LOUISIANA DEPARTMENT OF HEALTH

Emerging Treatments

Healthy Aging & ADRD Echo

June 17,2025

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Disclosure(s)

- **Anne-Foundas, MD**

In the past 24 months, I have NOT had any financial relationships with any ineligible companies.

- **Elizabeth Disbrow, Phd**

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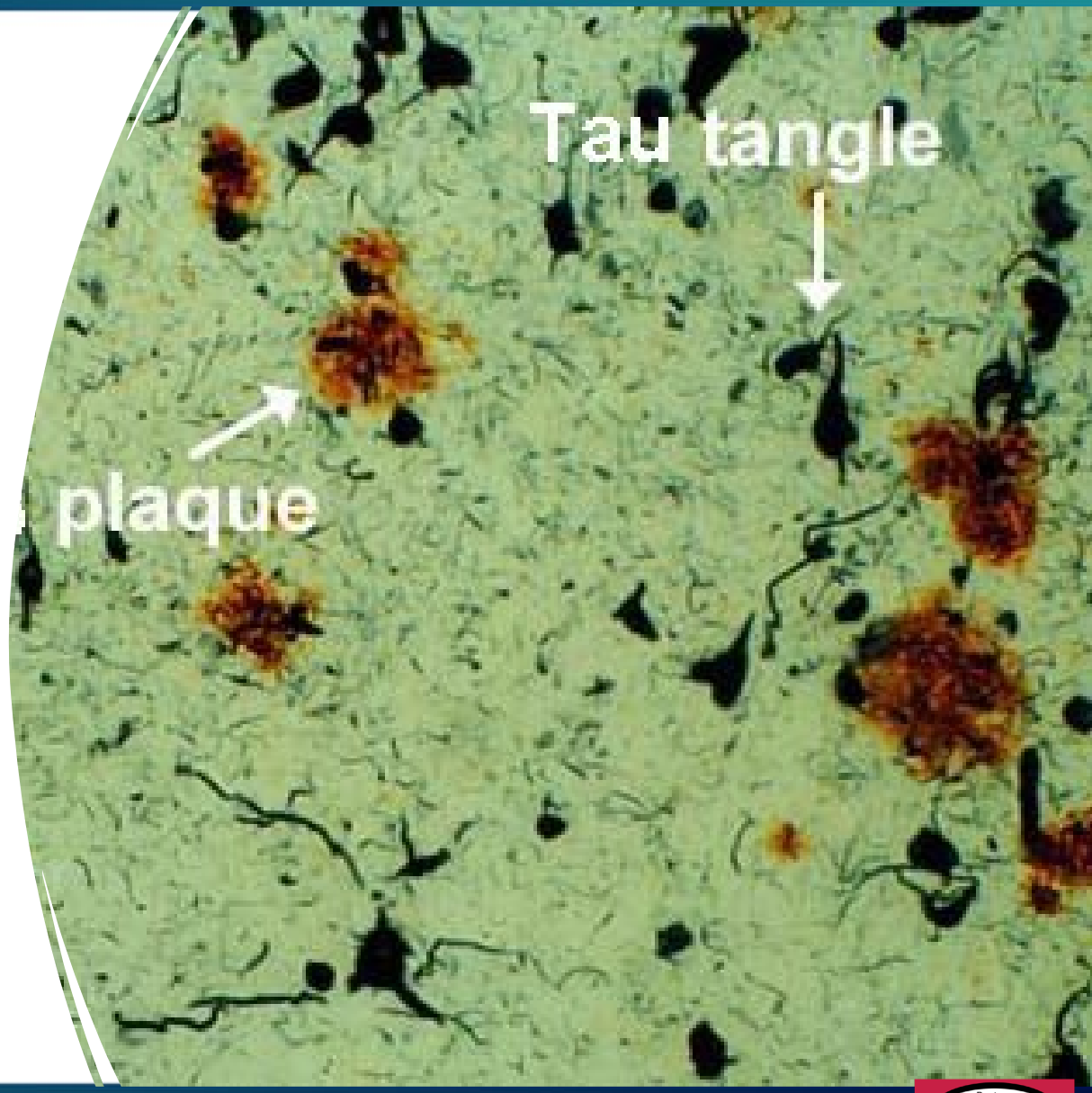
Objectives

