Leveraging Clinical & Research Imaging Data in a New Era of AD Treatments and Increased Engagement of Diverse Populations

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SCHOOL OF **MEDICINE**

Disclosures/Acknowledgements

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  - **I want to thank the other Neuroimaging Steering Committee members who helped to plan this session, especially Emily Rogalski (U Chicago, Chair) and Annie Cohen (Pittsburgh ADRC, Vice-Chair), as well as our excellent panelists who agreed to be part of this session: Adam Brickman, Gil Rabinovici, and Duygu Tosun**

Outline

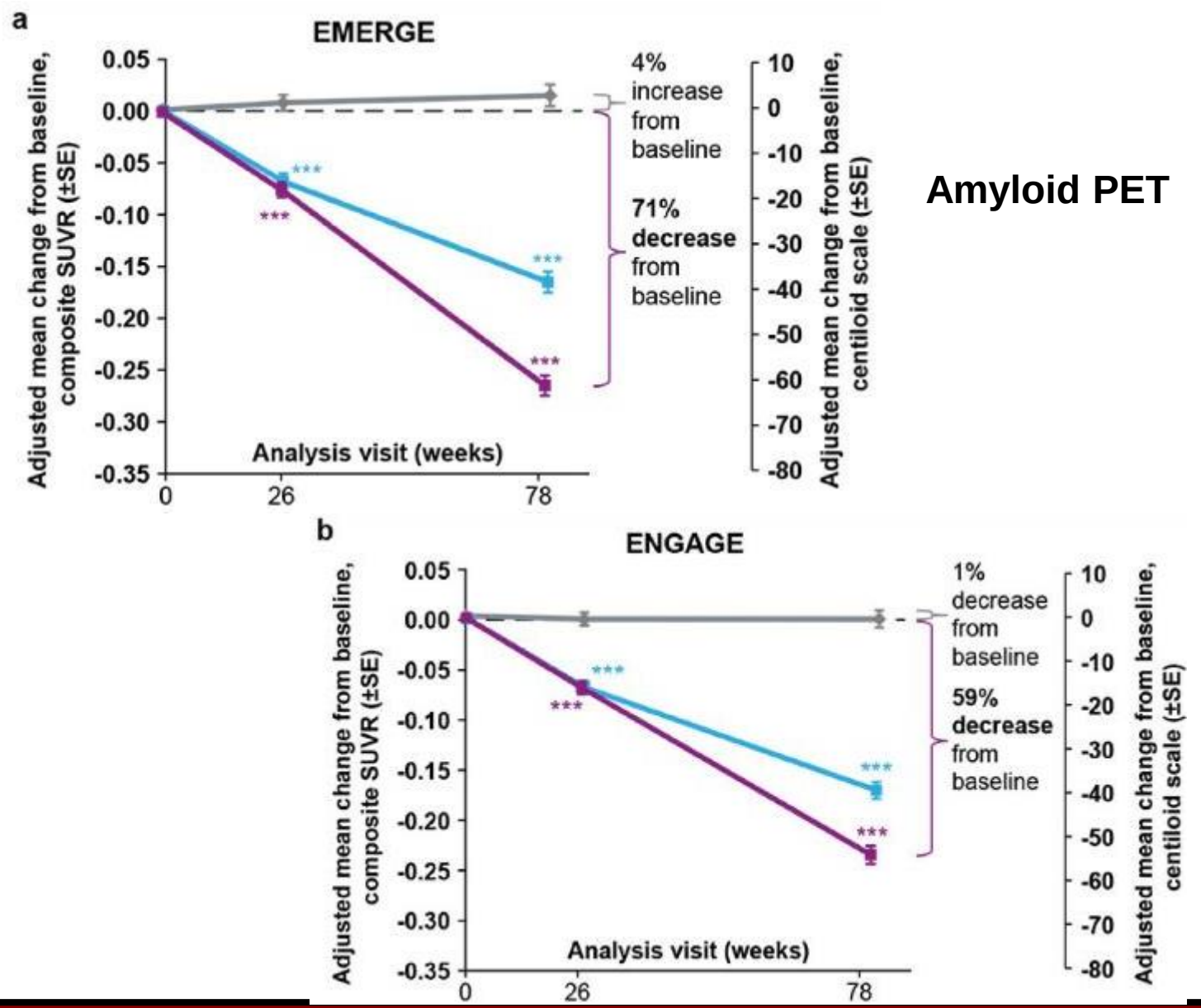
- Introduction of the approved/under review anti-amyloid monoclonal antibody (mAb) treatments
- Amyloid-related Imaging Abnormality (ARIA)
- Diversity of clinical trials samples
- Examples of future questions that could be studied with neuroimaging
- Questions/topics for the panel discussion

Aducanumab (Aduhelm)

- Ran two essentially simultaneous Phase 3 RCTs, ENGAGE (n=548 placebo, 543 low dose, 547 high dose) and EMERGE (545 placebo, 547 low dose, 555 high dose)
- Amyloid PET positive MCI or mild AD
- MRI scans to screen for ARIA done repeatedly throughout the trial (pre-treatment, 14, 22, 30, 42, 54, 66, 78 weeks)
- Accelerated approval by FDA in June 2021; Biogen announced in early 2024 that they would not longer be supporting aducanumab (Aduhelm)

Budd Haeberlein et al. (2022) J Prev Alzheimers Dis 9, 197–210
https://doi.org/10.14283/jpad.2022.30

Endpoint	EMERGE		ENGAGE	
	Difference vs placebo (%)		Difference vs placebo (%)	
	Placebo decline ± SE (n=548)	High dose (n=547)	Placebo decline ±; SE (n=545)	High dose (n=555)
Primary				
CDR-SB*	1.74±0.11	-0.39 (-22%)	1.56±;0.11	0.03 (2%)
		-0.69, -0.09		-0.26, 0.33
p-value		.012		.833
Secondary				
MMSE†	-3.3±0.2	0.6 (-18%)	-3.5±;0.2	-0.1 (3%)
		0.0, 1.1		-0.6, 0.5
p-value		.049		.811
ADAS-Cog 13‡	5.16±0.40	-1.40 (-27%)	5.14±;0.38	-0.59 (-11%)
		-2.46, -0.34		-1.61, 0.43
p-value		.010		.258
ADCS-ADL-MCI§	-4.3±0.4	1.7 (-40%)	-3.8±;0.3	0.7 (-18%)
		0.7, 2.7		-0.2, 1.6
p-value		<.001		.151



