Updates on the Treatment of Alzheimer's Disease: Focus on Anti-amyloid Therapies

2021-11-03 |

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Advocate Health Care®

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Disclosures

- Consultant for Novartis
- Research Support from: AbbVie, Biogen, Eisai, Lilly, Roche, Suven, Alzheimer's Association, NIA

- Investments: None to disclose

- Boards: None

- Speakers' bureau: Biogen (but not for therapeutics)

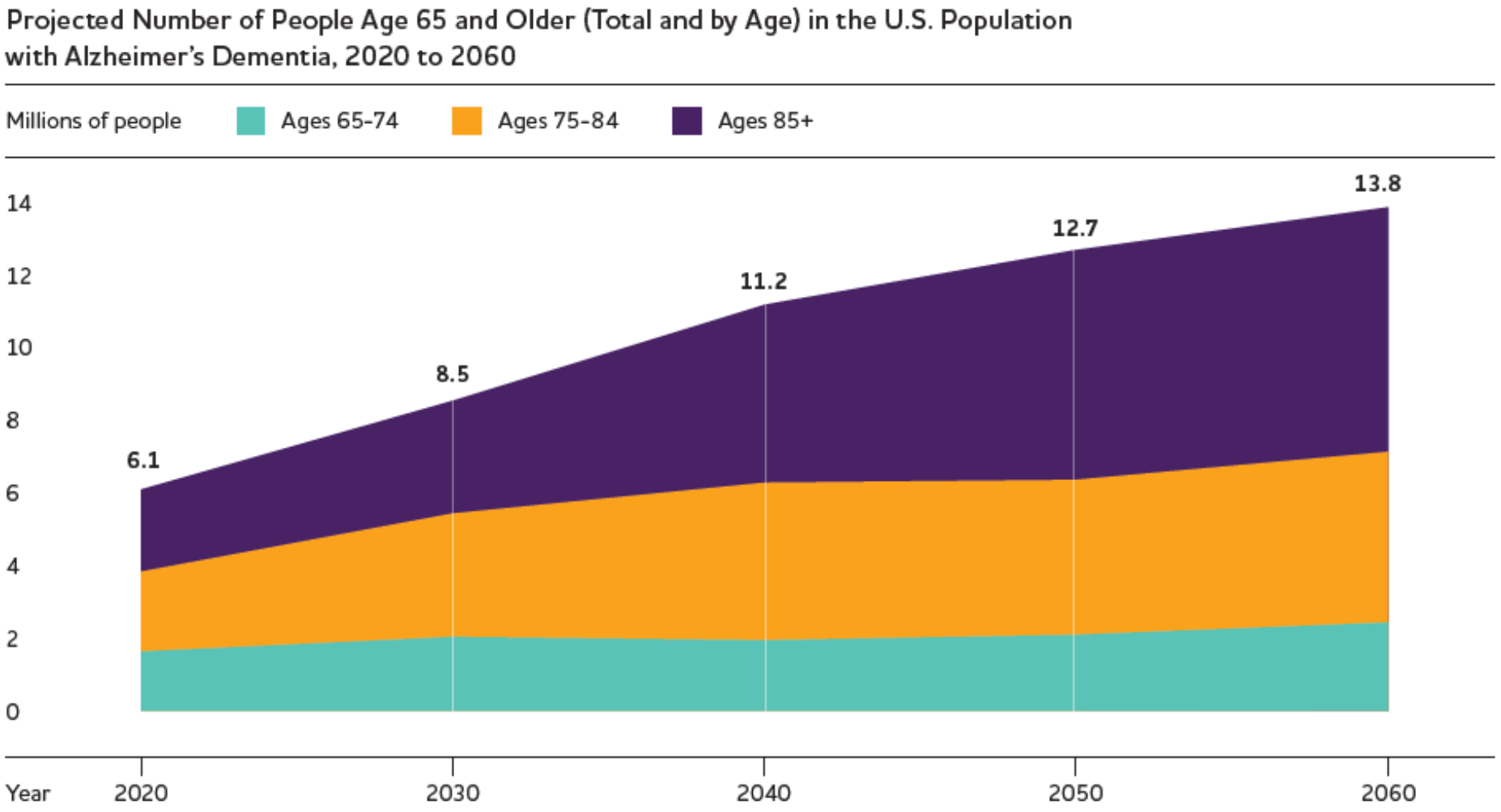
Alzheimer's Disease Burden

The **BURDEN** is **LARGE**

- **5.8 million with Alzheimer's in 2020**
- **$259 billion costs in 2017**
- **5th leading cause of death among Americans aged 65 and older**
- **AD results in memory loss, changes in behavior and loss of functional independence**
- **Patients become completely dependent as the disease advances**
- **There is no treatment that alters the disease course**

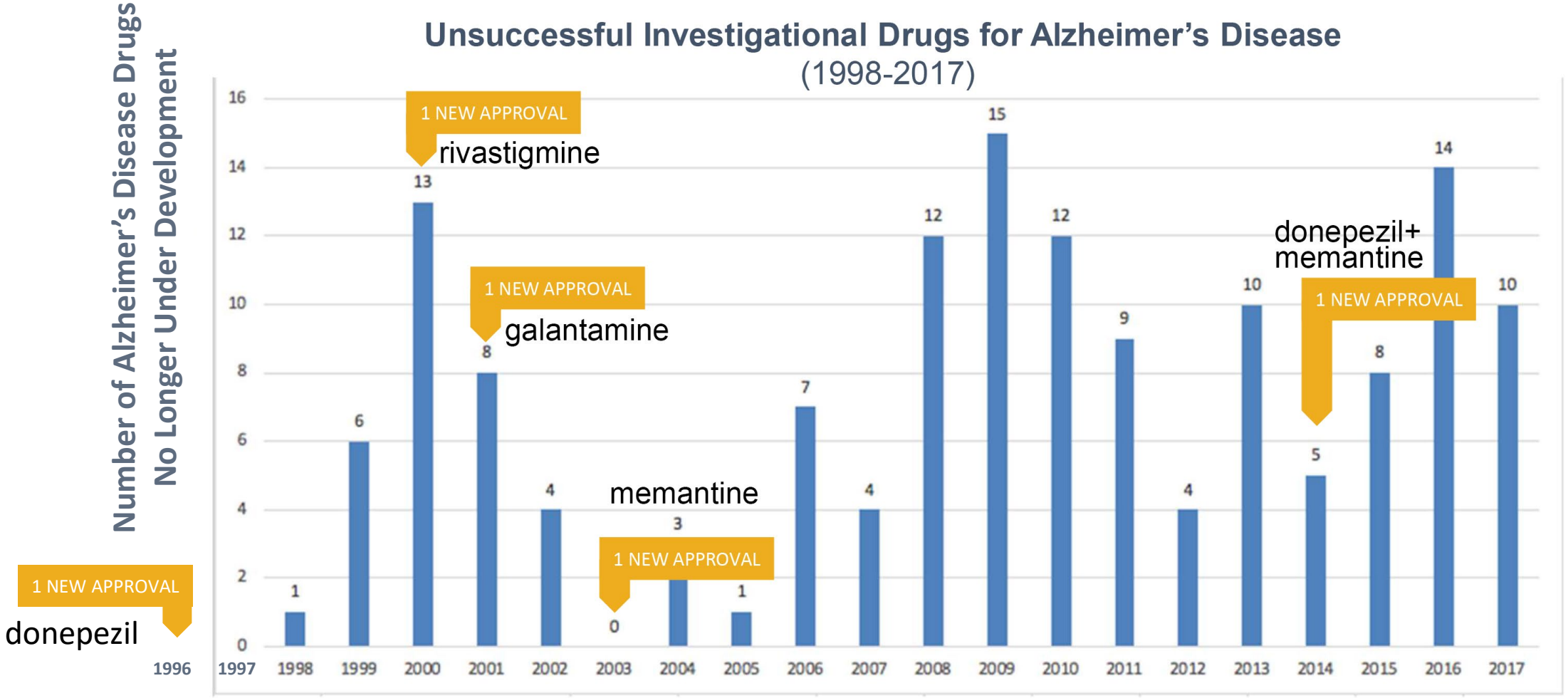
Hurd et al. N Engl J Med. 2013
MMWR Morb Mortal Wkly Rep. 2017
Alz. Dis. Facts and Figures, Alzheimer's & Dementia (2017)

U.S. Alzheimer's disease projections



Alzheimer's Assoc., Alz & Dement, 2021

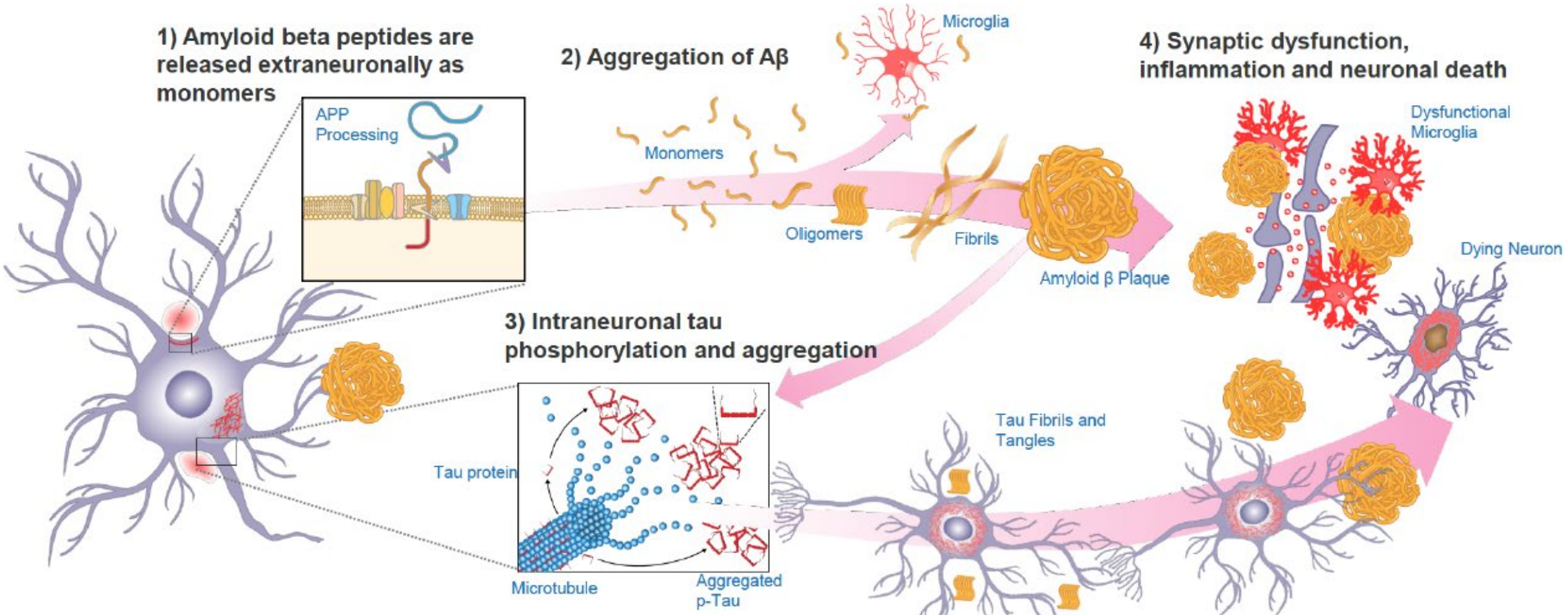
Results



146 Total Unsuccessful Drugs | **4** Total Approved Medicines

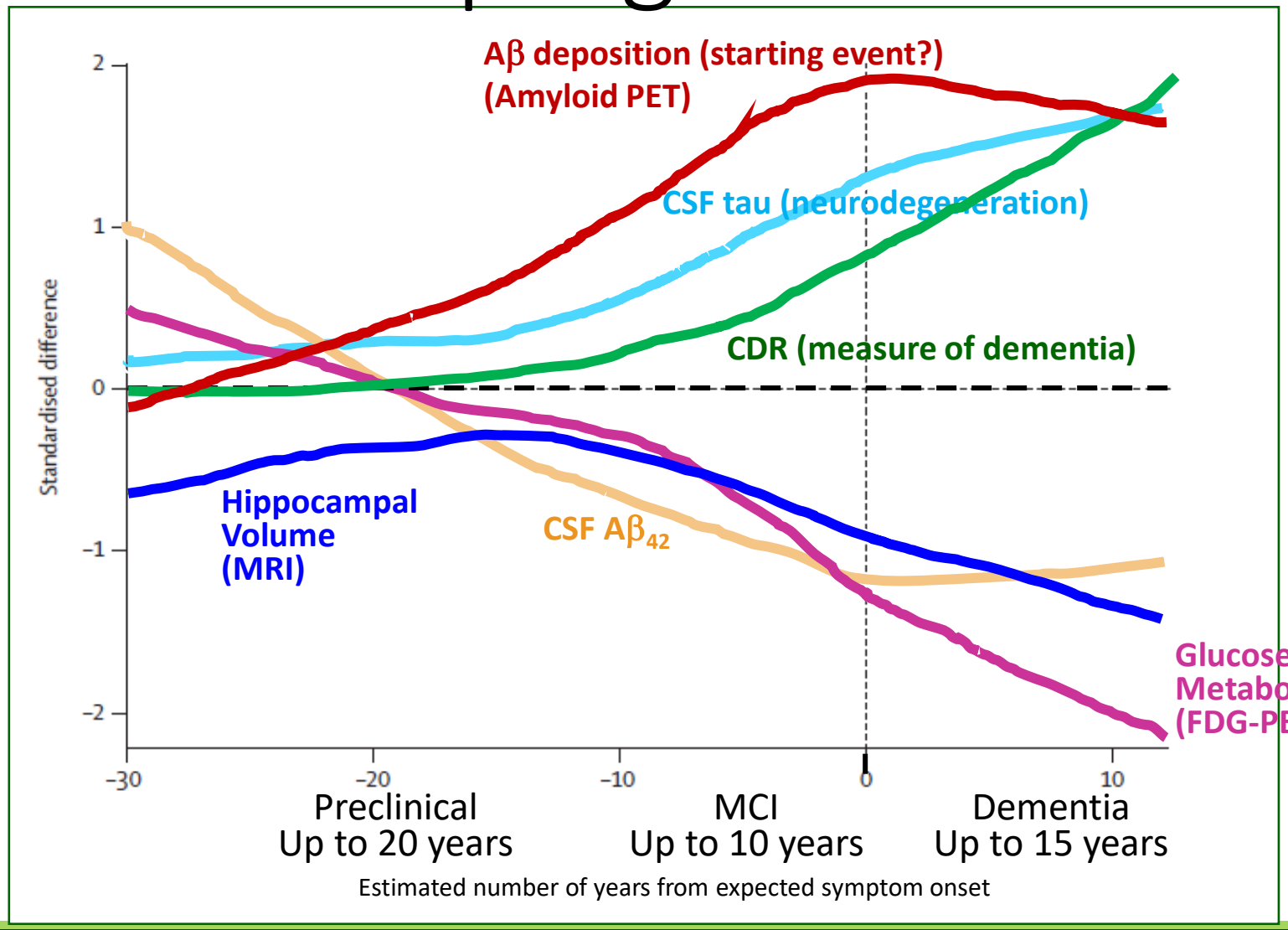
Source: PhRMA analysis of Adis R&D Insight Database, 25 January 2018

The Two Pathological Hallmarks of Alzheimer's Disease in the Brain Are Aβ Plaques and Neurofibrillary Tangles



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

Biomarker progression in AD



Adapted from Jack et al., Lancet Neurology, 2013

CLINICAL DEMENTIA RATING (CDR™):	0	0.5	1	2	3

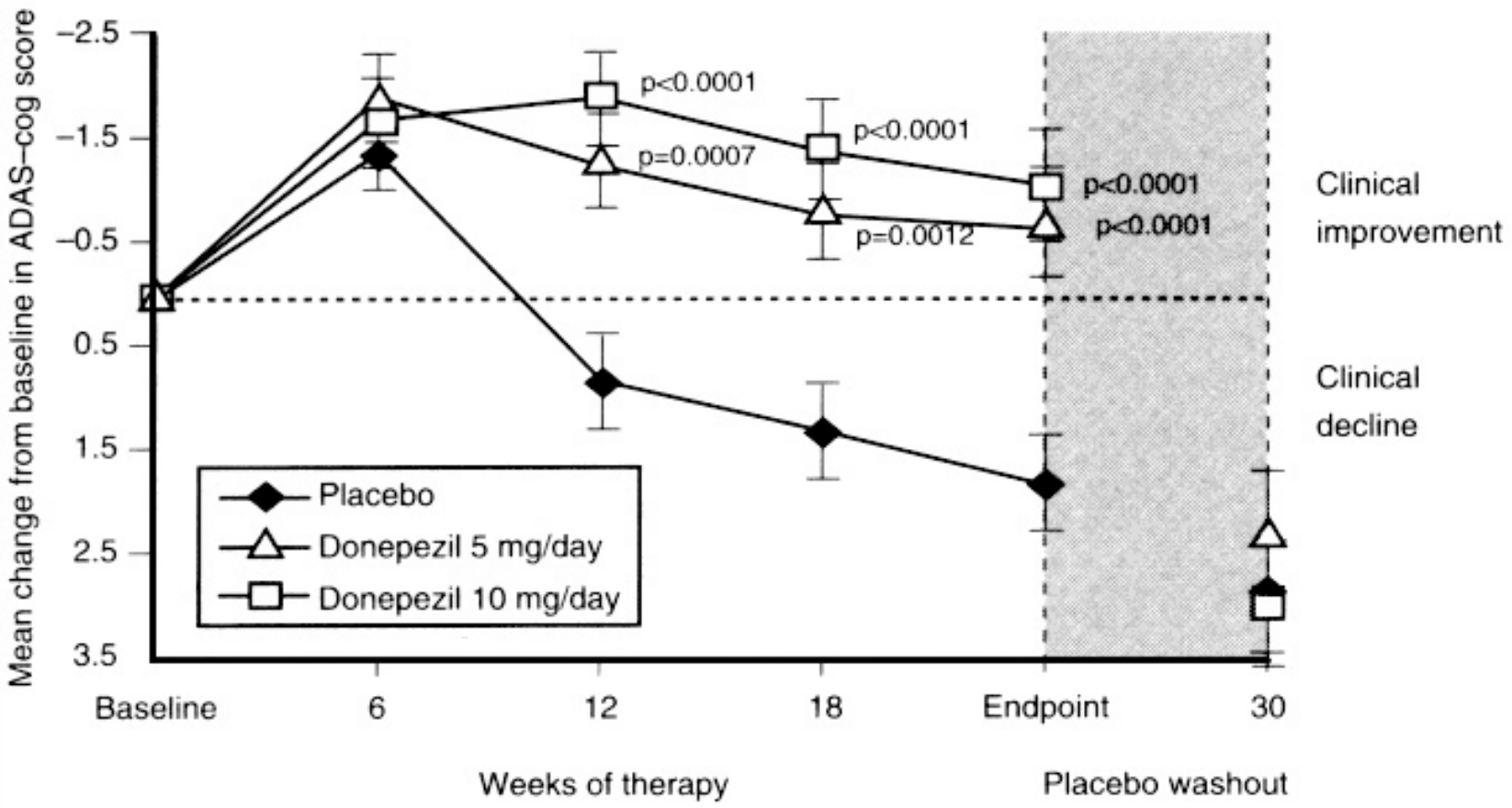
Global vs. Sum of Boxes Scores

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
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 relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a 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 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

Current Alzheimer's Disease Treatments

- Approved therapies
  - Cholinesterase inhibitors (donepezil, galantamine, rivastigmine)
  - NMDA antagonists (memantine)
- Modest effect on cognitive symptoms
- Approved for mild, moderate and severe dementia due to AD, but not MCI due to AD
- No effects on the underling brain pathology or disease course