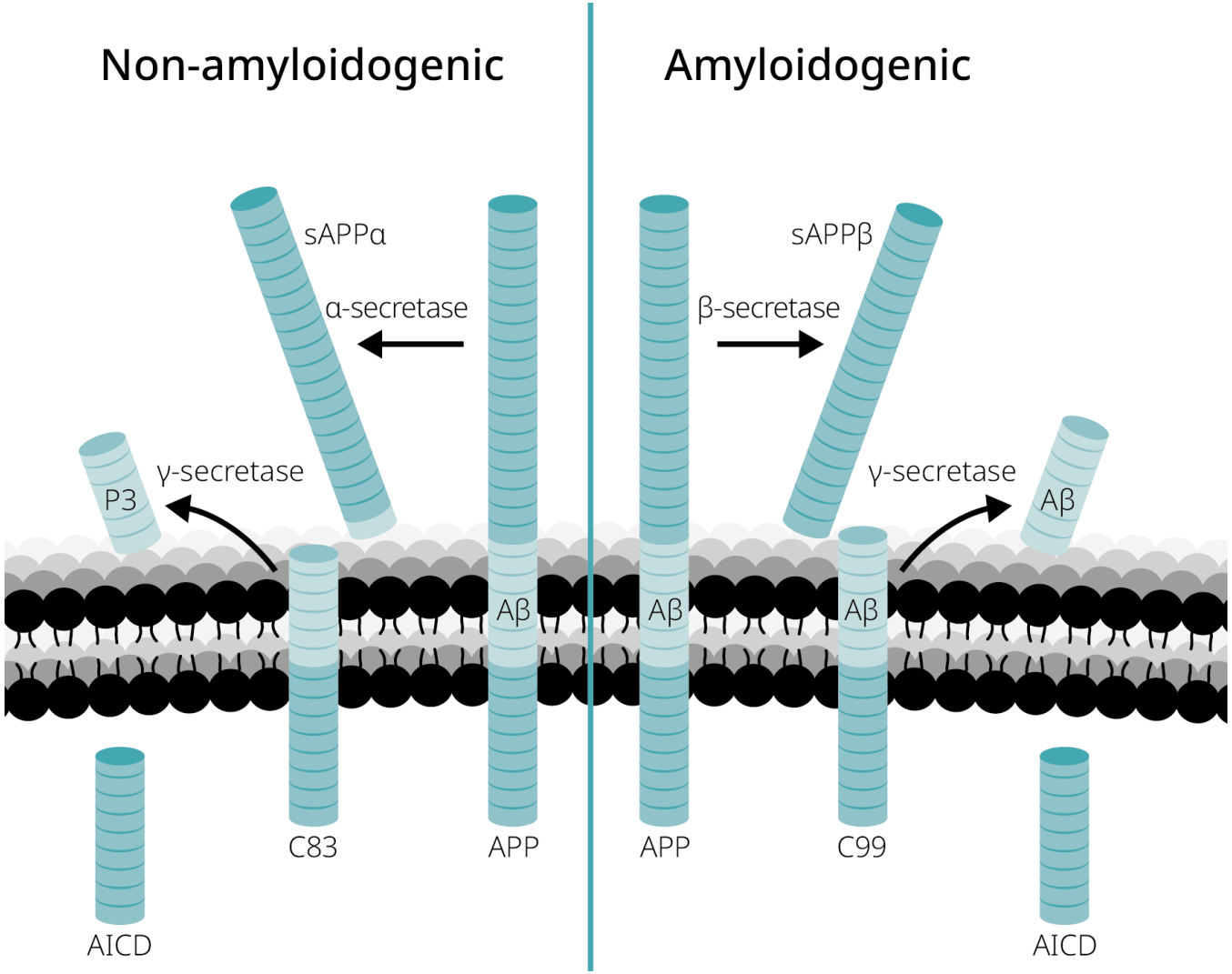
1. Understand the mechanism, effectiveness and side effects of available treatments

2. Learn more about treatments currently under investigation

Background



Modifiable Disease Mechanism



- Most of the Aβ peptides are 40 residues in length (Aβ 1–40)
- A small percentage contain 42 residues (Aβ 1–42).
- Aβ 1–42 is considered the more neurotoxic form because the extra two amino acids provide a greater tendency to misfold and subsequently aggregate
- Elevated plasma levels of Aβ 1–42 have been correlated with Alzheimer's disease
- A low Aβ 42/40 ratio also suggests a higher risk of AD

Adapted from: abcam.com/neuroscience/beta-amyloid-and-tau-in-alzheimers-disease

JAMA Neurology | Original Investigation

Prevalence and Outcomes of Amyloid Positivity Among Persons Without Dementia in a Longitudinal, Population-Based Setting

- One-quarter of people with normal cognition or subjective cognitive decline had amyloid plaques
- Half of people with mild cognitive impairment had amyloid plaques
- Nearly 90 percent of people with a clinical diagnosis of AD had amyloid plaques
- A third of cognitively normal people over 70 have amyloid
- ApoE4 carriers have steeper increases with age

JAMA Neurol. 2018 Aug 1;75(8):970-979

THE GENETICS OF ALZHEIMER'S DISEASE

- The APOE gene makes proteins that carry cholesterol and other types of fat in the blood stream.
- The APOE 4 allele is the best studied risk-factor gene for late onset AD
- About 25% of people have one copy of the APOE 4 allele
- 40-65% of people with AD have at least one copy of the APOE 4 allele

