0. What was the first name of the man who identified the first case of what became known as Alzheimer’s disease?

A. Karl
B. Alois
C. Hans
D. Wilhelm
Aducanumab for Alzheimer’s Disease: Effectiveness and Value

Public Meeting — July 15, 2021
The Joanne H. Pearson Memorial Award in Environmental Public Advocacy is a grant of up to $1,000 established in the memory of Joanne H. Pearson, a San Diego land use and environmental activist. It is awarded annually to a Sierra Club of San Diego volunteer who is committed to protecting public rights as they relate to land use or environmental protections in the greater San Diego region.

From 1997 to 2005, Joanne chaired the San Diego Sierra Club’s Coastal Committee playing a lead role in addressing coastal projects before the San Diego City Council and California Coastal Commission. In 2004, she organized an environmental coalition to testify successfully before the California Coastal Commission for adoption of the La Jolla Local Coastal Program Update, which resulted in acceptance by the City of San Diego and the California Coastal Conservancy of all outstanding public accesses along the La Jolla coastline. In 1994, Joanne received recognition from the California State Assembly “in honor of her commitment to preserve and enhance our coastal environment, and for her in-depth research and effective testimony before the California Coastal Commission.” In 1997, she was named the California State Assembly “Woman of the Year” for the 78th Assembly District.
Why Are We Here Today?

• Patients and families hope for a future with effective ways to prevent and treat Alzheimer’s disease

• What happens the day new treatments are approved by the FDA?
  • There are questions about who should use the new treatment
  • There are coverage questions
  • There are concerns about the price and the cost for patients

• What happens to other patients in the health care system?
The Impact of Rising Health Care Costs

Leonard Edloe
Richmond, Virginia

The Whitman family
Bird City, Alaska

The Maccoux family
Brooklyn Park, Minnesota
Organizational Overview

- California Technology Assessment Forum (CTAF)
- The Institute for Clinical and Economic Review (ICER)
Sources of Funding, 2021
https://icer.org/who-we-are/independent-funding/

- Nonprofit Foundations: 68%
- Manufacturer Contributions: 12%
- Health Plans and Provider Group Contributions: 9%
- Government Contributions: 10%
- Other*: 1%

*Individual / matching contributions and speech stipends.

ICER Policy Summit and non-report activities only
How Was the ICER Report Developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis and cost-effectiveness modeling
- Public comment and revision
- Expert reviewers
  - Victor W. Henderson, MD, MS, Professor of Epidemiology and Population Health and of Neurology and Neurological Sciences; Director, Stanford Alzheimer’s Disease Research Center, Stanford University
  - Sarah A. Kremen, MD, Director, Neurobehavior Program, Jona Goldrich Center for Alzheimer’s and Memory Disorders, Cedars-Sinai Medical Center
  - Peter J. Neumann, ScD, Director, Center for Evaluation of Value and Risk in Health, Institute for Clinical Research and Health Studies, Tufts Medical Center
  - Alzheimer’s Association Review Panel
- How is the evidence report structured to support CTAF voting and policy discussion?
Value Assessment Framework: Long-Term Value for Money

- Special Social/Ethical Priorities
- Potential Benefits Beyond “Health”
- Total Cost Overall
  - Including Cost Offsets
- Health Benefits:
  - Return of Function; Slower Decline
- Health Benefits:
  - Longer Life
<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00am</td>
<td>Meeting Convened and Opening Remarks</td>
</tr>
<tr>
<td>9:15am</td>
<td>Presentation of the Evidence</td>
</tr>
<tr>
<td>10:45am</td>
<td>Manufacturer Public Comments and Discussion</td>
</tr>
<tr>
<td>11:15am</td>
<td>Public Comments and Discussion</td>
</tr>
<tr>
<td>11:45am</td>
<td>Lunch</td>
</tr>
<tr>
<td>12:30pm</td>
<td>CTAF Deliberation and Vote</td>
</tr>
<tr>
<td>1:30pm</td>
<td>Break</td>
</tr>
<tr>
<td>1:45pm</td>
<td>Policy Roundtable Discussion</td>
</tr>
<tr>
<td>3:30pm</td>
<td>Reflections from CTAF</td>
</tr>
<tr>
<td>4:00pm</td>
<td>Meeting Adjourned</td>
</tr>
</tbody>
</table>
Clinical and Patient Experts

Victor W. Henderson, MD, MS, Professor of Epidemiology and Population Health and of Neurology and Neurological Sciences; Director, Stanford Alzheimer’s Disease Research Center, Stanford University

- No conflicts of interest to disclose.

Sarah A. Kremen, MD, Director, Neurobehavior Program, Jona Goldrich Center for Alzheimer’s and Memory Disorders, Cedars-Sinai Medical Center

- Dr. Kremen served as a site PI for aducanumab trials PRIME and ENGAGE.

