THE CHANGING LANDSCAPE

In the Treatment of Alzheimer's Disease

VV-Canada Medical-US-DEL-0350

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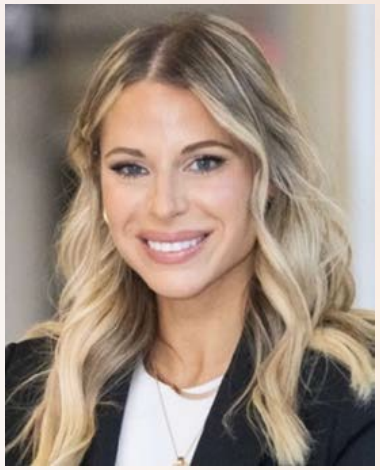
Introduction

Dr. Sara Mitchell

Scientific Planning Committee



Sara B. Mitchell, MD, FRCPC, MPH
Neurologist, Toronto, ON

Paolo Vitali, MD, PhD
Neurologist, Montreal, QC

Andrew Frank, MD, BScH, FRCPC
Cognitive Neurologist, Ottawa, ON

Presenter Disclosures

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	Sara B. Mitchell, MD, FRCPC, MPH	Paolo Vitali, MD, PhD	Andrew Frank, MD, BScH, FRCPC
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Learning Objectives

By the end of this course, participants will be able to:

- Review the latest research and clinical updates on Alzheimer's disease.
- Discuss diagnostic tools and imaging techniques in the identification and treatment of Alzheimer’s disease.
- Examine the safety and efficacy of new therapeutic strategies.
- Promote a collaborative discussion among professionals in the field.

Agenda

Welcome & Introductions, *Dr. Sara Mitchell*	2 mins
The State of AD in Canada, *Dr. Sara Mitchell*	5 mins
Diagnosis and Biomarkers, *Dr. Paolo Vitali*	15 mins
Panel Discussion, *All*	7 mins
DMTs - Trial Design and Efficacy, *Dr. Andrew Frank*	15 mins
Safety and ARIAs, *Dr. Paolo Vitali*	15 mins
Panel Discussion, *All*	7 mins
Canadian Readiness for DMTs, *Dr. Sara Mitchell*	15 mins
Panel Discussion, *All*	7 mins
Conclusion, *Dr. Sara Mitchell*	2 mins

Housekeeping

- There are a few interactive questions in this presentation; Slido will be used

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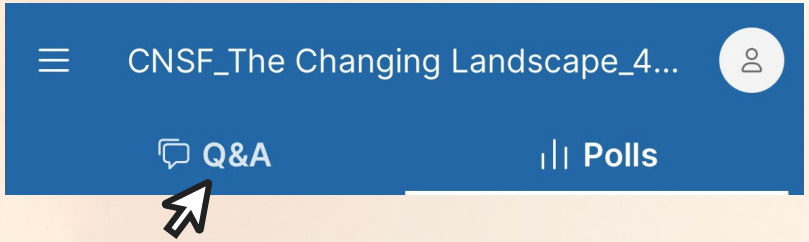


- Please complete the evaluation questionnaire at the end of the session (QR codes can be found on the tables)

THE CHANGING LANDSCAPE

In the Treatment of Alzheimer's Disease

The State of Alzheimer's Disease (AD) in Canada

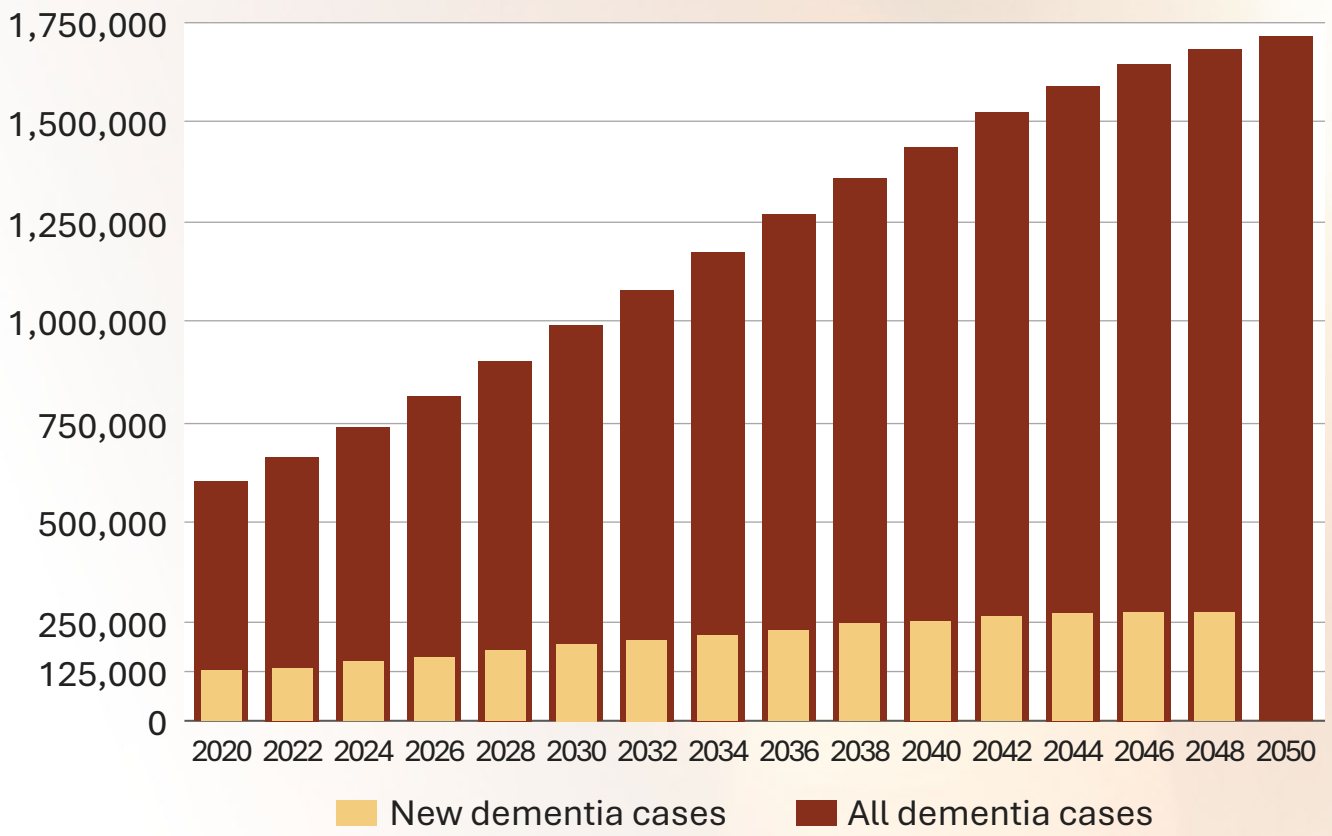
Dr. Sara Mitchell

Are you aware of the new medication options soon becoming available for Alzheimer’s disease in Canada?

In one word, what do you think about these medications becoming available in Canada?

The Upward Trend of Dementia in Canada

Dementia per year in Canada, 2020 to 2050[1]



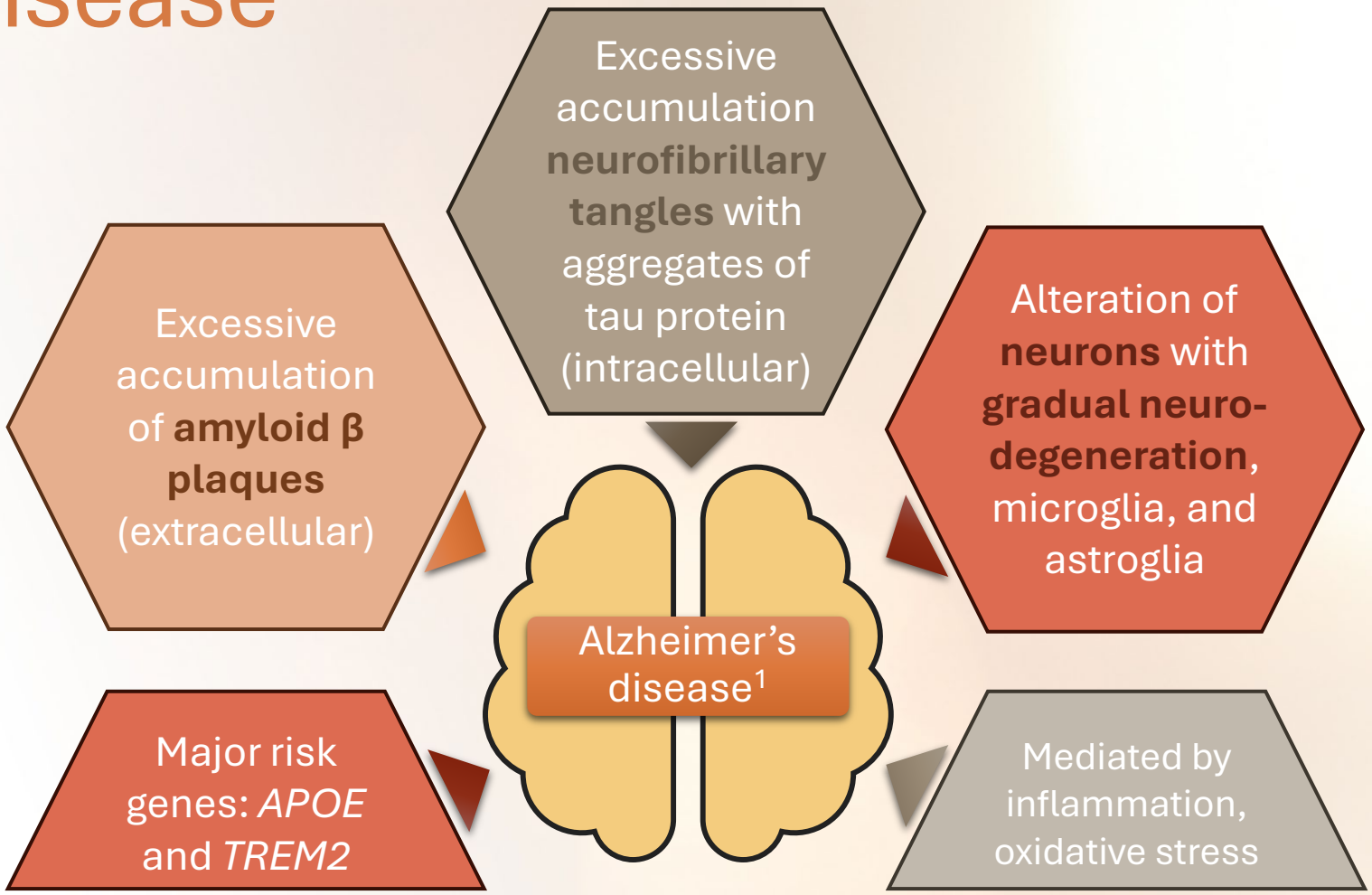
- In 2020, ~600,000 individuals living with dementia and 124,000 new cases
- By 2030, ~1 million of Canadians will be diagnosed with dementia
- By 2050, 1 in 2 who develop dementia will be of European origin and 1 in 4 of Asian origin

60-80% cases of dementia are from Alzheimer's disease

In 2024, ~750,000 Canadians lived with Alzheimer's disease

Data from: Alzheimer Society Canada. The many faces of dementia in Canada, The Landmark Study, Path, 2022

Defining Pathological Features of Alzheimer's Disease



Despite known defining features and mechanisms, the underlying cause of Alzheimer's disease is not fully known.

Current Hypotheses[2]

- **Amyloid cascade hypothesis**
- Tau hypothesis
- Cholinergic hypothesis
- Others (e.g., metabolic, immunologic)

APOE, Apolipoprotein E.; TREM2, Triggering receptor expressed on myeloid cells 2.

1. Scheltens P, et al. Lancet. 2021 Apr 24;397(10284):1577-1590; **2.** Du X, et al. Transl Neurodegener. 2018 Jan 30;7:2.

Alzheimer's Disease is Multifactorial[1-3]

Fixed risk factors	Advancing age	Over 65 years, the risk double every 5 years ~ 1 in 4 affected over 85 years
	Sex at birth	Higher tau load in women despite a similar amyloid β burden as men
	Genetics	60-80% dependent on heritable factors (APOE ε4)
Modifiable risk factors	Lifestyle	Physical, social, and mental activities
	Cardiovascular health	Hypertension, diabetes, midlife obesity, smoking
	Education	"Cognitive reserve" from longer education

Modifiable factors account for 40% of the risk.

Data from: **1.** Alzheimer Society Canada. The many faces of dementia in Canada, The Landmark Study, People, 2024. **2.** Scheltens P, et al. Lancet. 2021;397(10284):1577-1590. **3.** 2023 Alzheimer's disease facts and figures. Alzheimers Dement. 2023 Apr;19(4):1598-1695.

Perspective of Patients and Caregivers on Current Care Options

Most important outcomes for patients and caregivers:

- Maintaining the ability to care for themselves
- Preventing memory loss
- Maintaining quality of life
- Maintaining the ability to think clearly
- Slowing the worsening of symptoms

Uneven dementia care across Canada

- Different experiences (resources, psychological outcomes, caregiver self-care)
- Varying perception:
  - Dementia seen as a consequence of aging, not as a disease
  - Potential social stigma (e.g., being at increased risk, being diagnosed)
- Communication barriers (e.g., people may revert to native language)

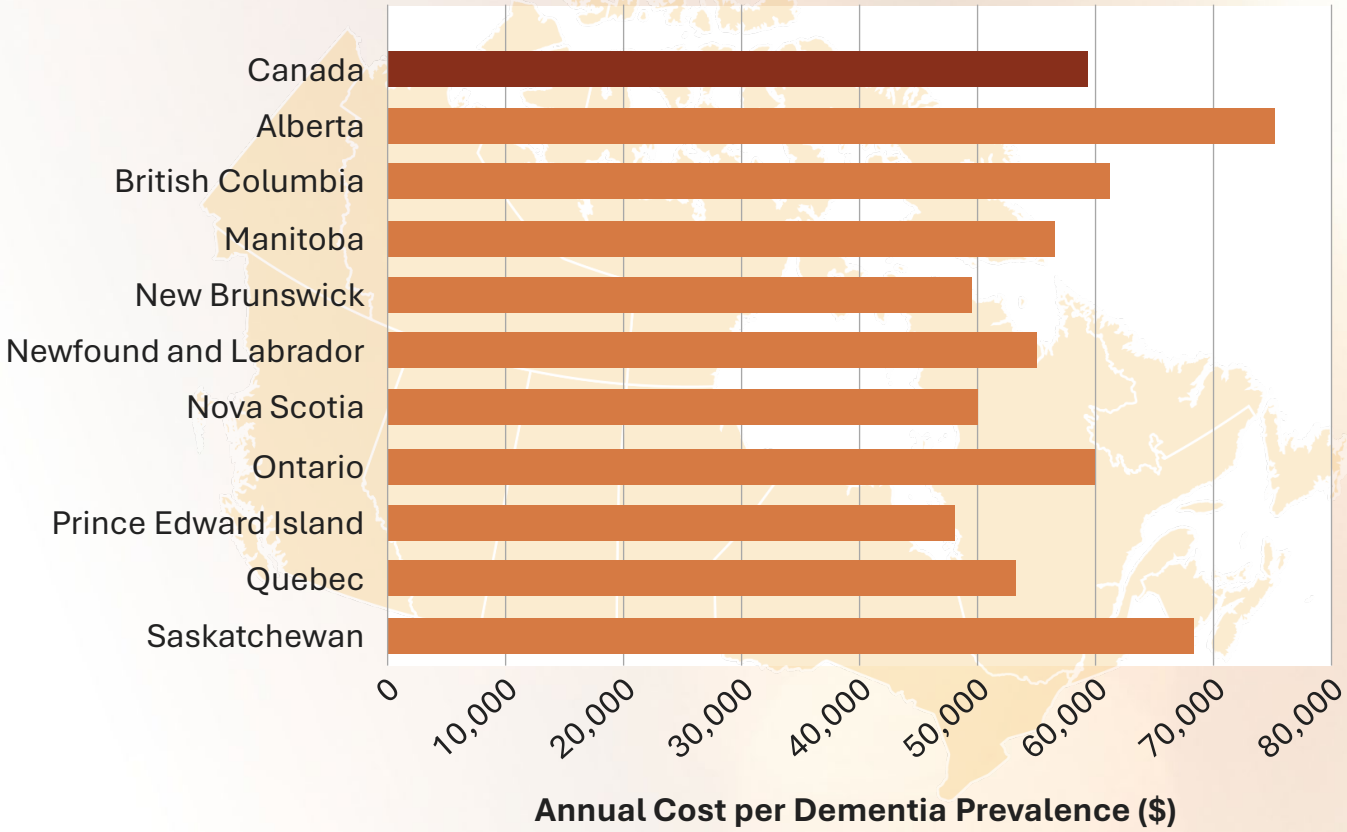
"Just getting an answer as to where he is on the spectrum of cognitive illness is very difficult. Getting access to any kind of support is challenging. The message we hear most often is, I wish we could do more. Goodbye."

- Caregiver

Alzheimer Society Canada. The many faces of dementia in Canada, The Landmark Study, People, 2024

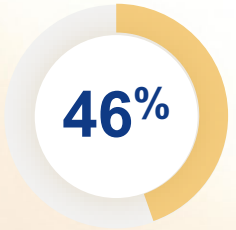
The Heavy Economic Burden of Dementia

Provincial economic burden per dementia case in 2020[2]

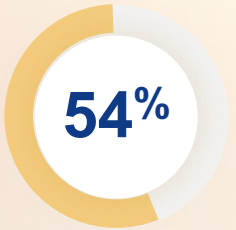


- Total annual cost of dementia in Canada is $40.1 billion in 2020 (estimate)
- Expected to grow to $110.3 billion over the next 30 years

$67,200 **Cost per patient with dementia**



Direct cost:
- Additional hospital stays
- ER visits
- Long-term care



Informal caregiver cost:
- Includes 472 million hours of informal caregiving

Data from: Canadian Centre for Economic Analysis, Dementia in Canada: Economic Burden: 2020 to 2050, 2023

Challenges in the Diagnosis and Treatment of AD in Canada

Current

- **Under-diagnosed** and **lack of timely and accurate** of **early-stage diagnosis** in primary care
- Nihilism due to lack of available treatment options, symptom management only
- **Biomarker testing** limited to a small number of specialists in limited geographic regions
- Management risk/benefits

Future

- Lack of access to specialist care to manage the patients eligible for DMT treatment
- Potential burden of ARIA monitoring and managing on radiological services

New treatment options should trigger a shift in the diagnosis of Alzheimer's from **optional** to **critical and prioritized**

AD, Alzheimer's disease; ARIA, Amyloid-related imaging abnormality; DMT, Disease-modifying therapy.

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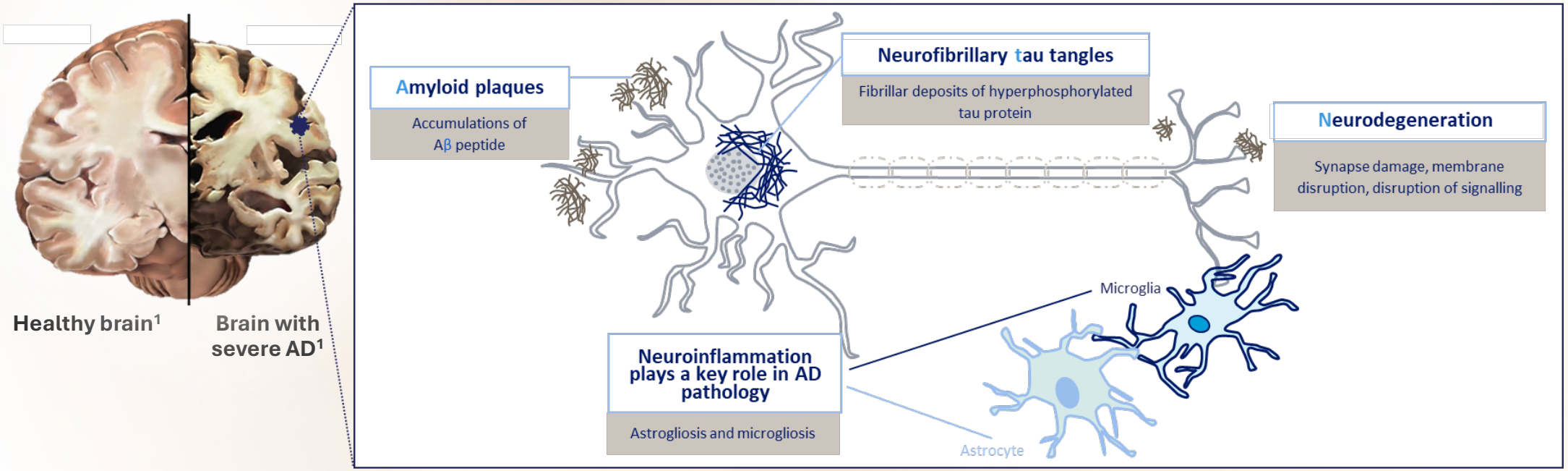
In the Treatment of Alzheimer's Disease

Diagnosis and Biomarkers

Dr. Paolo Vitali

Amyloid β and p-tau in Alzheimer's Disease[1-4]

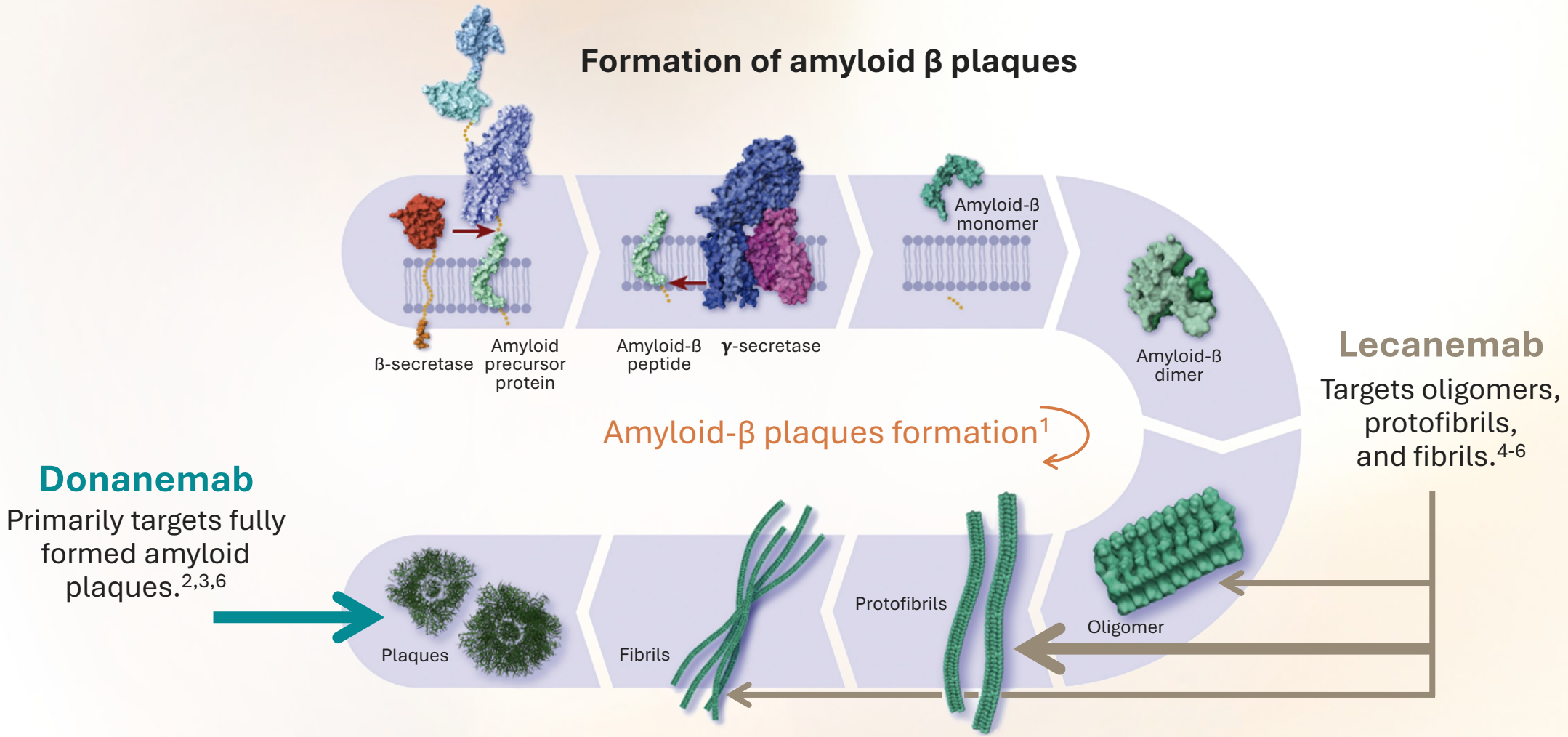
Accumulation of **amyloid plaque** → **Neuroinflammation** (microglia and astrocyte activation) → ← Hyperphosphorylation of **tau protein**



Aß, amyloid beta; AD, Alzheimer's disease.

1. De Castro AKA et al. Int J Comput Intell Syst 2012;4:88–89; **2** .Alzheimer's Association. Alzheimers Dement 2022;18:700–789; **3.** Kinney JW et al. Alzheimers Dement (N Y). 2018;4:575–590; **4.** Minter MR et al. J Neurochem 2016;136:457–474

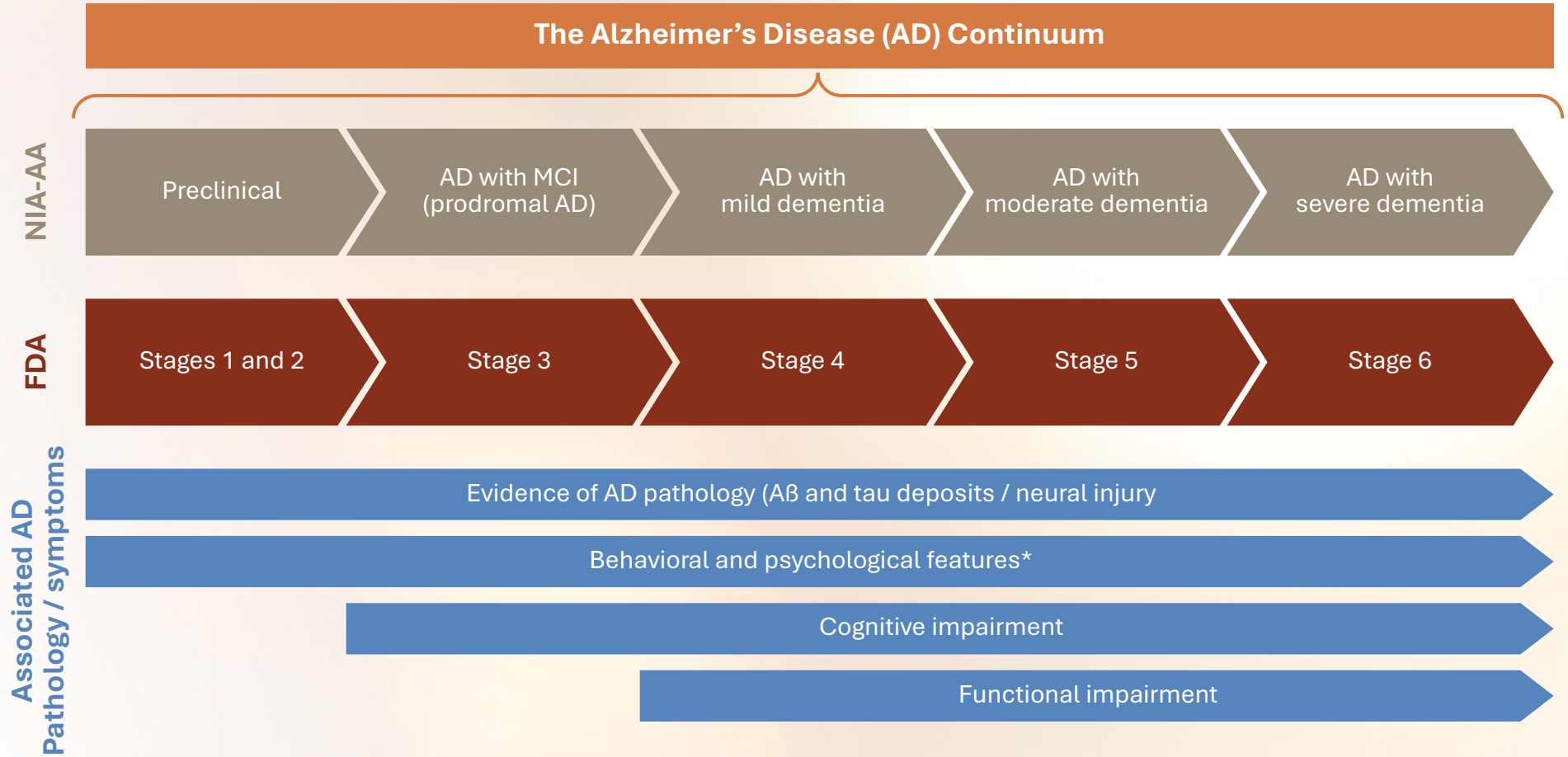
Amyloid β Structures Targeted by DMT Monoclonal Antibodies



Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada

Data from: **1.** Hampel H, et al. Mol Psychiatry 2021;26:5481-5503; 2. Kisunla (donanemab-azbt). Prescribing Information. Lilly USA, LLC. 3. Drolle E, et al. Drug Metab Rev. 2014;46(2):207-223. 4. Lequembi (lecanemab-irmb). Prescribing Information. Eisai Inc. Revised July, 2023. 5. Soederberg L, et al. Neurotherapeutics. 2023;20(1):195-206. 6. Plotkin SS, et al. Neurobiol Dis. 2020 Oct;144:105010).

Clinical and Neuropathological Phases and Staging of AD

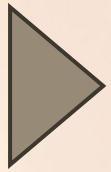


*Mild behavioral impairment is a construct that describes the emergence of sustained and impactful neuropsychiatric symptoms that may occur in patients ≥50 years old before cognitive decline and dementia. AD, Alzheimer's disease; Aβ, Amyloid β; MCI, mild cognitive impairment.
Data from: Kumar A, et al. Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK568805/

Challenges in Diagnosing MCI due to AD[1,2]

- Difficulty of attributing symptoms of MCI to AD and defining clinically meaningful changes in early stages.
  - The early-stage progression is slow
  - Patients show high variability in initial symptoms and presentation
- Cognitive screening tests used in healthcare cannot accurately differentiate between SCD and MCI.
- Modelling shows that the relative MCI prevalence is far too low and MCI is underdiagnosed.

Late diagnosis: 1-2 years of time lost until diagnosis or all-clear



Earlier diagnosis will allow patients to benefit from DMTs

AD, Alzheimer's disease; DMT, Disease-modifying therapy; MCI, mild cognitive impairment; SCD, Subjective cognitive decline.
Liss JL, et al. J Intern Med. 2021;290(2):310-334. Petrazzuoli F, et al. Alzheimers Dis. 2020;75(4):1191-1201.