Donepezil in mild to moderate AD: ADAS-Cog

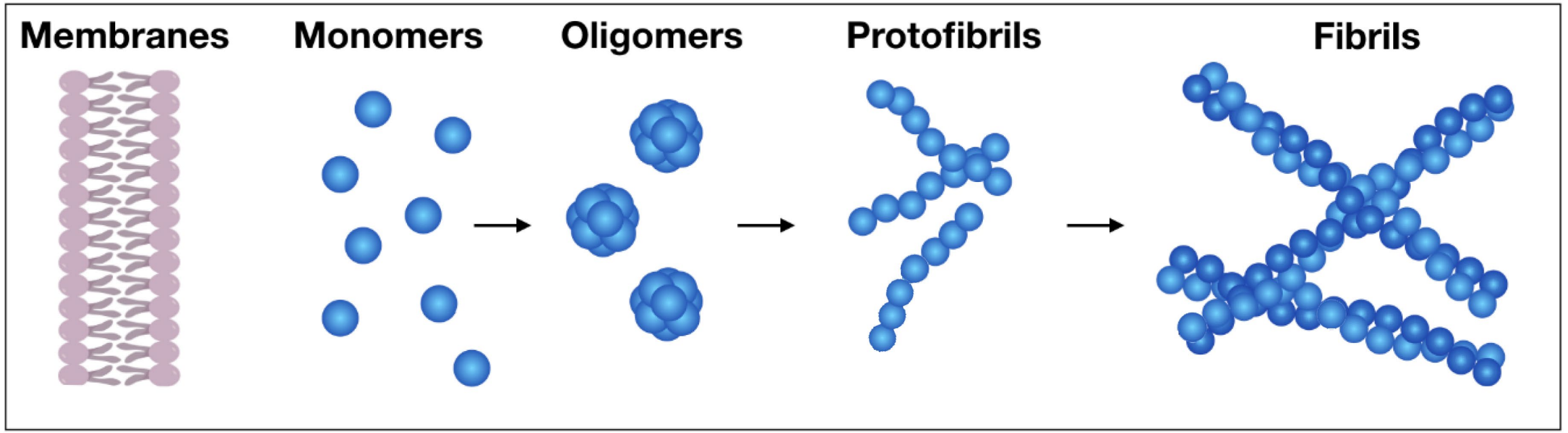


Rogers et al., Neurology, 1998

Anti-amyloid therapy potential

- Accumulation of amyloid may be the initiating factor that leads to Alzheimer's Disease.
- Removal of amyloid may interrupt this pathologic cascade.
- Early initiation of therapy before extensive neurodegeneration has taken place may be more successful

β-Amyloid aggregation pathway



- Aducanumab is a human IgG1 monoclonal antibody that binds aggregated forms of β-amyloid (oligomers, fibrils and plaques)
- Lecanemab (BAN2401) is a humanized IgG1 monoclonal antibody that binds to soluble Aβ aggregates (oligomers and protofibrils)
- Donanemab humanized IgG1 antibody directed at an N-terminal pyroglutamate Aβ epitope that is present only in established plaques

ARTICLE

doi:10.1038/nature19323

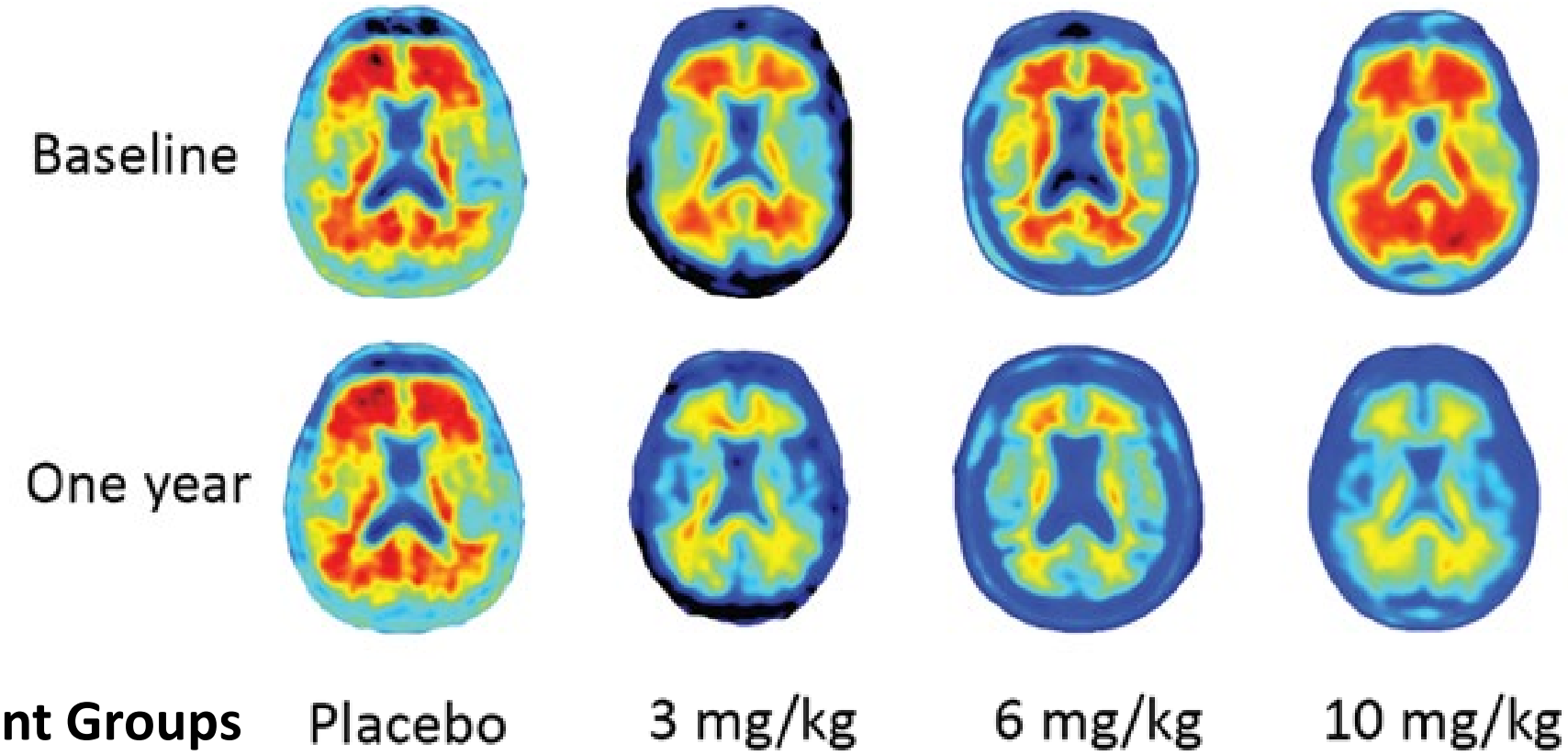
The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

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]§

Alzheimer's disease (AD) is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against Aβ to trigger its clearance or mitigate its neurotoxicity has so far been unsuccessful. Here we report the generation of aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ. In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.

Sevigny et al., Nature, 2016

Aducanumab: Amyloid Scan Results: Phase 1b: 103



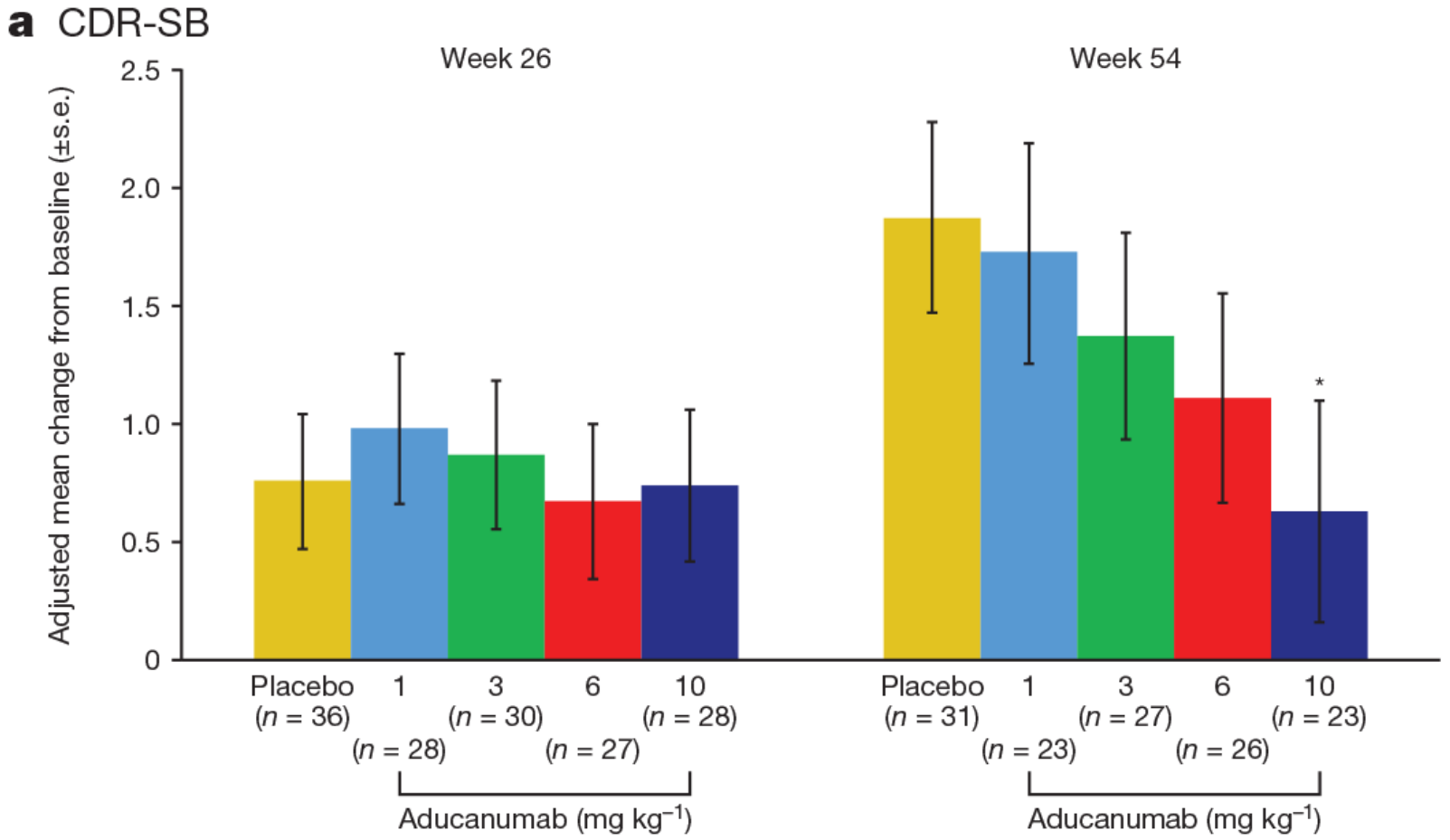
Sevigny et al., Nature, 2016

Aducanumab: Clinical Dementia Rating Scale: Phase 1b: 103

CDR

- Orientation
- Memory
- Judgment & Problem Solving
- Community Affairs
- Home and Hobbies
- Personal Care

- Normal = 0
- Higher numbers = worse



Dose-response $P < 0.05$ at week 54 based on a linear contrast test

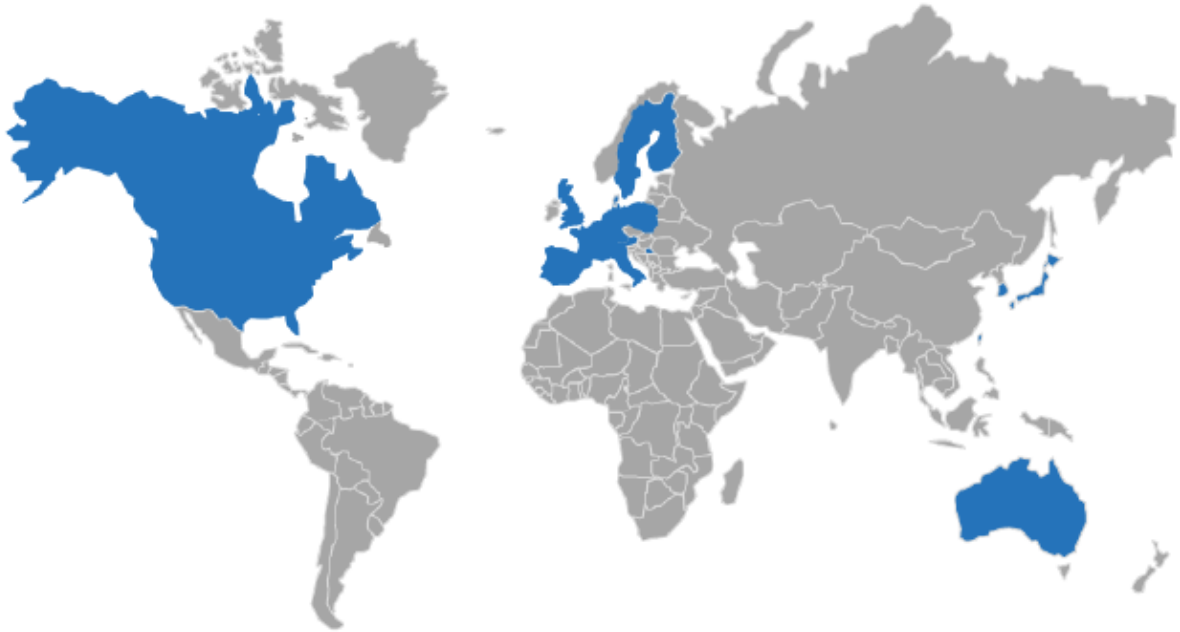
Sevigny et al., Nature, 2016

Aducanumab Phase 3 Trial Design

Studies 301 and 302

Engage and Emerge

Studies	Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
Geography/ Sample size	3285 patients at 348 sites in 20 countries
Population	• Early Alzheimer's disease (MCI due to Alzheimer's disease + mild Alzheimer's disease dementia) – MMSE 24-30, CDR-G 0.5, RBANS ≤ 85, with confirmed amyloid pathology
Doses	• Two dosing regimens (low and high) and placebo; randomized 1:1:1
Primary endpoint	• CDR-SB at 18 months
Other endpoints	• Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI • Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers



Countries with active sites included:
Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

Exclusion criteria

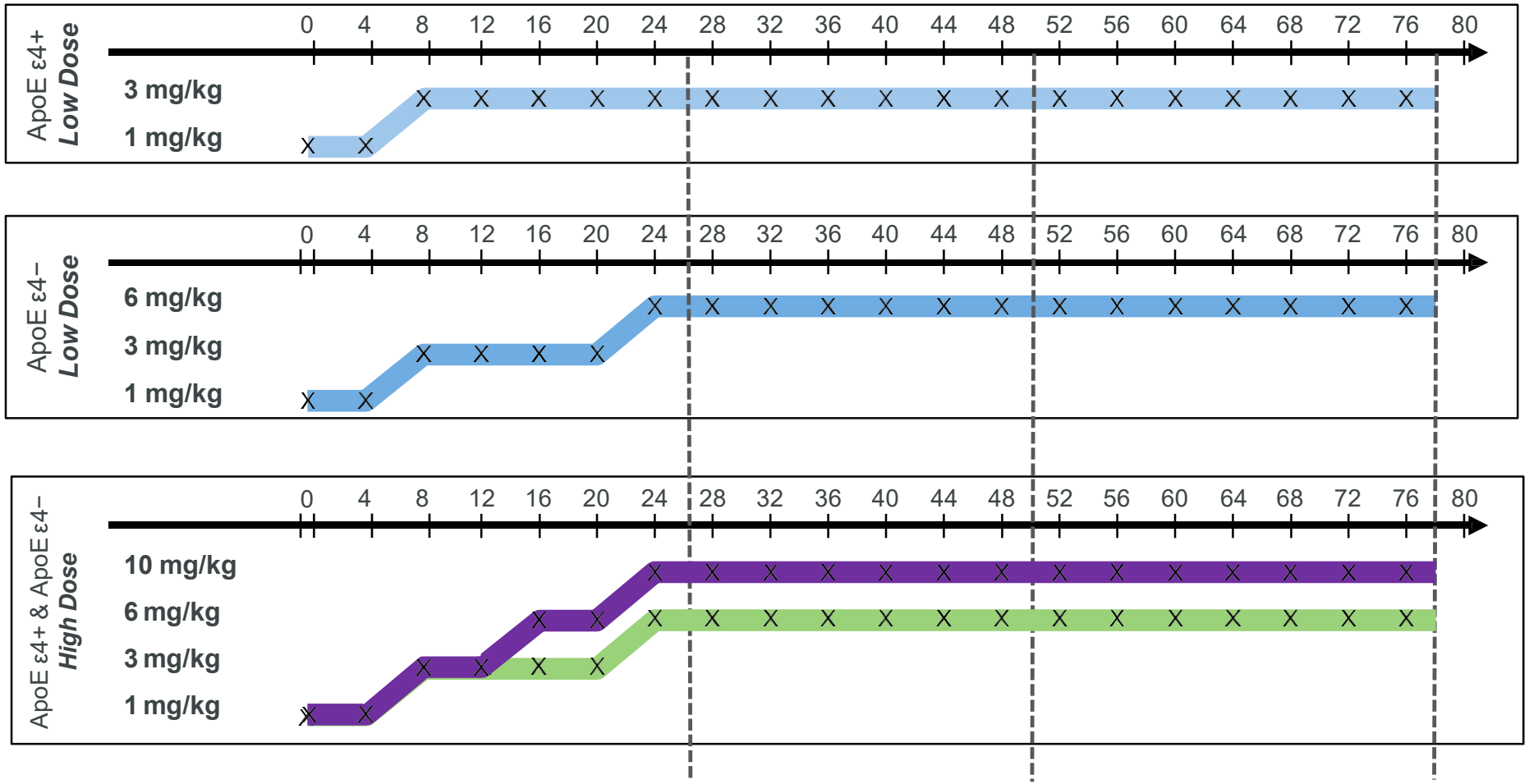
- Significant medical, neurological or psychiatric disease
- Contraindications to having a brain MRI scan
- MRI
  - Acute or subacute hemorrhage
  - Prior macrohemorrhage (>1 cm on T2* sequence) or prior subarachnoid hemorrhage unless not due to vascular lesion
  - > 4 microhemorrhages
  - Superficial siderosis
- Use of medications with platelet anti-aggregant or anti-coagulant properties except aspirin at a max dose of 325 mg/day

Baseline Demographics and Disease Characteristics

Studies 301 and 302

	Study 301				Study 302			
	Placebo N=545	Low dose N=547	High dose N=545	Total N=1647	Placebo N=548	Low dose N=543	High dose N=547	Total N=1638
Age, years, mean (SD)	69.8 (7.72)	70.4 (6.96)	70.0 (7.65)	70.1 (7.45)	70.8 (7.40)	70.6 (7.45)	70.6 (7.47)	70.7 (7.43)
Sex, female, n (%)	287 (52.7)	284 (51.9)	292 (52.6)	863 (52.4)	290 (52.9)	269 (49.5)	284 (51.9)	843 (51.5)
Race, n (%)								
Asian	55 (10.1)	55 (10.1)	65 (11.7)	175 (10.6)	47 (8.6)	39 (7.2)	42 (7.7)	128 (7.8)
White	413 (75.8)	412 (75.3)	413 (74.4)	1238 (75.2)	431 (78.6)	432 (79.6)	422 (77.1)	1285 (78.4)
Education, years, mean (SD)	14.7 (3.66)	14.6 (3.77)	14.6 (3.72)	14.6 (3.71)	14.5 (3.68)	14.5 (3.63)	14.5 (3.60)	14.5 (3.63)
AD medications used, n (%)	299 (54.9)	317 (58.0)	313 (56.4)	929 (56.4)	282 (51.5)	281 (51.7)	285 (52.1)	848 (51.8)
ApoE ε4, n (%)								
Carriers	376 (69.0)	391 (71.5)	378 (68.1)	1145 (69.5)	368 (67.2)	362 (66.7)	365 (66.7)	1095 (66.8)
Non-carriers	167 (30.6)	156 (28.5)	176 (31.7)	499 (30.3)	178 (32.5)	178 (32.8)	181 (33.1)	537 (32.8)
Clinical stage, n (%)								
MCI due to AD	443 (81.3)	440 (80.4)	442 (79.6)	1325 (80.4)	446 (81.4)	452 (83.2)	438 (80.1)	1336 (81.6)
Mild AD	102 (18.7)	107 (19.6)	113 (20.4)	322 (19.6)	102 (18.6)	91 (16.8)	109 (19.9)	302 (18.4)
CDR-SB, mean (SD)	2.40 (1.012)	2.43 (1.014)	2.40 (1.010)	2.41 (1.012)	2.47 (0.999)	2.46 (1.011)	2.51 (1.053)	2.48 (1.021)
MMSE, mean (SD)	26.4 (1.73)	26.4 (1.78)	26.4 (1.77)	26.4 (1.76)	26.4 (1.78)	26.3 (1.72)	26.3 (1.68)	26.3 (1.73)