Matthew Baumgart, Vice President of Health Policy, Alzheimer’s Association

- In FY 2020, the Association received $275,000 in contributions from Biogen. Total contributions from the pharmaceutical industry make up less than 1% of the Association’s total revenue.

Laura Jones, Caregiver and Advocate

- No conflicts of interest to disclose.
Presentation of the Clinical Evidence

Grace A. Lin, MD

Associate Professor of Medicine and Health Policy

University of California, San Francisco
Key Collaborators

• Patricia G. Synnott, MS, MALD, Senior Manager, CEA Registry and Global Health Initiatives, Center for the Evaluation of Value and Risk in Health

• Avery McKenna, Research Assistant III, Evidence Synthesis, ICER

• Emily Nhan, Research Assistant, ICER

**Disclosures:**

Grace Lin received funding from ICER for the report.

The Center for Evaluation of Value and Risk in Health receives funding from Biogen.
Alzheimer’s Disease (AD): A Common and Expensive Disease

Projected Total Population, by Age

Estimated Direct Health Care Costs, By Payer

Source: 2021 Alzheimer’s Facts and Figures

Total cost: $355 Billion (B)
- Medicare $181B, 51%
- Medicaid, $59B, 17%
- Out of pocket, $76B, 21%
- Other, $39B, 11%

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Stages and Symptoms of AD

Preclinical AD

- No symptoms
- ApoE+ Amyloid plaques

MCI* due to AD

- Very mild symptoms that do not interfere with everyday activities
  - Memory loss
  - Impaired judgment
- Symptoms interfere with some everyday activities
  - Language problems
  - Mood swings
  - Personality changes

Mild

- Symptoms interfere with many everyday activities
  - Unable to recall new information
  - Long-term memory loss
  - Wandering
  - Agitation, aggression
  - Assistance with ADLs

Moderate

- Symptoms interfere with most everyday activities
  - Gait instability
  - Incontinence
  - May be bedridden
  - Unable to perform ADLs
  - Placement in long-term care

Severe

Dementia due to AD
Impact on Patients and Caregivers

Patient Impact

• Loss of independence (e.g., driving, managing finances, ADLs)
• Loss of "self"

Caregiver Impact

• Estimated 15.3 billion hours of unpaid caregiving
• Impacts on caregiver physical and mental health
• Larger care impact than other diseases
Standard of Care and Management

• Supportive care
  • Non-pharmacologic treatments – e.g., physical exercise, strategies to mitigate behavioral symptoms
  • Care planning and coordination

• Non-disease modifying drugs to treat cognitive and behavioral symptoms
  • Acetylcholinesterase inhibitors (e.g., donepezil)
  • Memantine
  • Psychotropic drugs (e.g., antidepressants, antipsychotics)
Scope of Review

• **Scope:** Clinical and cost effectiveness of adding aducanumab to supportive care

• **Patient population:** Patients with MCI due to AD or mild AD

• **Comparator:** Supportive care, including non-pharmacologic and non-disease-modifying pharmacologic interventions for symptom management
Key Outcomes from Clinical Trials

• Primary outcome:
  • Clinical Dementia Rating-Sum of Boxes (CDR-SB)
    • 6 domains of cognitive and functional performance in AD
    • Higher scores indicate progression

• Secondary outcomes:
  • Cognitive and Functional Scales (e.g., MMSE, ADAS-Cog 13, etc.)
  • Biomarkers including amyloid and tau (PET and CSF)
Insights from Discussions with Patients

- Main goal of treatment: Maintain independence and identity
- Substantial caregiver burden
- Care gaps
  - Underdiagnosis
  - Coordination of care, future planning
  - Lack of disease-modifying therapy
- Limitations of current outcome measures
  - Objective assessment difficult
  - Measures focus on cognition and function, not quality of life
Clinical Evidence
## ENGAGE and EMERGE: Contemporaneous, Identical RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>N</th>
<th>F/U Months</th>
<th>Age, Years</th>
<th>Baseline CDR-SB, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENGAGE (Study 301)</td>
<td>MCI due to AD or mild AD</td>
<td>Total: 1,647 70% ApoE+ 80% MCI</td>
<td>Planned 18 months*</td>
<td>70.1</td>
<td>2.41 (1.0)</td>
</tr>
<tr>
<td>EMERGE (Study 302)</td>
<td></td>
<td>Total: 1,638 67% ApoE+ 82% MCI</td>
<td></td>
<td>70.7</td>
<td>2.48 (1.0)</td>
</tr>
</tbody>
</table>

*Pre-specified futility analysis with data collected until December 2018.
Aducanumab Dosing

