alliance for Aging Research receives more than 25% of it's funding from health care companies.*



James Taylor, MBA
President & CEO, Voices of Alzheimer's

Conflicts of Interest:

- *Voices of Alzheimer's receives more than 25% of its funding from health care companies including 25% from Eisai Co. and 25% from Eli Lilly & Co.*
- *Voices of Alzheimer's collaborated with High Lantern Group in developing their statement.*



Lunch

Meeting will resume at 11:50 am PT

ICER
INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

Voting Questions

Clinical Evidence Questions

Patient population for all questions: Adults with early Alzheimer's disease (i.e., Mild Cognitive Impairment due to Alzheimer's disease and mild Alzheimer's dementia).

1. Is the evidence adequate to demonstrate that the net health benefit of lecanemab added to supportive care is superior to that provided by supportive care alone?

A. Yes

B. No

Contextual Considerations and Potential Other Benefits or Disadvantages

When making judgements of overall long-term value for money, what is the relative priority that should be given to any effective treatment for early Alzheimer's disease with evidence of Alzheimer's disease pathology, on the basis of the following contextual considerations:

2. Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability

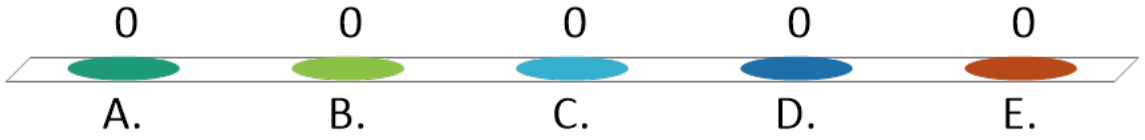
A. Very low priority

B. Low priority

C. Average priority

D. High priority

E. Very high priority



When making judgements of overall long-term value for money, what is the relative priority that should be given to any effective treatment for early Alzheimer's disease with evidence of Alzheimer's disease pathology, on the basis of the following contextual considerations:

3. Magnitude of the lifetime impact on individual patients of the condition being treated

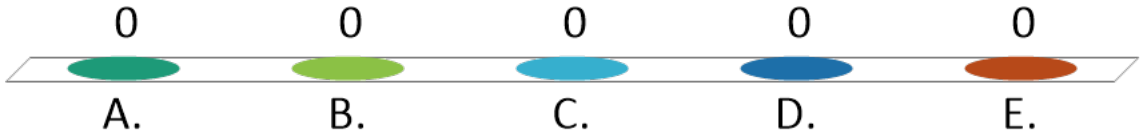
A. Very low priority

B. Low priority

C. Average priority

D. High priority

E. Very high priority



What are the relative effects of lecanemab added to supportive care versus supportive care alone on the following outcomes that inform judgement of the overall long-term value for money of lecanemab added to supportive care?

4. Patients' ability to achieve major life goals related to education, work, or family life

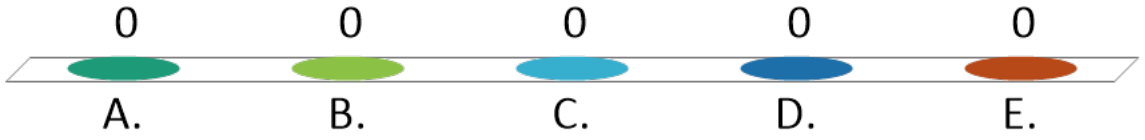
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



What are the relative effects of lecanemab added to supportive care versus supportive care alone on the following outcomes that inform judgement of the overall long-term value for money of lecanemab added to supportive care?

5. Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life

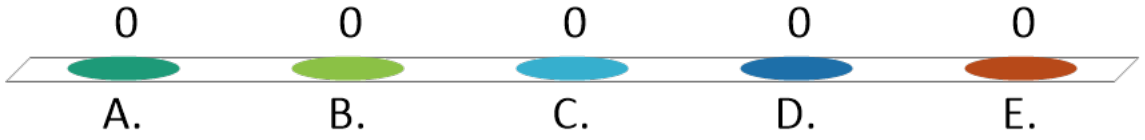
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



What are the relative effects of lecanemab added to supportive care versus supportive care alone on the following outcomes that inform judgement of the overall long-term value for money of lecanemab added to supportive care?

6. Society's goal of reducing health inequities

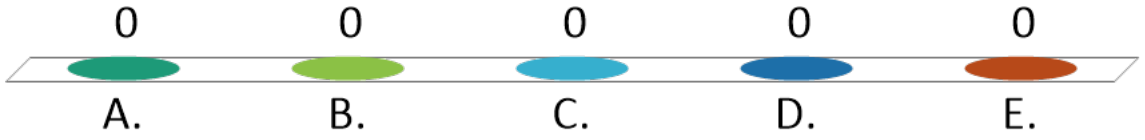
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



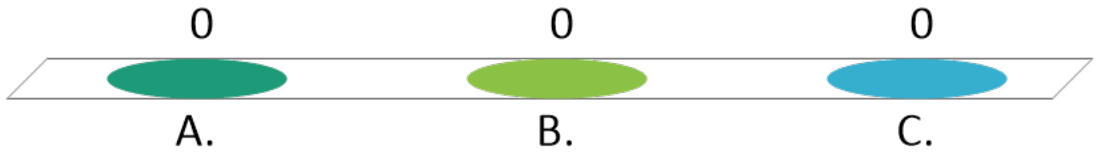
Long-Term Value for Money

7. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment at current pricing with lecanemab added to supportive care versus supportive care alone?

A. Low long-term value for money at current price

B. Intermediate long-term value for money at current price

C. High long-term value for money at current price



Break

Meeting will resume at 1 pm PT

ICER
INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

Policy Roundtable

Participant	Affiliation	Conflict of Interest
Victor Henderson, MD, MS Professor of Neurology	Stanford University	No conflicts to disclose.
Jason Karlawish, MD Professor of Medicine	University of Pennsylvania	Dr. Karlawish has received manufacturer support of research in the clinical area of this meeting. Dr. Karlawish has served as a site investigator for clinical trails sponsored by Eli Lilly & Co. and Biogen Inc.
Doreen Monks, RN, MSN Patient Advocate	Patient Advocate	No conflicts to disclose.
Russ Paulsen, MA Chief Operating Officer	UsAgainstAlzheimer's	UsAgainstAlzheimer's receives funding from companies, including less than 25% from Eisai.
Gail Ryan, PharmD Director of Pharmaceutical Transformation	Point32Health	Dr. Ryan is a full-time employee of Point32Health.
Amir A. Tahami, MD, MSc, Ph.D, Global Value & Access Head, Alzheimer's Disease and Brain Health	Eisai Co., Ltd.	Dr. Tahami is a full-time employee of Eisai Co., Ltd.
Susan Wojcicki, PharmD, BCOP Interim Director, Humana Pharmacy Solutions Clinical Drug Evaluation & Policy Strategies	Humana	Dr. Wojcicki is a full-time employee of Humana.

CTAF Council Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around April 17, 2023
  - Includes description of CTAF votes, deliberation, policy roundtable discussion
- Materials available at: https://icer.org/assessment/alzheimers-disease-2022/

Adjourn

ICER
INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW