MAYO CLINIC

NAPA 2023
HAVE WE MADE RESEARCH PROGRESS?

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CORA KANOW PROFESSOR OF ALZHEIMER'S DISEASE RESEARCH

MAYO CLINIC COLLEGE OF MEDICINE

ROCHESTER, MN

ADVISORY COUNCIL ON RESEARCH, CARE AND SERVICES
NATIONAL PLAN TO ADDRESS ALZHEIMER'S DISEASE

MAY 8, 2023

DISCLOSURES

- Roche, Inc.
- Genentech, Inc.
- Eisai, Inc.
- Eli Lilly, Inc.
- Nestle, Inc.
- NIH:
  - U01 AG006786
  - P30 AG062677
  - U01 AG024904
  - U24 AG057437
  - R01 AG011378
  - UF1 NS125417
  - GHR Foundation
  - Mayo Medical Foundation for Education and Research

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MAYO CLINIC

Outline

Overview of AD

AD Therapies

Expectations

Progress?

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NAPA Goals

Prevent and Effectively Treat AD/ADRD by 2025

Enhance Care Quality and Efficiency

Expand Supports for People with AD/ADRD and Their Families

Enhance Public Awareness and Engagement

Improve Data to Track Progress

(NEW) Accelerate Action to Promote Healthy Aging and Reduce Risk Factors for AD/ADRD

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ALZHEIMER'S DISEASE

2018 NIA-AA RESEARCH FRAMEWORK TO INVESTIGATE THE ALZHEIMER'S DISEASE CONTINUUM

- Biological definition
- Term AD refers to pathologic change – not specific syndrome
- AD is identified at post mortem by pathologic changes and/or in vivo by biomarkers of amyloid and tau
  - Symptoms are part of the disease continuum not its definition
  - Major shift in thinking

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Therapies for Alzheimer's Disease

Symptomatic

Disease modifying

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Disease Modifying Therapies

AMYLOID

AMYLOID LOWERING THERAPIES IN MCI/MILD DEMENTIA

- Aducanumab
- Lecanemab
- Donanemab

EMERGE: Primary and secondary endpoints from final data set at Week 78

	Placebo decline (n=548)	Difference vs. placebo (%)[a] p-value	
		Low dose (n=543)	High dose (n=547)
CDR-SB	1.74	**-0.26** (-15%) 0.0901	**-0.39** (-22%) 0.0120
MMSE	-3.3	**-0.1** (3%) 0.7578	**0.6** (-18%) 0.0493
ADAS-Cog 13	5.162	**-0.701** (-14%) 0.1962	**-1.400** (-27%) 0.0097
ADCS-ADL-MCI	-4.3	**0.7** (-16%) 0.1515	**1.7** (-40%) 0.0006

ITT population. [a]Difference vs placebo at Week 78. Negative percentage means less progression in the treated arm.
ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; ITT, intent to treat; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

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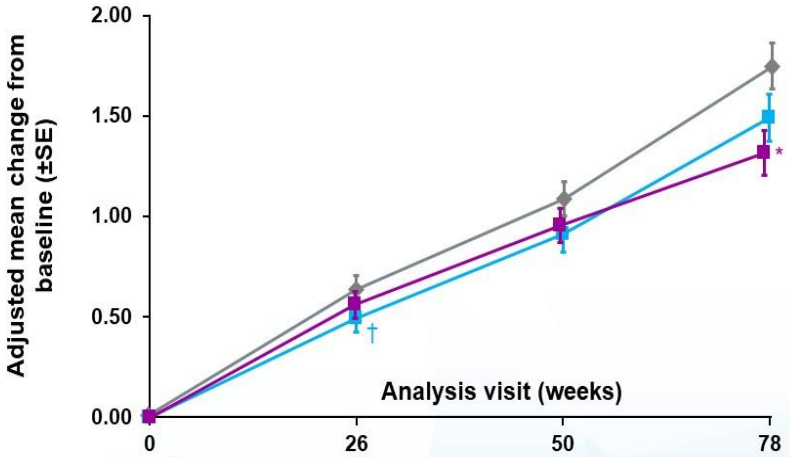
EMERGE: Longitudinal change from baseline in CDR-SB



Placebo	n=547	531	429	288
Low dose aducanumab	n=543	512	420	289
High dose aducanumab	n=547	513	431	299

ITT population. *p <0.05, †p<0.1 and ≥0.05 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status. ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; ITT, intent to treat; MMRM, mixed model for repeated measure; MMSE, Mini Mental State Examination; SE, standard error.