Diagnostic Tools for Staging Dementia: The CDR-SB Scale

CDR-SB: Validated scale to assess six domains that patients and caregivers identify as important: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care.[1,2]

	Rating scale for each domain*	0 - None	0.5 - Questionable	1 - Mild	2 - Moderate	3 - Severe
COGNITION	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
	Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationship; 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
	Judgement/ Problem-solving	Solves everyday problems, handles business and financial affairs well; judgment good in relation to past performance	Slight impairment in these activities	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
FUNCTION	Community affairs	Independent function at usual level in job, shopping, volunteer and social groups	Life at home, hobbies and intellectual interests slightly impaired.	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	Appears too ill to be taken to functions outside the family home
	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
	Personal care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score overview

- The total score ranges from 0 to 18.
- Higher scores indicate greater impairment.
- A score of 0.5 to 6 indicates early AD.[1,2]

AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes.

1. Van Dyck CH, et al. N Engl J Med 2023;388(1):9-21. **2.** Morris JC. Neurology.1993;43(11):2412-4.

Diagnostic Tools for Staging Dementia: The iADRS Scale[1-3]

- The Phase 3 TRAILBLAZER-ALZ 2 clinical trial utilized the iADRS—a validated, integrated scale of cognition and function, comprised of items from the ADAS-Cog_{13} and ADCS-iADL.*The iADRS measures AD severity and reflects the impact of cognitive loss on the ability to complete daily tasks.

COGNITIVE ABILITY (ADAS-Cog_{13})[a]

- Memory
- Language
- Orientation
- Attention
- Planning and execution of movements

FUNCTIONAL ABILITY (ADCS-iADL)

- Clearing dishes
- Disposing of garbage
- Making meals
- Obtaining beverages
- Using household appliances

- Writing
- Reading
- Keeping appointments
- Shopping
- Getting around
- Finding belongings
- Selecting clothes
- Engaging in hobbies

- Having conversations
- Using the telephone
- Talking about current events
- Watching television
- Being left alone

***The total score ranges from 0 to 144, with lower scores reflecting a greater global AD severity.[2]**

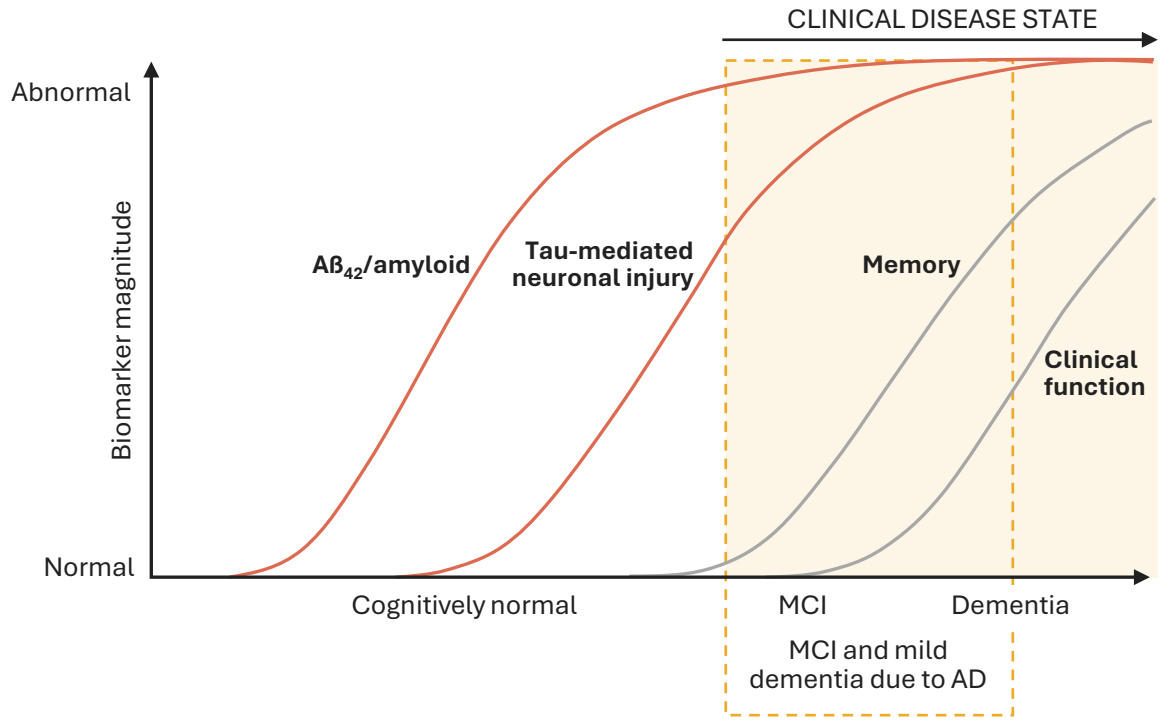
[a]Examples include domains assessed under cognitive ability and individual items assessed for functional ability.[1]

ADAS-Cog_{13}=Alzheimer's disease Assessment Scale-Cognitive Subscale; ADCS-iADL=Alzheimer's disease Cooperative Study-instrumental Activities of Daily Living; iADRS=Integrated Alzheimer's disease Rating Scale.

1. Wessels AM, et al. Neurol Clin Pract. 2023;13(2):e200127. **2.** Sims JR, et al. JAMA. 2023;330(6):512-527. **3.** Kisunla (donanemab-azbt). Prescribing Information. Lilly USA, LLC.

Targeting Amyloid Unlocks an Opportunity to Treat Early and Slow Disease Progression in Symptomatic AD[1-6]

Biomarker Changes in AD: Timeline of Biomarker Accumulation and Neurodegeneration[3]



- Abnormal accumulation of amyloid plaques in the brain initiates a complex cycle of synaptic loss and neuronal death that results in cognitive decline[1-5]

- **Targeting amyloid plaques early may benefit patients with early symptomatic AD (MCI and mild dementia due to AD)[1,6]**

Aβ, Amyloid Beta; Alzheimer's disease; MCI, Mild Cognitive Impairment.

Data from: **1.** Alzheimer's Association. Alzheimer's disease facts and figures. *Alzheimers Dement.* 2023;19(4):1598-1695. **2.** Jack CR Jr, et al. *Lancet Neurol.* 2013;12(2):207-216. **3.** Jack CR Jr, et al. *Lancet Neurol.* 2010;9(1):119-128. **4.** Villemagne VL, et al. *Lancet Neurol.* 2013;12(4):357-367. **5.** Raskin J, et al. *Curr Alzheimer Res.* 2015;12(8):712-722. **6.** Porsteinsson AP, et al. *J Prev Alzheimers Dis.* 2021;8(3):371-386.

Biological Staging of Alzheimer's Disease

Categorization of fluid analyte and imaging biomarkers

Biomarker category	CSF or plasma analytes	Imaging
Core markers		
Core 1		
A (Aß proteinopathy)	Aß 42	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	p-tau217, p-tau181, p-tau231[a]	
Core 2		
T_2 (AD tau proteinopathy)	MTBR-tau243[a], other phosphorylated tau forms (e.g., p-tau205[a]), non-phosphorylated mid-region tau fragments[a,b]	Tau PET
Biomarkers of nonspecific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MRI, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD copathology		
V vascular brain injury		Infarction on MRI or CT, WMH
S α-synuclein	αSyn-SAA[a]	

(s) Did not undergo the same level of validation testing as other Core biomarkers. (b) A fluid analyte that is presently informative only when measured in CSF.
Aβ, amyloid beta; AD, Alzheimer's disease; αSyn-SAA, alphasynuclein seed amplification assay; CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; GFAP, glial fibrillary acidic protein; MRI, magnetic resonance imaging; MTBR, microtubule-binding region; NfL, neurofilament light chain; PET, positron emission tomography; WMH,white matter hyperintensity.
Data from: Jack CR, J. et al. Alzheimer's & dementia. 2024;20(8).

Shifting From a Clinical to a Biomarker-Based Diagnostic Approach

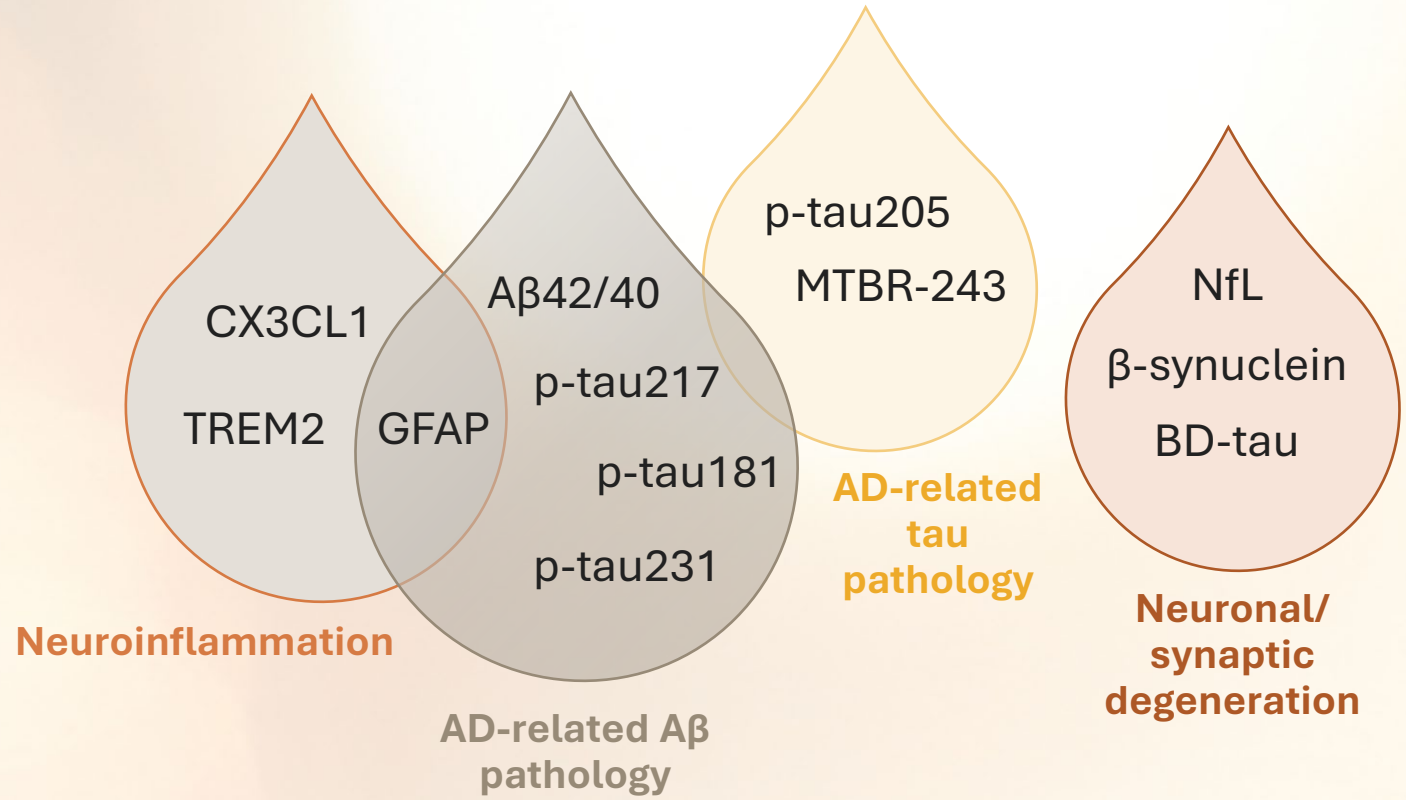
Amyloid PET
Non-invasive imaging to confirm amyloid deposition in the brain.

Tau PET
Provides insight into tau pathology, complementing amyloid imaging.

CSF Analysis
Lumbar puncture for measuring amyloid-beta and tau levels, offering a cost-effective alternative to PET scans.

Serum p-tau
Emerging blood biomarkers may serve as a less invasive screening tool.

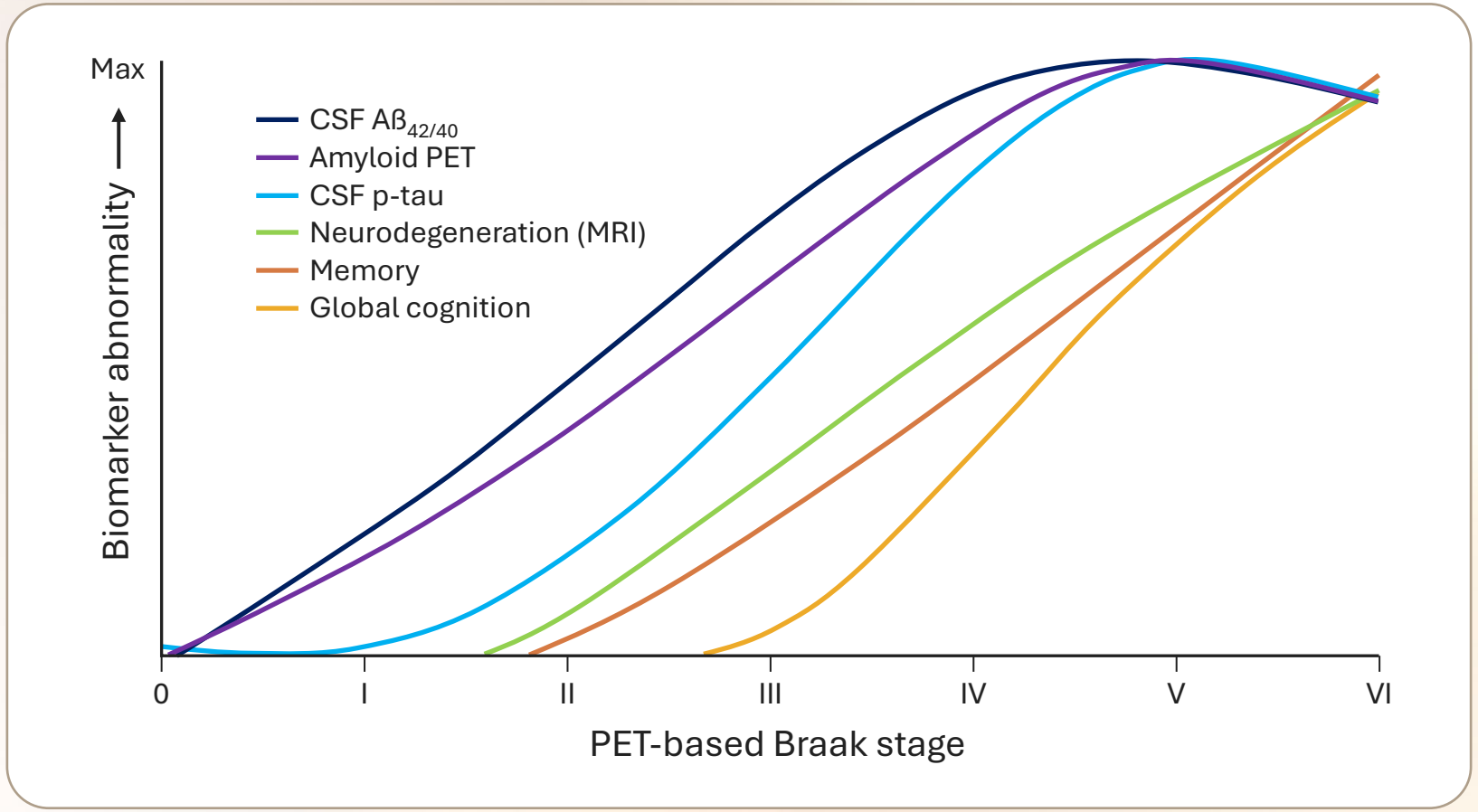
Blood biomarkers



Aß, Amyloid ß; AD, Alzheimer's disease; BD-Tau, Brain-derived tau; CSF, Cerebrospinal fluid; CX3CL1, C-X3-C motif chemokine ligand 1; GFAP, Glial fibrillary acidic protein; MTBR-243, Microtubule binding region with residue 243; NfL, Neurofilament light chain; PET, Positron emission tomography; p-tau, Phosphorylated tau; TREM2, triggering receptor expressed on myeloid cells 2.Data from: 1. Smith EE, et al. J Prev Alzheimers Dis. 2025;12(3):100068. 2. Schöll M, et al. Lancet Healthy Longev. 2024;5(10):100630.

Using Biomarkers to Stage AD Neuropathology

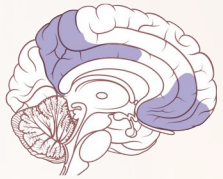
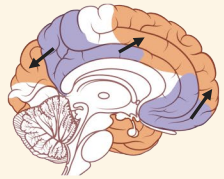
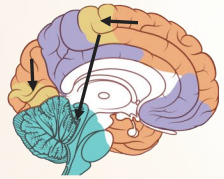
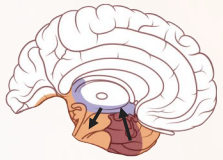
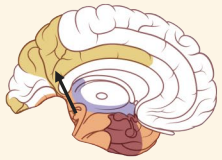
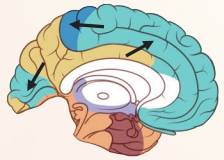
Clinical and biomarker changes in relation to AD pathological stage severity



Aβ, Amyloid β; AD, Alzheimer's disease; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography.
Data from: Therriault J, et al. Nat Rev Neurol. 2024;20(4):232-244.

Significance of Blood Biomarker Testing

Key blood-based biomarkers for the diagnosis of AD.[1]

	Cognitively unimpaired	MCI	Dementia
Aß pathology			
Tau pathology			
AD diagnosis	p-tau231 (or p-tau217) + Aß42/Aß40	p-tau217 (+MTBR-tau)	p-tau217 (+MTBR-tau)
Predicting AD dementia	p-tau217 + cognitive tests (+MTBR-tau)	p-tau217 + cognitive tests (+MTBR-tau)	NA

Aβ42/40[2]

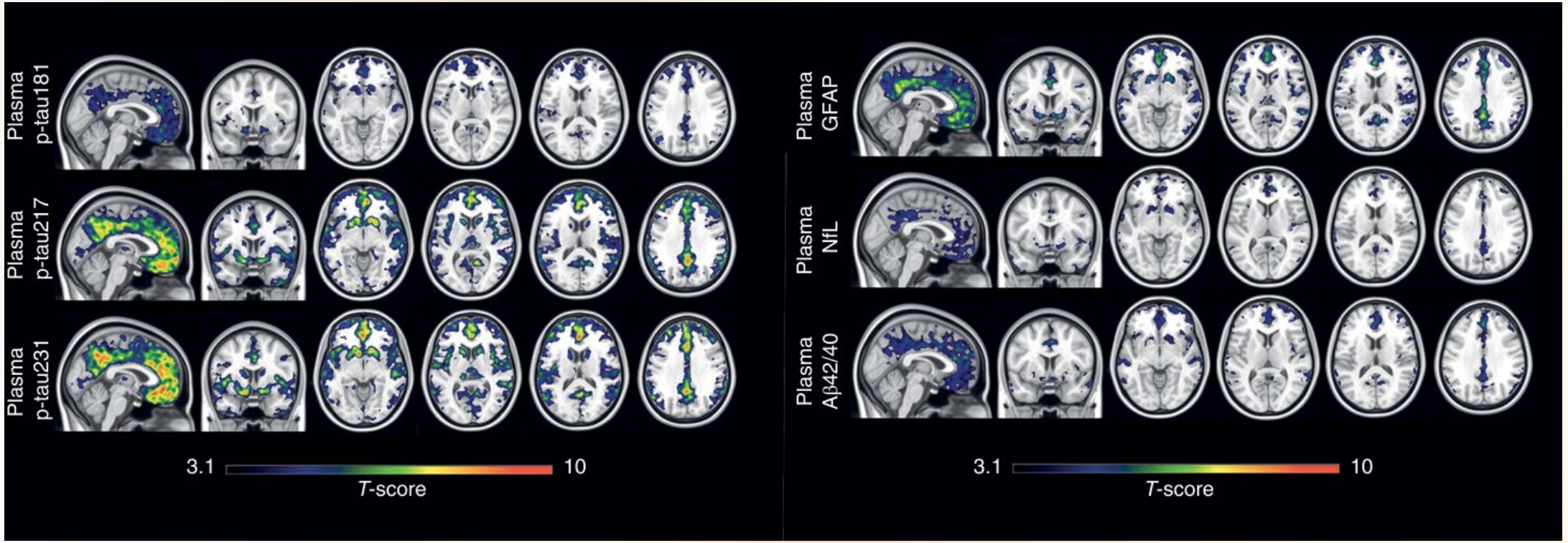
- Decrease in blood correlates with cerebral Aβ pathology (PET or CSF), especially in the early stages.
- Better differentiation between AD and other neurodegenerative diseases.
- Low fold change between amyloid β-positive and amyloid β-negative individuals, based on measurements of PET or CSF amyloid β.

Phosphorylated-tau (p-tau)[2]

- Strong performance of different isoforms (e.g., p-tau181, p-tau231, p-tau217) in detecting AD.
- p-tau217: best-performing blood biomarker (equivalent to CSF testing for identifying amyloid β-positivity).
- p-tau231: potential for early detection of AD.

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
Aß, Amyloid ß; AD, Alzheimer's disease; CSF, Cerebrospinal fluid; MCI, Mild cognitive impairment; MTBR, Microtubule binding region; PET, Positron emission tomography; p-tau, Phosphorylated tau. Data from: 1. Hansson O, et al. Nat Aging. 2023;3(5):506-519. 2. Schöll M., et al. The Lancet Healthy Longevity, Volume 5, Issue 10, 100630

Plasma p-tau as an Early Biomarker for AD, Cont'd



p-tau217 had the strongest association with Aβ PET in areas known to show early Aβ accumulation

Aβ, Amyloid β; AD, Alzheimer's disease; NfL, Neurofilament light chain; PET, positron emission tomography.
Data from: Milà-Alomà M, et al. Nat Med. 2022 Sep;28(9):1797-1801. Copyright © licensed under CC-BY-4.0 (https://creativecommons.org/licenses/by/4.0/)

Blood-Based Biomarkers Currently Available

Clinically validated, regulation-compliant diagnostic tests *

Target	Biomarker	Platform (Company)
β-Amyloid	Aβ40, Aβ42	CLEIA (Sysmex)
Tau	p-tau181	SIMOA (Quanterix) #
Panel	p-tau181, APOE status	ECLIA (Roche) #
	Aβ42/Aβ40, APOE status, %p-tau	LC-MS/MS (C_2N Diagnostics) #

p-tau217 / Aß42 plasma ratio (Fujirebio) received FDA clearance

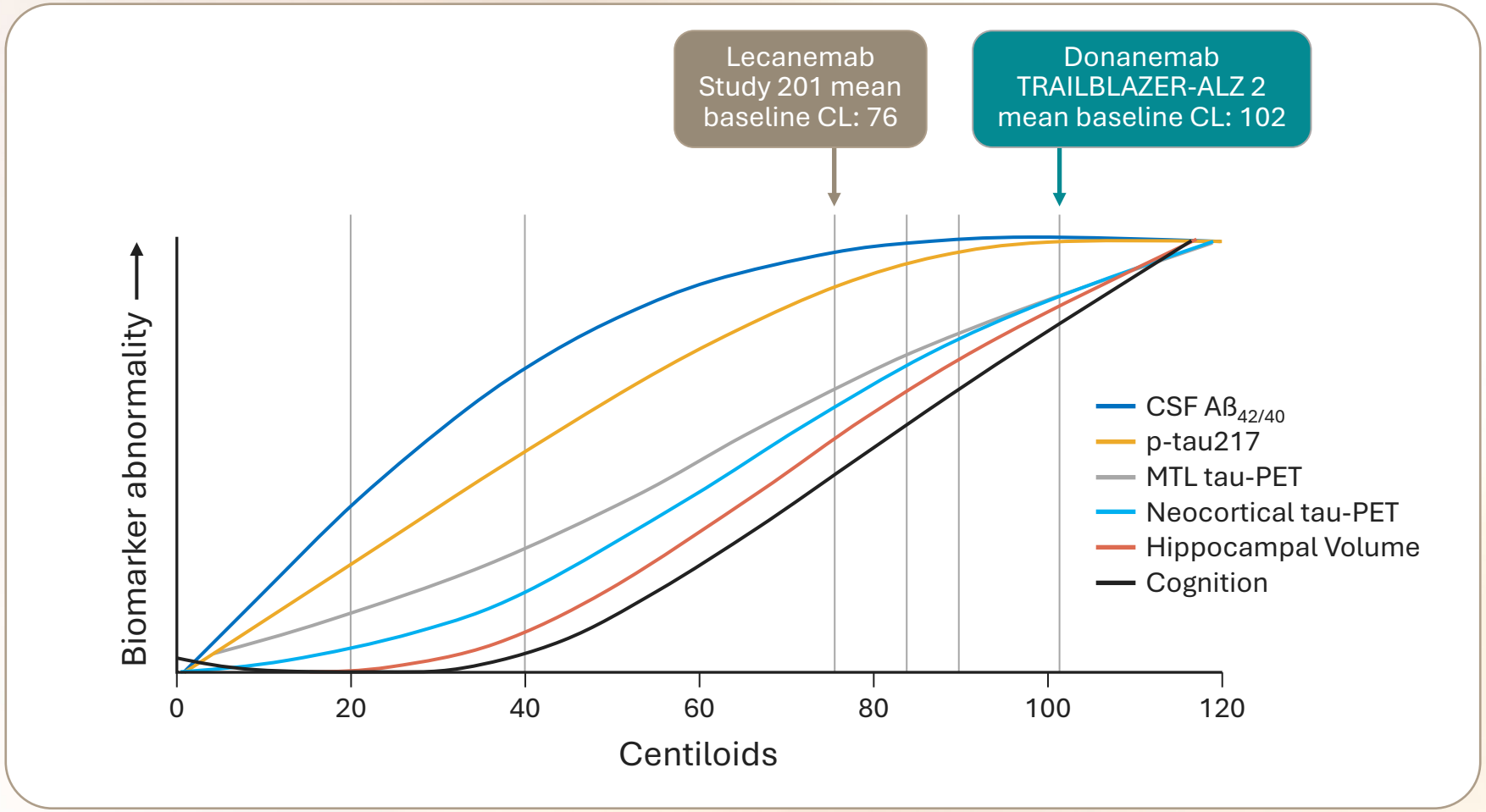
- Other tests and platforms are available for research use only or have been validated in local clinical settings.
- Tests under development require validation in heterogenous cohorts to ensure their robustness of accuracy against factors that can affect results (e.g., sample stability, comorbidities).

Blood-based biomarkers will help accelerate early detection and provide more accurate diagnosis. However, standardization will be needed.

* The tests undergo extensive clinical validation and full regulatory review; † Under review; # FDA breakthrough device; ‡ Laboratory-developed test.
Data from: Schöll M, et al. J Prev Alzheimers Dis. 2025 Apr;12(4):100056.

Window for DMT Treatment

Biomarker-based staging informs the design and expectations of DMTs



Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted CL, Centiloid; CSF, cerebrospinal fluid; DMT, Disease-modifying therapy; MTL, Medial temporal lobe; PET, positron emission tomography.
Data from: Therriault J, et al. Nat Rev Neurol. 2024 Apr;20(4):232-244.

THE CHANGING LANDSCAPE

In the Treatment of Alzheimer's Disease

Panel Discussion: Diagnosis and Biomarkers

Dr. Mitchell, Dr. Vitali, Dr. Frank

THE CHANGING LANDSCAPE

In the Treatment of Alzheimer's Disease

Disease-Modifying Treatments – Clinical Trial Efficacy Results

Dr. Andrew Frank

Changing the Future of How We View and Treat AD

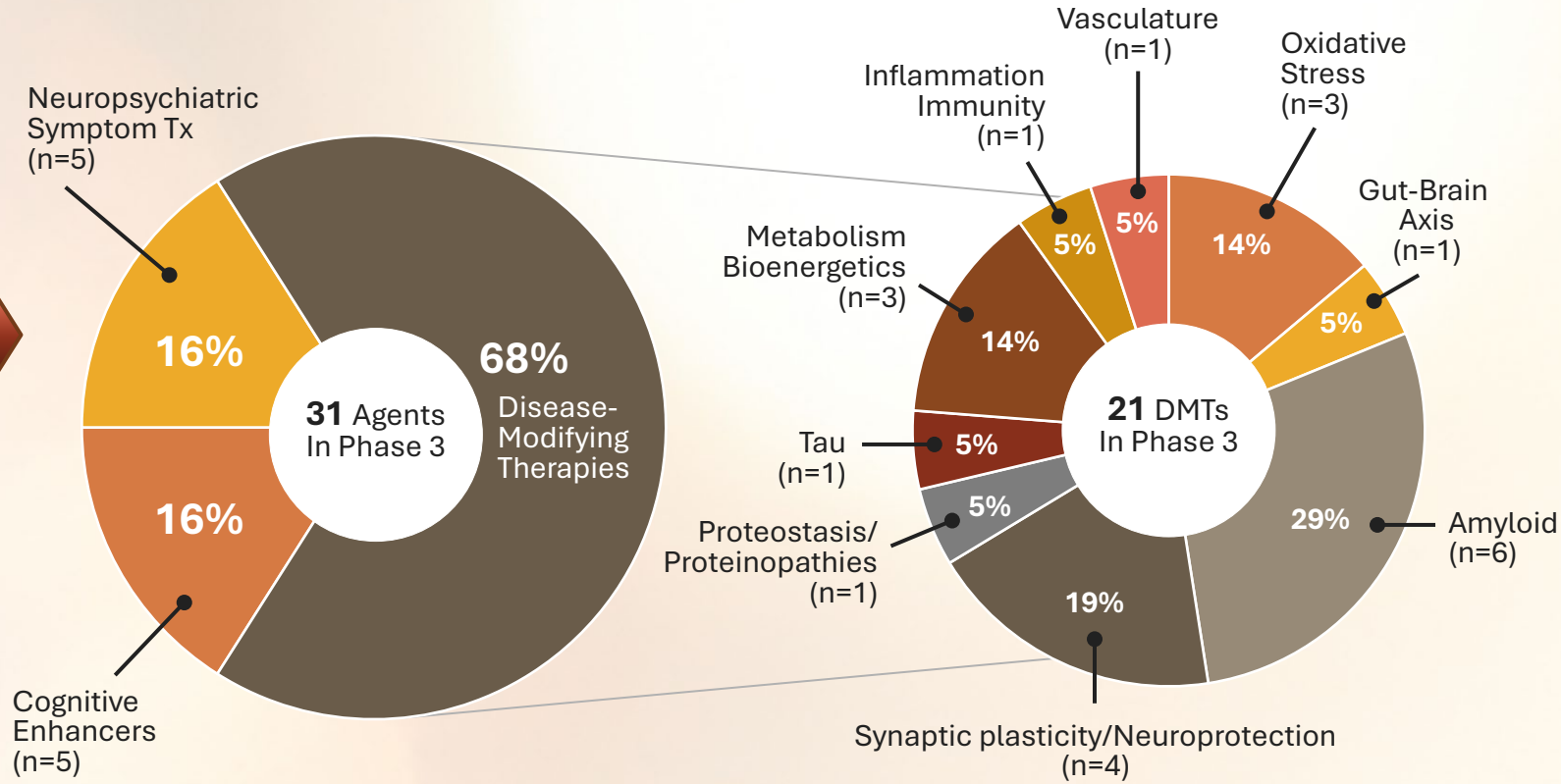
- Previous treatments focused on AD symptoms and stabilization of cognitive and functional impairment (e.g., Cholinesterase inhibitors, memantine).
- 30 years of research, starting from the discovery of amyloid precursor protein (APP) mutations, lead to the development of DMTs.

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada. AD, Alzheimer's disease; APP, Amyloid precursor protein; Aβ, Amyloid-β; CSF, cerebrospinal fluid; DMT, Disease-modifying therapy; PET, positron emission tomography. Boxer AL, et al. Cell. 2023;186(22):4757-4772.