Amyloid PET

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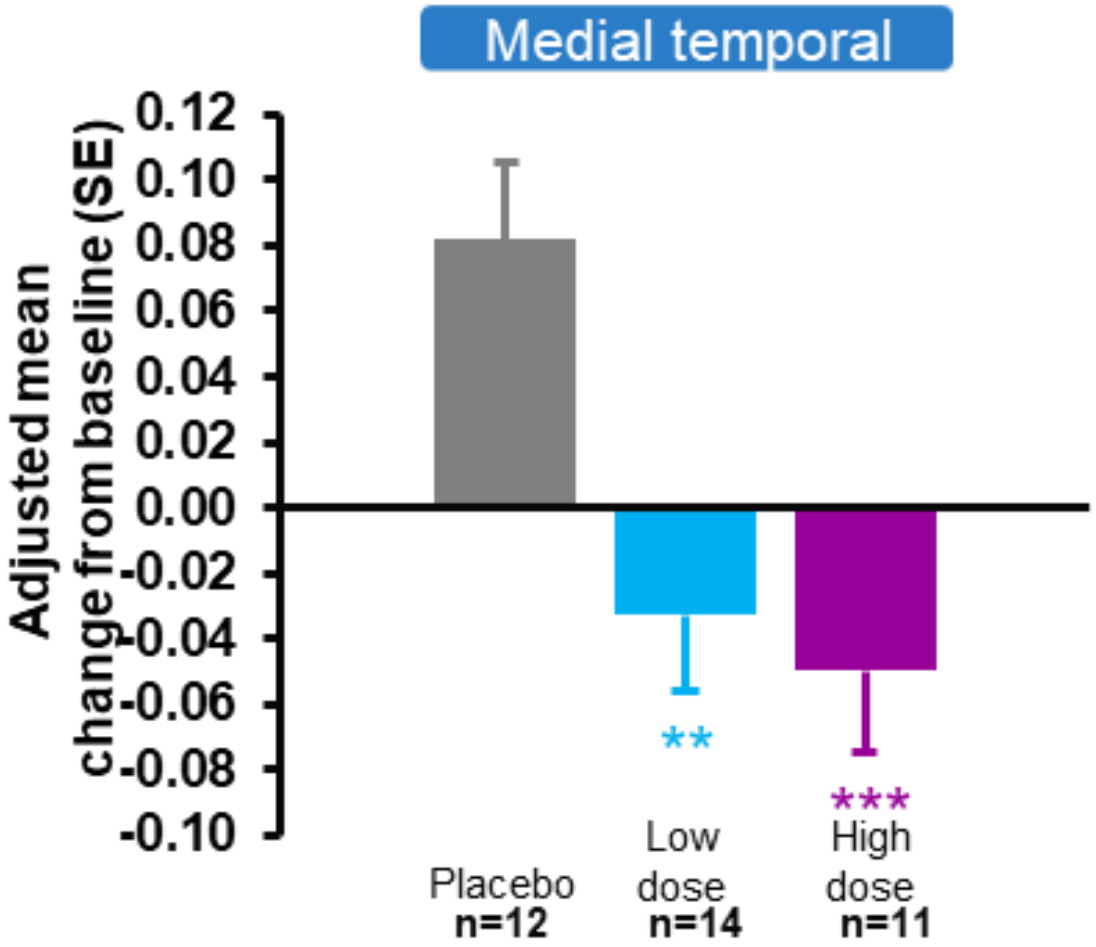
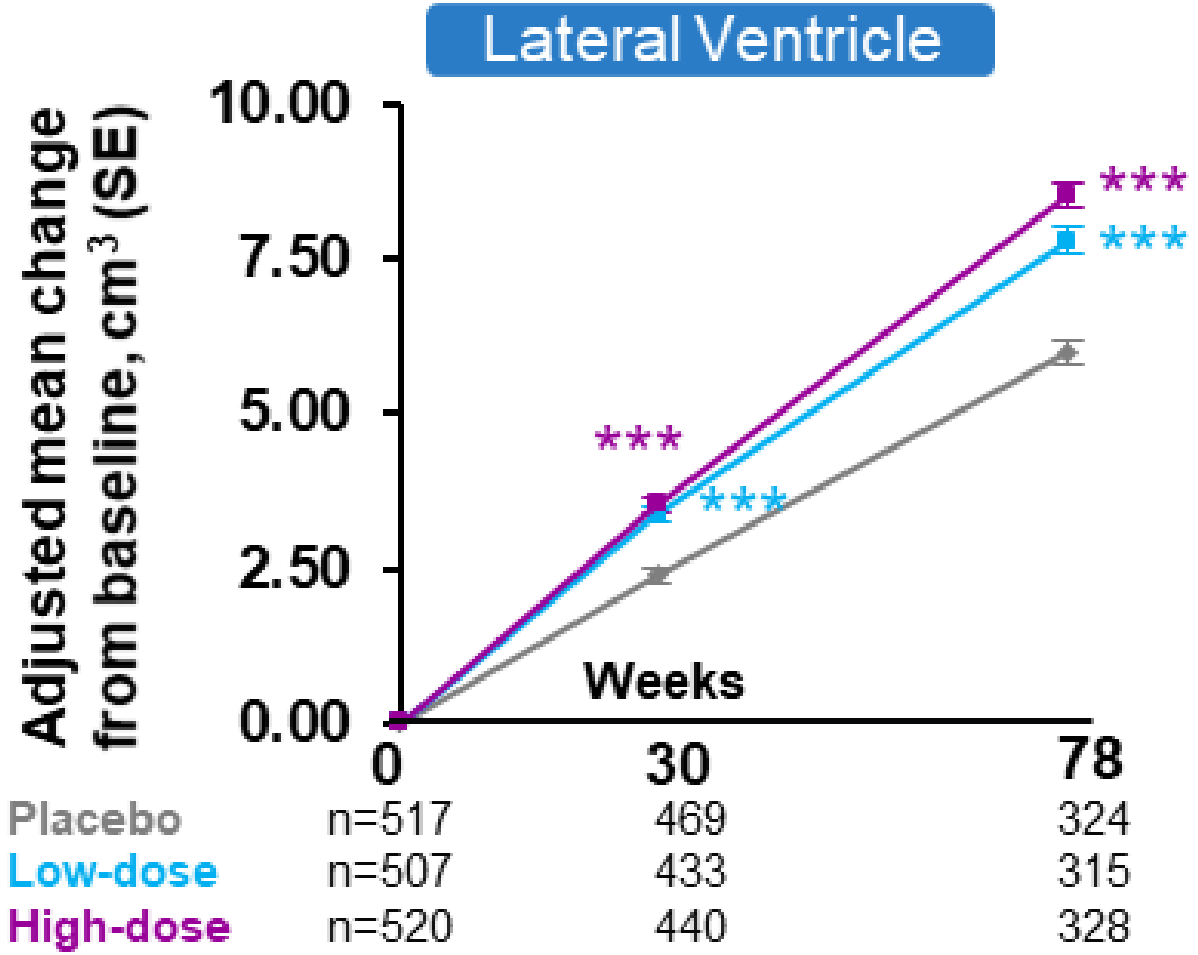
Aducanumab Other Imaging Outcomes





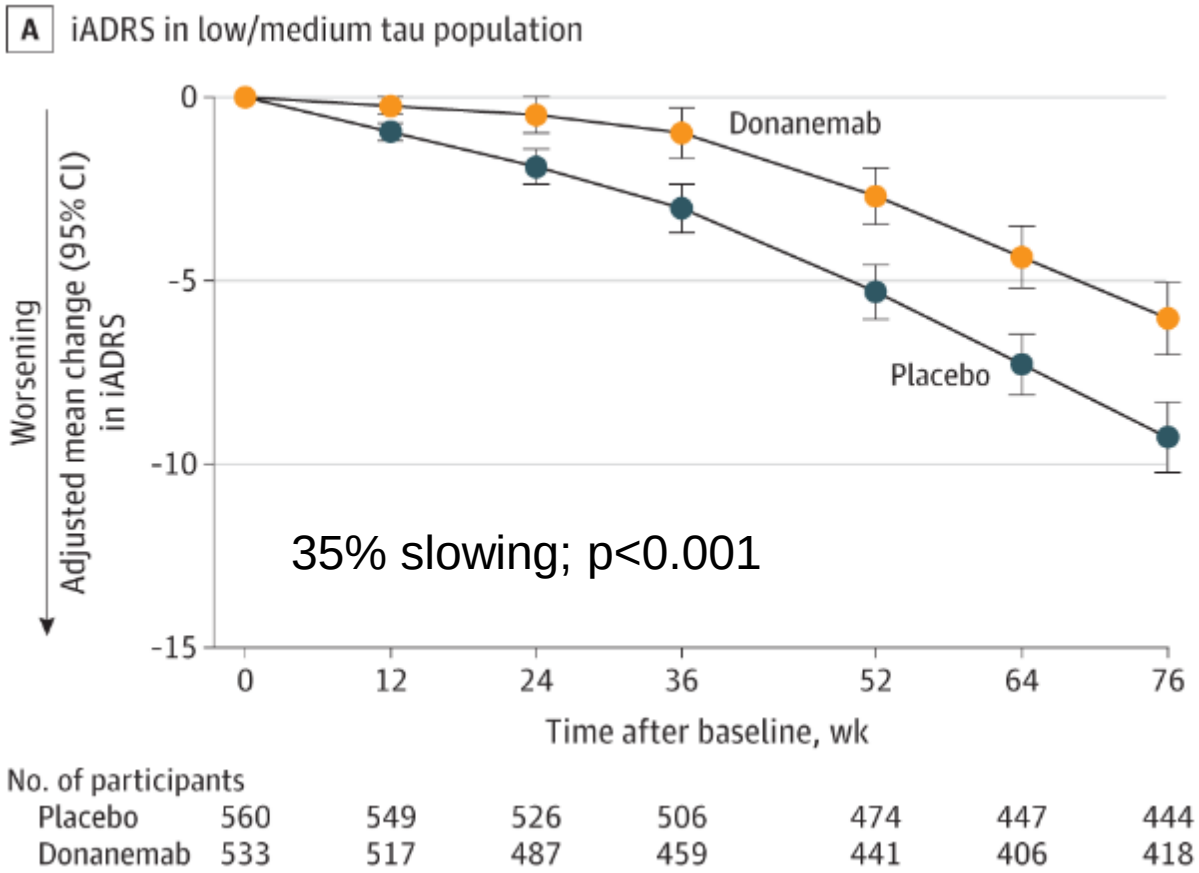
Budd Haeberlein et al. (2022) J Prev Alzheimers Dis 9, 197–210
https://doi.org/10.14283/jpad.2022.30

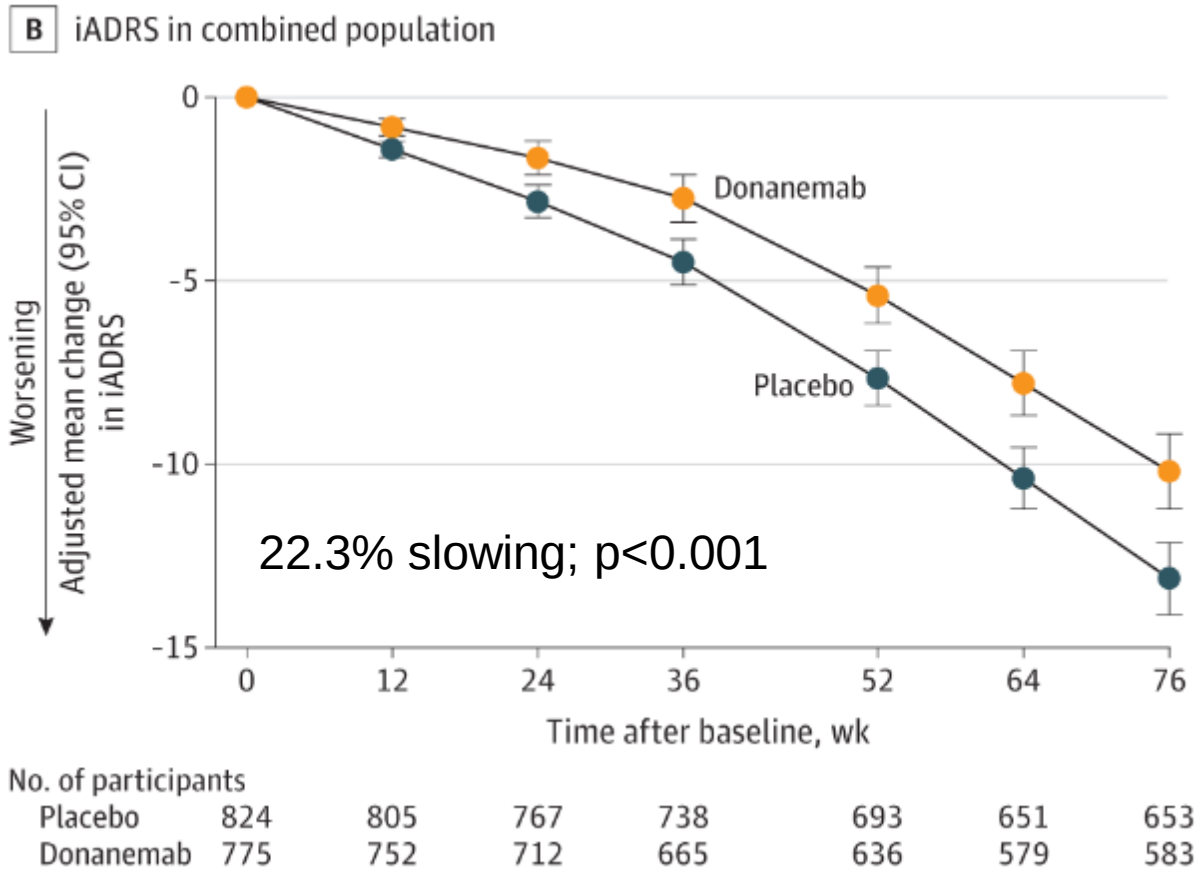
Donanemab

- Initial Phase 2 study (TRAILBLAZER-ALZ) showed clearance of amyloid and less decline in a clinical/cognitive measure
- Phase 3 study (TRAILBLAZER-ALZ 2) was initiated
  - 1736 participants (860 donanemab, 876 placebo)
  - Ages 60-85; amyloid positive on PET (≥37 Centiloids); diagnosed as either MCI due to AD or mild dementia due to AD
  - Participants underwent tau PET with flortaucipir and were sub-categorized into a low/medium tau group (n=588 donanemab, 594 placebo) and high tau group (n=272 donanemab, 282 placebo)

Mintun et al. (2021) NEJM; doi: 10.1056/NEJMoa2100708
Sims et al. (2023) JAMA; doi:10.1001/jama.2023.13239

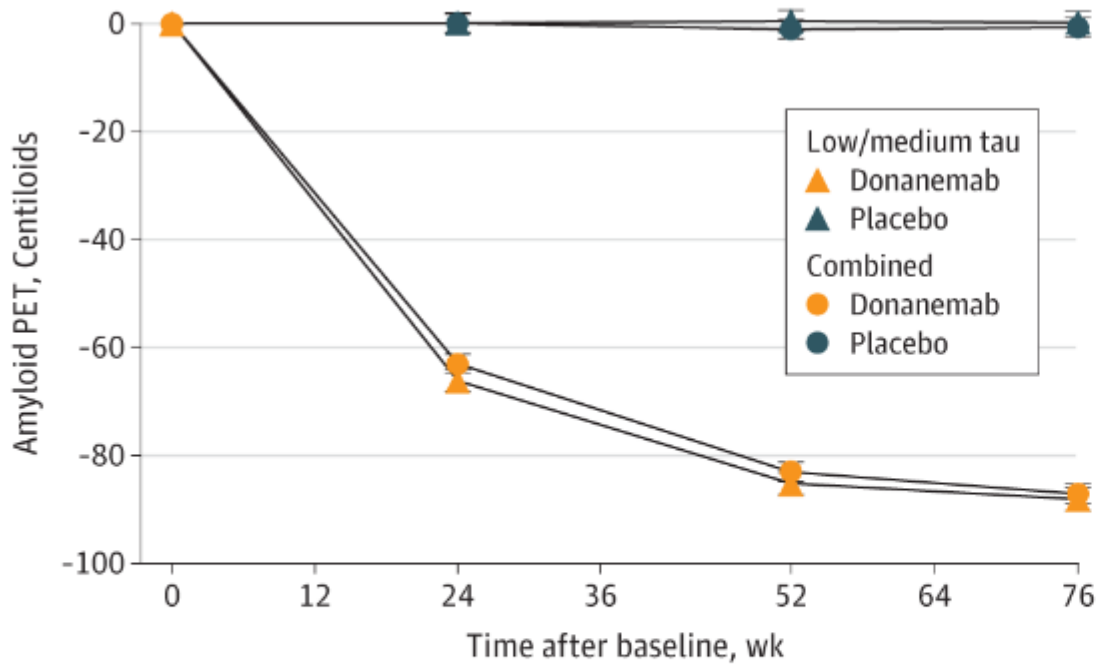
Donanemab


A
iADRS in low/medium tau population
Worsening
Adjusted mean change (95% CI) in iADRS
0
-5
-10
-15
Donanemab
Placebo
35% slowing; p<0.001
0
12
24
36
52
64
76
Time after baseline, wk
No. of participants
Placebo 560 549 526 506 474 447 444
Donanemab 533 517 487 459 441 406 418


B
iADRS in combined population
Worsening
Adjusted mean change (95% CI) in iADRS
0
-5
-10
-15
Donanemab
Placebo
22.3% slowing; p<0.001
0
12
24
36
52
64
76
Time after baseline, wk
No. of participants
Placebo 824 805 767 738 693 651 653
Donanemab 775 752 712 665 636 579 583

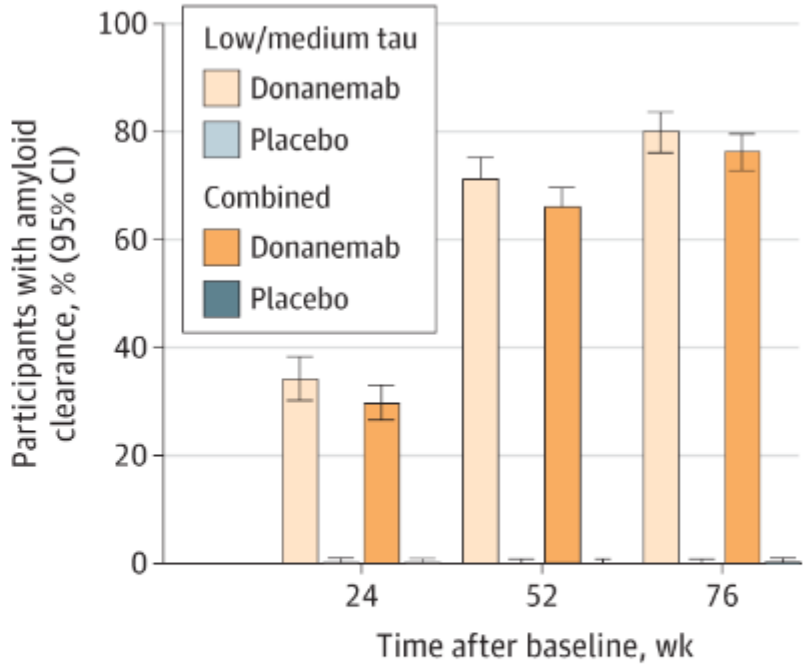
Donanemab

A Adjusted mean change (95% CI) in amyloid PET



No. of participants					76-wk value, Centiloids	Difference from baseline %
Low/medium tau						
Donanemab	525	521	463	433	-88.0	-85.5
Placebo	556	552	498	470	0.2	0.2
Combined						
Donanemab	765	760	670	614	-87.0	-83.7
Placebo	812	805	729	690	-0.7	-0.7

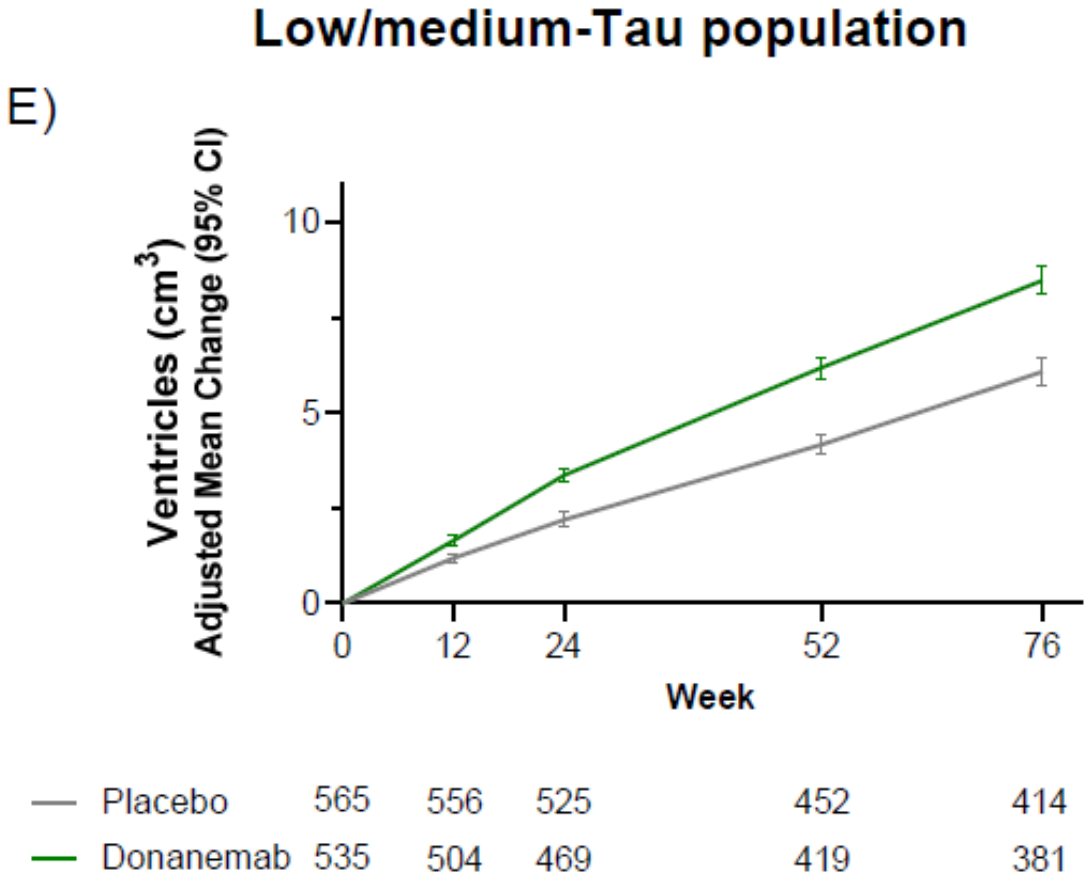
B Participants with amyloid clearance (<24.1 Centiloids)

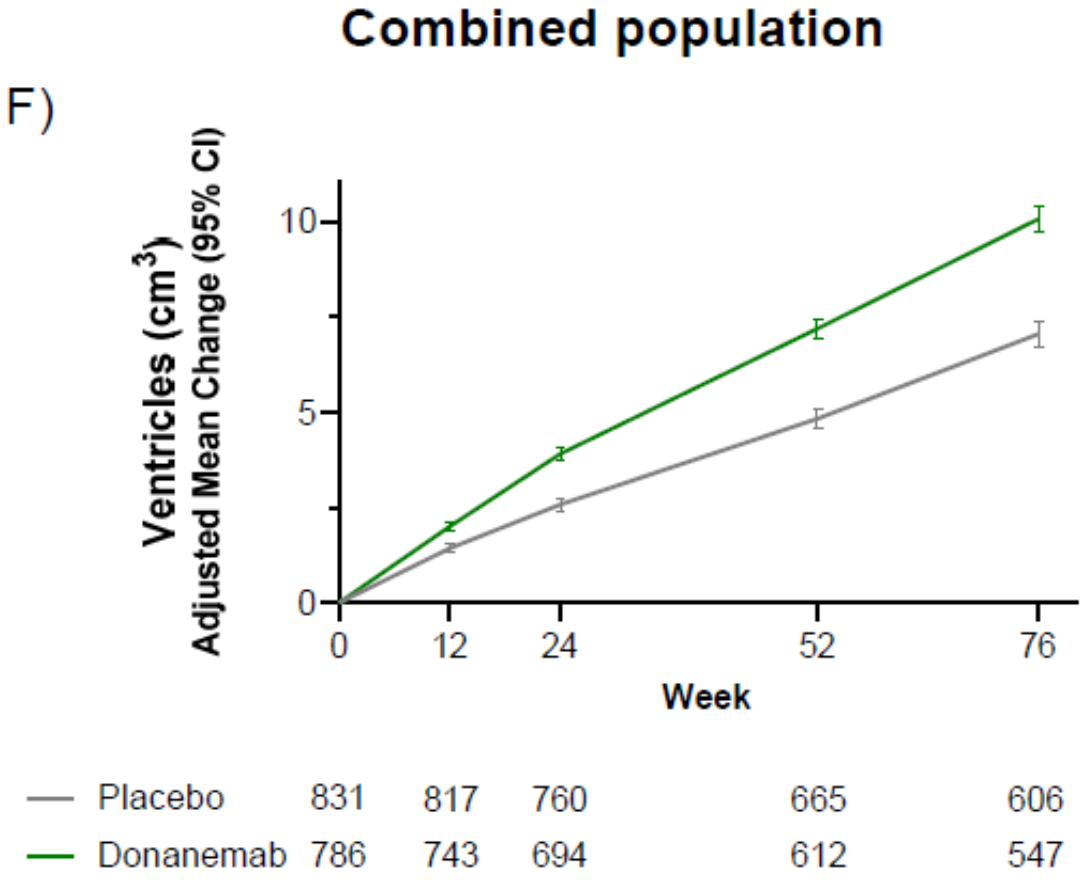


No. of participants			
Low/medium tau			
Donanemab	521	463	433
Placebo	553	498	470
Combined			
Donanemab	761	670	614
Placebo	805	730	690