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ADUCANUMAB

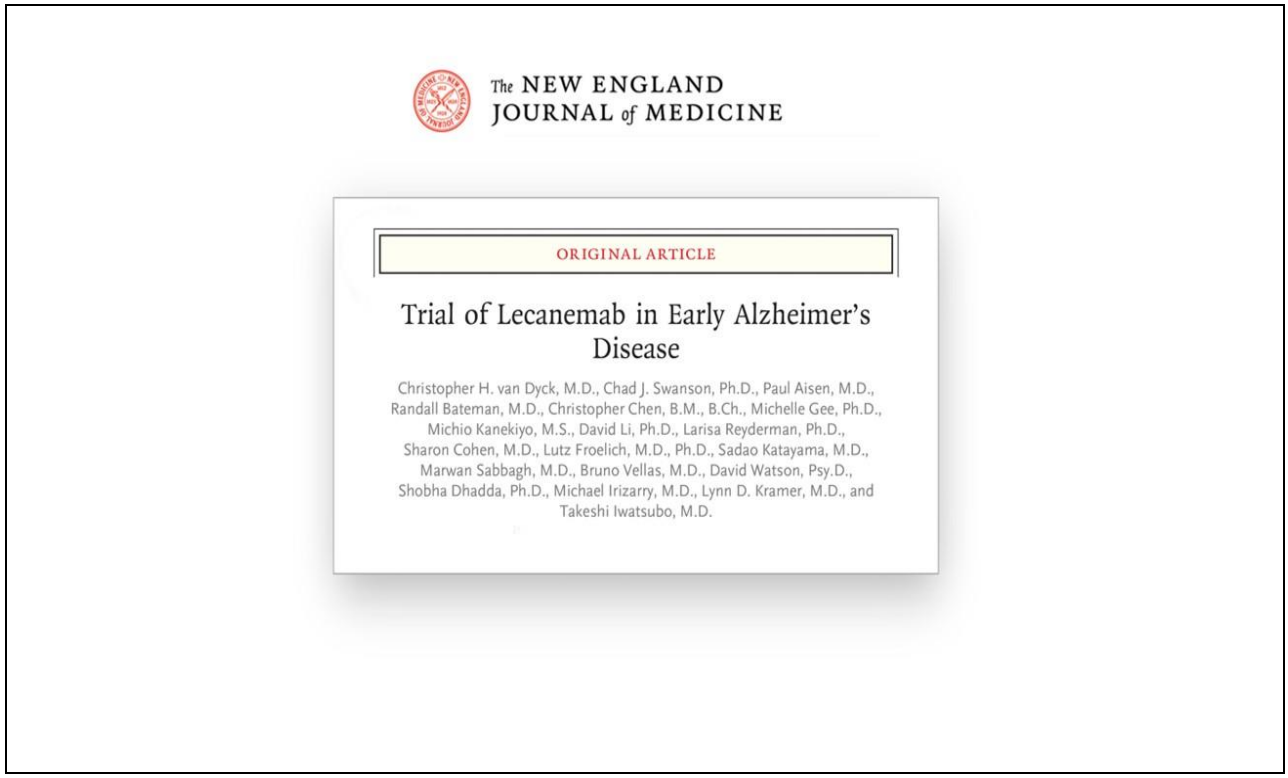
ONE POSITIVE

ONE NEGATIVE

ONE SUGGESTIVE

LECANEMAB

CLARITY AD



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 (18 months)

R 1:1

- Lecanemab 10 mg/kg biweekly (IV infusion)
- Placebo Biweekly (IV infusion)

Extension Phase (open-label)

- Lecanemab 10 mg/kg biweekly (IV infusion)

Randomization Phase Primary Outcome Measure:

CDR-SB: 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)

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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.

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

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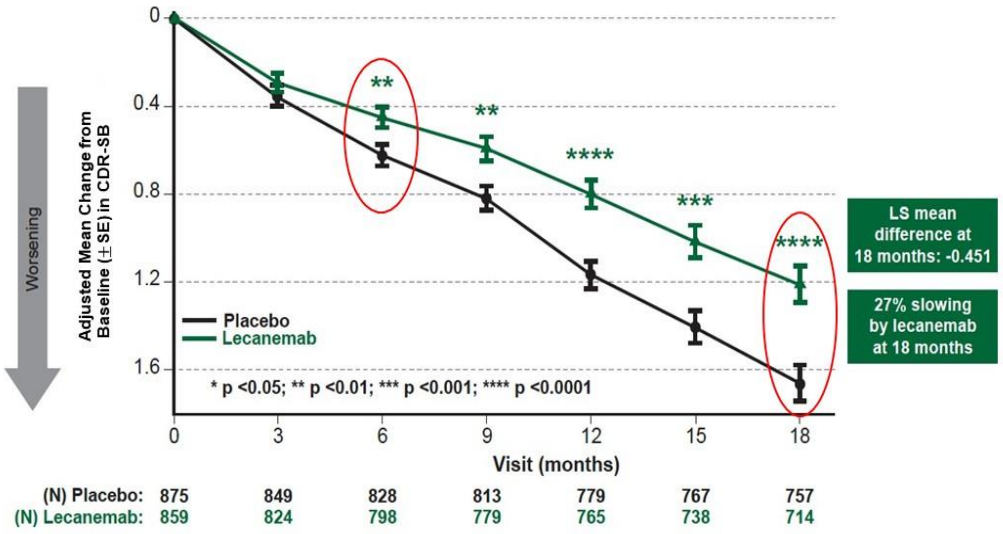
ADAS-Cog14, Alzheimer's Disease Assessment Scale–cognitive subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS ADL-MCI: Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for mild cognitive impairment (MCI) subjects; CDR-SB, Clinical Dementia Rating, sum of boxes;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

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



(N) Placebo:	875	849	828	813	779	767	757
(N) Lecanemab:	859	824	798	779	765	738	714

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.

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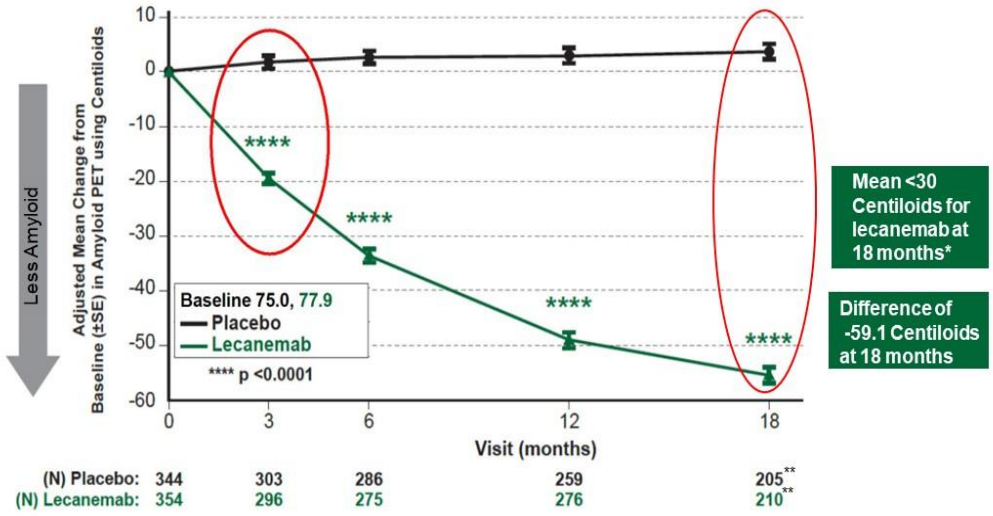
Amyloid PET:

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



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

*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.