A Vast Drug Development Pipeline

Trials	Number of Agents	Number of trials
Phase 1	31	47
Phase 2	82	94
Phase 3	30	31

Mechanism of action of agents in Phase 3 trials



DMTs represent 83.2% of the total number of agents in trials

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
DMT, Disease-modifying therapy.
Data from: Cummings J, et al. Alzheimers Dement (N Y). 2022;8(1):e12295.

Current, Ongoing, and Future Targeted Changes in Biomarkers

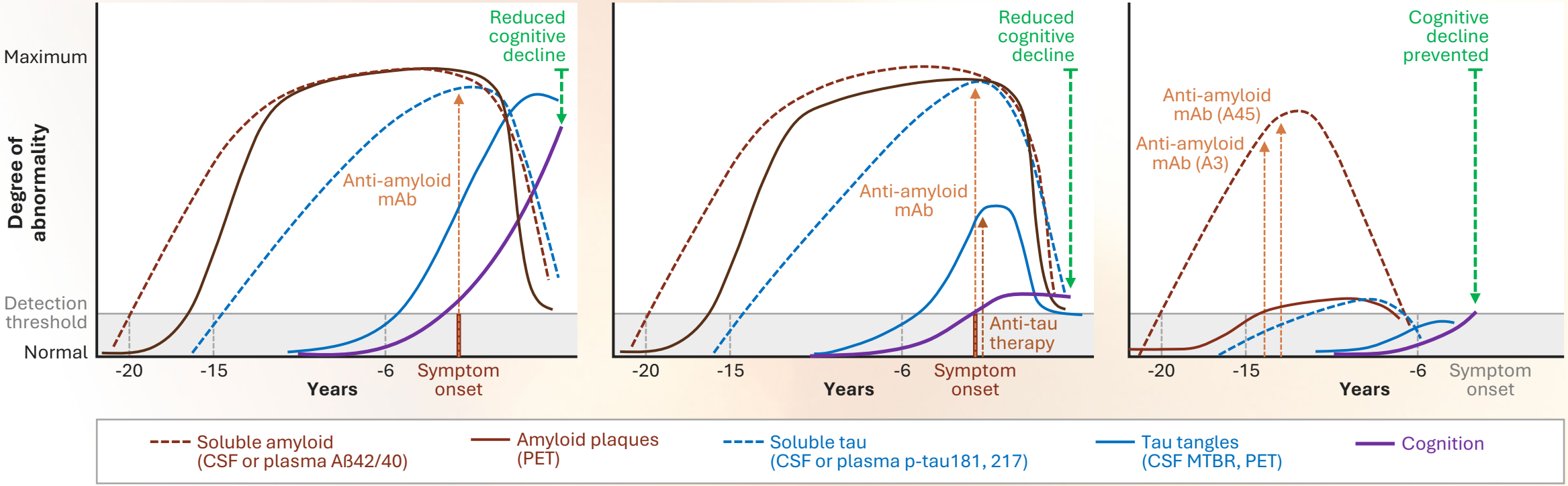
Reported changes in biomarkers

Biomarker and cognitive changes after treatment with **lecanemab** or **donanemab**

Predicted changes in biomarkers

Alzheimer's Tau Platform (ATP) study (planned)

Ongoing A3-45 (AHEAD) prevention study

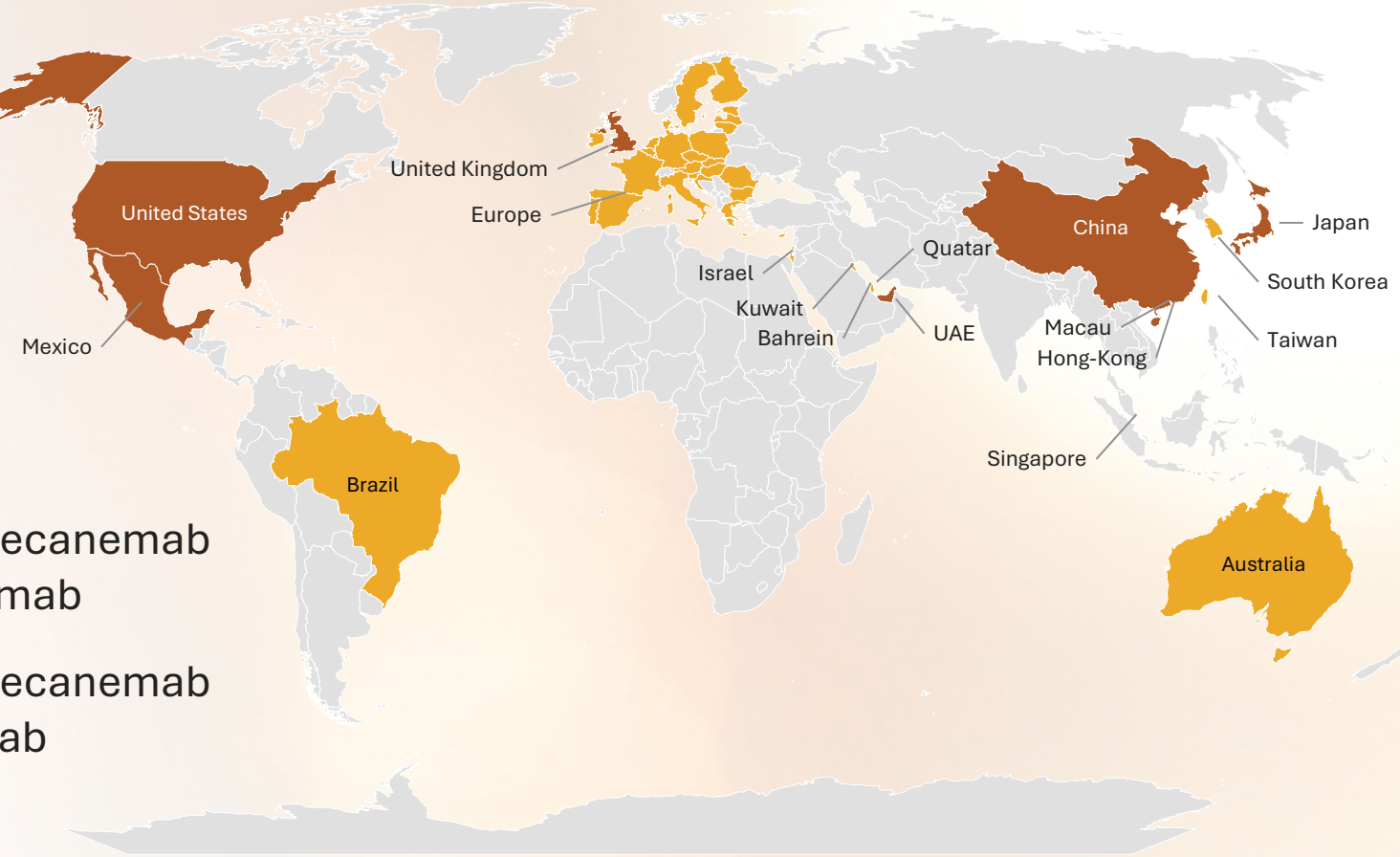


Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada

Aβ, Amyloid β; CSF, cerebrospinal fluid; mAb, Monoclonal antibody; MTBR, Microtubule binding region; PET, positron emission tomography.

Data from: Boxer AL, et al. Cell. 2023;186(22):4757-4772.

Approval of Monoclonal Antibodies Against Amyloid β*



Approval of lecanemab **and** donanemab

Approval of lecanemab **or** donanemab

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada

* Approval as of May 2025

Overview of the Two Positive Phase 3 Trials

	CLARITY-AD (lecanemab)[1]	TRAILBLAZER ALZ 2 (donanemab)[2]
Study design	Double-blind, placebo-controlled	
Study duration	18 months + OLE up to 2 years	76 weeks + 78-week LTE
Number of participants	**1795**	**1736**
Treatment frequency	**Every 2 weeks**	**Every 4 weeks**
Treatment duration	Continuous	Discontinued if amyloid fell below a pre-specified threshold
Participant Age	50-90 years	60-85 years
Participant MMSE	22 to 30 (MCI or Mild AD)	20 to 28 (MCI or Mild AD)
Confirmed AD pathology	Amyloid PET or CSF	Amyloid PET and Tau PET
Baseline MRI inclusion criteria	≤4 cerebral microhemorrhages, ≤1 area of superficial siderosis, no ARIA-E, no macrohemorrhage, and no severe white matter disease	
Primary outcome	**CDR-SB change**, baseline to 18 months	**iADRS change**, baseline to 76 weeks
Key secondary outcome measures	ADAS-Cog$_{14}$, ADCOMS, ADCS-MCI-ADL (Substudy: Amyloid burden on PET)	**CDR-SB**, ADCS-iADL, ADAS-Cog$_{13}$, CDR-GS (gated biomarker outcomes: amyloid PET, tau PET)
Special trial features		Two primary analysis populations: (1) low-medium tau and (2) combined population

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* low-medium tau level population: SUVR of ≥1.10 and ≤1.46. See notes for definition of acronyms. **1.** Van Dyck CH, et al. *N Engl J Med* 2023;388(1):9-21. **2.** Sims JR, et al. *JAMA.* 2023;330(6):512-527.

CLARITY-AD: Double-Blind, Placebo-Controlled Design

Pre-randomization → **Double-blind treatment period – IV administration** → **Follow-up** → **Open-Label Extension Phase**

*Up to **65 days*** | ***18 months*** | ***3 months*** | ***Up to 2 years****

(n=1734)

(n=859) → **Lecanemab** / 10 mg/kg Q2W

Randomization stratified by clinical subgroup, concomitant use of approved symptomatic AD medication at baseline, *ApoEε4* status, and geographic region.

(n=875) → **Placebo** Q2W

Months	0	3	6	12	13	18
Safety MRI	★ ★	★	★	★		★
CSF analysis	★			★		★
Amyloid PET scan	★	★	★	★		★
Tau PET scan	★				★	★

Optional sub-studies to evaluate:
- Changes in brain amyloid burden
- Brain tau pathologic features
- CSF biomarkers

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*Extension Phase scheduled to continue for up to 2 years, or until commercial availability of lecanemab, or until a positive risk-benefit assessment in this indication was not demonstrated.

AD, Alzheimer's disease; ApoEε4, Apolipoprotein E ε4; CSF, Cerebrospinal fluid; IV, intravenous; MRI, Magnetic Resonance Imaging; OLE, open-label extension; PET, Positron Emission Tomography; Q2W, Once Every 2 Weeks.

Van Dyck CH, et al. N Engl J Med 2023;388(1):9-21 and Appendix (Study Protocol).

CLARITY-AD: Outcome Measures

PRIMARY OUTCOME

CDR-SB

Clinical Dementia Rating – Sum of Boxes: Obtained by interviewing patients to assess cognition and function in six domains (Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care).

[*scores range from 0-18 with higher score=greater impairment*]

- Change from baseline to 18 months

Key secondary end points

- Amyloid burden on PET (substudy)
- ADAS-Cog_{14}
- ADCOMS
- ADCS-MCI-ADL

Biomarker Assessments

- CSF biomarkers (Aβ1-40, Aβ1-42, total tau, p-tau181, neurogranin, and NfL)
- Plasma biomarkers (Aβ42/40 ratio, p-tau181, GFAP, and NfL)
- Tau PET
- Volumetric MRI

Exploratory Outcome

Time to worsening of the global CDR score*

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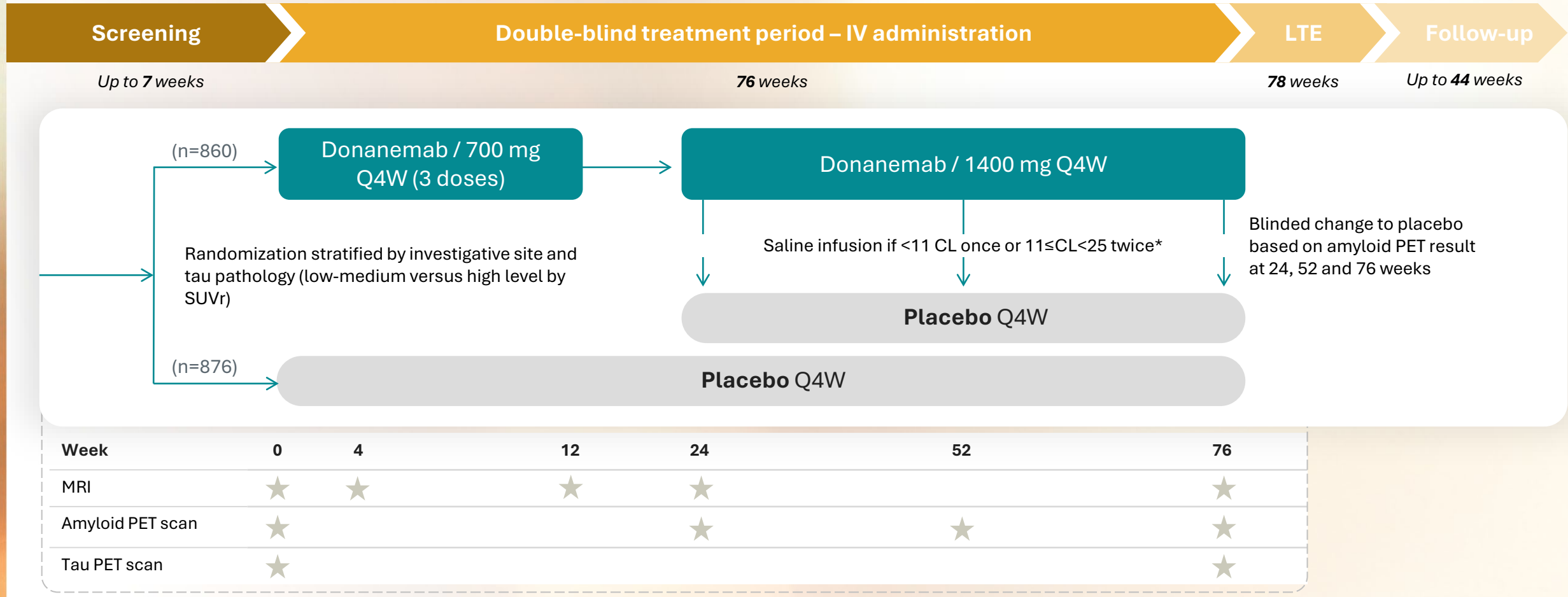
* Defined as the time to the first increase of at least 0.5 points in the global CDR score on two consecutive visits.

AD, Alzheimer's disease; ADAS-Cog14, Alzheimer's disease Assessment Scale–14-item Cognitive Subscale; ADCS-MCI-ADL, Alzheimer's disease Cooperative Study Activities of Daily Living scale for Mild Cognitive Impairment; CDR-G, Clinical Dementia Rating Global Score; CDR-SB, Clinical Dementia Rating Scale-Sum of Boxes; CSF, cerebrospinal fluid; GFAP. glial fibrillary acidic protein; iADRS, Integrated Alzheimer's disease Rating Scale; MRI, magnetic resonance imaging; NfL, neurofilament light chain; PET, Positron Emission Tomography; p-tau217, Phosphorylated tau 217. Van Dyck CH, et al. N Engl J Med 2023;388(1):9-21.

TRAILBLAZER-ALZ 2: Double-Blind, Placebo-Controlled Design, with Limited-Duration Donanemab Dosing Based on Amyloid Clearance[1,2]



Week	0	4	12	24	52	76
MRI	★	★	★	★		★
Amyloid PET scan	★			★	★	★
Tau PET scan	★					★

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*In the protocol, if the amyloid plaque level was <11 CL on a single PET scan or 11 to <25 CL on 2 consecutive PET scans, the patient was eligible to be switched to placebo1,2
For reference, <24.1 CL on an amyloid PET scan is consistent with a negative visual read3
CL, Centiloids; IV, Intravenous; LTE, Long Term Extension; MRI, Magnetic Resonance Imaging; PET, Positron Emission Tomography; Q4W, Once Every 4 Weeks; SUVr, Standardized Uptake Value ratio. Data from: 1. Kisunla (donanemab-azbt). Prescribing Information. Lilly USA, LLC. 2. Sims JR, et al; for TRAILBLAZER-ALZ 2 Investigators. JAMA. 2023;330(6):512-527. 3. Navitsky M, et al. Alzheimers Dement. 2018;14(12):1565-1571.

TRAILBLAZER-ALZ 2: Outcome Measures

PRIMARY OUTCOME

iADRS

Integrated assessment of cognition and daily function comprised of items from the ADAS-Cog_{13} and the ADCS-iADL, measuring global AD severity across the AD continuum

[*scores range from 0-144 with lower score=greater impairment*]

- Change from baseline to Week 76 in either low-medium tau pathology population or combined population

Gated Clinical Outcomes

- CDR-SB
- ADCS-iADL
- ADAS-Cog13
- CDR-GS

Gated Biomarker Outcomes

- Amyloid PET
- Tau PET

Exploratory Outcomes

CDR-GS – Progression risk[a]

CDR-SB – Participants with no progression at 1 year; clinical progression delay (months saved with treatment)*

iADRS – Clinical progression delay (months saved with treatment)*

Change in plasma p-tau217 at Week 76

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
*Gated in low-medium tau population; (a) Progression risk defined as any increase from baseline in CDR-G at consecutive visits.
AD, Alzheimer's disease; ADAS-Cog13, Alzheimer's disease Assessment Scale–13-item Cognitive Subscale; ADCS-iADL, Alzheimer's disease Cooperative Study-instrumental Activities of Daily Living Inventory; CDR-G, Clinical Dementia Rating Global Score; CDR-SB, Clinical Dementia Rating Scale-Sum of Boxes; iADRS, Integrated Alzheimer's disease Rating Scale; PET, Positron Emission Tomography; p-tau217, Phosphorylated tau 217.
Sims JR, et al. JAMA. 2023; 330(6):512-527.

Baseline Demographics and Clinical Characteristics in the Overall Trial Populations

		CLARITY-AD[1]		TRAILBLAZER ALZ 2[2]	
		LECANEMAB (n=859)	PLACEBO (n=875)	DONANEMAB (n=860)	PLACEBO (n=876)
Female, n (%)		443 (51.6%)	464 (53.0%)	493 (57.3%)	503 (57.4%)
Mean age, years (SD)		71.4 ± 7.9	71.0 ± 7.8	73.0 ± 6.2	73.0 ± 6.2
White race, n (%)[a]		655 (76.3%)	677 (77.4%)	781 (90.9%)	807 (92.1%)
APOEε4 carrier, n (%)		592 (68.9%)	600 (68.6%)	598 (69.8%)	621 (71.2%)
APOEε4 homozygotes, n (%)		136 (15.8%)	132 (15.1%)	143 (16.7%)	146 (16.7%)
Use of medication for symptoms of AD, n (%)		447 (52.0%)	468 (53.5%)	521 (60.6%)	538 (61.4%)
MMSE score, mean (SD)[g]		25.5 ± 2.2	25.6 ± 2.2	22.4 (3.8)	22.2 (3.9)
Clinical subgroup, n (%)					
• MCI due to AD*		528 (61.5%)	544 (62.2%)	146 (17.0%)	137 (15.7%)
• Mild dementia due to AD*		331 (38.5%)	331 (37.8%)	713 (82.9%)	738 (84.3%)
CDR-SB baseline score, mean, (SD)[b]		3.17 ± 1.34	3.22 ± 1.34	4.0 ± 2.1	3.9 ± 2.1
Amyloid PET baseline burden in Centiloids, mean (SD)[c]		77.92 ± 44.84	75.03 ± 41.82	103.5 ± 34.5	101.6 ± 34.5
ADAS-Cog14 baseline score, mean, (SD)[d]	iADRS baseline score, mean, (SD)	24.45 ± 7.08	24.37 ± 7.56	104.1 ± 14.3	103.6 ± 14.0
ADCOMS baseline score, mean, (SD)[e]		0.398 ± 0.147	0.400 ± 0.147		
ADCS-MCI-ADL baseline score, mean (SD)[f]		41.2 ± 6.6	40.9 ± 6.9		

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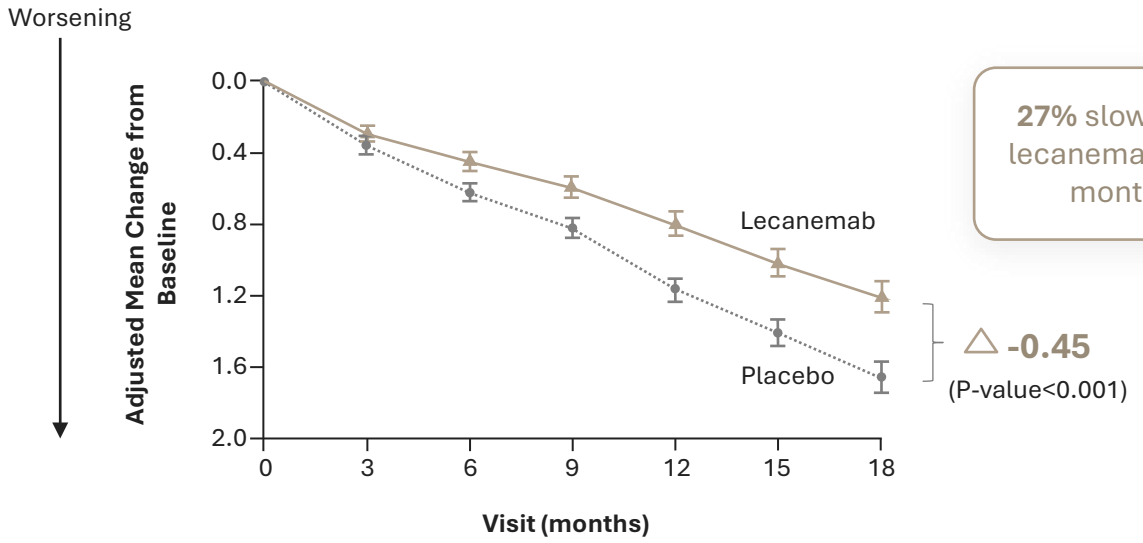
See slide notes for qualifying information and abbreviations. Data from: **1.** Van Dyck CH, et al. N Engl J Med 2023;388(1):9-21. **2.** Sims JR, et al. JAMA. 2023;330(6):512-527.

CLARITY-AD: Lecanemab Demonstrated to Slow Progression in Patients With Early Symptomatic AD[1,2]

CDR-SB change from baseline through 18 months[1]

Primary Endpoint: CDR-SB (Modified ITT Population)[1]



27% slowing by lecanemab at 18 months

No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

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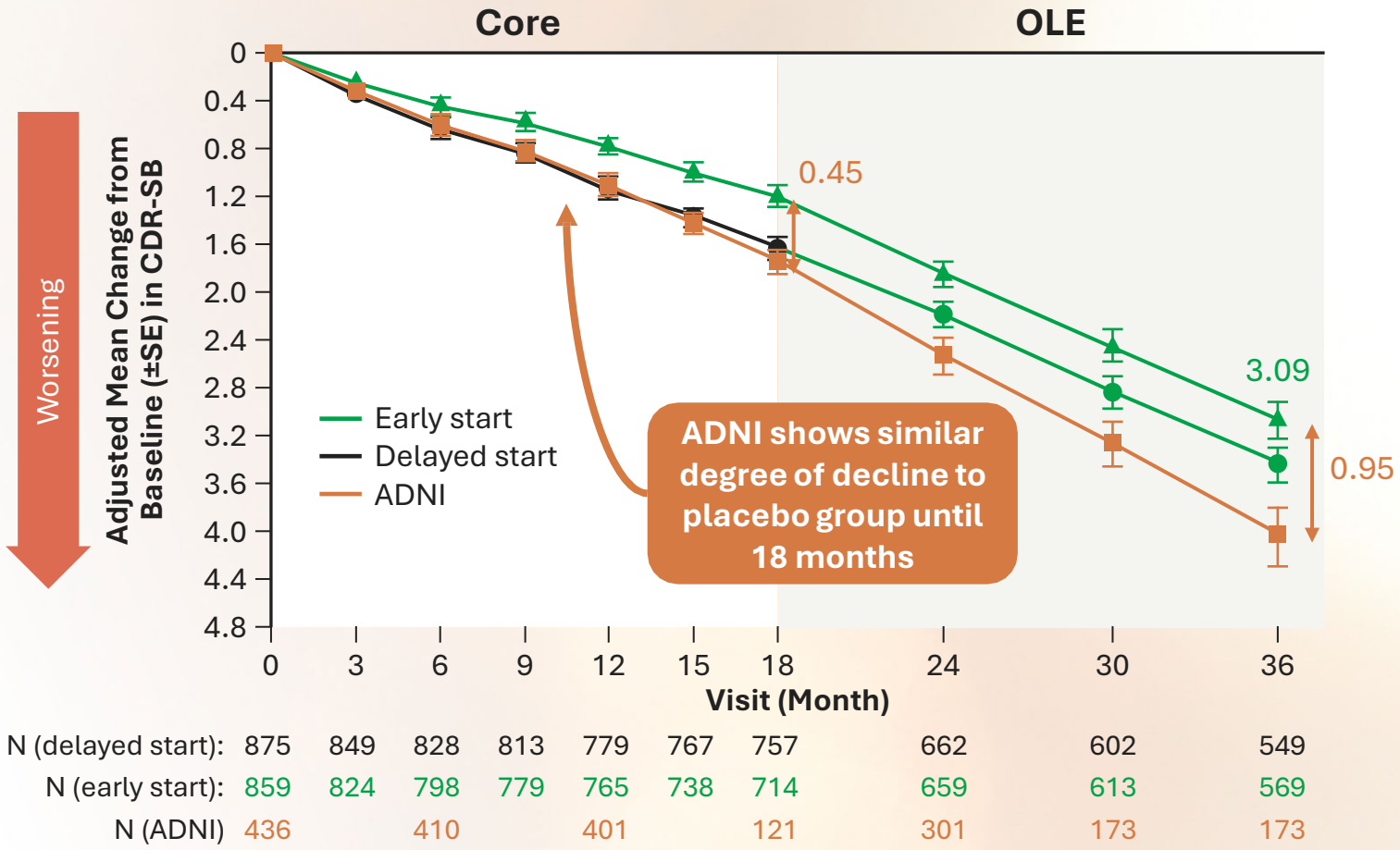
AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; iADRS, Integrated Alzheimer's disease Rating Scale; ITT, intent to treat; NCS2, Natural Cubic Spline with 2 Degrees of Freedom; SE, Standard Error.

Data from: **1.** Van Dyck CH, et al. N Engl J Med 2023;388(1):9-21. **2.** Tarawneh R, Pankratz VS. Alzheimers Res Ther. 2024;16(1):37.

CLARITY-AD OLE: Change in CDR-SB Through 36 Months[1,2]



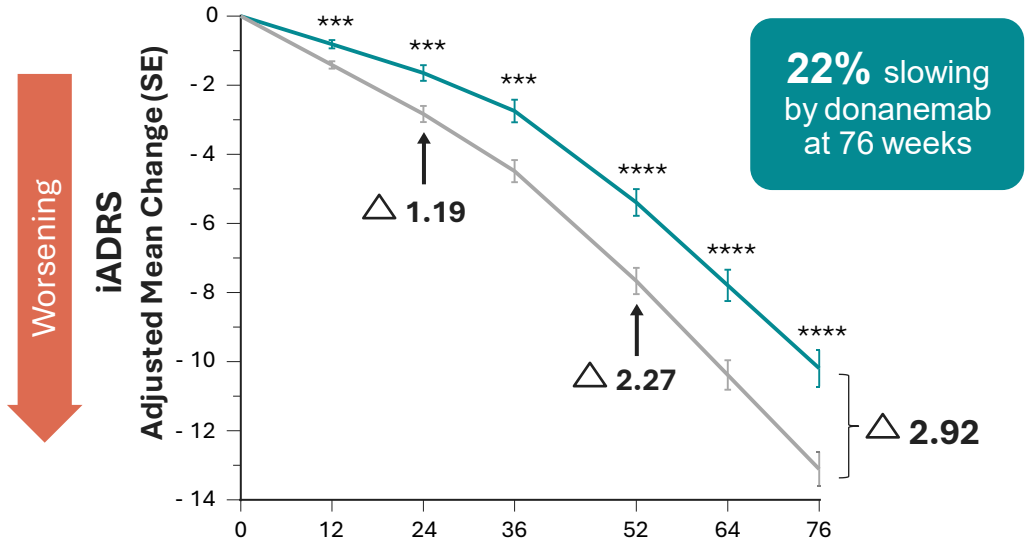
Alzheimer's Disease Neuroimaging Initiative (ADNI) observational cohort represents population of CLARITY-AD

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
ADNI, Alzheimer's Disease Neuroimaging Initiative. CDR-SB, Clinical Dementia Rating-sum of boxes. OLE, open-label extension; SE, standard error.
Data from: van Dyck C. Is there evidence for a continued benefit for long-term lecanemab treatment? A benefit/risk update from long-term efficacy, safety and biomarker data. AAIC. Philadelphia. 2024.

TRAILBLAZER-ALZ 2: Donanemab Demonstrated to Slow Progression in Patients With Early Symptomatic AD

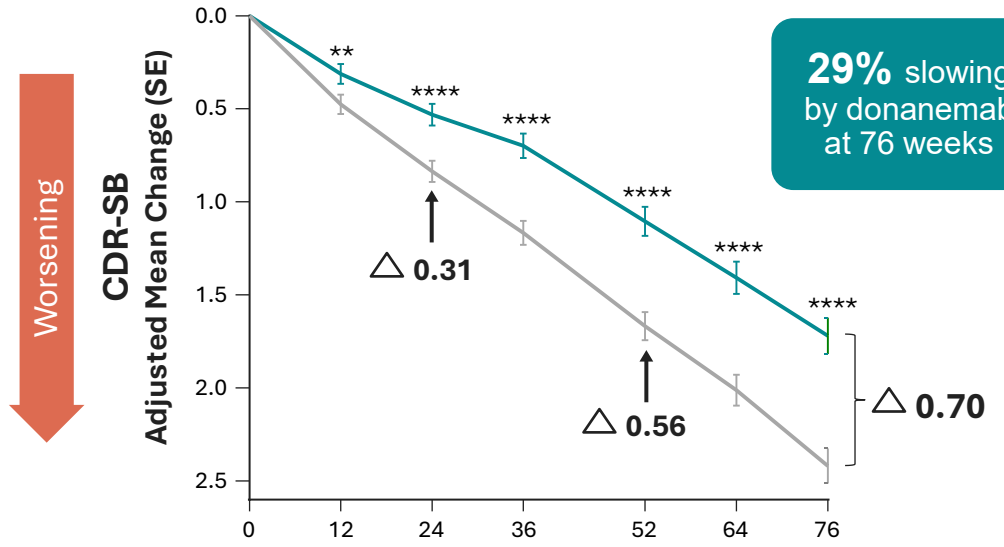
iADRS and CDR-SB change from baseline through 76 weeks

Primary Endpoint: iADRS (Overall Population)[a]



Placebo	824	805	767	738	693	651	653
Donanemab	775	752	712	665	636	579	583

Key Secondary Endpoint: CDR-SB (Overall Population)[b]



Placebo	838	825	784	752	713	678	672
Donanemab	794	774	731	682	650	603	598

- The treatment effect of donanemab continued to widen over 76 weeks vs. placebo
- Donanemab achieved statistically significant separation from placebo as early as week 12

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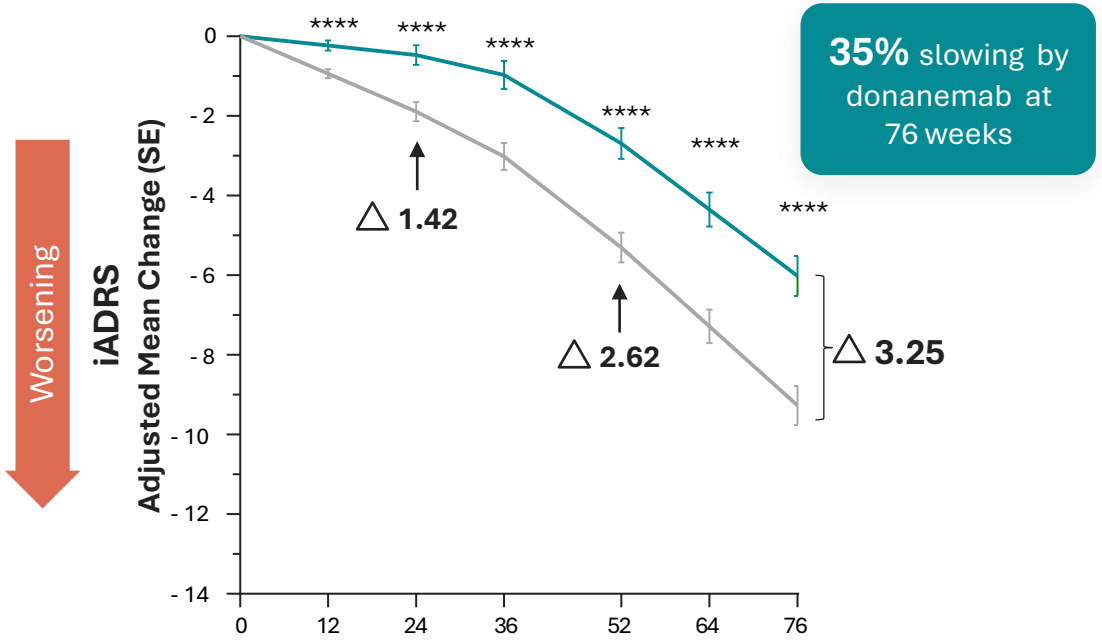
** P-value<0.01, *** P-value<0.001, **** P-value<0.0001. (a) Assessed using NCS2 analysis.1 (b) Assessed using pre-specified mixed model repeated measures methodology.