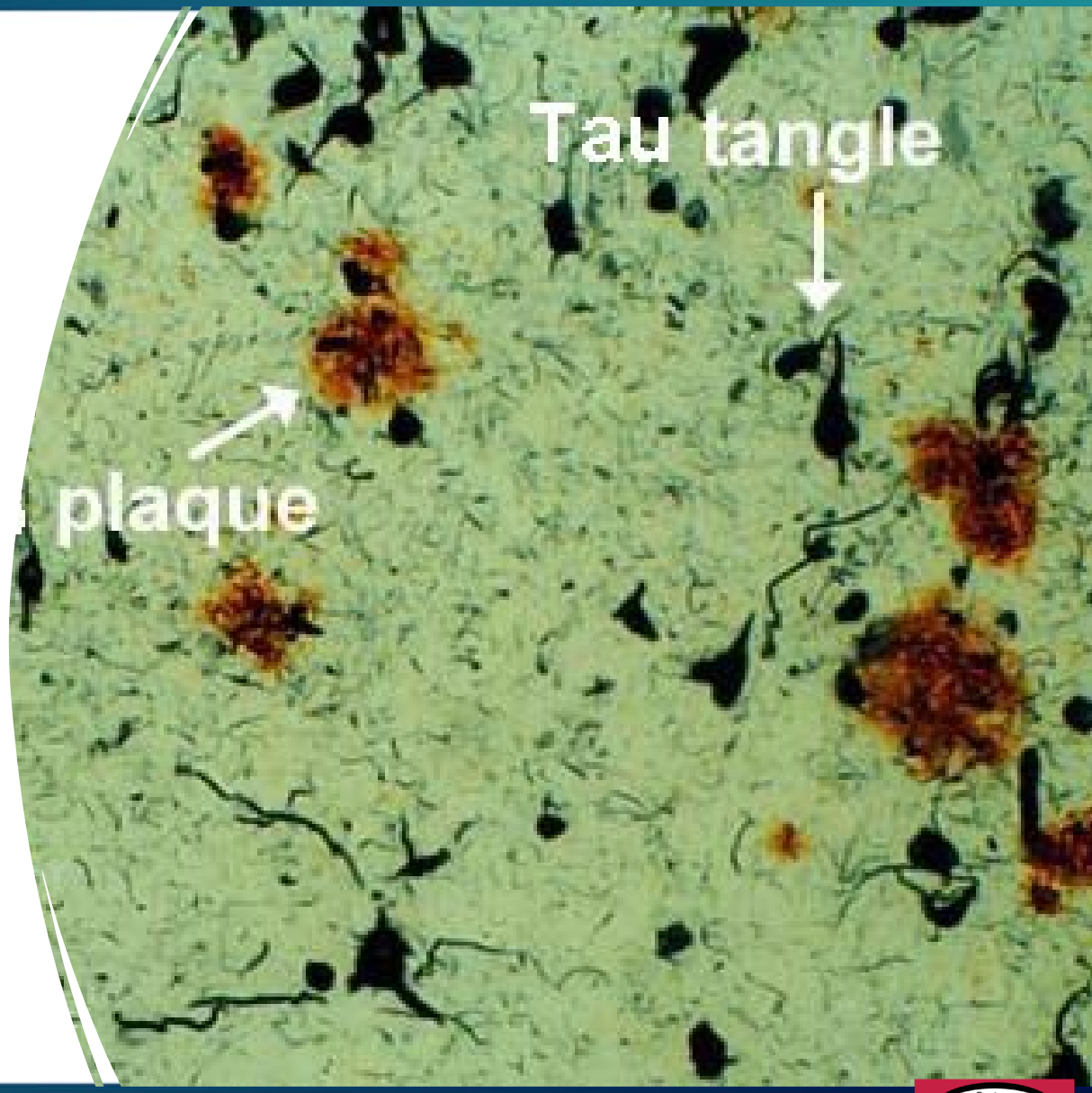
Medical Xpress

Current Treatments

Monoclonal antibodies bind and remove amyloid plaques from the brain

They target and clear the most neurotoxic form of Aβ

They induce an immune response to remove continuously accumulating as well as existing plaques



There are currently two FDA approved monoclonal antibodies:

1. **Lecanemab (Leqembi)** from Eisai
2. **Kisuna (Donanemab)** from Eli Lilly & Co.

- They should be used for people with mild cognitive impairment or mild dementia, as these were the individuals who participated in the clinical trials testing the drug.
- There is no evidence of benefit for individuals in the moderate to severe stages of Alzheimer's disease or other types of dementia.
- They are not a cure for Alzheimer's disease, but it may help to slow the progression of the disease.

