UT Southwestern
Medical Center

Advances in Dementia

Brain Summit 2023 Symposium: Current Trends in Neurology

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Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.

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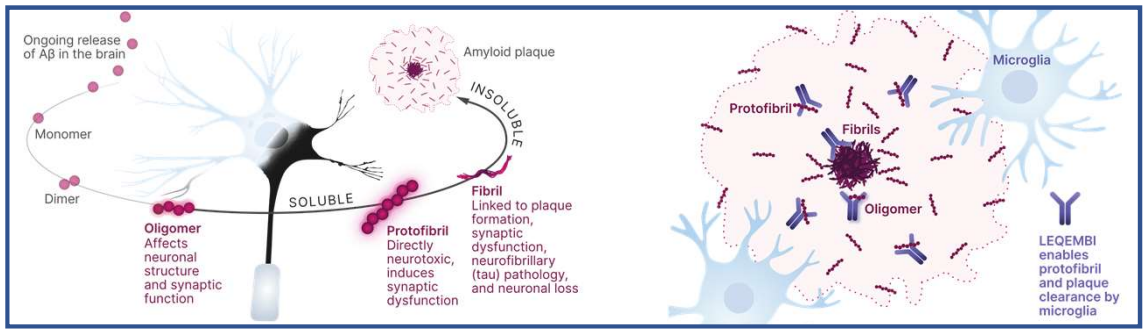
  - Biogen (site PI for ENVISION)
  - Alzheimer's Disease Neuroimaging Initiative (ADNI 4)

Objectives

- Understand the indications and patient selection criteria for lecanemab
- Describe the benefits and side effects of lecanemab
- Know how to recognize and manage amyloid-related imaging abnormalities (ARIA) related to lecanemab

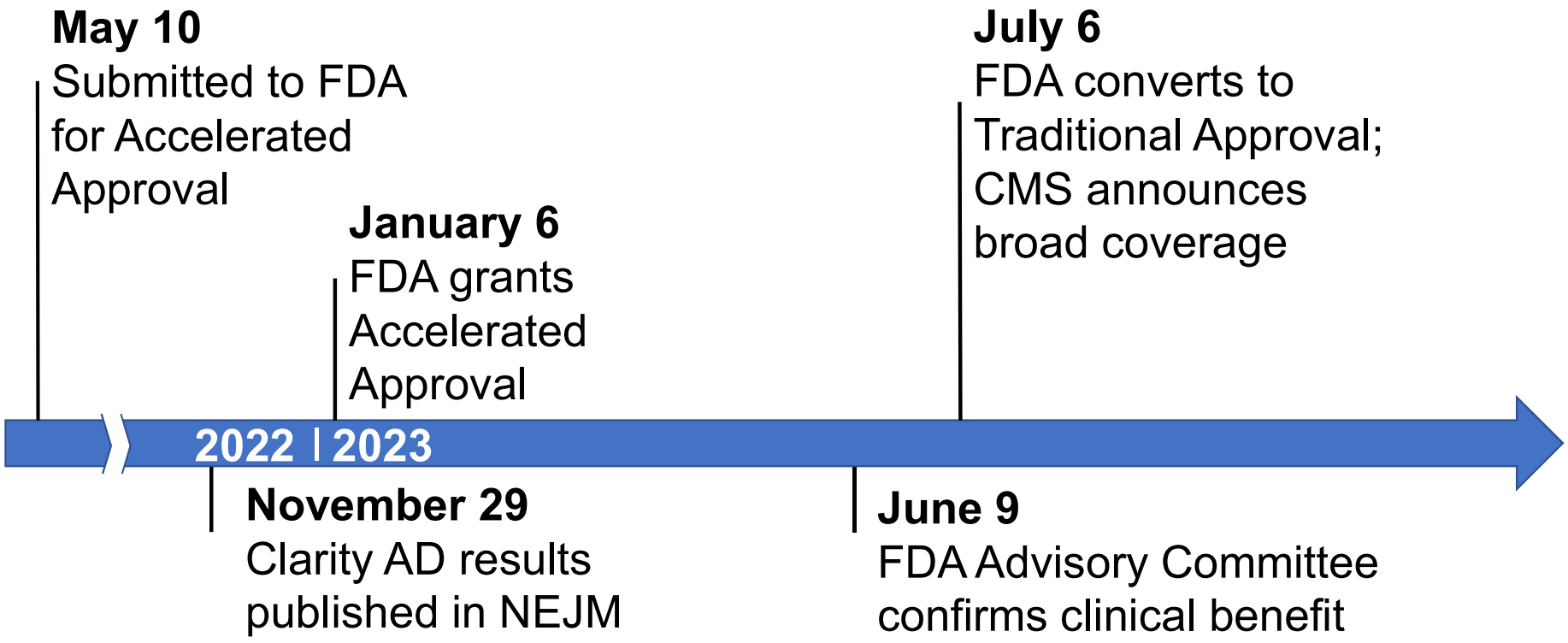
What is Lecanemab / LEQEMBI?

- Treatment of Alzheimer's disease (AD)
  - Mild cognitive impairment (MCI)
  - Mild dementia
- Anti-amyloid monoclonal antibody
  - Amyloid-beta protofibrils
  - 10 mg/kg infusion over 1 hr every two weeks



LEQEMBI (lecanemab-irmb) Prescribing Information; leqembihcp.com

Timeline of Lecanemab



Lecanemab:
Clinical Trial Data

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

Clarity AD

- Trial design: 18-month, multicenter, double-bind, placebo-controlled, parallel-group
- Inclusion
  - 50 – 90 years of age
  - MCI or mild dementia due to AD
  - Amyloid (+) by PET or CSF
- Primary endpoint: Clinical Dementia Rating – Sum of Boxes (CDR-SB)
- Secondary endpoints:
  - Change in amyloid PET
  - Clinical scales (ADAS-cog14, ADCOMS, ADCS-MCI-ADL)
  - CSF, plasma, tau PET and MRI biomarkers

van Dyck, et al. (2023) *NEJM*

Clinical Dementia Rating – Sum of Boxes

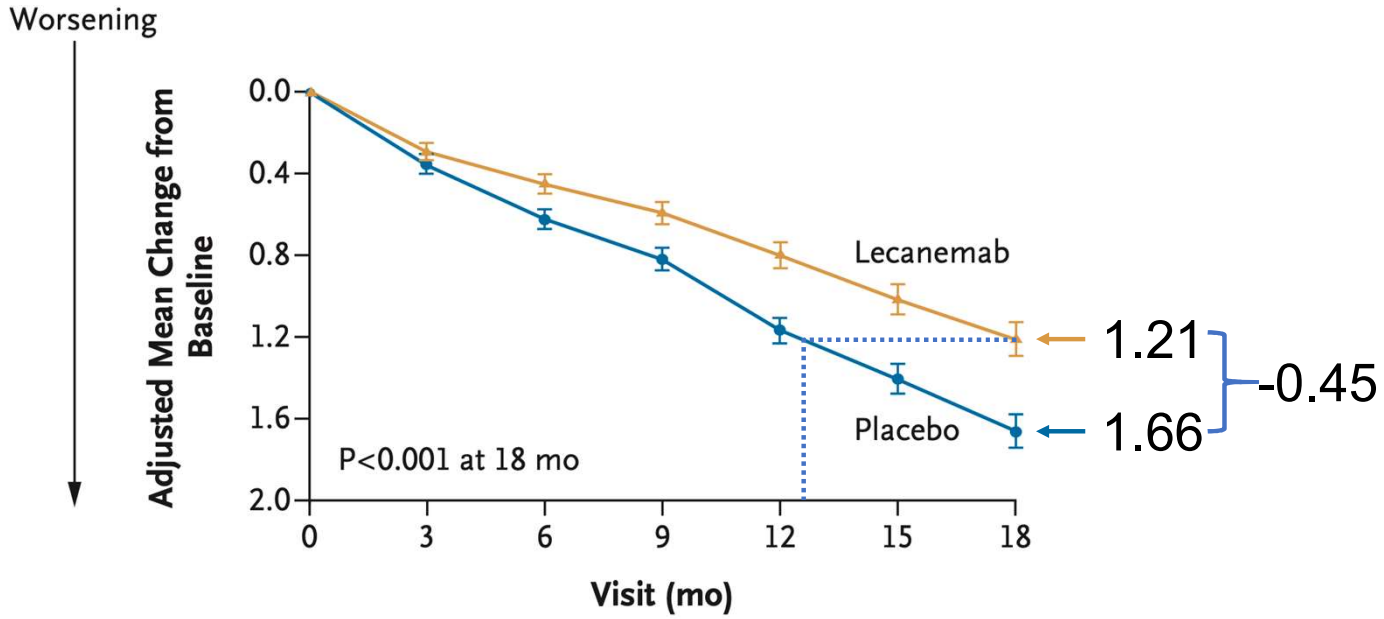
SECTION 1: CDR® DEMENTIA STAGING INSTRUMENT[1]