AD, Alzheimer's disease; CDR-SB, Clinical dementia rating–sum of boxes; iADRS, Integrated AD rating scale; NCS2, Natural cubic spline with 2 degrees of freedom; SE, Standard error.

Data from: Sims JR, et al. Donanemab in Early Symptomatic Alzheimer's Disease: Clinical Efficacy Results from TRAILBLAZER-ALZ 2. Presented at the Alzheimer's Association International Conference (AAIC) 2003, Amsterdam, Netherlands

TRAILBLAZER-ALZ 2: Donanemab Efficacy in Subjects With Less AD Pathology (Low-Medium Tau) is Consistent With the Overall Population[1]

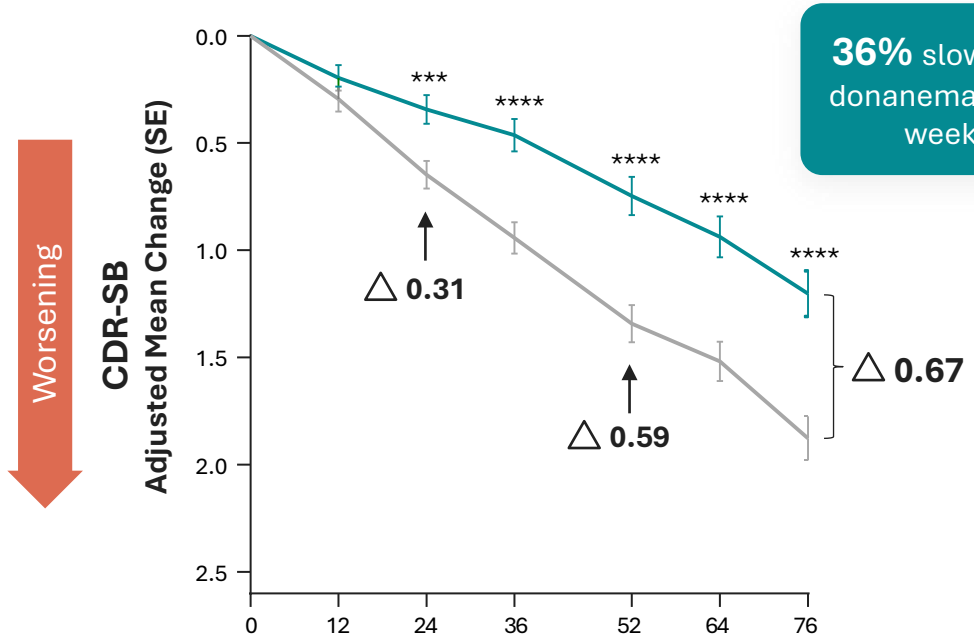
Primary Endpoint: iADRS (Low-medium Tau Population)[a]



35% slowing by donanemab at 76 weeks

Placebo	560	549	526	506	474	447	444
Donanemab	533	517	487	459	441	406	418

Key Secondary Endpoint: CDR-SB (Low-Medium Tau Population)[b]



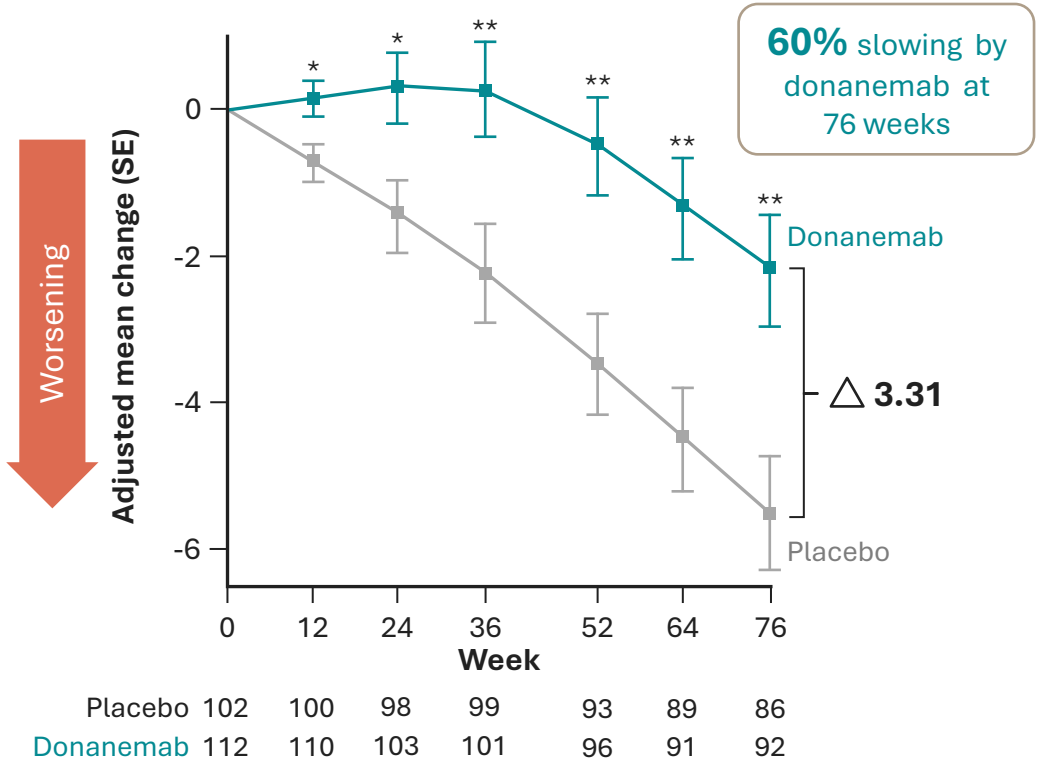
36% slowing by donanemab at 76 weeks

Placebo	569	561	540	516	486	461	459
Donanemab	546	530	499	741	451	418	424

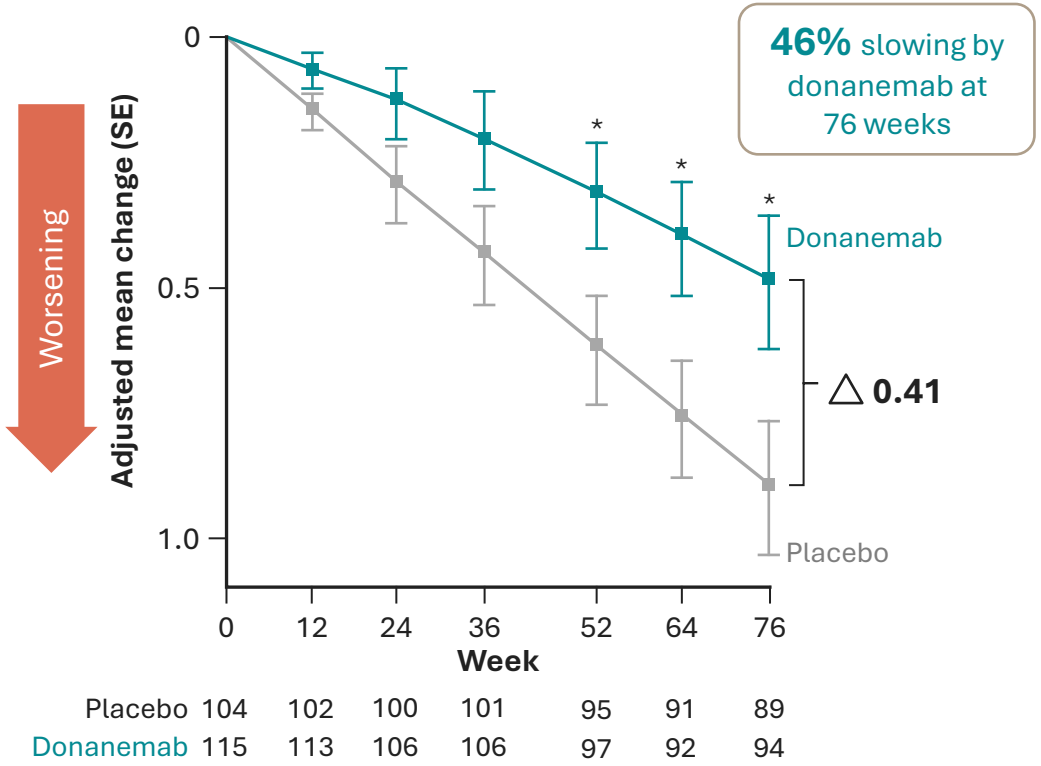
Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
*** P-value<0.001, **** P-value<0.0001. (a) Assessed using NCS2 analysis.1 (b) Assessed using pre-specified mixed model repeated measures methodology.
AD, Alzheimer's disease; CDR-SB, Clinical dementia rating–sum of boxes; iADRS, Integrated AD rating scale; NCS2, Natural cubic spline with 2 degrees of freedom; SE, Standard error
AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; iADRS, Integrated Alzheimer's Disease Rating Scale; P, Probability value; SE, Standard Error.
Data from: 1. Sims JR. Donanemab in Early Symptomatic Alzheimer's Disease: Clinical Efficacy Results from TRAILBLAZER-ALZ 2. Presented at the Alzheimer's Association International Conference (AAIC) 2023, Amsterdam, Netherlands.

TRAILBLAZER-ALZ 2: Donanemab Showed Greater Clinical Impact in Earlier Disease Stage in Pre-specified Subpopulation - MCI, Low Medium Tau[1]

iADRS



CDR-SB



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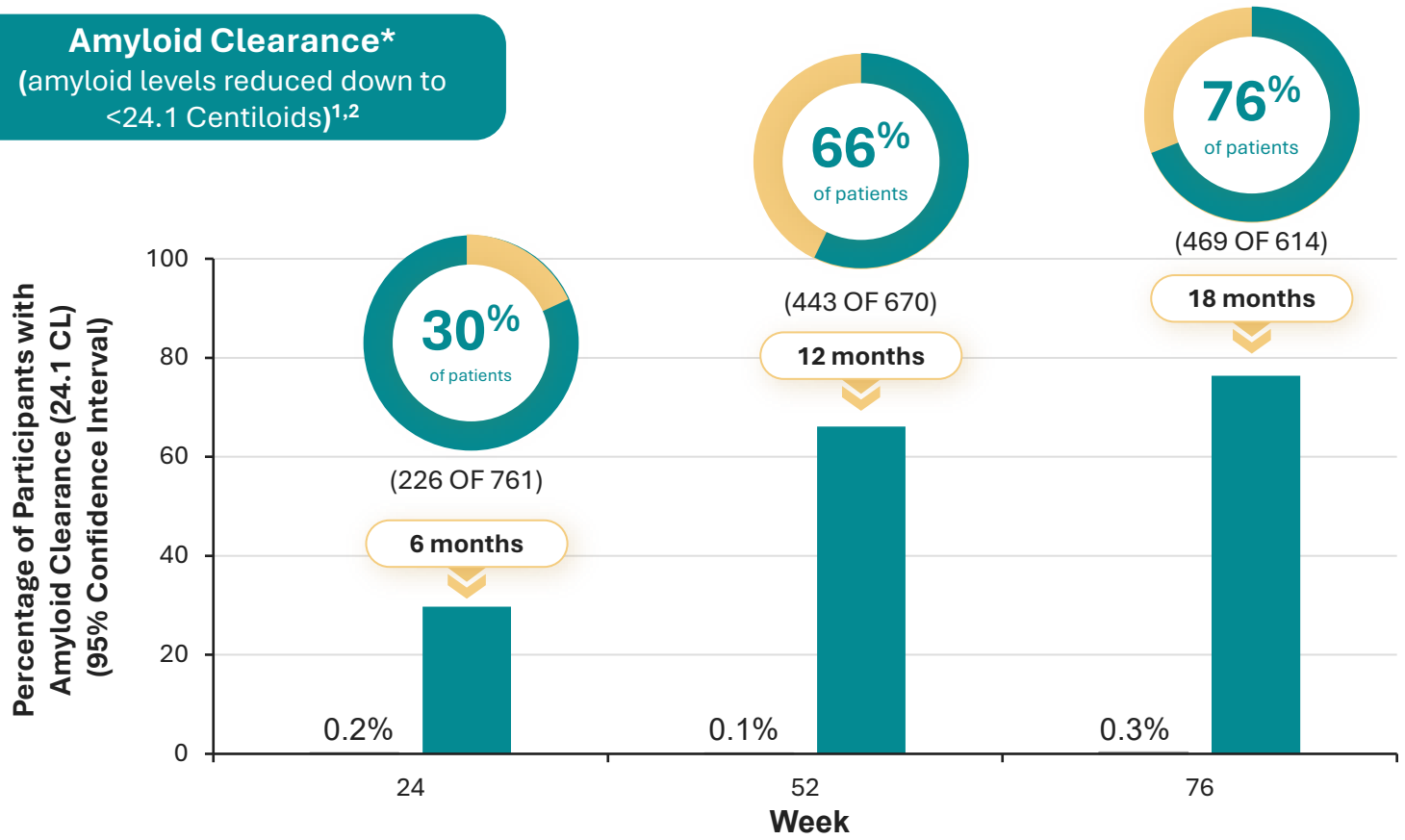
MCI, MMSE ≥27 at baseline. SE, 95% CI and p-value are derived using NCS model with 2 degree of freedom. The model was adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction and covariates for age at baseline, pooled investigator, and baseline acetylcholinesterase inhibitor/memantine use. Nominal P-values: * P<0.05, ** P<0.01.

CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, Confidence Interval; iADRS, Integrated Alzheimer's disease Rating Scale; MCI, Mild Cognitive Impairment; MMSE, Mini–Mental State Examination; NCS, Natural Cubic Spline; P-value, Probability value; SE, Standard Error.

Data from: 1. Sims JR. Donanemab in Early Symptomatic Alzheimer's Disease: Clinical Efficacy Results from TRAILBLAZER-ALZ 2. Presented at the Alzheimer's Association International Conference 2023 (AAIC 2023), Amsterdam, Netherlands, and Online: 16 - 20 July 2023.

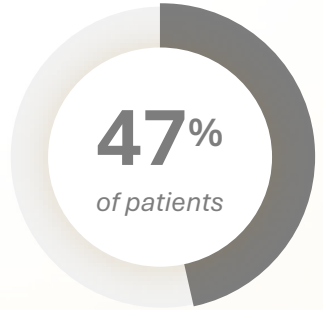
TRAILBLAZER-ALZ 2: At one Year, the Majority of Patients Achieved Amyloid Clearance*,[1,2]

Amyloid Clearance*
(amyloid levels reduced down to <24.1 Centiloids)[1,2]



Placebo (N)	805	730	690
Donanemab (N)	761	670	614

Switch to placebo
(Eligibility: amyloid plaque level <11 Centiloids on a single PET scan or 11 to <25 Centiloids on 2 consecutive PET scans)[1]



met criteria to switch to placebo† and **completed treatment** at 1 year[1,2]

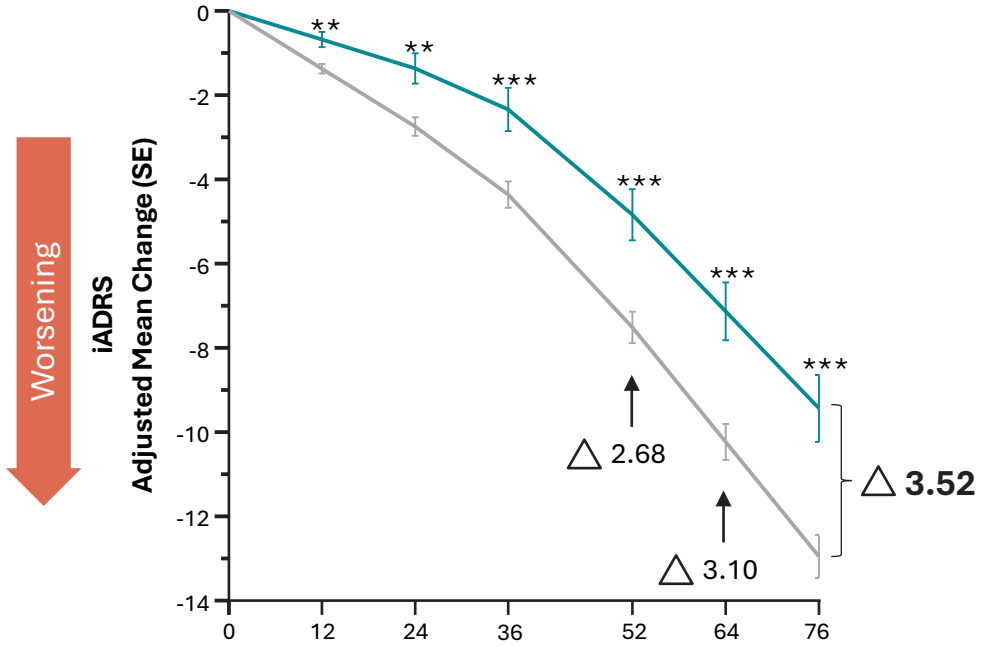
Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
*For reference, <24.1 CL on an amyloid PET scan is consistent with a negative visual read.[3] CL, Centiloids.
1. Kisunla (donanemab-azbt). Prescribing Information. Lilly USA, LLC. 2. Sims JR, et al. JAMA. 2023;330(6):512-527. 3. Navitsky M, et al. Alzheimers Dement. 2018;14(12):1565-1571.

TRAILBLAZER-ALZ 2: Widening Between Group Difference After Treatment Completion Supports Limited-Duration Dosing[1,2]

Mean time in trial prior to switch to placebo for these participants: **47 weeks**

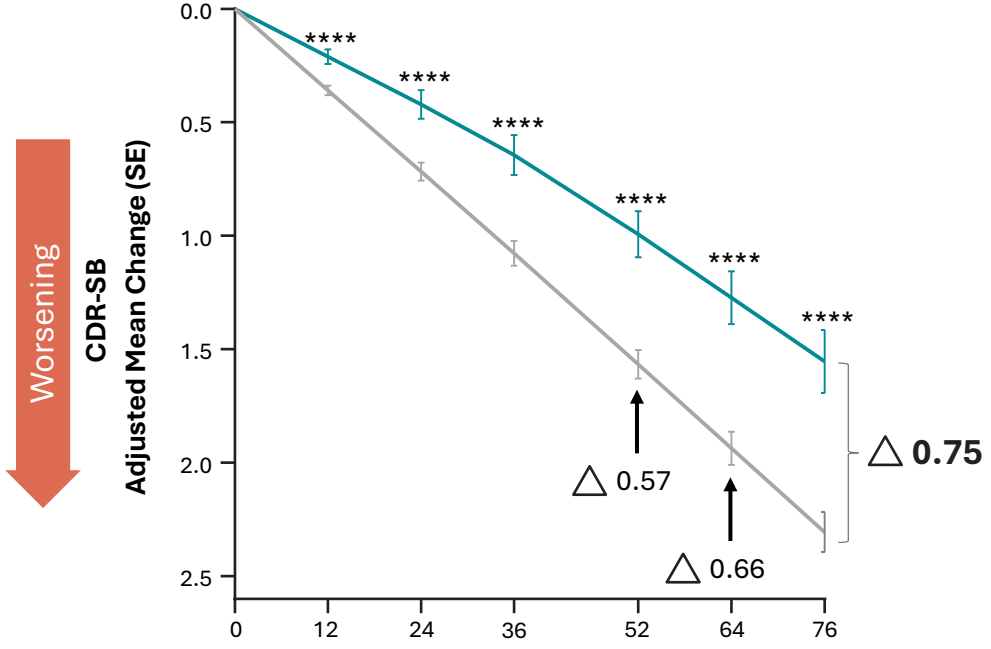
A post-hoc, sub-group analysis of patients who switched to placebo‡ at 24 or 52 weeks

iADRS Change From Baseline Through 76 Weeks



Placebo	797	779	761	738	693	651	653
Donanemab	296	290	288	285	282	266	268

CDR-SB Change From Baseline Through 76 Weeks



Placebo	810	798	778	752	713	678	672
Donanemab	301	297	294	292	290	275	275

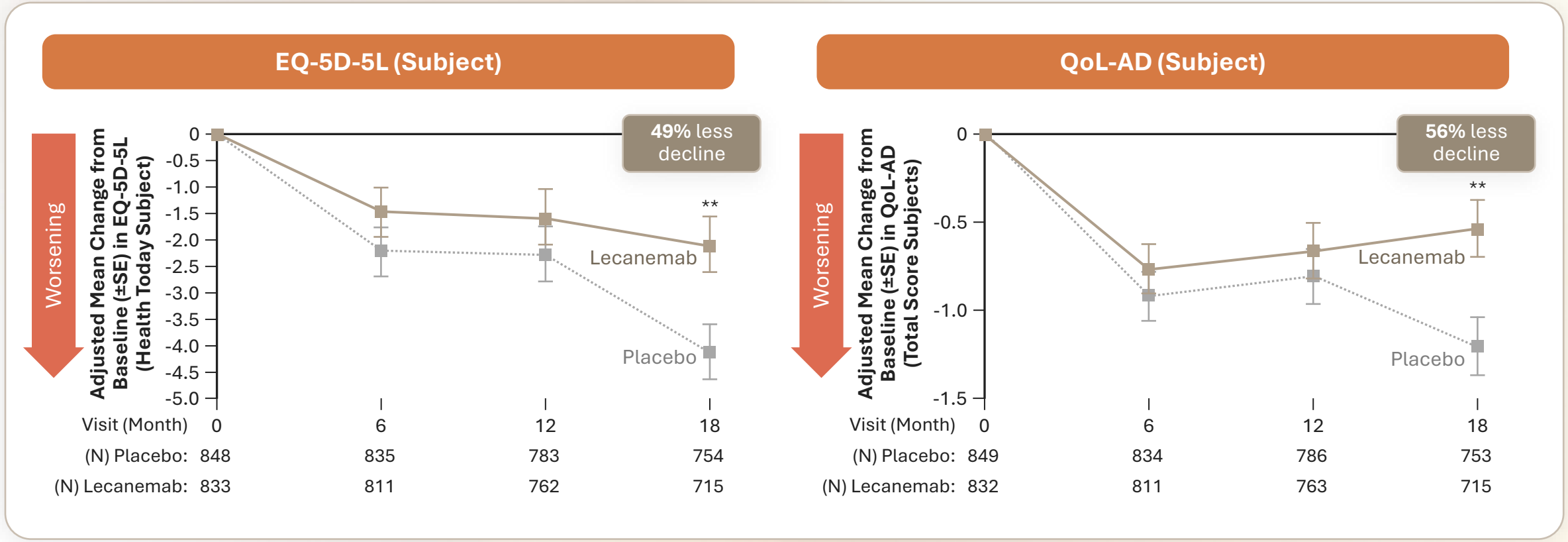
Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada

‡If the amyloid plaque level was <11 Centiloids on a single PET scan or 11 to <25 Centiloids on 2 consecutive PET scans, it was considered cleared and the patient was eligible to be switched to placebo.[2]

Assessed using NCS2 analysis. Nominal P-values: ** P<0.01, *** P<0.001, **** P<0.0001. CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; iADRS, Integrated Alzheimer's disease Rating Scale; NCS2, Natural Cubic Spline with 2 Degrees of Freedom; SE, Standard Error; PET, Positron Emission Tomography.

Data from: **1.** Sims JR. Donanemab in Early Symptomatic Alzheimer's Disease: Clinical Efficacy Results from TRAILBLAZER-ALZ 2. Presented at the Alzheimer's Association International Conference (AAIC) 2023, Amsterdam, Netherlands. **2.** Kisunla (donanemab-azbt). Prescribing Information. Lilly USA, LLC.

CLARITY-AD: Statistically Significant Difference Between Placebo and Lecanemab on Change From Baseline in Participant-Rated Quality of Life Scores

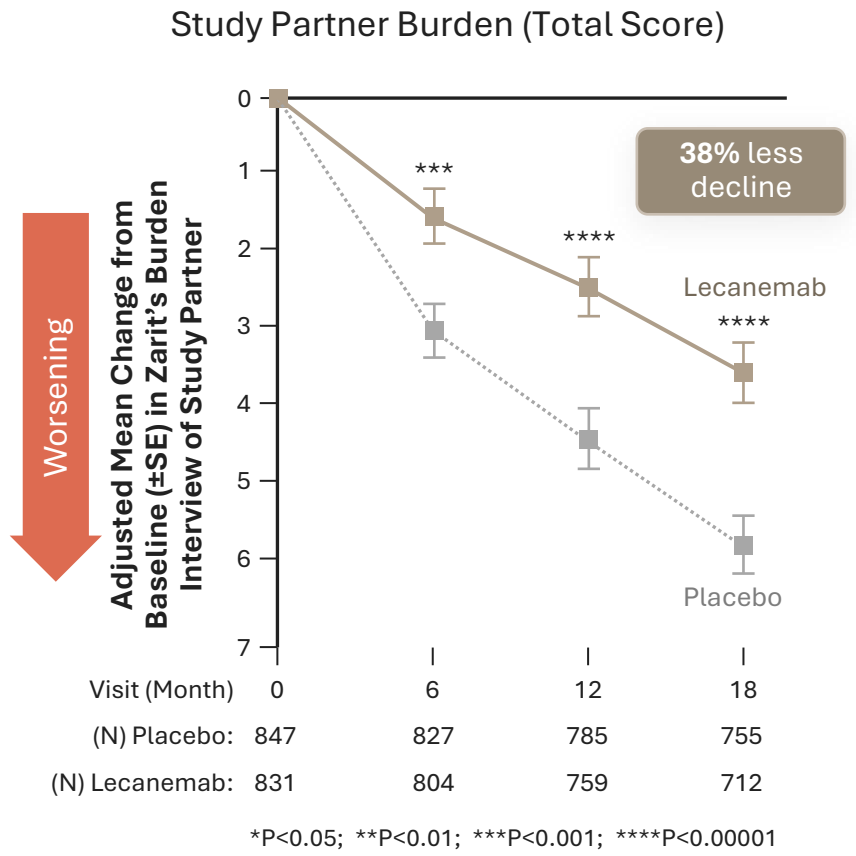


Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada

**P<0.01. AD, Alzheimer's disease; EQ-5D-5L, European Quality of Life–5 Dimensions by subject; CI, Confidence Interval; QOL-AD, Quality of Life in AD; N, Number of Participants; PET, Positron Emission Tomography. Data from: Cohen S, et al. J Prev Alz Dis 2023;4(10):771-777.