EMERGE and ENGAGE: Initial dose regimen



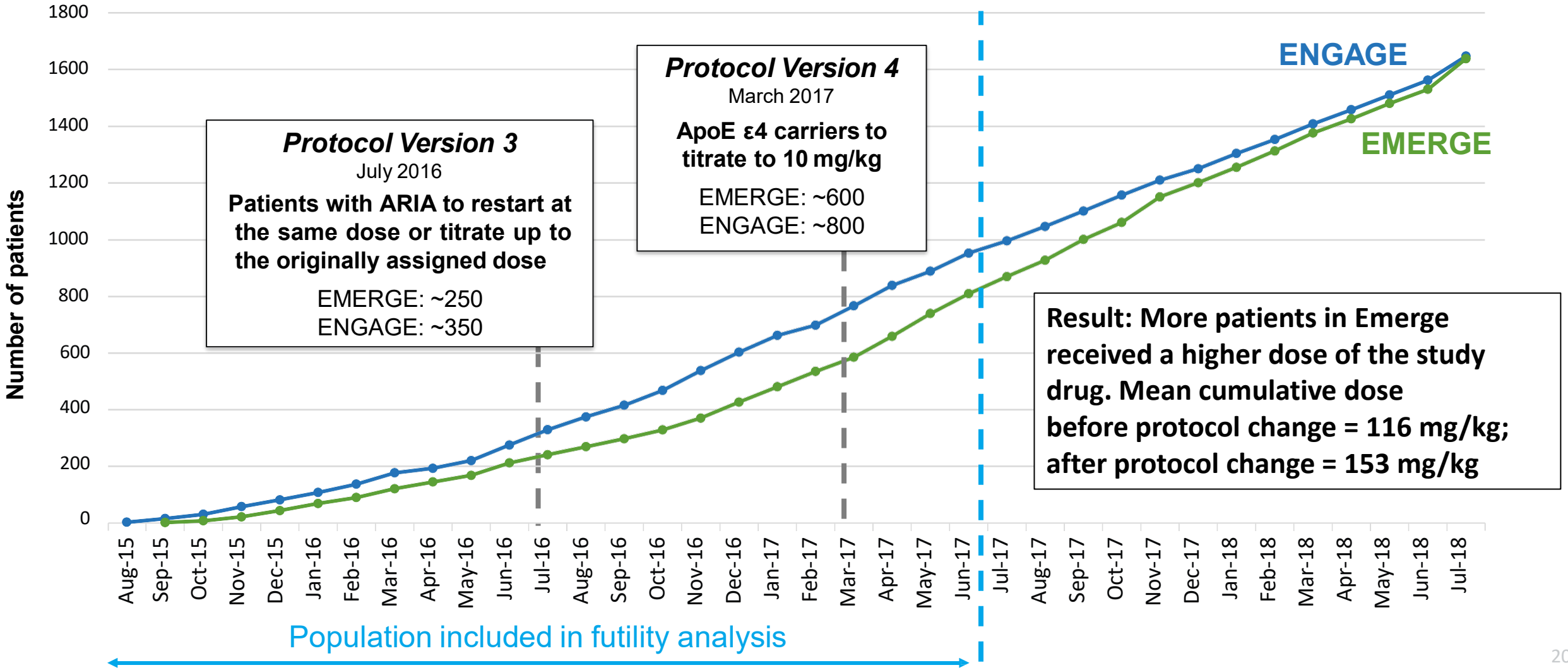
- Low dose titrated to 3 or 6 mg/kg
- Maintained throughout study

- High dose titrated to 6 or 10 mg/kg for Protocol Versions 1-3
- High dose titrated to 10 mg/kg for Protocol Version 4 and higher

Expected # of 10 mg/kg in high dose group ***by Week 26*: 1 dose** ***by Week 50*: 7 doses** ***by Week 78*: 14 doses**

ApoE, apolipoprotein E.

Enrollment and timing of key protocol amendments



ApoE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities.

Biogen presentation, CTAD 2019

An Alzheimer's Drug Trial Gave Me Hope, and Then It Ended

I was a small piece in the search to find a cure. Now I feel as if I'm getting erased, and medical science doesn't have any answers.

Stuart Bradford

By Phillip S. Gutis

March 22, 2019

212

I knew that participating in a clinical trial for an Alzheimer's drug was unlikely to help me. But it gave me hope.

- Futility analysis results announced March 21, 2019
- "Independent data monitoring committee advises aducanumab unlikely to meet primary endpoints."
- The trial was stopped… but data collection continued.

Gutis, NYT, March 22, 2019

‘Reports of My Death Are Greatly Exaggerated.’

Signed, Aducanumab (alzforum 10/24/19)

- October 22, 2019: Aducanumab resurrected
- Additional data collected after futility analysis → Full analysis
- Full analysis hits primary endpoint and secondary outcomes, in 1/2 Phase 3 trials (Emerge: 302)
- Second trial (Engage: 301) negative, but is said to show supportive data from those with adequate exposure (high dose)
- Biogen files for a biologics licensing application with the FDA

November 9, 2020: FDA advisory committee for aducanumab votes against approval, as there is no reason to favor the positive result in one phase 3 trial over the negative result in the other.

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Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019

David S. Knopman, David T. Jones, Michael D. Greicius

First published: 01 November 2020 | https://doi.org/10.1002/alz.12213 | Citations: 5

See related article here https://doi.org/10.1002/alz.12235

Alzheimer's Research & Therapy

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Viewpoint | Open Access | Published: 10 May 2021

Aducanumab produced a clinically meaningful benefit in association with amyloid lowering

Jeffrey Cummings, Paul Aisen, Cynthia Lemere, Alireza Atri, Marwan Sabbagh & Stephen Salloway

Alzheimer's Research & Therapy **13**, Article number: 98 (2021) | Cite this article

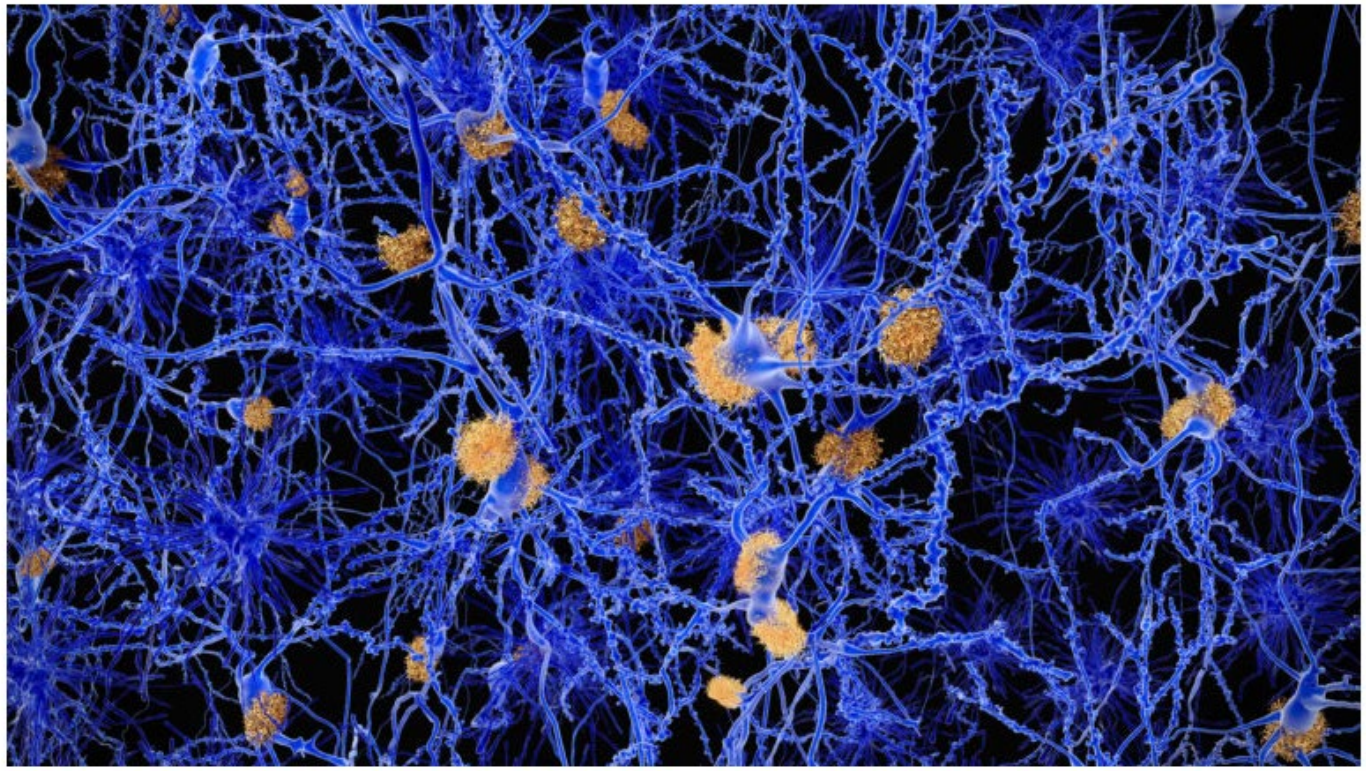
4250 Accesses | **106** Altmetric | Metrics

FIRST OPINION

If the FDA approves Biogen's Alzheimer's treatment, I won't prescribe it

By Jason Karlawish May 30, 2021

Reprints



Biogen's experimental drug, aducanumab, may clear amyloid plaque from the brain, but the company hasn't made a convincing case that it slows the progression of Alzheimer's disease.

https://www.statnews.com/2021/05/30/if-the-fda-approves-biogens-alzheimers-treatment-i-wont-prescribe-it/

FDA NEWS RELEASE

FDA Grants Accelerated Approval for Alzheimer's Drug

More Press Announcements

For Immediate Release: June 07, 2021

Today, the U.S. Food and Drug Administration approved Aduhelm (aducanumab) for the treatment of Alzheimer's, a debilitating disease affecting 6.2 million Americans. Aduhelm was approved using the accelerated approval pathway, which can be used for a drug for a serious or life-threatening illness that provides a meaningful therapeutic advantage over existing treatments. Accelerated approval can be based on the drug's effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients, with a required post-approval trial to verify that the drug provides the expected clinical benefit.

"Alzheimer's disease is a devastating illness that can have a profound impact on the lives of people diagnosed with the disease as well as their loved ones," said Patrizia Cavazzoni, M.D., director of the FDA's Center for Drug Evaluation and Research. "Currently available therapies only treat symptoms of the disease; this treatment option is the first therapy to target and affect

Content current as of:
06/07/2021

Regulated Product(s)
Drugs

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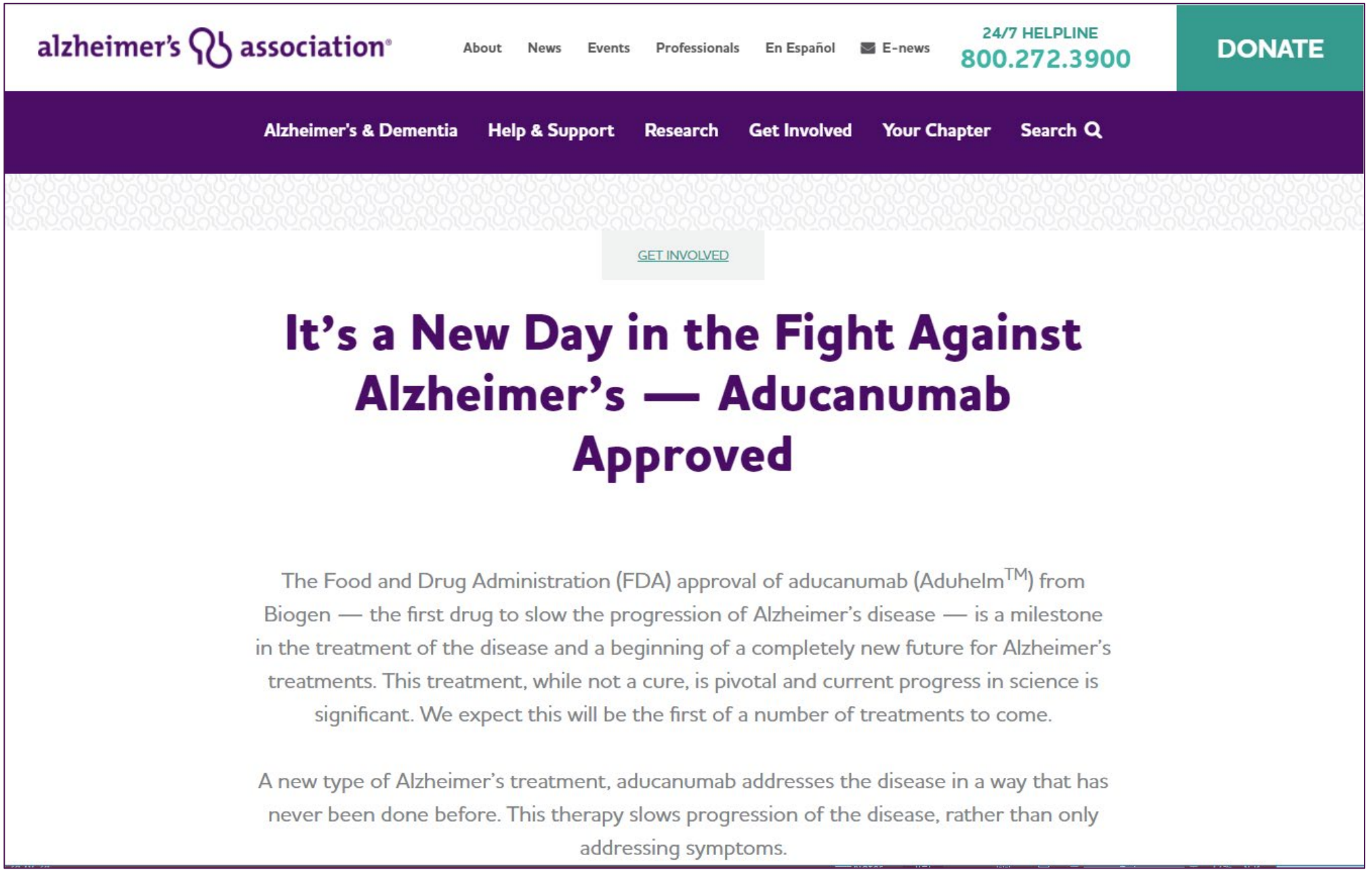

https://www.alz.org/get-involved-now/new-day

VIEWPOINT

Aducanumab, Amyloid Lowering, and Slowing of Alzheimer Disease

Stephen Salloway, MD, MS, and Jeffrey Cummings, MD, ScD

Neurology® 2021;97:543-544. doi:10.1212/WNL.0000000000012451

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VIEWPOINT

Prescribing Aducanumab in the Face of Meager Efficacy and Real Risks

David S. Knopman, MD, and Joel S. Perlmutter, MD

Neurology® 2021;97:545-547. doi:10.1212/WNL.0000000000012452

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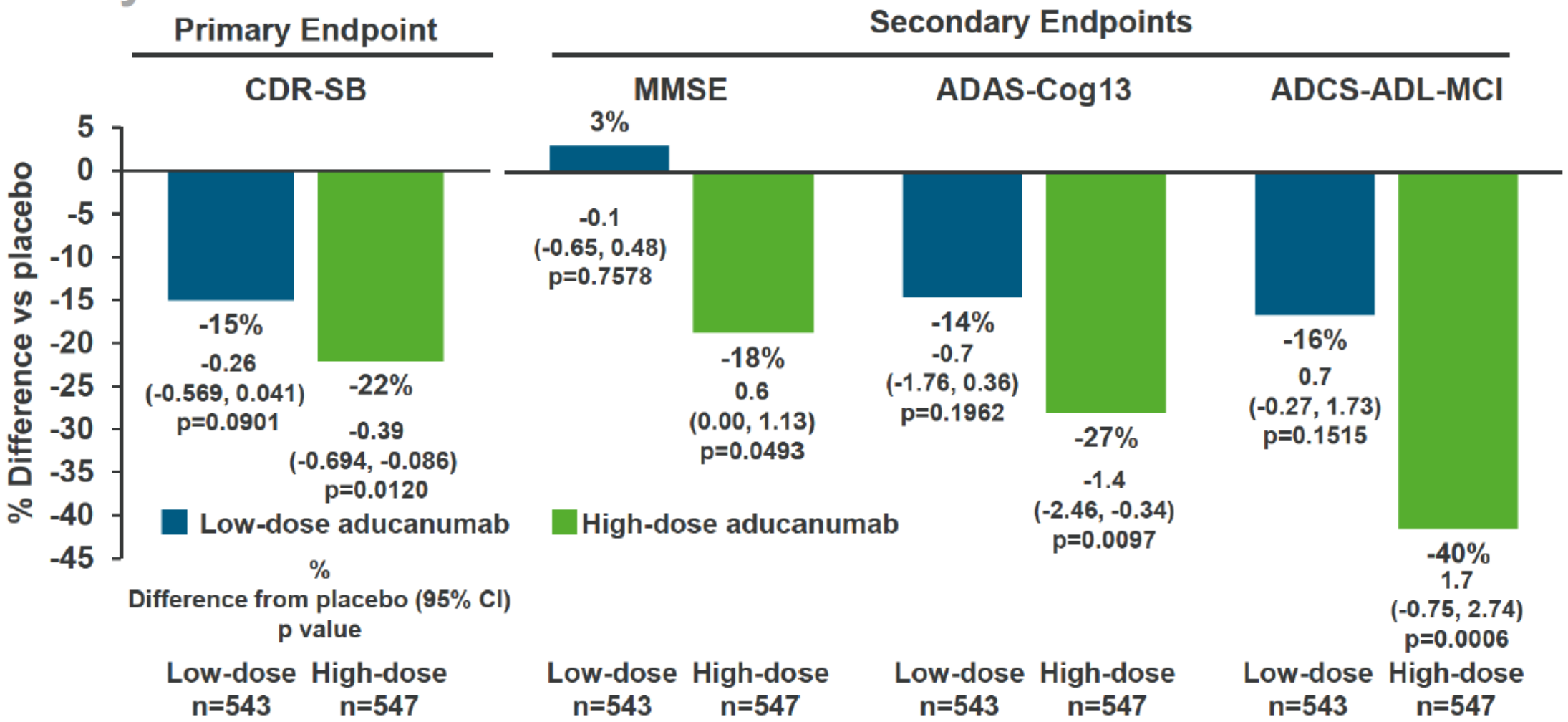
High-dose Aducanumab Met All Clinical Endpoints Assessing Cognition and Function at Week 78