Trial Entry

ENGAGE
August 2015

EMERGE
September 2015

ApoE+

Low dose: 3 mg/kg

High dose: 6 mg/kg

High dose: 10 mg/kg

ApoE-

Low dose: 6 mg/kg

High dose: 10 mg/kg

Protocol Version 4
March 2017
Change in Amyloid (PET SUVR)
EMERGE Results: CDR-SB (ITT)

Adjusted Mean Change from Baseline

Week

0 26 50 78

Better
Worse

Diff. HD vs. Placebo:
-0.39 (-0.69, -0.09)

-22%
(favors aducanumab)
ENGAGE Results: CDR-SB (ITT)

Adjusted Mean Change from Baseline

Week

Diff. HD vs. Placebo: +0.03 (-0.26, +0.33)
+2%
(no benefit)
Harms

• Amyloid-related imaging abnormalities (ARIA)
  • Both edema (more common) and hemorrhage (less common)
  • Diagnosed by MRI, majority asymptomatic (74%)
  • Most resolved with brief interruption in therapy
  • More common in ApoE+ and high-dose groups

• Discontinuation: 9%

• Other harms: Headache, falls, diarrhea
ENGAGE & EMERGE: Can We Reconcile the Discordant Results?
Why Did Two Identically Designed Trials Give Different Answers?

• Similar baseline characteristics, trials ran in parallel

• Stopped based on predicted futility

• Manufacturer analyzed larger dataset, found positive results in EMERGE
  • Assumption that EMERGE result was correct, ENGAGE was wrong
  • Post-hoc subgroup analyses done to explain above results
Can Dosing Explain the Discordant Results?

- ENGAGE started 1 month before EMERGE

- Protocol Version 4 influenced more participants in EMERGE (56%) than ENGAGE (49%)

- Participants who received all 14 doses of 10 mg/kg
  - EMERGE 29%
  - ENGAGE 22%
% Difference from Placebo by Number of 10 mg/kg Doses

Number of Doses: 
- >=6
- >=8
- >=10
- >=12
- =14 (full dose)

Number of subjects and Adjusted mean at Week 78

<table>
<thead>
<tr>
<th></th>
<th>Placebo 102</th>
<th>Placebo 185</th>
<th>Placebo 157</th>
<th>Placebo 120</th>
<th>Placebo 77</th>
<th>Placebo 220</th>
<th>Placebo 201</th>
<th>Placebo 177</th>
<th>Placebo 144</th>
<th>Placebo 98</th>
</tr>
</thead>
<tbody>
<tr>
<td>adjusted mean</td>
<td>1.42</td>
<td>1.36</td>
<td>1.49</td>
<td>1.54</td>
<td>1.58</td>
<td>1.56</td>
<td>1.45</td>
<td>1.54</td>
<td>1.38</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>BIT5037 102</td>
<td>BIT5037 185</td>
<td>BIT5037 157</td>
<td>BIT5037 120</td>
<td>BIT5037 77</td>
<td>BIT5037 220</td>
<td>BIT5037 201</td>
<td>BIT5037 177</td>
<td>BIT5037 144</td>
<td>BIT5037 98</td>
</tr>
<tr>
<td>adjusted mean</td>
<td>1.45</td>
<td>1.43</td>
<td>1.21</td>
<td>1.14</td>
<td>1.08</td>
<td>1.07</td>
<td>1.02</td>
<td>0.57</td>
<td>0.89</td>
<td>0.87</td>
</tr>
</tbody>
</table>
Name that Dose: CDR-SB, Post-PV4, by ApoE Status
Name that Dose: CDR-SB, Post-PV4, by ApoE Status
Name that Dose: CDR-SB, Post-PV4, by ApoE Status
Name that Dose: CDR-SB, Post-PV4, by ApoE Status

ENGAGE ApoE-

Placebo
Low Dose
High Dose

Worse
Better

EMERGE ApoE-

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Name that Dose: CDR-SB, Post-PV4, by ApoE Status

ENGAGE ApoE-

EMERGE ApoE-

Better

Worse

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Name that Dose: CDR-SB, Post-PV4, by ApoE Status

ENGAGE ApoE-

Worse
Better

0.00
0.50
1.00
1.50
2.00
2.50
3.00

Placebo
Low Dose
High Dose

ENGAGE ApoE+

Worse
Better

0.00
0.50
1.00
1.50
2.00
2.50
3.00

Placebo
Low Dose
High Dose

EMERGE ApoE-

0.00
0.50
1.00
1.50
2.00
2.50
3.00

Low Dose
High Dose
Placebo

© 2021 Institute for Clinical and Economic Review
Name that Dose: CDR-SB, Post-PV4, by ApoE Status