Sims et al. (2023) JAMA; doi:10.1001/jama.2023.13239

Donanemab – Other Imaging Findings





Sims et al. (2023) JAMA; doi:10.1001/jama.2023.13239

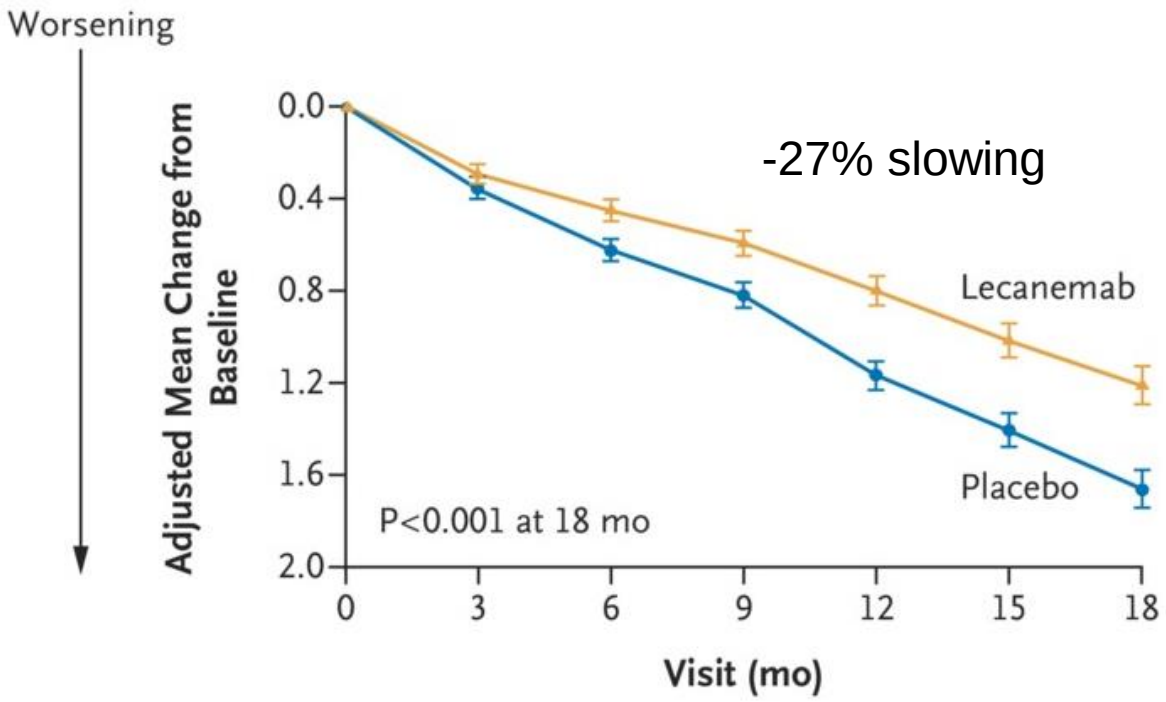
Lecanemab (Leqembi)

- Phase 2 trial (n=247 placebo, 552 on various doses) demonstrated amyloid clearance and positive changes in fluid biomarkers and clinical/cognitive outcomes; also identified 10mg/kg bi-weekly as most effective
- This trial also include an open-label extension after a 24-month gap period (on average)
  - Gap period showed clinical progression similar to placebo, some amyloid re-accumulation, and AD-like changes on plasma biomarkers
- Phase 3 trial (CLARITY; n=897 placebo, n=898 lecanemab)

McDade et al. (2022) Alz Res & Therapy; doi: 10.1186/s13195-022-01124-2
Swanson et al. (2021) Alz Res & Therapy; doi: 10.1186/s13195-021-00813-8
Van Dyck et al. (2023) NEJM; doi: 10.1056/NEJMoa2212948

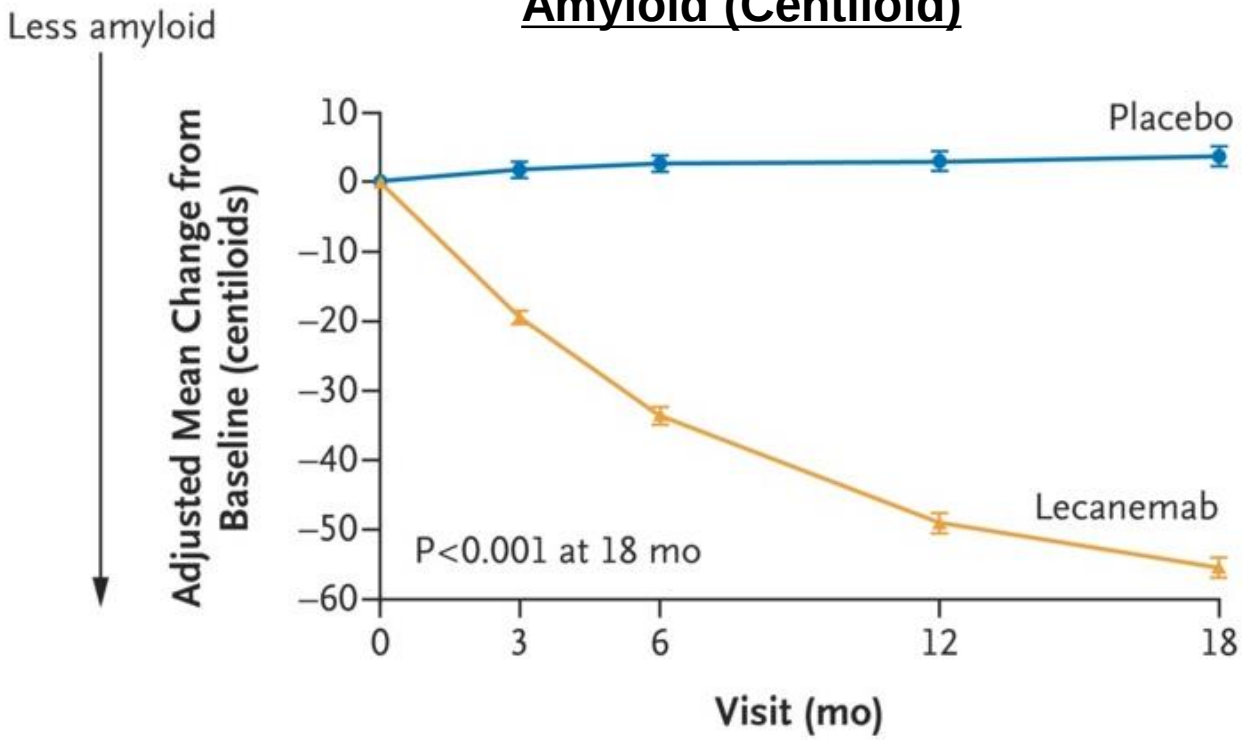
Lecanemab (Leqembi)