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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.

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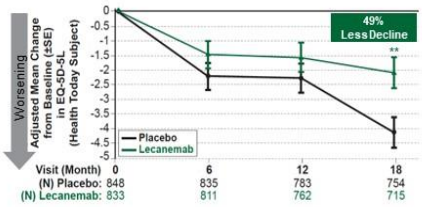
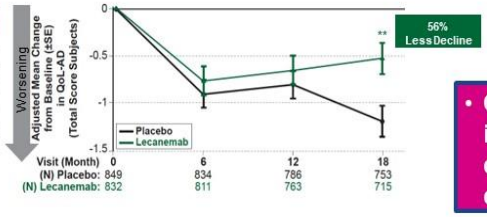
Health-Related Quality of Life Measures

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

EQ-5D-5L (Subject)



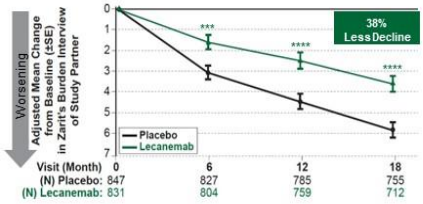
QOL-AD (Subject)



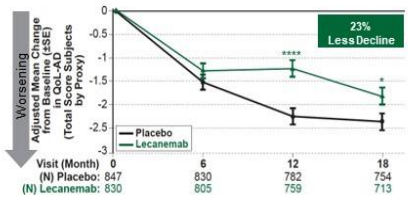
- **Consistent benefits seen in quality of life and caregiver burden across different scales**

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.

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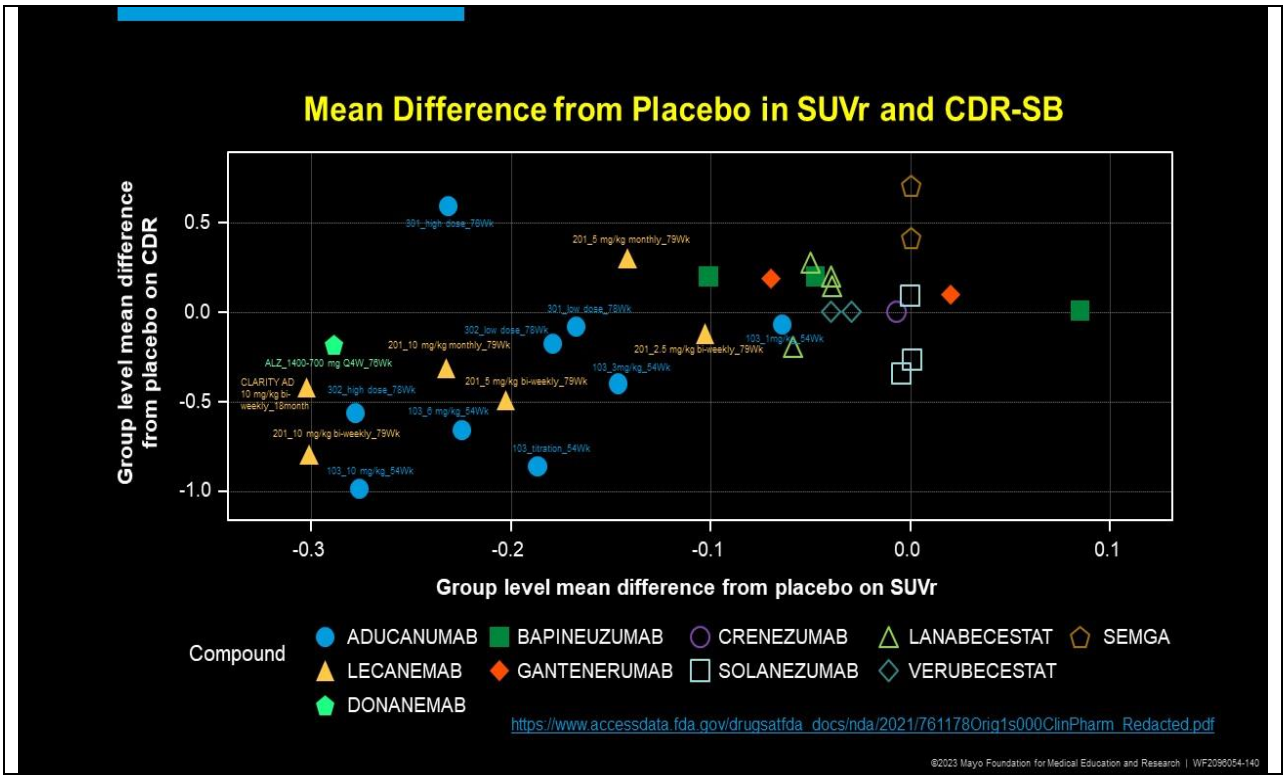
* P<0.05; ** P<0.01; *** P<0.001; **** P<0.0001

CLARITY AD
TOPLINE RESULTS

- N = 1795
- MCI and mild dementia due to AD
- 18 month study
- 27% slowing
- CDR-SB change of -0.45 SB relative to placebo
- Secondary measures: PET, ADAS-Cog 14, ADCOMS, ADCS-ADL significant
- ARIA E: 12.5% (2.8%) vs 1.7% (0.0%)
- ARIA H: 17% (0.7%) vs 8.7% (0.2%)

