Key Milestones in Alzheimer's Disease

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Disclosures

- SBH is an employee and shareholder of Biogen.
- Writing and editorial support for the preparation of this presentation was provided by MediTech Media (Atlanta, GA, USA); funding for medical writing was provided by Biogen
- This work was funded by Biogen and Eisai

Aducanumab is approved for use in the following markets: the United States, the United Arab Emirates, and Qatar. In the rest of the world, it is an investigational drug. Its efficacy and safety have not been established in Spain.

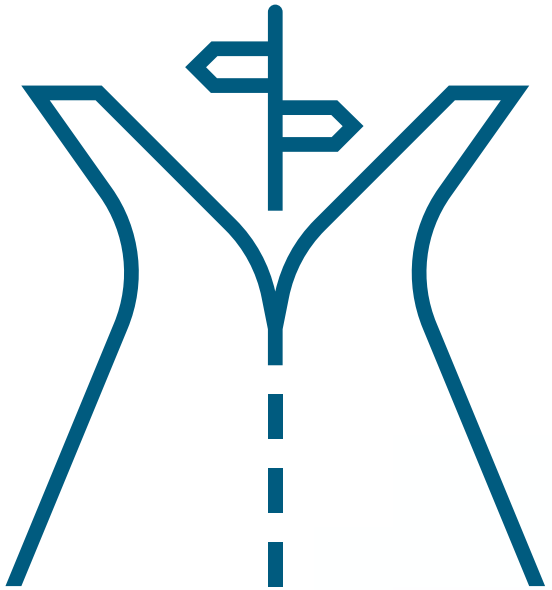
Forward-looking statements

This presentation contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, about the potential clinical effects of ADUHELM; the potential benefits, safety and efficacy of ADUHELM; the treatment of Alzheimer's disease; the anticipated benefits and potential of Biogen's collaboration arrangements with Eisai; clinical development programs, clinical trials and data readouts and presentations; and risks and uncertainties associated with drug development and commercialization. These statements may be identified by words such as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "intend," "may," "plan," "possible," "potential," "will," "would" and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical trials may not be indicative of full results or results from later stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements, or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including without limitation unexpected concerns that may arise from additional data, analysis or results obtained during clinical trials; the occurrence of adverse safety events; risks of unexpected costs or delays; the risk of other unexpected hurdles; failure to protect and enforce Biogen's data, intellectual property and other proprietary rights and uncertainties relating to intellectual property claims and challenges; risks associated with current and potential future healthcare reforms; product liability claims; third party collaboration risks; and the direct and indirect impacts of the ongoing COVID-19 pandemic on Biogen's business, results of operations and financial condition. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from Biogen's expectations in any forward-looking statement. Investors should consider this cautionary statement as well as the risk factors identified in Biogen's most recent annual or quarterly report and in other reports Biogen has filed with the U.S. Securities and Exchange Commission. These statements are based on Biogen's current beliefs and expectations and speak only as of the date of this news release. Biogen does not undertake any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise.

Introduction:
Advances in Alzheimer’s disease research

It has been over 25 years since the first symptomatic treatment for Alzheimer's disease was approved by the US Food and Drug Administration (FDA) in 1993



- In 1993, the FDA approved tacrine, a cholinesterase inhibitor, as the first drug to treat the cognitive symptoms of Alzheimer's disease
- Over the next 10 years, 4 additional symptomatic therapies for Alzheimer's disease were approved
- **During the last 26 years, the Alzheimer's disease community has made large strides with respect to:**
  - Diagnosis, monitoring and management of disease
  - Biomarkers of underlying pathophysiology
  - Clinical trial design and diversity of therapeutic targets

FDA, US Food and Drug Administration; MCI, mild cognitive impairment.

1. Cummings J, et al. *Alzheimer's Dement.* 2021;1-9.

Changes in biomarkers reflect underlying pathologic changes in the brain that can occur decades before cognitive symptoms of Alzheimer's disease are evident

Amyloid β

CSF and plasma assays[1,2,3,8]
- CSF and plasma Aβ42
- CSF and plasma Aβ40
- CSF and plasma ratios (Aβ42/Aβ40, Aβ42/p-tau)

Amyloid PET[6]
- β-amyloid neuritic plaque density in the brain

Tau

CSF and plasma assays[1,4,5,8]
- CSF and plasma p-tau[181]
- CSF and plasma p-tau[217]

Tau PET[7]
- Pathologic tau in the brain

Neurodegeneration

CSF and plasma assay[8,9]
- CSF and plasma NfL

Structural MRI[6]
- Brain atrophy

CT[10]
- Brain atrophy

FDG PET[6]
- Brain metabolism and synaptic activity

Aβ, amyloid beta; AD, Alzheimer's disease; ATN, amyloid β, tau, neurodegeneration; CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; NfL, neurofilament light; PET, positron emission tomography; p-tau, phosphorylated tau.

1. Molinuevo JL, et al. *Acta Neuropathol.* 2018;136:821–853; 2. Nakamura A, et al. *Nature*. 2018;554:249-254; 3. Pérez-Grijalba V, et al. *Alzheimer's Res.Ther.* 2019;11:96; 4. Karikari TK, et al. *Lancet Neurol*. 2020;19:422–433; 5. Palmqvist S, et al. *JAMA*. 2020;324:772–881; 6. Johnson KA, et al. *Col Spring Harb Perspect Med*. 2012;2:a006213–a006213; 7. Chandra A, et al. *Human Brain Mapping*. 2019;40:5424–5442; 8. Zetterberg H and Blennow K. *Mol Neurodegener*. 2021;16:10; 9. Cullen N, et al. *Nat Commun*. 2021;12:3555; 10. Albert M, et al. https://www.alz.org/national/documents/imaging_consensus_report.pdf. Alzheimer's Assoc Chicago, IL. 2005;1:1–5. Accessed March 3, 2022.

Alzheimer’s disease clinical trial design and focus have evolved

Targeting earlier stages of Alzheimer’s disease

Prodromal Alzheimer’s disease → Mild Alzheimer’s disease dementia → Moderate Alzheimer’s disease dementia

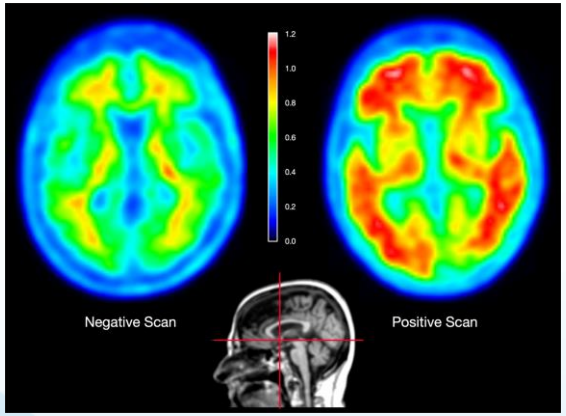
- Previous clinical trials of anti-amyloid monoclonal antibodies enrolled patients with **mild to moderate Alzheimer’s disease dementia**[1,2]

Prodromal Alzheimer’s disease → Mild Alzheimer’s disease dementia → Moderate Alzheimer’s disease dementia

- ✓ Intervening at earlier stages of disease may increase the likelihood of clinical benefit by perturbing the Aβ pathophysiological cascade prior to extensive, and possibly irreversible, neurodegeneration[2,3]

Targeting the underlying course of disease

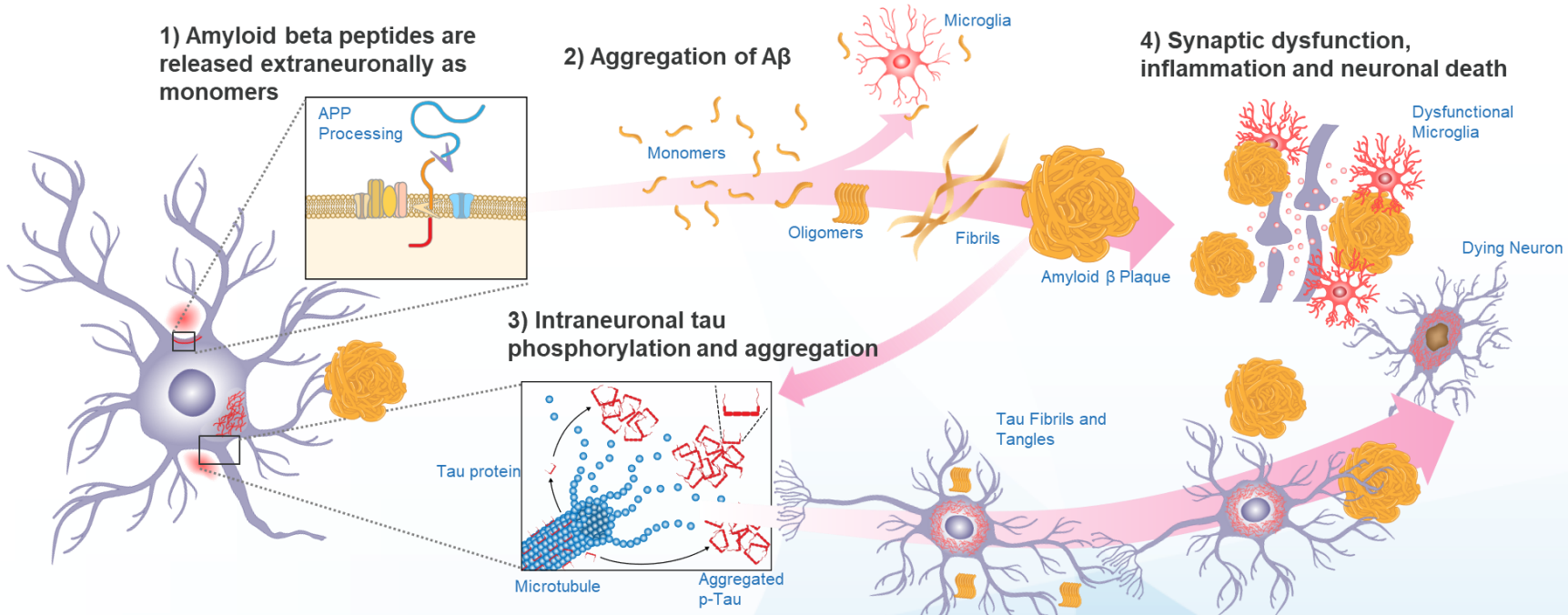
- Previously, all approved Alzheimer’s disease treatments were “symptomatic” agents that aimed to improve cognitive and behavioral symptoms[4]
- ✓ Currently, the development of Alzheimer’s disease therapies is focused on targeting the underlying pathology of the disease[5-7]



Aβ, amyloid beta; PET, positron emission tomography.

1. Salloway S, et al. *N Engl J Med.* 2014;370:322–333; 2. Doody R, et al. *N Engl J Med*. 2014;370:311–321; 3. Budd Haeberlein S, et al. *J Prev Alzheimers Dis*. 2017;4(4):255–263; 4. Cummings, J. *Mol Neurodegeneration*. 2021;16(2); 5. Sevigny J, et al. *Nature*. 2016;537:50–56; 6. Swanson C, et al. *Alzheimers Res Ther*. 2021;13:80; 7. Mintun M, et al. *N Engl J Med*. 2021; 384:1691–1704;

Targeting the amyloid cascade



Aβ=amyloid beta; APP=amyloid precursor protein.
Based on Pospich S, Raunser S. *Science.* 2017;358(6359):45-46.

Accumulation of pathological Aβ in the brain is a characteristic pathology and early event in Alzheimer's disease

Targeting the amyloid cascade has been a key focus for many clinical development programs with the goal of slowing the pathological cascade before significant, irreversible neurodegeneration has taken place[1]

- Abnormal accumulation of Aβ in the brain can be **detected 20 years before clinical symptoms of Alzheimer's disease dementia**[2]
- **Accumulation of Aβ** is believed to initiate a cascade of pathological changes that lead to **neurodegeneration**[3,4]
- **Genetic, neuropathological, and cell biological evidence** suggest a key role for **Aβ in the pathogenesis of Alzheimer's disease**[5,6]

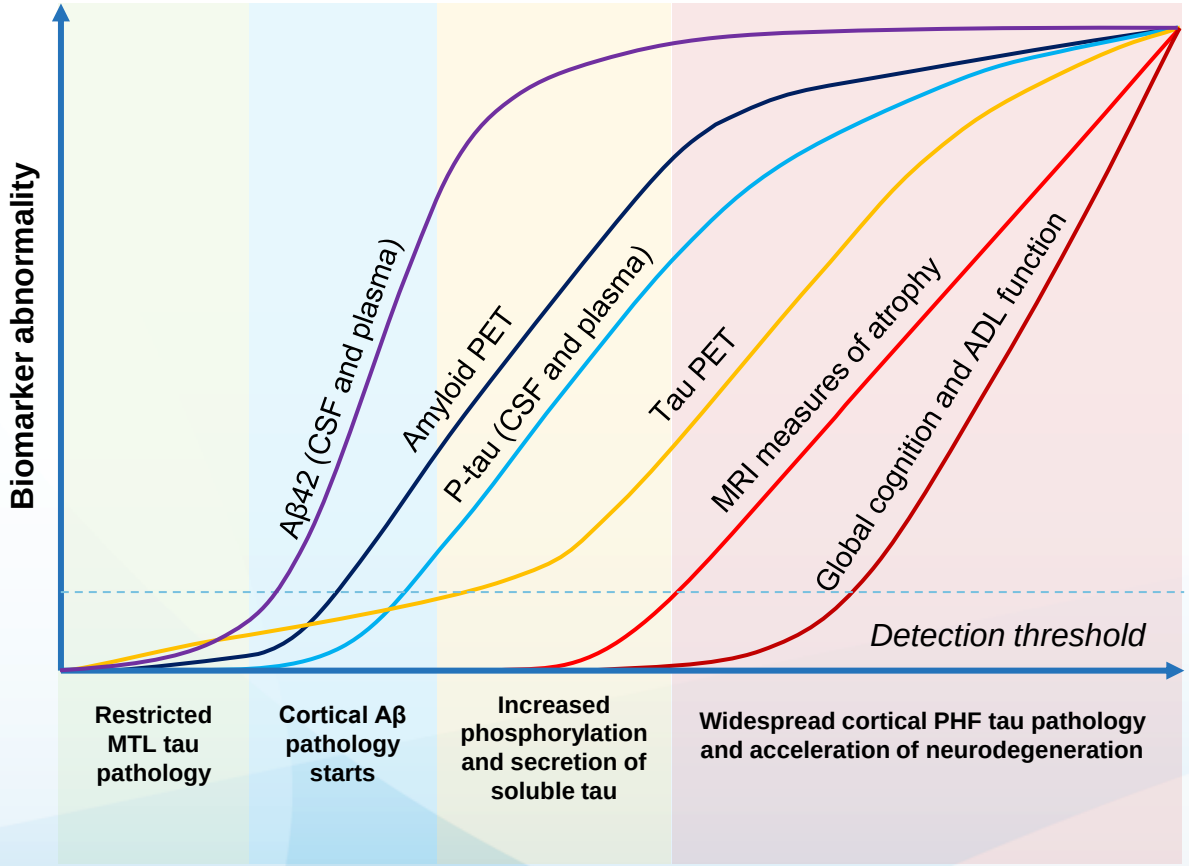


Figure adapted from Hansson O. *Nat Med*. 2021;27:954-963.[7]

Aβ, amyloid beta; ADL, activities of daily living; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; MTL, median temporal lobe; PET, positron emission tomography; PHF, paired helical filaments; p-tau, phosphorylated tau.

1. Selkoe DJ, Hardy J. *EMBO Mol Med*. 2016;8:595–608; 2.Dubois B, et al. *Alzheimers Dement*. 2016;12:292–323; 3. Haas C, Selkoe DJ. *Nature Reviews*. 2007;8:101–112; 4. Hardy J, Selkoe DJ. *Science*. 2002;297:353–356; 5. Ising C, et al. *Clin Pharmacol Ther*. 2015;98:469–471; 6. Selkoe DJ. *Ann Neurol*. 2013;74:328–336; 7. Hansson O. *Nat Med*. 2021;27:954–963.

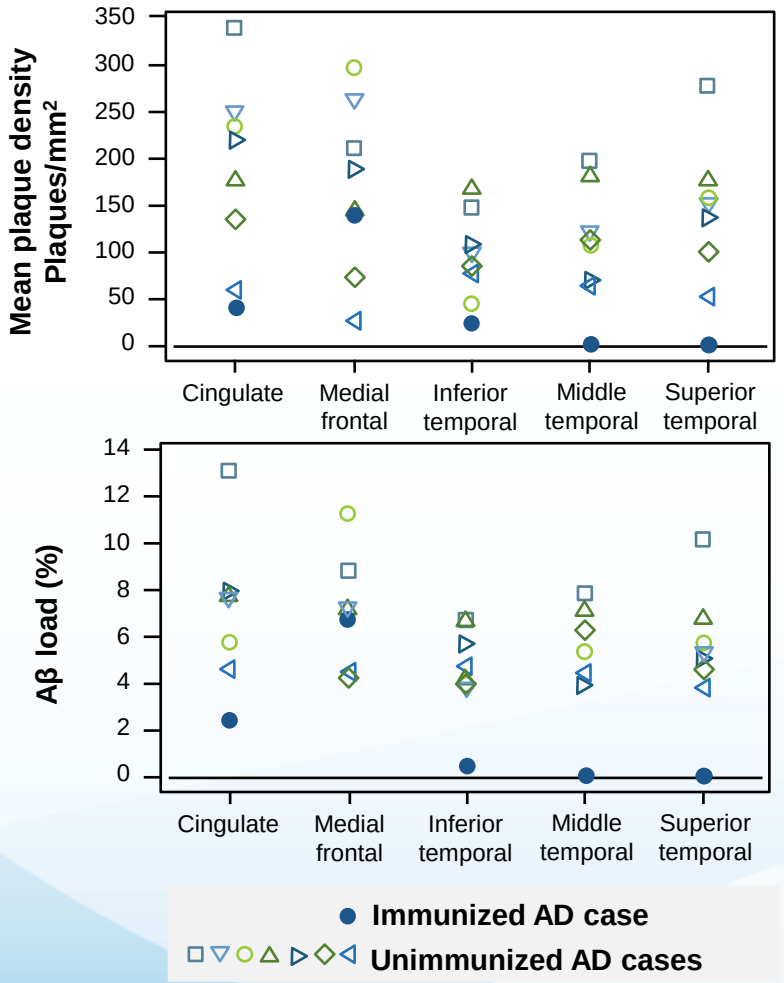
AN-1792, a vaccine, was the first agent targeting brain amyloid investigated for Alzheimer's disease[1,2]

Proof of concept

- Development terminated due to ~6% of patients developing meningoencephalitis[3]
- ✓ **However, post-mortem examination revealed that the vaccine had markedly cleared plaque from the brain[3,4]**

- The Phase 2a study was conducted in participants **with later stage disease (mild to moderate Alzheimer's disease dementia)**[3]
- A 4.6 year follow up of 159 patients from the Phase 2a trial reported **functional benefit in responders**[4]
- This study occurred **before the widespread use of imaging biomarkers in clinical trials of Alzheimer's disease**; assessment of target engagement was limited to post-mortem[4]

AV-1792 Phase 2a trial: Quantitative image analysis[4]



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

1. Bayer AJ, et al. *Neurology*. 2005;64(1):94-101; 2. Nicoll JAR, et al. *Brain*. 2019;142(7):2113-2126; 3. Vellas B, et al. *Curr Alzheimer Res*. 2009;6:144–151; 4. Nicoll JA, et al. *Nat Med*. 2003;9:448–452.

The evolution of targeting amyloid:

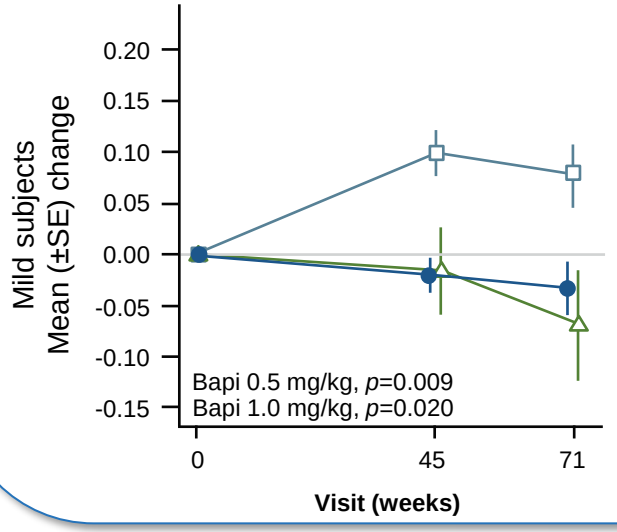
First generation anti-Aβ agents

Bapineuzumab[1]

Clinical Trial > Neurology. 2015 Aug 25;85(8):692-700. doi: 10.1212/WNL.0000000000001877. Epub 2015 Jul 24.

Amyloid-β 11C-PiB-PET imaging results from 2 randomized bapineuzumab phase 3 AD trials

Enchi Liu [1], Mark E Schmidt [2], Richard Margolin [2], Reisa Sperling [2], Robert Koeppe [2], Neale S Mason [2], William E Klunk [2], Chester A Mathis [2], Stephen Salloway [2], Nick C Fox [2], Derek L Hill [2], Andrea S Les [2], Peter Collins [2], Keith M Gregg [2], Jianing Di [2], Yuan Lu [2], I Cristina Tudor [2], Bradley T Wyman [2], Kevin Booth [2], Stephanie Broome [2], Eric Yuen [2], Michael Grundman [2], H Robert Brashear [2], Bapineuzumab 301 and 302 Clinical Trial Investigators

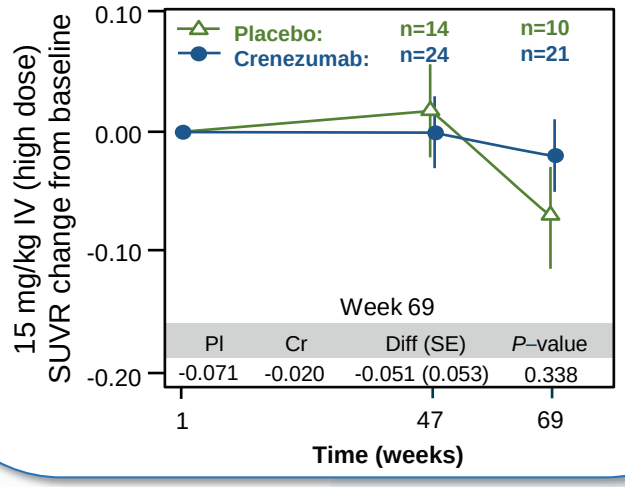


Crenezumab[2]

Clinical Trial > Alzheimers Res Ther. 2018 Sep 19;10(1):96. doi: 10.1186/s13195-018-0424-5.

Amyloid positron emission tomography and cerebrospinal fluid results from a crenezumab anti-amyloid-beta antibody double-blind, placebo-controlled, randomized phase II study in mild-to-moderate Alzheimer's disease (BLAZE)

Stephen Salloway [1], Lee A Honigberg [2], William Cho [2], Michael Ward [2], Michel Friesenhahn [2], Flavia Brunstein [2], Angelica Quartino [2], David Clayton [2], Deborah Mortensen [2], Tobias Bittner [3], Carole Ho [2], Christina Rabe [2], Stephen P Schauer [2], Kristin R Wildsmith [2], Reina N Fuji [2], Shehnaaz Suliman [2], Eric M Reiman [4], Kewei Chen [4], Robert Paul [2]



Solanezumab[3]

Clinical Trial > Alzheimers Dement. 2016 Feb;12(2):110-120. doi: 10.1016/j.jalz.2015.06.1893. Epub 2015 Aug 1.

Phase 3 solanezumab trials: Secondary outcomes in mild Alzheimer's disease patients

Eric R Siemers [1], Karen L Sundell [2], Christopher Carlson [2], Michael Case [2], Gopalan Sethuraman [2], Hong Liu-Seifert [2], Sherie A Dowsett [2], Michael J Pontecorvo [3], Robert A Dean [2], Ronald Demattos [2]

"78% (195/251) of individuals with mild Alzheimer's disease who participated in an optional amyloid imaging addendum and had interpretable baseline scans were amyloid positive at baseline (assessed via PET scan visual read). The treatment group difference in baseline to endpoint change in composite summary SUVR normalized to mean whole cerebellum was not significant in these amyloid positive individuals given solanezumab vs placebo (P = 0.17)."

Most first generation anti-Aβ agents had little effect on lowering Aβ plaques in clinical trials[1–3]

Aβ, amyloid beta; ^{11}C-PiB, ^{11}C-labeled Pittsburgh Compound-B; IV, intravenous; PET, positron emission tomography; Pl, placebo; Cr, crenezumab; SE, standard error; SUVR, standardized uptake value ratio.

1. Liu E, et al. *Neurology*. 2015;85:692–700; 2. Salloway S, et al. *Alzheimers Res Ther.* 2018;10:96; 3. Siemers ER, et al. *Alzheimers Dement.* 2016;12:110–120.

Earlier trials testing first generation anti-Aβ monoclonal antibodies did not demonstrate efficacy

Possible reasons for lack of efficacy in past trials of other anti-Aβ monoclonal antibodies:[1]

Population: lack of biomarker evidence of Aβ pathology[2]

Disease stage: treatment was not initiated early enough in the disease process to capture an effect[2-5]

Insufficient target engagement: brain Aβ was insufficiently lowered by the monoclonal antibody[5-6]

Dosing: dose of monoclonal antibody was too low[2,4,5,7]

Second generation anti-Aβ monoclonal antibodies clinical study designs incorporated these key learnings

Aβ, amyloid beta.

1. Budd Haeberlein S, et al. *J Prev Alzheimers Dis*. 2017;4(4):255–263; 2. Lannfelt L, et al. *Alzheimers Res Ther.* 2014;6:16; 3. Panza F, et al. *Expert Rev Clin Immunol.* 2014;10:405–419; 4. Salloway S, et al. *N Engl J Med.* 2014;370:322–333; 5. van Dyck CH. *Biol Psychiatry.* 2018;83:3; 6. Moreth J, et al. *Immun Ageing.* 2013;10:18; 7. Ostrowitzki S, et al. *Alzheimers Res Ther.* 2017;9:95.

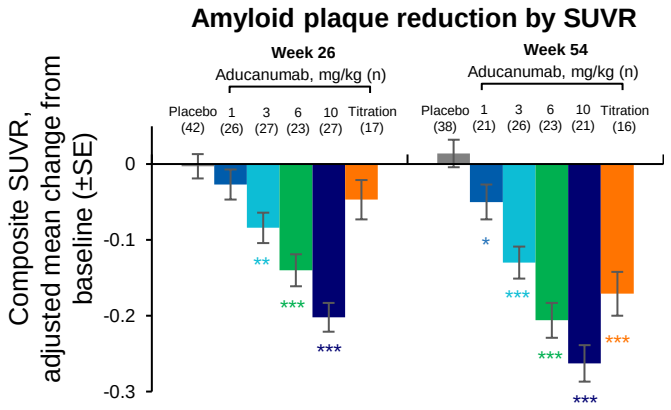
Second generation anti-Aβ monoclonal antibodies demonstrate robust target engagement and strong support for amyloid as a therapeutic target[1-4]

Aducanumab[1,2]

› Nature. 2016 Sep 1;537(7618):50-6. doi: 10.1038/nature19323.

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny [1], Ping Chiao [1], Thierry Bussière [1], Paul H Weinreb [1], Leslie Williams [1], Marcel Maier [2], Robert Dunstan [1], Stephen Salloway [3], Tianle Chen [1], Yan Ling [1], John O'Gorman [1], Fang Qian [1], Mahin Arastu [1], Mingwei Li [1], Sowmya Chollate [1], Melanie S Brennan [1], Omar Quintero-Monzon [1], Robert H Scannevin [1], H Moore Arnold [1], Thomas Engber [1], Kenneth Rhodes [1], James Ferrero [1], Yaming Hang [1], Alvydas Mikulskis [1], Jan Grimm [2], Christoph Hock [2 4], Roger M Nitsch [2 4], Alfred Sandrock [1]

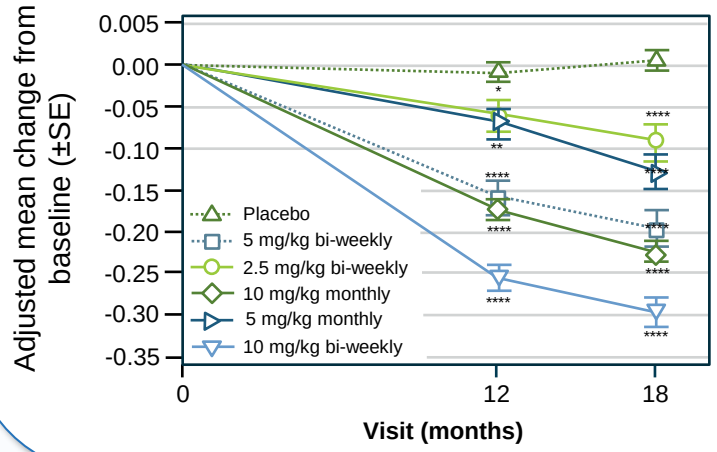


Lecanemab[3]

Clinical Trial › Alzheimers Res Ther. 2021 Apr 17;13(1):80. doi: 10.1186/s13195-021-00813-8.

A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody

Chad J Swanson [1], Yong Zhang [1], Shobha Dhadda [1], Jinping Wang [1], June Kaplow [1], Robert Y K Lai [2], Lars Lannfelt [3 4], Heather Bradley [1], Martin Rabe [1], Akihiko Koyama [1], Larisa Reyderman [1], Donald A Berry [5], Scott Berry [5], Robert Gordon [2], Lynn D Kramer [1], Jeffrey L Cummings [6]



Donanemab[4]

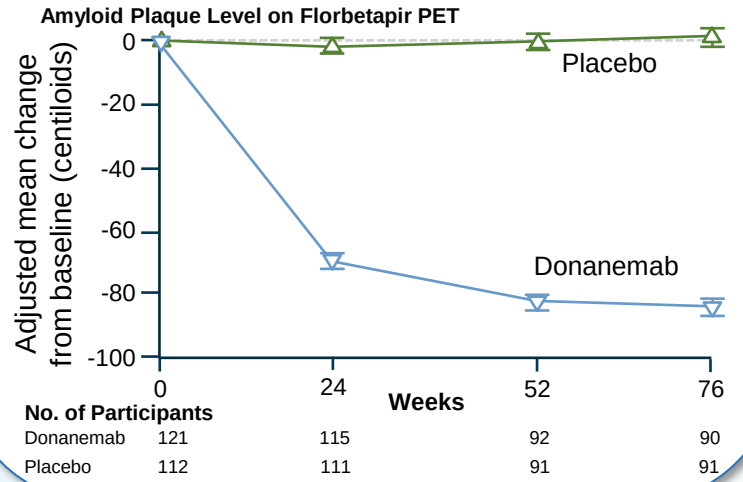
Clinical Trial › N Engl J Med. 2021 May 6;384(18):1691-1704. doi: 10.1056/NEJMoa2100708. Epub 2021 Mar 13.

Donanemab in Early Alzheimer's Disease

Mark A Mintun [1], Albert C Lo [1], Cynthia Duggan Evans [1], Alette M Wessels [1], Paul A Ardayfio [1], Scott W Andersen [1], Sergey Shcherbinin [1], JonDavid Sparks [1], John R Sims [1], Miroslaw Brys [1], Liana G Apostolova [1], Stephen P Salloway [1], Daniel M Skovronsky [1]

Affiliations + expand

PMID: 33720637 DOI: 10.1056/NEJMoa2100708



High doses of second generation anti-Aβ antibodies robustly reduce Aβ plaques to below pathological levels[1–3]

Aducanumab is only authorized in USA, UAE and Qatar. Lecanemab is being co-developed by Eisai and Biogen.
Aβ, amyloid beta; PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.
1. Sevigny J, et al. *Nature*. 2016;537:50–56; 2. Budd Haeberlein S. Data presented at CTAD 2018; 3. Swanson C, et al. *Alzheimers Res Ther*. 2021;13:80; 4. Mintun M, et al. *N Engl J Med*. 2021;384:1691–1704.