CDR-SB



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

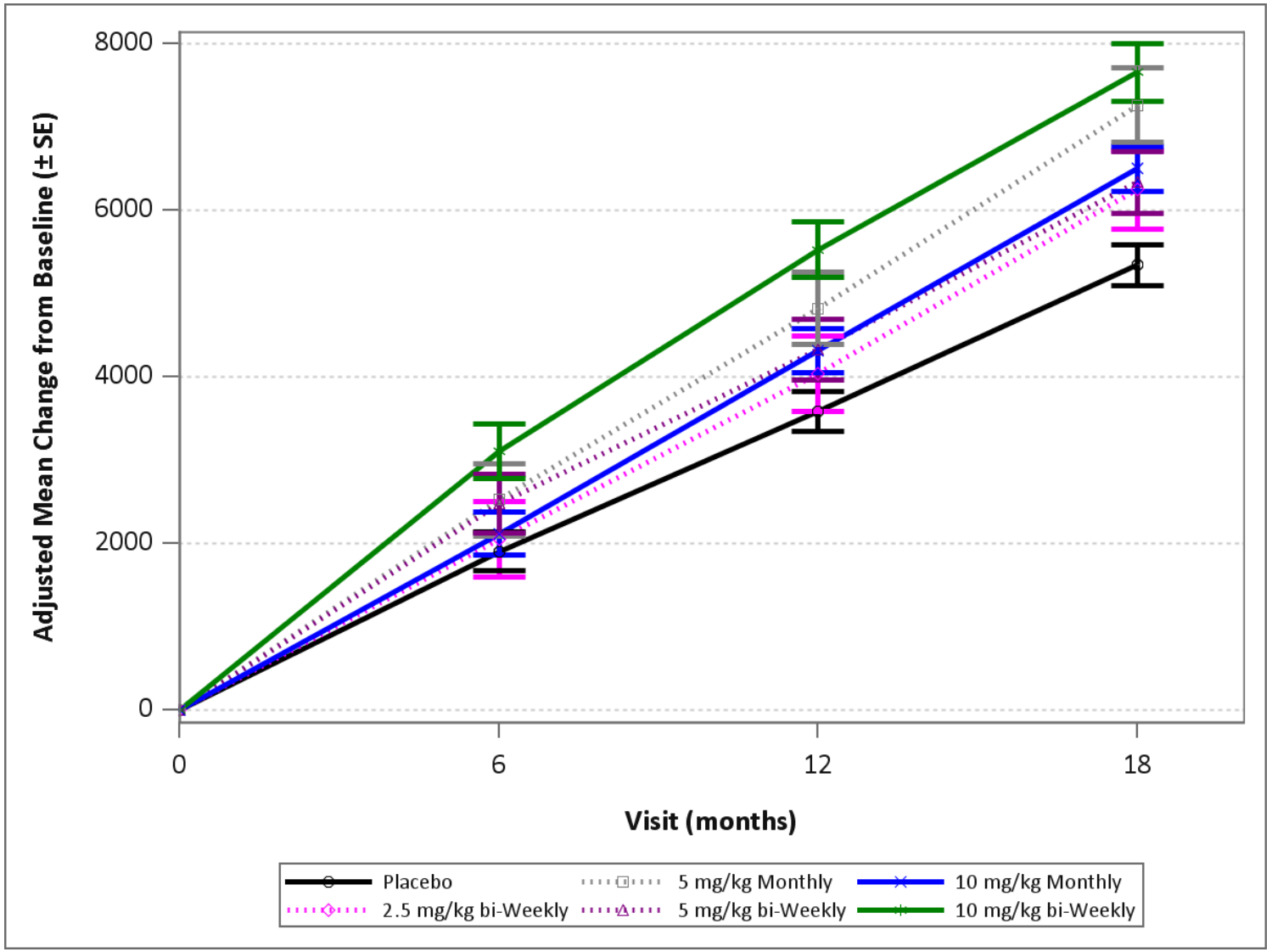
Amyloid (Centiloid)



No. of Participants					
Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

Van Dyck et al. (2023) NEJM; doi: 10.1056/NEJMoa2212948

Lecanemab (Leqembi) – Other Imaging Outcomes



Swanson et al. (2021) Alz Res & Therapy; doi: 10.1186/s13195-021-00813-8

Lecanemab (Leqembi)

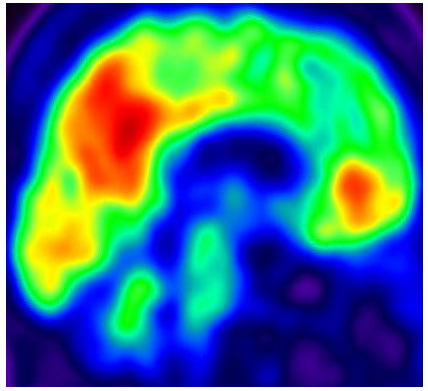
- Lecanemab received full FDA approval in June 2023
- Appropriate Use Recommendations (Cummings et al. (2023))
  - Amyloid-positive via PET or CSF individuals with MCI due to AD or mild AD
  - Notable exclusions (see AUR for all exclusions): anticoagulant medications; stroke, TIA, or bleeding disorder in the last 12 months; any history of seizure; CAA-related inflammation or amyloid-beta related angiitis (ABRA)
  - >4 microhemorrhages (<11mm), macrohemorrhage (>10 mm), superficial siderosis, vasogenic edema, >2 lacunar infarcts or stroke in major vascular territory, severe subcortical hyperintensities (Fazekas score of 3)
  - APOE genotyping suggested for risk assessment (no formal restrictions)

Cummings et al. (2023) J Prevention of Alzheimer's Disease
doi: 10.14283/jpad.2023.30

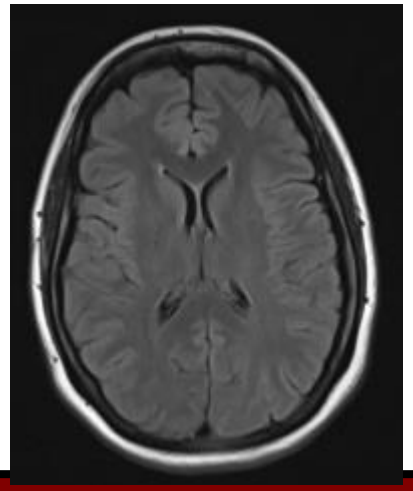
Suggested Imaging Protocols

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26…..

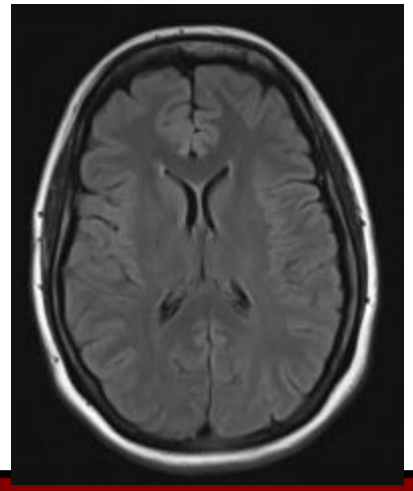
Eligibility (Amyloid PET)



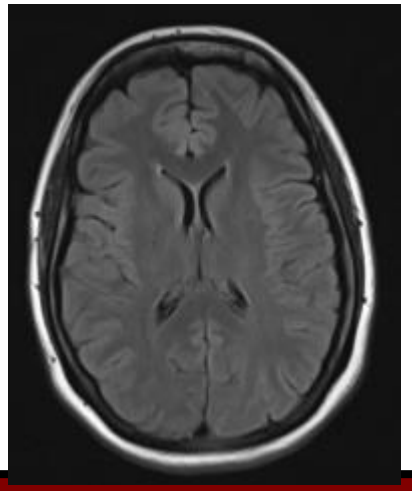
Eligibility and Safety MRI (within 12 months)



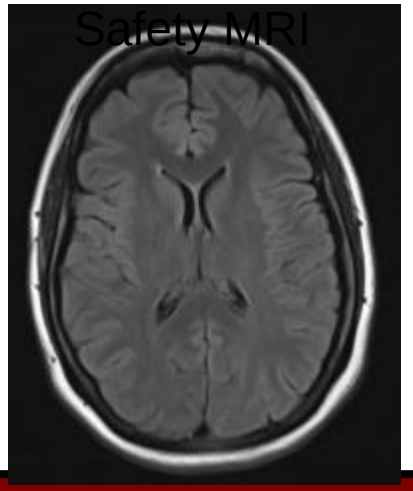
Before 5th infusion Safety MRI



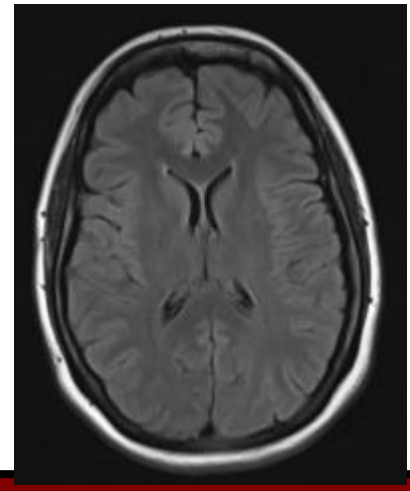
Before 7th infusion Safety MRI



Before 14th infusion Safety MRI



Possible Safety MRI (for those with resolved ARIA and APOE4 carriers)



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Cummings et al. (2023) J Prevention of Alzheimer's Disease
doi: 10.14283/jpad.2023.30

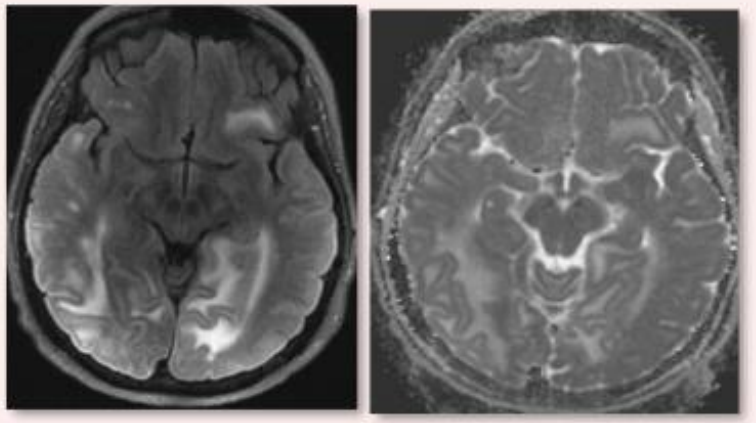
Lecanemab Prescribing Information: https://www.leqembi.com/-/media/Files/Leqembi/Prescribing-Information.pdf

