# The Latest Achievements in Alzheimer's Treatment & Research

Elizabeth Disbrow, PhD

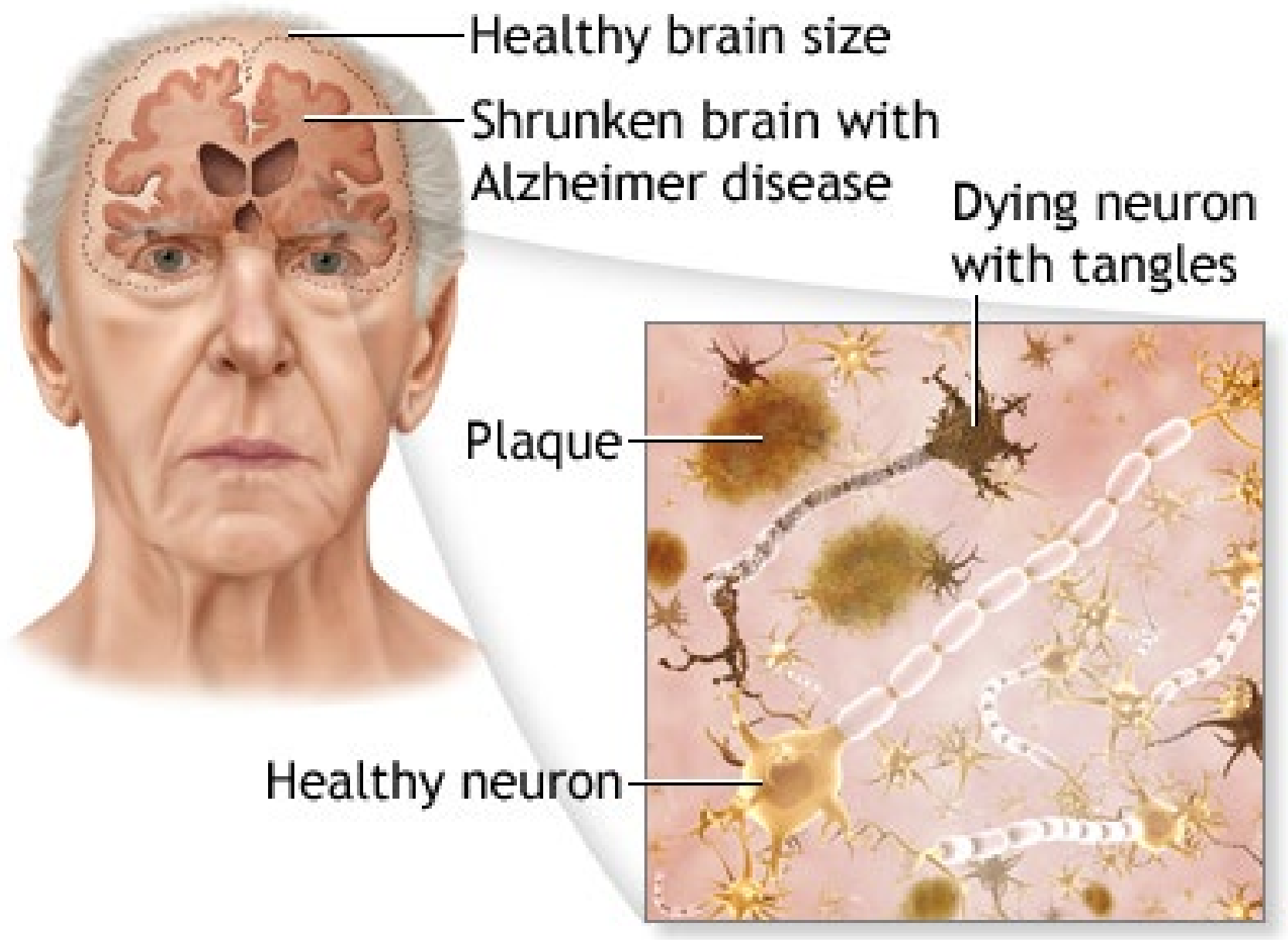
Department of Neurology

LSU Health Shreveport

# New FDA approved drugs and test

- Lecanemab or Leqembi can slow disease progression
- Beta Amyloid/Tau diagnostic tests
- Brexpiprazole or Rexulti is approved for agitation due to Alzheimer’s dementia

# PLAQUES & TANGLES



Research

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 had amyloid
- ApoE4 carriers have steeper increases with age

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

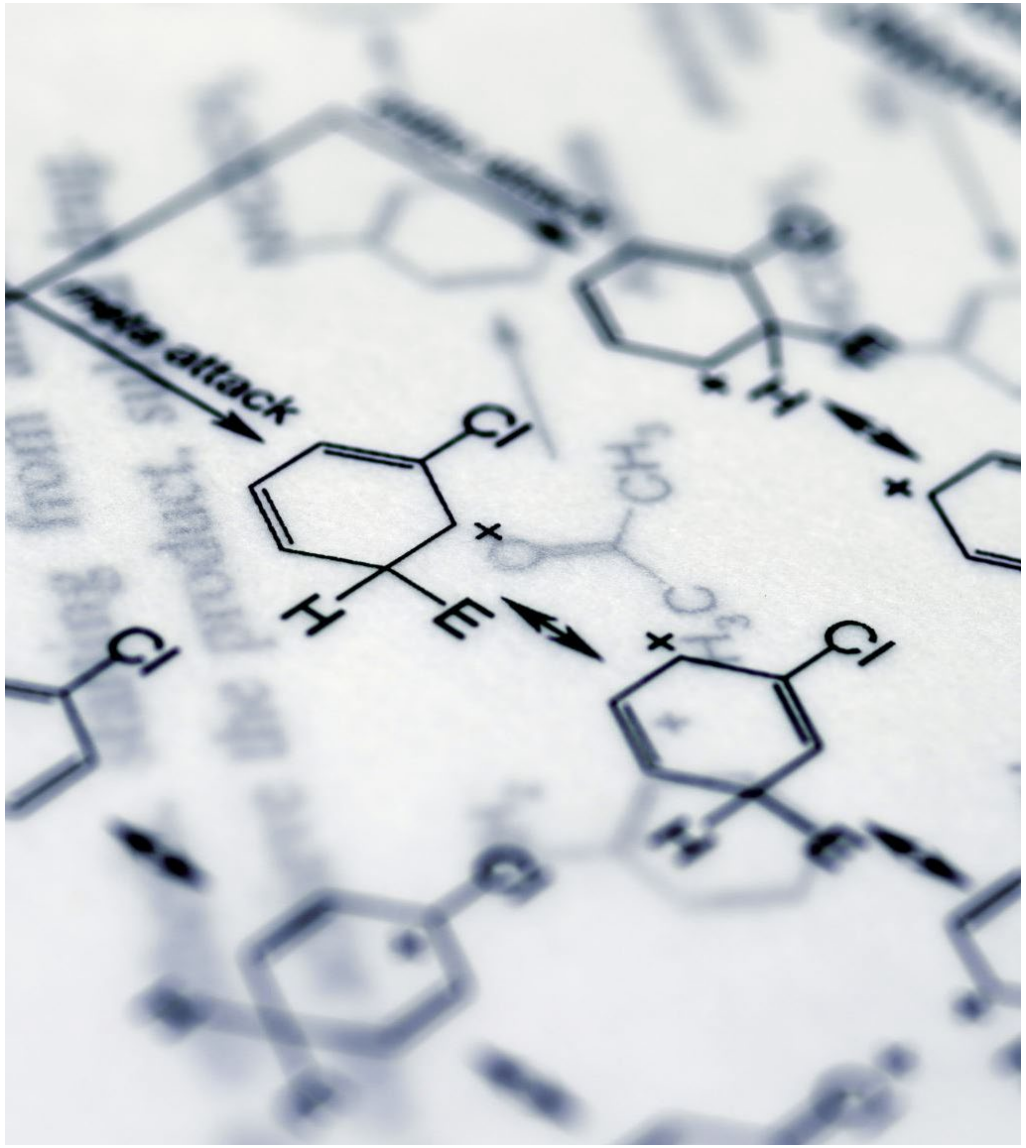
# WHAT WE KNOW ABOUT THE GENETICS OF ALZHEIMER'S DISEASE

- 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

# New FDA approved drugs and test

- Lecanemab or Leqembi can slow disease progression
- Beta Amyloid/Tau diagnostic test
- Brexpiprazole or Rexulti is approved for agitation due to Alzheimer's dementia




# What is Lecanemab (Leqembi)?

- Lecanemab or Leqembi the first FDA approved disease modifying drug for Alzheimer's disease
- It is a monoclonal antibody that binds and removes amyloid plaques from the brain
- It targets and clears the most neurotoxic form of Aβ that continuously accumulates and removes the existing plaques

## What is Lecanemab (Leqembi)?

- It 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.
- Lecanemab is not a cure for Alzheimer’s disease, but it may help to slow the progression of the disease.

## Screening involves:

*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 involves:

*Intravenous (IV) infusion every two 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*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2023 VOL. 388 NO. 1

# Lecanemab in Early Alzheimer's Disease

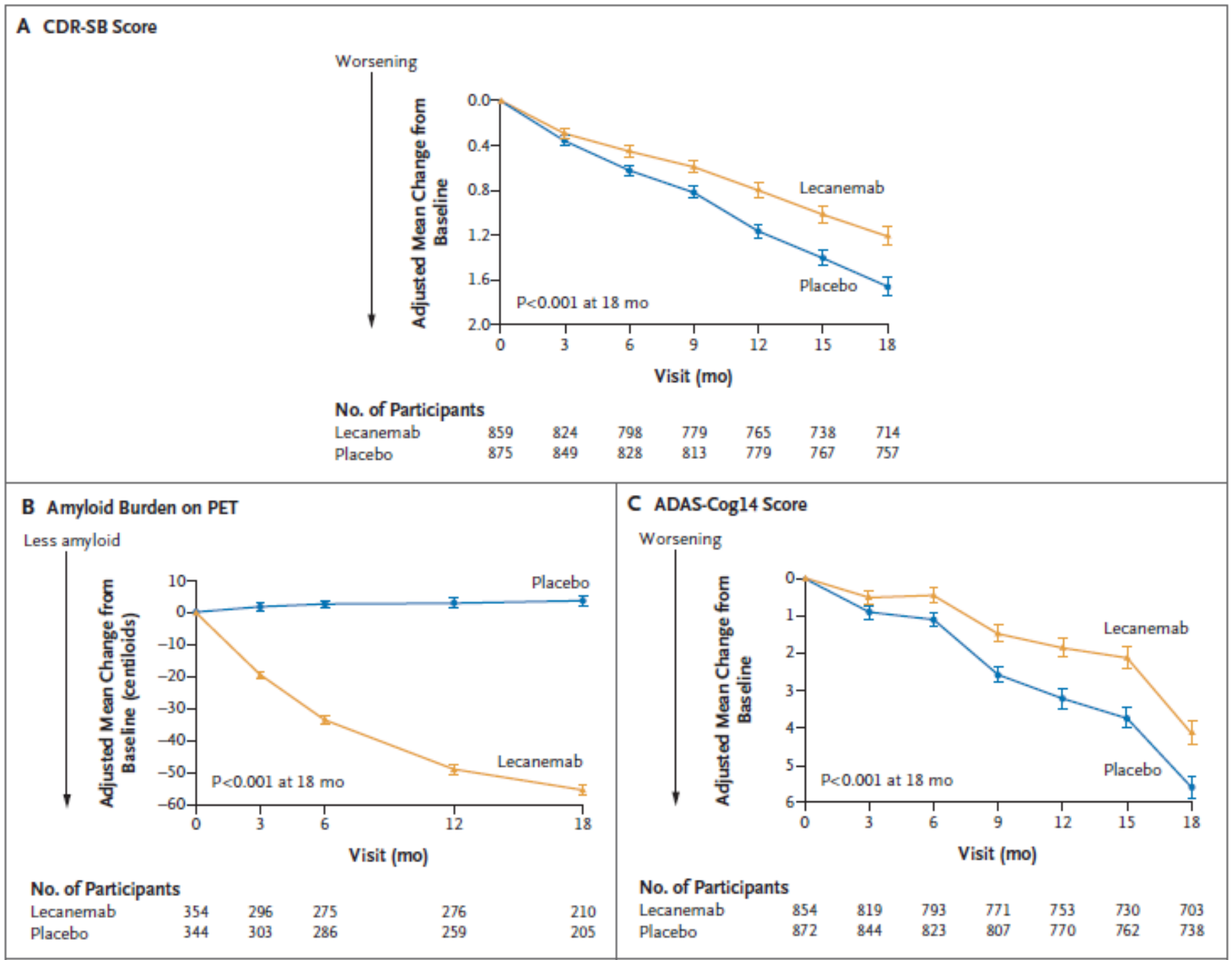
C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

## 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 (10 mg per kilogram of body weight every 2 weeks) or placebo.

The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating–Sum of Boxes. Key secondary end points were the change in amyloid burden on PET, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale and other cognitive tests.