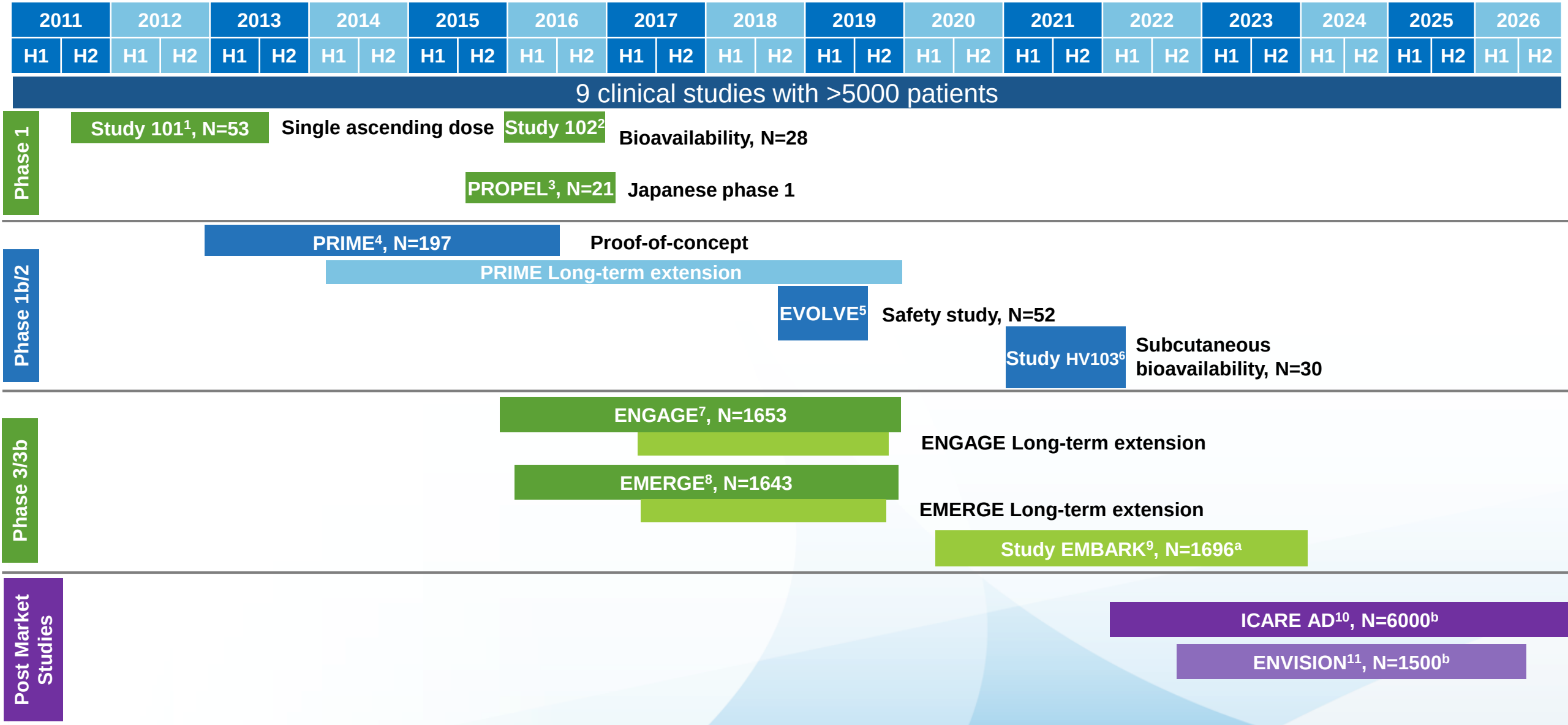
Aducanumab:
First FDA approval for an agent that targets underlying disease pathophysiology

Aducanumab was approved by the US Food and Drug Administration for the treatment of Alzheimer's disease. According to the US Prescribing Information, aducanumab should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.[1]

Aducanumab is only authorized in USA, UAE and Qatar.

1. Aduhelm. Prescribing information. Biogen, Inc.; 2021.

Aducanumab clinical development program is extensive



Aducanumab is only authorized in USA, UAE and Qatar.

[a] As of December 23, 2021; all enrolled patients participated in previous aducanumab studies; [b] Estimated enrollment.

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/ 1. NCT01397539; 2. NCT02782975; 3. NCT02434718; 4. NCT01677572; 5. NCT03639987; 6. NCT04924140; 7. NCT02477800; 8. NCT02484547. Accessed March 8, 2022; 9. Cohen S, et al. CTAD 2021; 10. ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT05097131. Accessed March 8, 2022; 11. Update on the Phase 4 ENVISION Confirmatory Study of ADUHELM® Biogen website. Published January 27, 2022, Accessed March 8, 2022; 12. Aducanumab Summary Memorandum. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf. Accessed March 8, 2022.

Aducanumab clinical development program is extensive

2011		2012		2013		2014		2015		2016		2017		2018		2019		2020		2021		2022		2023		2024		2025		2026	
H1	H2	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2	H1	H2

9 clinical studies with >5000 patients

Phase 1

Study 101[1], N=53 Single ascending dose

Study 102[2] Bioavailability, N=28

PROPEL[3], N=21 Japanese phase 1

Phase 1b/2

PRIME[4], N=197 Proof-of-concept

Number exposed to date: >3600 patients

Number with safety data at filing: >3000 patients[12]

Number being dosed today/coming years: >9000 patients

Phase 3/3b

EMERGE Long-term extension

Study EMBARK[9], N=1694[a]

Post Market Studies

ICARE AD[10], N=6000

ENVISION[11], N=1300

Aducanumab is only authorized in USA, UAE and Qatar.

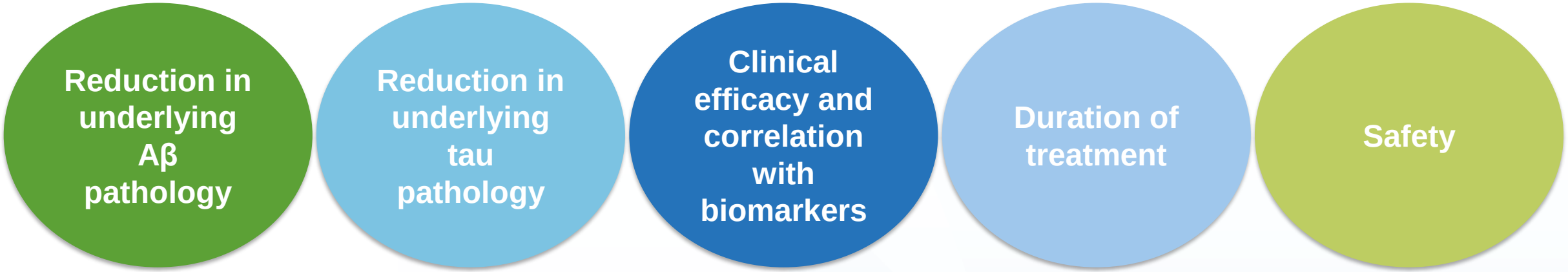
[a] As of July 15, 2021.

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/ 1. NCT01397539; 2. NCT02782975; 3. NCT02434718; 4. NCT01677572; 5. NCT03639987; 6. NCT04924140; 7. NCT02477800; 8. NCT02484547. Accessed March 8, 2022; 9. Cohen S, et al. CTAD 2021; 10. ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT05097131. Accessed March 8, 2022; 11. Update on the Phase 4 ENVISION Confirmatory Study of ADUHELM® Biogen website. Published January 27, 2022, Accessed March 8, 2022; 12. Aducanumab Summary Memorandum. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf. Accessed March 8, 2022.

Anti-Aβ antibodies: What have we learned?

Aducanumab is only authorized in USA, UAE and Qatar.
Aβ, amyloid beta.

What do the data tell us?



What do the data tell us?

Reduction in underlying Aβ pathology

Reduction in underlying tau pathology

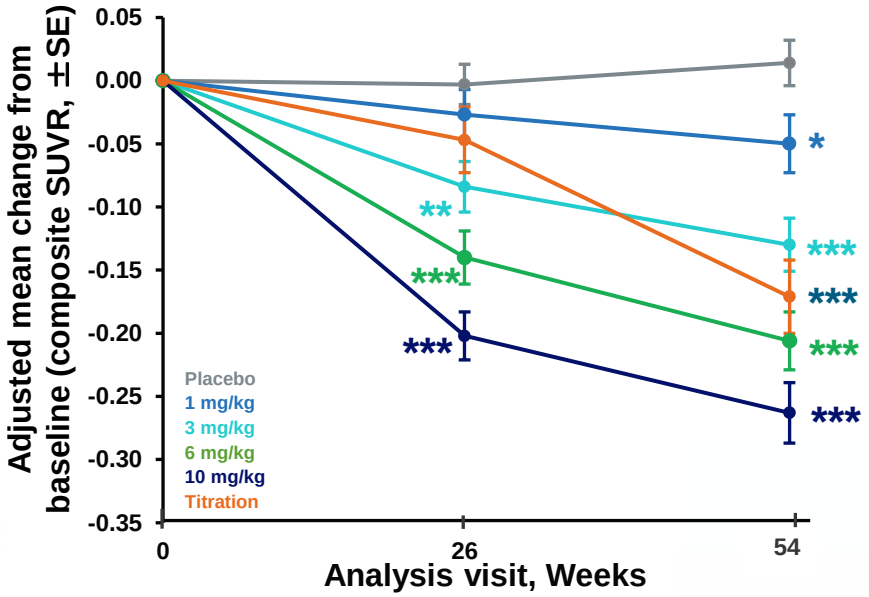
Clinical efficacy and correlation with biomarkers

Duration of treatment

Safety

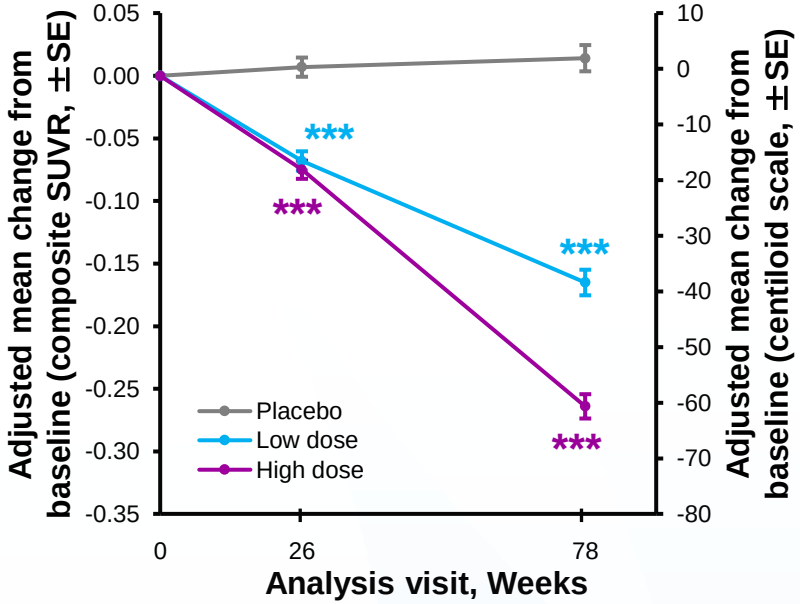
Aducanumab reduced amyloid PET SUVR in a dose- and time-dependent manner in clinical trials of aducanumab

PRIME[1]



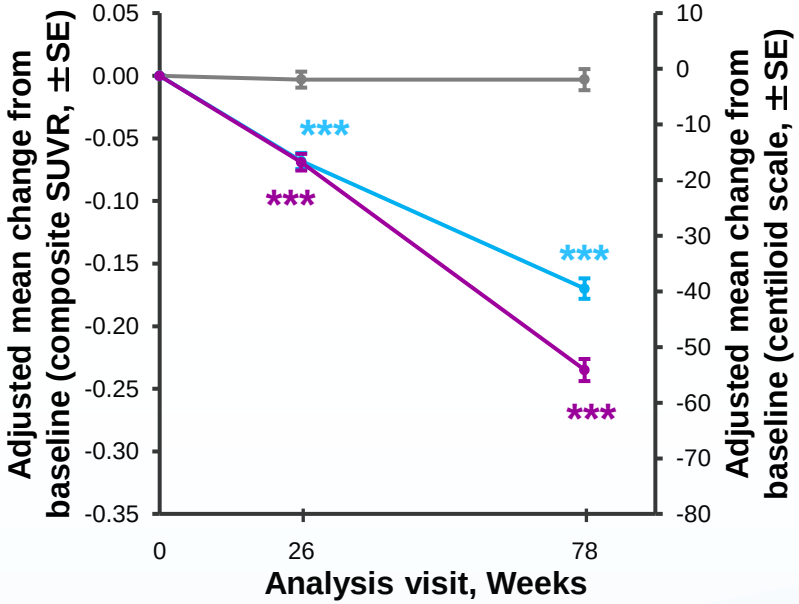
Placebo	n=42	42	38
1 mg/kg	n=26	26	21
3 mg/kg	n=29	27	26
6 mg/kg	n=24	23	23
10 mg/kg	n=28	27	21
Titration	n=18	17	16

EMERGE[2,3,a]



Placebo	n=159	129	93
Low-dose adu	n=159	129	100
High-dose adu	n=170	138	109

ENGAGE[2,3,a]

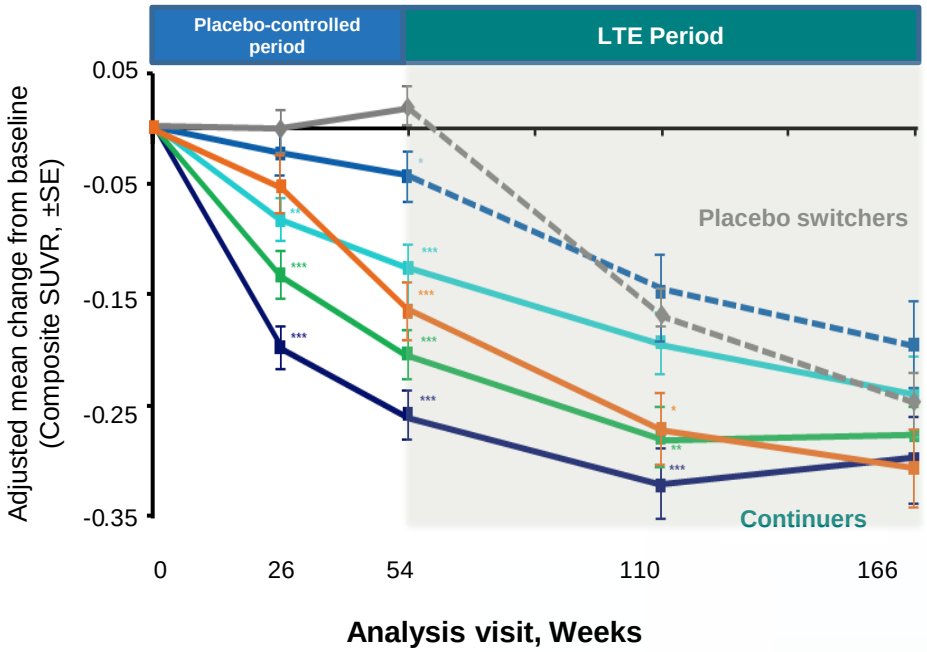


n=204	168	124	
n=198	169	138	
n=183	156	112	

Aducanumab is only authorized in USA, UAE and Qatar. *p<0.05, **p<0.01, *** p<0.001 (nominal); [a]18F-florbetapir amyloid PET analysis population. Values at each time point were based on an MMRM model, with change from baseline in MMSE as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline SUVR, baseline SUVR-by-visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.
adu, aducanumab; ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; MMRM, mixed model for repeated measure; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.
1. Budd Haeberlein S, et al. Data presented at CCFDIE 2021; 2. Budd Haeberlein S, et al. (2021). Manuscript submitted. Figure 1; 3. Budd Haeberlein S, et al. Data presented at ADPD 2021.