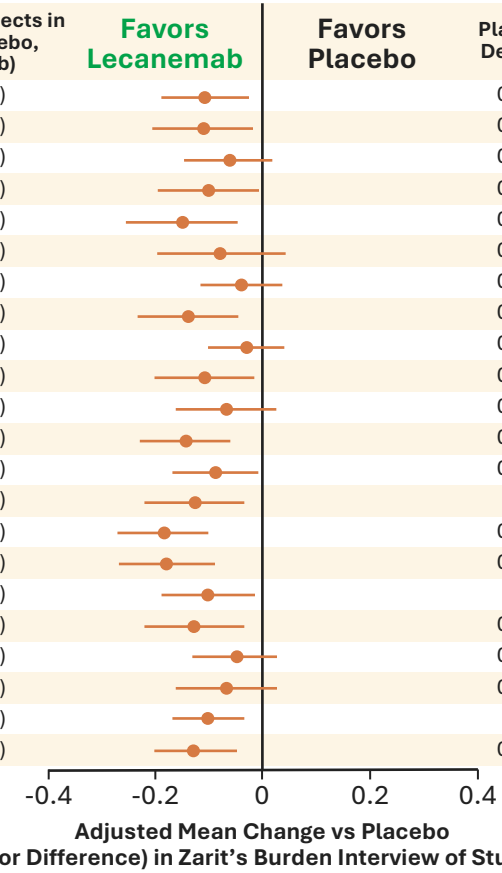
CLARITY-AD: Statistically Significant Difference Between Placebo and Lecanemab on Change From Baseline in Partner Burden Score

Zarit Burden Interview



Zarit Burden Interview Item Scores

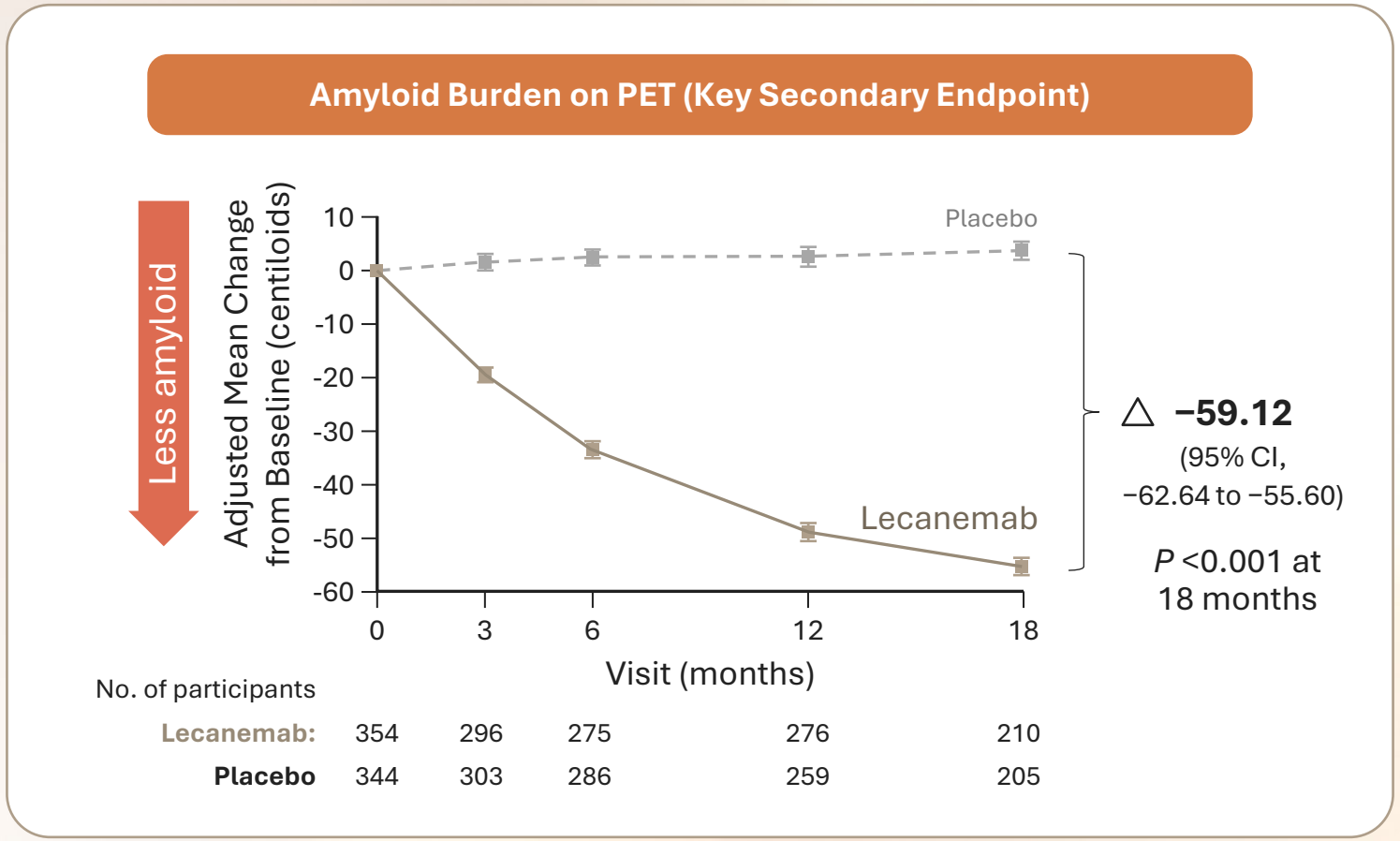
Item	Number of Subjects in MMRM (placebo, lecanemab)	Placebo Decline	Difference vs Placebo	% Less Decline
Affects relationships negatively	(847, 831)	0.22	-0.11	48.2
Afraid of future of cared-for person	(847, 831)	0.11	-0.11	98.2
Angry around cared-for person	(847, 831)	0.21	-0.06	30.5
Ask for help than needed	(847, 831)	0.26	-0.1	38.2
Cared-for person is dependent on you	(847, 831)	0.43	-0.15	35
Cared-for person's expectations	(847, 831)	0.37	-0.08	21.1
Don't have enough money	(847, 831)	0.12	-0.04	32.9
Don't have enough time for yourself	(847, 831)	0.39	-0.14	35.4
Embarrassed over person's behavior	(847, 831)	0.22	-0.03	14.5
Feel you could do a better job	(847, 831)	0.22	-0.11	48.5
Feel you should be doing more	(847, 831)	0.19	-0.07	36.1
Health has suffered	(847, 831)	0.35	-0.14	39.9
How burdened overall do you feel	(847, 831)	0.32	-0.09	27
Lack of privacy	(847, 831)	0.4	-0.13	31.4
Lost control of your life	(847, 831)	0.39	-0.18	46.5
Social life has suffered	(847, 831)	0.42	-0.18	42.6
Strained around cared-for person	(847, 831)	0.2	-0.1	51.5
Stressed between care and other duties	(847, 831)	0.35	-0.13	36.5
Unable to take care of for much longer	(847, 831)	0.24	-0.05	21.4
Uncertain about what to do about person	(847, 831)	0.24	-0.07	28.6
Uncomfortable having friends over	(847, 831)	0.2	-0.1	50.4
Wish to leave care to someone else	(847, 831)	0.28	-0.13	45.3



Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada

AD, Alzheimer's disease; EQ-5D-5L, European Quality of Life–5 Dimensions by subject; CI, Confidence Interval; QoL, Quality of life; QOL-AD, QoL in AD; N, Number of Participants; PET , Positron Emission Tomography. Data from: Cohen S, et al. J Prev Alz Dis 2023;4(10):771-777.

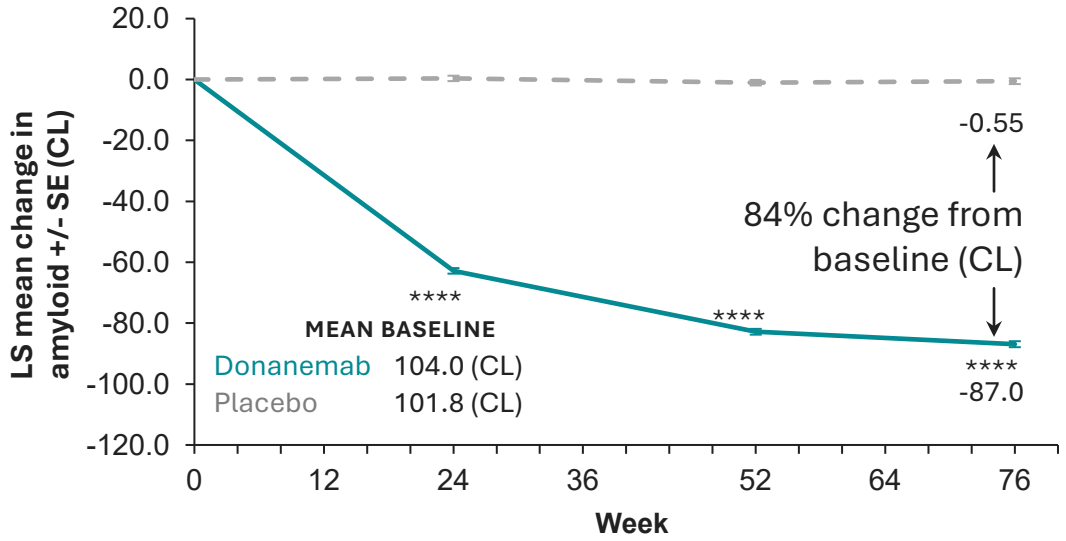
CLARITY-AD: Statistically Significant Amyloid Clearance Seen on PET at 18 Months[1]



Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
For reference, <24.1 Centiloid on an amyloid PET scan is consistent with a negative visual read.[2]
CI, Confidence interval; PET, Positron emission tomography.
Data from: **1.** Van Dyck CH, et al. N Engl J Med 2023;388(1):9-21. **2.** Navitsky M, et al. Alzheimers Dement. 2018;14(12):1565-1571.

TRAILBLAZER-ALZ 2: Significant Biomarkers Changes Were Observed in the Overall Population[1-3]

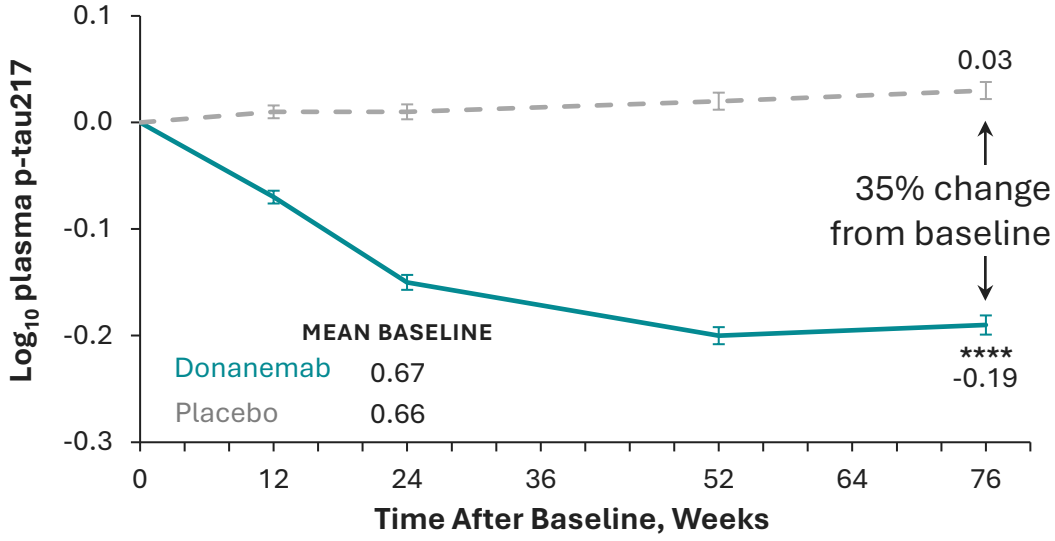
Change from Baseline in Brain Amyloid Beta Plaque level on Amyloid PET Imaging[1,2]



Number of participants

Placebo	754	740	680	642
Donanemab	712	702	627	571

Plasma P-tau217 Change From Baseline Through 76 Weeks[3]



Number of participants

Placebo	786	758	734	658	620
Donanemab	758	717	686	602	568

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**** P<0.0001. CL, Centiloids; LS, Least Squares; p-tau217, Phosphorylated tau 217; PET, Positron Emission Tomography; SE, Standard Error.

Data from: **1.** Kisunla (donanemab-azbt). Prescribing Information. Lilly USA, LLC. **2.** Sims JR, et al. JAMA. 2023;330(6):512-527. **3.** Hansson O. Donanemab in Early Symptomatic Alzheimer's Disease: Biomarker Results from TRAILBLAZER-ALZ 2. Presented at Alzheimer's Association International Conference (AAIC) 2023, Amsterdam, Netherlands.

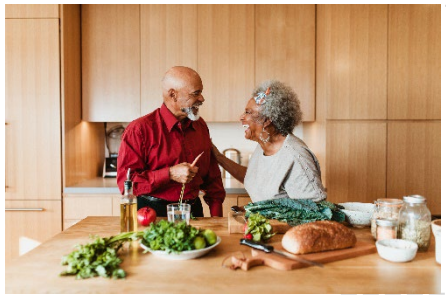
What Matters Most to Patients and Care Partners?

- Clinical trial endpoints may be challenging to interpret.[1]
- Estimating the **delay in progression to the next stage** of Alzheimer's disease (AD) represents a more patient centric perspective on the clinical relevance of treatment.[1-5]

To slow progression early to allow:

- ✔ Maintain independence
- ✔ To continue engaging in what matters the most

If they could stop it right now, then I could continue to function like I am… (patient)[3]



Ideally it would just stop the memory loss. I could definitely live and survive the way I am now. But you don't know what's going to happen in the future, how it progresses…(patient)[3]

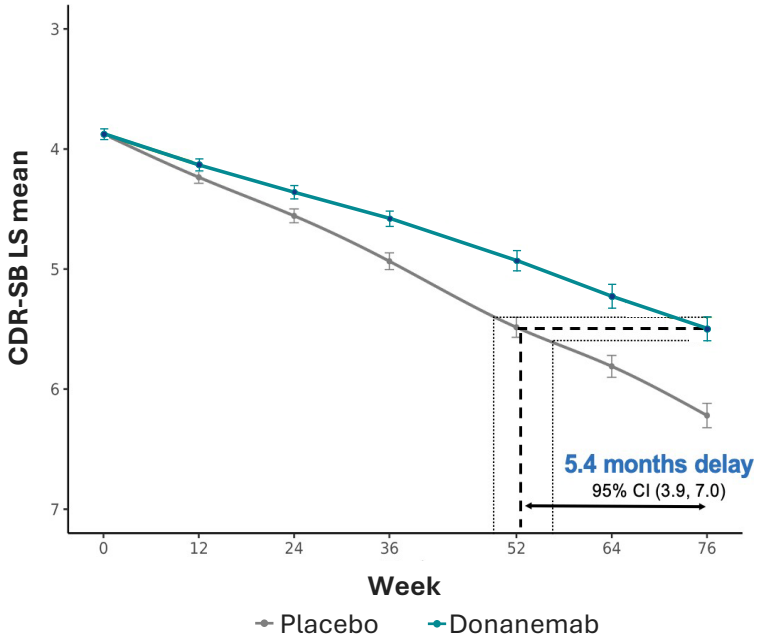
Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada

AD, Alzheimer's disease.

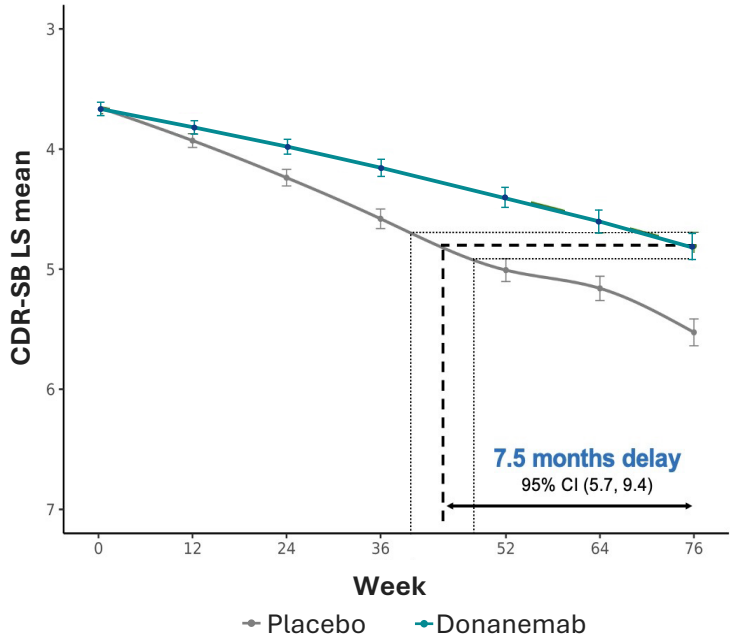
1. Murray AL, et al. Alzheimers Res Ther. 2021;13(1):26. 2. Tochel C, et al. Alzheimers Dement. 2019;7:11:231-247. 3. DiBenedetti DB, et al. Alzheimers Res & Ther. 2020;12:90. 4. Hauber B, et al. Neurol Ther. 2023;12:505-527. 5. Watson J, et al. Health Expect. 2019 22:504-517.

TRAILBLAZER-ALZ 2: Donanemab Delayed Disease Progression, Especially in the Low-Medium Tau Group[1]

CDR-SB
Overall Population[1]



CDR-SB
Low-Med Tau Population[1]



Proportional time slowing PMRM analysis. Error bars indicate ±1 standard error. P<0.001 vs placebo.[1]

Prespecified analyses of delay in disease progression based on CDR-SB showed that, compared with placebo, donanemab resulted in **5.4 months saved** (overall population) and **7.5 months saved** (low-medium tau population) in **18 months of treatment.**[1]

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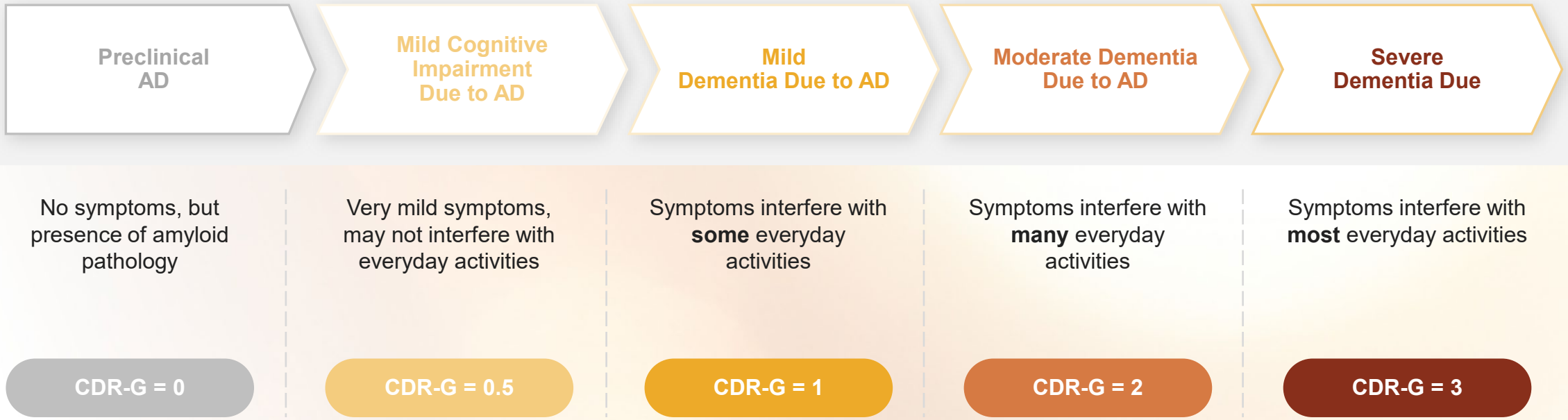
AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, Confidence Interval; LS, Least Squares; PMRM, Progression Model for Repeated Measures.
Data from: Sims JR, et al. JAMA. 2023;330(6):512-527. Suppl 3.

Evaluating Progression to Next Clinical Stage of AD

In the TRAILBALZER-ALZ 2 and CLARITY-AD studies, patients were assessed by CDR-Global Score every 3 months for progression to next stage of AD.[1-3]



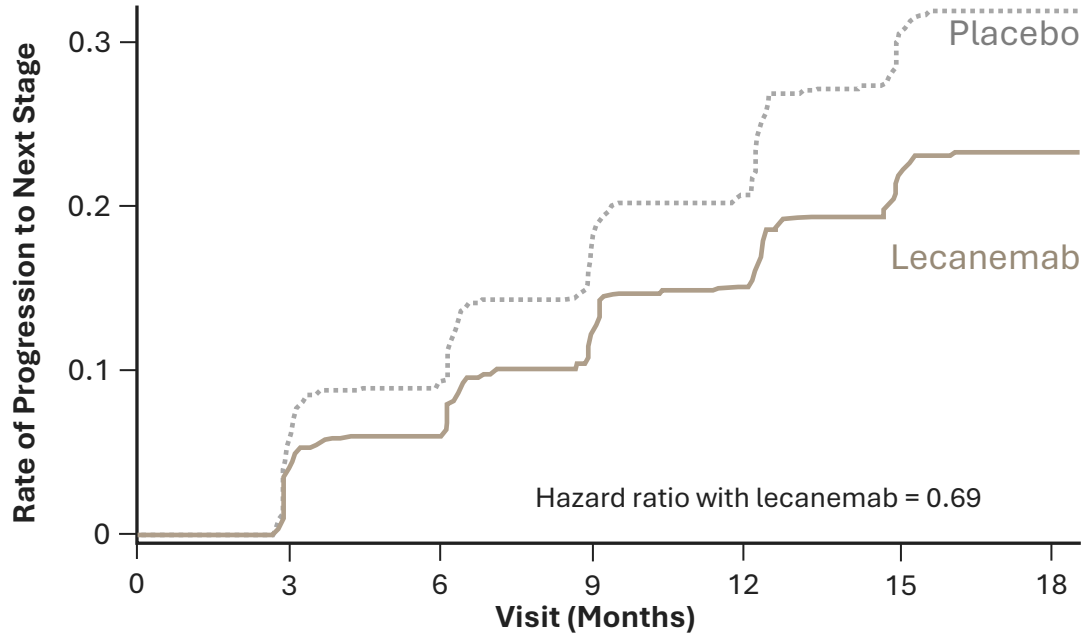
- A patient's condition was considered worsened or advanced to the next stage of the disease with two consecutive scores higher than baseline.

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
AD, Alzheimer's disease; CDR-GS, Clinical Dementia Rating-Global Score; TB2, TRAILBLAZER-ALZ 2.

1. Sims JR, et al. JAMA. 2023;330(6):512-527. 2. Eli Lilly and Company. Peripheral and Central Nervous System Drugs Advisory Committee Briefing Document. Available from: https://www.fda.gov/media/179167/download (Accessed Sep 2024). 3. Van Dyck CH, et al. N Engl J Med 2023;388(1):9-21 and Supplement (Protocol). .

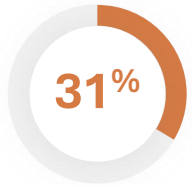
CLARITY-AD: Patients Progressing to the Next Stage of AD

CDR-GS: Time to worsening of disease | Modified ITT population



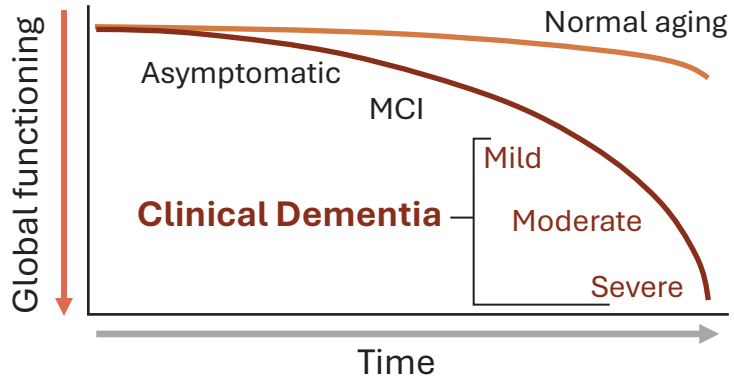
(N) Placebo:	875	792	757	649	603	524	265
(N) Lecanemab:	859	801	765	677	642	554	299

Hazard ratio and P-value were generated using a Cox proportional hazards model adjusted for baseline age, baseline value, and baseline acetylcholinesterase inhibitor/memantine use and stratified by pooled investigator and baseline tau level.



REDUCED RISK *of progressing to the next stage of disease*

In a prespecified, multiplicity-unadjusted analysis of the time to worsening of the global CDR score, the hazard ratio for progression to the next stage of dementia (0.69) numerically favored lecanemab over placebo.

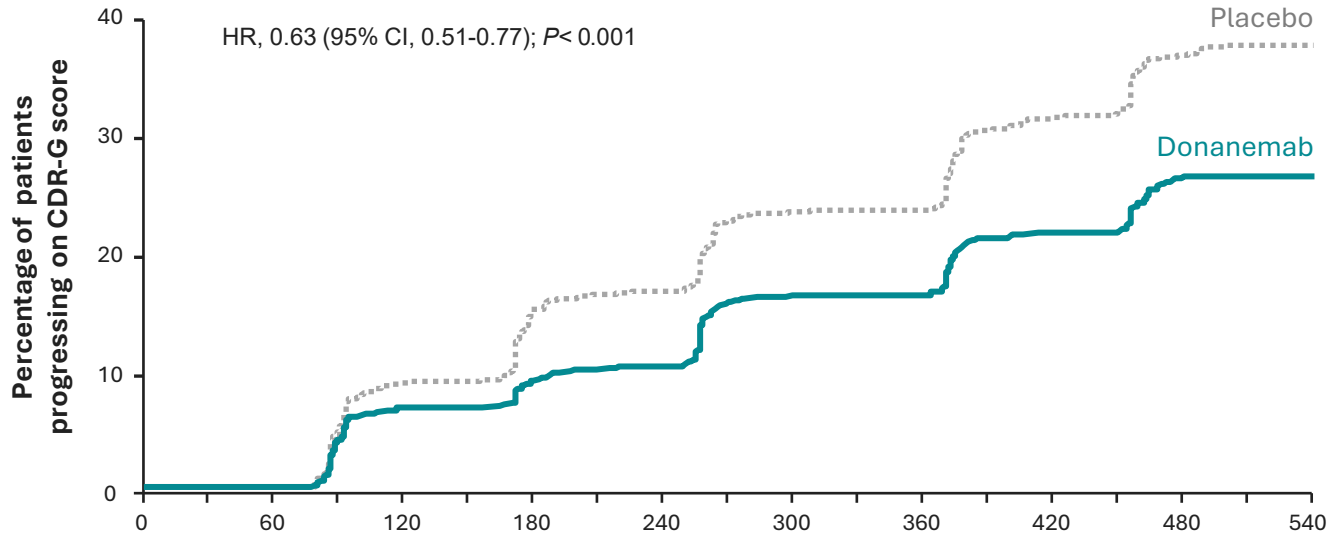


Modified from Sperling A, et al. *Alzheimer's Dement.* 2011;7(3):280–292. Available from: https://doi.org/10.1016/j.jalz.2011.03.003.

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
Clinical progression was defined as an increase from baseline in CDR-G score at 2 consecutive visits.[1] ‡The HR is the relative risk reduction for substantial decline achieved by Donanemab vs placebo.[1] CDR-GS, Clinical Dementia Rating Global Score; CI, Confidence Interval; d, Days; HR, Hazard Ratio; MCI, Mild Cognitive Impairment; P, Probability value.
Data from: Van Dyck CH, et al. N Engl J Med 2023;388(1):9-21.

TRAILBLAZER-ALZ 2: Patients Progressing to the Next Stage of AD[1]

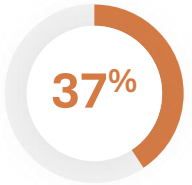
CDR-GS: Time to worsening of disease | Overall population



No. of participants at risk

Treatment	60 d	120 d	180 d	240 d	360 d	480 d
Placebo	840	764	700	671	587	462
Donanemab	801	737	696	696	575	474

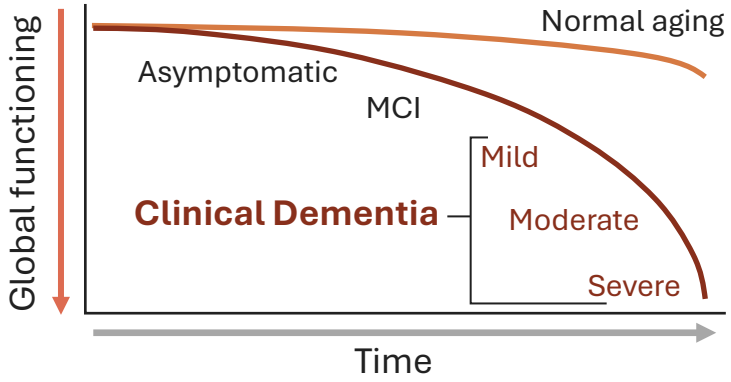
Hazard ratio and P-value were generated using a Cox proportional hazards model adjusted for baseline age, baseline value, and baseline acetylcholinesterase inhibitor/memantine use and stratified by pooled investigator and baseline tau level.



REDUCED RISK *of progressing to the next stage of disease*

In the low-medium tau population, a **39%** reduced risk of progressing vs placebo was observed at 76 weeks; P<0.001[1]

- *HR: Low-medium tau=0.61‡; 95% CI: 0.47, 0.80[1]*



Modified from Sperling A, et al. *Alzheimer's Dement.* 2011;7(3):280–292. Available from: https://doi.org/10.1016/j.jalz.2011.03.003.

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Clinical progression was defined as an increase from baseline in CDR-G score at 2 consecutive visits.[1]
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CDR-GS, Clinical Dementia Rating Global Score; CI, Confidence Interval; d, Days; HR, Hazard Ratio; MCI, Mild Cognitive Impairment; P, Probability value.
Data from: 1. Sims JR, et al. JAMA. 2023;330(6):512-527.

THE CHANGING LANDSCAPE

In the Treatment of Alzheimer's Disease

Safety and ARIAs

Dr. Paolo Vitali

Treatment-Emergent Adverse Events[1,2]

For illustrative purposes only. Comparisons cannot be made in the absence of head-to-head trials.

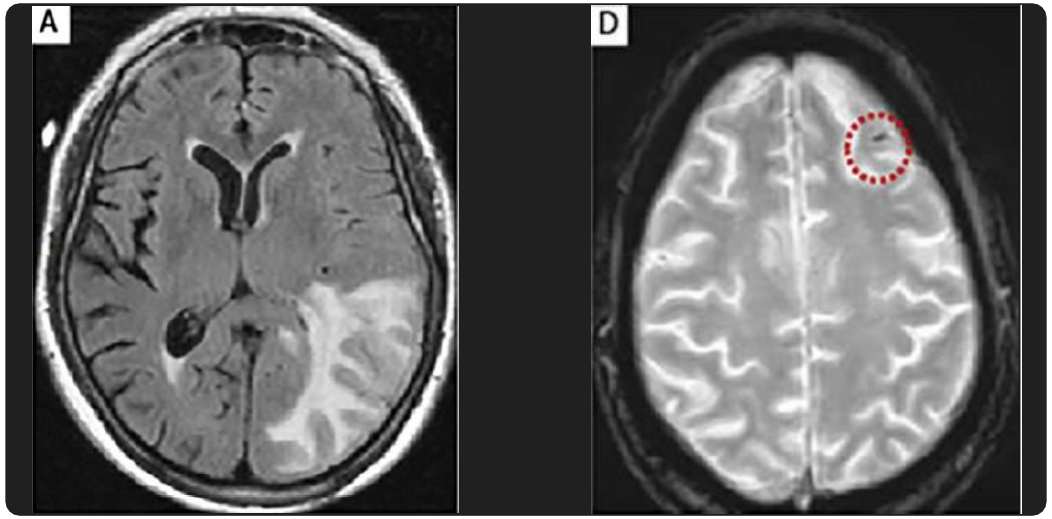
Treatment-Emergent AE ≥5%#	CLARITY-AD (lecanemab)[1]		TRAILBLAZER-ALZ 2 (donanemab)[2]	
	Placebo (N=897)	Lecanemab (N=898)	Placebo (N=874)	Donanemab (N=853)
ARIA-E	**15 (1.7)**	**113 (12.6)**	**17 (1.9)**	**205 (24.0)**
ARIA-H	**69 (7.7)**	**126 (14.0)**	**65 (7.4)**	**168 (19.7)**
COVID-19	60 (6.7)	64 (7.1)	154 (17.6)	136 (15.9)
Headache	**73 (8.1)**	**100 (11.1)**	**86 (9.8)**	**119 (14.0)**
Fall	86 (9.6)	93 (10.4)	110 (12.6)	114 (13.4)
Infusion-related reaction	**66 (7.4)**	**237 (26.4)**	**4 (0.5)**	**74 (8.7)**
Superficial siderosis of CNS	**22 (2.5)**	**50 (5.6)**	**10 (1.1)**	**58 (6.8)**
Dizziness	46 (5.1)	49 (5.5)	48 (5.5)	53 (6.2)
Arthralgia	62 (6.9)	53 (5.9)	42 (4.8)	49 (5.7)
Urinary tract infection	82 (9.1)	78 (8.7)	59 (6.8)	45 (5.3)
Diarrhea	58 (6.5)	48 (5.3)	50 (5.7)	43 (5.0)
Serious Adverse Events				
Any serious adverse event	101 (11.3)	126 (14.0)	138 (15.8)	148 (17.4)
Death	6 (0.7)	7 (0.8)	10* (1.1)	16* (1.9)

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
Serious adverse event defined as an event that results in death, is life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, or based on other medical/scientific judgment.
* Only 1 death in the placebo group and 3 deaths in the donanemab group were considered treatment-related.
# in treatment groups afterrounding. Not shown in table: anxiety reported in CLARITY-AD (4.2% placebo vs. 5.0% lecanemab) and fatigue reported in TRAILBLAZER ALZ 2 (5.1% placebo vs. 4.9% donanemab) . See notes for abbreviations.
Data from: 1. van Dyck CH, et al. N Engl J Med 2023;388;9-21. 2. Sims JR, Zimmer JA, Evans CD, et al. JAMA. 2023; 330(6): 512-27.