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

## RESULTS

- Eisai and Biogen, the drug developers, found lecanemab slowed cognitive decline associated with Alzheimer's disease by 27%.

- Of 1734 participants who completed a study evaluating lecanemab/Leqembi (859 in the lecanemab group and 875 in the placebo group), most were white, 2.5% were Black, 12.4% were Hispanic, and 17% were Asian.

**Monoclonal antibodies directed against aggregated forms of amyloid beta, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA).**

## Incidence of ARIA

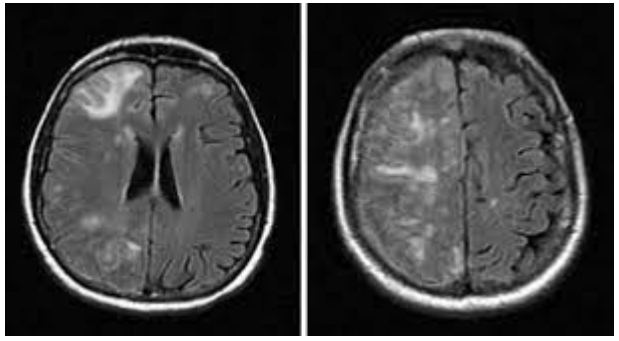
•Including asymptomatic radiographic events, ARIA was observed in LEQEMBI: 21% (191/898); placebo: 9% (84/897).

•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 in 9% of ApoE ε4 homozygotes compared with 2% of heterozygotes and 1% noncarriers. Serious 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

# Medicare Coverage for Leqembi: Things to know for people with Medicare

- Leqembi is covered by Medicare Part B. People with Original Medicare will pay the standard 20% coinsurance of the Medicare-approved amount for the medication after they meet the Part B deductible. If you have Medicare supplemental coverage (like a Medigap plan) or other secondary insurance, or if you're enrolled in a Medicare Advantage plan, your costs may be different. Contact your plan for details about your coverage. In addition to medication costs, you may need additional scans and tests before and/or during treatment that could add to your overall costs.
- Medicare will now provide additional coverage for an imaging test, called an amyloid PET scan, that can be used to help diagnose and monitor Alzheimer's disease. Oct 20, 2023
- Another beta-amyloid testing method, cerebrospinal fluid analysis, also lacks national Medicare coverage. Oct 13, 2023
- Private insurance coverage varies by carrier.

# How to sign up for Leqembi screening in our area:

Fax a referral from primary care provider to (318) 675-7805 including:

- Name of referring physician
- Patient demographics
- Notes from most recent office visit
- Any recent test results (lab, CT, MRI etc.)
- Make a note about interest in Leqembi

Eisai has established a Patient Assistance Program to provide LEQEMBI at no cost, for eligible uninsured and underinsured patients, including Medicare beneficiaries, who meet financial need and other program criteria.

Eisai offers patient support for improving access through Patient Navigators, who will provide information about accessing LEQEMBI, help patients and their families understand their insurance coverage and options, and identify financial support programs for eligible patients.

People in the U.S. can learn more about these services by visiting LEQEMBI.com, calling 1-833-4-LEQEMBI (1-833-453-7362), Mon-Friday, 8 a.m. to 8 p.m. EST or faxing an enrollment form to 1-833-770-7017.