Please enter score below:	IMPAIRMENT				
	None — 0	Questionable — 0.5	Mild — 1	Moderate — 2	Severe — 3
1. Memory ⌊_⌋.⌊_⌋	No memory loss, or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss, more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
2. Orientation ⌊_⌋.⌊_⌋	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
3. Judgment and problem solving ⌊_⌋.⌊_⌋	Solves everyday problems, handles business and financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
4. Community affairs ⌊_⌋.⌊_⌋	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities, although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside the home; appears well enough to be taken to functions outside the family home	No pretense of independent function outside the home; appears too ill to be taken to functions outside the family home
5. Home and hobbies ⌊_⌋.⌊_⌋	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in the home
6. Personal care ⌊_⌋.0	Fully capable of self-care (=0).		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence
7. ⌊_⌋⌊_⌋.⌊_⌋	**CDR SUM OF BOXES**				
8. ⌊_⌋.⌊_⌋	**GLOBAL CDR**				

National Alzheimer's Coordinating Center, www.naccdata.org

Clarity AD Primary Outcome: CDR-SB

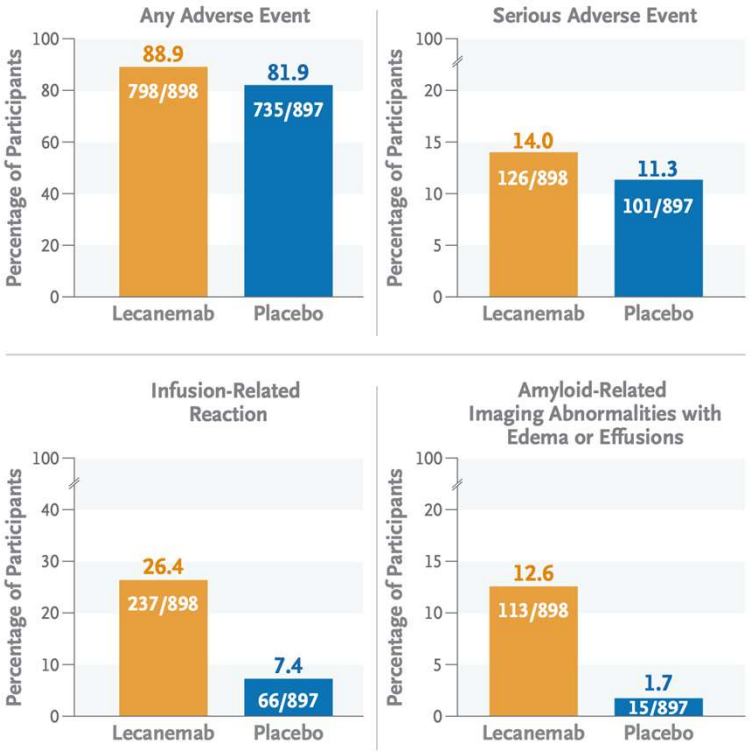
Baseline CDR-SB: 3.2