Suggested Clinical Imaging Protocols

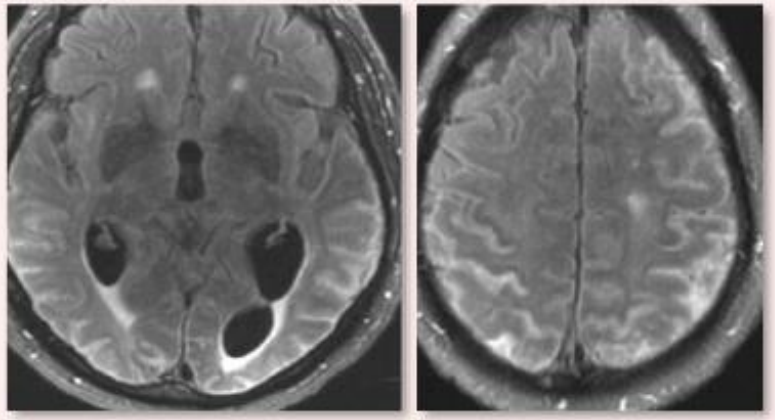
- Amyloid PET – use one of the FDA-approved tracers (FBB, FBP, Flutemetamol); follow prescribing information
- Eligibility and Safety MRI minimum sequence (non-contrast; preferably on a 3T magnet):
  - T1-weighted
  - T2 fluid-attenuated inversion recovery (FLAIR)
  - T2* gradient recalled echo (GRE) or similar scan (i.e., susceptibility weighted imaging (SWI)
  - Diffusion weighted imaging (DWI)

Amyloid-Related Imaging Abnormality (ARIA)

Amyloid-related imaging abnormalities (ARIA)

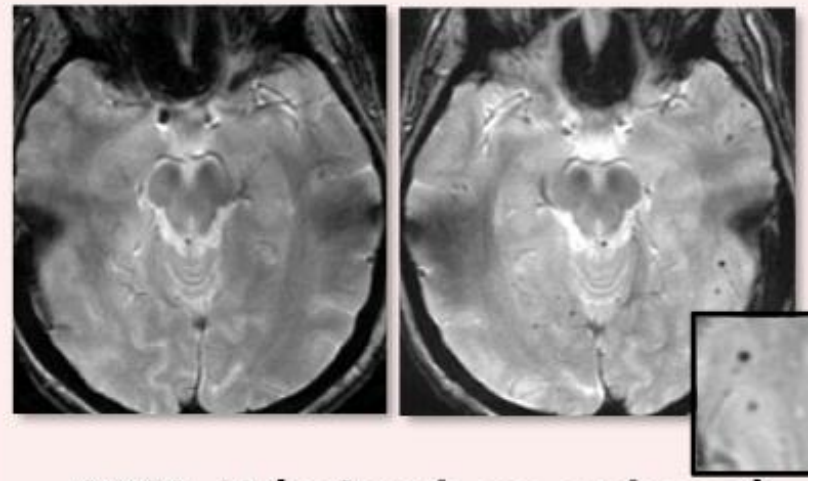


ARIA-E (edema)



ARIA-E (effusion)

ARIA-E is characterized by parenchymal edema and/or sulcal effusion. This is the most common side effect of monoclonal antibodies.



ARIA-H (microhemorrhage)

ARIA-H is characterized by parenchymal microhemorrhages and/or superficial siderosis.

Agarwal A et al. Published online: August 31, 2023
https://doi.org/10.1148/rg.230009

Amyloid-Related Imaging Abnormality (ARIA)

Agent	Phase	ARIA-E (%)	ARIA-H (%)	Symptomatic ARIA (%)	ARIA-E in APOE4 heterozygotes (%)	ARIA-E in APOE 4/4 (%)
Aducanumab (high dose)[1]	III	35.9	18.8	20.8 (headache)	E4 Carrier: 42.1 non-E4 carrier: 22.7	62.2
Aducanumab (high dose)[1]	III	34.8	20	19.8 (headache)	E4 Carrier: 43.2 non-E4 carrier: 17.9	58.7
Aducanumab (high dose)[2]	III	35.2	19.1	26	35.9	66
Donanemab[3]	II	26.7	30.5	6.1	30.9	44
Donanemab[4]	III	24	31.4	6.1	NA	NA
Lecanemab (10mg/kg BW)[5]	IIb	9.9	6.8	1.2 (all ARIA-E)	14.3*	
Lecanemab[6]	III	12.6	17.3	3.5	10.9	32.6

*APOE4 heterozygotes and homozygotes were grouped in this study (APOE4+)

1) Budd Haeberlein et al. (2022) J Prev AD; https://doi.org/10.14283/jpad.2022.30
2) Salloway et al. (2022) JAMA Neurology; doi:10.1001/jamaneurol.2021.4161
3) Mintun et al. (2021) NEJM; doi: 10.1056/NEJMoa2100708
4) Sims et al. (2023) JAMA; doi:10.1001/jama.2023.13239
5) Swanson et al. (2021) Alz Res & Therapy; doi: 10.1186/s13195-021-00813-8
6) Van Dyck et al. (2023) NEJM; doi: 10.1056/NEJMoa2212948

Ethnoracial Diversity of Clinical Trials

Agent	Grp	n	White	Asian	Afr. Am./ Black	Pac. Island./ Nat. Hawaii.	Am. Indian/ Alaskan	Other/Not Disclosed	Non-Hispanic	Hispanic
Aducanumab (EMERGE)[1]	Plac	548	431 (78.6%)	47 (8.6%)	1 (0.2%)	0 (0%)	1 (0.2%)	68 (12.4%)	470 (85.8%)*	22 (4.0%)*
	Treat	1090	854 (78.3%)	81 (7.4%)	10 (0.9%)	0 (0%)	0 (0%)	144 (13.2%)	931 (85.4%)*	45 (4.1%)*
Aducanumab (ENGAGE)[1]	Plac	545	413 (75.8%)	55 (10.1%)	5 (0.9%)	0 (0%)	0 (0%)	72 (13.2%)	489 (89.7%)*	13 (2.4%)*
	Treat	1102	825 (74.9%)	120 (10.9%)	3 (0.2%)	1 (0.1%)	0 (0%)	153 (13.9%)	991 (89.9%)*	24 (2.2%)*
Donanemab (Phase 2)[2]	Plac	126	121 (96.0%)	2 (1.6%)	3 (2.4%)	n/a	n/a	0 (0%)	n/a**	3 (2.4%)
	Treat	131	122 (93.1%)	1 (0.8%)	5 (3.8%)	n/a	n/a	3 (2.3%)	n/a**	5 (3.8%)
Donanemab (Phase 3)[3]	Plac	876	807 (92.1%)	47 (5.4%)	21 (2.4%)	n/a	0 (0%)	1 (0.1%)	596 (94.3%)***	35 (5.7%)***
	Treat	860	781 (90.0%)	57 (6.6%)	19 (2.2%)	n/a	2 (0.2%)	1 (0.1%)	584 (94.3%)***	36 (5.7%)***
Lecanemab (Phase 3)[4]	Plac	875	677 (77.4%)	148 (16.9%)	24 (2.7%)	n/a	n/a	26 (3.0%)	n/a**	108 (12.3%)
	Treat	859	655 (76.3%)	147 (17.1%)	20 (2.3%)	n/a	n/a	37 (4.3%)	n/a**	107 (12.5%)
TOTAL		7012	5686 (81.1%)	705 (10.1%)	111 (1.6%)	1 (0.01%)	3 (0.04%)	505 (7.2%)	>90%****	398 (5.7%)

* Remaining individuals (~10%) did not disclose their ethnicity
*** These percentages are for the US only sample (n=632 placebo, n=619 Donanemab)

** Only Hispanic ethnicity participant counts were available (not Non-Hispanic or other/not disclosed)
**** Calculated as mean of the percentages since number counts are missing for some studies