# New FDA approved drugs and test

- Lecanemab or Leqembi can slow disease progression
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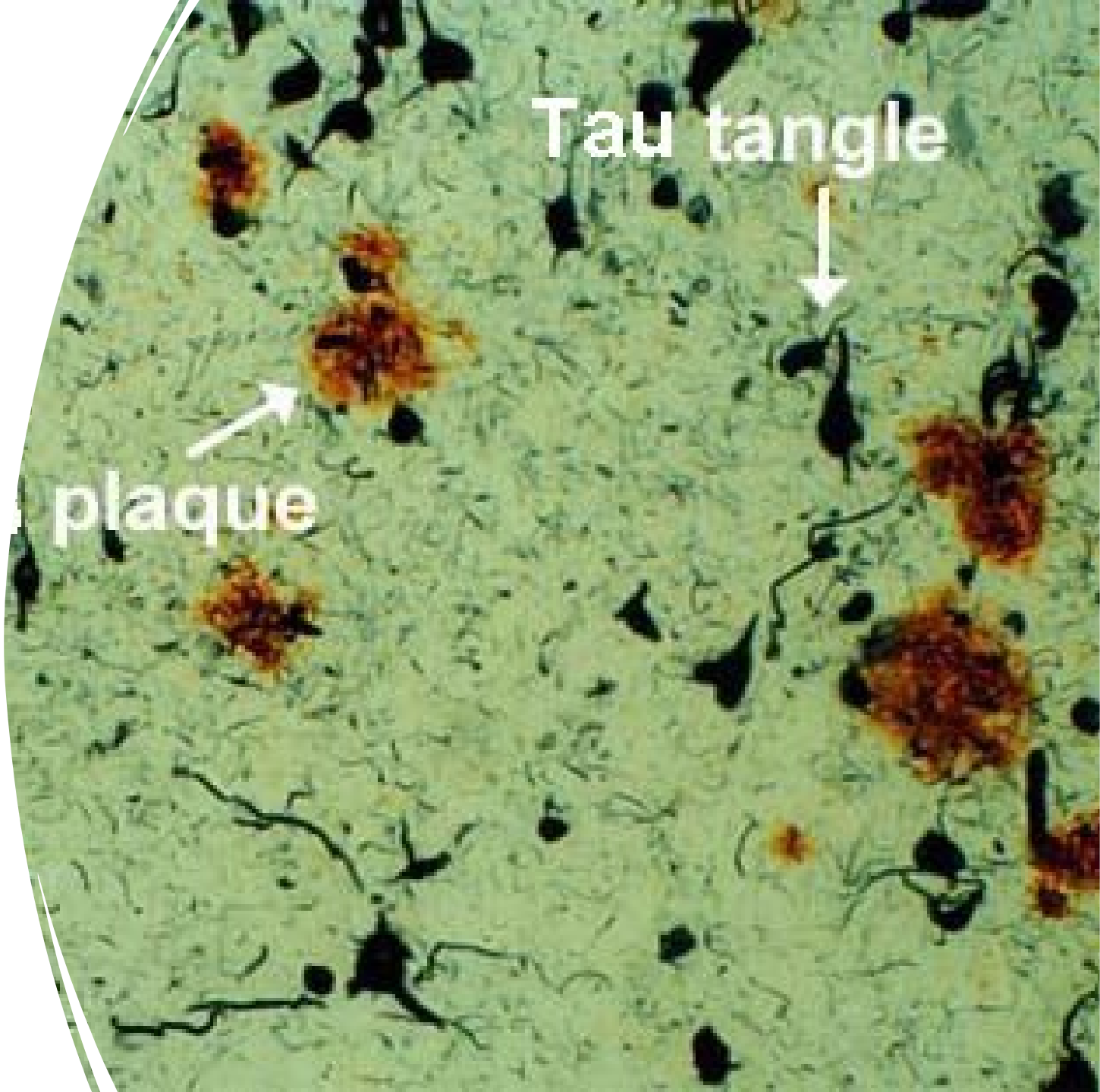
# Test for Alzheimer's diagnosis granted FDA Clearance

June 30, 2023

- Roche has two FDA approved tests that compare the ratio of beta-amyloid (plaques) and phospho-tau (tangles)
- The tests are cleared for use in adults aged 55 years and older who are being evaluated for Alzheimer's
- CSF test results were similar to amyloid PET scan imaging
- Roche is teaming up with Lilly to develop an assay that measures biomarkers in blood samples



# What is the amyloid blood test from Quest Diagnostics? Aug. 1, 2023

- QUEST AD-Detect™ Amyloid Beta 42/40 Ratio in plasma for Alzheimer's Disease on questhealth.com –
- The first blood test available for consumer purchase, and it uses the same technology as the test Quest provided for doctors last year.
- The test has not been cleared or approved by FDA, and it costs $399.
- Users must first pay for the test on Quest's website.  A telemedicine doctor will review the purchase to ensure it is medically necessary and place an order on their behalf. Patients can review their results online and have the option to speak to a physician at no extra cost.
- "One of the advantages of having an amyloid test is that it lets you know, potentially years in advance of even being symptomatic, that you are at risk for Alzheimer's," said Michael Racke, MD, Quest's medical director of neurology to Reuters.

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- Brexpiprazole or Rexulti is approved for agitation due to Alzheimer’s dementia

# Brexpiprazole (Rexulti®) is the first FDA-approved medication for agitation associated with dementia due to Alzheimer's

Agitation is an emotional, physical, and often verbal acting-out of anxiety, loss of control, physical discomfort, and fear.