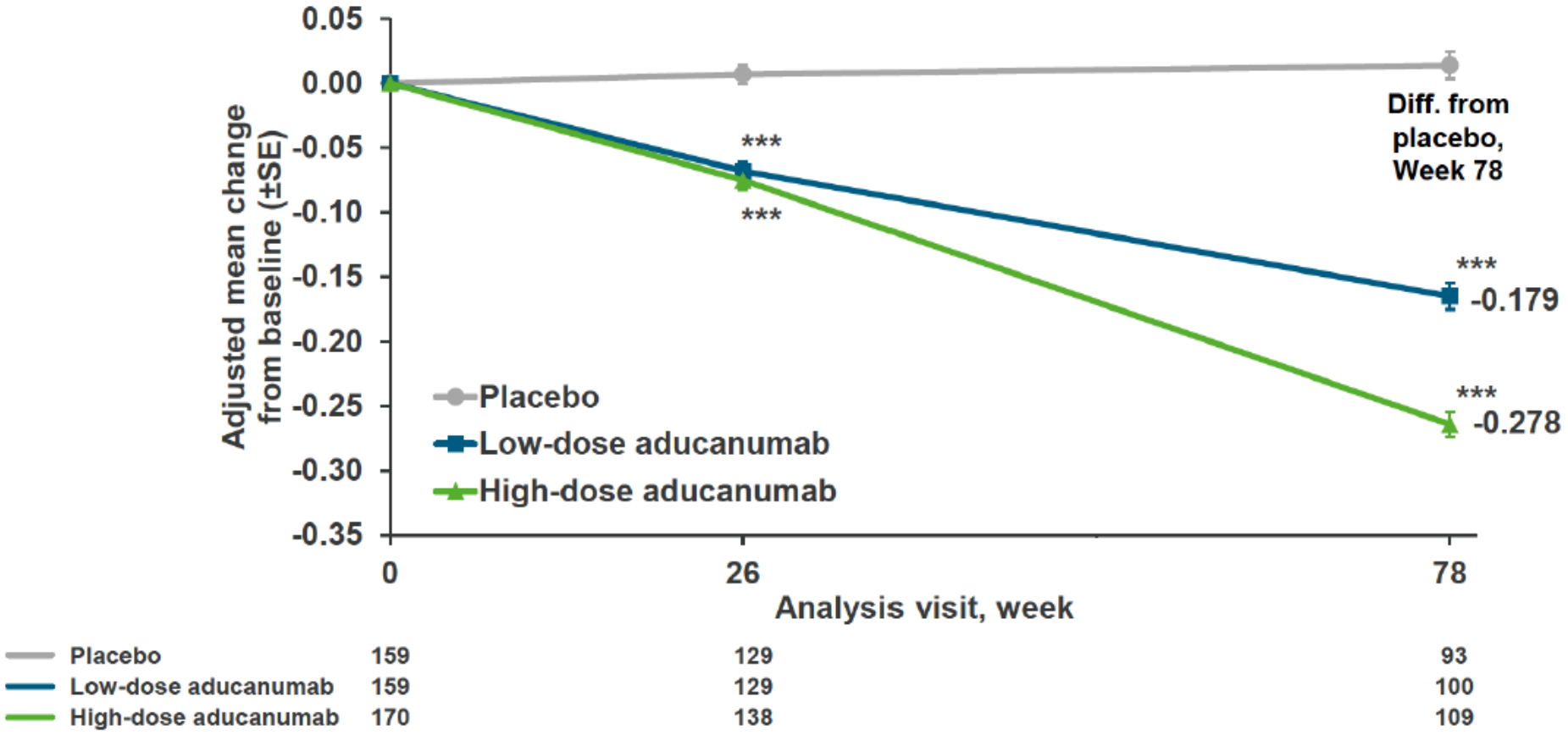
Study 302



n=numbers of randomized and dosed participants included in the analysis

Study 302 Amyloid PET Confirms Dose-Dependent Target Engagement as Demonstrated in Study 103

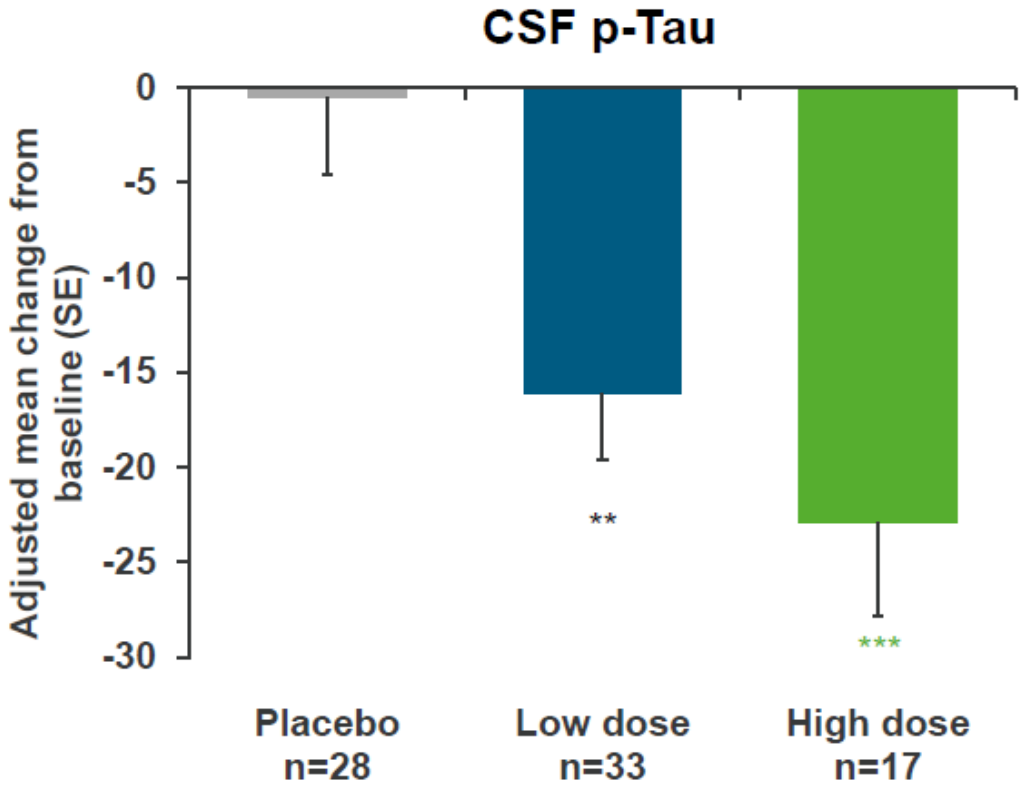
Study 302



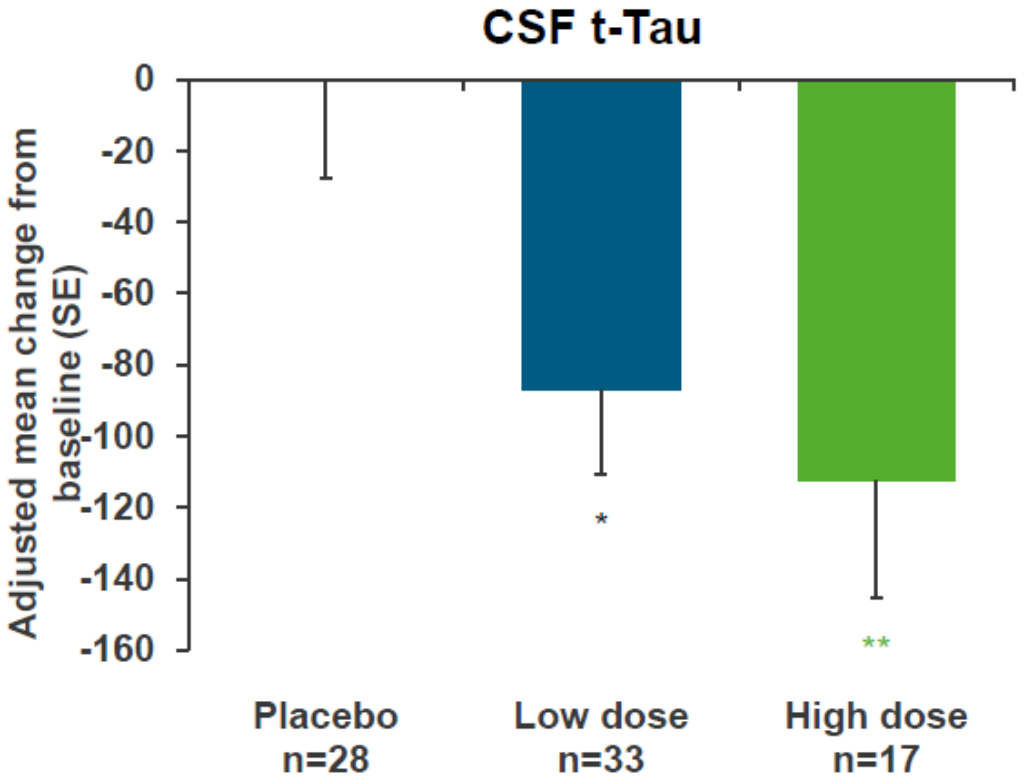
*** p<0.001 (nominal).

Study 302: Aducanumab Reduced Biomarkers of Alzheimer's Disease-specific Tau Pathophysiology and Neurodegeneration

Tau pathophysiology



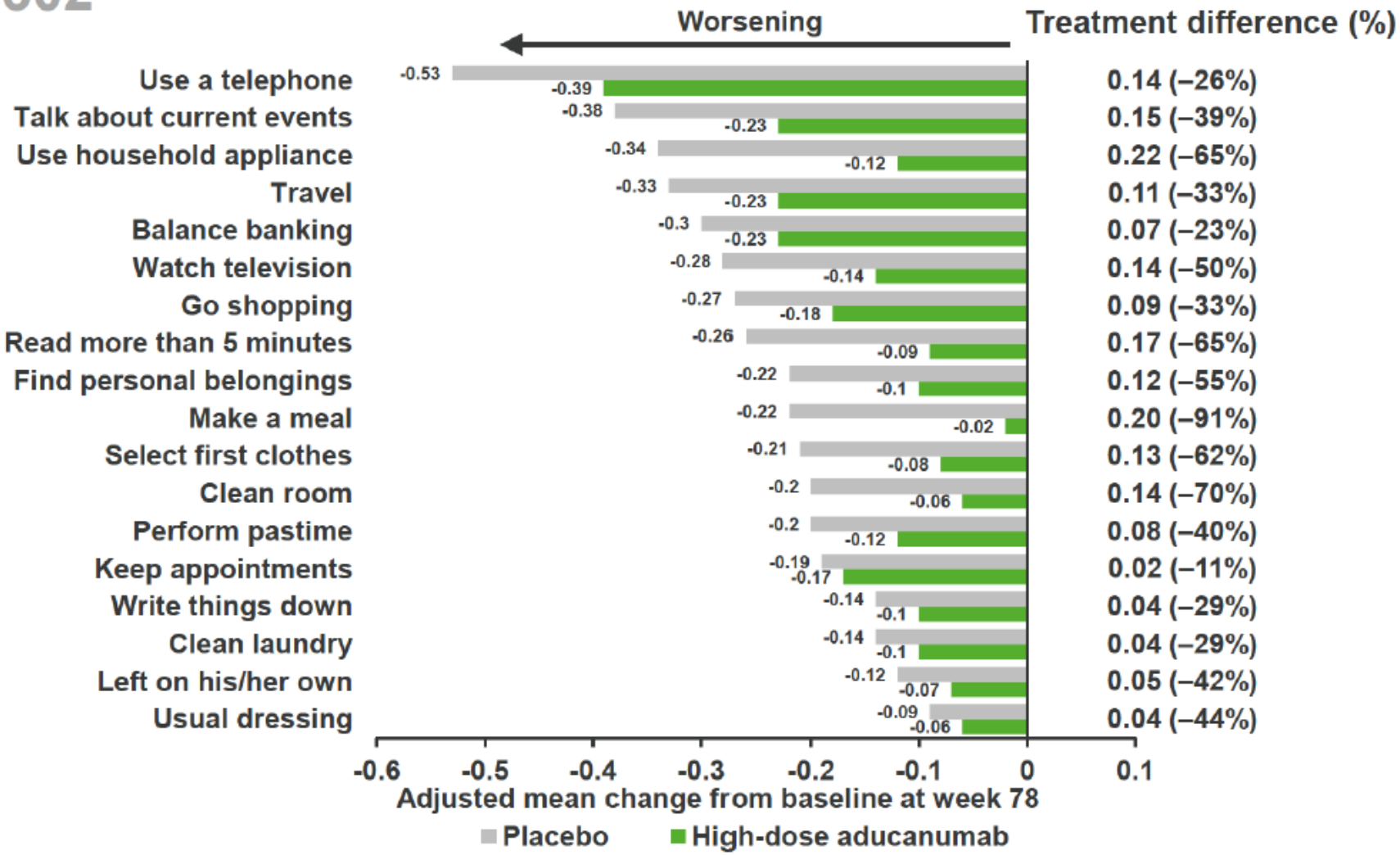
Neurodegeneration



*p<0.05, ** p<0.01 , *** p<0.001 (nominal)
n=numbers of randomized and dosed participants included in the analysis

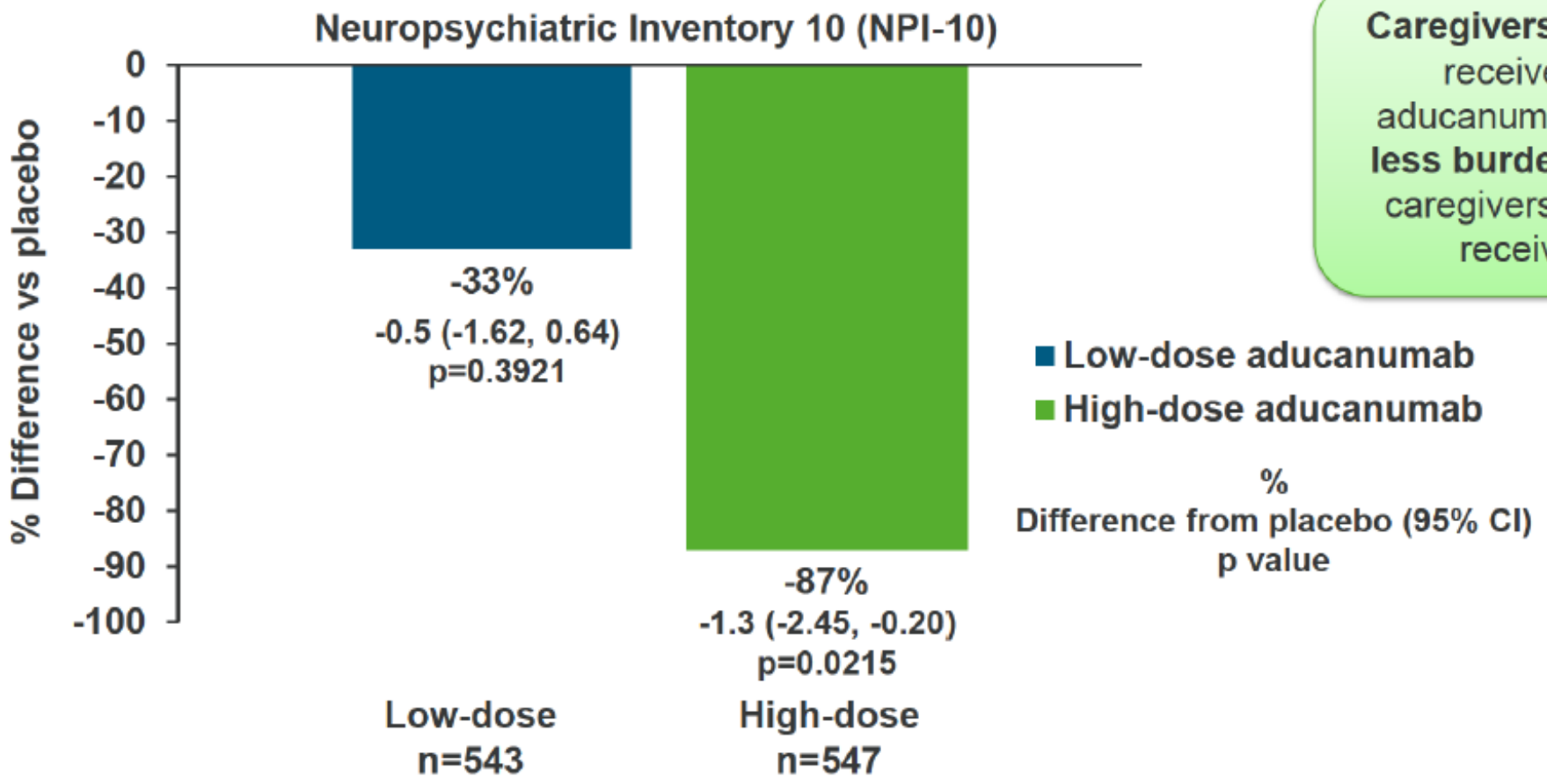
Aducanumab Reduced Functional Decline in Activities of Daily Living: ADCS-ADL-MCI

Study 302



Treatment Effect Observed in Exploratory Clinical Endpoint of NPI-10 Assessing Behavior at Week 78

Study 302



Caregivers of patients who received high-dose aducanumab reported **84% less burden** compared with caregivers of patients who received placebo

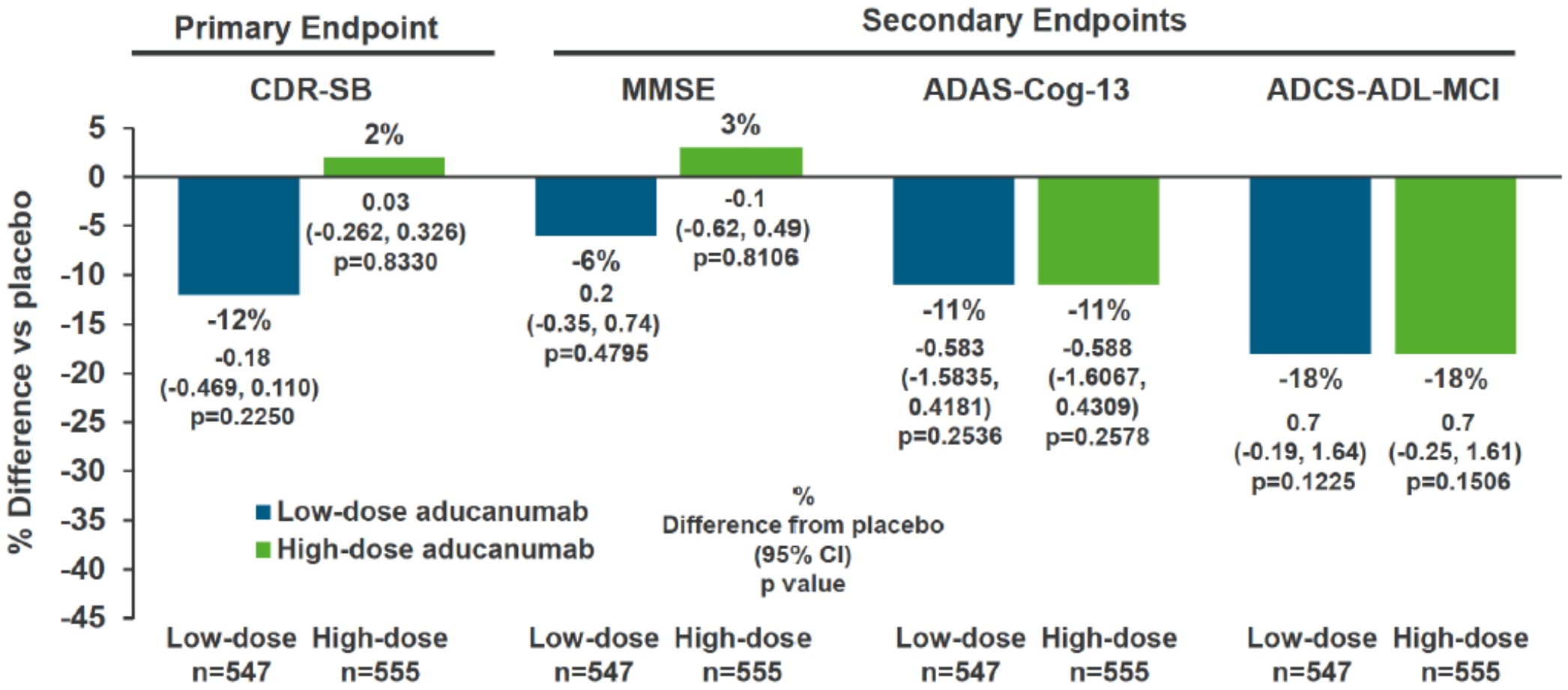
n=numbers of randomized and dosed participants included in the analysis

Summary of 302 study: Emerge

- Met its primary and secondary objectives in the high dose arm
- Intermediate effect observed in the low-dose group, indicative of a dose-response relationship
- Substantial effects on objective measures of underlying Alzheimer’s disease pathophysiology