TRAILBLAZER-ALZ 2
TOPLINE RESULTS

- N = 1736
- MCI and mild dementia due to AD
- 18 month study
- Two levels of tau PET (intermediate and high)
- 40% slowing in intermediate; 23% combined
- Secondary measures: CDR-SB, ADCS iADL, ADAS Cog, significant
- 72% reduced to negative amyloid levels at 18 mo
- ARIA E: 24.0% (6.1%)
- ARIA H: 31.4% vs 13.6%


Mean Difference from Placebo in SUVr and CDR-SB
Group level mean difference from placebo on CDR
0.5
0.0
-0.5
-1.0
-0.3
-0.2
-0.1
0.0
0.1
Group level mean difference from placebo on SUVr
301_high dose_78Wk
201_5 mg/kg monthly_79Wk
301_low dose_78Wk
302_low dose_78Wk
201_10 mg/kg monthly_79Wk
103_1mg/kg_54Wk
201_2.5 mg/kg bi-weekly_79Wk
ALZ_1400-700 mg Q4W_76Wk
103_3mg/kg_54Wk
CLARITY AD 10 mg/kg bi-weekly_18month
302_high dose_78Wk
201_5 mg/kg bi-weekly_79Wk
103_6 mg/kg_54Wk
201_10 mg/kg bi-weekly_79Wk
103_titration_54Wk
103_10 mg/kg_54Wk
Compound
ADUCANUMAB
BAPINEUZUMAB
CRENEZUMAB
LANABECESTAT
SEMGA
LECANEMAB
GANTENERUMAB
SOLANEZUMAB
VERUBECESTAT
DONANEMAB
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000ClinPharm_Redacted.pdf
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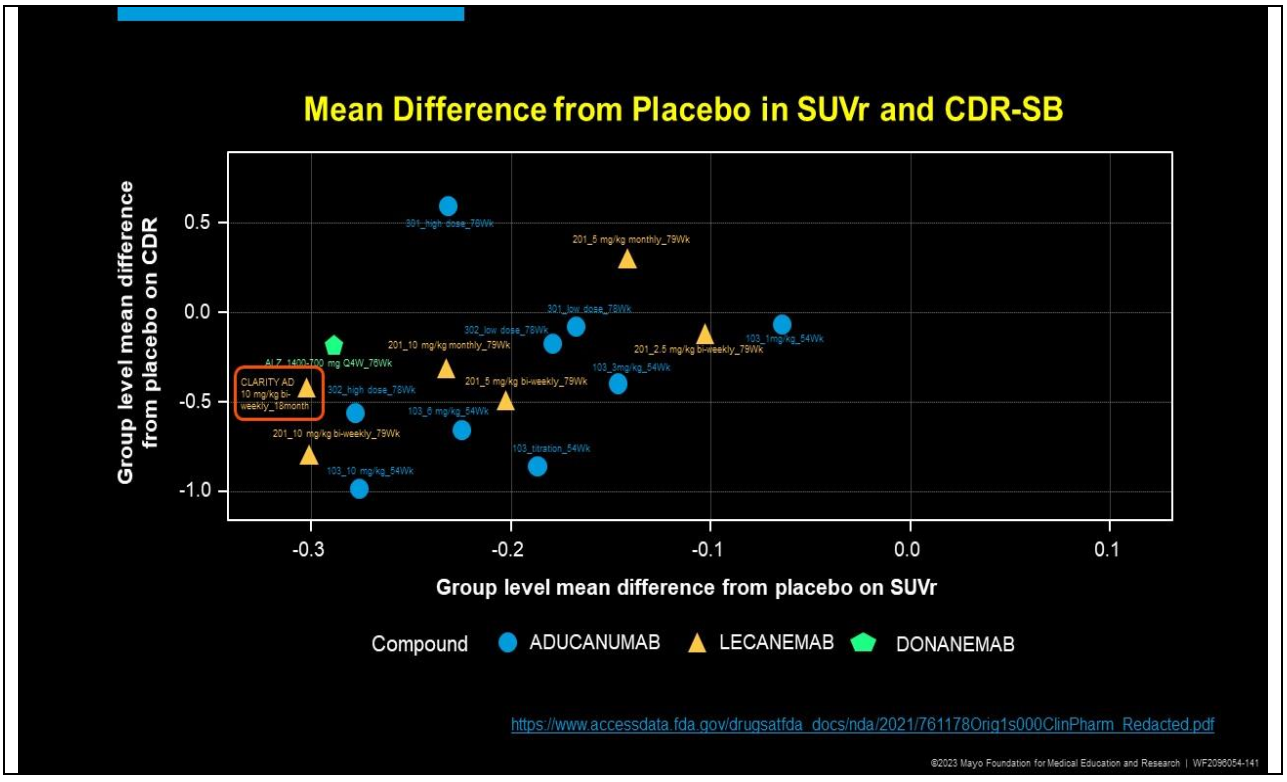
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201_2.5 mg/kg bi-weekly_79Wk
ALZ_1400-700 mg Q4W_76Wk
103_3mg/kg_54Wk
CLARITY AD 10 mg/kg bi-weekly_18month
302_high dose_78Wk
201_5 mg/kg bi-weekly_79Wk
103_6 mg/kg_54Wk
201_10 mg/kg bi-weekly_79Wk
103_titration_54Wk
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Compound
ADUCANUMAB
LECANEMAB
DONANEMAB
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000ClinPharm_Redacted.pdf
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WHAT ARE REASONABLE CLINICAL EXPECTATIONS OF INTERVENTIONS WITH ALZHEIMER'S DISEASE THERAPIES?