No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

van Dyck, et al. (2023) *NEJM*

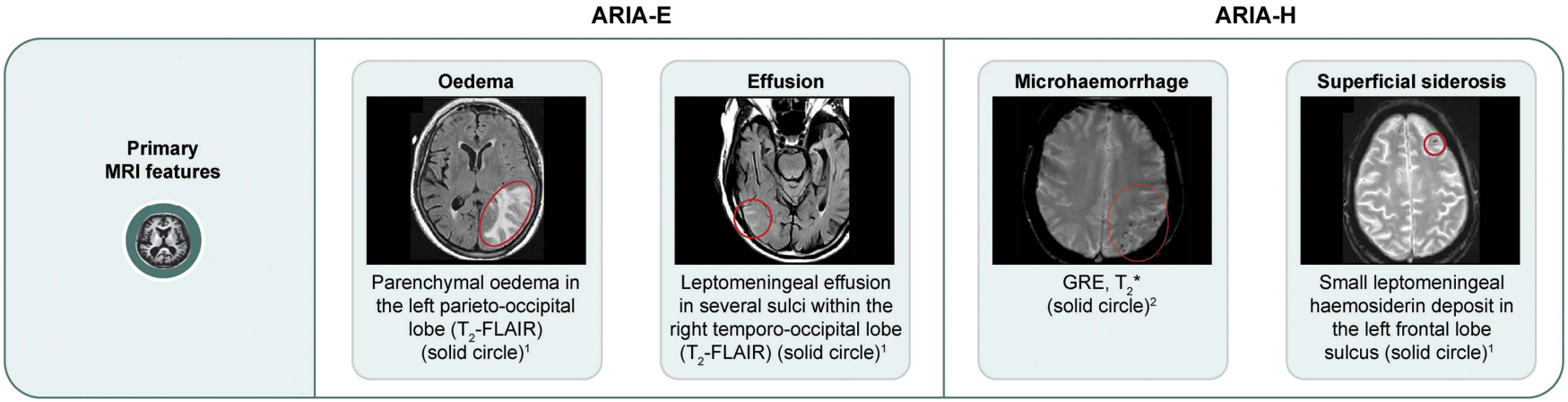
Clarity AD Safety



van Dyck, et al. (2023) *NEJM*

Amyloid-Related Imaging Abnormalities (ARIA)

- ARIA-E
  - Edema
  - Effusions
- ARIA-H
  - Micro- or macrohemorrhages
  - Superficial siderosis



Hampel, et al. (2023) *Brain*

Clarity AD: ARIA-E

Event	Lecanemab (N=898)	Placebo (N=897)
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)

van Dyck, et al. (2023) *NEJM*

Clarity AD: ARIA-H

Event	Lecanemab (N = 898)	Placebo (N = 897)
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)
ARIA-H according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	33/278 (11.9)	12/286 (4.2)
ApoE ε4 carrier	122/620 (19.7)	69/611 (11.3)
ApoE ε4 heterozygote	67/479 (14.0)	41/478 (8.6)
ApoE ε4 homozygote	55/141 (39.0)	28/133 (21.1)

van Dyck, et al. (2023) *NEJM*

Clarity AD: ARIA-E and/or ARIA-H

Event	Lecanemab (N=898)	Placebo (N=897)
ARIA-E or ARIA-H — no. (%)	193 (21.5)	85 (9.5)
Concurrent ARIA-E and ARIA-H — no. (%)	74 (8.2)	9 (1.0)

van Dyck, et al. (2023) *NEJM*

Lecanemab:
Identifying Appropriate Patients

J Prev Alz Dis 2023;3(10):362-377
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Review