Study Did Not Meet Primary and Secondary Clinical Endpoints

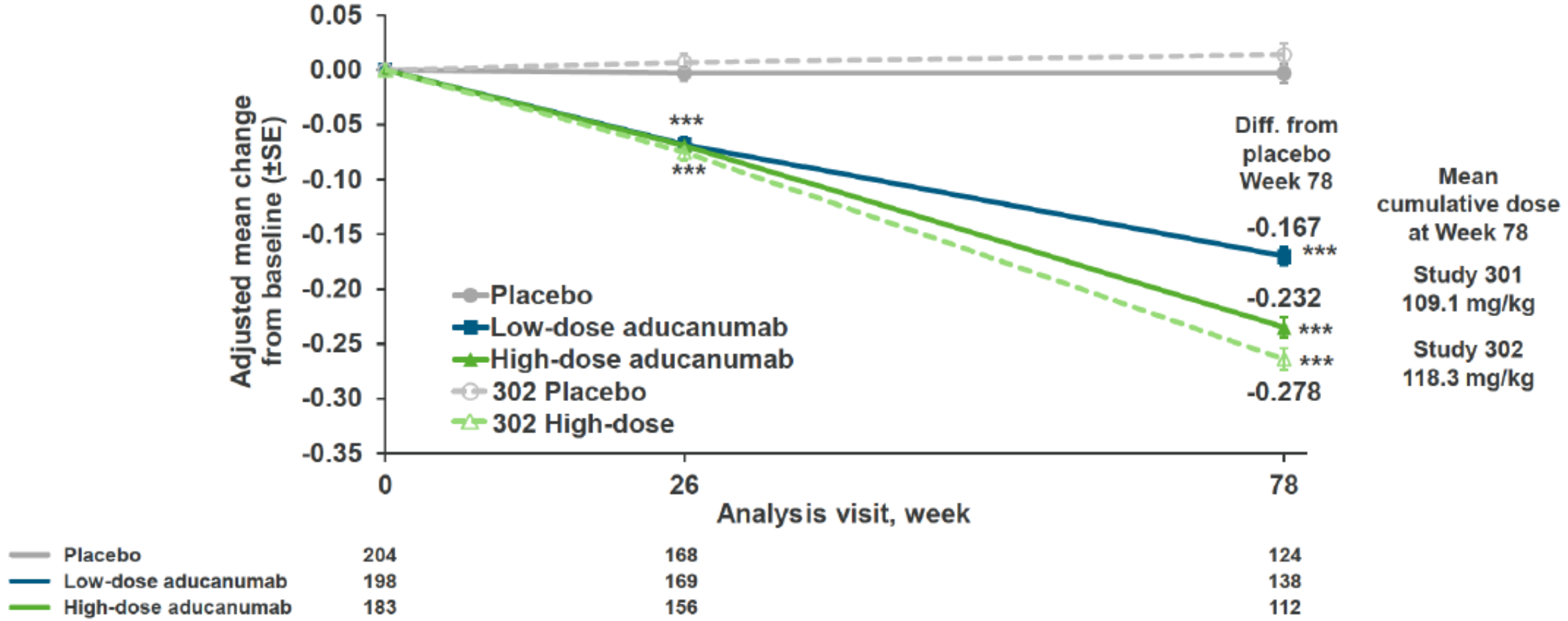
Study 301



n=numbers of randomized and dosed participants included in the analysis

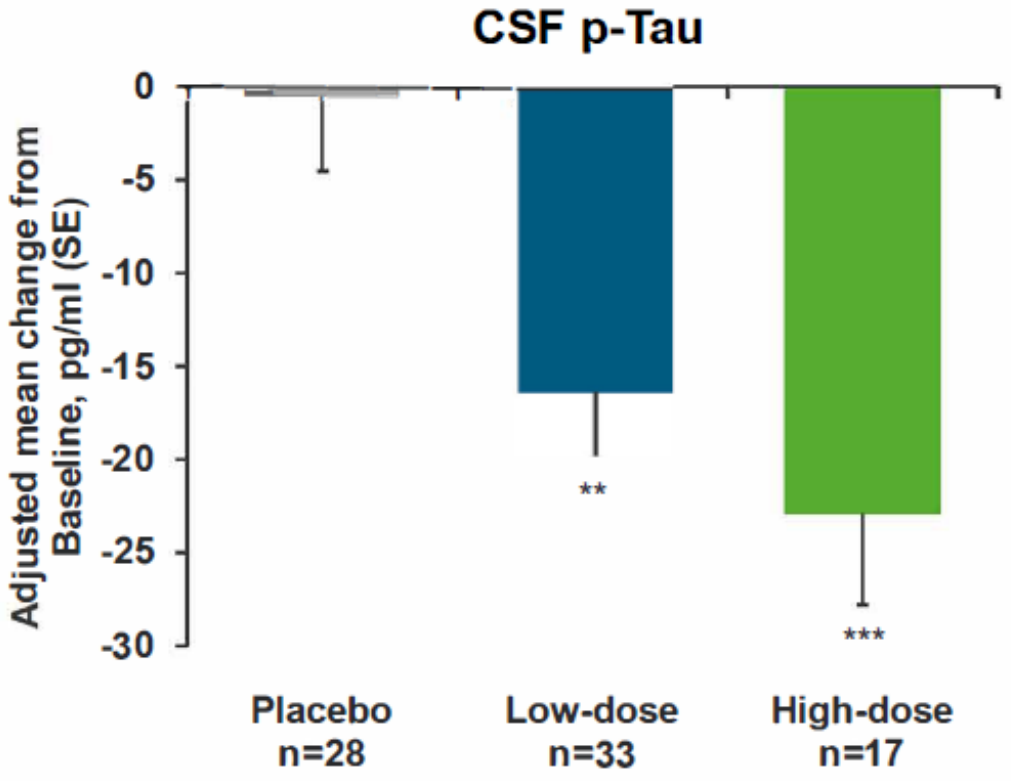
Amyloid PET Demonstrated Dose-Dependent Target Engagement With High-Dose Group Lower Than in Study 302

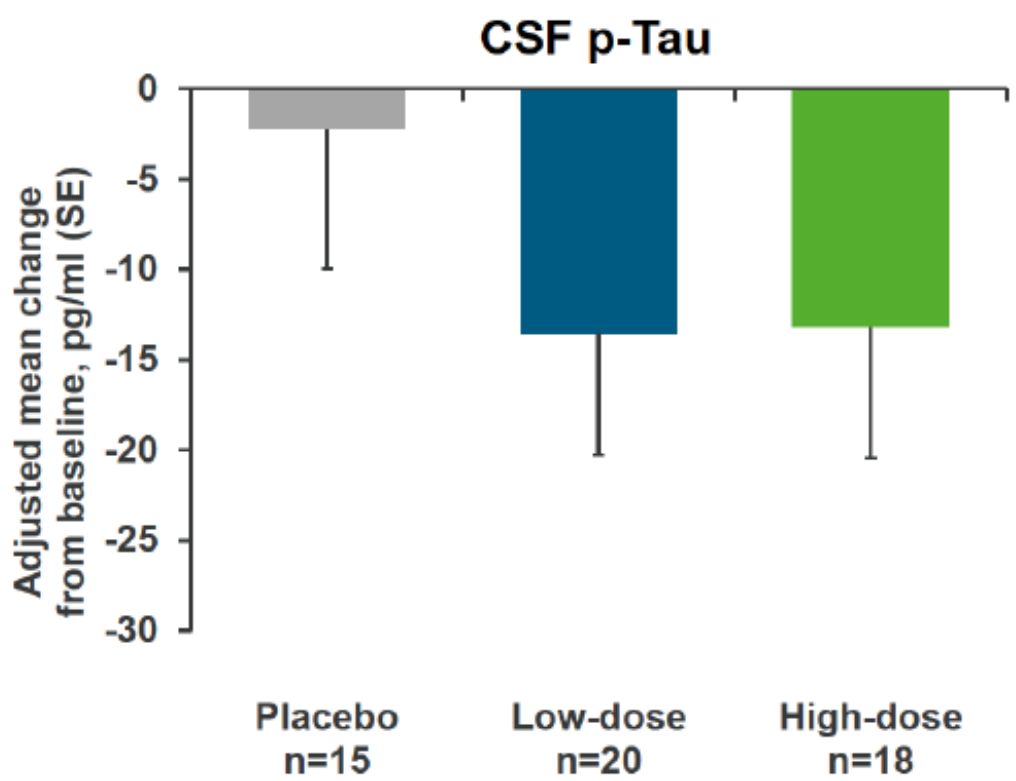
Study 301



*** p<0.001 (nominal).
n=numbers of randomized and dosed participants included in the analysis

Aducanumb effects on Biomarkers of Alzheimer's Disease-Specific Tau Pathophysiology: study 302 vs. 301



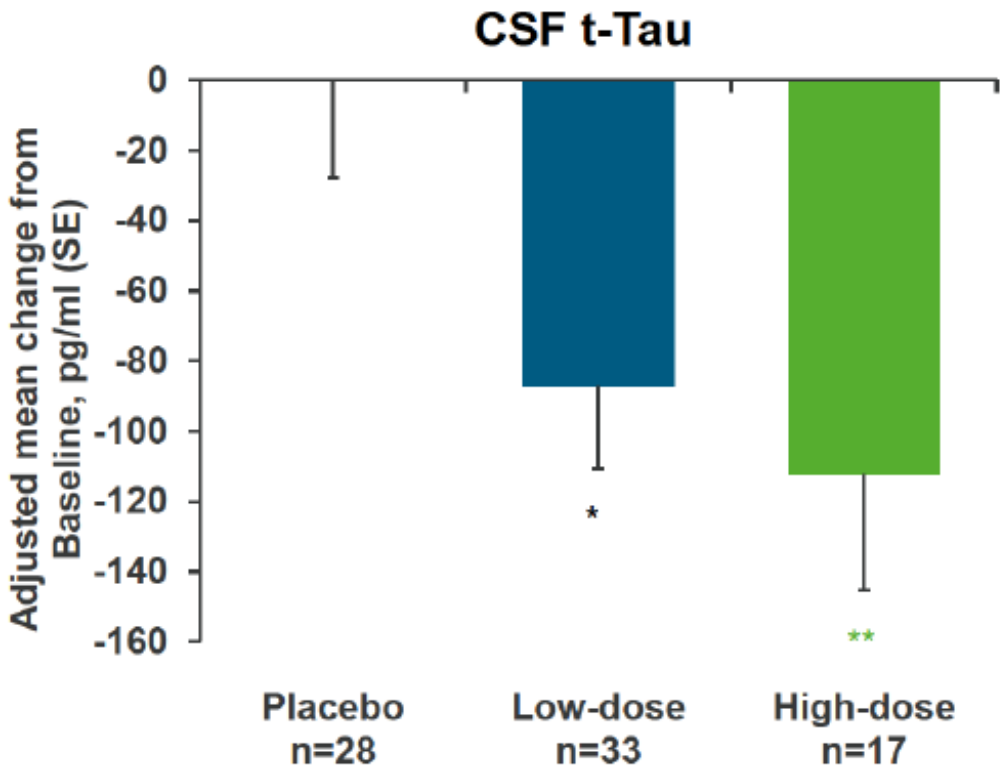


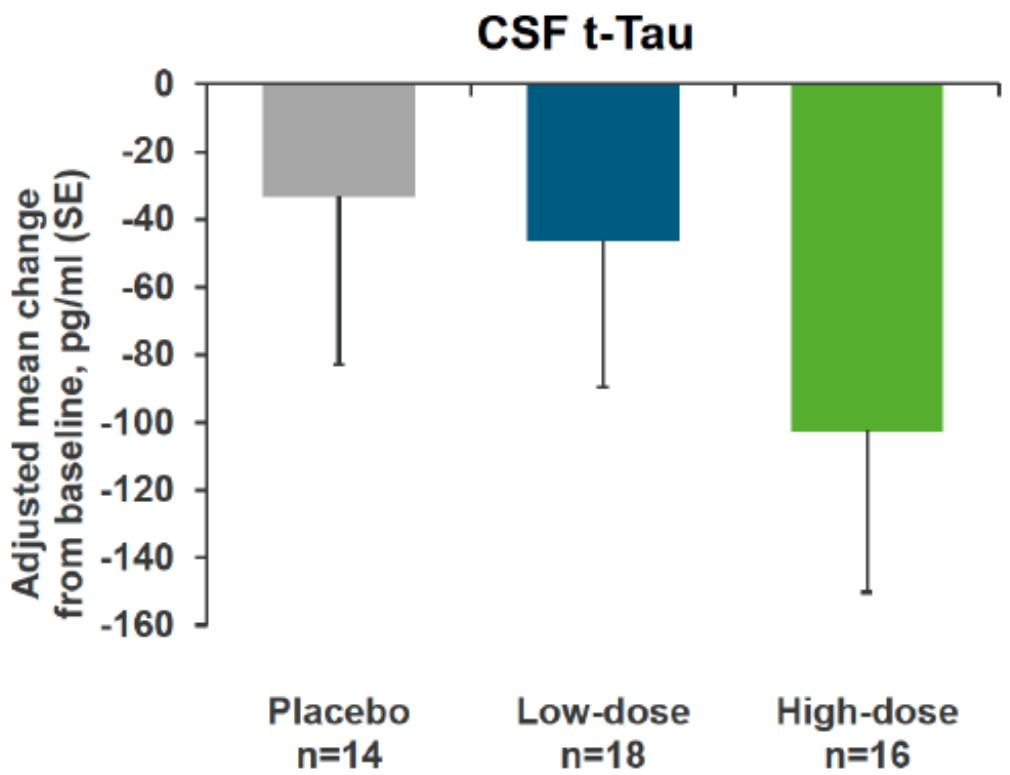
** p<0.01, *** p<0.001 (nominal).
n=numbers of randomized and dosed participants included in the analysis

Study 302

Study 301

Aducanumb effects on Biomarkers of Neurodegeneration: studies 302 vs. 301





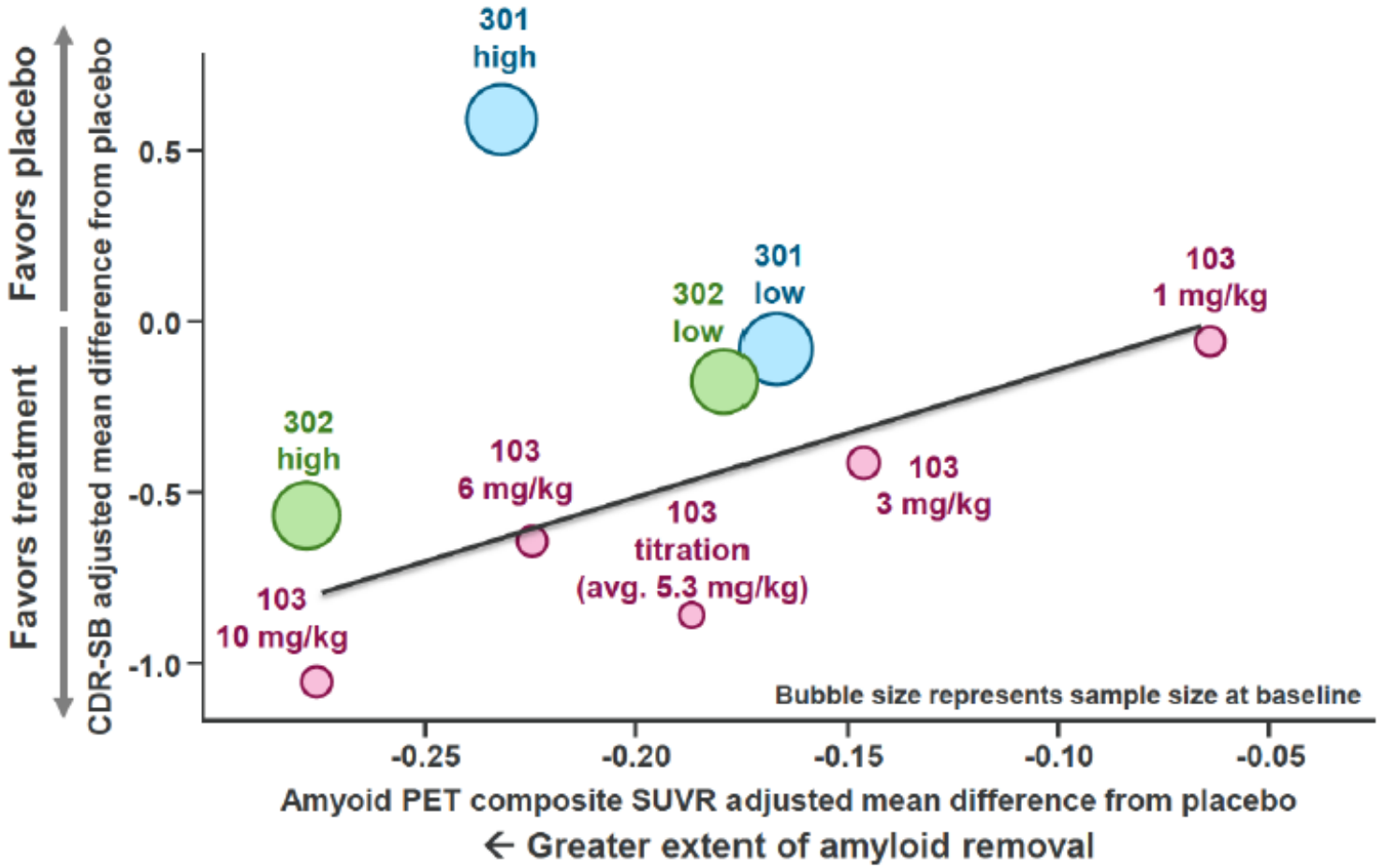
* p<0.05, ** p<0.01 (Nominal)
n=numbers of randomized and dosed participants included in the analysis

Study 302

Study 301

Study 301 High-Dose Group Diverged From an Otherwise Consistent Association Between Aβ Reduction and Slowing of Clinical Decline

Studies 301, 302, and 103



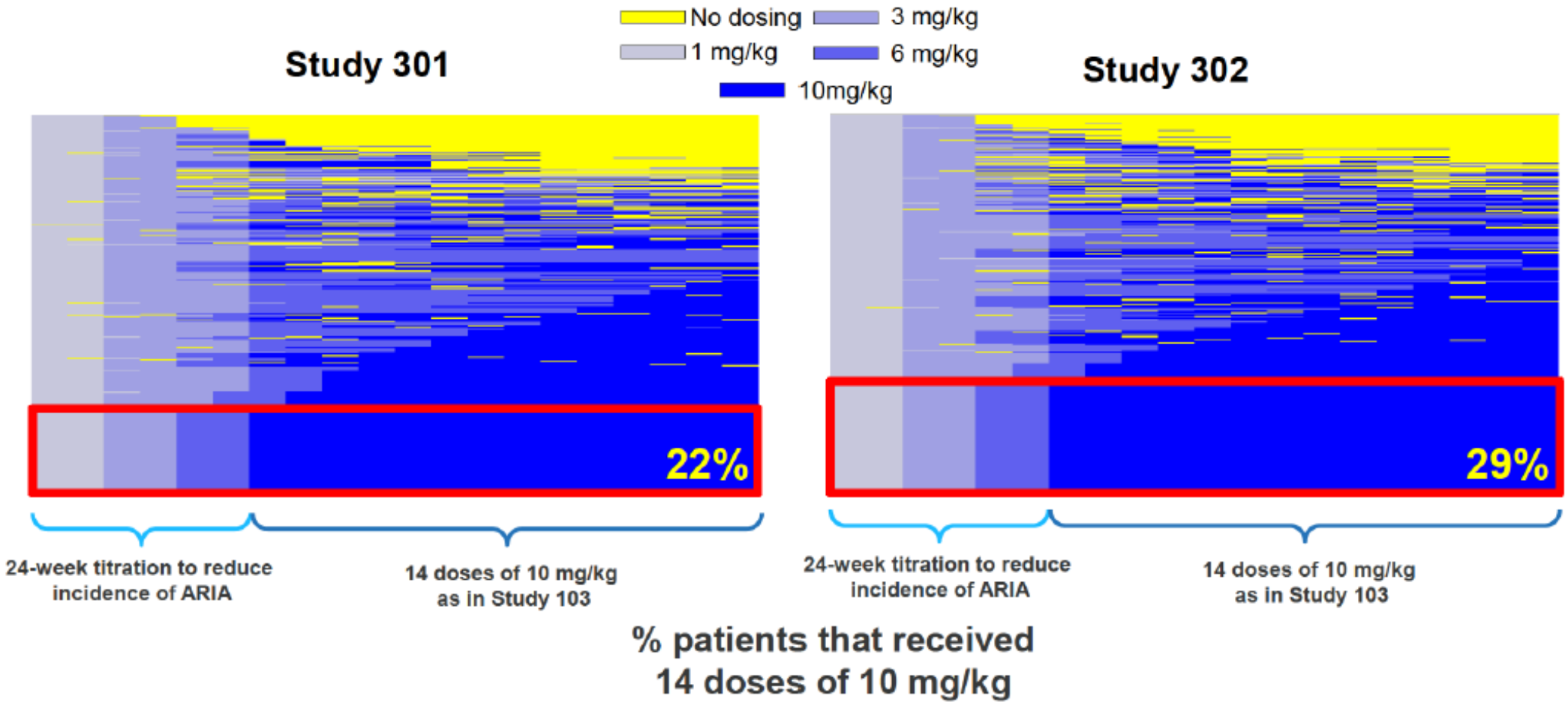
Summary of study 301: Engage

- Study 301 failed to meet its primary or secondary objectives

- Methodologic concerns
  - Lower amount of study drug received in study 301
  - More rapid progressors in study 301