The International Psychogeriatric Association workgroup defined agitation in cognitive disorders as:

A) occurring in patients with a cognitive impairment or dementia syndrome;
B) exhibiting behavior consistent with emotional distress: excessive motor activity (e.g., pacing, rocking, or gesturing), verbal aggression (e.g., yelling, excessive loudness, or using profanity), and/or physical aggression (e.g., grabbing, shoving, or pushing);
C) causing excess disability with regard to interpersonal relationships, social functioning, or activities of daily living; and
D) not solely being attributable to another disorder (psychiatric, medical, or substance-related).

From: Cummings J, et al: Int Psychogeriatr 2015; 27:7–17

The prevalence of agitation in Alzheimer's is as high as 86% in care homes depending on how "agitation" is defined, and it increases with disease severity

Cohen-Mansfield J, et al., J Gerontol 1989; 44:M77–M84

# Brexpiprazole (Rexulti®) is an FDA-approved atypical antipsychotic for agitation associated with dementia due to Alzheimer's.

Atypical antipsychotics are a group of antipsychotic drugs that target the serotonin and dopamine chemical pathways in the brain.

Serotonin, dopamine, and noradrenaline neurotransmitter systems are implicated in behavioral symptoms of dementia, including agitation, and thus it is hypothesized that brexpiprazole may provide a benefit to these patients.

Brexpiprazole is efficacious and well tolerated in adults as a treatment for schizophrenia, and as adjunctive treatment to antidepressants for the treatment of major depressive disorder.

Brexpiprazole has a low propensity for activating and sedating side effects.

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Am J of Geriatric Psychiatry 28:4 (2020) 383–400

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ScienceDirect

journal homepage: www.ajgponline.org

Regular Research Article

# Efficacy and Safety of Brexpiprazole for the Treatment of Agitation in Alzheimer's Dementia: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled Trials

*George T. Grossberg, M.D., Eva Kohegyi, M.D., Victor Mergel, Ph.D., Mette Krog Josiassen, Ph.D., Didier Meulien, M.D., Mary Hobart, Ph.D., Mary Slomkowski, Pharm.D., Ross A. Baker, Ph.D., Robert D. McQuade, Ph.D., Jeffrey L. Cummings, M.D., Sc.D.*

The objective of the two Phase 3 studies was to assess the efficacy, safety, and tolerability of brexpiprazole in patients with AAD

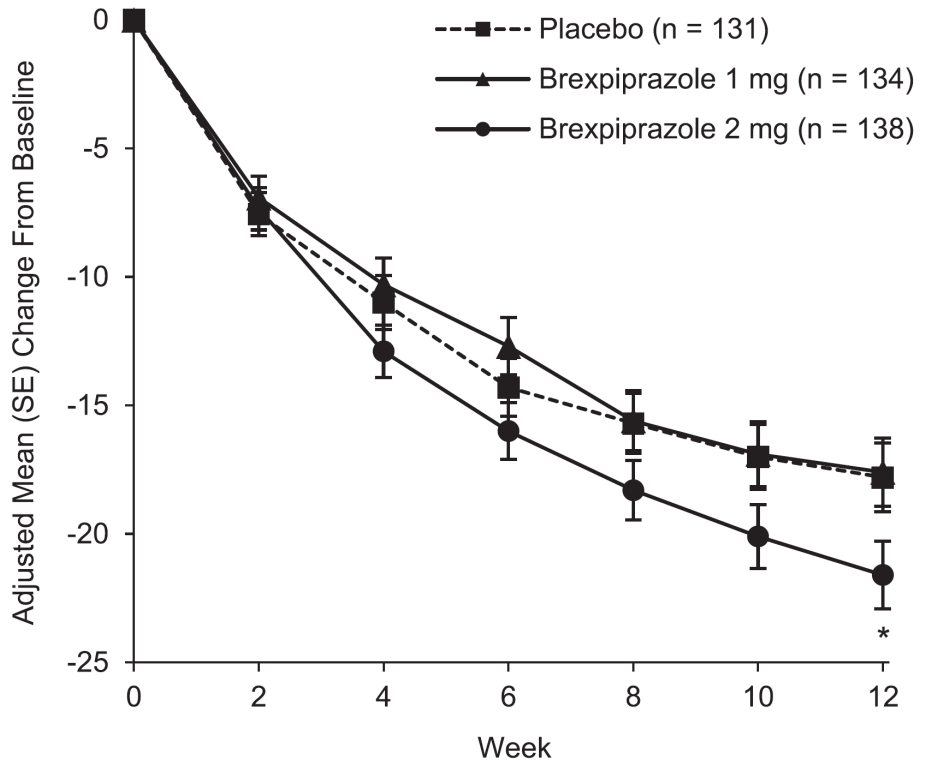
## Study Design

Two 12 week, randomized, double blind, placebo-controlled studies with about 140 people per group.