ENGAGE ApoE-

EMERGE ApoE-

ENGAGE ApoE+

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Name that Dose: CDR-SB, Post-PV4, by ApoE Status

ENGAGE ApoE-

- Placebo
- Low Dose
- High Dose

EMERGE ApoE-

- Low Dose
- High Dose
- Placebo

ENGAGE ApoE+

- Placebo
- Low Dose
- High Dose

EMERGE ApoE+

- Low Dose
- High Dose
Name that Dose: CDR-SB, Post-PV4, by ApoE Status

ENGAGE ApoE-

Placebo
Low Dose
High Dose

Worse
Better

ENGAGE ApoE+

Placebo
Low Dose
High Dose

Worse
Better

EMERGE ApoE-

Placebo
Low Dose
High Dose

Worse
Better

EMERGE ApoE+

Placebo
Low Dose
High Dose

Worse
Better
Pooled Estimated Effect of Amyloid Reduction on MMSE
Why Might Aducanumab Have Shown Positive Results When Others Did Not?

- Mechanism of action
  - Aducanumab targets aggregated forms of amyloid – could oligomer be the toxic form?

- Trial design
  - Recruited patients earlier in disease course
  - Confirmed beta-amyloid pathology
  - Dose titration to decrease risk of ARIA
## Controversies and Uncertainties

<table>
<thead>
<tr>
<th>Category</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methodologic Threats to Validity</td>
<td>- Inconsistent results between two identical trials</td>
</tr>
<tr>
<td></td>
<td>- Post-hoc analyses</td>
</tr>
<tr>
<td></td>
<td>- Potential functional unblinding due to ARIA</td>
</tr>
<tr>
<td>Clinical Significance of Results</td>
<td>- Minimal clinically important difference for CDR-SB?</td>
</tr>
<tr>
<td></td>
<td>- Uncertain link between amyloid reduction and clinical efficacy</td>
</tr>
<tr>
<td>Safety</td>
<td>- Intensive monitoring for ARIA in trial not required in real world</td>
</tr>
<tr>
<td>Generalizability</td>
<td>- No data in more severe AD population</td>
</tr>
<tr>
<td></td>
<td>- Lack of diversity and younger age in clinical trial population</td>
</tr>
</tbody>
</table>
Potential Other Benefits and Contextual Considerations

• High unmet need for effective disease-modifying therapy

• High impact on patients’ and caregivers’ quality of life, ability to achieve major life goals

• Every 4 week IV infusion plus additional MRI monitoring may be burdensome

• Impact on health inequities is unclear

• Impact on long-term care need
Public Comments Received

• ARIA harm is not severe, since most cases are asymptomatic and/or resolve

• Innovation and “first-in-class” to show potential efficacy should not be minimized

• Treatment could have value in reducing health disparities related to diagnosis and treatment of AD
Summary

• EMERGE met primary endpoint, ENGAGE did not

• Post-hoc analyses were more supportive of positive result, but concerns remain about validity of such analyses
  • Post-hoc analyses usually exploratory due to loss of randomization
  • Possible that EMERGE was chance finding

• ARIA—while mostly mild—was common

• Clinical significance of findings?
ICER Evidence Ratings for Aducanumab

• “Insufficient” for MCI and mild AD
Questions
Long-Term Cost Effectiveness

Melanie D. Whittington, PhD, MS

Associate Director of Health Economics

Institute for Clinical and Economic Review
Key Review Team Members

• Jon Campbell, PhD, MS, Senior Vice President for Health Economics, ICER

• Noemi Fluetsch, MPH, Research Assistant, Health Economics and Outcomes, ICER

Disclosures:

We have no conflicts of interest relevant to this report.
Objective

• Estimate the cost effectiveness of aducanumab in addition to supportive care as compared to supportive care alone
Methods in Brief
Population

- In alignment with the clinical evidence and updated FDA label, the starting population for the economic evaluation included adults with early AD, defined as MCI due to AD or mild AD.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, years</td>
<td>70</td>
<td>Weighted average of participants in ENGAGE and EMERGE</td>
</tr>
<tr>
<td>Percent Female, %</td>
<td>52%</td>
<td>Weighted average of participants in ENGAGE and EMERGE</td>
</tr>
<tr>
<td>Clinical Stage, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI Due to AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild AD</td>
<td>55%</td>
<td>AD population with underlying beta-amyloid pathology</td>
</tr>
<tr>
<td></td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Setting of Care, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>92%</td>
<td>Percent of population ages 65-74 who received long-term services and supports</td>
</tr>
<tr>
<td>Long-Term Care</td>
<td>8%</td>
<td></td>
</tr>
</tbody>
</table>
Methods Overview