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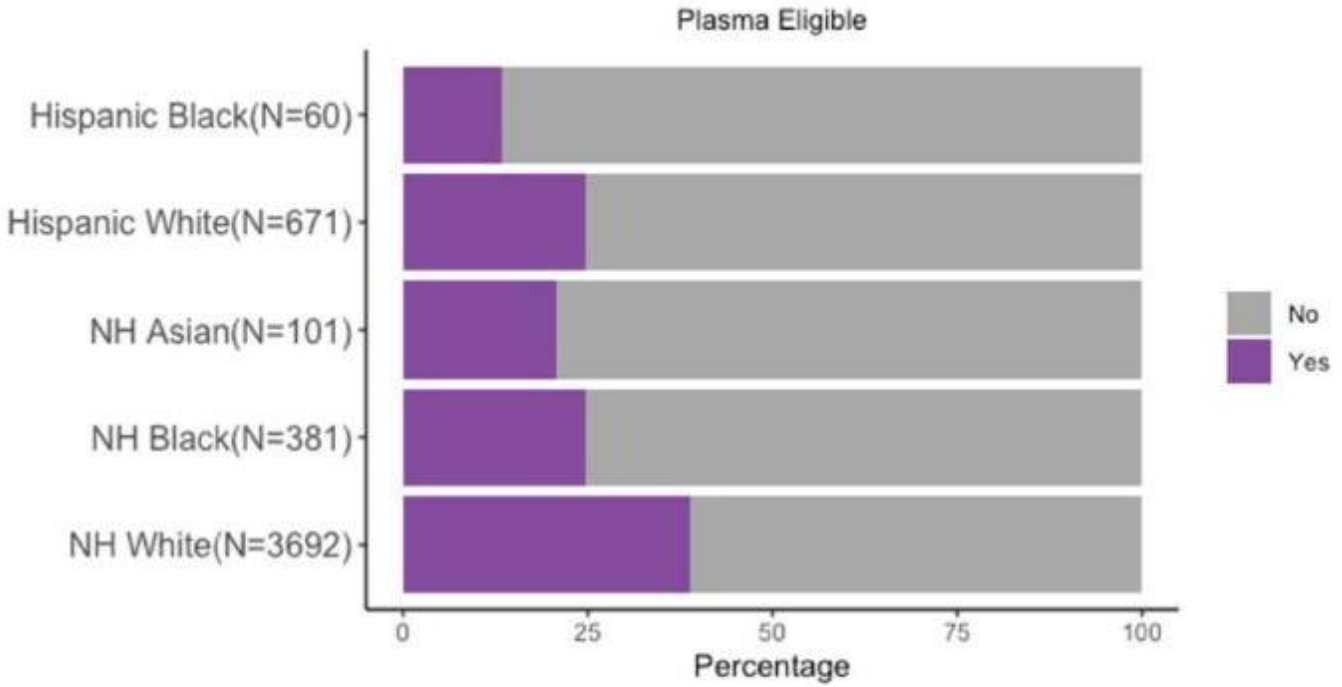
1) Budd Haeberlein et al. (2022) J Prev AD; https://doi.org/10.14283/jpad.2022.30
2) Mintun et al. (2021) NEJM; doi: 10.1056/NEJMoa2100708
3) Sims et al. (2023) JAMA; doi:10.1001/jama.2023.13239
4) Van Dyck et al. (2023) NEJM; doi: 10.1056/NEJMoa2212948

Ethnoracial Diversity of Clinical Trials

AHEAD 3-45



Plasma Eligibility	Race and Ethnicity No. (%)						P-value
	Hispanic Black (N=60)	Hispanic White (N=671)	NH Asian (N=101)	NH Black (N=381)	NH White (N=3692)	Total (N=4905)	
Yes	8 (13.3)	166 (24.7)	21 (20.8)	94 (24.7)	1435 (38.9)	1724 (35.1)	<0.001
No	52 (86.7)	505 (75.3)	80 (79.2)	287 (75.3)	2257 (61.1)	3181 (64.9)	

Molina-Henry DP, Raman R, Liu A, et al. (2024) *Alzheimer's Dement*. https://doi.org/10.1002/alz.13803

Future (Neuroimaging) Studies

- AlzNet – Centralized resource for monoclonal antibody treatment for patients/researchers (https://www.alz-net.org/)

Introduction to ALZ-NET

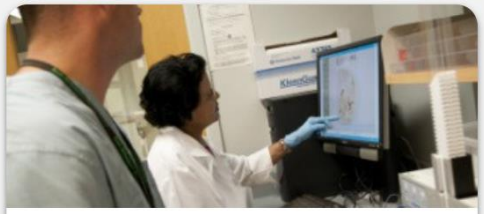
Millions Affected

More than 6 million Americans are living with Alzheimer's disease. By 2050, this number is projected to rise to nearly 13 million.

More than 140 new therapies are being tested in clinical trials or are currently under regulatory review.

Treatments

The Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) seeks to connect clinical data from Alzheimer's patients to our network of medical professionals and researchers to encourage robust information sharing and education, and to drive innovation in the ways we care for and treat Alzheimer's disease and other dementia.



Patient Registry

ALZ-NET is a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer's disease from patients being evaluated for or treated with novel FDA-approved Alzheimer's therapies. ALZ-NET is also a platform for patients to access resources about Alzheimer's, including locating ALZ-NET participating sites.

Payer Coverage

ALZ-NET is approved by the Centers for Medicare and Medicaid Services (CMS) as a Coverage with Evidence Development (CED) study and can be used as a pathway to Medicare coverage for anti-amyloid Alzheimer's therapies that have received traditional FDA approval.

Future (Neuroimaging) Studies

- Neuroimaging studies in the ADRC network (with Alznet or independently) could answer a number of research questions:
  - Prediction of ARIA risk – novel neuroimaging sequences or PET tracer targets that could predict ARIA risk
  - Impact of treatment on other neuroimaging biomarkers (i.e., functional brain scans, tau PET, other PET targets)
  - Longer-term follow-up (i.e., >18 or 24 months) of participants with amyloid and/or tau PET, advanced MRI techniques
  - Many more research questions…

Panelists

Adam Brickman, PhD

Professor of Neuropsychology (in Neurology) at the Taub Institute for Research on AD and the Aging Brain and the Gertrude H. Sergievsky Center, Columbia University

Gil Rabinovici, MD

Edward Fein and Pearl Landrith Distinguished Professorship in Memory & Aging in the UCSF Department of Neurology

Duygu Tosun-Turgut

Professor of Radiology and Biomedical Imaging at UCSF; the Founding Director of Medical Imaging Informatics and AI at the SF Veterans Affairs Medical Center

Questions/Topics for Discussion

- How can Neuroimaging Cores best integrate with clinical treatment with mAb?
  - Use of ADRC scans for treatment eligibility (i.e., amyloid PET, baseline MRI) – can we use even when non-FDA approved tracer
  - Reducing the need for repeat scans for research and clinical purposes and clearly educating participants about these differences.
  - Is pre-treatment baseline imaging needed for enrollment in the ADRC or should post-treatment participants also be included?
  - Other considerations?

Questions/Topics for Discussion

- How can Neuroimaging Cores contribute to answering additional research questions about mAbs?
  - Standardizing clinical scans for research use
  - Longer term follow-up; repeat amyloid/tau PET imaging
  - Change in other neuroimaging measures (fMRI, DTI, other PET)
  - Neuroimaging measures for ARIA prediction
  - Novel measures to help with eligibility screening (i.e., portable MRI, validation of plasma, etc.)
  - Other opportunities?

Questions/Topics for Discussion

- How can Neuroimaging Cores/neuroimaging research help to promote diversity and equity in mAb treatment?
  - New technologies to expand the reach of screening techniques for anti-Aβ mAb to underserved communities (i.e., portable MRI, fluid biomarkers, etc.)
  - Developing culturally-appropriate dialogue with diverse communities about the imaging and biomarkers involved in anti-Aβ mAb treatment
  - Other discussion topics?

Questions/Topics for Discussion

- How can Neuroimaging Cores best integrate with clinical treatment with mAb?
- How can Neuroimaging Cores contribute to answering additional research questions about mAbs?
- How can Neuroimaging Cores/neuroimaging research help to promote diversity and equity in mAb treatment?