Aducanumab continued to decrease amyloid plaque levels beyond 2 years

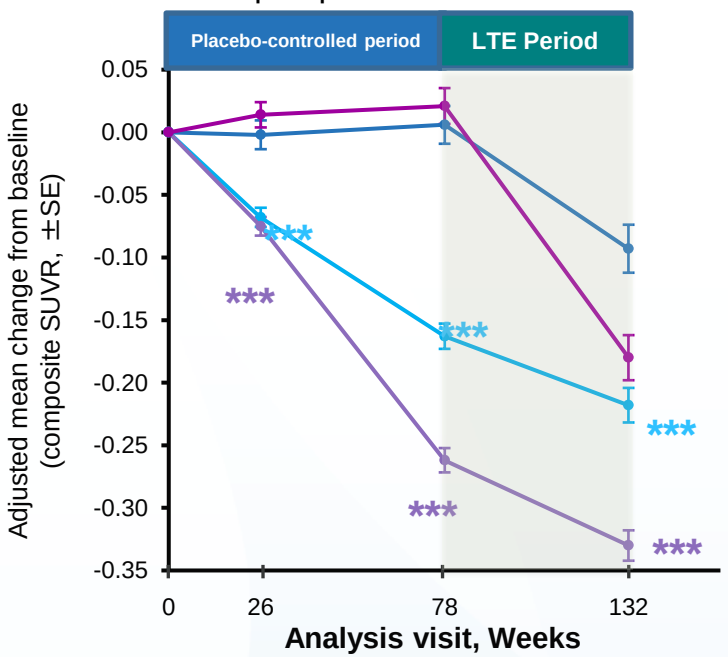
PRIME[1,a]



Aducanumab (mg/kg)							
PBO	n=42	42	38	PBO switchers[b]	26		22
1	n=26	26	21	3 mg/kg	13		6
3	n=29	27	26		18		12
6	n=24	23	23		18		15
10	n=28	27	21		13		7
Titration	n=18	17	16		15		13

EMERGE[c]

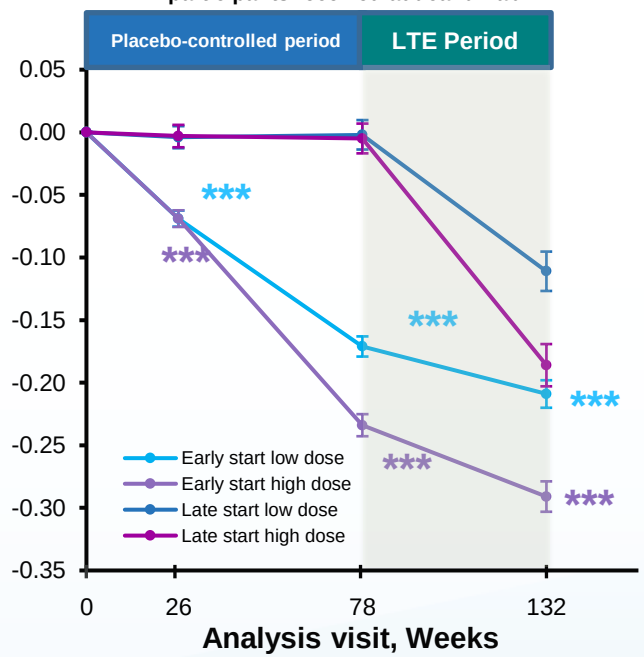
All participants received aducanumab



Early start low dose	n=159	129	100	34
Early start high dose	n=170	138	109	47
Late start low dose	n=74	56	44	19
Late start high dose	n=85	73	49	21

ENGAGE[c]

All participants received aducanumab



	n=198	169	138	65
	n=183	156	112	52
	n=100	84	63	31
	n=104	84	61	28

Aducanumab is only authorized in USA, UAE and Qatar. [a] Mean amyloid plaque levels in the 10 mg/kg fixed-dose cohort reached and remained at a SUVR level below 1.1, which is considered the quantitative cut-point suggested to discriminate between a positive and negative scan.[2] * P < 0.05; ** P < 0.01; *** P < 0.001 vs placebo in the placebo-controlled period and vs placebo switchers in the LTE; [b] Placebo switchers received aducanumab 3 mg/kg or titration (3 mg/kg → 6 mg/kg or 1 mg/kg → 10 mg/kg) in the LTE; [c] Early start participants are those assigned to aducanumab in both PC and LTE periods, and late start participants are those assigned to placebo in PC period and aducanumab in LTE period; the reference group is late start low dose for early start low dose, and late start high dose for early start high dose. Results were based on an MMRM model, with change from baseline as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline SUVR value, baseline SUVR value by visit interaction, baseline MMSE, baseline age and laboratory ApoE status. *** p<0.001 compared with late start group. ApoE, apolipoprotein E; LTE, long-term extension; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; PC, placebo-controlled; PBO, placebo; PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.

1. Budd Haeberlein S, et al. Data presented at CCFDIE 2021; 2. Joshi AD, et al. *J Nucl Med*. 2015;56:1736–1741.

What do the data tell us?

Reduction in underlying Aβ pathology

Reduction in underlying tau pathology

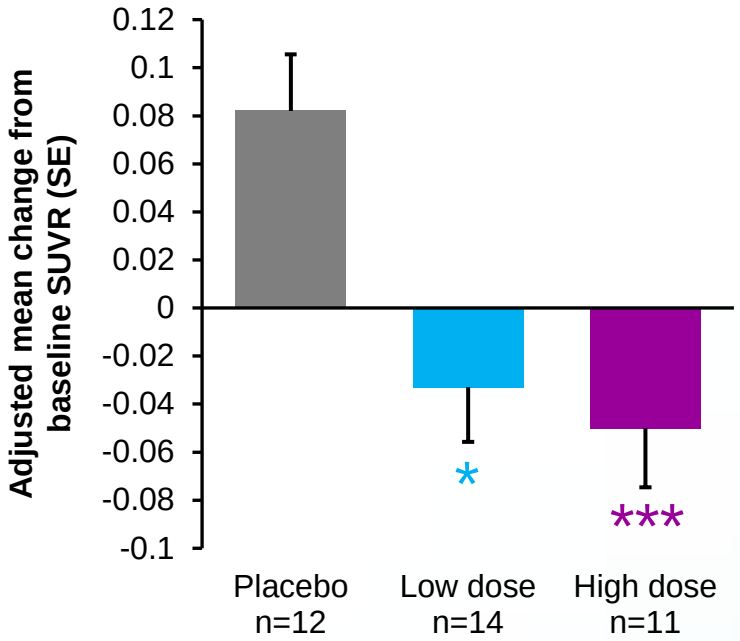
Clinical efficacy and correlation with biomarkers

Duration of treatment

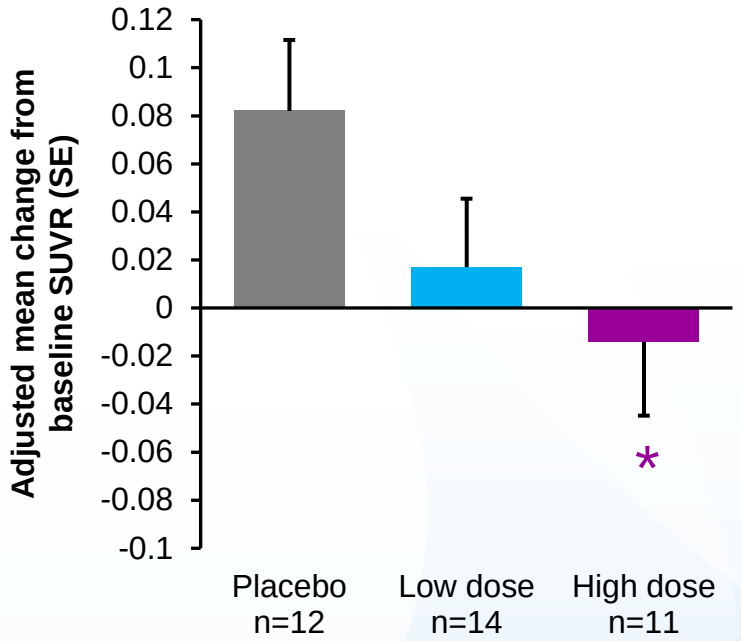
Safety

Aducanumab reduced tau pathology, as measured by MK-6240 tau PET (EMERGE and ENGAGE)

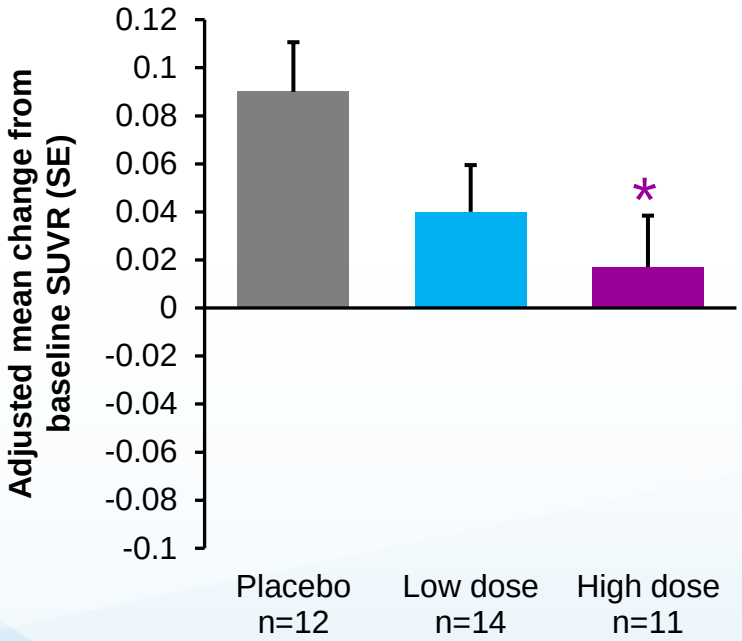
Medial temporal composite



Temporal composite



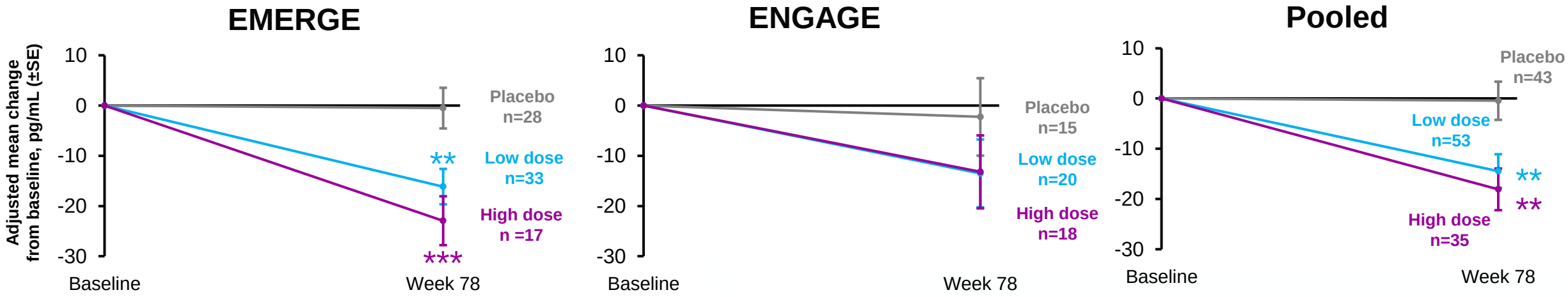
Frontal composite



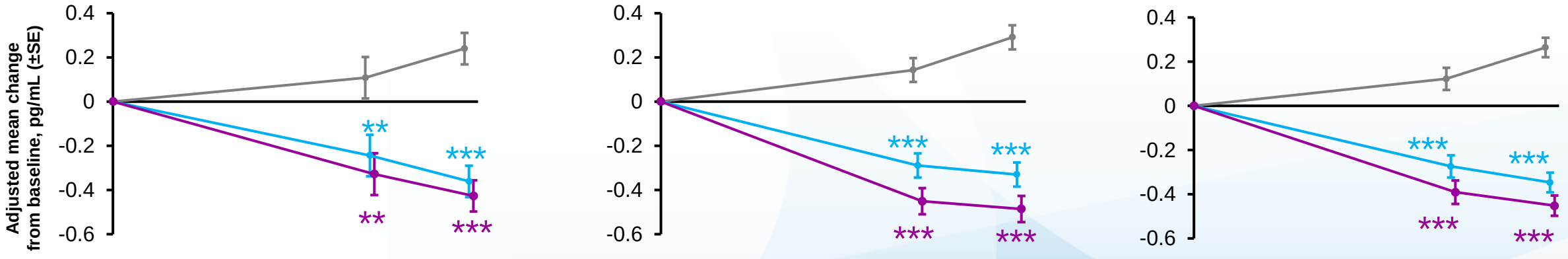
Pooled tau PET analysis population. ^{18}F-MK6240 Tau PET tracer. *p<0.05; ***p<0.0001 compared with placebo (nominal).
PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.
Budd Haeberlein S, et al. Data presented at ADPD 2021.

Aducanumab reduced fluid biomarkers linked to tau pathology at Week 78 in EMERGE and ENGAGE

CSF[a]



Plasma p-tau[181] [b]



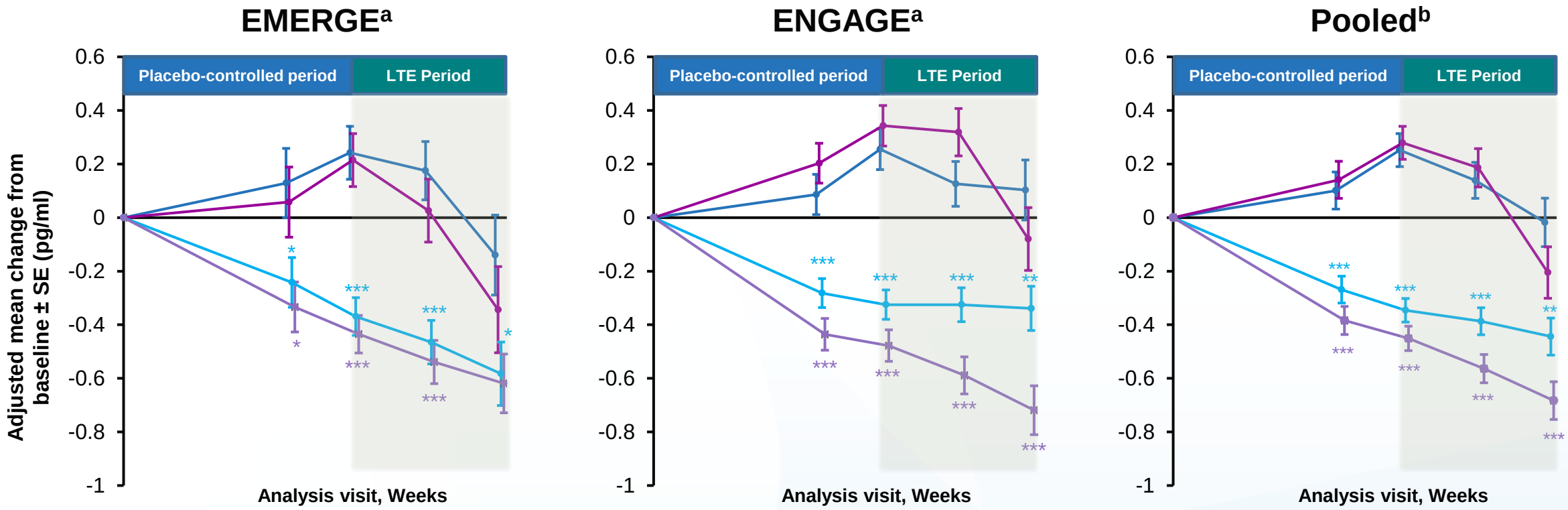
		EMERGE		ENGAGE		Pooled	
		Week 56	Week 78	Week 56	Week 78	Week 56	Week 78
placebo	n=287	177	273	333	301	325	620	478	598
Low dose	n=293	172	269	331	299	322	624	471	591
High dose	n=290	168	271	281	242	274	571	410	545

Aducanumab is only authorized in USA, UAE and Qatar.

*p<0.05, ** p<0.01, *** p<0.001 compared with placebo (nominal). [a] CSF modified analysis population (patients with both baseline and post-baseline CSF assessments). Results were based on an ANCOVA model at Week 78, fitted with change from baseline as dependent variable, and with categorical treatment, study, baseline biomarker value, baseline age and laboratory ApoE status (carrier and non-carrier) as independent variables; [b] Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline value, baseline value by visit interaction, baseline age and laboratory ApoE status.

ANCOVA, analysis of covariance; ApoE, apolipoprotein E; CSF, cerebrospinal fluid; MMRM, mixed model for repeated measures; PET, positron emission tomography; pg/ml, picograms per milliliter; p-tau, phosphorylated tau 181; SE, standard error; SUVR, standardized uptake value ratio; t-tau, total tau.

Aducanumab continued to decrease plasma p-tau^{181} levels beyond 2 years



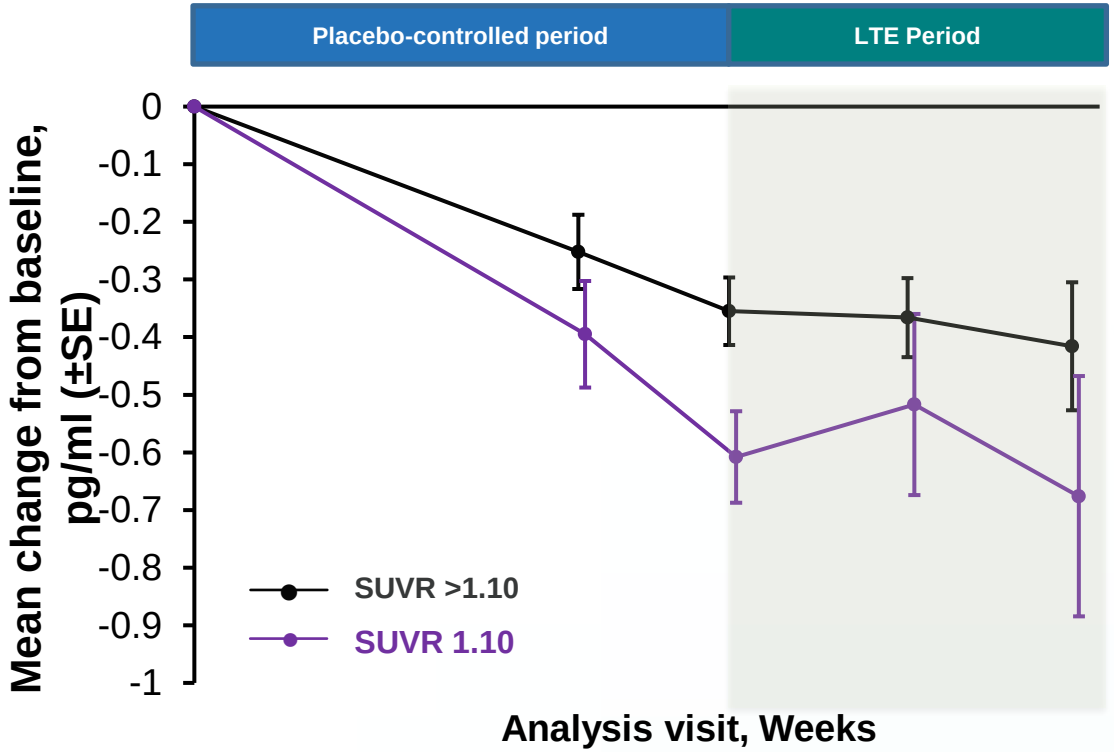
		0	56	78	104	128	0	56	78	104	128	0	56	78	104	128
Late start low dose	n=144		90	136	75	41	165	147	161	109	53	309	237	297	184	94
Late start high dose	n=143		87	137	59	34	168	154	164	93	48	311	241	301	152	82
Early start low dose	n=293		172	269	130	62	331	299	322	187	98	624	471	591	317	160
Early start high dose	N=290		168	271	132	74	281	242	274	150	79	571	410	545	282	153

Aducanumab is only authorized in USA, UAE and Qatar. *p<0.05, **p<0.01, *** p<0.001 compared with late start group. Early start participants are those assigned to aducanumab in both placebo-controlled and LTE periods, and late start participants are those assigned to placebo in placebo-controlled period and aducanumab in LTE period; the reference group is late start low dose for early start low dose, and late start high dose for early start high dose. [a] Results were based on an MMRM model, with change from baseline as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline value, baseline value by visit interaction, baseline age and laboratory ApoE status. [b] Results were based on an MMRM model, with change from baseline as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, study, study by visit interaction, baseline value, baseline value by visit interaction, baseline age and laboratory ApoE status.

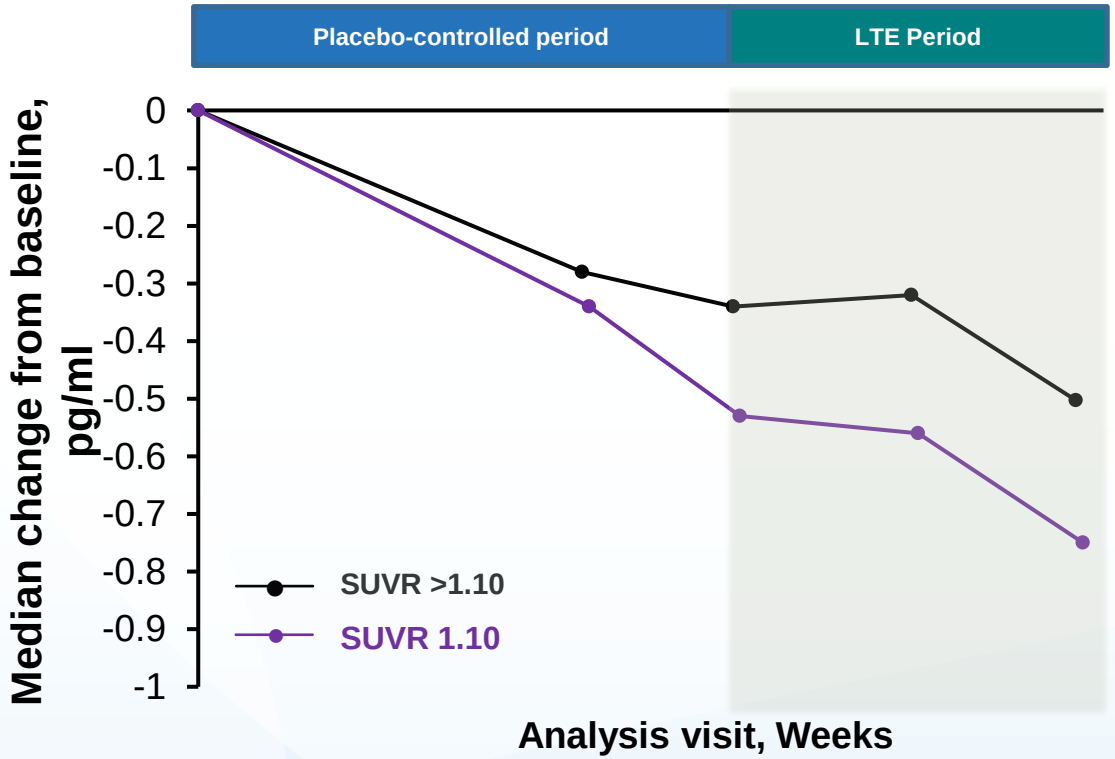
ApoE, apolipoprotein E; LTE, long-term extension; MMRM, mixed model for repeated measures; pg/ml, picograms per milliliter; p-tau, phosphorylated tau 181; SE, standard error.

Reduction in plasma p-tau^{181} levels was greater in aducanumab-treated patients who had an amyloid PET SUVR ≤1.10 at Week 78

Pooled low dose and high dose groups



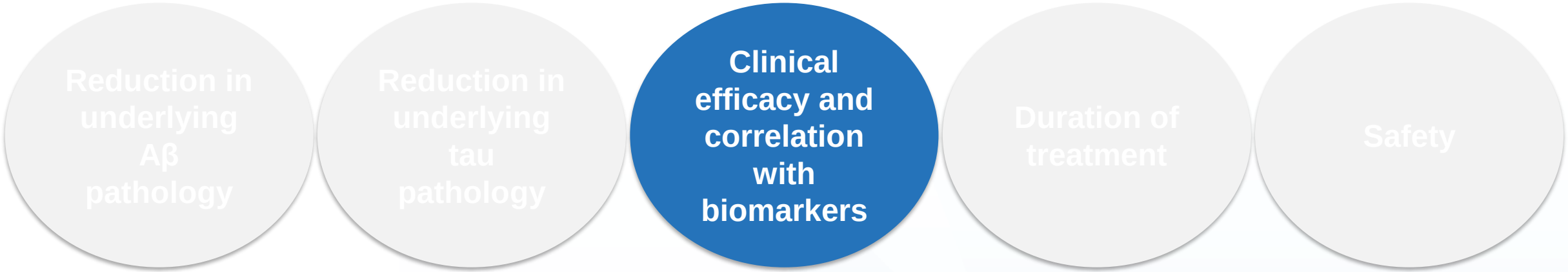
		0	56	78	104	128
SUVR >1.10	n=287	247	287	173	102
SUVR <1.10	n=117	98	117	73	41



		0	56	78	104	128
SUVR >1.10	n=287	247	287	173	102
SUVR <1.10	n=117	98	117	73	41

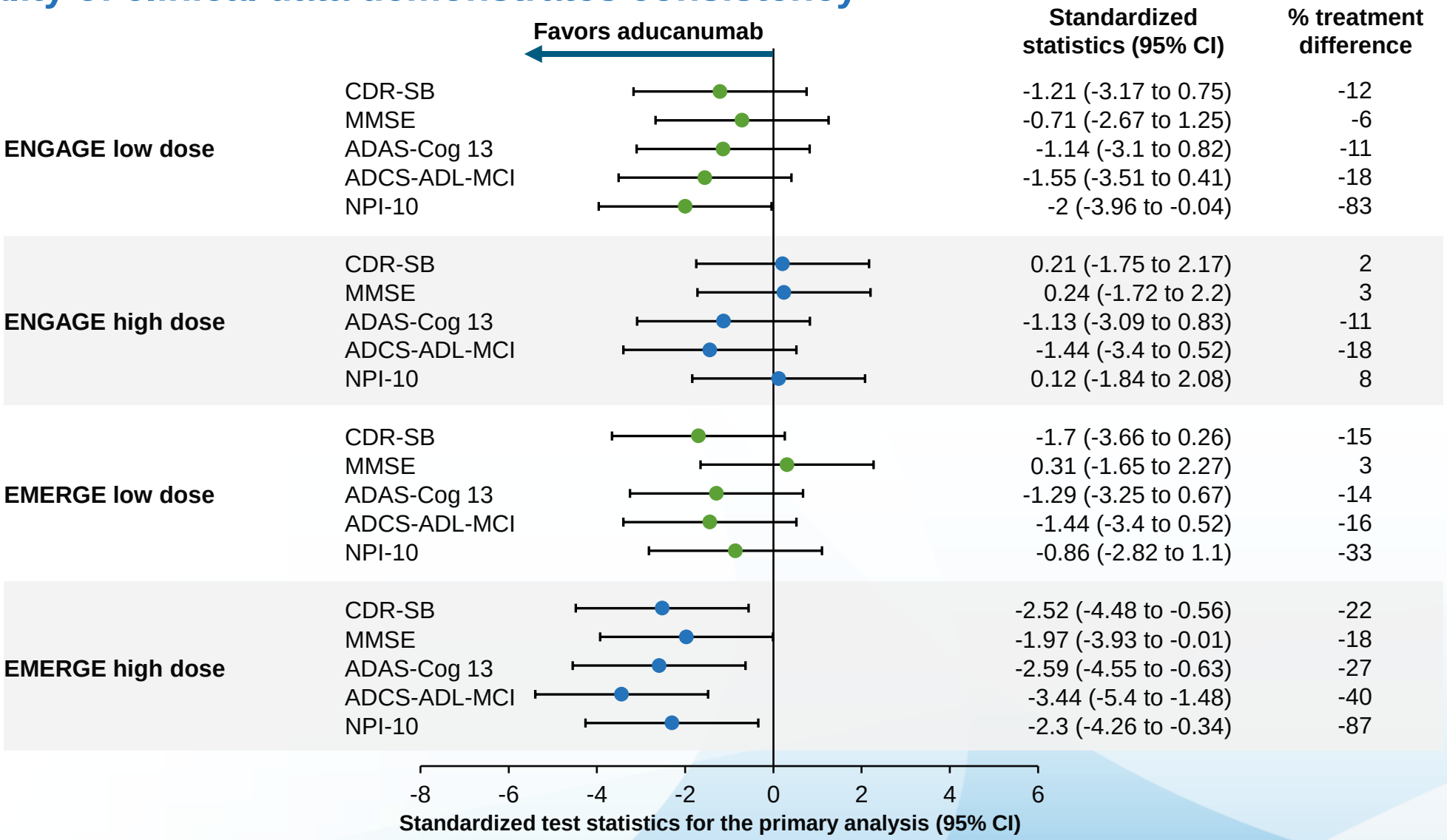
Aducanumab is only authorized in USA, UAE and Qatar.
Assessed in pooled low- and high-dose aducanumab-treated groups. 1.10 is the SUVR cut-point for florbetapir in Landau SM, et al. *J Nucl Med*. 2013;54(1):70-77.
PET, positron emission tomography; pg/ml, picograms per milliliter; p-tau, phosphorylated tau 181; SE, standard error; SUVR, standardized uptake value ratio.

What do the data tell us?



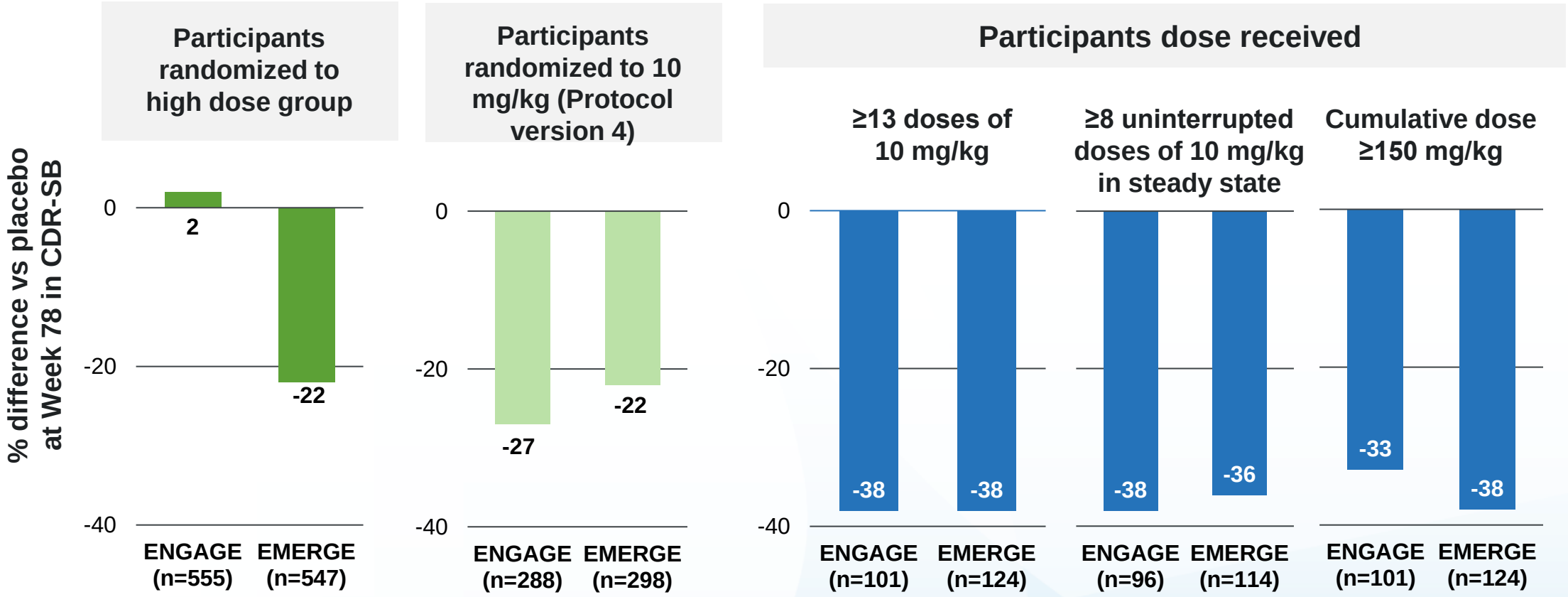
Clinical endpoints in early Alzheimer's disease:

The totality of clinical data demonstrates consistency



A correlation of 0.3 to 0.5 was observed between endpoints.
Results for CDR-SB were based on an MMRM, with change from baseline CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status. The change from baseline in MMSE, ADAS-Cog 13 and ADCS-ADL-MCI scores were also analyzed using MMRM.
AD, Alzheimer's disease; ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; NPI-10, Neuropsychiatric Inventory (10 items).