The NEW ENGLAND JOURNAL of MEDICINE

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Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

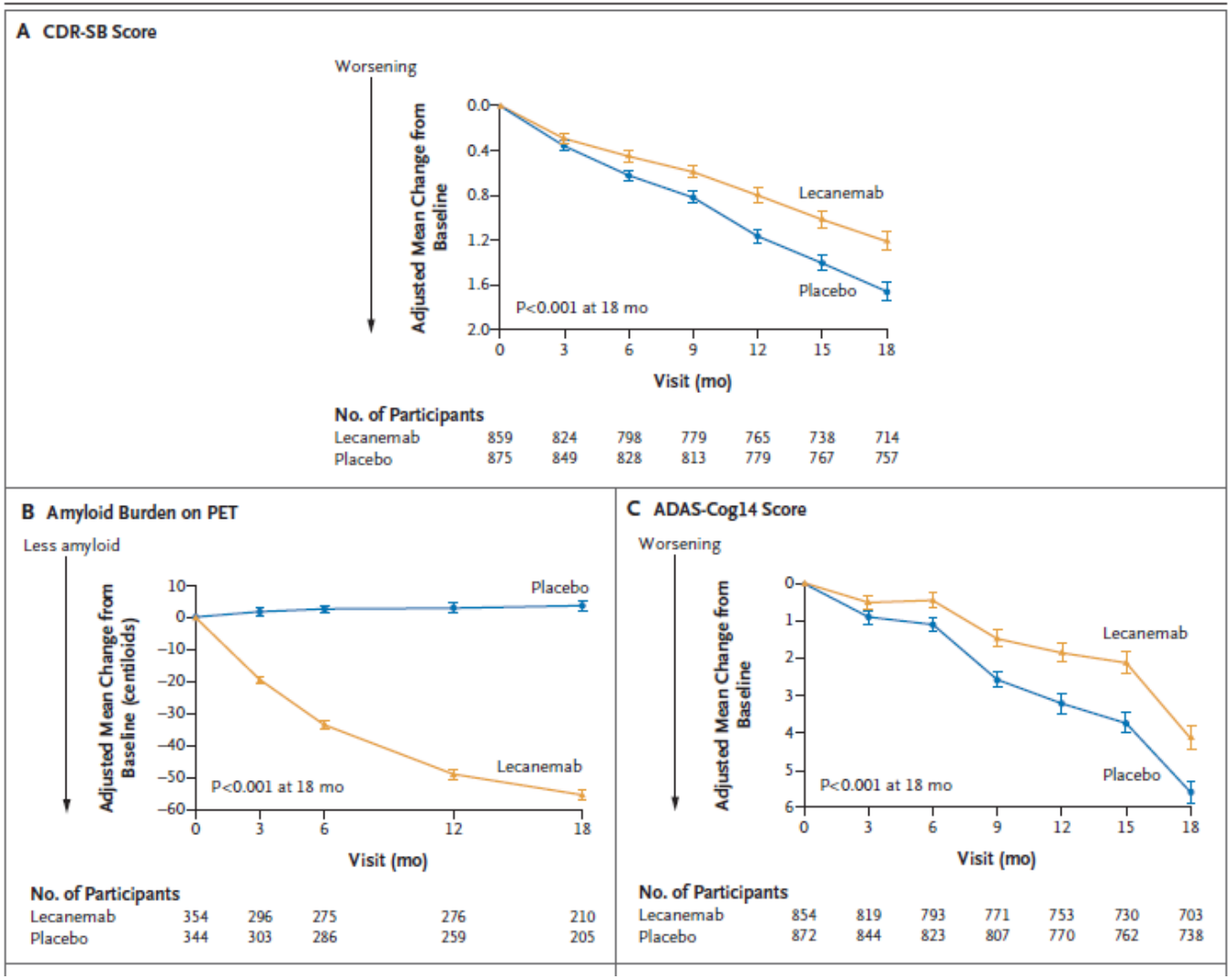
METHODS

The study was an 18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years of age with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on positron emission tomography (PET) or by cerebrospinal fluid testing.

Participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab or placebo. A total of 1795 participants were enrolled, with 898 assigned to receive lecanemab and 897 to receive placebo.

The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating–Sum of Boxes. CDR measures six different cognitive and behavioral domains such as memory, orientation, judgment and problem solving, community affairs, home and hobbies performance, and personal care.

The NEW ENGLAND JOURNAL of MEDICINE



A.Clinical dementia rating – sum of boxes baseline score was 3.2 in both groups, MCI 0.5-6