Exposure to Aducanumab 10 mg/kg Was Lower in Study 301 Than in Study 302

Studies 301 and 302

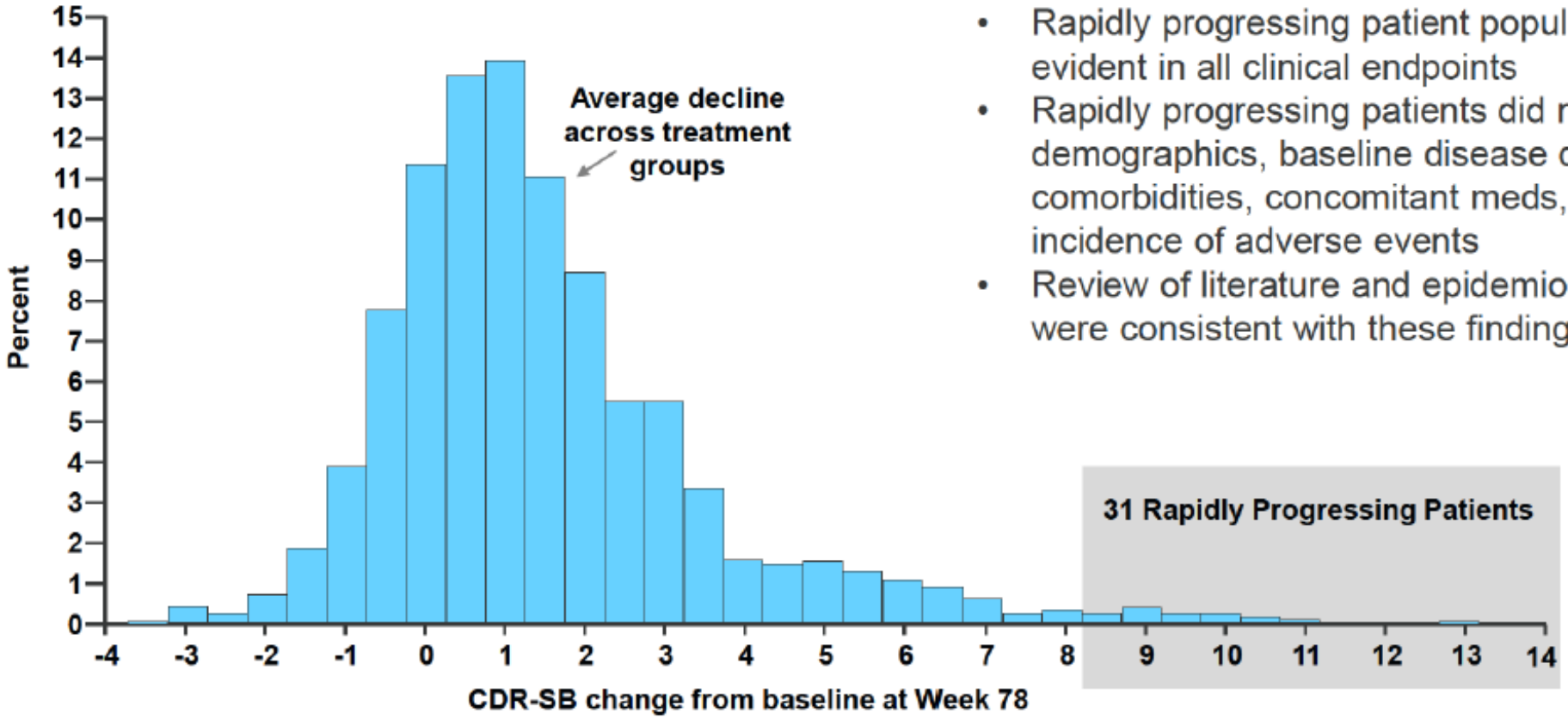


Patients who have had the opportunity to complete week 78 visit by 20 March 2019.

Distribution of CDR-SB Changes Include a Small Number of Especially Rapidly Progressing Patients

CR-8

Studies 301 and 302



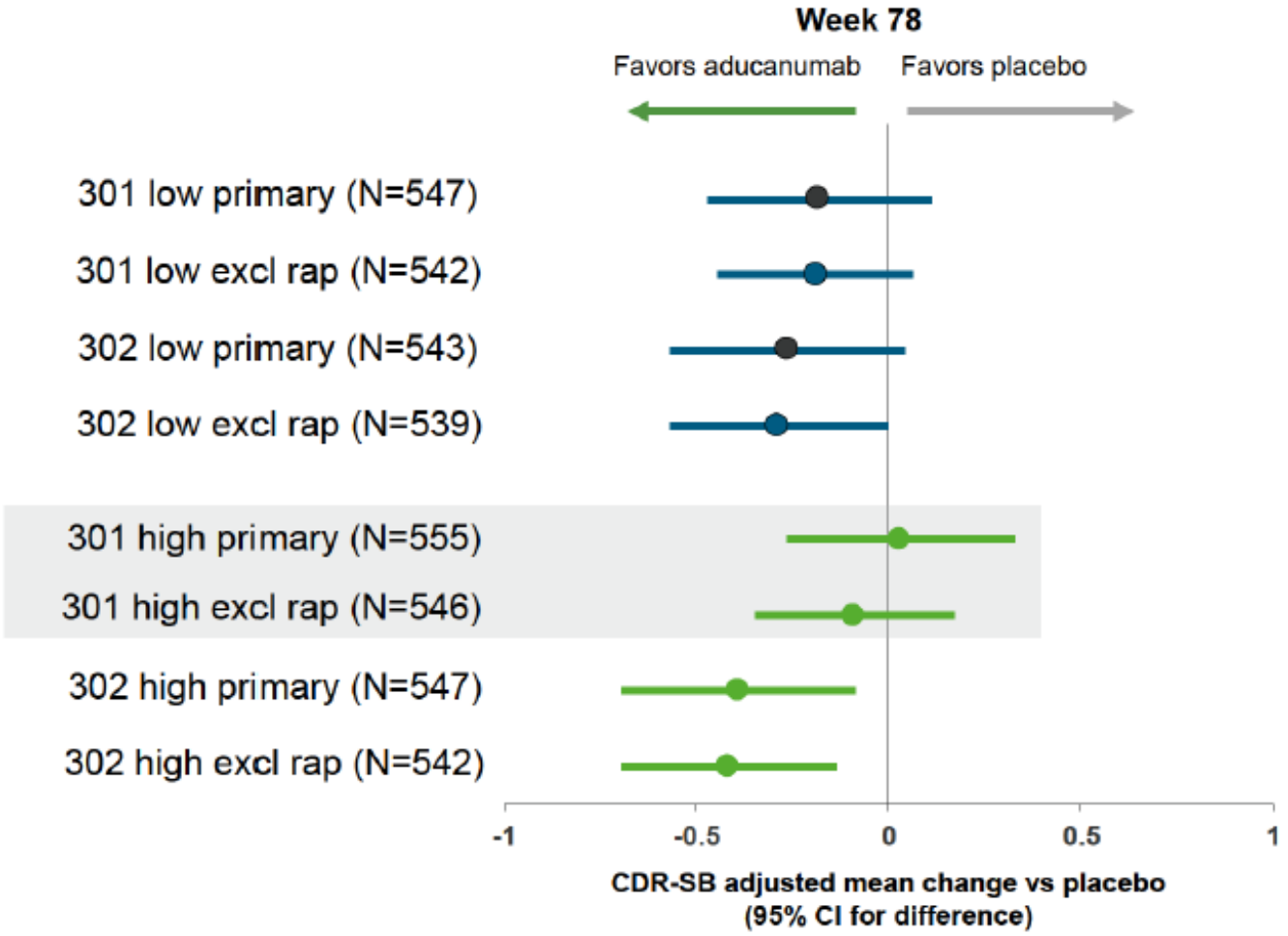
- Rapidly progressing patient population was evident in all clinical endpoints
- Rapidly progressing patients did not differ in demographics, baseline disease characteristics, comorbidities, concomitant meds, exposure, or incidence of adverse events
- Review of literature and epidemiologic studies were consistent with these findings

Histogram displays data pooled from all three treatment groups from both studies.

Excluding Rapid Progressors Had the Greatest Impact on CDR-SB in Study 301 High-Dose Group

Studies 301 and 302

Study	Rapid progressors, n	
	302	301
Placebo	4	4
low	4	5
high	5	9



Biogen Says:

CR-3

Differences in Study 301 Are Sufficiently Understood so as Not to Detract From Study 302

- Demographics disease characteristics, and frequency, severity and management of ARIA were all similar between studies

- Differences between studies were largely driven by
  - Lower exposure to 10 mg/kg dosing in Study 301
  - Imbalance in number and distribution of rapid progressing Alzheimer's disease patients

… "Nothing to see here. Move along."

Establishing the Substantial Effectiveness of Aducanumab

Study 302	A positive study with robust and internally consistent results
Study 103	An independent, second study providing supportive evidence
Study 301	A failed study with reasons for difference between studies in results understood and post hoc subgroups supportive of Study 302 and 103

Consistent exposure to 10 mg/kg aducanumab is effective at reducing the clinical decline in patients with early symptomatic Alzheimer's disease

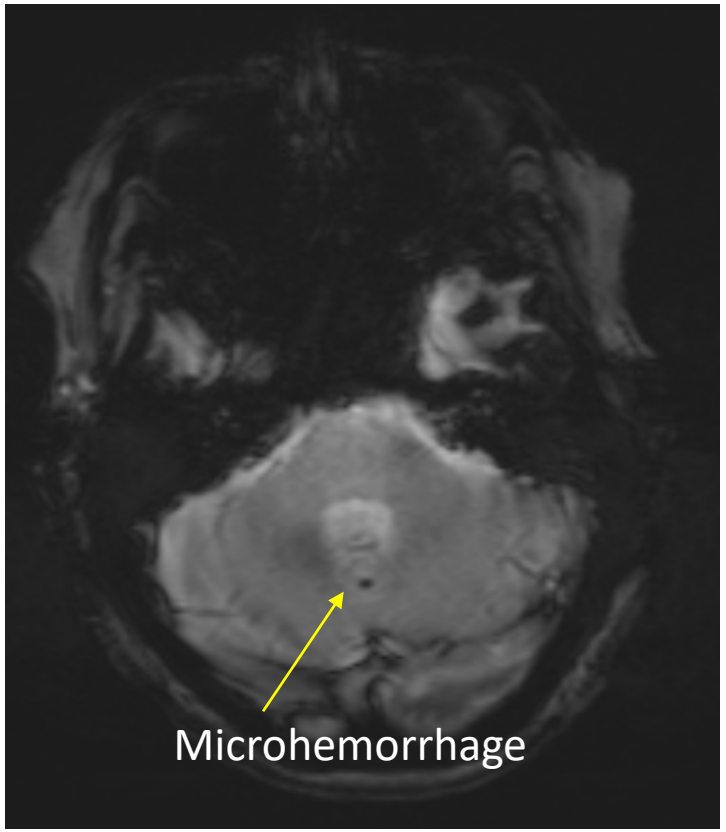
Methodologic concerns

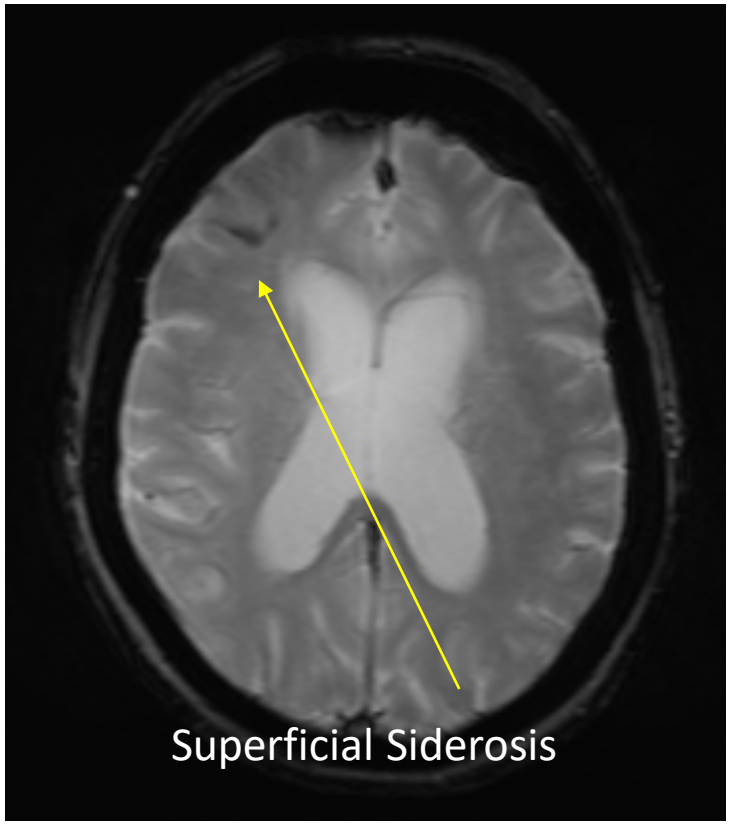
- Analysis of a trial stopped for futility
  - More likely to under- rather than overestimate an effect.
- Use of the Phase 1b trial to provide a “second” positive trial
  - Phase 1b - independent but small. Not the same as a positive phase 3 trial.
- Analyses excluding “rapid progressors”
  - No prior definition of rapid progressors. No prior plan to analyze data this way. It is not valid to remove subjects based on outcomes of a trial.
- Effect of functional unblinding due to ARIA
  - Potentially could affect CDR particularly in ApoE4+, but unlikely to affect MMSE. Future studies might account for this in the placebo group.
- Lack of racial and ethnic diversity in the clinical trials

Methodologic concerns

- Post-hoc analysis of trial results.
  - Biogen started with premise that drug was effective, and used an exploratory analysis as evidence (i.e., Looked at Engage PV4 with OTC). Increases risk of type 1 error due to multiple comparisons. Story was still not consistent.)
- Use of CDR as an endpoint
  - Scale is not used in clinical practice. What is clinically significant? (1-2 points)
- Was follow-up long enough (78 weeks)?
  - Is the drug effective in the long term? What is the long-term safety profile?
- Unknown duration of treatment – stopping not assessed

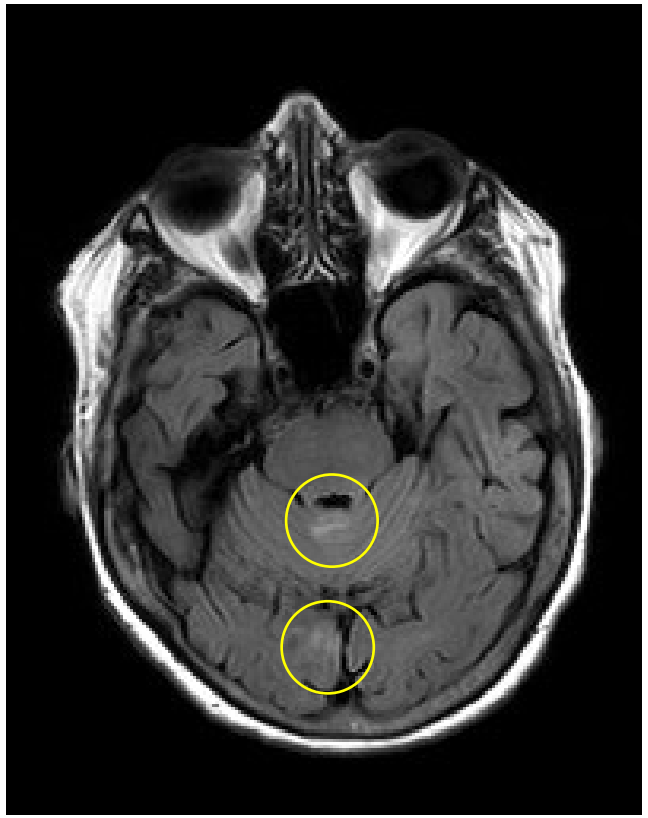
ARIA–H





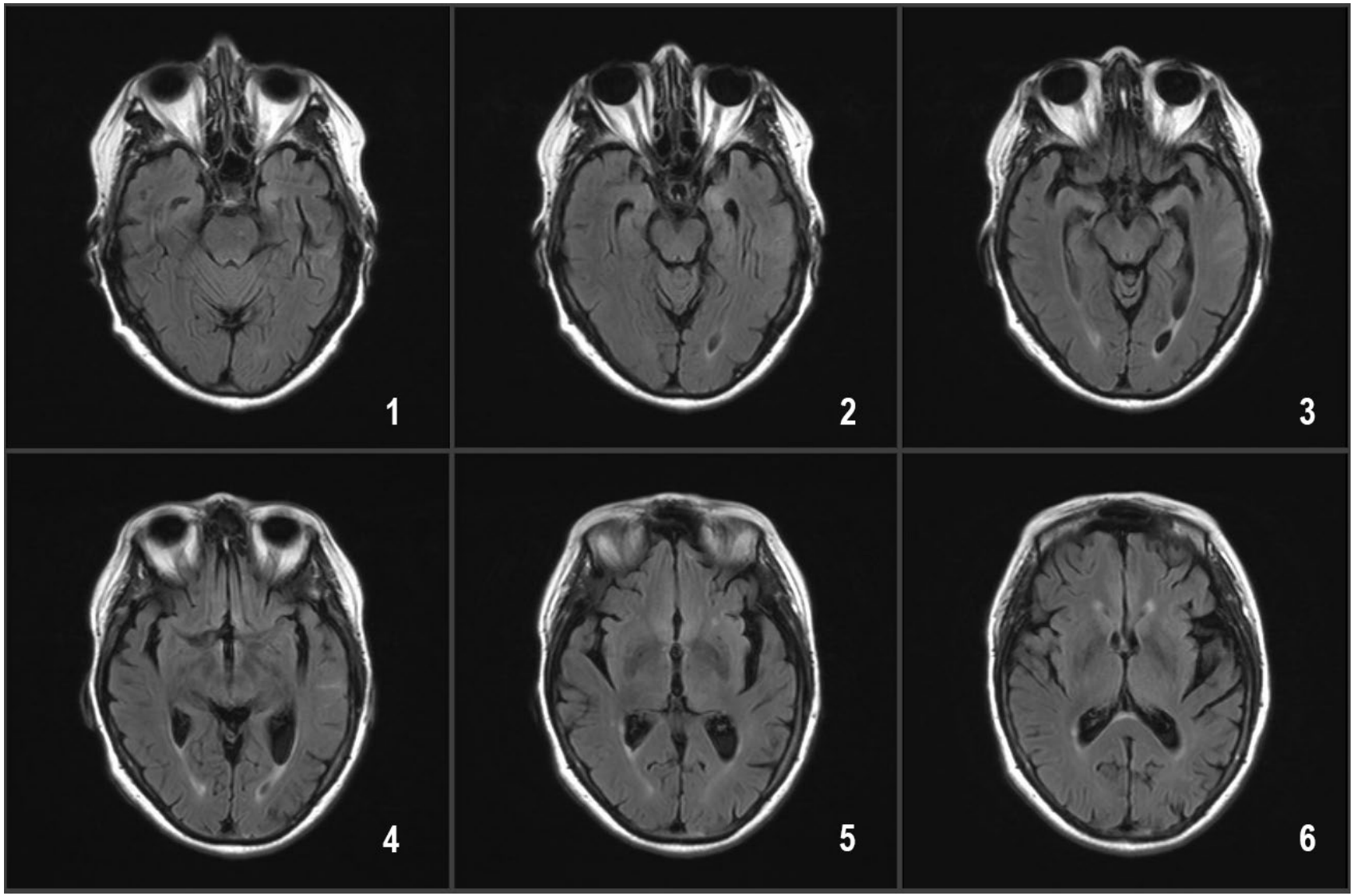
Best viewed on gradient echo and susceptibility weighted sequences

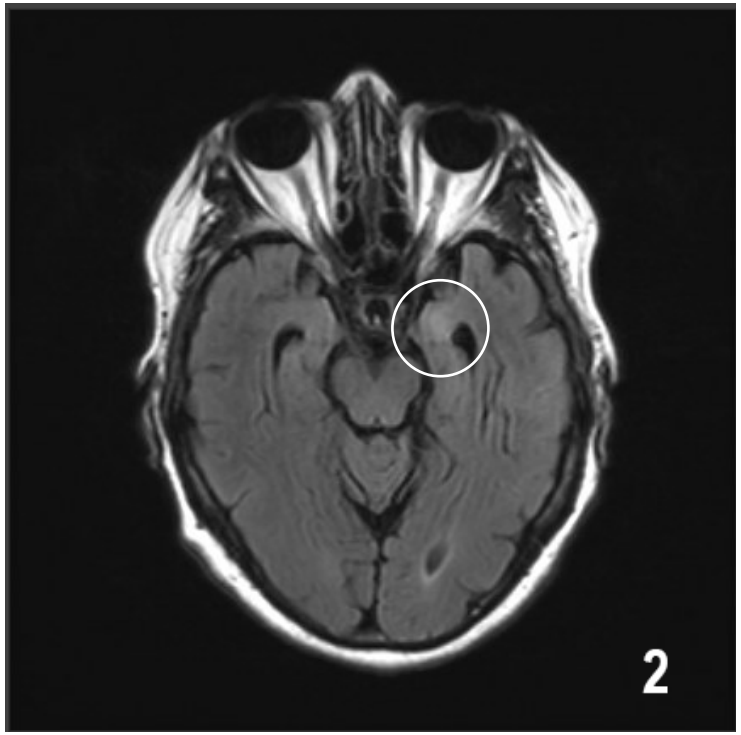
ARIA-E



Best viewed on a FLAIR sequence

Where’s the ARIA?