Dose / exposure to sufficient doses of 10mg/kg provides consistent efficacy in EMERGE and ENGAGE

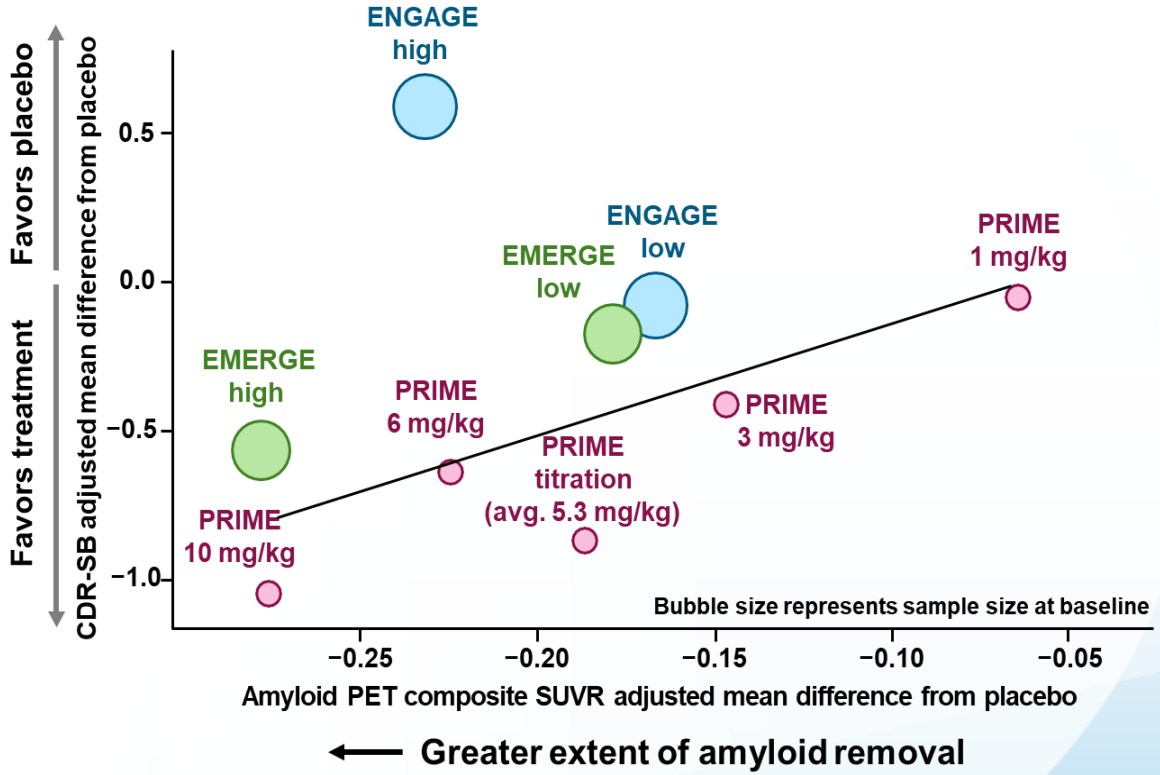


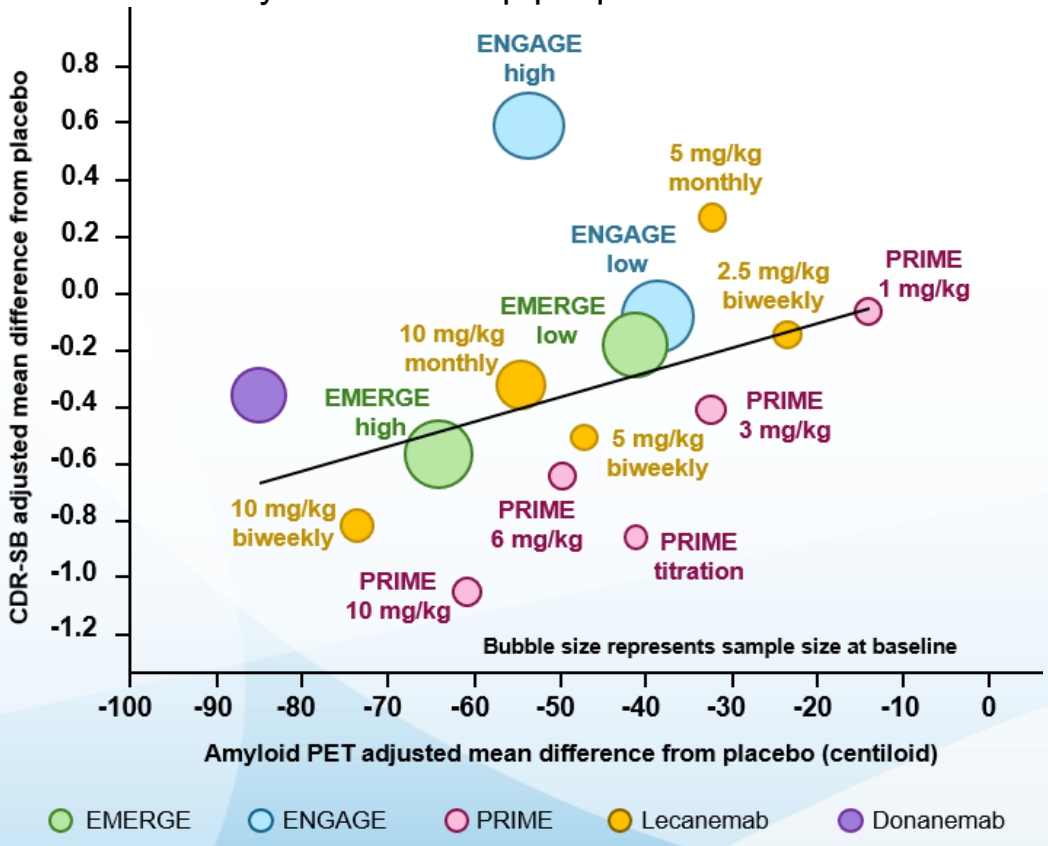
Note: Propensity score matching approach using matched placebo (based on baseline demographic and illness characteristics)

Aducanumab is only authorized in USA, UAE and Qatar.
n=number of subjects in the aducanumab group.
CDR-SB, Clinical Dementia Rating Scale-Sum of Boxes
Budd Haeberlein S, et al. Data presented at JSDR 2021.

Reduction in brain Aβ plaque levels is associated with slowing of clinical decline

- The Pop/PK-PD model of aducanumab using the PRIME, EMERGE, and ENGAGE data showed a dose-proportional reduction in brain Aβ plaque levels[1]
- EMERGE, ENGAGE, and PRIME data demonstrate a correlation between treatment effects on amyloid PET and CDR-SB, indicating that a greater treatment effect on brain Aβ plaque levels is associated with a greater clinical benefit[2]
- Similar correlation analysis across contemporary anti-Aβ agents demonstrated to robustly lower brain Aβ plaques levels[2]

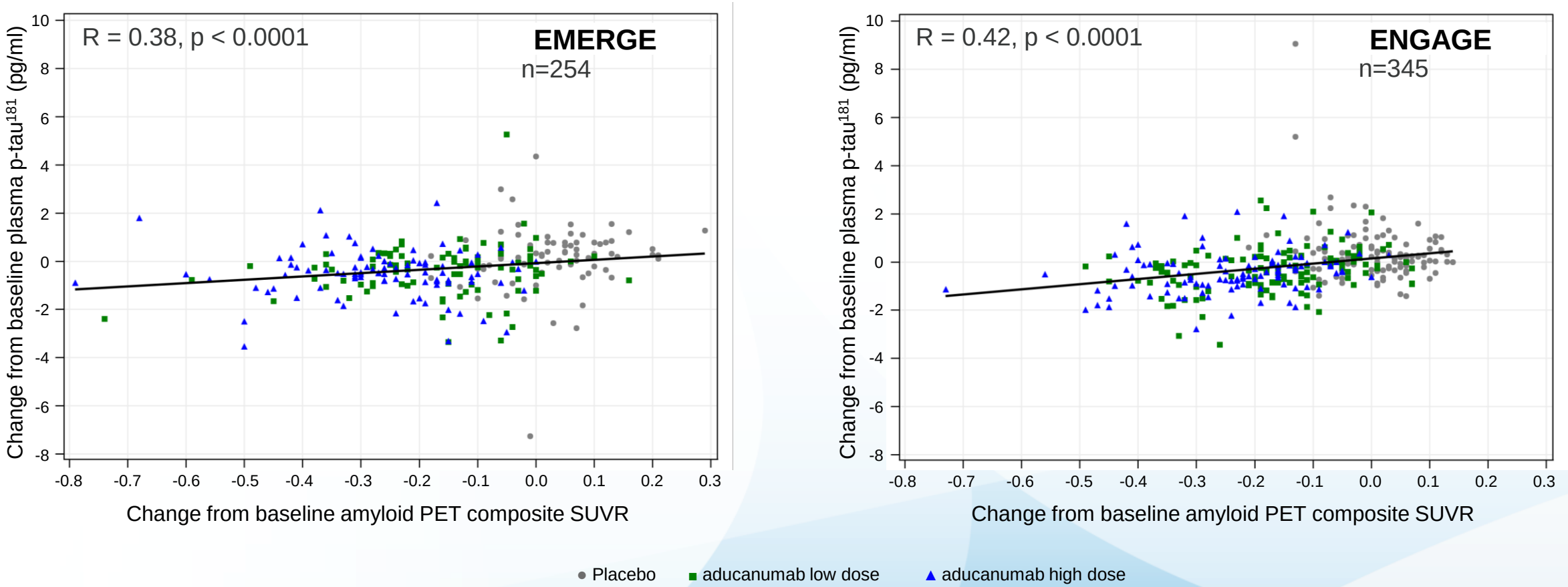




Aducanumab is only authorized in USA, UAE and Qatar.
Results for the aducanumab studies were from the Aβ PET substudy population, in which longitudinal Aβ PET data was available. The high-dose group in ENGAGE was not included for the regression line in the figure on the left.
Aβ, amyloid beta; CDR-SB, Clinical Dementia Rating Scale-Sum of Boxes; PET, positron emission tomography; PopPK-PD; population pharmacokinetics-pharmacodynamics; SUVR, standardized uptake value ratio.
1. Kandadi Muralidharan K,. *CPT Pharmacometrics Syst Pharmacol.* 2022;11(1):7-19; 2. Rajagovindan R, et al. Data presented at AAIC 2021.

Change in plasma p-tau^{181} levels is correlated with change in amyloid PET SUVR at Week 78 in EMERGE and ENGAGE

Scatterplots of change from baseline plasma p-tau^{181} vs change from baseline ^{18}F-florbetapir amyloid PET composite SUVR (reference region = cerebellum) at Week 78



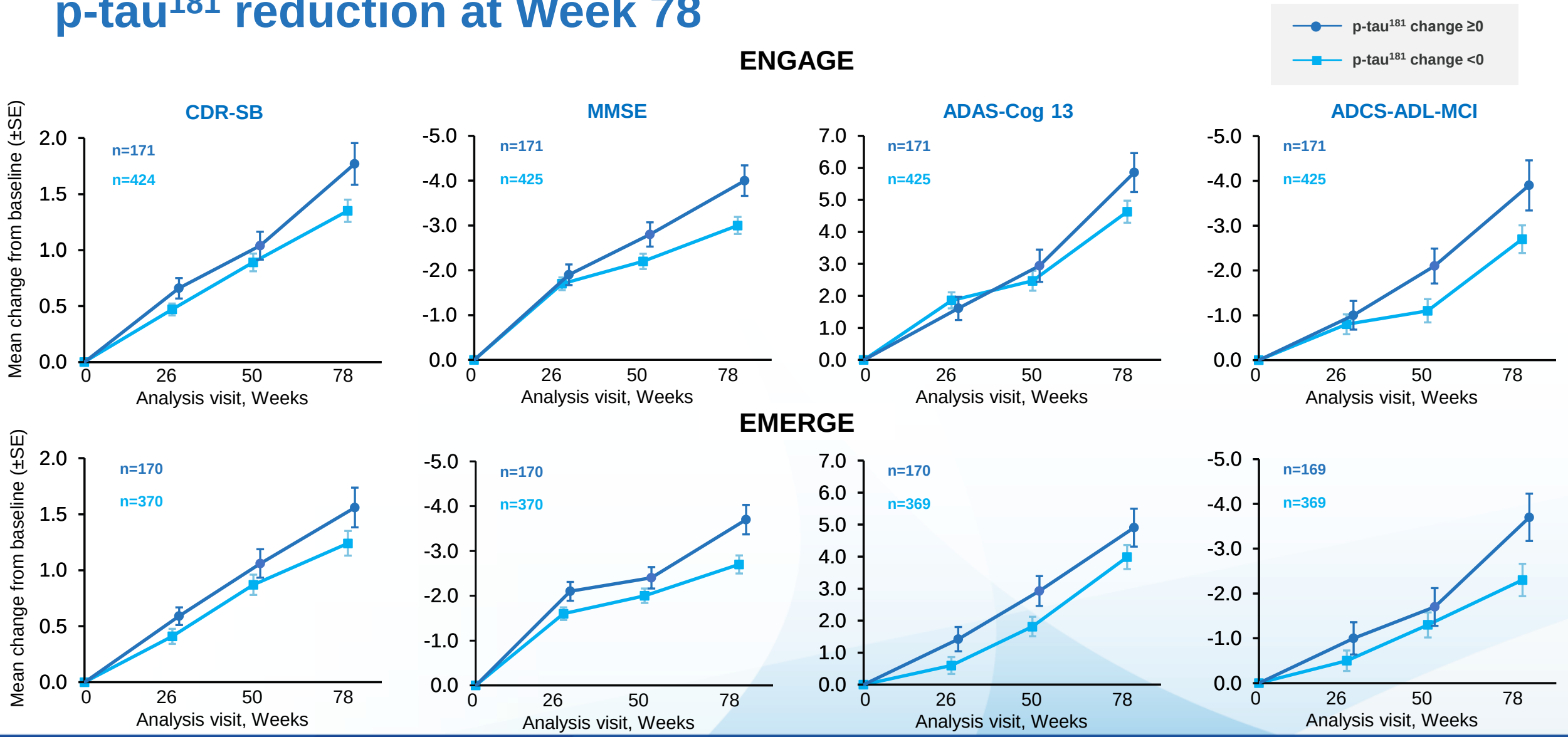
Aducanumab is only authorized in USA, UAE and Qatar.
R: Spearman correlation adjusted for baseline p-tau, baseline amyloid PET, and age. Correlations calculated based on all arms.
PET, positron emission tomography; pg/ml, picograms per milliliter; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio.
Hansson O, et al. Data presented at CTAD 2021.

Aducanumab-induced reduction in plasma p-tau^{181} levels was associated with less clinical decline in both EMERGE and ENGAGE

Association between change in p-tau^{181} and efficacy at Week 78		Hypothesized correlation	Correlation (p-value)	
			EMERGE (n = 514–521)	ENGAGE (n = 577–581)
p-tau^{181}	CDR-SB	Positive	**0.11** (0.0166)	**0.14** (0.0005)
	MMSE	Negative	**-0.21** (<0.0001)	**-0.15** (0.0002)
	ADAS-Cog13	Positive	**0.17** (0.0001)	**0.15** (0.0002)
	ADCS-ADL-MCI	Negative	**-0.12** (0.0086)	**-0.14** (0.0010)

Aducanumab is only authorized in USA, UAE and Qatar.
Correlations are partial Spearman correlations assessed in pooled low and high dose aducanumab-treated groups, adjusting for baseline p-tau, baseline clinical endpoint, and age. ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau.
Hansson O, et al. Data presented at CTAD 2021.

Clinical progression was slower in participants who had plasma p-tau^{181} reduction at Week 78

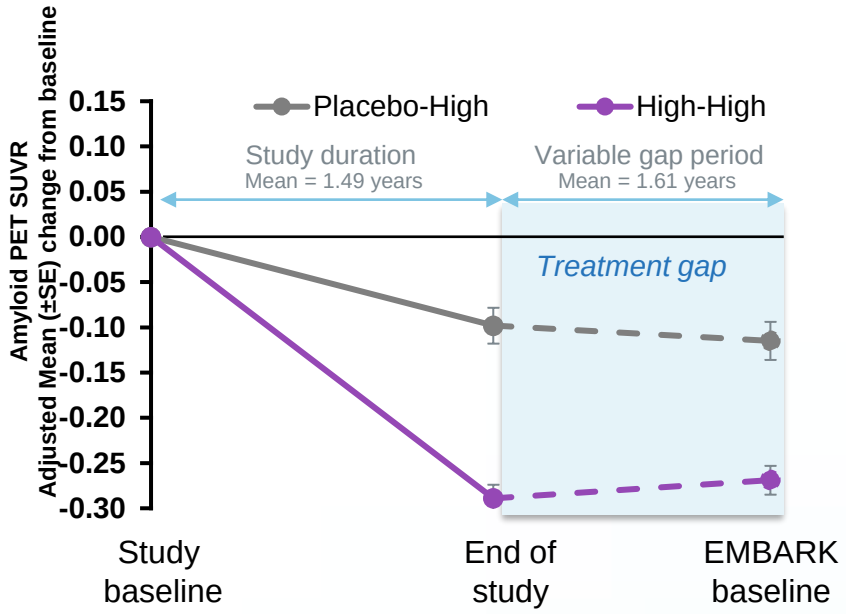


Aducanumab is only authorized in USA, UAE and Qatar. Assessed in pooled low and high dose aducanumab-treated groups.
ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; SE, standard error.

What do the data tell us?