ARIA: Definition and Subtypes

- Amyloid-related imaging abnormalities (ARIA) are a spectrum of MRI signal abnormalities associated with Aβ clearance in the aging brain[1-3]
- ARIA can occur spontaneously, but is more frequently observed with ATT[1-3]
- There are two types of ARIA[2,5]:
  - ARIA-E refers to vasogenic edema and/or sulcal effusion[2-4]
  - ARIA-H refers to hemosiderin deposits[1,4]

ARIA-E and ARIA-H can occur together[5]



ARIA-E
Left parieto-occipital lobe (T2-FLAIR)[4]

ARIA-H
Left frontal lobe sulcus (GRE/T2*)[4]

Figure adapted from Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211-220. Copyright © licensed under CC-BY-4.0 (https://creativecommons.org/licenses/by/4.0/). Modified from original by cutting.

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada

Aβ, Amyloid Beta; AD, Alzheimer's disease; ARIA, Amyloid-Related Imaging Abnormalities; ARIA-E, Amyloid-Related Imaging Abnormalities-Edema/Effusions; ARIA-H, Amyloid-Related Imaging Abnormalities-Hemorrhage/Hemosiderin Deposition; DMT, Disease-Modifying Therapy; FLAIR, Fluid-Attenuated Inversion Recovery; GRE, Gradient Recalled Echo; MRI, Magnetic Resonance Imaging.

Data from: **1.** Salloway S, et al. JAMA Neurol. 2022;79(1):13-21. **2.** Filippi M, et al. JAMA Neurol. 2022;79(3):291-304. **3.** Sperling RA, et al. Alzheimers Dement. 2011;7(4):367-385. **4.** Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211-220. Copyright © licensed under CC-BY-4.0 (https://creativecommons.org/licenses/by/4.0/). Modified from original by cutting. **5.** Cogswell PM, et al. Am J Neuroradiol. 2022;43(9):E19-E35.

ARIA Clinical Manifestations[1-3]

Most common

Headache

Common

Confusion

Nausea / Dizziness

Gait Disturbance

Less Frequent

Neuropsychiatric Symptoms

Visual Symptoms

Rare symptoms:

- *Seizure / status epilepticus*
- *Focal deficits*
- *Encephalopathy*

In Phase 3 clinical trials, the majority of cases of ARIA-E (75% in TRAILBLAZER ALZ 2 and 78% in CLARITY-AD) were asymptomatic[1,3]

Severity rating of clinical symptoms of ARIA-E[2]

Mild
Discomfort noticed
No disruptions of daily activity

Moderate
Discomfort sufficient to reduce or affect normal daily activity

Severe
Incapacitating Inability to work or to perform normal daily activity

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada Abbreviations: ARIA, Amyloid-related Imaging

1. Sims JR, et al. JAMA. 2023;330(6):512-527. 2. Kisunla (donanemab-azbt). Prescribing Information. Lilly USA, LLC. 3. van Dyck CH, et al. N Engl J Med 2023;388;9-21.

Timing and Resolution of ARIA-E

For illustrative purposes only. Comparisons cannot be made in the absence of head-to-head trials.

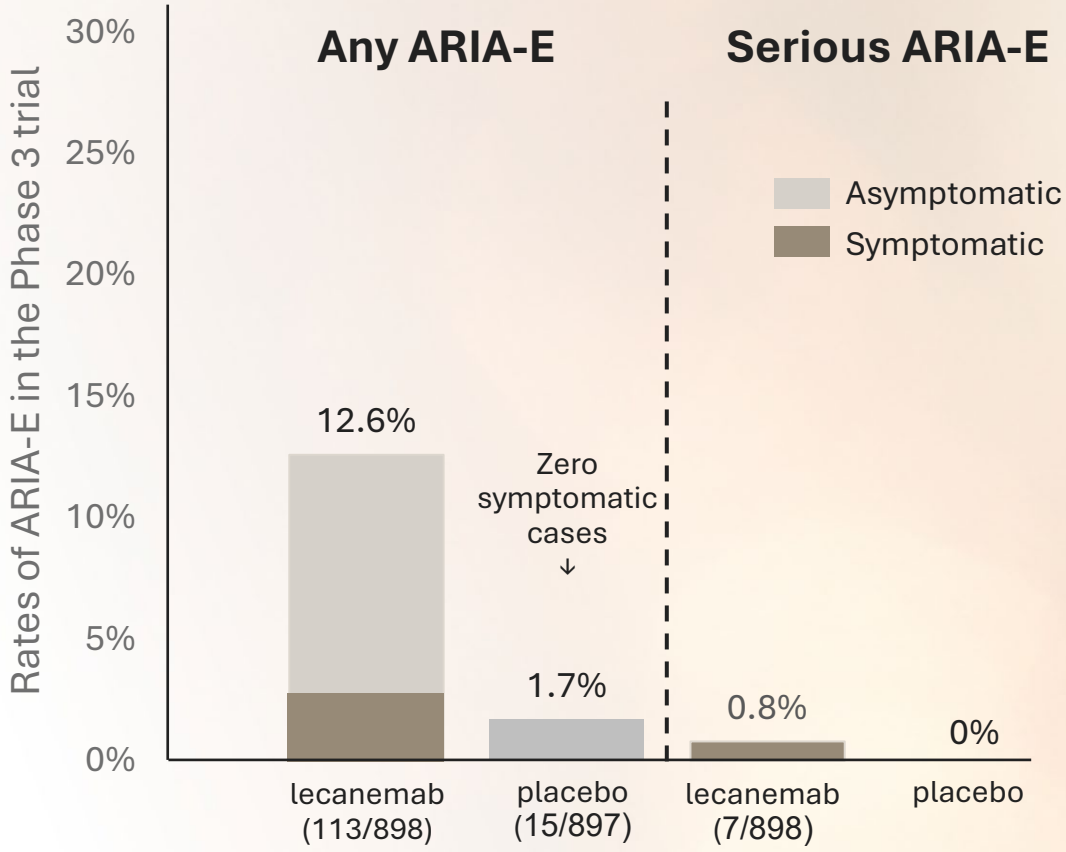
	TRAILBLAZER-ALZ 2 Donanemab[1]	CLARITY-AD Lecanemab[2]
Timing	**57.9%** occurred after receiving up to 3 infusions within 12 weeks	**71%** were detectable on the first or second MRIs obtained at weeks 9 and 13
Resolution	**98.0%** of first events of ARIA-E resolved within ~72.4 days	**81%** resolved spontaneously within 4 months of radiographic detection

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
ARIA, amyloid-related imaging abnormality; ARIA-E, ARIA – edema; MRI, Magnetic resonance imaging.
1. Sims JR, et al. JAMA. 2023;330(6):512-527; 2. Cummings J et al. J Prev Alzheimers Dis., 2023;10(3):352-377

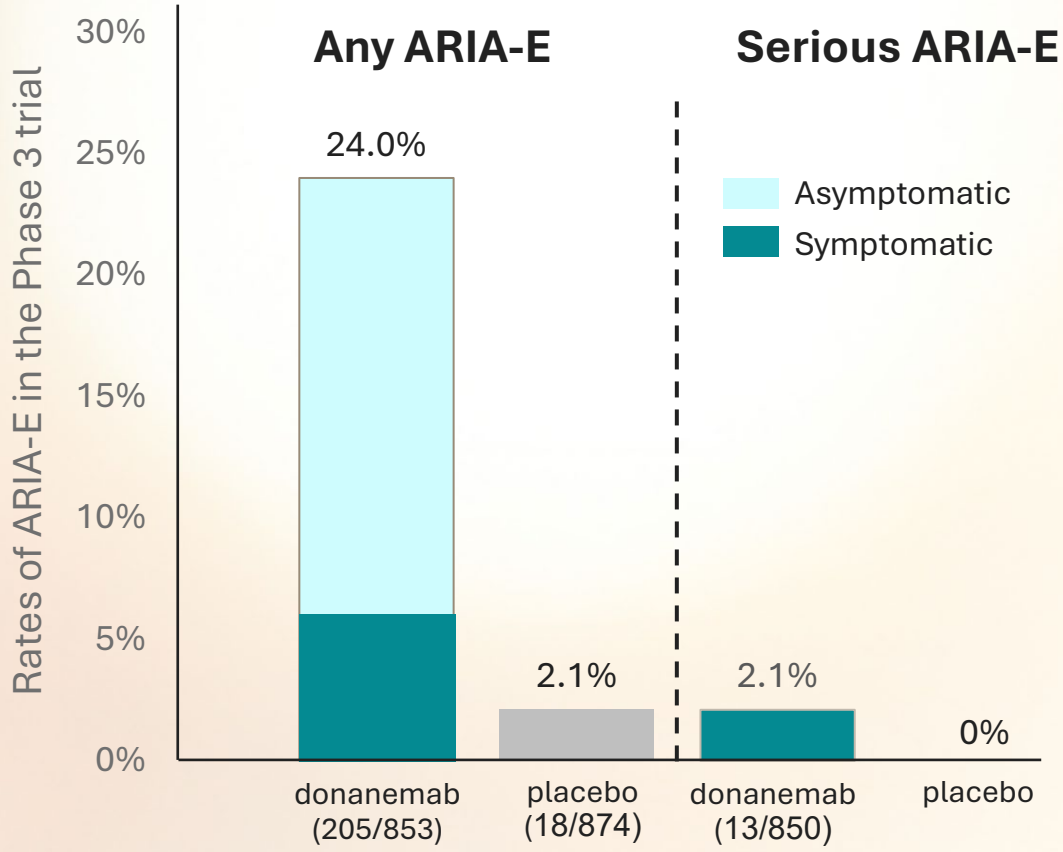
Most Cases of ARIA-E (≥75%) Were Asymptomatic

For illustrative purposes only. Comparisons cannot be made in the absence of head-to-head trials.

CLARITY-AD (lecanemab)[1]



TRAILBLAZER-ALZ 2 (donanemab)[2]



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* One placebo-treated participant had ARIA-E during the placebo-controlled period; however, the participant developed symptoms during the long-term extension period.

Serious adverse event defined as an event that results in death, is life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, or based on other medical/scientific judgment.

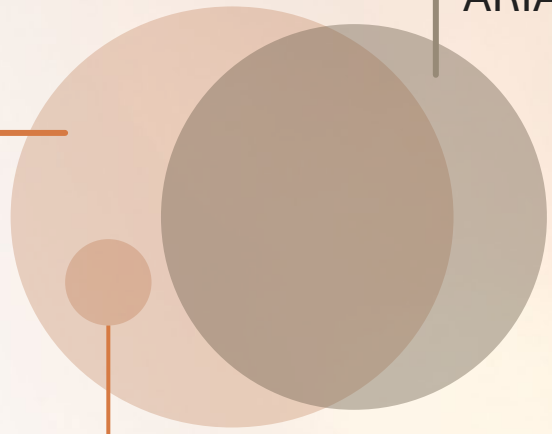
AD, Alzheimer's disease; APOE4, apolipoprotein E4; ARIA-E, amyloid-related imaging abnormality – edema.

1. van Dyck CH, et al. N Engl J Med 2023;388;9-21. 2. Sims JR, et al. JAMA. 2023;330(6):512-527 and Supplement 3 eTable8.

Rates of Isolated ARIA-H

For illustrative purposes only. Comparisons cannot be made in the absence of head-to-head trials.

Among **lecanemab**-treated participants[2]
CLARITY-AD



12.6% had ARIA-E

8.9% had ARIA-H only

vs. **7.8%** of placebo-treated participants

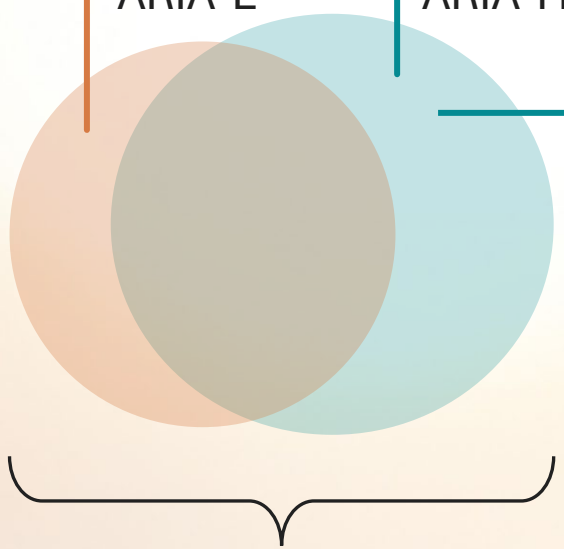
Most common symptom: Dizziness

0.7% of **isolated symptomatic** ARIA-H

vs. **0.2%** of placebo-treated participants

Isolated ARIA-H occurred throughout the trial.

Among **donanemab**-treated participants[1]
TRAILBLAZER-ALZ 2



24.0% had ARIA-E

31.4% had ARIA-H

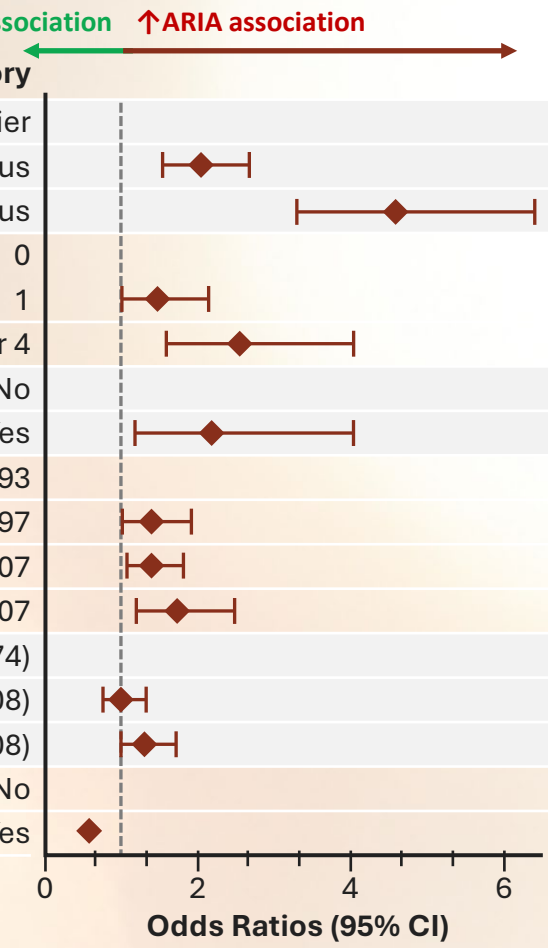
12.7% had ARIA-H only

vs. **12.4%** of placebo-treated participants

36.8% had ARIA
(ARIA-E or ARIA-H)

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
ARIA-E, amyloid-related imaging abnormality – edema; ARIA-H, amyloid-related imaging abnormality – hemorrhage.
1. Sims JR, et al. JAMA. 2023;330(6):512-527, 2. van Dyck CH, et al. N Engl J Med 2023;388;9-21.

APOEε4 Genotype and Baseline MRI are the Greatest Contributing Factors to ARIA-E*



Variable	Category	Odds Ratio (95% CI)	p-value
APOEε4 genotype	Non carrier		
	heterozygous	2.0 (1.5, 2.7)	<0.001
	homozygous	4.6 (3.3, 6.4)	<0.001
Microhemorrhages	0		
	1	1.4 (1.0, 2.1)	0.047
	2,3, or 4	2.5 (1.6, 4.0)	<0.001
Superficial siderosis	No		
	Yes	2.2 (1.2, 4.0)	0.013
Mean arterial pressure	<93		
	≥93 & <97	1.4 (1.0, 1.9)	0.042
	≥97 & <107	1.4 (1.1, 1.8)	0.014
	≥107	1.7 (1.2, 2.5)	0.003
Amyloid PET† Centiloids	tercile 1 (<74)		
	tercile 2 (≥74 & <108)	1.0 (0.8, 1.3)	0.971
	tercile 3 (≥108)	1.3 (1.0, 1.7)	0.048
Antihypertensives	No		
	Yes	0.6 (0.5, 0.7)	<0.001

Total sample size N=2021; With ARIA-E n=446.
Pseudo R-square=7.44%

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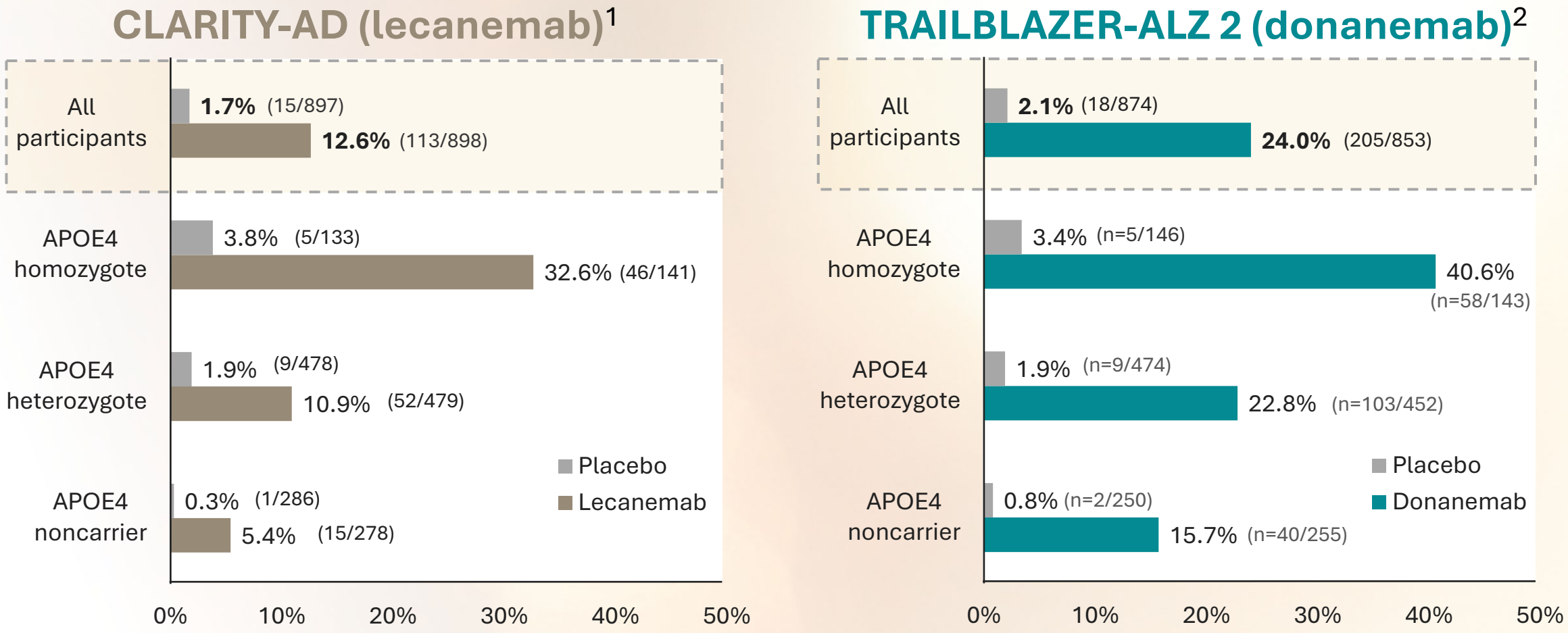
*Analyses completed with multiple logistic regression using TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2, and Addendum populations. †Cerebellum used as reference region.
APOE ε4, Apolipoprotein E type ε4; ARIA-E, Amyloid-related imaging abnormalities - edema/effusions; CI, Confidence interval; PET, Positron emission tomography.
Data from: Biffi A. Presented at the Alzheimer's Association International Conference 2024 (AAIC 2024) - Philadelphia, US, and Online; July 28 - August 1, 2024.

Rates of ARIA-E by *ApoE4* Genotype

For illustrative purposes only. Comparisons cannot be made in the absence of head-to-head trials.



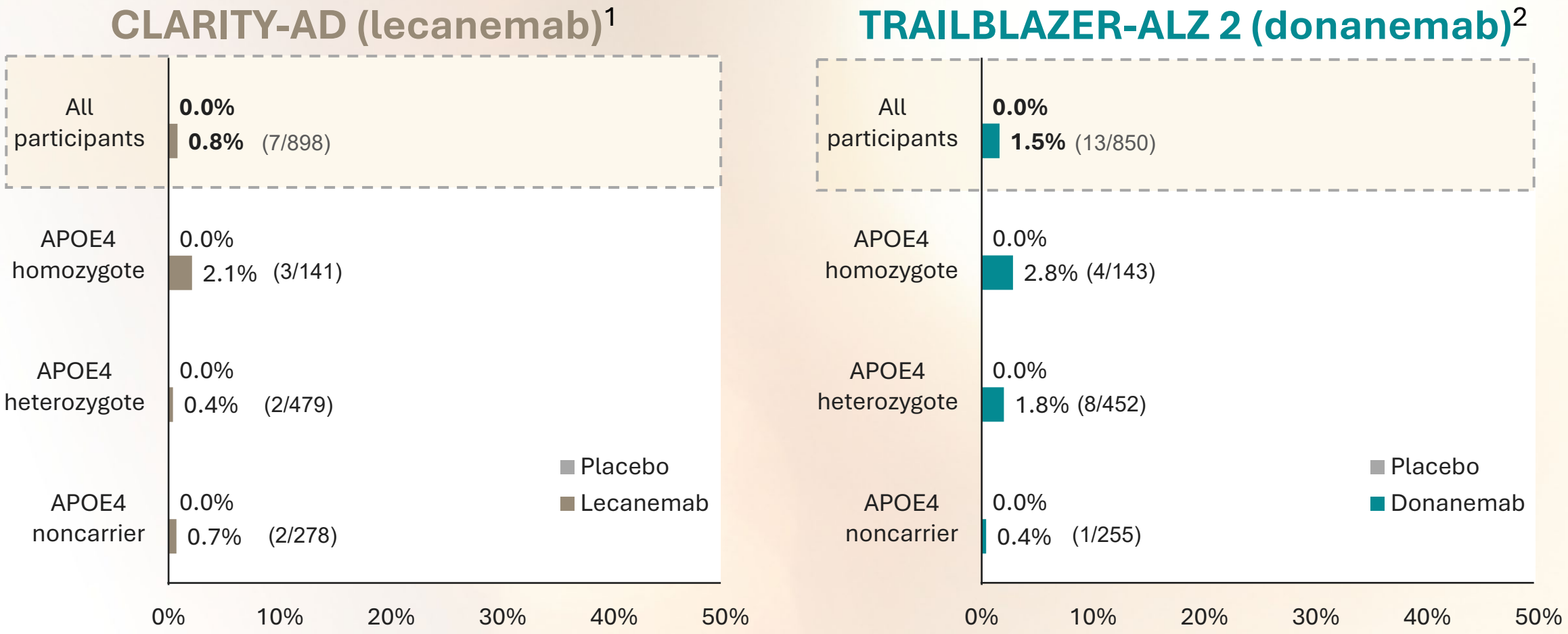
Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada

AD, Alzheimer's disease; APOE4, apolipoprotein E4; ARIA-E, amyloid-related imaging abnormality – edema.

1. van Dyck CH, et al. N Engl J Med 2023;388;9-21. 2. Sims JR, et al. JAMA. 2023;330(6):512-527 and Supplement 3 eTable8.

Rates of Serious ARIA-E by *ApoE4* Genotype

For illustrative purposes only. Comparisons cannot be made in the absence of head-to-head trials.



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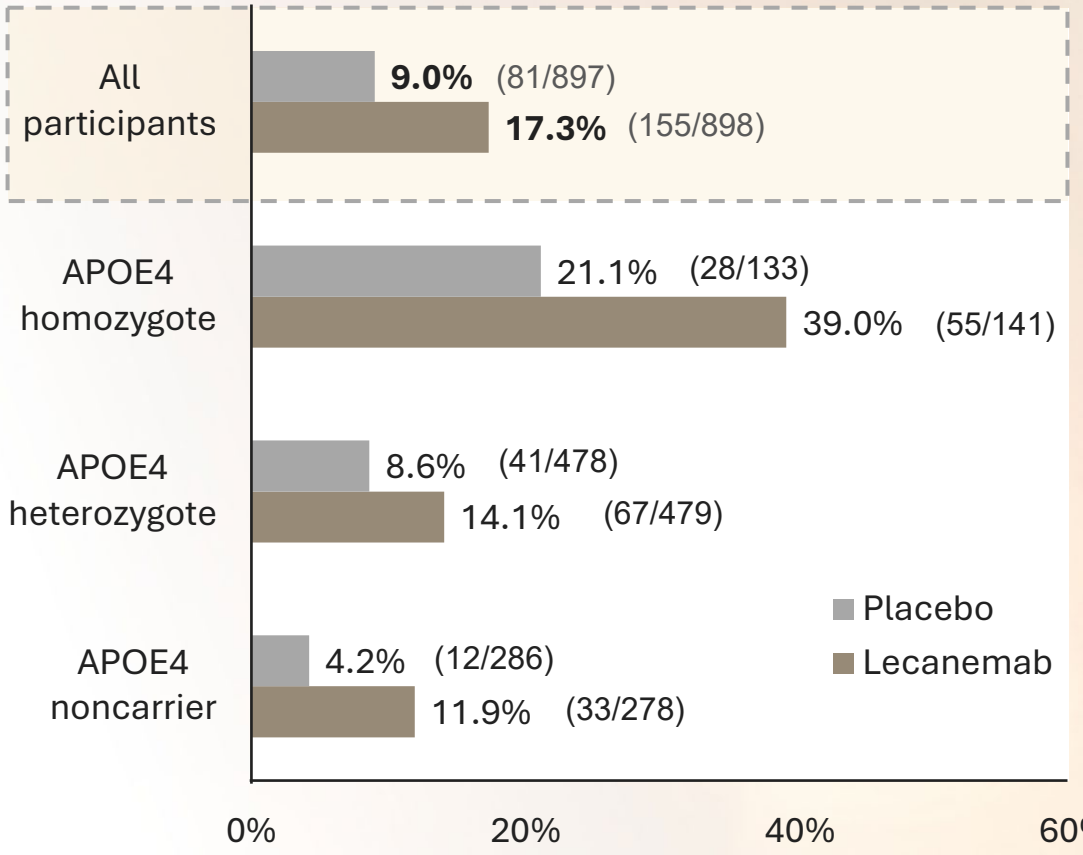
Serious adverse event defined as an event that results in death, is life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, or based on other medical/scientific judgment.
AD, Alzheimer's disease; APOE4, apolipoprotein E4; ARIA-E, amyloid-related imaging abnormality – edema.
1. Cummings J et al. J Prev Alzheimers Dis., 2023;10(3):352-377. 2. Sims JR, et al. JAMA. 2023;330(6):512-527 and Supplement 3 eTable8.

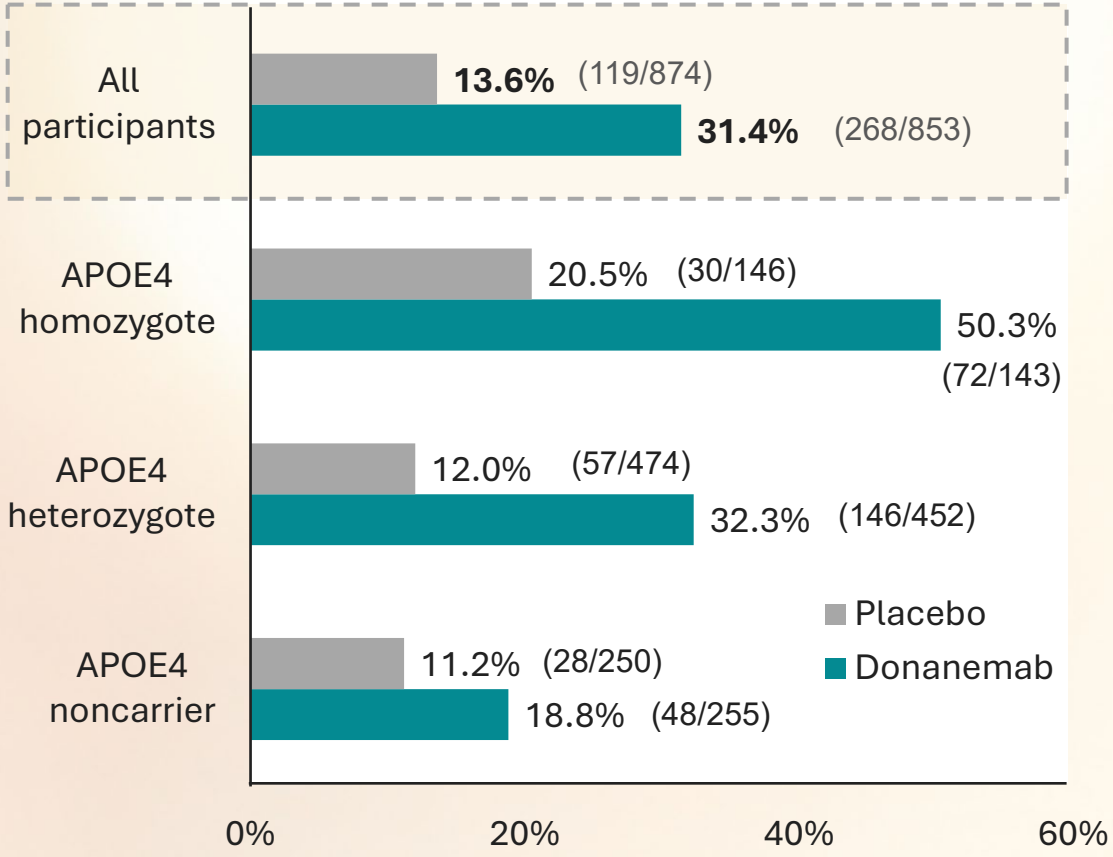
Rates of ARIA-H by *ApoE4* Genotype

For illustrative purposes only. Comparisons cannot be made in the absence of head-to-head trials.