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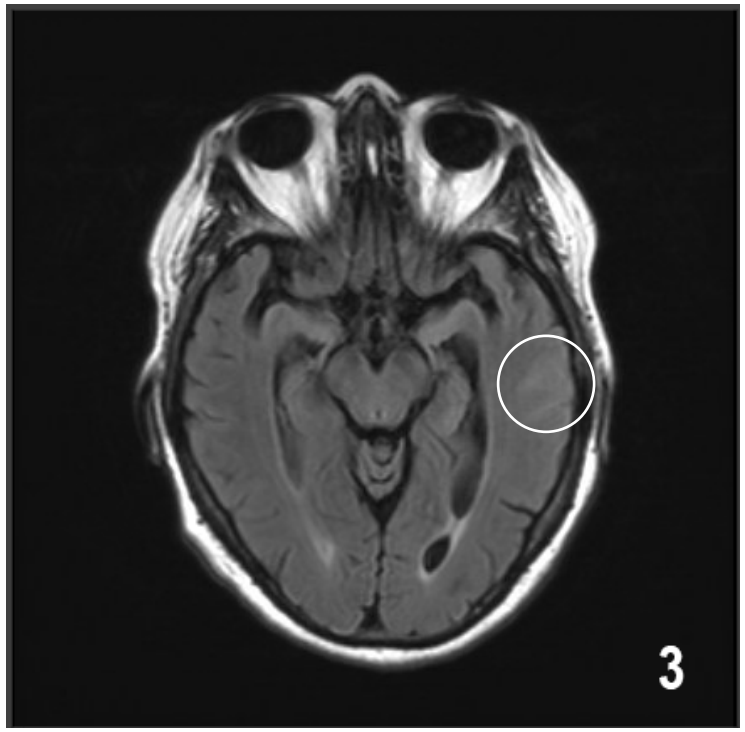
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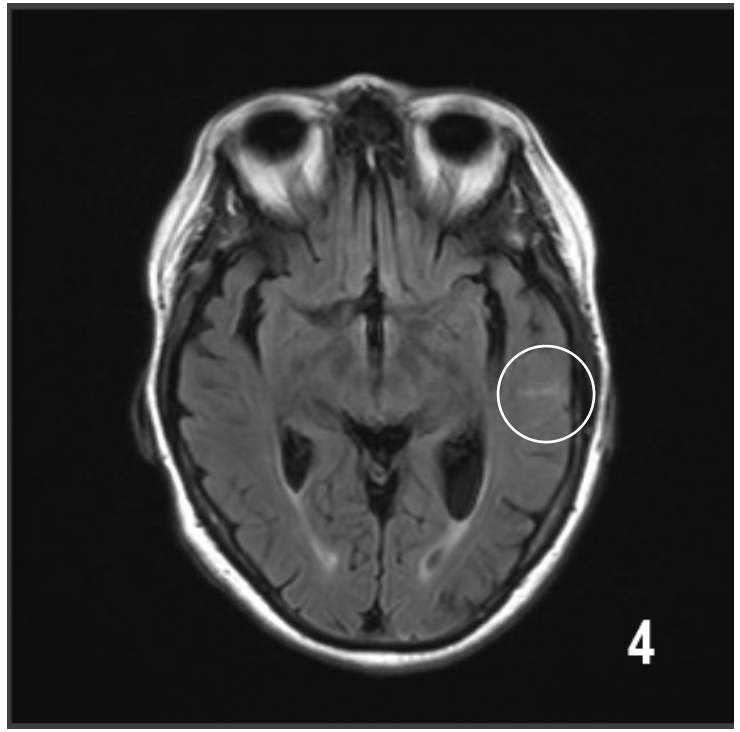
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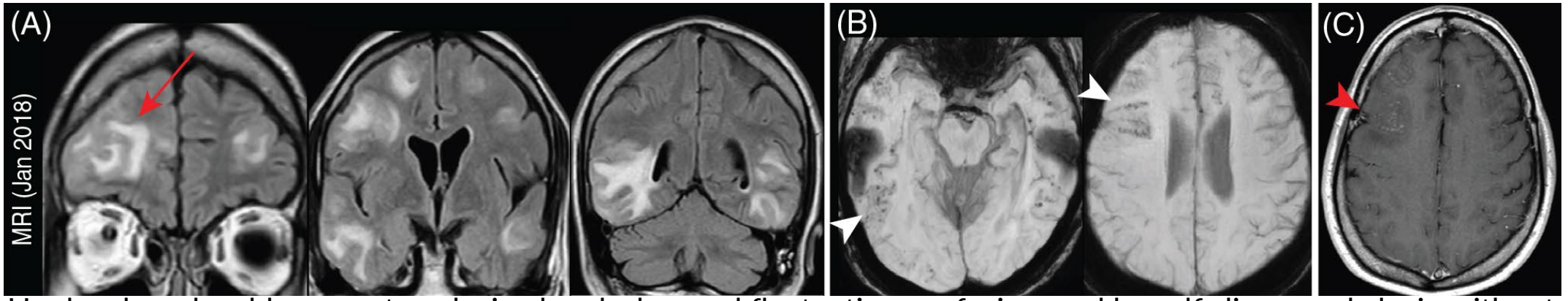
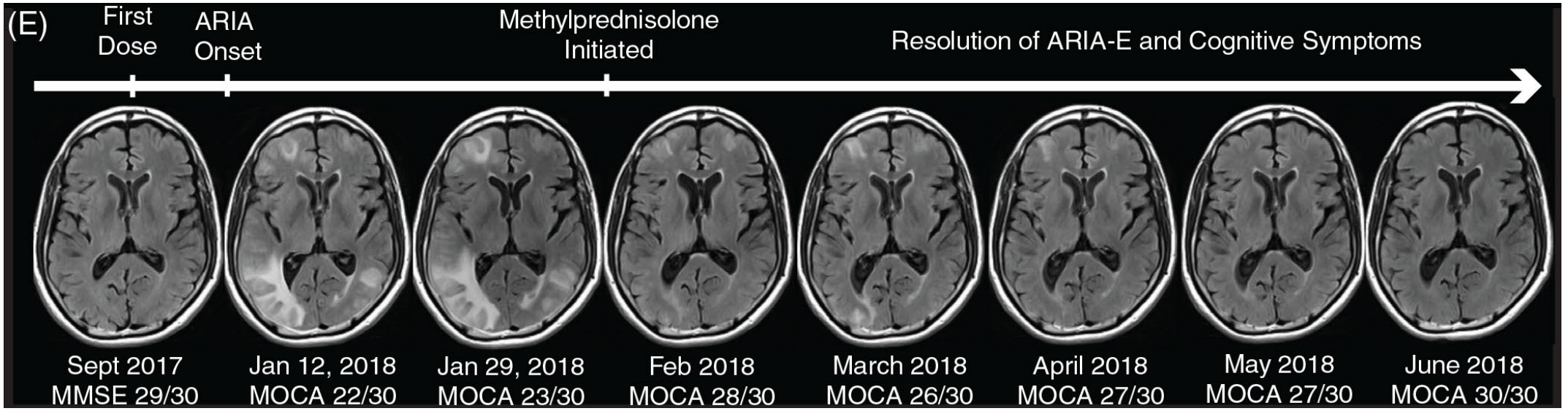


He developed sudden-onset explosive headaches and fluctuating confusion, and he self-diagnosed alexia without agraphia. He presented to the hospital, where his systolic blood pressure was 206/116 on admission to the intensive care unit (ICU), where he received intravenous nicardipine.



Note: Methylprednisolone has not been definitively shown to treat ARIA-E

Table 3. Occurrence of ARIA in the entire population and in participants with and without the APOE-4 allele in the two pivotal trials combined (10 mg/kg dose) (5)

Participant Group	Placebo	Aducanumab
ARIA-E and ARIA-H (overall population)	10%	41%
ARIA-E (overall population)	2.7%	35.2%
ARIA-E with symptoms	10.3%	26%
ARIA-H (overall population)	8.7%	28.3%
ARIA-E APOE-4 carriers	2.2%	43%
ARIA-E APOE-4 noncarriers	3.9%	20.3%
Trial discontinuations due to ARIA	0.6%	6.2%

Symptomatic ARIA-E: mild 67.7%, moderate 28.3%, and severe 4%
The most common symptoms reported were confusion or altered mental status (5%), dizziness (4%), visual disturbances (2%), and nausea (2%).

See paper for ARIA management.

J Prev Alz Dis 2021;
Published online July 20, 2021, http://dx.doi.org/10.14283/jpad.2021.41

Special Article

Aducanumab: Appropriate Use Recommendations

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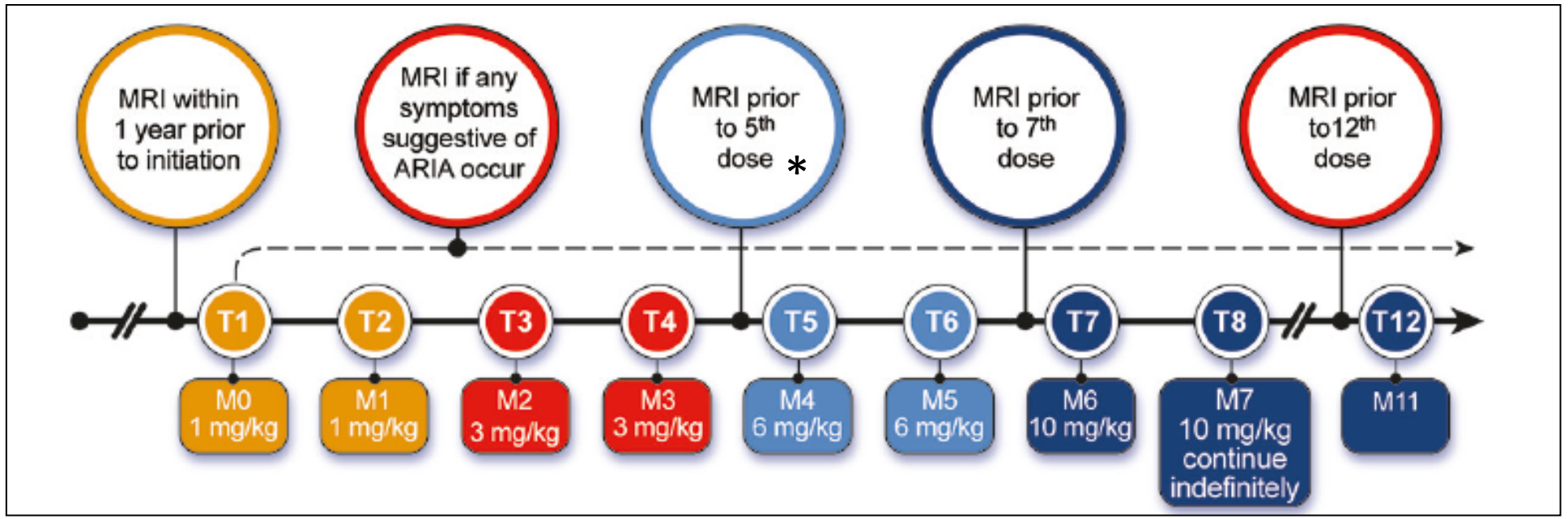
Corresponding Author: Jeffrey Cummings, MD, ScD, 1380 Opal Valley Street, Henderson, NV 89052, jcummings@cnsinnovations.com, T: 702-902-3939

Patient item	Appropriate use in clinical practice
Age	50-85 (consider older/younger if all other criteria met)
Diagnosis	Clinical criteria for MCI due AD or mild AD dementia
Scale scores	MMSE: 21-30 or equivalent, such as MoCA: 17-30
Amyloid status	Amyloid PET positive (visual read), CSF consistent with AD
ApoE genotyping	Discuss. Inform greater ARIA risk with ApoE4 positive
Neuro exam	Exclude non-AD neurological disorders
Cardiovascular history	Stable cardiovascular status (clinical judgment)
Medical history	Stable medical conditions (clinical judgment)
Psychiatric history	Stable psychiatric status (clinical judgment)
Reproductive status	Exclude if pregnant or breast feeding; if female patient of childbearing age, practice contraception.
Clotting status	Max aspirin 325 mg/day, no other anti-platelet, anticoagulant medications
Concomitant meds	Can be on standard cholinesterase inhibitors and/or memantine
Baseline MRI	Exclude if acute or subacute hemorrhage, macrohemorrhage, >4 microhemorrhages, cortical or lacunar infarct (>1.5 cm), >1 area superficial siderosis, diffuse WM disease or cannot have an MRI
Care support	May live independently or with a care partner
Informed consent	Document understanding of requirements for therapy (monthly) and expected outcome (slowing of decline, not symptomatic improvement)

Special populations

Consider aducanumab although information is incomplete	Avoid using aducanumab
Autosomal Dominant AD	**Alzheimer's disease but not in trials**
Atypical AD (logopenic aphasia, posterior cortical atrophy, frontal AD, corticobasal syndrome)	Moderate AD
	Severe AD
	Preclinical AD
	Amyloid positive but not in trials
	Down syndrome
	Dementia with Lewy bodies
	Cerebral amyloid angiopathy

Aducanumab dosing and MRI schedule



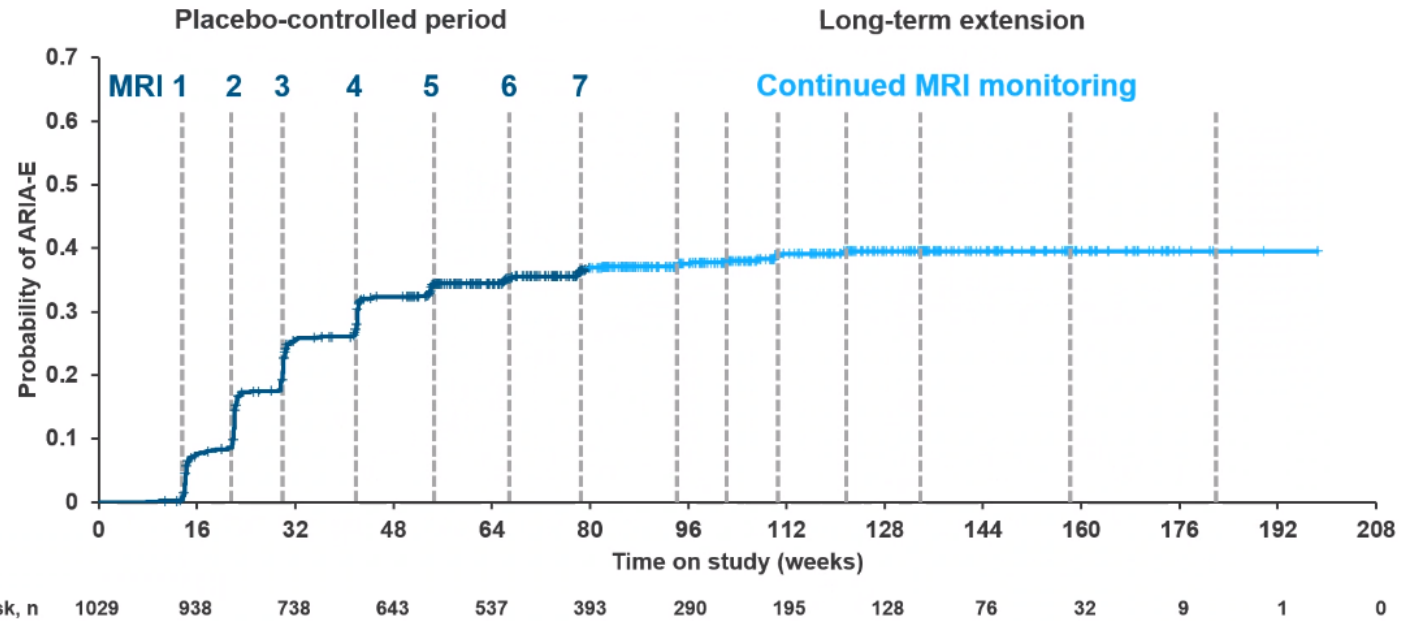
* Added in appropriate use recommendations

Time to first ARIA-E

CS-90

Kaplan-Meier Analysis of Time to First ARIA-E

Studies 301 and 302, 10 mg/kg

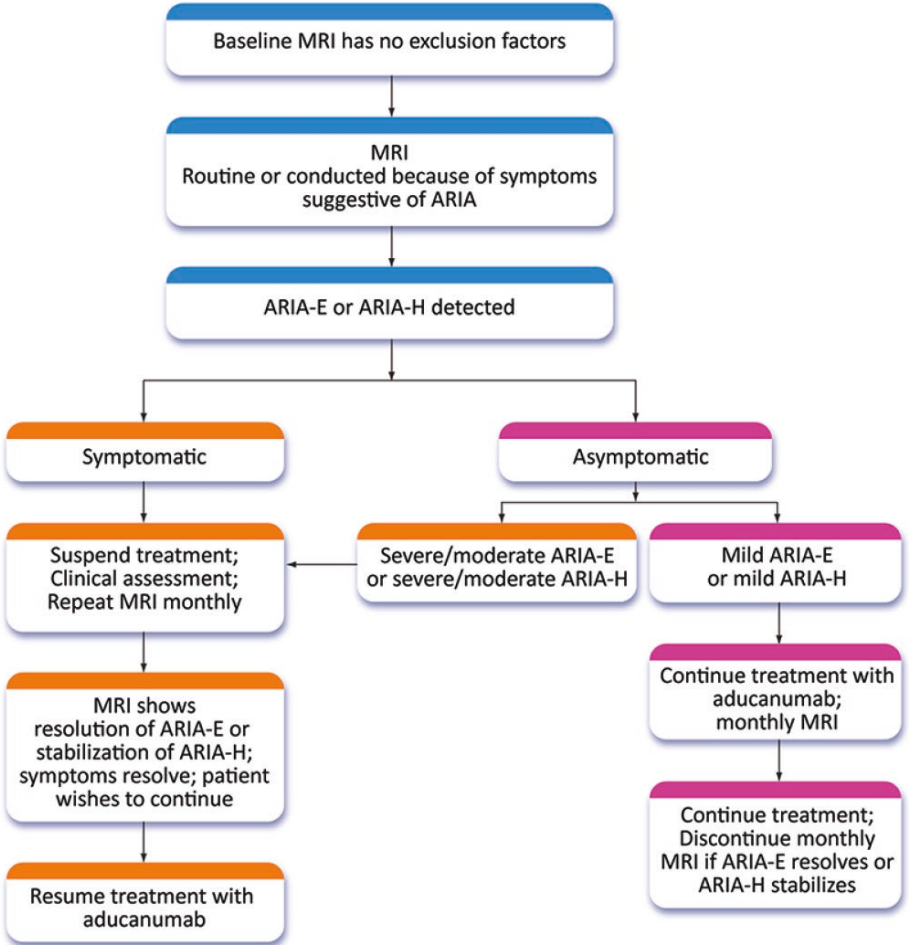


ARIA Management

- **ARIA-E**
  - Mild: mild FLAIR hyperintensity, affecting an area max <5 cm. Only a single region of involvement
  - Moderate: FLAIR hyperintensity measuring max 5-10 cm or more than one site
  - Severe: FLAIR hyperintensity max >10 cm in one or more areas

- **ARIA-H**
- Superficial Siderosis Severity
  - Mild: single focus of hemosiderosis
  - Moderate: 2 focal areas of hemosiderosis
  - Severe: more than 2 focal areas of hemosiderosis

- Microhemorrhage Severity
  - Mild: 1-4 microhemorrhages
  - Moderate: 5-9 microhemorrhages
  - Severe: 10 or more microhemorrhages



Cost considerations

- Drug cost = $56,000 per year
- Additional costs = MRI scans, infusions, examinations, care of complications
- Paid for under Medicare part B = 20% copay
- Currently available only to wealthy patients (Biogen does have a support program)
- Medicare National Coverage Determination – pending
- If covered by Medicare treatment will still have steep costs for many patients.
- What about treatment of younger patients not yet on Medicare?