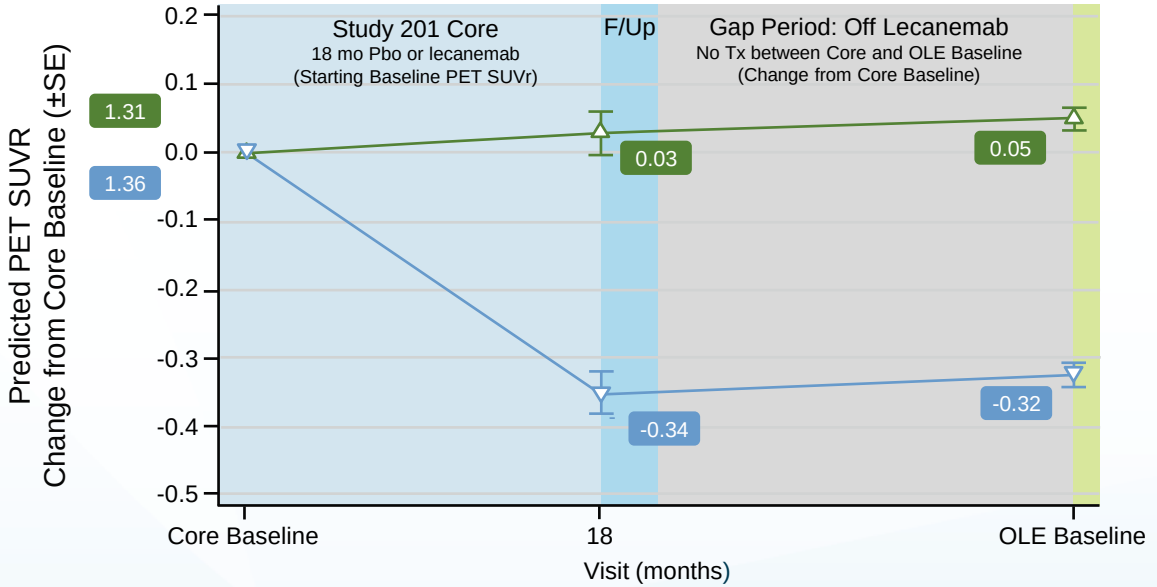
Reduction of amyloid plaque levels was maintained for at least 2 years following stopping treatment

Pooled EMERGE and ENGAGE



Placebo-High	37	37	37
High-High	64	64	64

Lecanemab Phase 2[a]

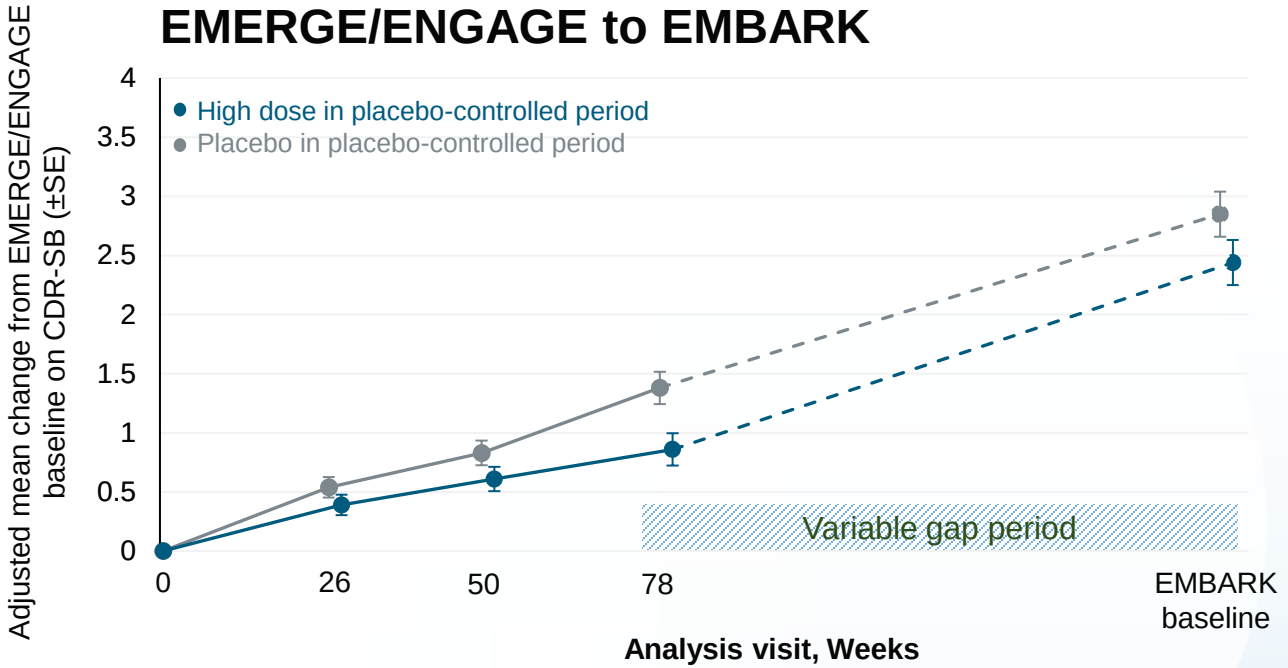


Placebo	10	10	10
10 bi-weekly	10	19	10

Aducanumab is only authorized in USA, UAE and Qatar.
Aducanumab: The end-of-feeder-study amyloid PET SUVR was defined as the last non-missing post-baseline amyloid PET SUVR in the feeder study. Some subjects may receive aducanumab doses after the date of the last post-baseline amyloid PET in the feeder study. For the pooled EMERGE/ENGAGE analyses, adjusted mean changes were based on an MMRM with change from feeder-study baseline amyloid PET composite SUVR as outcomes using fixed effects of treatment group, time (categorical), treatment group-by-time interaction, feeder-study baseline SUVR value, feeder-study baseline SUVR value by time interaction, feeder-study baseline MMSE, feeder-study baseline age, and laboratory ApoE status (carrier/noncarrier).
[a] Gap period is off-treatment (on average 24 months, with min 9 & max 59 months).
ApoE, apolipoprotein E; LTE, long-term extension; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio. Cohen S, et al. Data presented at CTAD 2021. Lecanemab: Predicted PET SUVR change from Core baseline was based on piecewise regression for the OLE enrolled subjects with Core baseline and post-baseline in PET sub study in Core Study and OLE phase. Swanson C, et al. Data presented at CTAD 2021.

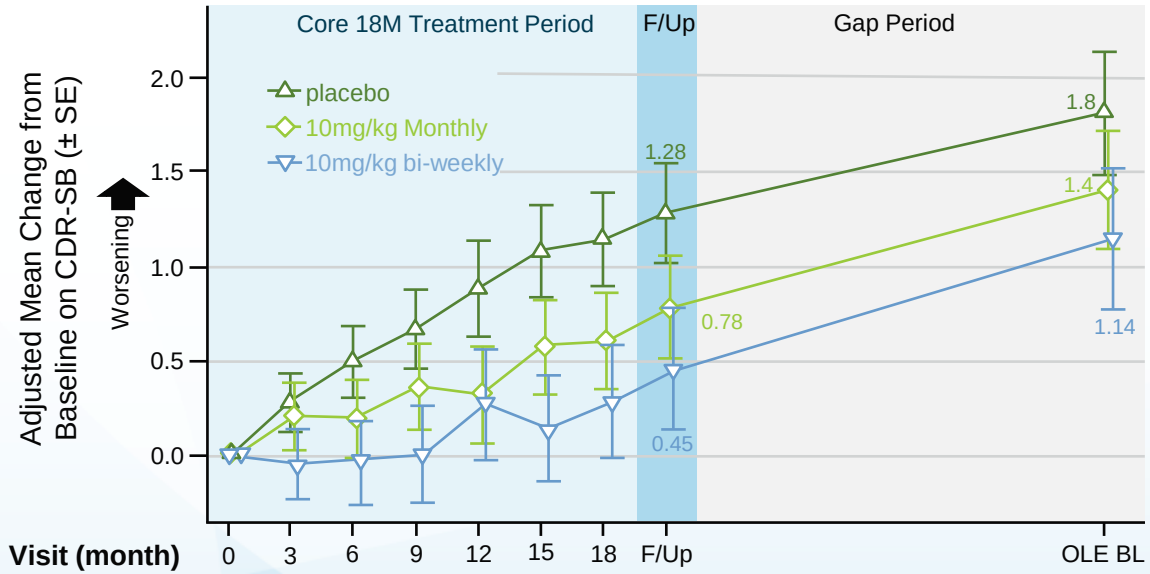
After stopping treatment, clinical measures continue to decline, albeit maintaining a numerical advantage over placebo during the treatment gap[1,2]

EMERGE/ENGAGE to EMBARK



Placebo	237	237	232	133	230
High dose	259	253	248	153	254

Lecanemab OLE[a]



N (placebo)	40	40	38	39	39	38	38	38	40
N (10 Monthly)	48	47	46	46	45	43	43	43	48
N (10 bi-weekly)	31	30	30	30	29	29	29	29	31

Adjusted mean and standard errors at each time point were based on an MMRM, with change from feeder-study baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, feeder-study baseline CDR-SB, feeder-study baseline CDR-SB by visit interaction, feeder-study baseline MMSE, AD symptomatic medication use at feeder-study baseline, region, and laboratory ApoE status.

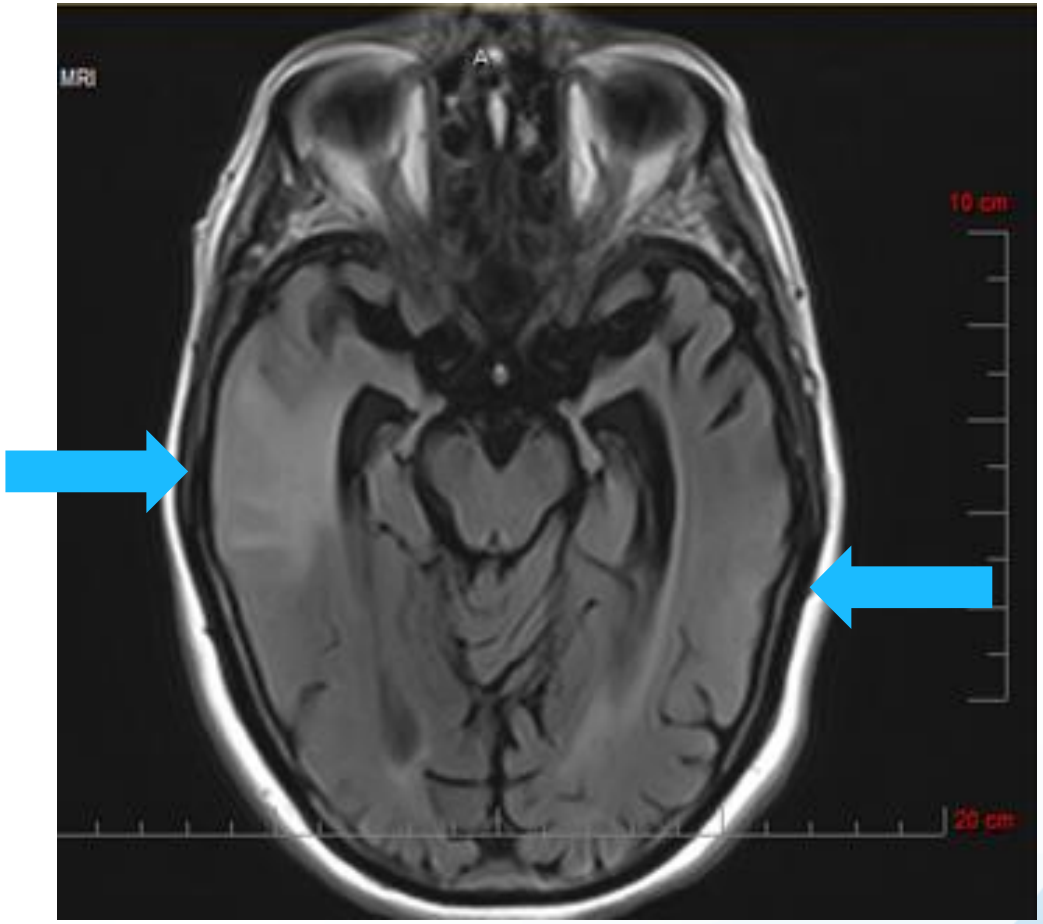
[a] Adjusted mean change in clinical endpoints by Core treatment group during Core, 3-month Follow-Up & Gap.[2]

AD, Alzheimer's disease; ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; SE, standard error. 1. Cohen S, et al. Data presented at CTAD 2021; 2. Swanson C, et al. Data presented at AAIC 2021.

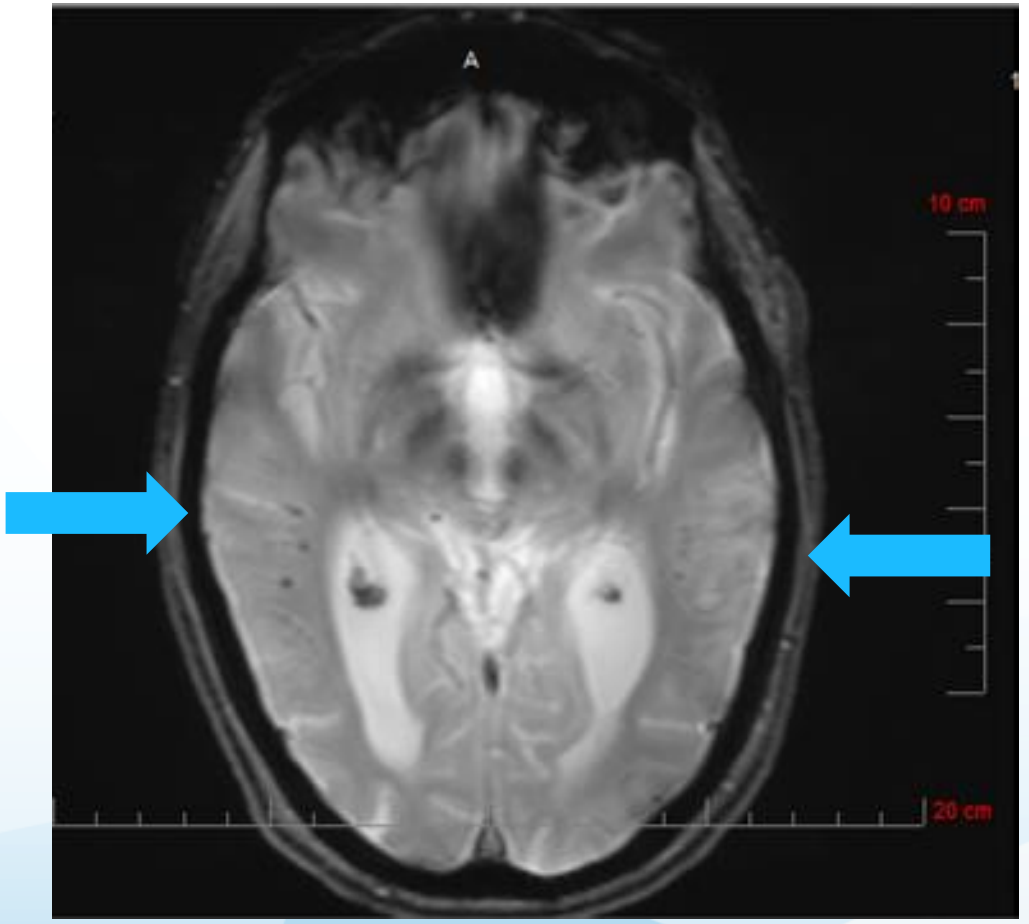
What do the data tell us?