CLARITY-AD (lecanemab)[1]



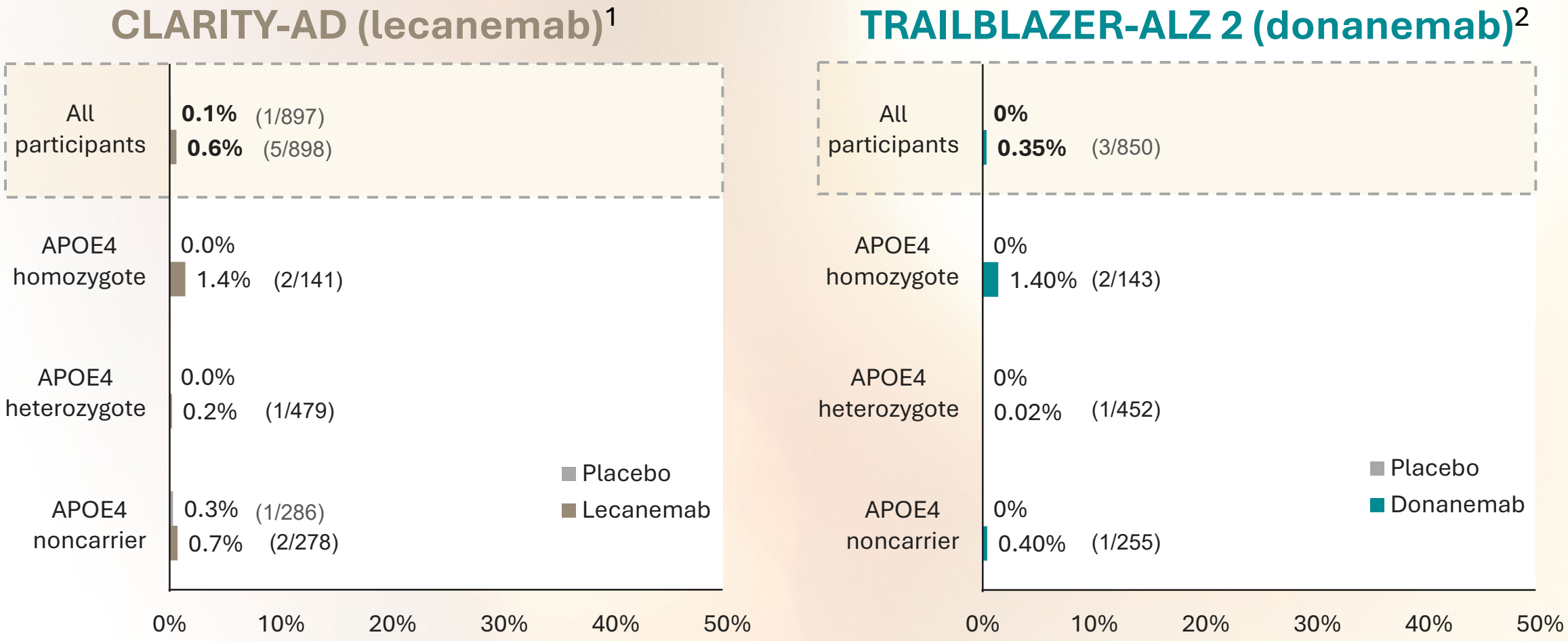
TRAILBLAZER-ALZ 2 (donanemab)[2]



Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
AD, Alzheimer's disease; APOE4, apolipoprotein E4; ARIA-H, amyloid-related imaging abnormality – hemorrhage.
1. van Dyck CH, et al. N Engl J Med 2023;388;9-21. 2. Sims JR, et al. JAMA. 2023;330(6):512-527 and Supplement 3 eTable8.

Rates of Serious ARIA-H by *ApoE4* genotype

For illustrative purposes only. Comparisons cannot be made in the absence of head-to-head trials.



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AD, Alzheimer's disease; APOE4, apolipoprotein E4; ARIA-H, amyloid-related imaging abnormality – hemorrhage.
1. van Dyck CH, et al. N Engl J Med 2023;388;9-21. 2. Sims JR, et al. JAMA. 2023;330(6):512-527 and Supplement 3 eTable8.

Lecanemab: Infusion-Related Reactions

CLARITY-AD + OLE data[1]

- **Rates of infusion-related reactions:**
  - 24.7% of participants overall (398/1612)
  - 19.9% of newly-treated lecanemab participants in OLE
- **Severity and Timing:**
  - 96.5% were mild-to-moderate (73% on the first dose)
  - 65.1% had only one IRR
  - 0.6% had a severe reaction (grade 3-4) and all severe reactions occurred with the first dose
- **Common symptoms:** fever and flu-like symptoms*, nausea, vomiting, hypotension, hypertension, oxygen desaturation.

Prophylactic medication (e.g., acetaminophen, antihistamine, hydrocortisone):

- Taken by 46.9% of participants after a first IRR
  - Only 39.3% had subsequent infusion reactions
- Of the participants who did take a preventative medication, only 32.7% had subsequent infusion reactions

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*Chills, generalized aches, feeling shaky, and joint pain.
IRR, Infusion-Related Reaction.
1. Honig LS, et al. Alzheimers Res Ther. 2024;16(1):105.

Donanemab: Infusion-Related Reactions

IRRs were reported by 8.5% (84/984) vs. 0.4% (4/999) in the placebo arm.

- 82 immediate (≤24 h post-infusion)
  - 92.1% < 30 min after infusion
- Nearly all were mild or moderate

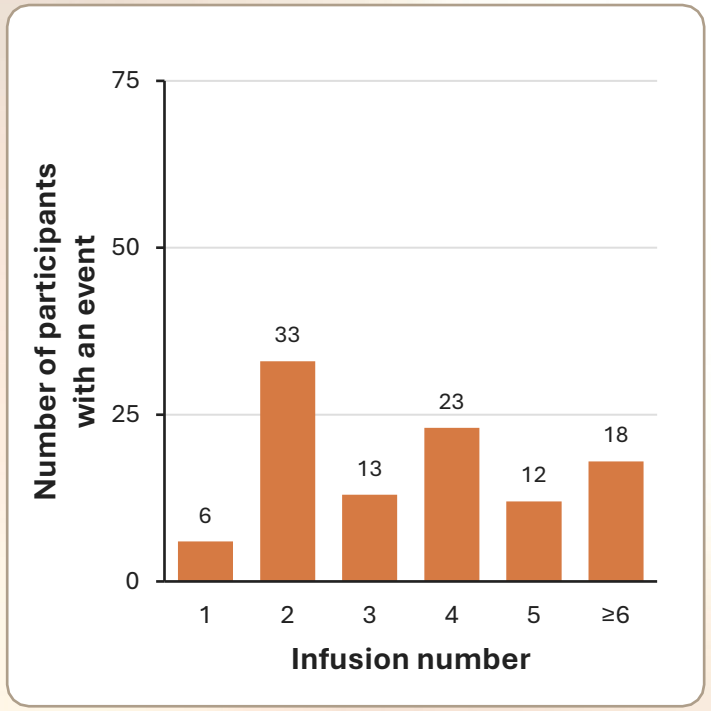
Occurrence by participants:

- Hypersensitivity: 1.0%
- Anaphylactic reactions: 0.3%
- Serious IRRs or hypersensitivity: 0.6% (6/984)

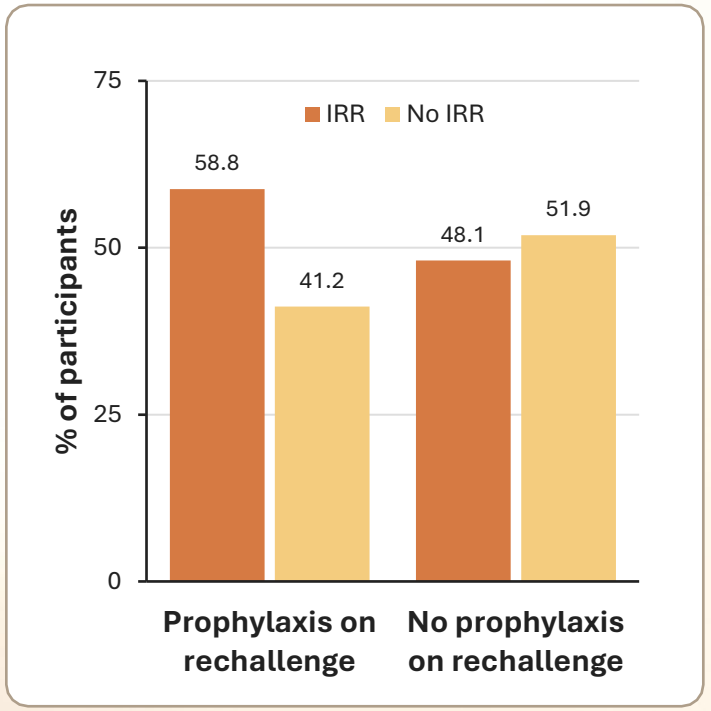
3.9% participants discontinued donanemab due to IRR

Most common IRR symptoms:

- Erythema (4.7%), chills (4.0%), nausea/vomiting (4.0%), sweating (2.3%), and difficulty breathing/dyspnea (2.1%)



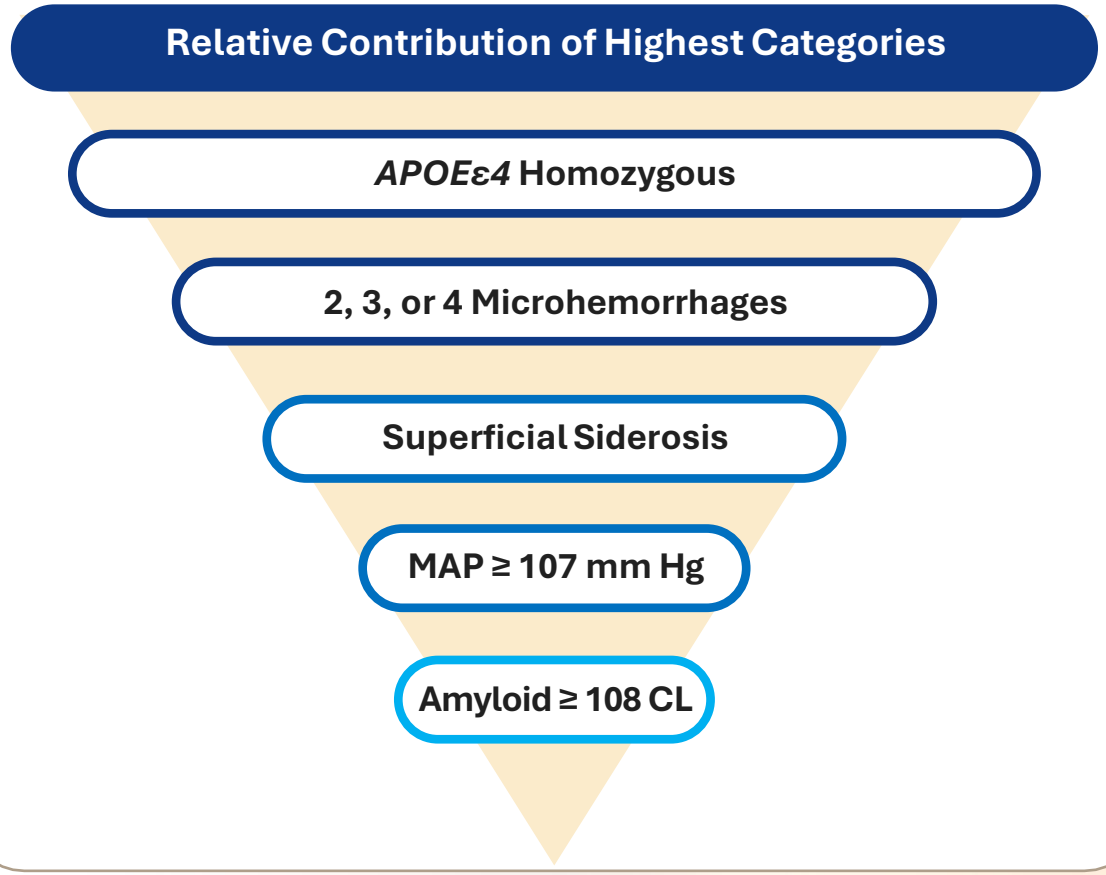
First IRR relative to donanemab infusion number



Percent of participants reporting IRRs during a rechallenge infusion with or without prophylaxis medication

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
IRR, Infusion-Related Reaction; PC, Placebo Controlled.
Reference: Ardayfio P, et al. Poster LP029 presented at Clinical Trials on Alzheimer's Disease (CTAD); Boston, Massachusetts, USA; October 24-27, 2023

Strategy for ARIA Mitigation



ARIA Risk Management

- **Identifying higher risk patients prior to treatment**
- **Adhering to MRI monitoring schedule**
- **Dose titration, interruption, or discontinuation**
- **Use of steroids for serious or symptomatic ARIA**

(E.g., high dose glucocorticoid for 5 days followed by oral steroid taper over several weeks)

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*Analyses completed with multiple logistic regression using TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2, and Addendum populations. †Cerebellum used as reference region
APOE, Apolipoprotein E; ARIA, Amyloid-Related Imaging Abnormalities; ARIA-E, Amyloid-Related Imaging Abnormalities-Edema/Effusions; CI, Confidence Interval; MAP, Mean Arterial Pressure; MRI, Magnetic Resonance Imaging; N,n, Number of Participants; p-value, Probability-Value; PET, Positron Emission Tomography.
Data from: Biffi A. Presented at the Alzheimer's Association International Conference 2024 (AAIC 2024) - Philadelphia, US, and Online; July 28 - August 1, 2024.

TRAILBLAZER-ALZ 6: Reduction of ARIA Risk

Objectives Assess the impact of different donanemab dosing options on the frequency of ARIA-E (primary) and ARIA-H in relation to amyloid reduction.

Study Design Randomization stratified by *APOE* and by baseline amyloid PET

Primary Outcome

	Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
	Study Week	Screening	0	2	4	6	8	10	12	14	16	20	24
Treatment Arm	Standard			PBO		PBO		PBO		PBO			
	Modified Titration			PBO		PBO		PBO		PBO			
	Dose Skipping			PBO	PBO	PBO		PBO		PBO			
	Cmax												
	Amyloid PET Scan	√											√
	MRI	√			√				√				√

350 mg
700 mg
1050 mg
1400 mg

Cumulative donanemab exposure was the same for the 4 dosing regimens by week 16.

Placebo was given at the indicated visits to preserve the blind for the different dosing regimens.

After week 16, all participants received 1400 mg of donanemab monthly until dose stopping criteria was met or until the end of the study.

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ARIA, Amyloid-related imaging abnormality; ARIA-E, ARIA – edema; ARIA-H, ARIA – hemorrhage. APOE, Apolipoprotein E; MRI, Magnetic resonance imaging; PBO, Placebo; PET, Positron emission tomography.
Data from: Sims J. Presented at the 17th Clinical Trials on Alzheimer's Disease (CTAD) Madrid (Spain) October 29 - November 1, 2024

TRAILBLAZER-ALZ 6: Baseline Characteristics

Category	Standard (N=208)	Modified Titration (N=212)	Dose Skipping (N=210)	Cmax (N=213)
Sex, female, n (%)*	121 (58.2)	126 (59.4)	117 (55.7)	123 (57.7)
Age, mean (SD), in years	73.3 (5.7)	74.3 (5.7)	73.4 (5.8)	73.2 (6.0)
Race, n (%)*				
Asian	0 (0)	3 (1.4)	3 (1.4)	3 (1.4)
Black or African American	11 (5.3)	14 (6.6)	8 (3.8)	13 (6.1)
White	197 (94.7)	193 (91.0)	197 (93.8)	196 (92.0)
Ethnicity, n (%)*, Hispanic/Latino	11 (5.3)	11 (5.2)	9 (4.3)	15 (7.0)
Country, n (%)*, United States	188 (90.4)	192 (90.6)	182 (86.7)	186 (87.3)
APOEε4* carrier, n (%)	133 (64.6)	136 (64.5)	137 (65.2)	137 (64.3)
ε4 homozygous, n (%)*	21 (10.2)	21 (10.0)	22 (10.5)	21 (9.9)
Screening amyloid in centiloid, mean (SD)	85.3 (36.6)	84.4 (37.6)	83.1 (35.3)	84.9 (39.4)
Microhemorrhage or superficial siderosis, n (%)*, yes	50 (24.2)	55 (25.9)	44 (21.0)	49 (23.0)
MMSE, mean (SD)	24.6 (2.5)	25.1 (2.3)	24.7 (2.5)	24.5 (2.6)
Screening MMSE by clinical category				
Mild cognitive impairment (27-28), n (%)*	59 (28.4)	73 (34.4)	69 (32.9)	57 (26.8)
Mild AD (20-26), n (%)*	149 (71.6)	139 (65.6)	141 (67.1)	155 (72.8)
Time since onset of AD symptom, mean (SD), in years	3.8 (3.3)	3.9 (3.2)	4.1 (3.3)	3.8 (2.3)
AChEI and/or Memantine use, n (%)*, yes	84 (40.4)	70 (33.0)	69 (32.9)	85 (39.9)

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* Denominator of percentage calculation is the number of participants with non-missing data.

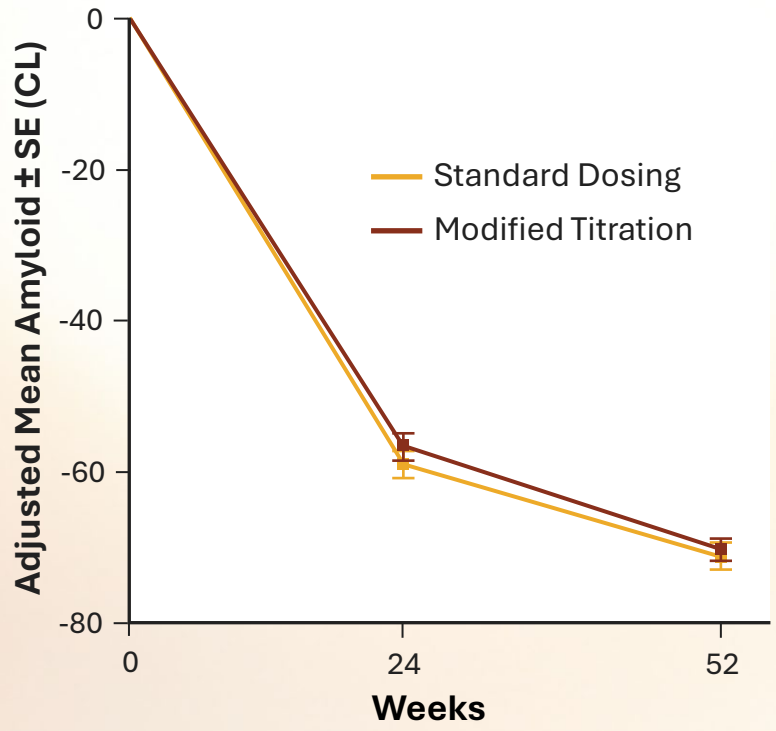
AChEI, acetyl-cholinesterase-inhibitor; AD, Alzheimer's disease; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; N,n: number of participants; SD: standard deviation.

Data from: Sims J. Presented at the 17th Clinical Trials on Alzheimer's Disease (CTAD) Madrid (Spain) October 29 - November 1, 2024

TRAILBLAZER-ALZ 6: Comparable Amyloid Reduction Achieved With Modified Titration

	24 weeks		52 weeks	
	Standard (N=194)	Modified Titration (N=201)	Standard (N=173)	Modified Titration (N=178)
Adjusted mean change from baseline*, CL (SE)	-58.8 (1.8)	-56.3 (1.7)	-71.2 (1.6)	-70.3 (1.6)
Amyloid level below 24.1 CL, n (%)	110 (56.7)	102 (50.7)	138 (79.8)	137 (77.0)
Dose stopping criteria met, n (%)	66 (34.0)	65 (32.3)	116 (67.1)	117 (65.7)

* Adjusted mean change from baseline and SE are derived using ANCOVA mode at 24 weeks and MMRM at 52 weeks. The ANCOVA model is: postbaseline amyloid CL = baseline amyloid CL + dosing regimen + baseline age. MMRM model: with fixed factors being treatment, visit, treatment-by-visit interaction, baseline PET value, baseline PET value-by-visit interaction, and baseline age. Variance-covariance structure is Unstructured.



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ANCOVA, analysis of covariance; CL, Centiloid; MMRM, mixed model repeated measures methodology; N, number of participants in the analysis population; n, number of participants within each specific category; PET, positron emission tomography; SE, standard error.
Data from: Wang H. et al, Alzheimers Dement. 2025.

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TRAILBLAZER-ALZ 6: Modified Titration Arm Significantly Lowered ARIA-E

	24 weeks		52 weeks	
	Standard (N=207) n (%)	Modified Titration N=212 n (%)	Standard (N=207) n (%)	Modified Titration N=212 n (%)
Any ARIA (either E or H) [a,b,c]	67 (32.4)	50 (23.6)	71 (34.3)	61 (28.8)
Concurrent ARIA-E and ARIA-H [d]	32 (15.5)	21 (9.9)	34 (16.4)	23 (10.8%)
ARIA-E [a,b]	49 (23.7)	29 (13.7)	50 (24.2)	33 (15.6)
Symptomatic [a,b,*]	10 (4.8)	6 (2.8)	10 (4.8)	6 (2.8)
SAE of ARIA-E[e]	0 (0)	0 (0)	0 (0)	1 (0.5)
ARIA-H [a,c]	52 (25.1)	43 (20.3)	57 (27.5)	53 (25)
Symptomatic [a,c,f]	0 (0)	1 (0.5)	0 (0)	1 (0.5)
Microhemorrhage [d]	41 (19.8)	36 (17.0)	44 (21.3)	48 (22.6)
Superficial siderosis [d]	26 (12.6)	14 (6.6)	31 (15.0)	18 (8.5)
Macrohemorrhages [a,e]	1 (0.5)	2 (0.9)	1 (0.5)	2 (0.9)

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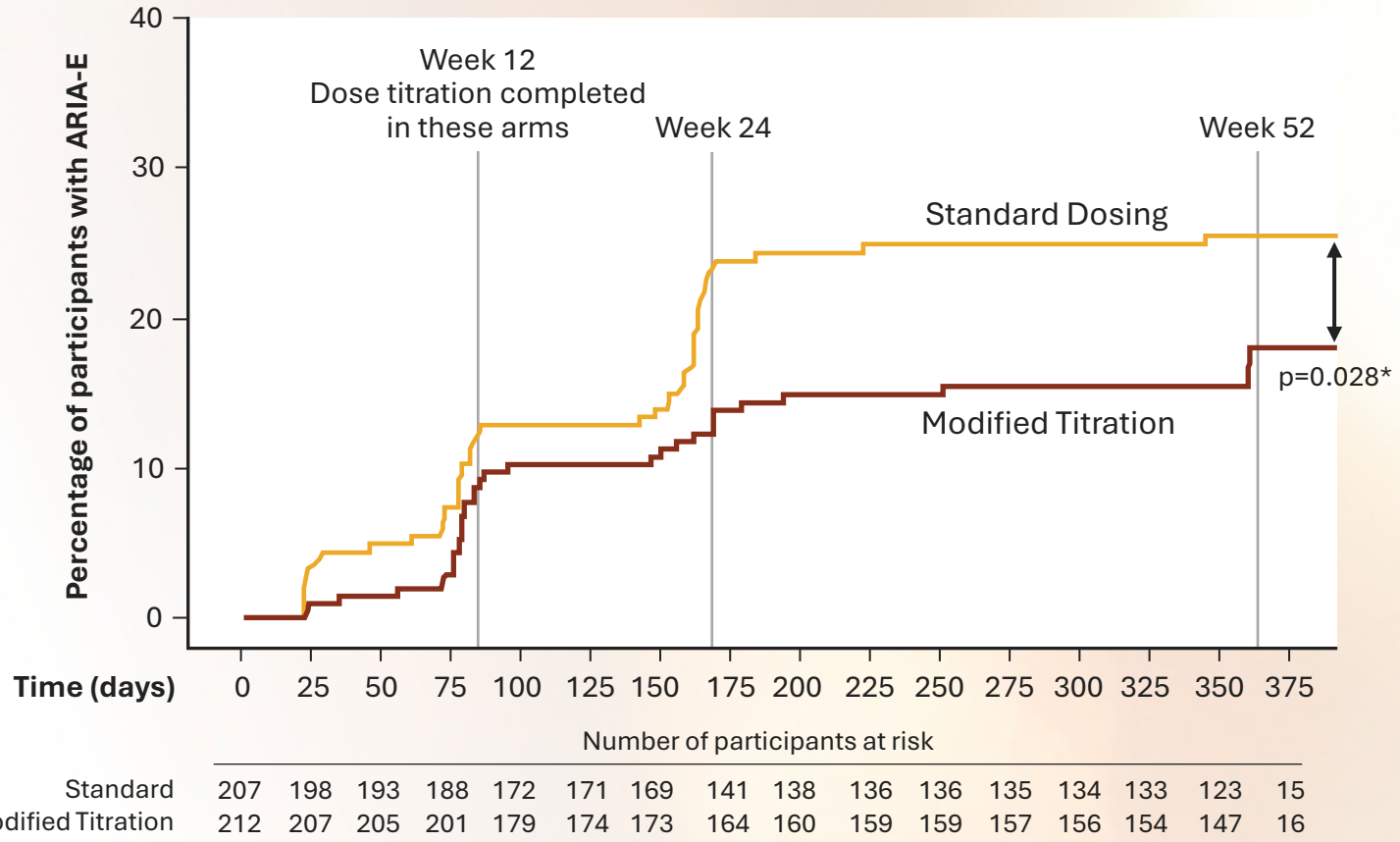
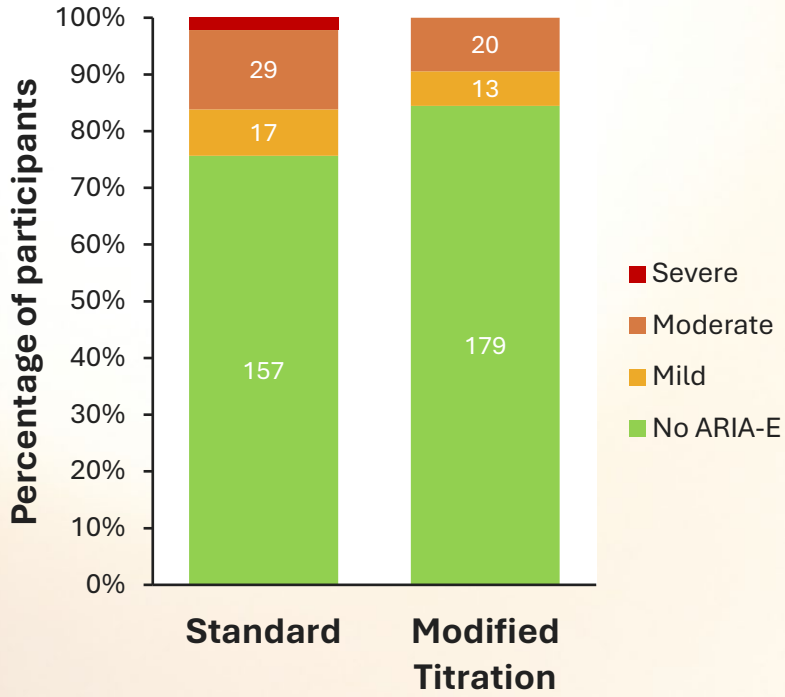
(a) Based on MRI or treatment-emergent adverse event cluster; (b) ARIA-E treatment-emergent adverse event cluster preferred terms are: ARIA - oedema/effusion; brain oedema; vasogenic cerebral oedema; (c) ARIA-H treatment-emergent adverse event cluster preferred terms are: ARIA - microhemorrhage and hemosiderin deposits; brainstem microhemorrhage; cerebellar microhemorrhage; cerebral hemosiderin deposit; cerebral microhemorrhage; and superficial siderosis of the central nervous system; (d) Based on magnetic resonance imaging only; (e) Based on treatment-emergent adverse event cluster; (f) Symptomatic ARIA-H Low Level Term includes symptomatic ARIA-H, symptomatic ARIA-microhemorrhages and haemosiderin deposits, symptomatic ARIA-microhemorrhages and hemosiderin deposits, and symptomatic ARIA-superficial siderosis; (g) Macrohemorrhage preferred term are cerebral hemorrhage; and hemorrhagic stroke.
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA with edema/effusion; ARIA-H, ARIA with hemorrhages/hemosiderin deposition; MRI, Magnetic resonance imaging; SAE, serious adverse event. Data from: Wang H. et al, Alzheimers Dement. 2025.

TRAILBLAZER-ALZ 6: Significantly Lower ARIA-E Risk Over Time and Radiographic Severity in the Modified Titration Arm

Cumulative hazard of time to first ARIA-E



ARIA-E Radiographic Severity at 52 weeks



ARIA-E severity distribution significantly shifted favoring the modified titration arm with p=0.015 (Cochran-Mantel-Haenszel)

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*Log-rank unstratified p-value (2-sided). ARIA-E, Amyloid-related imaging abnormalities - edema; MRI, Magnetic resonance imaging

Data from: Sims J. Presented at the 17th Clinical Trials on Alzheimer's Disease (CTAD) Madrid (Spain) October 29 - November 1, 2024

Real-World Data: Experience with DMTs at Tel Aviv Medical Center *

169 patients were evaluated for suspected early-stage AD → 156 completed evaluation → **86 initiated treatment by Jan. 2025** → 17 discontinued treatment

29 patients excluded for medical reasons:

- 14 *ApoEε4* homozygous
- 7 progressed to moderate dementia
- 3 were found to have contraindications in MRI repeated review
- 4 had inconclusive biomarkers results
- 1 required surgery for other medical condition

41 patients did not start for other reasons:

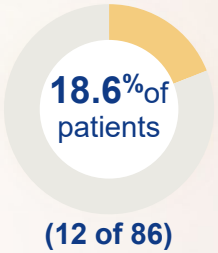
- 5 are currently considering treatment
- 12 are in the process of securing insurance approval
- 16 chose not to proceed with treatment
- 6 are scheduled to begin treatment soon
- 2 opted for a different anti-amyloid therapy

Baseline Characteristics

Age (years) (SD)	71.99 (8.20)
Sex (N, % women)	53 (62%)
Mean MMSE score (SD)	23.96 (2.69)
Number of *ApoEε4* carriers (N, %)	46 (53%)
Mean CSF t-tau (pg/ml) (SD)	569.74 (279.27)
Mean CSF p-tau (pg/ml) (SD)	154.17 (340.04)
Mean CSF Amyloid beta 42 (pg/ml) (SD)	324.89 (159.75)

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
AD, Alzheimer's disease; APOE, Apolipoprotein E; DMT, Disease-modifying therapy; MMSE, Mini mental state examination; SD, Standard deviation.
* Data reproduced with the permission of Dr. Noa Bregman, MD, Director, Cognitive Neurology Unit, Tel Aviv Medical Center

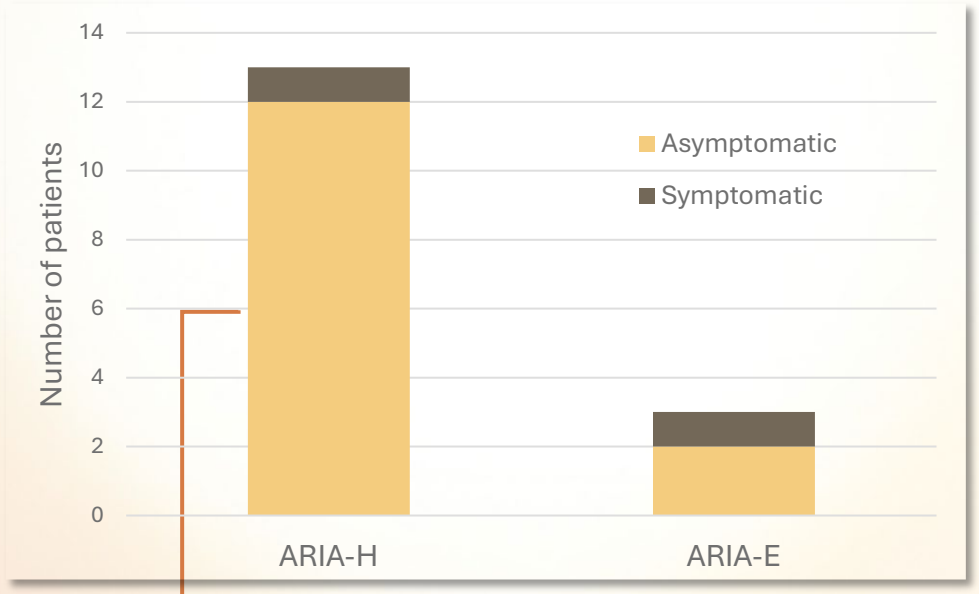
Real-World Data: Adverse Events *

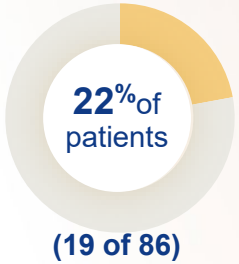


(12 of 86)

Total ARIA

- **13** patients had ARIA-H
  - **12** asymptomatic micro-hemorrhages
- **3** patients had ARIA-E
  - **2** mild, asymptomatic
  - **1** moderate, symptomatic





(19 of 86)

Infusion-related reaction (mild)

Reported only after the first and/or second dose

- **2** 2 events of asymptomatic micro-hemorrhages
  - **1** developed superficial siderosis on subsequent MRI (treatment was discontinued)
  - **1** ARIA-E/H was detected - moderate

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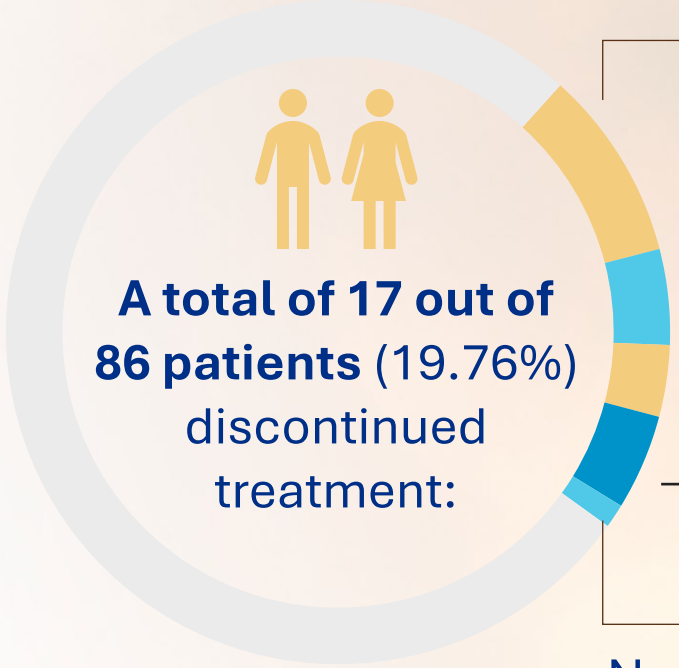
ARIA, Amyloid-related imaging abnormality; ARIA-E, ARIA – edema; ARIA-H, ARIA – hemorrhage; MRI, magnetic resonance imaging.