B.Amyloid baseline was about 75

C. Baseline score was 24

Van Dyke et al., 2023

Incidence of ARIA

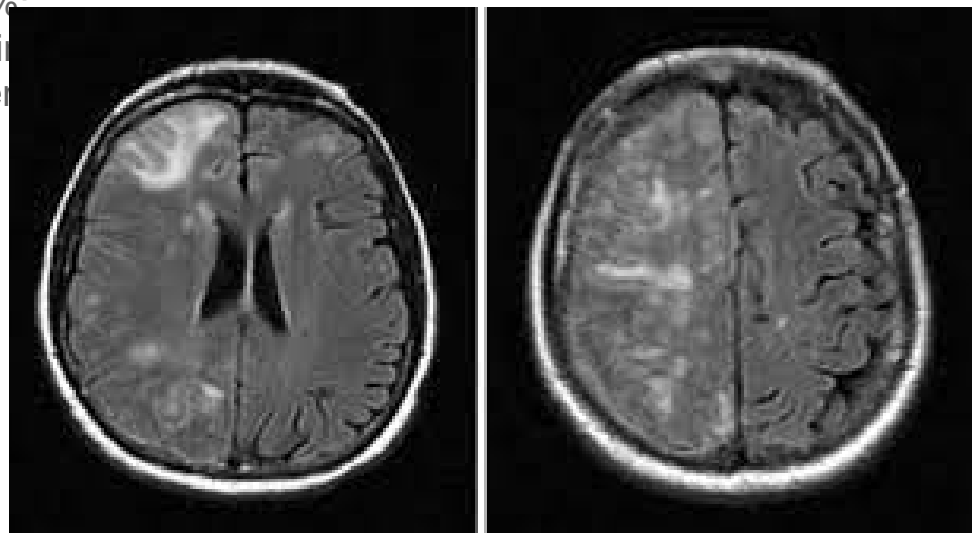
•Including asymptomatic radiographic events, ARIA was observed in LEQEMBI: 21% (191/898); placebo: 9% (84/897).

•In Study 2, symptomatic ARIA occurred in 3% (29/898) of LEQEMBI-treated patients. Serious symptoms associated with ARIA were reported in 0.7% (6/898) of patients treated with LEQEMBI. Clinical symptoms associated with ARIA resolved in 79% (23/29) of patients during the period of observation.

ApoE ε4 Carrier Status and Risk of ARIA

•In Study 2, 16% (141/898) of patients in the LEQEMBI arm were ApoE ε4 homozygotes, 53% (479/898) were heterozygotes, and 31% (278/898) were noncarriers.

•The incidence of ARIA was higher in ApoE ε4 homozygotes (LEQEMBI: 45%; placebo: 22%) than in heterozygotes (LEQEMBI: 19%; placebo: 9%) and noncarriers (LEQEMBI: 13%; placebo: 4%). Among patients treated with LEQEMBI, symptomatic ARIA-E occurred i of ApoE ε4 homozygotes compared with 2% of heterozygotes and 1% noncarriers. Se events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and noncarriers.



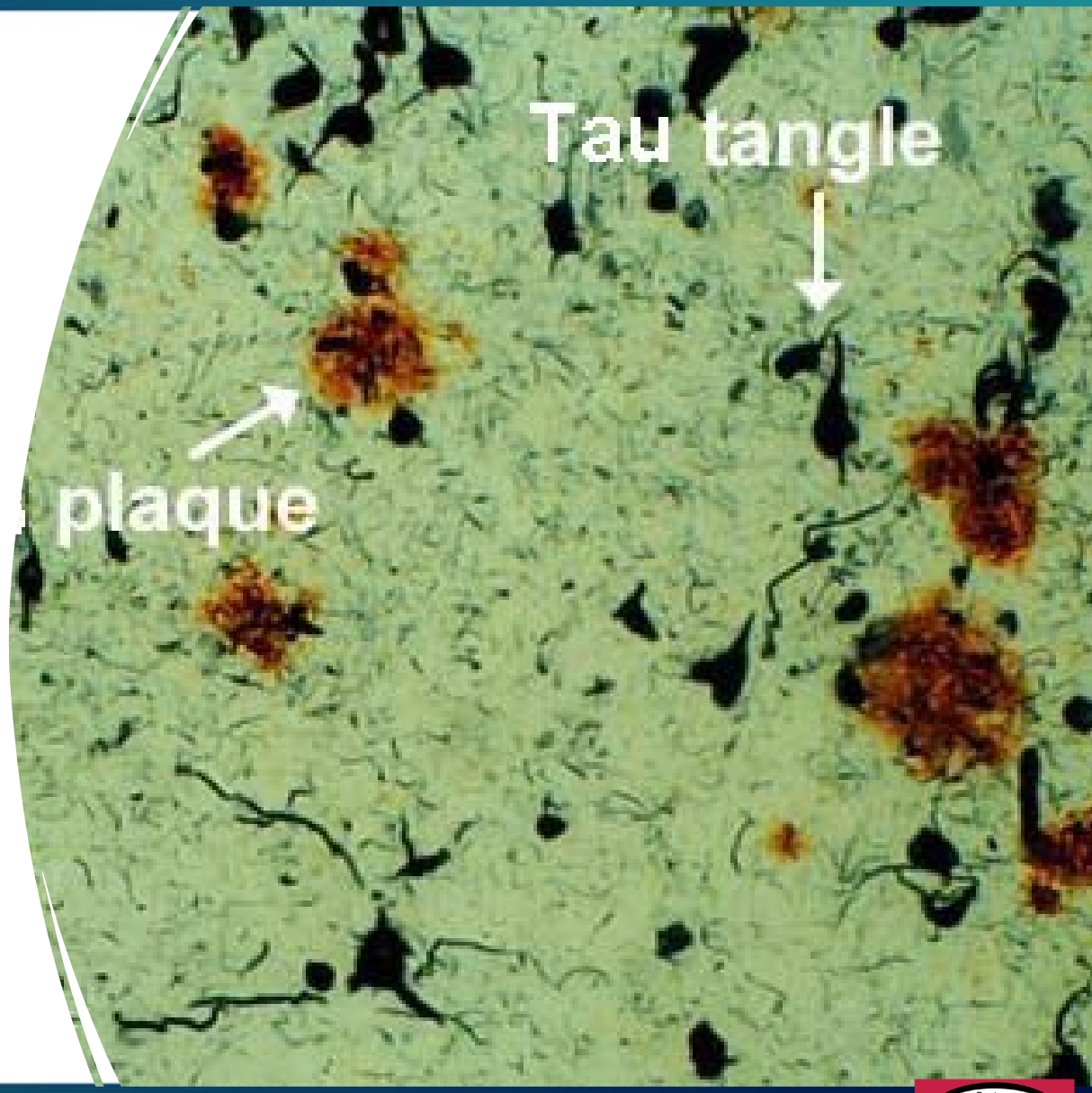
ARIA is a side effect that does not usually cause any symptoms, but serious symptoms can occur. ARIA is most commonly seen as temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain, and infrequently, larger areas of bleeding in the brain can occur. Most people with this type of swelling in the brain do not get symptoms, however some people may have symptoms, such as:

- headache
- confusion
- dizziness
- vision changes
- nausea
- difficulty walking
- seizures
- hemorrhage

- Results (both benefits and side effects) are similar for Kisunla and can be seen here: https://kisunla.lilly.com/hcp/efficacy#riskreductiondata

- An important difference is that Kisunla is administered once a month, compared to Leqembi, which is administered every 2 weeks.

Screening Process



Screening:

Cognitive evaluation (MOCA or MMSE ≥21)

Confirmation of the presence of beta amyloid – PET or CSF w/in 1 year

APOE4 test recommended but not required

Rule out other causes: Lewy body dementia, vascular dementia, frontotemporal dementia, Parkinson's disease, med interaction, vitamin deficiency, stroke

Med Check:

antiplatelet meds OK: aspirin, clopidogrel, ticagrelor, and prasugrel, cilostazol, and dipyridamole.

anticoagulants not OK: unfractionated and low molecular weight heparin, warfarin, and direct thrombin inhibitors

Screening can take weeks!

Treatment:

Intravenous infusion every two (Leqembi) or 4 (Kisunla) weeks that takes about an hour

Periodic imaging to evaluate side effects

Your doctor will submit data to better understand how well the new medication works as part of the process for ensuring coverage by Medicare

Coverage:

Both are covered by Medicare Part B and Advantage plans but cost for the drug will vary by plan

PET screening is also covered, while CSF analysis lacks national coverage at this time.

Drugs Under Investigation

Phases of Clinical Research

Phase 1: Testing safety and determining dosage in a small group of healthy volunteers.

Phase 2: Testing effectiveness and side effects in a larger group of patients with the target condition.

Phase 3: Testing effectiveness and safety compared to existing treatments in a large group of patients.