Lecanemab: Appropriate Use Recommendations

J. Cummings[1], L. Apostolova[2], G.D. Rabinovici[3], A. Atri[4], P. Aisen[5], S. Greenberg[6], S. Hendrix[7], D. Selkoe[8], M. Weiner[9], R.C. Petersen[10], S. Salloway[11], For the Alzheimer's Disease and Related Disorders Therapeutics Work Group

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Clinical Diagnosis and Features

- Age: 50 – 90 years old
- AD with amyloid confirmation
  - Amyloid PET
  - CSF elevated p-tau and low Aβ42 level (increased p-tau:Aβ42)
  - Blood biomarker not considered adequate
- APOE for risk stratification
- Stage: MCI or mild dementia
  - MMSE 22 – 30
  - Safety/efficacy not defined for preclinical or more advanced disease
- Syndrome type:
  - Memory-predominant
  - Atypical syndromes not specifically excluded

Cummings, et al. (2023) *J Prev Alz Dis*

MRI Brain (within 12 mo) Exclusion:

- Macrohemorrhage (> 10 mm)
- > 4 microhemorrhages (< 10 mm)
- Superficial siderosis
- Vasogenic edema
- Significant white matter hyperintensities
- Multiple lacunar strokes
- Cerebral stroke involving major vascular territory
- Cerebral contusions
- Encephalomalacia
- Brain aneurysms or other vascular malformations
- CNS infection
- Brain tumor other than meningioma or arachnoid cysts
- CAA-ri / ABRA

Cummings, et al. (2023) *J Prev Alz Dis*

Other Exclusions

- Immunologic disorders
- Requiring immunotherapies
  - Immunoglobulins
  - Systemic monoclonal antibodies
  - Systemic immunosuppressants
  - Plasmapheresis
- Stroke, TIA, bleeding d/o, seizures in previous 12 mo
- Women who are pregnant or lactating
- Depression (GDS > 8)
- BMI > 35 or < 17
- Clotting disorders
- Cerebral amyloid angiopathy
- Unable to undergo MRI

Cummings, et al. (2023) *J Prev Alz Dis*

Medications

- Acceptable
  - Anti-dementia medications
  - Other medical or psychiatric medications
  - ASA up to 325 mg daily
  - Other antiplatelet agents at standard dosing
- Excluded
  - Aducanumab (or had severe or recurrent ARIA)
  - Anticoagulation
- AUR recommends avoiding treatment with acute thrombolytics until safety evidence with combined use is available

Cummings, et al. (2023) *J Prev Alz Dis*

Lecanemab:
Side Effect Management

Infusion-Related Reactions

- 26.4%
- Typically
  - Mild to moderate
  - First two treatments
  - During up to several hours after
  - Resolve in 24 hours
- Symptoms: fever, chills, headaches, rash, nausea, vomiting, GI discomfort, elevated blood pressure

- For more significant reactions
  - Stop infusion
  - Mild: diphenhydramine and acetaminophen
  - More severe: oral dexamethasone or methylprednisolone
  - Pretreatment with above

Cummings, et al. (2023) *J Prev Alz Dis*

ARIA Management

- MRI monitoring prior to 5th, 7th and 14th infusions
- If present, monthly MRI until ARIA-E resolves or ARIA-H stabilizes
- Symptoms: Headache, confusion, visual changes, dizziness, nausea gait difficulties
- Serious ARIA symptoms: seizures, status epilepticus, encephalopathy, stupor, lateralizing signs
- Exclude ischemic stroke
- Consider high-dose glucocorticoid
  - 1g IVSM x 5 days
  - Oral steroid taper over several weeks