- **Model**: Markov Model
- **Setting**: United States
- **Perspective**: Health Care System Perspective and Modified Societal Perspective
- **Time Horizon**: Lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: Yearly
- **Primary Outcomes**: Cost per quality-adjusted life year (QALY) gained; cost per equal value of life year gained (evLYG); cost per life year (LY) gained; cost per year in the community gained
Model Schematic

- MCI due to AD
- Mild AD
- Moderate AD
- Severe AD
- Dead
Key Model Assumptions

• *Effect on disease progression from MCI:* Blend of hazard ratio from EMERGE and relationship with CDR-SB from ENGAGE

• *Effect on disease progression from Mild:* Aducanumab is 50% less effective on transitions out of mild AD than it is on transitions out of MCI due to AD

• *Effect on disease progression from Moderate:* Aducanumab does not reduce or increase the rate of disease progression

• Patients stop receiving aducanumab once they enter the severe AD health state
# Key Model Inputs: Clinical Inputs

<table>
<thead>
<tr>
<th>Input</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab HR from MCI</td>
<td>[Redacted]</td>
<td>Used 1.02 for ENGAGE trial based on CDR-SB and [Redacted] based on health state transition HR provided by Biogen</td>
</tr>
<tr>
<td>Aducanumab HR from Mild AD</td>
<td>50% as effective as HR from MCI</td>
<td>Applied to mild to moderate and mild to severe transition</td>
</tr>
<tr>
<td>Aducanumab HR from Moderate AD</td>
<td>1.0</td>
<td>Applied to moderate to severe transition</td>
</tr>
<tr>
<td>Probability of Symptomatic ARIA/Discontinuation Due to Adverse Events</td>
<td>10%</td>
<td>Occurred within first 18 months of starting aducanumab; discontinuation not related to AEs occurred as individuals transitioned to severe AD over the time horizon</td>
</tr>
<tr>
<td>Duration of ARIA</td>
<td>12 weeks</td>
<td>Duration influenced disutility and monitoring costs</td>
</tr>
</tbody>
</table>
# Key Model Inputs: Utilities

<table>
<thead>
<tr>
<th>Input</th>
<th>Community Dwelling</th>
<th>Long-Term Care Dwelling</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Disutilities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI Due to AD</td>
<td>-0.17</td>
<td>-0.17</td>
</tr>
<tr>
<td>Mild AD</td>
<td>-0.22</td>
<td>-0.19</td>
</tr>
<tr>
<td>Moderate AD</td>
<td>-0.36</td>
<td>-0.42</td>
</tr>
<tr>
<td>Severe AD</td>
<td>-0.53</td>
<td>-0.59</td>
</tr>
<tr>
<td><strong>Caregiver Disutilities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI Due to AD</td>
<td>-0.03</td>
<td>-0.03</td>
</tr>
<tr>
<td>Mild AD</td>
<td>-0.05</td>
<td>-0.05</td>
</tr>
<tr>
<td>Moderate AD</td>
<td>-0.08</td>
<td>-0.08</td>
</tr>
<tr>
<td>Severe AD</td>
<td>-0.10</td>
<td>-0.10</td>
</tr>
</tbody>
</table>
## Key Model Inputs: Costs

<table>
<thead>
<tr>
<th>Costs</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab</td>
<td>$56,000 + 6% per year</td>
<td>Year 1 cost lower due to titration</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>$255.33 per scan</td>
<td>3 brain MRIs in first year and 3 brain MRIs for each ARIA occurrence</td>
</tr>
<tr>
<td>Caregiver Time Spent Caregiving</td>
<td></td>
<td>Values are for community-dwelling patients; time spent for LTC-dwelling patients was 44% of these values</td>
</tr>
<tr>
<td>MCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild AD</td>
<td>69 hours/month</td>
<td></td>
</tr>
<tr>
<td>Moderate AD</td>
<td>113 hours/month</td>
<td></td>
</tr>
<tr>
<td>Severe AD</td>
<td>169 hours/month</td>
<td></td>
</tr>
<tr>
<td></td>
<td>298 hours/month</td>
<td></td>
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</table>
Results
# Base-Case Results: Undiscounted Years in Health States

<table>
<thead>
<tr>
<th>Health State</th>
<th>Aducanumab</th>
<th>Supportive Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI</td>
<td>2.48 years</td>
<td>2.20 years</td>
</tr>
<tr>
<td>Mild AD</td>
<td>2.07 years</td>
<td>2.00 years</td>
</tr>
<tr>
<td>Moderate AD</td>
<td>1.23 years</td>
<td>1.29 years</td>
</tr>
<tr>
<td>Severe AD</td>
<td>1.61 years</td>
<td>1.71 years</td>
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</tbody>
</table>
## Base-Case Results: Model Outputs