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DOI: 10.1002/alz.12959

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

PERSPECTIVE

Expectations and clinical meaningfulness of randomized controlled trials

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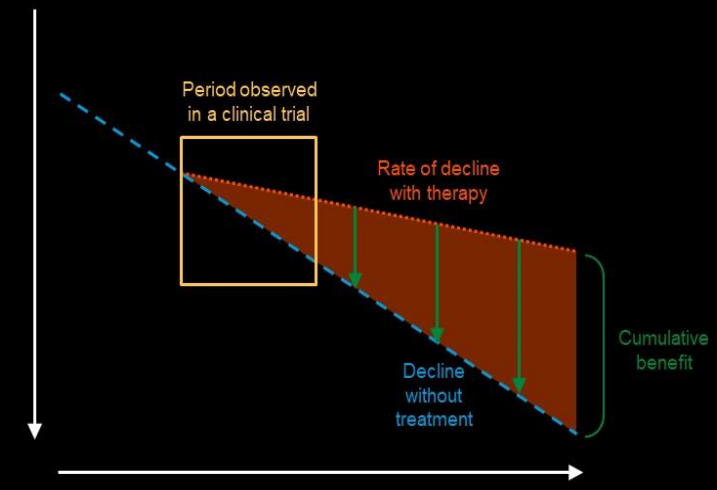
Abstract

Alzheimer's disease (AD) clinical trials are designed and powered to detect the impact of a therapeutic intervention, and there has been considerable discussion on what constitutes a clinically meaningful change in those receiving treatment versus placebo. The pathology of AD is complex, beginning many years before clinical symptoms are detectable, with multiple potential opportunities for therapeutic engagement. Introducing treatment strategies early in the disease and assessing meaningful change over the course of an 18-month clinical trial are critical to understanding the value to an effective intervention. With new clinical trial data expected soon on emerging therapeutics from several AD studies, the Alzheimer's Association convened a work group of experts to discuss key considerations for interpreting data from cognitive and

CLINICAL EXPECTATIONS AND MEANINGFULNESS

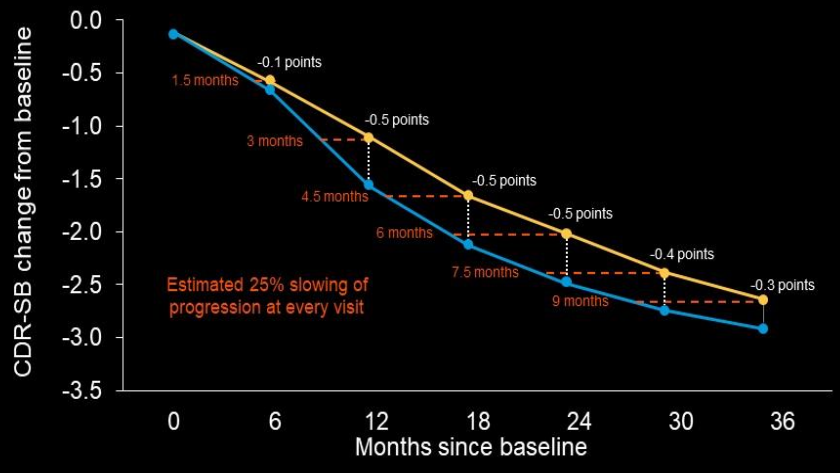
- Temporal evolution of pathophysiology
- Length of RCT
- Cumulative benefit over time
- Meaningfulness of clinical benefit
- Multiple pathologies active

CUMULATIVE BENEFIT OVER TIME FROM A DMT



Petersen et al: Alzheimer's and Dementia, 2023

POTENTIAL PRESERVATION OF FUNCTION

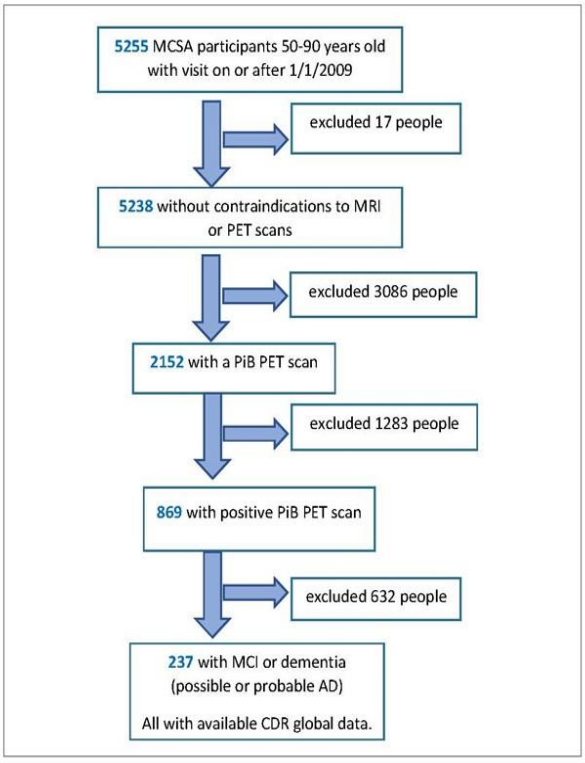


Petersen et al: Azheimer's and Dementia, 2023)

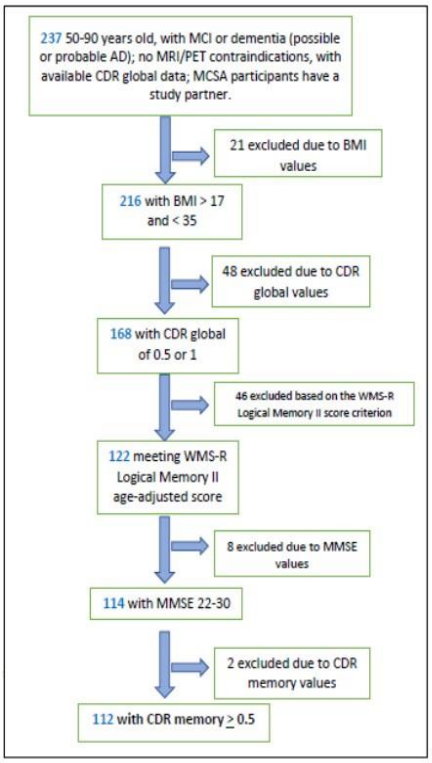
Mayo Clinic Study of Aging

Population-based study of 6000+ (3000 active) persons without dementia ages 30-89 years in Olmsted County, MN

Selection of the study sample.