Cummings, et al. (2023) *J Prev Alz Dis*

ARIA Management

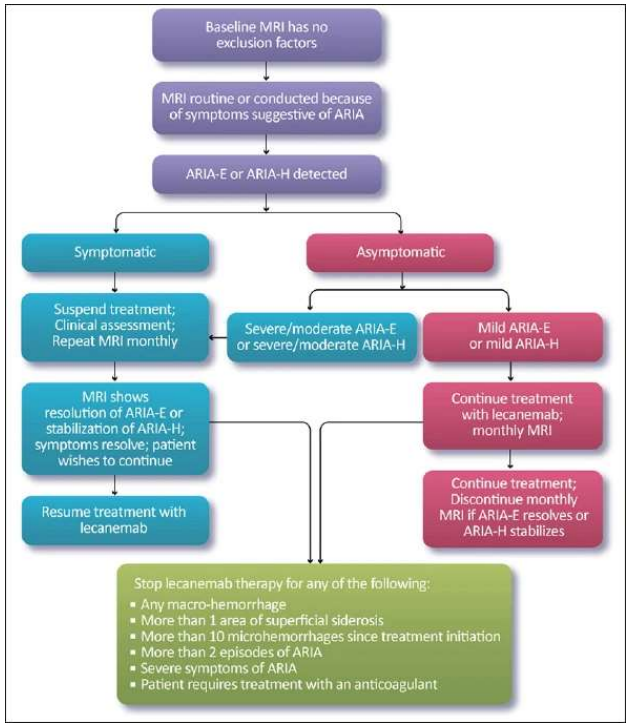

Table 7. Description of mild, moderate, and severe radiographic ARIA (from the Prescribing Information)

	Radiographic Severity		
ARIA Type	**Mild**	**Moderate**	**Severe**
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted
ARIA-H Microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H Superficial Siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 areas of superficial siderosis

Table 8. Management of ARIA depending on the severity of symptoms and the severity of the radiographic ARIA-E or ARIA-H on MRI

	Symptom Description			
	No Symptoms	**Mild Symptoms**	**Moderate Symptoms**	**Severe Symptoms**
Severity of Changes Observed on MRI	None	Discomfort noted; no disruption of daily activity	Discomfort sufficient to reduce or affect normal daily activity	Incapacitating, with inability to work or to perform normal daily activity
ARIA-E on MRI				
Mild	Continue dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Moderate	Suspend dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Severe	Discontinue dosing	Discontinue dosing	Discontinue dosing	Discontinue dosing
ARIA-H on MRI				
Mild	Continue dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Moderate	Suspend dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Severe	Discontinue dosing	Discontinue dosing	Discontinue dosing	Discontinue dosing

Cummings, et al. (2023) *J Prev Alz Dis*

Conclusion

Summary

- Lecanemab is:
  - Antibody infusion every 2 wks
  - AD with biomarker confirmation
  - MCI and mild dementia
  - MMSE 22-30
- Clarity AD (18 months):
  - 27.1% less decline
  - Approximately 5 months slower
- Side effects include
  - Infusion reactions (26.4%)
  - ARIA (21.5%)
  - Risk depends on *APOE*
- Serious ARIA may require hospital admission to manage cerebral edema and associated symptoms

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  - Brendan Kelley, M.D.
  - Alka Khera, M.D.
  - Natalie Martinez
  - Rebecca Logan

Post-Credit Scene

Any Day Now: Donanemab

- Antibody infusion every 4 wks
  - 700 mg x 3 mo, then 1400 mg
  - Stop after amyloid PET clearance
- AD biomarkers
  - Amyloid PET
  - Tau PET
- MCI and mild dementia
- MMSE 20-28

- TRAILBLAZER-ALZ 2 CDR-SB (secondary):
  - 28.9% less decline
  - Approximately 5 months slower
- Safety
  - Infusion reactions: 8.7%
  - ARIA: 36.8% (14.9% placebo)
  - ARIA-E in ε4/ε4: 40.6%
  - Symptomatic ARIA-E: 6.1%
  - 3 deaths due to ARIA

Sims, et al. (2023) *JAMA*