Radiographic appearance and colocalization of ARIA-E and ARIA-H

ARIA-E



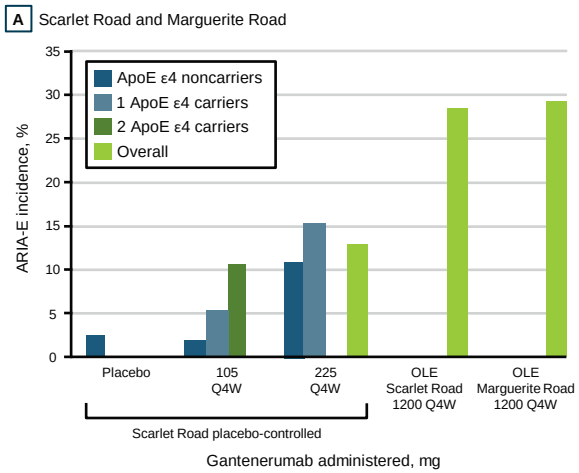
Bi-temporal superficial siderosis and microhemorrhages

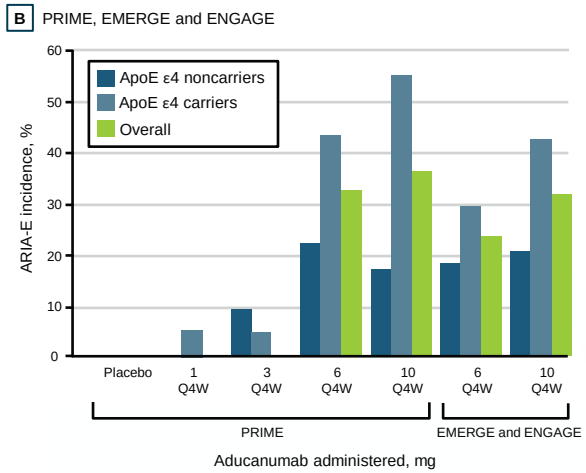


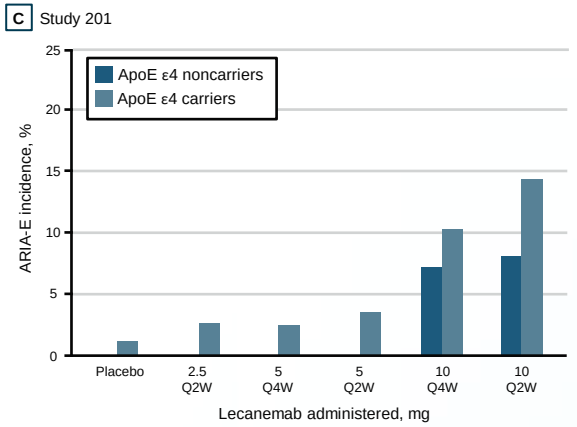
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema; ARIA-H, ARIA–microhemorrhages, macrohemorrhages, or superficial siderosis.

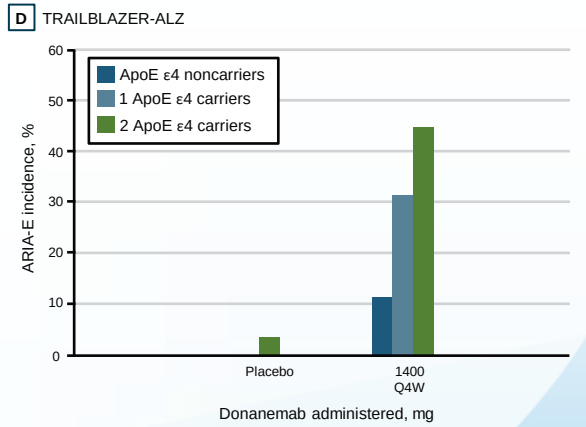
ARIA events are associated with anti-Aβ antibodies that lower amyloid plaque levels[1]

ARIA-E

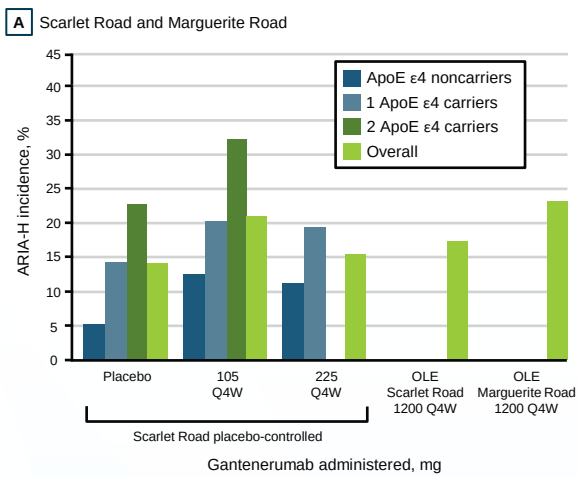


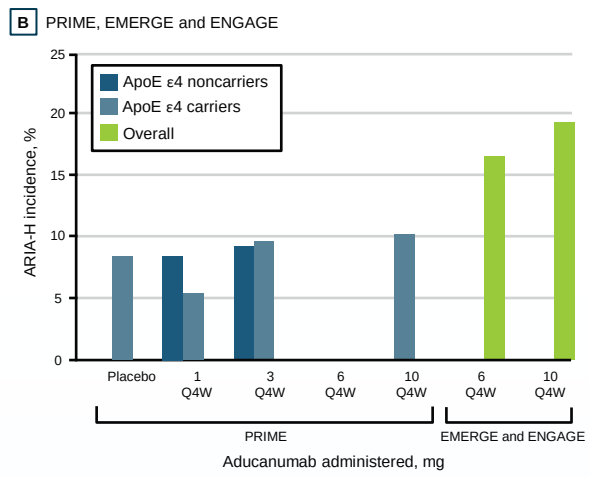


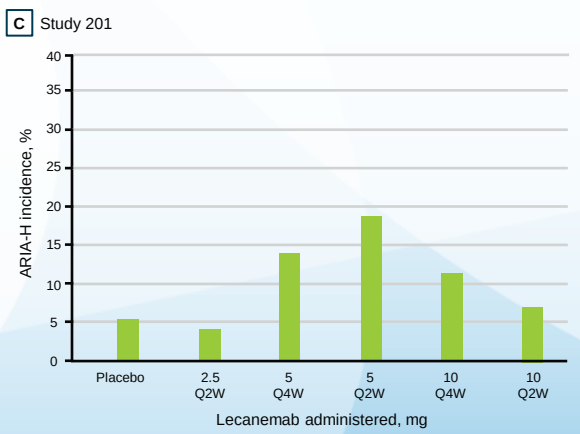


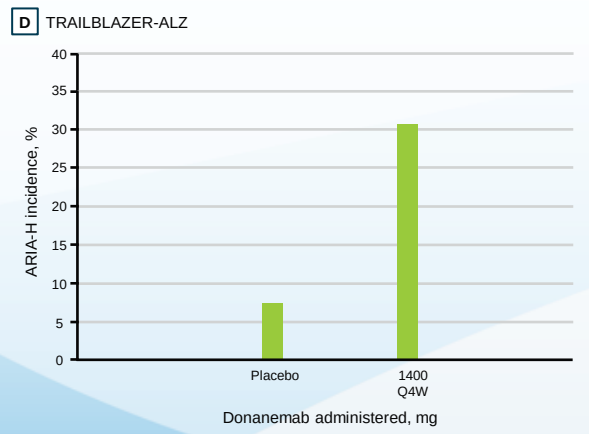


ARIA-H









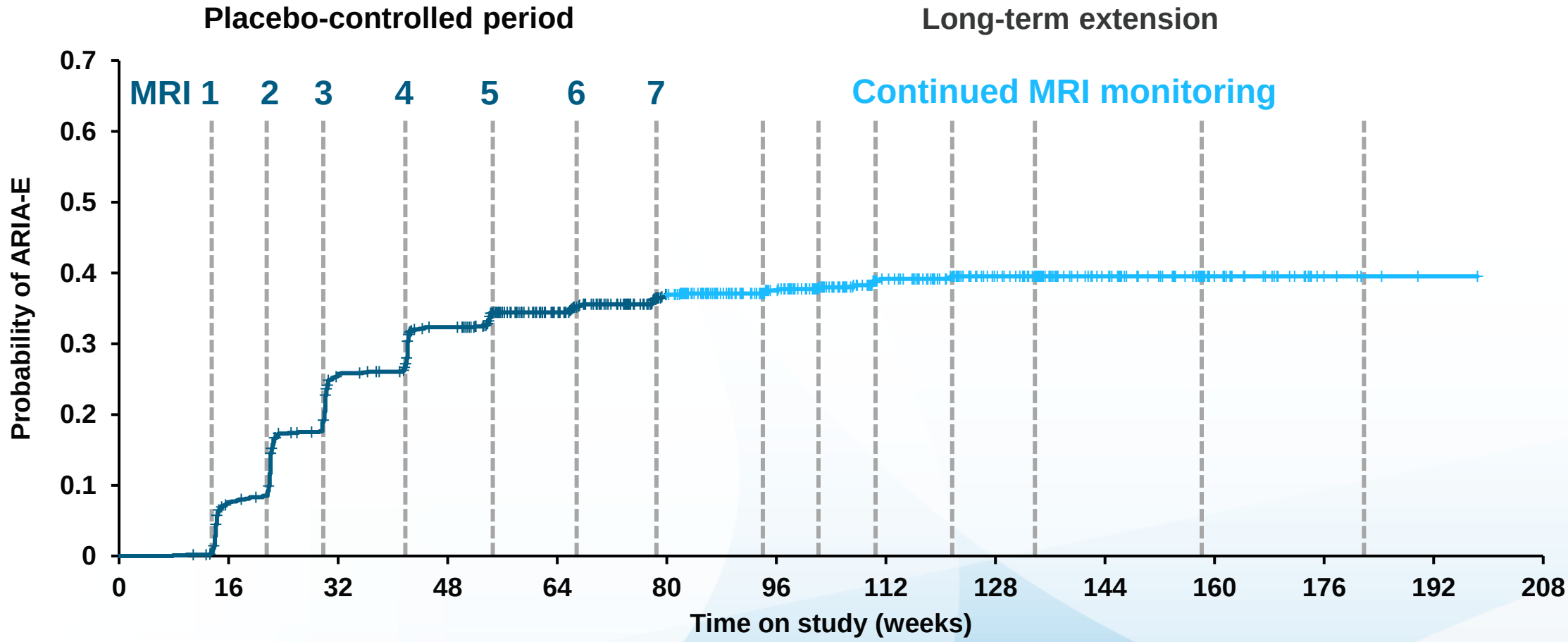
Aducanumab is only authorized in USA, UAE and Qatar.

Aβ, amyloid beta; ApoE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema; ARIA-H, ARIA–microhemorrhages, macrohemorrhages, or superficial siderosis.

1. Filippi M, et al. *JAMA Neurol.* [published online ahead of print, January 31, 2022].

ARIA-E events occurred mostly prior to the 8th dose[1]

Analysis of time to first ARIA-E with 10 mg/kg aducanumab treatment in EMERGE and ENGAGE



Participants at risk, n	1029	938	738	643	537	393	290	195	128	76	32	9	1	0

ARIA-E, amyloid-related imaging abnormalities edema; MRI, magnetic resonance imaging.

1. Aduhelm. Prescribing information. Biogen, Inc.; 2021; 2. Chalkias S, et al. Data presented at ADPD 2021.

ARIA-E is most commonly mild or moderate in radiographic severity and most commonly asymptomatic

EMERGE and ENGAGE integrated safety data set (placebo-controlled period)

Total number of participants in the 10 mg/kg group, N=1029

Participants with ARIA-E detected in brain MRI, n=362

Mild = 109 (30%)

Moderate = 209 (58%)

Severe = 44 (12%)

Radiographic severity of ARIA[a]

Number who experienced symptomatic ARIA-E, n = 94 (26%)

Number who experienced asymptomatic ARIA-E, n = 268 (74%)

Symptomatic severity of ARIA[b]

98% of ARIA-E events resolved on study

- 69% resolved within 12 weeks, 83% resolved within 16 weeks

- The most common symptoms were headache, confusion, dizziness, and nausea
- Most symptoms during ARIA were mild (67.7%) or moderate (28.3%) in clinical severity
- Severe symptoms were uncommon and included rare reports of seizures

[a] Each participant counted once, at maximum radiographic severity; [b] Each participant counted once, at maximum symptomatic status and severity.
ARIA-E, amyloid-related imaging abnormalities edema; MRI, magnetic resonance imaging.
Chalkias S, et al. Data presented at ADPD 2021.

The incidence of ARIA is highest in ApoE ε4 homozygous participants in EMERGE and ENGAGE

n (%)	Aducanumab 10 mg/kg		
	ApoE ε4 homozygote (n=159)	ApoE ε4 heterozygote (n=515)	ApoE ε4 noncarrier (n=355)
ARIA-E	105 (66.0)	185 (35.9)	72 (20.3)
ARIA-H	95 (59.7)	134 (26.0)	62 (17.5)
Microhemorrhage	68 (42.8)	85 (16.5)	44 (12.4)
Superficial siderosis	55 (34.6)	74 (14.4)	22 (6.2)
Macrohemorrhage	0	1 (0.2)	2 (0.6)
Discontinued treatment due to ARIA	29 (18.2)	26 (5.0)	9 (2.5)

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ApoE, apolipoprotein E; ARIA, amyloid-related imaging abnormality; ARIA-E, ARIA-edema; ARIA-H, ARIA-microhemorrhage or superficial siderosis.

For participants with ARIA, radiographic severity and symptomatic status were generally similar regardless of ApoE ε4 genotype

	Aducanumab 10 mg/kg		
	ApoE ε4 homozygote (N=159)	**ApoE ε4 heterozygote (N=515)**	**ApoE ε4 non-carrier (N=355)**
Number of subjects with ARIA-E	105	185	72
Radiographic severity			
Mild	24 (22.9)	63 (34.1)	22 (30.6)
Moderate	65 (61.9)	102 (55.1)	42 (58.3)
Severe	16 (15.2)	20 (10.8)	8 (11.1)
Symptomatic status			
Asymptomatic	82 (78.1)	131 (70.8)	55 (76.4)
Symptomatic	23 (21.9)	54 (29.2)	17 (23.6)
Serious ARIA-E events	2/159 (1.3)	5/515 (1.0)	6/355 (1.7)

Aducanumab is only authorized in USA, UAE and Qatar.
ApoE, apolipoprotein E; ARIA, amyloid-related imaging abnormality; ARIA-E, ARIA-edema; ARIA-H, ARIA-microhemorrhage or superficial siderosis.

Safety data collection and risk evaluation will continue in post-marketing settings

Safety data collection

- Enhanced pharmacovigilance for ARIA, including specific data collection and ongoing analyses
- Clinical Studies (EMBARK, ENVISION)
- Real-world data, including ICARE AD

ARIA risk minimization and management

- Dose titration
- MRI monitoring (routine and ad hoc)
- Dose management
- Education of prescribers, radiologists, patients and caregivers

Aducanumab is only authorized in USA, UAE and Qatar.
ARIA, amyloid-related imaging abnormality; MRI, magnetic resonance imaging.

Future research and key questions

Aducanumab is only authorized in USA, UAE and Qatar.

Future research questions

Long term outcomes of treatment

- The **long-term outcomes of aducanumab treatment** are currently being investigated in the Phase 3b study EMBARK[1]

Real-world data generation

- Real-world data generation will further inform **duration of treatment, patient selection, assessment of disease progression and measuring clinically meaningful change**
- ICARE AD-US is collecting longitudinal clinical, imaging, and pharmacoeconomic data to evaluate the safety and effectiveness of aducanumab in **real-world clinical practice**[2]
- ENVISION, a Phase 4 confirmatory study, will begin patient screening May 2022[3]
- ICARE-AD and ENVISION aim to enroll 16% and 18%, respectively, of its US participants from Black/African American and Latinx population.

Promising anti-Aβ monoclonal antibodies under development

- Other promising anti-Aβ monoclonal antibodies in **Phase 3 development that demonstrate robust target engagement**
- Study population includes those with early Alzheimer's disease (MCI due to Alzheimer's disease and mild Alzheimer's disease) and in preclinical stages

Generation of new research hypotheses

- As more is known about the underlying pathology of Alzheimer's disease, it is expected that **new research hypotheses and drug targets will emerge**
- Potential for anti-Aβ monoclonal antibodies to be **used in to target amyloid accumulation** (e.g., Down's syndrome)

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Aβ, amyloid beta.
1. ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT04241068. Accessed February 23, 2022; 2. Galvin J, et al. Data presented at AAIC 2021; 3. Update on the Phase 4 ENVISION Confirmatory Study of ADUHELM [Press Release]. Available at https://investors.biogen.com/news-releases/news-release-details/update-phase-4-envision-confirmatory-study-aduhelmr. Accessed March 2022;

Acknowledgments

We thank the Alzheimer’s disease community, all the patients and their family members participating in the aducanumab studies, as well as the investigators and their staff conducting these studies

Available Resources

ARIA

Salloway S, et al.

Amyloid related imaging abnormalities in 2 Phase 3 studies evaluating Aducanumab in patients with early Alzheimer's disease.

JAMA Neurol. 2022; 79(1):13–21

Population/PK-PD model

Kandadi Muralidharan K, et al.

Population pharmacokinetics and standard uptake value ratio of aducanumab, an amyloid plaque–removing agent, in patients with Alzheimer's disease.

CPT Pharmacometrics Syst Pharmacol. 2022; 11(1):7-19

Phase 3 Clinical Trials

Budd Haeberlein S, et al.

Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease.

J Prev Alz Disease. 2022; Published online