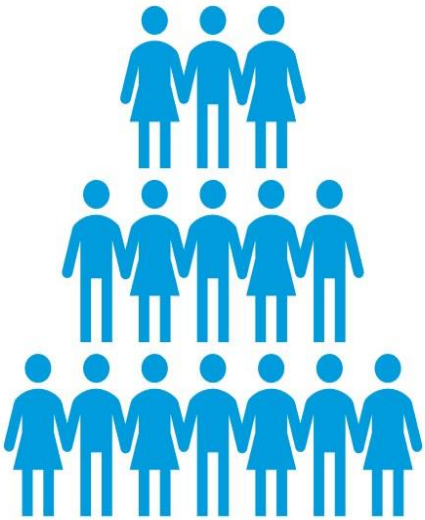
Inclusion criteria used in present study for lecanemab



CONCLUSION

Modifying the inclusion criteria to include all participants with MCI (instead of applying additional cognitive criteria) **increased the fraction** of potentially eligible participants from **8% to 17.4%**.

Implication: Many fewer people will actually be eligible for treatment than suspected



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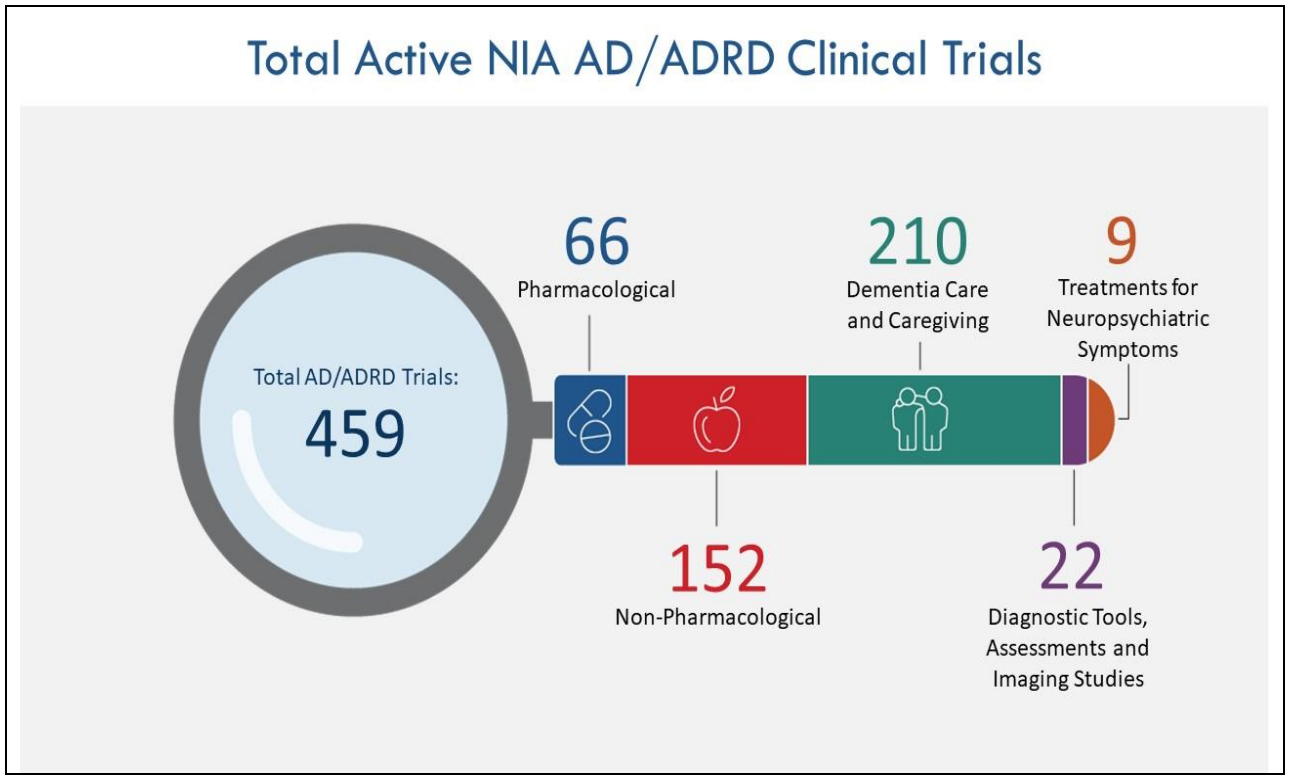
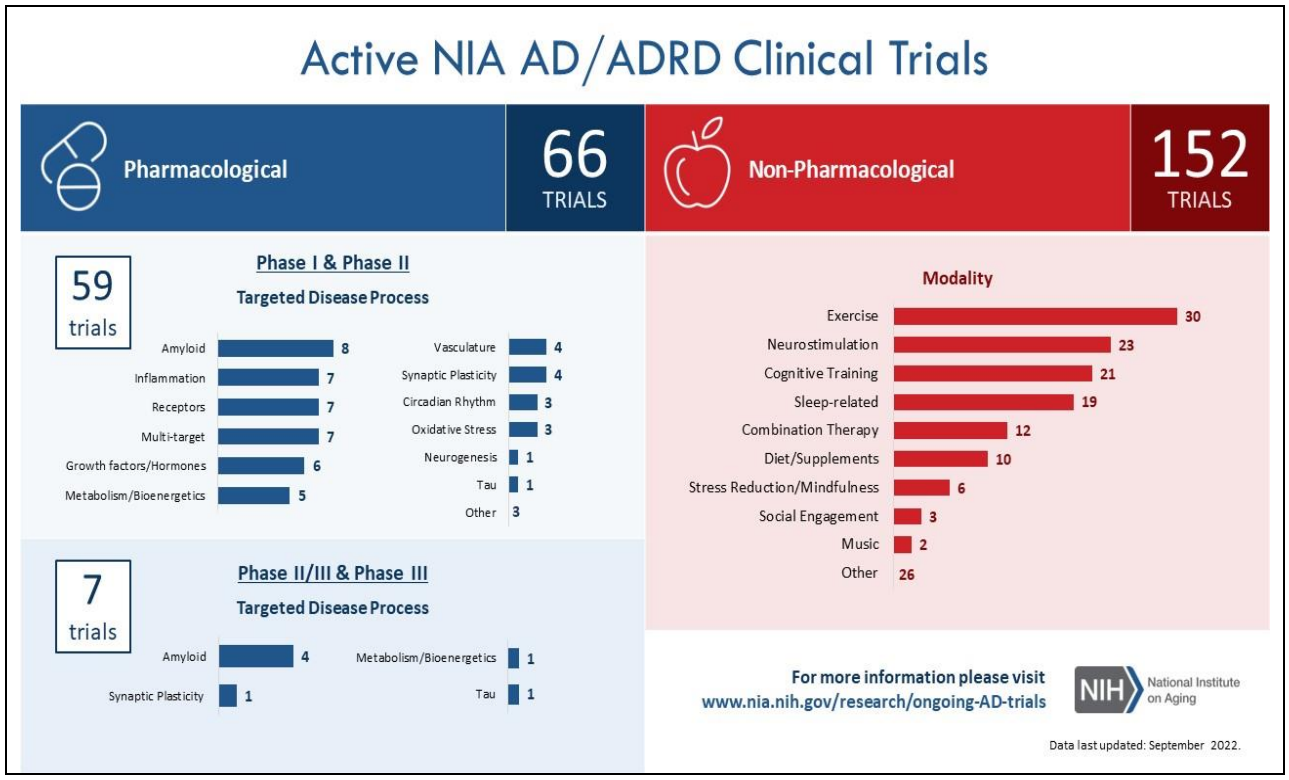
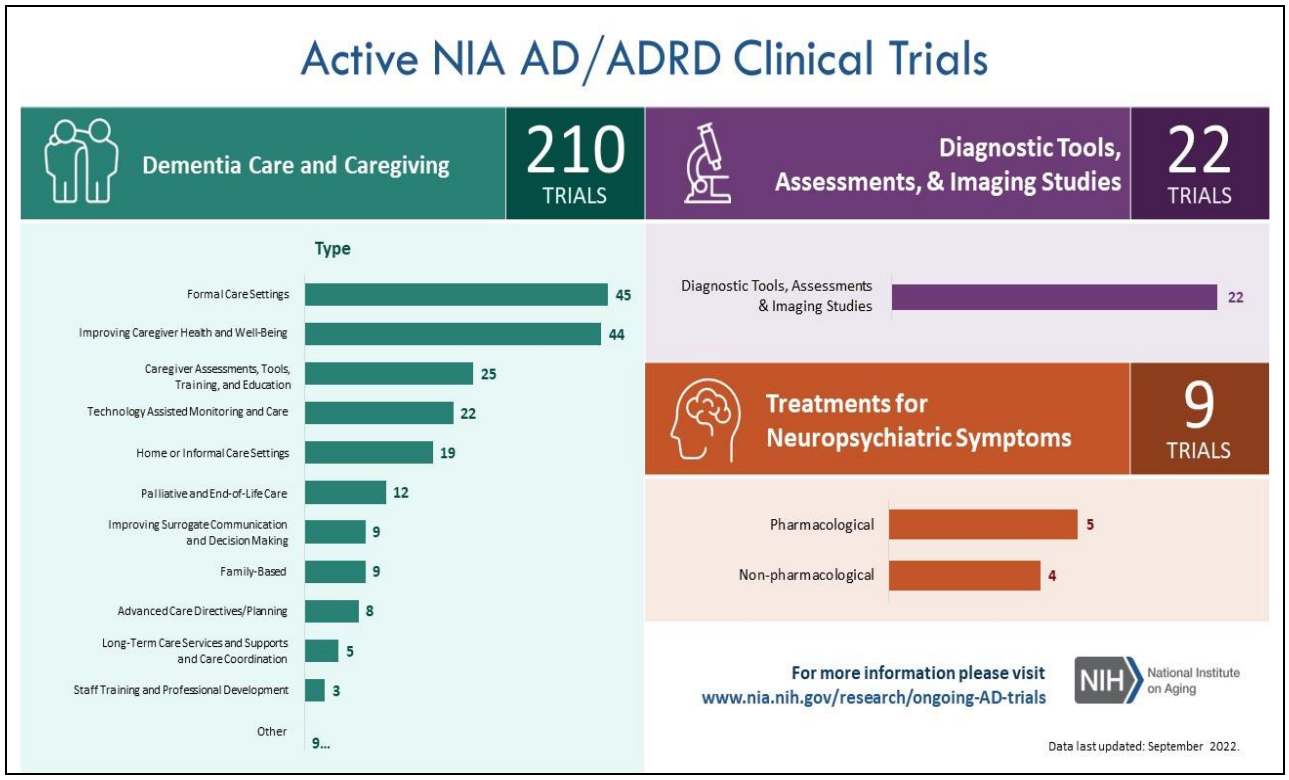
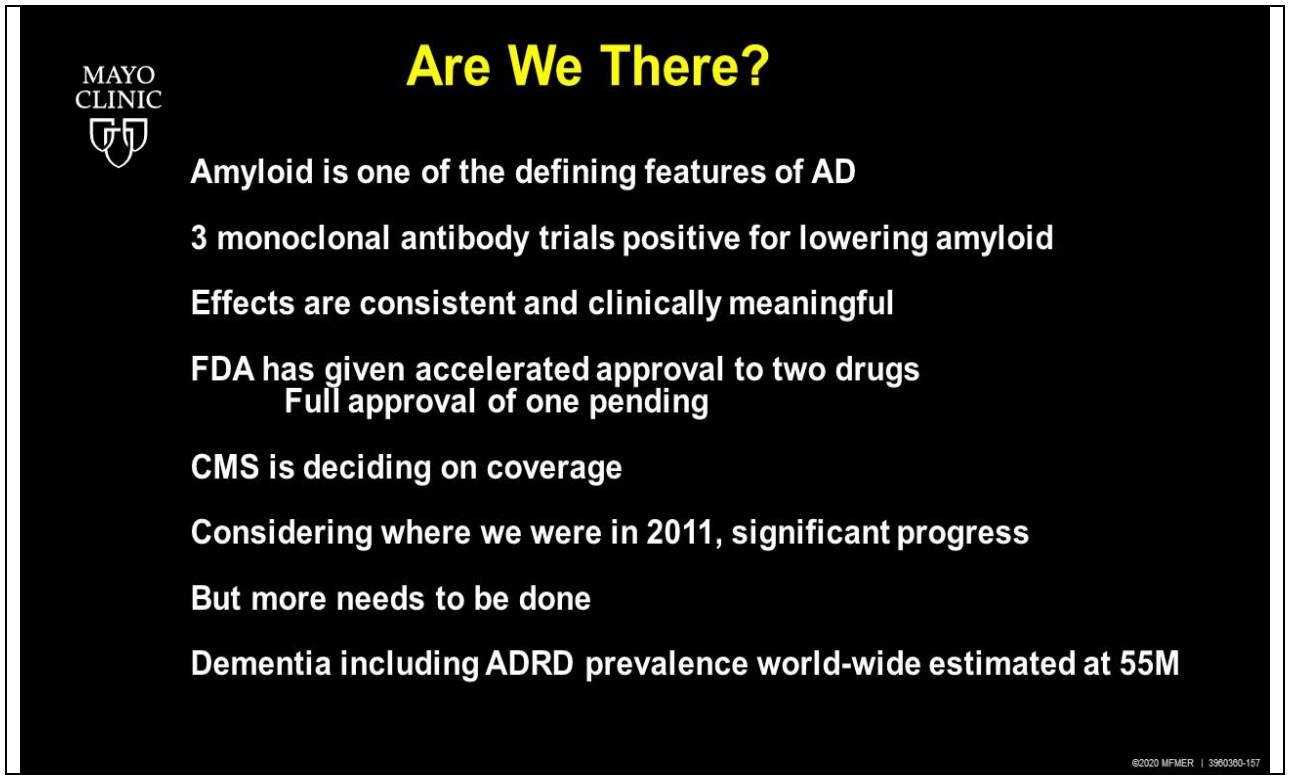
Have We Made Progress?