<table>
<thead>
<tr>
<th>Health Care System Perspective</th>
<th>Total Cost</th>
<th>QALYs</th>
<th>evLYs</th>
<th>Life Years</th>
<th>Life Years in Community</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aducanumab</td>
<td>$546,000</td>
<td>3.467</td>
<td>3.513</td>
<td>5.969</td>
<td>3.789</td>
</tr>
<tr>
<td>Supportive Care</td>
<td>$342,000</td>
<td>3.313</td>
<td>3.313</td>
<td>5.827</td>
<td>3.628</td>
</tr>
<tr>
<td>Incremental</td>
<td>$204,000</td>
<td>0.154</td>
<td>0.201</td>
<td>0.143</td>
<td>0.161</td>
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</table>

<table>
<thead>
<tr>
<th>Societal Perspective</th>
<th>Total Cost</th>
<th>QALYs</th>
<th>evLYs</th>
<th>Life Years</th>
<th>Life Years in Community</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Aducanumab</td>
<td>$838,000</td>
<td>3.097</td>
<td>3.154</td>
<td>5.969</td>
<td>3.789</td>
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<td>Supportive Care</td>
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<tr>
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<td>$202,000</td>
<td>0.159</td>
<td>0.215</td>
<td>0.143</td>
<td>0.161</td>
</tr>
</tbody>
</table>
## Base-Case Results: Incremental Cost-Effectiveness Ratios

<table>
<thead>
<tr>
<th></th>
<th>Health Care System Perspective</th>
<th>Societal Perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per QALY Gained</td>
<td>$1,330,000</td>
<td>$1,270,000</td>
</tr>
<tr>
<td>Cost per evLYG Gained</td>
<td>$1,020,000</td>
<td>$938,000</td>
</tr>
<tr>
<td>Cost per Life Year Gained</td>
<td>$1,430,000</td>
<td>$1,420,000</td>
</tr>
<tr>
<td>Cost per Additional Year in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>the Community</td>
<td>$1,270,000</td>
<td>$1,260,000</td>
</tr>
</tbody>
</table>
One Way Sensitivity Analysis

- Aducanumab treatment effectiveness most influential input
  - Incremental cost-effectiveness ratios ranged from dominated to approximately $600,000 per QALY gained
## Probabilistic Sensitivity Analysis

<table>
<thead>
<tr>
<th>Outcome = QALYs Gained</th>
<th>Cost-Effective at $50,000</th>
<th>Cost-Effective at $100,000</th>
<th>Cost-Effective at $150,000</th>
<th>Cost-Effective at $200,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome = evLYGs</th>
<th>Cost-Effective at $50,000</th>
<th>Cost-Effective at $100,000</th>
<th>Cost-Effective at $150,000</th>
<th>Cost-Effective at $200,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Scenario Analyses

1. Optimistic Treatment Benefit
   - Hazard ratio from EMERGE for transitions from MCI
   - Hazard ratio from EMERGE for transitions from mild AD

2. Conservative Treatment Benefit
   - Blended hazard ratio for transitions from MCI only
Optimistic Treatment Benefit Scenario

- Hazard ratio from EMERGE for transitions from MCI
- Hazard ratio from EMERGE for transitions from mild AD

<table>
<thead>
<tr>
<th></th>
<th>Cost per QALY Gained</th>
<th>Cost per evLYG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Care System Perspective</td>
<td>$454,000</td>
<td>$360,000</td>
</tr>
<tr>
<td>Societal Perspective</td>
<td>$431,000</td>
<td>$329,000</td>
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</tbody>
</table>
Conservative Treatment Benefit Scenario

- Blended hazard ratio for transitions from MCI only

<table>
<thead>
<tr>
<th>Perspective</th>
<th>Cost per QALY Gained</th>
<th>Cost per evLYG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Care System Perspective</td>
<td>$1,960,000</td>
<td>$1,490,000</td>
</tr>
<tr>
<td>Societal Perspective</td>
<td>$1,860,000</td>
<td>$1,360,000</td>
</tr>
</tbody>
</table>
Limitations

• Evidence on the effectiveness of aducanumab is inconsistent between the 2 pivotal trials

• Evidence on aducanumab’s effect on health state transitions is limited

• Utilities for the patient and caregiver are from cross-sectional studies
Public Comments Received

- Threshold above commonly used thresholds for Alzheimer’s disease
- Pooling effect from EMERGE and ENGAGE
Conclusions

• An annual price of $56,000 for aducanumab is not in alignment with its clinical benefits, even under a scenario with optimistic treatment benefit assumptions

• Uncertainty in the effectiveness of aducanumab percolates through to a wide range in potential cost-effectiveness estimates, ranging from dominated to around $350,000 per evLYG
Questions
Manufacturer Public Comment and Discussion
Chris Leibman, Senior Vice President of Value and Access, Biogen and Maha Radhakrishnan, MD, Chief Medical Officer, Biogen