Primary outcome measure was the Cohen-Mansfield Agitation Inventory (CMAI) a clinically validated agitation rating scale that measures the frequency of 29 agitated behavior items:

- physically and verbally aggressive behavior (e.g., hitting or cursing),
- physically nonaggressive behavior (e.g., pacing or restlessness), and
- verbally agitated behavior (e.g., complaining or constant requests for attention).

**FIGURE 3. Primary endpoint in Study 1: effects of brexpiprazole on symptoms of agitation (CMAI Total).**



## Side Effects

Possible side effects included headache, dizziness, urinary tract infection and sleep disturbances.

There is an FDA boxed warning for mortality associated with atypical antipsychotics, as well as a warning for cerebrovascular events, based on meta-analyses that show an increased risk of such events in elderly patients with dementia

> Increased risk of death in elderly people with dementia-related psychosis. Medicines like REXULTI can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). REXULTI is not approved for the treatment of people with dementia-related psychosis without agitation that may happen with dementia due to Alzheimer's disease.

If you have questions, contact us at the LSU Center for Brain Health:

elizabeth.disbrow@lsuhs.edu
(318) 813-3610
1521 Wilkinson St.

LSU Health Shreveport
CENTER FOR BRAIN HEALTH

See our table: We are conducting a short caregiver survey!

https://www.einpresswire.com/article/665244469/rethinking-alzheimer-s-treatment-experts-challenge-efficacy-and-safety-of-anti-amyloid-drugs

**Table 3. Adverse Events.***

| Event | Lecanemab (N=898) | Placebo (N=897) |
|---|---|---|
| **Overall — no. (%)** | | |
| Any adverse event | 798 (88.9) | 735 (81.9) |
| Adverse event related to lecanemab or placebo† | 401 (44.7) | 197 (22.0) |
| Serious adverse event | 126 (14.0) | 101 (11.3) |
| Death | 6 (0.7) | 7 (0.8) |
| Adverse event leading to discontinuation of the trial agent | 62 (6.9) | 26 (2.9) |
| Adverse event that occurred in ≥5% of participants in either group | | |
| Infusion-related reaction | 237 (26.4) | 66 (7.4) |
| ARIA with microhemorrhages or hemosiderin deposits | 126 (14.0) | 69 (7.7) |
| ARIA-E | 113 (12.6) | 15 (1.7) |
| Headache | 100 (11.1) | 73 (8.1) |
| Fall | 93 (10.4) | 86 (9.6) |
| Urinary tract infection | 78 (8.7) | 82 (9.1) |
| Covid-19 | 64 (7.1) | 60 (6.7) |
| Back pain | 60 (6.7) | 52 (5.8) |
| Arthralgia | 53 (5.9) | 62 (6.9) |
| Superficial siderosis of central nervous system | 50 (5.6) | 22 (2.5) |
| Dizziness | 49 (5.5) | 46 (5.1) |
| Diarrhea | 48 (5.3) | 58 (6.5) |
| Anxiety | 45 (5.0) | 38 (4.2) |
| **ARIA‡** | | |
| ARIA-E — no. (%) | 113 (12.6) | 15 (1.7) |
| Symptomatic ARIA-E — no. (%)§ | 25 (2.8) | 0 |
| ApoE ε4 noncarrier — no./total no. (%) | 4/278 (1.4) | 0/286 |
| ApoE ε4 carrier — no./total no. (%) | 21/620 (3.4) | 0/611 |
| ApoE ε4 heterozygote | 8/479 (1.7) | 0/478 |
| ApoE ε4 homozygote | 13/141 (9.2) | 0/133 |
| ARIA-E according to ApoE ε4 genotype — no./total no. (%) | | |
| ApoE ε4 noncarrier | 15/278 (5.4) | 1/286 (0.3) |
| ApoE ε4 carrier | 98/620 (15.8) | 14/611 (2.3) |
| ApoE ε4 heterozygote | 52/479 (10.9) | 9/478 (1.9) |
| ApoE ε4 homozygote | 46/141 (32.6) | 5/133 (3.8) |
| ARIA-H — no. (%) | 155 (17.3) | 81 (9.0) |
| Microhemorrhage | 126 (14.0) | 68 (7.6) |
| Superficial siderosis | 50 (5.6) | 21 (2.3) |
| Macrohemorrhage | 5 (0.6) | 1 (0.1) |
| Symptomatic ARIA-H§ | 6 (0.7) | 2 (0.2) |
| Isolated ARIA-H: no concurrent ARIA-E | 80 (8.9) | 70 (7.8) |