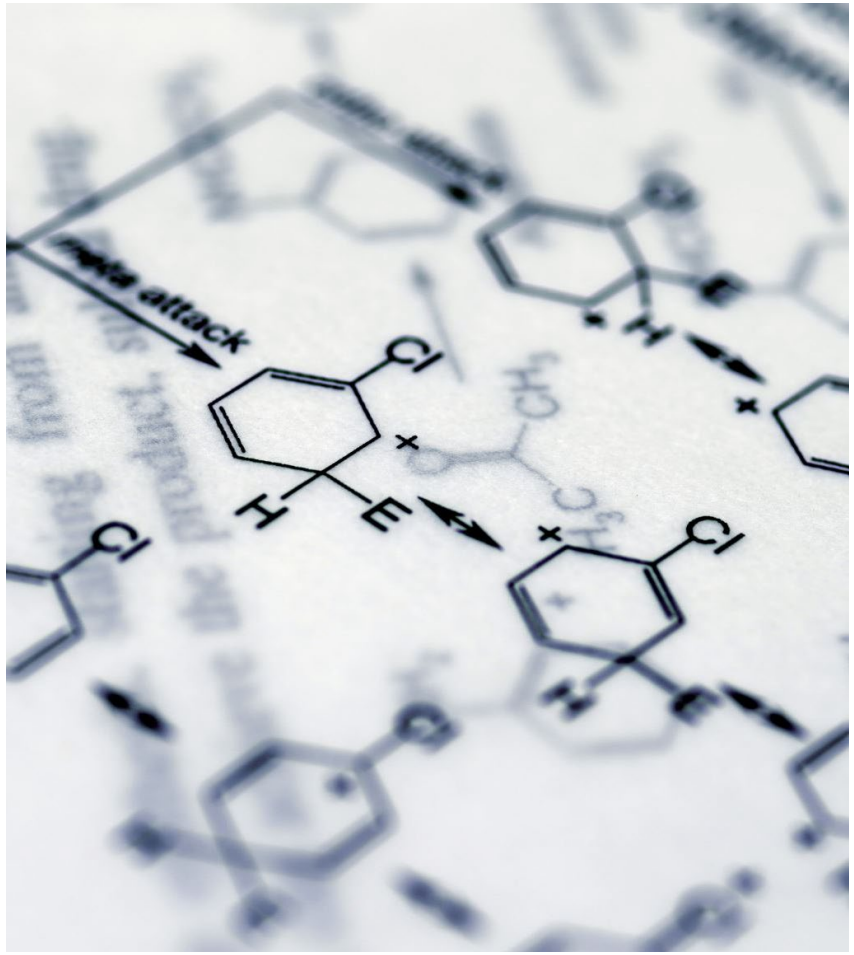
4. FDA Review: The drug developer submits a New Drug Application (NDA) to the FDA for review.

5. Post-Market Safety Monitoring: Once approved, the FDA continues to monitor the drug's safety and effectiveness after it's available on the market. This can include Phase 4 clinical trials.

Additional Anti-Amyloid Treatments

- Lilly is currently testing Remternetug, another anti-amyloid antibody, in a 1,667-person Phase 3 trial. They are concurrently testing an intravenous and an injectable version, which uses a delivery device similar to an EpiPen. The trial will finish in early 2026.
- Investigators at the Washington University School of Medicine are studying Remternetug as a preventative in a trial called DIAN-TU-002. The trial is specifically focused on people at high risk for early-onset Alzheimer's due to genetic mutations (homozygous APOE 4), aiming to intervene before significant symptoms emerge. This long-term, placebo control Phase 2/3 clinical study is enrolling 240 participants as young as 18. This trial will test Remternetug against a placebo for 3.5 years, giving all participants the option to take the drug after the study ends. Results from this study are expected in 2034.

Pill for Amyloid Treatment



- A 325-person Phase 3 trial of a disease-modifying pill valiltramiprosate, or ALZ-801 was completed last year by Alzheon.
- Rather than removing toxic plaques like anti-amyloid drugs, this pill prevents healthy forms of beta-amyloid from turning toxic.
- The drug is being tested as a treatment for people with two copies of the Alzheimer's risk gene ApoE4.
- The company has not yet published the results.
- Alzheon has not yet disclosed when they plan to file for FDA approval in the U.S. and Europe.

Anti-Tau Treatments

BIIB080 (Biogen):

This investigational therapy is designed to reduce tau protein production by targeting the mRNA of the microtubule-associated protein tau. Phase 1b trials showed positive cognitive trends and reduced tau levels in the cerebrospinal fluid. Phase 2 CELIA trials are ongoing, with data expected in 2026.

Posdinemab (Johnson & Johnson):

This monoclonal antibody targets phosphorylated tau to potentially slow cognitive decline in early Alzheimer's disease. The FDA has granted a Fast Track designation for posdinemab, highlighting its potential as a treatment for early-stage Alzheimer's. The AuTonomy study, a Phase 2b trial, uses a plasma biomarker to screen patients and evaluate posdinemab's efficacy.

Vaccines

ACI-24.060 (AC Immune SA in partnership with Takeda):

An amyloid-targeting vaccine is being evaluated for AD prevention in people with Down syndrome. In a phase 2 study, 140 people will be tested over 1.5 years to confirm efficacy and safety, with results expected in 2026. If successful, a Phase 3 trial would follow.

JNJ-2056 (AC Immune, in partnership with Jannsen)

Testing of an experimental tau vaccine Phase 2 study is in the planning stage. The four-year trial will involve 498 cognitively healthy participants.

Repurposed Drugs

Alzforum AR1001 (AriBio)

There is accumulating evidence that Viagra reduces risk for AD, possibly due to beneficial vascular effects. To test this hypothesis, AriBio will finish a 1,150-person Phase 3 trial testing AR1001, a pill originally developed for erectile dysfunction, in early AD. The trial will finish at the end of 2025.

Semaglutide (Novo Nordisk)

The diabetes drug semaglutide (brand names Wegovy, Ozempic) a GLP-1 agonist used to treat diabetes and weight loss and potentially heart attacks and stroke. A 1,840-person Phase 3 trial ending in Sept. of 2025 will show whether a pill form of the drug could successfully treat the early stages of AD.