Conflicts of Interest:

- Chris Leibman and Maha Radhakrishnan are employees of Biogen.
Conflicts of Interest:

• No conflicts of interest to disclose.
Conflicts of Interest:

- No conflicts of interest to disclose.
Laura Jones, Caregiver and Advocate

Conflicts of Interest:

- No conflicts of interest to disclose.
Matthew Baumgart, Vice President of Health Policy
Alzheimer’s Association

Conflicts of Interest:

- The Alzheimer’s Association received 0.89% of its total 2020 contributed revenue from the biotechnology, pharmaceutical, diagnostics, and clinical research industry, including 0.15% from Biogen and Eisai.
Russ Paulsen, Chief Operating Officer
Us Against Alzheimer’s

Conflicts of Interest:

- Us Against Alzheimer’s receives financial support from Biogen, Eisai, and their competitors.
- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000.
Conflicts of Interest:

- No conflicts of interest to disclose.
Lunch

Meeting will resume at 12:30 pm PT
Voting Questions
1. Is the available evidence adequate to demonstrate that the net health benefit of aducanumab plus supportive care is superior to that provided by supportive care alone?

A. Yes

B. No
When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* effective treatment for Alzheimer’s disease, on the basis of the following contextual considerations:

2. Acuity of need for treatment of individual patients based on the severity of the condition being treated

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>A.</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>Very Low Priority</td>
</tr>
<tr>
<td>B.</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Low priority</td>
</tr>
<tr>
<td>C.</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Average priority</td>
</tr>
<tr>
<td>D.</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>High priority</td>
</tr>
<tr>
<td>E.</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>Very High Priority</td>
</tr>
</tbody>
</table>

![Priority Scale]

- 1 Very Low Priority
- 2 Low priority
- 3 Average priority
- 4 High priority
- 5 Very High Priority
3. Magnitude of the lifetime impact on individual patients of the condition being treated

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<td>4</td>
<td>High priority</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>5</td>
<td>5</td>
<td>Very High Priority</td>
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</tbody>
</table>

![Priority Scale Diagram]
What are the relative effects of aducanumab plus supportive care versus supportive care alone on the following outcomes that inform judgment of the overall long-term value for money of aducanumab?

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

A. 1
   1. Major Negative Effect
B. 2
   2. Minor Negative Effect
   3. No Difference
C. 3
   4. Minor Positive Effect
D. 4
   5. Major Positive Effect
5. Caregivers’ quality of life and/or ability to achieve major life goals related to education, work, or family life

A. 1
   1. Major Negative Effect

B. 2
   2. Minor Negative Effect
   3. No Difference

C. 3
   4. Minor Positive Effect

D. 4
   5. Major Positive Effect

E. 5
### 6. Society’s goal of reducing health inequities

<p>| | |</p>
<table>
<thead>
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<tbody>
<tr>
<td>A</td>
<td>1</td>
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<tr>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
</tr>
<tr>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>E</td>
<td>5</td>
</tr>
</tbody>
</table>

![Graph showing the distribution of effects](chart.png)
7. Given the available evidence...what is the long-term value for aducanumab plus 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 pricing

C. High long-term value for money at current pricing
Break

Meeting will resume at 1:45 pm PT
Policy Roundtable
## Policy Roundtable

<table>
<thead>
<tr>
<th>Participant</th>
<th>Title and Affiliation</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matthew Baumgart</td>
<td>Vice President, Health Policy, Alzheimer’s Association</td>
<td>The Association received 0.89% of its total 2020 revenue from biotechnology, pharmaceutical, diagnostics, and clinical research industries, including 0.15% from Biogen and Eisai.</td>
</tr>
<tr>
<td>Leslie Fish, RPh, PharmD</td>
<td>Vice President, Clinical Pharmacy, IPD Analytics</td>
<td>Leslie Fish is a full-time employee of IPD Analytics.</td>
</tr>
<tr>
<td>Patrick Gleason, PharmD</td>
<td>Assistant Vice President, Health Outcomes, Prime Therapeutics</td>
<td>Patrick Gleason is an employee of Prime Therapeutics.</td>
</tr>
<tr>
<td>Victor W. Henderson, MD, MS</td>
<td>Professor, Epidemiology and Population Health and Neurology and Neurological Sciences; Director, Alzheimer’s Disease Research Center, Stanford University</td>
<td>No conflicts of interest to disclose.</td>
</tr>
<tr>
<td>Laura Jones</td>
<td>Caregiver</td>
<td>No conflicts of interest to disclose.</td>
</tr>
<tr>
<td>Sarah Kremen, MD</td>
<td>Director, Neurobehavior Program, Jona Goldrich Center for Alzheimer’s and Memory Disorders, Cedars-Sinai Medical Center</td>
<td>Sarah Kremen served as a site PI for aducanumab trials PRIME and ENGAGE.</td>
</tr>
<tr>
<td>Chris Leibman, PharmD, MS</td>
<td>Biogen</td>
<td>Chris Leibman is an employee of Biogen.</td>
</tr>
<tr>
<td>Mark McClellan, MD, PhD</td>
<td>Director, Duke University Margolis Center for Health Policy</td>
<td>Receipt of monetary value, including salary and other payments for services such as consulting fees and honoraria. Equity interests in individual stocks, stock options, or other ownership interests in excess of $10,000. Status/position as an officer, board member, trustee, owner, or employee of a health care company, or an organization that receives more than 25% of its funding from health care companies.</td>
</tr>
</tbody>
</table>
The doctor-administered drugs Medicare spends the most on