## RESULTS

A total of 1795 participants were enrolled, with 898 assigned to receive lecanemab and 897 to receive placebo. The mean CDR-SB score at baseline was approximately 3.2 in both groups. The adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo (difference, −0.45; 95% confidence interval [CI], −0.67 to −0.23; P<0.001). In a substudy involving 698 participants, there were greater reductions in brain amyloid burden with lecanemab than with placebo (difference, −59.1 centiloids; 95% CI, −62.6 to −55.6). Other mean differences between the two groups in the change from baseline favoring lecanemab were as follows: for the ADAS-cog14 score, −1.44 (95% CI, −2.27 to −0.61; P<0.001); for the ADCOMS, −0.050 (95% CI, −0.074 to −0.027; P<0.001); and for the ADCS-MCI-ADL score, 2.0 (95% CI, 1.2 to 2.8; P<0.001). Lecanemab resulted in infusion-related reactions in 26.4% of the participants and amyloid-related imaging abnormalities with edema or effusions in 12.6%.

## CONCLUSIONS

Lecanemab reduced markers of amyloid in early Alzheimer's disease and resulted in moderately less decline on measures of cognition and function than placebo at 18 months but was associated with adverse events. Longer trials are warranted to determine the efficacy and safety of lecanemab in early Alzheimer's disease. (Funded by Eisai and Biogen; Clarity AD ClinicalTrials.gov number, NCT03887455.)

## WARNING: AMYLOID RELATED IMAGING ABNORMALITIES (ARIA)

- **Monoclonal antibodies directed against aggregated forms of amyloid beta, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA).**
- ARIA-E can be observed on MRI as brain edema or sulcal effusions, and ARIA-H as microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease
- **ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur,** including seizure. **Serious intracerebral hemorrhages >1 cm, some of which have been fatal, have been observed in patients treated with this class of medications.**
- Reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time
- **Apolipoprotein E ε4 (ApoE ε4) Homozygotes: Patients who are ApoE ε4 homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications, including LEQEMBI, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.**

## WARNINGS AND PRECAUTIONS

## AMYLOID RELATED IMAGING ABNORMALITIES

•LEQEMBI can cause ARIA-E and ARIA-H.. ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. ARIA-H and ARIA-E can occur together. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, status epilepticus, rarely can occur..

## ncidence of ARIA

•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.

•Including asymptomatic radiographic events, ARIA was observed in LEQEMBI: 21% (191/898); placebo: 9% (84/897). ARIA-E was observed in LEQEMBI: 13% (113/898); placebo: 2% (15/897). ARIA-H was observed in LEQEMBI: 17% (152/898); placebo: 9% (80/897). There was no increase in isolated ARIA-H for LEQEMBI vs placebo.

## 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 in 9% of ApoE ε4 homozygotes compared with 2% of heterozygotes and 1% noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and noncarriers.

•The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers.

## Radiographic Findings

•The majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses), although ARIA can occur at any time and patients can have more than 1 episode. The maximum radiographic severity of ARIA-E in patients treated with LEQEMBI was mild in 4% (37/898), moderate in 7% (66/898), and severe in 1% (9/898). Resolution on MRI occurred in 52% of ARIA-E patients by 12 weeks, 81% by 17 weeks, and 100% overall after detection. The maximum radiographic severity of ARIA-H microhemorrhage in LEQEMBI-treated patients was mild in 9% (79/898), moderate in 2% (19/898), and severe in 3% (28/898) of patients; superficial siderosis was mild in 4% (38/898), moderate in 1% (8/898) , and severe in 0.4% (4/898). Among LEQEMBI-treated patients, the rate of severe