* Data reproduced with the permission of Dr. Noa Bregman, MD, Director, Cognitive Neurology Unit, Tel Aviv Medical Center

Real-World Data: Discontinuation of Treatment*



A total of 17 out of 86 patients (19.76%) discontinued treatment:

5	Patients – ARIA
4	Patients discontinued due to other medical conditions: 1 DVT and 1 AF - requiring anticoagulation therapy | 1 – ischemic stroke | 1 - suicidal thoughts | 1 - severe weight loss
3	Financial difficulties
4	Chose to stop treatment and did not specify a specific reason
1	Patient moved abroad and continued treatment elsewhere

No patients discontinued treatment due to infusion related reactions

Conclusion

- Initial experience with **lecanemab** generally consistent with expectations from clinical trials
- Experience with **donanemab** has just started through special license program

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AF, Atrial fibrillation; ARIA, Amyloid-related imaging abnormality; DVT, Deep vein thrombosis.
* Data reproduced with the permission of Dr. Noa Bregman, MD, Director, Cognitive Neurology Unit, Tel Aviv Medical Center

THE CHANGING LANDSCAPE

In the Treatment of Alzheimer's Disease

Panel Discussion: Safety and Efficacy

Dr. Mitchell, Dr. Vitali, Dr. Frank

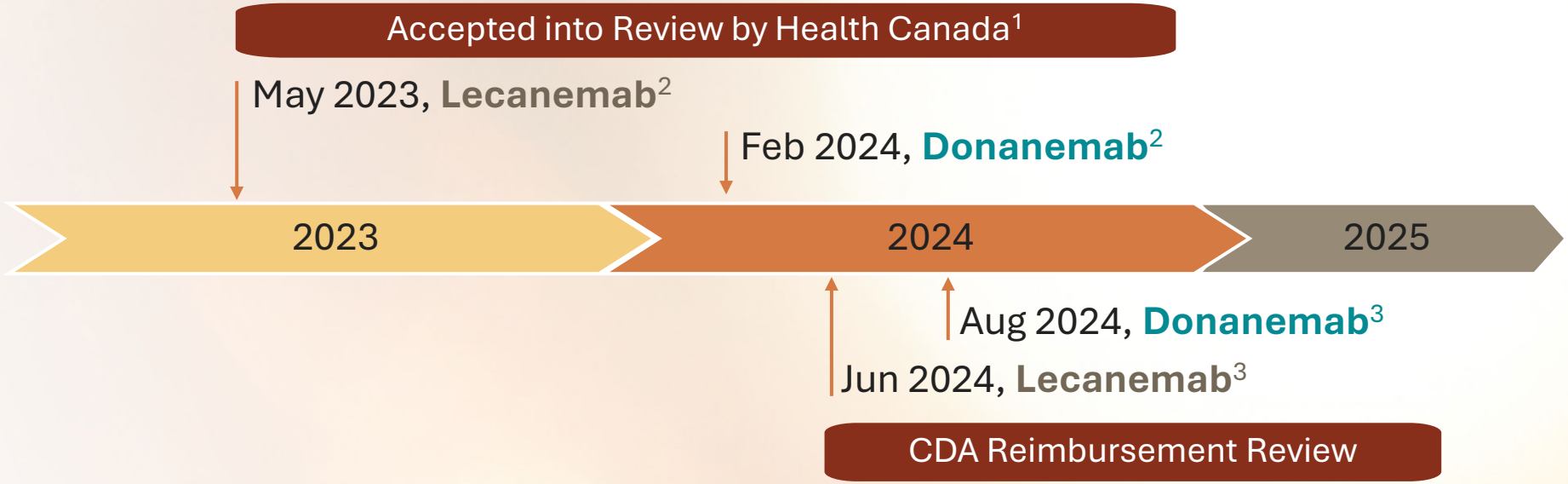
THE CHANGING LANDSCAPE

In the Treatment of Alzheimer's Disease

Canadian Readiness

Dr. Sara Mitchell

Approval Timeline of DMTs for AD in Canada



Standard review timeline

Health Canada Review[1]	NDS	Review ~ 1 year	Regulation Decision (e.g. NOC)
CDA Review	Pre-NOC review	Review ~ 6 mo	Reimbursement negotiations

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
CDA, Canadian Drug Agency; DMT, Disease-modifying drug; NDS, New drug submission; NOC, Notice of compliance

Practical Challenges Ahead

What needs to be done for Canada to be ready?

How to determine eligibility to DMTs?

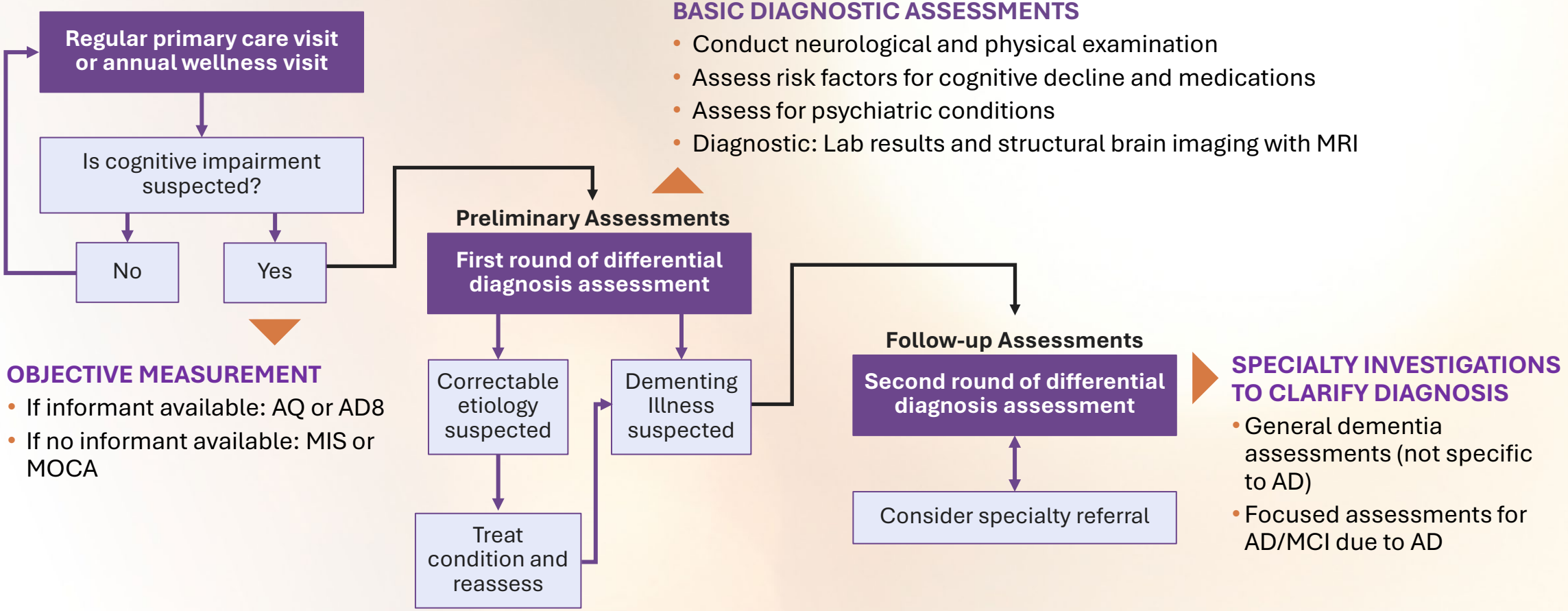
What current biomarker can support AD diagnosis?

How will the risk be monitored?

When to see a doctor?

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
AD, Alzheimer's disease; DMT, Disease-modifying therapy.

Step to Increase Timely Diagnosis: Monitor and Evaluate Patient at Risk of Cognitive Impairment



Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
AD, Alzheimer's disease; AD8, Ascertain Dementia 8-Item Informant Questionnaire; AQ, Alzheimer's Questionnaire; MCI, mild cognitive impairment; MIS, Memory Impairment Screen; MOCA, Montreal Cognitive Assessment. Liss JL, et al. 2021;290(2):310-334.

Consideration for Providing Treatment with DMTs in Clinical Practice

Selection of patients for treatment in practice will require simpler, more pragmatic criteria than the ones used in the trials.

1. • **Patient selection** (MCI, mild-stage dementia due to AD, APOE status*, anticoagulant/thrombolytic treatment status)

* Not routinely performed in Canada

2. • **Diagnostic confirmation** by biomarkers (amyloid-PET*, CSF Aβ42/total-tau* or Aβ42/p-tau, Aβ40*)

3. • **Neuroimaging Protocol** (pre-treatment and follow-up MRI**, amyloid-PET** [alternatively CSF])

** Limited access in Canada

4. • **Organizing clinical care and infusion** (trained professionals, response to IRR, duration of the therapy)

Standardization and practical recommendations are needed

Primary care will have a critical role in identifying potential candidates for DMTs and helping patients to understand potential benefits and harms of treatment

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada Aβ, Amyloid β; AD, Alzheimer's disease; APOE, Apolipoprotein E; CSF, cerebrospinal fluid; DMT, Disease-modifying therapy; IRR, Infusion-related reaction; MRI, magnetic resonance imaging; PET, positron emission tomography. Data from: 1. Smith EE, et al. J Prev Alzheimers Dis. 2025;12(3):100068.

Criteria to Meet Before Initiating Treatment

01

Identify early symptomatic AD

To consider DMTs, clinical symptoms must be consistent with either MCI or mild dementia associated with early AD.[1]
While many clinical assessment tools are available, in donanemab clinical trials, this included patients with MMSE scores of 20-28.[2]

02

Confirm amyloid presence

Presence of amyloid beta pathology can be confirmed via a variety of approved/cleared diagnostic tests, such as PET scan, CSF, and blood plasma.[3]
In TRAILBLAZER-ALZ-2 amyloid presence was confirmed via PET scan.[2]

03

Obtain baseline MRI

Obtain recent brain MRI (including both FLAIR and T2*GRE) prior to initiating treatment to monitor for preexisting ARIA.[1]

04

TEST for *APOEε4* carrier status

Testing for *ApoEε4* status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior testing, discuss with patients the risk of ARIA across genotypes. Prescribers should inform patients and families that if genotype testing is not performed, they can still be treated with donanemab; however, it cannot be determined if they are *APOEε4* homozygotes and at higher risk for ARIA.[1]

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada

AD, Alzheimer's Disease; ARIA, Amyloid-Related Imaging Abnormalities; CSF, Cerebrospinal Fluid; FLAIR, Fluid-Attenuated Inversion Recovery; GRE, Gradient-Recalled Echo Imaging; MMSE, Mini- Mental State Examination; PET, Positron Emission Tomography.

Data from: **1.** Kisunla (donanemab-azbt). Prescribing Information. Lilly USA, LLC. **2.** Sims JR, et al. *JAMA*. 2023;330(6):512-527 **3.** Porsteinsson AP, et al. *J Prev Alzheimers Dis*. 2021;8:371-386.

Access to AD Biomarker Testing Across Canada

Access to amyloid PET for AD diagnosis is limited and variable across Canada (80% are in ON and QC).[1]

AD biomarker testing is not done routinely in patients suspected of AD in Canada.[1]

- There are no Health Canada licensed blood-based diagnostic kits.[1]
- ~ 1.15 % of Canadian with mild dementia or MCI due to AD had access to testing.[2]
- Lack of resources for eligibility assessment would result in a waitlist of ~ 382,000 Canadians, one year after DMT introduction.[2]

AD CSF biomarkers testing significantly and positively effects change in clinical management (e.g., improving imaging resource availability).[3]

CSF testing is only available and reimbursed in BC, and in specialty dementia clinics in AB, ON, and QC.[1]

- Health Canada-approved CSF testing kits are used in a BC clinical laboratory.
- Elsewhere, testing occurs out of province (with special approvals sometimes required).

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada
AB, Alberta; AD, Alzheimer's disease; BC, British Columbia, CSF, Cerebrospinal fluid, DMT, Disease-modifying therapy, MCI, mild cognitive impairment; ON, Ontario, QC, Quebec.
Data from: 1. Smith EE, et al. J Prev Alzheimers Dis. 2025;12(3):100068. 2. Black SE, et al, Can J Neurol Sci. 2024;51(4):487-494. 3. Patel KJ, et al. Alzheimers Dement (N Y). 2024;10(2):e12464.

Discuss Genetic Risk and Treatment Considerations[1-3]

Discuss Logistics

Clarify infusion schedules, transportation needs, and expected time commitment to ensure treatment adherence.

APOEε4 and DMT Response

APOEε4 carriers have increased amyloid burden and may have different responses to DMT, requiring tailored monitoring.

Manage Expectations

Educate families about realistic treatment outcomes, potential risks, and the gradual nature of DMT effects.

Shared Decision-Making

Engage patients and families in a transparent discussion about benefits, risks, and alternative options.

Genetic Counseling

Discuss implications of APOE status with patients and families, ensuring informed consent and expectation management.

Risk of ARIA

APOEε4 homozygotes have a higher risk of amyloid-related imaging abnormalities (ARIA), necessitating enhanced surveillance.

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APOE ε4, Apolipoprotein E type ε4; ARIA, Amyloid-related imaging abnormalities; ATT, Amyloid-targeting therapy.
1. Smith EE, et al. J Prev Alzheimers Dis. 2025;12(3):100068.; 2. Rabinovici GD, et al. J Prev Alzheimers Dis. 2025;12(5):100150; 3. Cummings J, et al. J Prev Alzheimers Dis. 2023;10(3):362-377.

Initiating and Monitoring Patients on DMTs

Experienced Support Staff

Clinicians, nurses, and pharmacists with expertise in DMT are essential for patient safety and adherence.

Infusion Suite

Requires specialized facilities equipped for DMT administration, patient monitoring, and emergency response.

Patient Education

Pre-infusion counseling ensures patients understand the treatment process, potential side effects, and monitoring protocols.

Scheduled MRI Surveillance

Routine MRI scans are required to monitor for amyloid-related imaging abnormalities (ARIA) and other adverse effects.

Neurologic Symptom Monitoring

Any new cognitive or neurological symptoms warrant an unscheduled MRI to rule out ARIA or other complications.

Patient and Caregiver Reporting

Encourage patients and caregivers to report subtle changes in cognition, behavior, or function.

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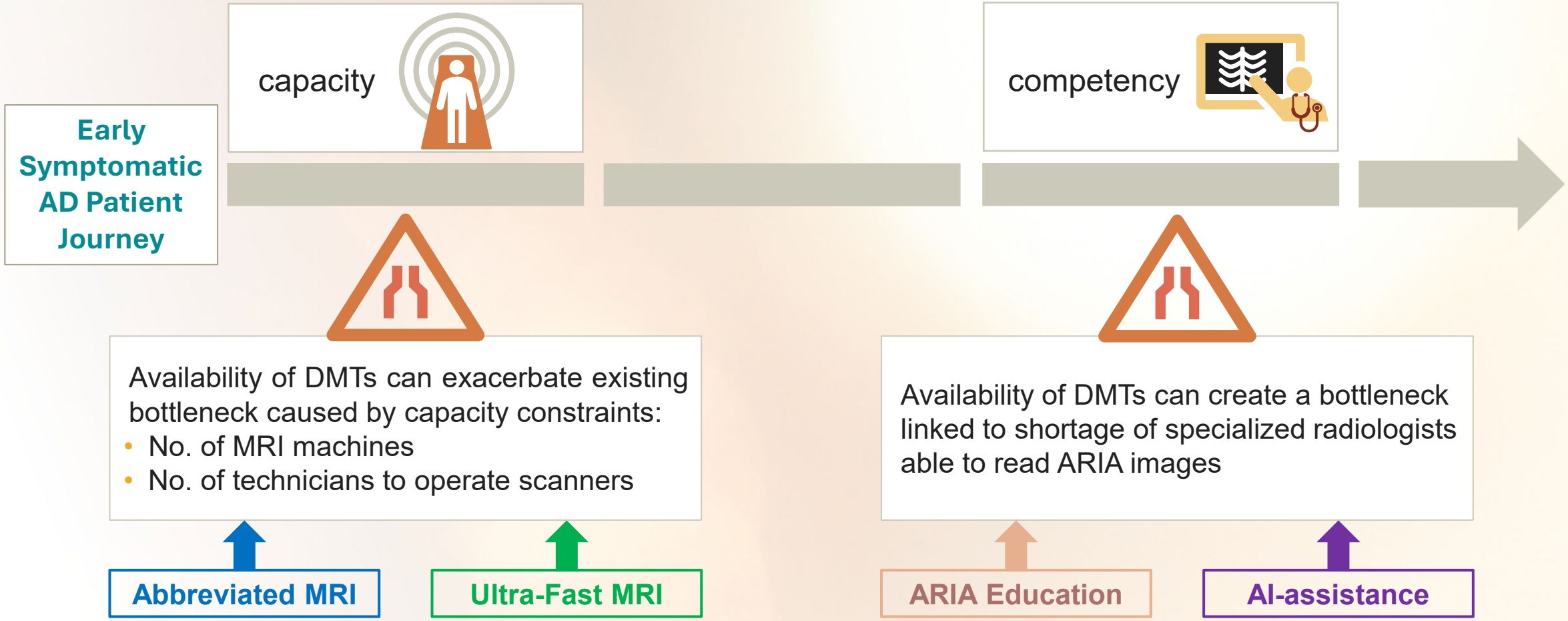
ARIA, Amyloid-related imaging abnormalities; ATT, Amyloid-targeting therapy; MRI, Magnetic resonance imaging.
Smith EE, et al. J Prev Alzheimers Dis. 2025;12(3):100068.

Facilitate ARIA Monitoring and Management: MRI-related Ecosystem Constraints



Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada

AD, Alzheimer's disease, AI, Artificial intelligence; ARIA, Amyloid-related imaging abnormalities; ATT, Amyloid-targeting therapy; MRI, Magnetic resonance imaging.

Improving MRI Access: Abbreviated and Ultra-Fast MRI protocol

3T scanner (recommended), 1.5T scanner (minimal)[1,2]	Greater sensitivity of high-field scanners but limited availability.
Slice thickness[2]: ≤5 mm D	Balance thinner slices (increased resolution) with loss of signal-to-noise ratio[2]
TE[2]: ≥20 ms	Longer TE increases sensitivity to detection[2]
2D T2* GRE or SWI[2,3]	To identify superficial siderosis and improve detection and visualization of microhemorrhages[2]
T2 FLAIR[2]	To monitor brain edema or sulcal effusion (ARIA-E)[3]
DWI[3]	Recommended for differential diagnosis[3]
3D t1-GE (optional)[1]	Anatomical[1]

The focus is on sequences relevant to ARIA identification, severity determination, and clinical decision-making[1-4]

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ARIA-E, Amyloid-related imaging abnormalities - edema/effusion; ARIA-H, Amyloid-related imaging abnormalities-hemosiderin deposits; DWI, Diffusion-weighted imaging; FLAIR, Fluid-attenuated inversion recovery; GRE, Gradient recalled echo; MRI, Magnetic resonance imaging; SWI, Susceptibility weighted imaging; TE, Time to echo.

1. Pinter NK et al. Alzheimer's Dement. 2022;18(Suppl. 5):e065547; 2. Cogswell PM et al. Am J Neurol. 2022;43:e19-35; 3. Sperling RA et al. Alzheimer's Dement. 2011;7:367-385; 4. Barakos J et al. J Prev Alz Dis. 2022;9:211-220

Recommendations on Imaging in the Context of Alzheimer's ATTs from the CCNA Imaging Workgroup

#	Recommendation	Agreement
1	Trials of AD ATTs should report complete MRI sequence parameters, in either the main trial publication or supplemental documents and in sufficient detail to allow their reproduction in clinical practice.	Strong
2	Tailored monitoring protocols should be used for each drug that follows regulatory guidelines if issued or appropriate use recommendations if regulatory guidelines are not available. A common protocol may be considered when more information becomes available on drug safety, efficacy, side effects and risk profiles.	Strong
3	Further studies of the safety, efficacy, side effects and risk profiles associated with various risk factors should be performed before deviating from the current monitoring protocols.	Strong
4	The monitoring protocol should not be changed even if treatment on any ATT is not shown to be optimally effective.	Strong
5	MRI screening and monitoring can be performed on either 1.5T or 3T scanners, provided that protocols are adapted to acquire similar contrasts at identical resolution.	Strong
6	Protocols should be standardized across platforms, scanner strength and ATTs.	Strong
7	Patients should be scanned at screening and then at follow-up/ARIA visits on the same scanner and with the same imaging protocol to ensure consistency (100% agreement).	Strong
8	Provided MR scanners are maintained to a contemporary standard with respect to software/hardware, a protocol lasting 20-30 minutes is both clinically feasible and sufficient with modern acquisition approaches to collect all relevant information.	Strong

Health Canada has not established the safety and effectiveness of an unauthorized health product and market authorization has not been granted in Canada

AD, Alzheimer's disease; ARIA, Amyloid-related imaging abnormalities; ATT, Amyloid-targeting therapy; CCNA, Canadian Consortium on Neurodegeneration in Aging; T, Tesla.

Duchesne S, et al. Can J Neurol Sci. 2024:1-9.

Recommendations on Imaging in the Context of Alzheimer's ATTs from the CCNA Imaging Workgroup

#	Recommendation	Agreement
9	The following acquisitions should be included in a base protocol: 3D T1-weighted, 2D FLAIR, 2D T2*GRE and diffusion-weighted imaging.	Strong
10	Centers are encouraged to perform a 3D rather than 2D FLAIR, as well as acquire a susceptibility-weighted image over and above a T2*GRE if possible.	Strong
11	Further studies on the sensitivity and specificity of high-resolution susceptibility imaging for ARIA-H detection should be performed.	Strong
12	A consensus conference should be convened on the operational definition of ARIA-H and ARIA-E.	Strong
13	Guidelines should be used to rate ARIA-E and ARIA-H.	Strong
14	Intra- and inter-rater variability in ARIA detection, cross-sectionally and longitudinally, should be studied further.	Strong
15	Further studies are necessary to provide information for imaging follow-up guidelines of ARIA-E and ARIA-H.	Strong
16	Acquisition of a PET scan before beginning therapy, even if the amyloid status of the patient has already been confirmed by other means, should be obtained whenever this is practically available, as repetition of this test during therapy would help directly assess the extent of plaque removal, guiding a decision on whether therapy should be continued or discontinued. Further research is needed to assess when a control scan should be obtained after ATT initiation.	Strong

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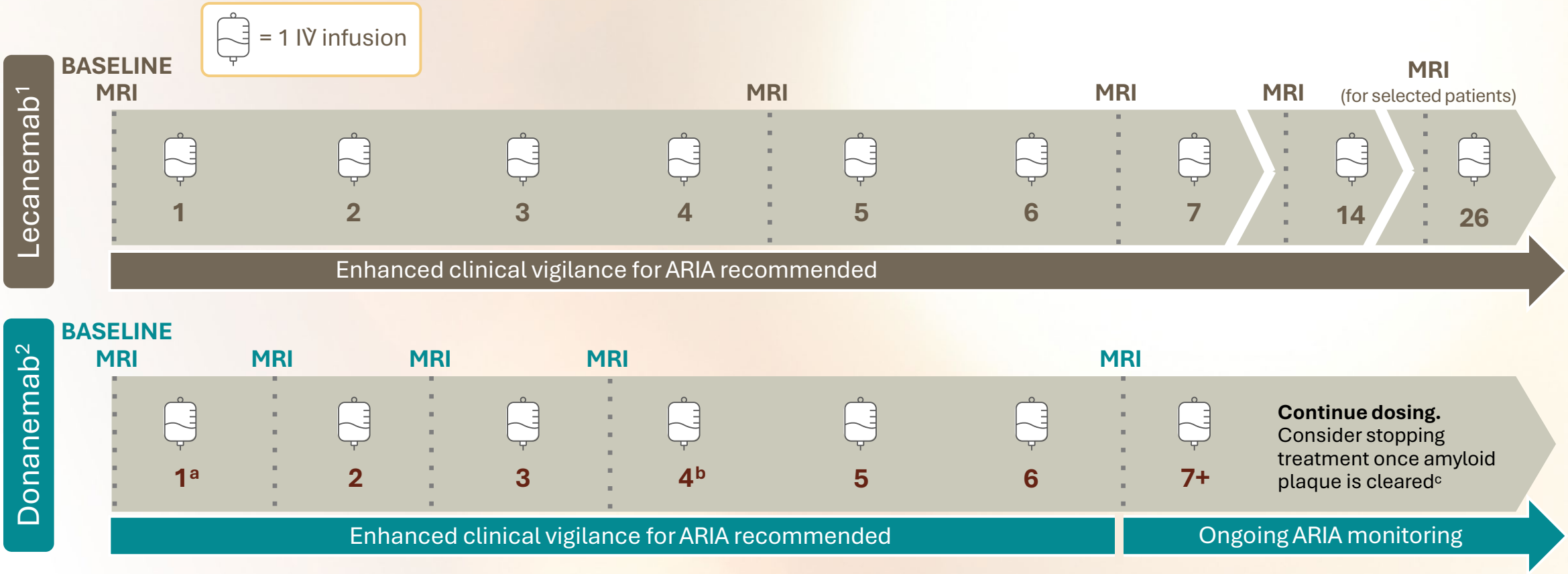
ARIA, Amyloid-related imaging abnormalities; ARIA-E, ARIA-edema; ARIA-H, ARIA-hemorrhagic; CCNA, Canadian Consortium on Neurodegeneration in Aging; ATT, Amyloid-targeting therapy; FLAIR, MRI fluid-attenuated inversion recovery; GRE, MRI T2*-weighted gradient recalled echo; MRI, Magnetic resonance imaging; PET, Positron emission tomography.
Duchesne S, et al. Can J Neurol Sci. 2024:1-9.

How To Monitor for ARIA



- Obtain recent brain MRI prior to initiating treatment. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including an MRI if indicated.

[a] Initial dose of 700 mg.[1] [b] Titrate up to 1400 mg.[1] [c] In TRAILBLAZER-ALZ 2, clearance was an outcome of amyloid assessment and was defined as <24.1 Centiloids on amyloid PET scan consistent with a negative visual read2. Clearance was assessed via amyloid PET at 6, 12, and 18 months.[1]

ARIA, Amyloid-Related Imaging Abnormalities; ARIA-E, ARIA-Edema/Effusion; ARIA-H, ARIA-Hemosiderin Deposits; IV, Intravenous; MRI, Magnetic Resonance Imaging; PET, Positron Emission Tomography.

1. Cummings J, et al. J Prev Alzheimers Dis. 2023;10(3):362-3772. 2. Rabinovici GD, et al. J Prev Alzheimers Dis. 2025:100150.

Managing ARIAs and Deciding When to Stop DMTs

Management Strategies

Mild cases may resolve with monitoring, while symptomatic cases may require temporary treatment discontinuation.

Patient or Family Decision

If benefits no longer outweigh risks, discontinuation may be considered in alignment with patient and family preferences.

Significant Clinical Decline

Progression beyond mild dementia (e.g., loss of independence, severe functional impairment) may indicate DMT discontinuation.

Severe ARIA

Persistent or symptomatic ARIA, particularly if associated with neurological deficits, may necessitate discontinuation.

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Smith EE, et al. J Prev Alzheimers Dis. 2025;12(3):100068.

THE CHANGING LANDSCAPE

In the Treatment of Alzheimer's Disease

Conclusion

Dr. Sara Mitchell

Conclusion

- DMTs lower amyloid-β and slow the rate of decline of cognition by 22-27 % over an 18 month period, with an effect on the rate of cognitive and functional decline.
- DMTs, approved in multiple countries, are currently under review by Health Canada.
- ARIA is a significant side effect that requires monitoring. Access to ultra-fast MRI and adjustment in titration schedule may help mitigate this effect.
- In Canada, substantial changes are needed to integrate DMTs into clinical practice, including:
  - Improvement of AD diagnosis, access to biomarker testing and specialists,
  - Determination of eligibility criteria for DMTs and access to treatment monitoring.

THE CHANGING LANDSCAPE

In the Treatment of Alzheimer's Disease

Panel Discussion: Canadian Readiness

Dr. Mitchell, Dr. Vitali, Dr. Frank

Evaluation 1/2

- Kindly complete the evaluation by scanning the QR code or clicking on the link in the chat.

VV-Canada Medical-US-DEL-0350

Evaluation 2/2

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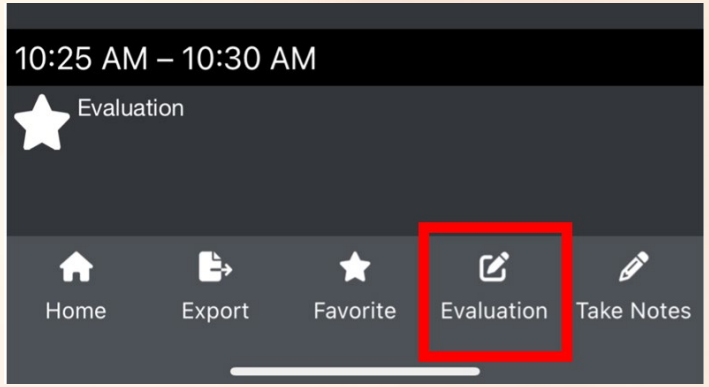

THE CHANGING LANDSCAPE

In the Treatment of Alzheimer's Disease

Thank You!