KFF ESTIMATE AT $5,600

$2.9B

Aduhelm
BIOPEN

Eylea
REGENERON

Keytruda
MERK

Opdivo
BMS

Rituxan
GENENTECH

Prolia
AMGEN

$2.91B

$2.67B

$1.78B

$1.73B

$1.61B

SOURCES: Centers for Medicare & Medicaid Services, Kaiser Family Foundation, Biogen
The doctor-administered drugs Medicare spends the most on

BIOGEN LOW ESTIMATE AT $5,600

$5.8B

- Aduhelm (BIOGEN)
- Eylea (REGENERON) $2.91B
- Keytruda (MERCK) $2.67B
- Opdivo (BMS) $1.78B
- Rituxan (GENENTECH) $1.73B
- Prolia (AMGEN) $1.61B

SOURCES: Centers for Medicare & Medicaid Services, Kaiser Family Foundation, Biogen
The doctor-administered drugs Medicare spends the most on

**BIOGEN HIGH ESTIMATE AT $5,600**

$11.5B

- **Aduhelm**
  - BIOGEN
  - $2.91B

- **Eylea**
  - REGENERON
  - $2.67B

- **Keytruda**
  - MERCK
  - $2.67B

- **Opdivo**
  - BMS
  - $1.78B

- **Rituxan**
  - GENENTECH
  - $1.73B

- **Prolia**
  - AMGEN
  - $1.61B

**SOURCES:** Centers for Medicare & Medicaid Services, Kaiser Family Foundation, Biogen
Aside from payer access and physician demand, there are a number of softer issues that could affect Gilead’s final pricing decision.

<table>
<thead>
<tr>
<th>Stakeholders</th>
<th>Wave 1 Regimen</th>
<th>Wave 1 SOF product (12 wks)</th>
<th>Wave 2 FDC (8 wks or 12 wks?)</th>
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<td>Payers</td>
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</tr>
<tr>
<td>Physicians</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Likelihood of applying directly observed therapy due to high price</td>
<td>Unlikely</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>Likelihood of delay treatment of GT-1 TN patients due to pricing</td>
<td>Unlikely</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>Likelihood of losing some KOL endorsement/support as price too high</td>
<td>Very Unlikely</td>
<td>Unlikely</td>
<td>Possible</td>
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<tr>
<td>Likelihood of getting rejection on TE patients and delay treatment for all due to misconception of restriction for SOF</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>Patients and Advocacy groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likelihood of AHF, FPC and other advocacy groups reacting negatively to price, and affecting public opinion</td>
<td>Likely</td>
<td>Likely</td>
<td>Very Likely</td>
</tr>
<tr>
<td>Treatment Guidelines</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Likelihood of AASLD develop treatment pathway to prioritize (staging) patients (per KOLs or/and professional community request)</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>Likelihood of a “price mention or asterisk” in AASLD (per KOLs or/and professional community request)</td>
<td>Unlikely</td>
<td>Unlikely</td>
<td>Possible</td>
</tr>
<tr>
<td>Others</td>
<td></td>
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<tr>
<td>Likelihood of public outcry if SOF revenue exceed $2B as government trying to control healthcare cost</td>
<td>Possible</td>
<td>Possible</td>
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<td>Likelihood of a letter from congress on SOF price</td>
<td>Possible</td>
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<td>Likely</td>
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<tr>
<td>Likelihood of a congressional hearing if SOF revenue exceed $2B</td>
<td>Unlikely</td>
<td>Unlikely</td>
<td>Unlikely</td>
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</table>
CTAF Reflections
Next Steps

• Meeting recording posted to ICER website next week

• Final Report published on or around August 5, 2021
  • Includes description of CTAF votes, deliberation, policy roundtable discussion

• Materials available at: https://icer.org/assessment/alzheimers-disease-2021
Adjourn