AD Prevention

<u>AHEAD 3-45</u>: Leqembi for Alzheimer's prevention (Biogen & Eisai)

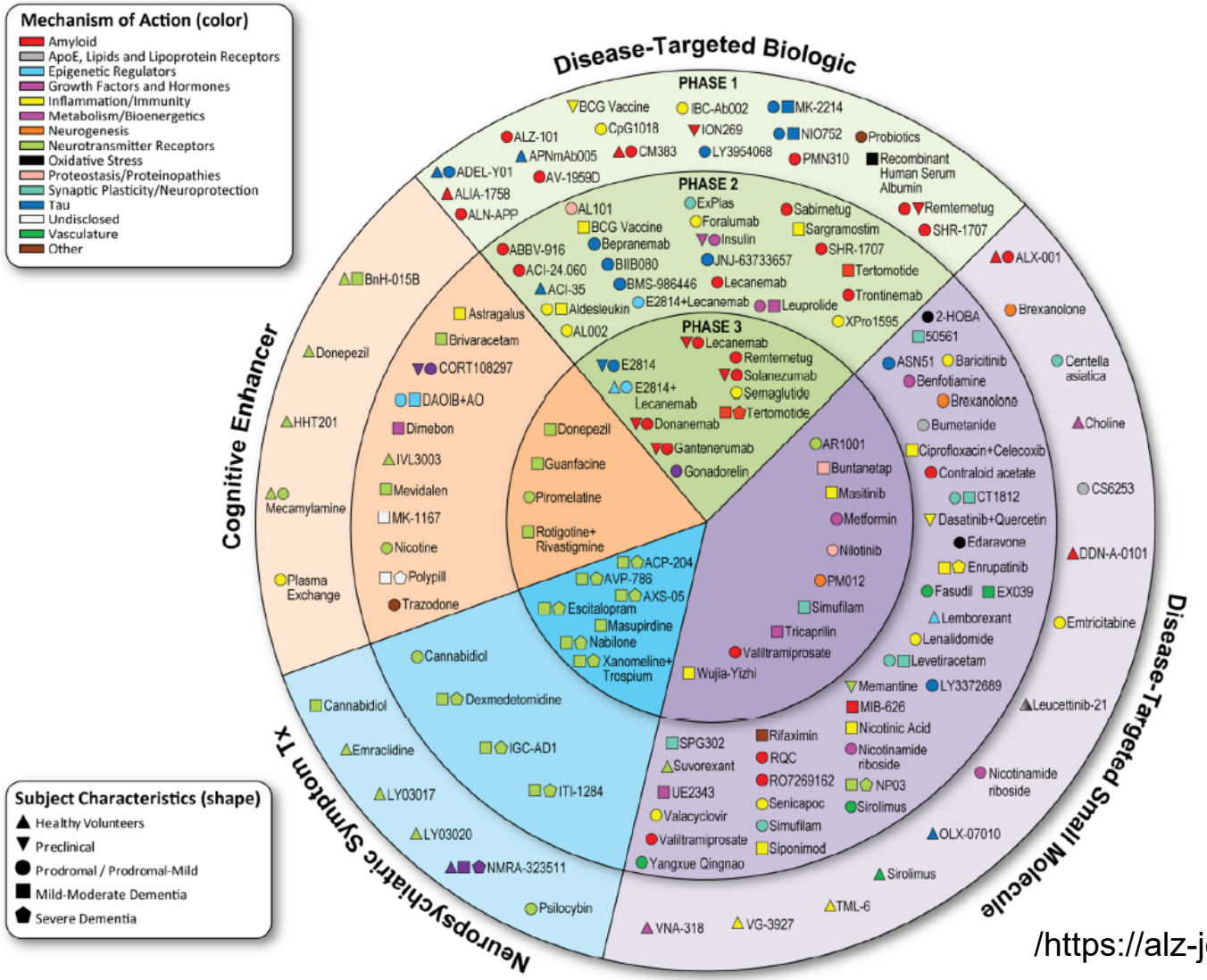
In the Phase 3 trial of Leqembi, the participants who had less severe symptoms at the start of the study appeared to benefit more from the treatment.

Two ongoing trials are testing whether four years of treatment could prevent cognitively healthy people with beta-amyloid plaques in their brains from developing Alzheimer's symptoms.

The Phase 2 trial within AHEAD 3 trial examines the effects of Leqembi on beta-amyloid in people with intermediate levels of plaque in the brain. The Phase 3 AHEAD 45 trial tests whether the drug could halt the disease in people with high levels of beta-amyloid plaques.

The study includes 1,400 participants. It is expected to conclude in late 2028.

2025 Alzheimer's Drug Development Pipeline



https://clinicaltrials.gov

/https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.70098

Questions?

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THANK YOU

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Contact us: WellAhead@la.gov

Please also feel free to visit the Well-Ahead website at:

http://wellaheadla.com

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