Total Active NIA AD/ADRD Clinical Trials
Total AD/ADRD Trials:
459
66
Pharmacological
152
Non-Pharmacological
210
Dementia Care and Caregiving
9
Treatments for Neuropsychiatric Symptoms
22
Diagnostic Tools, Assessments and Imaging Studies


Active NIA AD/ADRD Clinical Trials
Pharmacological
66
TRIALS
Non-Pharmacological
152
TRIALS
59
trials
Phase I & Phase II
Targeted Disease Process
Amyloid 8
Inflammation 7
Receptors 7
Multi-target 7
Growth factors/Hormones 6
Metabolism/Bioenergetics 5
Vasculature 4
Synaptic Plasticity 4
Circadian Rhythm 3
Oxidative Stress 3
Neurogenesis 1
Tau 1
Other 3
7
trials
Phase II/III & Phase III
Targeted Disease Process
Amyloid 4
Synaptic Plasticity 1
Metabolism/Bioenergetics 1
Tau 1
Modality
Exercise 30
Neurostimulation 23
Cognitive Training 21
Sleep-related 19
Combination Therapy 12
Diet/Supplements 10
Stress Reduction/Mindfulness 6
Social Engagement 3
Music 2
Other 26
For more information please visit
www.nia.nih.gov/research/ongoing-AD-trials
NIH National Institute on Aging
Data last updated: September 2022.


Active NIA AD/ADRD Clinical Trials
Dementia Care and Caregiving
210
TRIALS
Type
Formal Care Settings 45
Improving Caregiver Health and Well-Being 44
Caregiver Assessments, Tools, Training, and Education 25
Technology Assisted Monitoring and Care 22
Home or Informal Care Settings 19
Palliative and End-of-Life Care 12
Improving Surrogate Communication and Decision Making 9
Family-Based 9
Advanced Care Directives/Planning 8
Long-Term Care Services and Supports and Care Coordination 5
Staff Training and Professional Development 3
Other 9...
Diagnostic Tools, Assessments, & Imaging Studies
22
TRIALS
Diagnostic Tools, Assessments & Imaging Studies 22
Treatments for Neuropsychiatric Symptoms
9
TRIALS
Pharmacological 5
Non-pharmacological 4
For more information please visit
www.nia.nih.gov/research/ongoing-AD-trials
NIH National Institute on Aging
Data last updated: September 2022.


MAYO CLINIC
Are We There?
Amyloid is one of the defining features of AD
3 monoclonal antibody trials positive for lowering amyloid
Effects are consistent and clinically meaningful
FDA has given accelerated approval to two drugs
Full approval of one pending
CMS is deciding on coverage
Considering where we were in 2011, significant progress
But more needs to be done
Dementia including ADRD prevalence world-wide estimated at 55M
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Residual Issues

Who should administer these therapies initially?
- Specialists, generalists, PCP's?
- Screening: blood, PET, CSF?

Implications of a CED for coverage
- Might it increase disparities?
- Will it reduce access?
- Will its administrative requirements discriminate?

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THANK YOU