Swanson et al. Alzheimer's Research & Therapy (2021) 13:80
https://doi.org/10.1186/s13195-021-00813-8

Alzheimer's Research & Therapy

RESEARCH Open Access

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

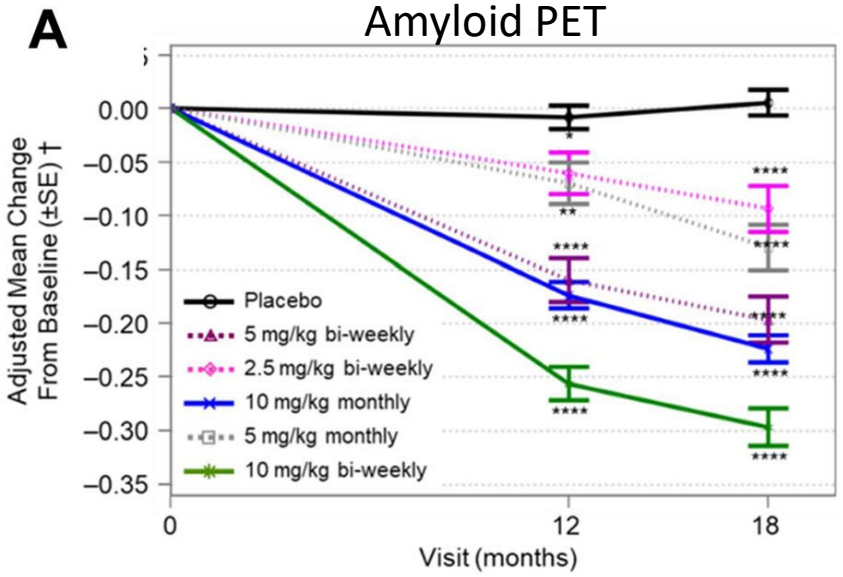
Chad J. Swanson[1], Yong Zhang[1], Shobha Dhadda[1], Jinping Wang[1], June Kaplow[1], Robert Y. K. Lai[2], Lars Lannfelt[3,4], Heather Bradley[1], Martin Rabe[1], Akihiko Koyama[1], Larisa Reyderman[1], Donald A. Berry[5], Scott Berry[5], Robert Gordon[2], Lynn D. Kramer[1] and Jeffrey L. Cummings[6*]

- Inclusion
  - Age 50- 90 years with mild cognitive impairment due to AD or mild AD dementia.
  - Confirmed amyloid positive via amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) Aβ1–42
  - Objective impairment in episodic memory (on Wechsler Memory Scale-IV Logical Memory II
  - Mini Mental State Examination (MMSE) score ≥ 22 at screening and baseline
  - Naïve to or on stable dose (12 weeks) of approved AD medications

Swanson et al., Alz Res & Ther, 2021

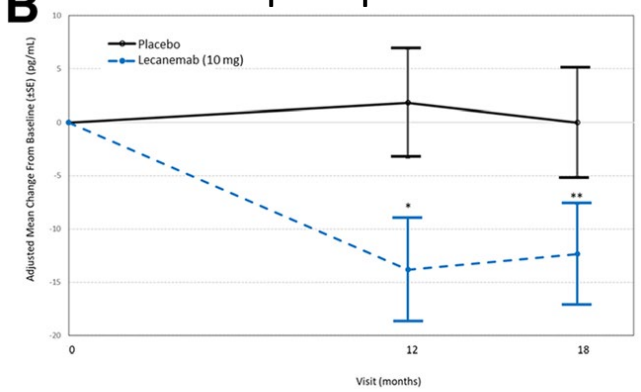
Lecanemab (BAN2401) Phase 2b

Amyloid PET



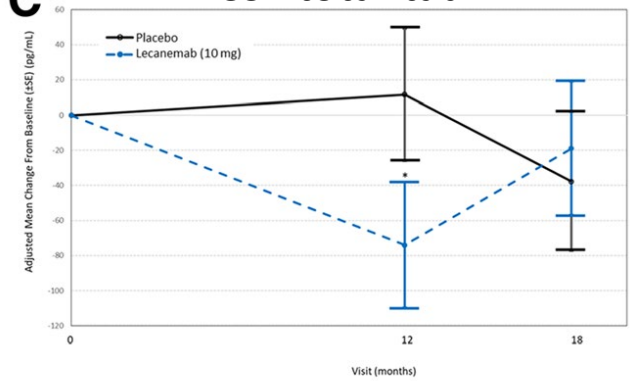
N (PET-SUVr)	0 Months	12 Months	18 Months
Placebo	99	96	88
2.5 mg/kg biweekly	28	27	23
5 mg/kg monthly	28	27	23
5 mg/kg biweekly	27	25	24
10 mg/kg monthly	89	88	82
10 mg/kg biweekly	44	43	37

CSF phospho-tau



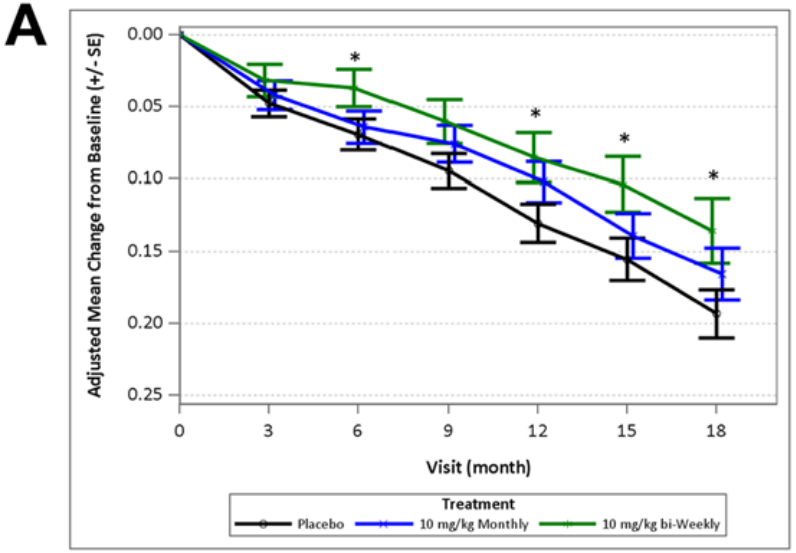
N with data	0 mo.	12 mo.	18 mo.
Placebo	24	22	18
Combined 10 mg/kg groups	28	26	23

CSF total-tau



N with data	0 mo.	12 mo.	18 mo.
Placebo	18	15	14
Combined 10 mg/kg groups	18	17	14

ADCOMS



N (ADCOMS)	0 Months	3 Months	6 Months	9 Months	12 Months	15 Months	18 Months
Placebo	238	226	216	201	187	172	160
10 mg/kg monthly	246	235	208	177	165	152	146
10 mg/kg biweekly	152	143	130	105	93	89	79

Swanson et al., Alz Res & Ther, 2021

Lecanemab adverse events

Category	Placebo (*n* = 245) *n* (%)	Lecanemab				
		2.5 mg/kg Biweekly (*n* = 52) *n* (%)	5 mg/kg Monthly (*n* = 51) *n* (%)	5 mg/kg Biweekly (*n* = 92) *n* (%)	10 mg/kg Monthly (*n* = 253) *n* (%)	10 mg/kg Biweekly (*n* = 161) *n* (%)
Any TEAE	216 (88.2)	46 (88.5)	48 (94.1)	81 (88.0)	238 (94.1)	39 (86.3)
Treatment-related TEAE	65 (26.5)	23 (44.2)	25 (49.0)	31 (33.7)	135 (53.4)	76 (47.2)
Serious adverse event	43 (17.6)	10 (19.2)	4 (7.8)	16 (17.4)	31 (12.3)	25 (15.5)
Deaths	2 (0.8)	2 (3.8)	0	1 (1.1)	2 (0.8)	0
AE leading to discontinuation	15 (6.1)	7 (13.5)	4 (7.8)	10 (10.9)	47 (18.6)	24 (14.9)
ARIA-E	2 (0.8)	1 (1.9)	1 (2.0)	3 (3.3)	25 (9.9)	16 (9.9)
ApoE4-positive (*n* = 436)	2 (1.1)	1 (2.6)	1 (2.5)	3 (3.6)	23 (10.2)	7 (14.3)
ApoE4-negative(*n* = 112)	0	0	0	0	2 (7.1)	9 (8.0)

TEAE, treatment emergent adverse event; *ARIA-E*, amyloid-related imaging abnormalities-edema; *ApoE4*, apolipoprotein E4

- ARIA-H (new cerebral microhemorrhages, cerebral macrohemorrhages, and superficial siderosis)
  - 13 (5.3%) subjects in the placebo group (N = 245)
  - 65 (10.7%) subjects in the lecanemab groups (N = 609).

Swanson et al., Alz Res & Ther, 2021

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 6, 2021 VOL. 384 NO. 18

Donanemab in Early Alzheimer's Disease

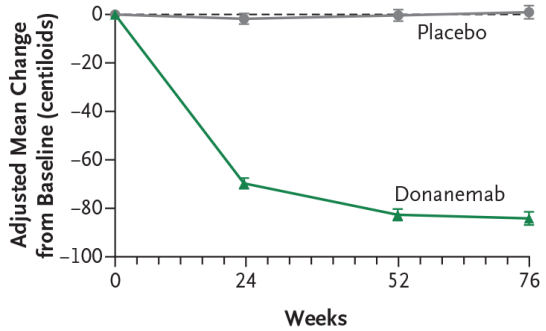
Mark A. Mintun, M.D., Albert C. Lo, M.D., Ph.D., Cynthia Duggan Evans, Ph.D., Alette M. Wessels, Ph.D., Paul A. Ardayfio, Ph.D., Scott W. Andersen, M.S., Sergey Shcherbinin, Ph.D., JonDavid Sparks, Ph.D., John R. Sims, M.D., Miroslaw Brys, M.D., Ph.D., Liana G. Apostolova, M.D., Stephen P. Salloway,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

- Age 60 – 85 years with mild cognitive impairment due to AD or mild AD dementia.
- Mini–Mental State Examination score of 20 to 28
- Confirmed amyloid positive via amyloid positron emission tomography (PET)
- Tau PET SUVR 1.10 – 1.46

Mintun et al., NEJM, 2021

Donanemab Outcomes

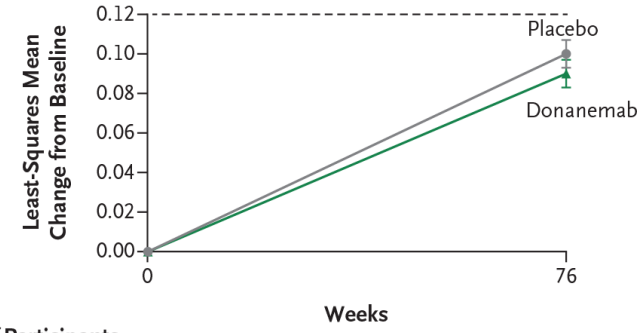
A Amyloid Plaque Level on Florbetapir PET



No. of Participants				
Donanemab	121	115	92	90
Placebo	112	111	91	91

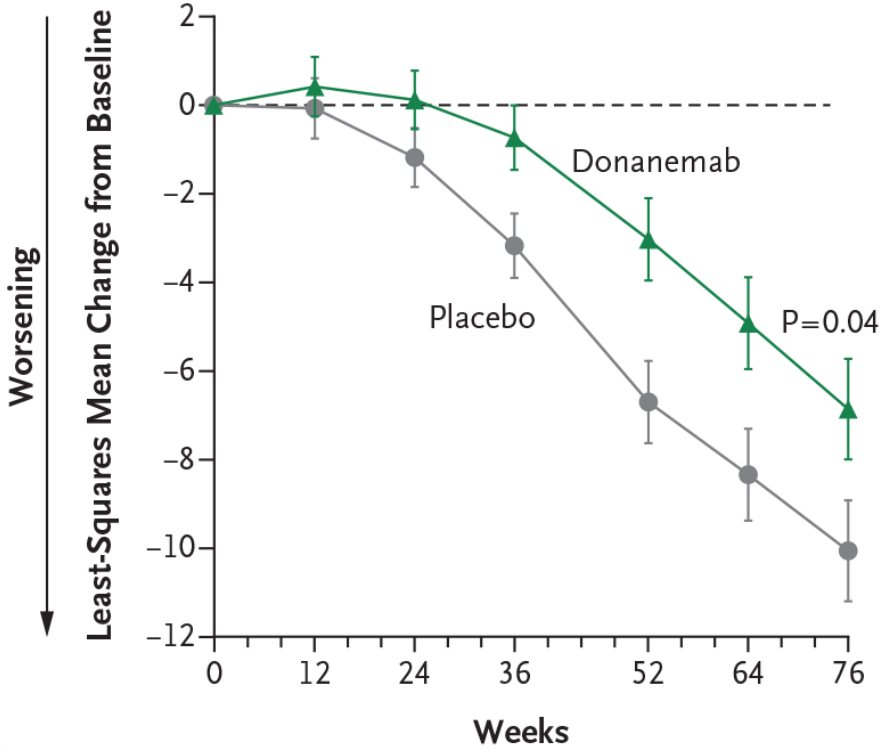
	Difference in Adjusted Mean Change		Amyloid-Negative Status, Donanemab
	Donanemab vs. placebo	95% CI	
	centiloids		*no. (%)*
Wk 24	−67.83±3.16	−74.04 to −61.61	46 (40.0)
Wk 52	−82.30±3.41	−89.02 to −75.59	55 (59.8)
Wk 76	−85.06±3.87	−92.68 to −77.43	61 (67.8)

B Global Tau Load on Flortaucipir PET



No. of Participants		
Donanemab	90	90
Placebo	87	87

A Primary Outcome: iADRS Score

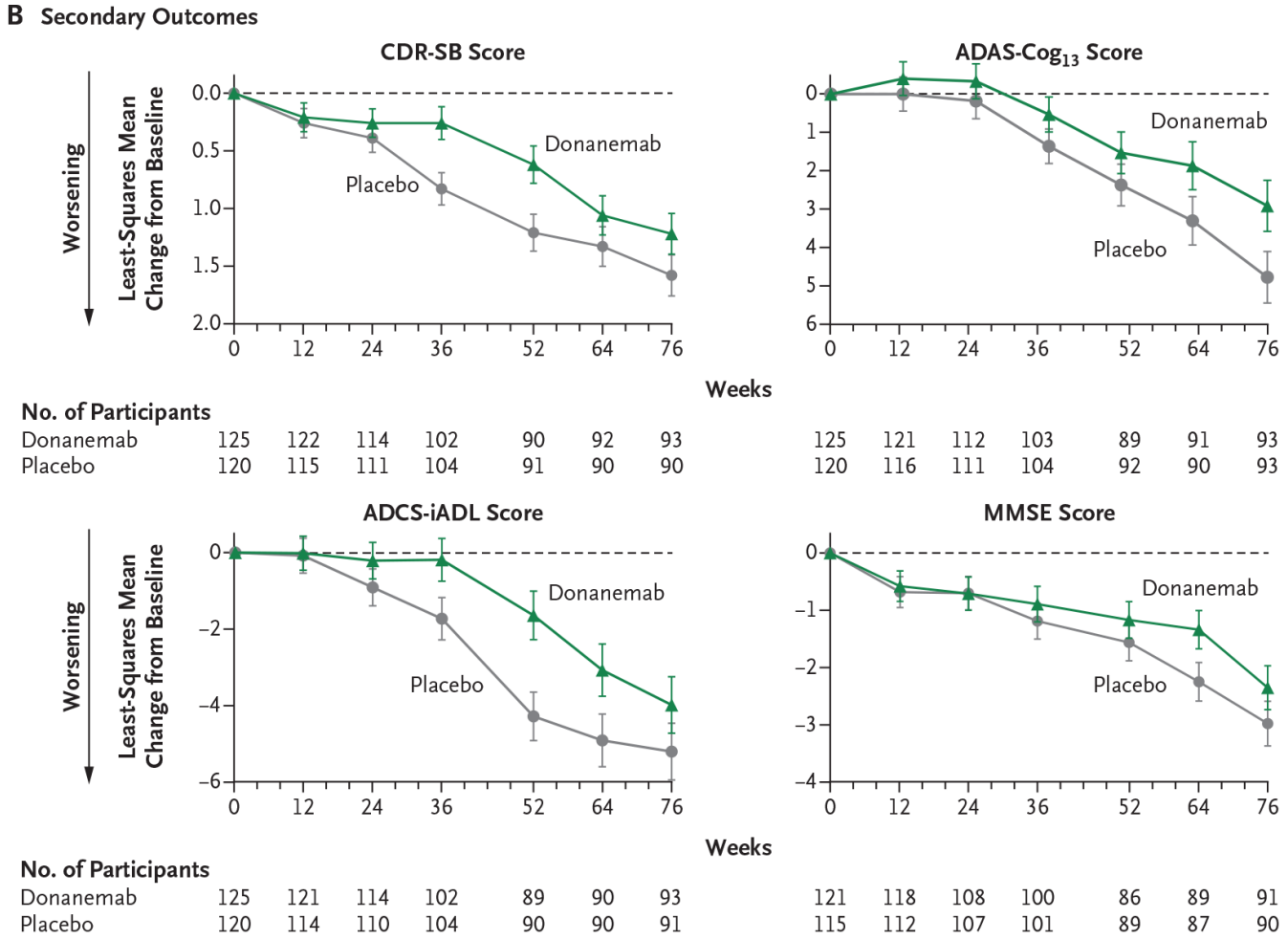


No. of Participants							
Donanemab	125	120	112	102	88	89	93
Placebo	120	113	110	103	90	90	91

Trial powered to show 50% slowing of decline

Mintun et al., NEJM, 2021

Donanemab Outcomes



Not significant

Mintun et al., NEJM, 2021

Donanemab Adverse events

ARIA Event§	Donanemab (N=131)	Placebo (N=125)
ARIA-E or ARIA-H — no. (%)	51 (38.9)	10 (8.0)
ARIA-E		
Any — no. (%)	36 (27.5)	1 (0.8)
Symptom status — no. (%)		
Asymptomatic	28 (21.4)	0
Symptomatic	8 (6.1)	1 (0.8)
APOE genotype — no./total no. (%)		
ε2/ε3	0/1	0/1
ε2/ε4	0/2	0/2
ε3/ε3	4/35 (11.4)	0/31
ε3/ε4	21/68 (30.9)	0/62
ε4/ε4	11/25 (44.0)	1/28 (3.6)
ARIA-H — no. (%)		
Any	40 (30.5)	9 (7.2)
Microhemorrhage	26 (19.8)	6 (4.8)
Superficial siderosis	23 (17.6)	3 (2.4)
Macrohemorrhage	0	0

Mintun et al., NEJM, 2021

Changes to practice

- Workup will need to be expedited. Prolonged evaluation may mean a patient becomes ineligible for treatment during the evaluation
- Alzheimer's disease previously a diagnosis of exclusion. Diagnostic workflow will need to include biomarkers in treatment eligible patients
    - Amyloid PET (no insurance), CSF (invasive), blood tests (early days, not reimbursed by insurance)
- Genetic testing – ApoE because of drug adverse event risks
- Treatment exclusions: MRI contraindicated, or patient on anti-coagulation
- Patients will need closer follow-up.
- Shared decision-making will be very important.

End