

## Alzheimer's disease and Aducanumab (Aduhelm™)

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**MANY STRENGTHS. ONE MISSION.**  
*A Seventh-day Adventist Organization*



## US FDA approves Aducanumab (Aduhelm™) for Alzheimer's disease on June 7<sup>th</sup> 2021


**CNN**  
**In controversial decision, FDA approves first new Alzheimer's disease drug in nearly 20 years**  
(CNN) The US Food and Drug Administration on Monday approved the use of the experimental drug aducanumab for early-stage Alzheimer's disease.  
1 day ago



**NPR**  
**Aducanumab: FDA Approves Controversial Alzheimer's Drug**  
The Food and Drug Administration approved the drug aducanumab to treat patients with Alzheimer's disease on Monday. It is the first new drug...  
2 days ago



**Reuters**  
**U.S. approval of Biogen Alzheimer's drug sends shares soaring, hailed as 'big day' for patients**  
U.S. regulators on Monday approved Biogen Inc's (BIIB.O) aducanumab as the first treatment to attack a likely cause of Alzheimer's disease...  
1 day ago



**BBC**  
**US approves first new Alzheimer's drug in 20 years**  
There has been controversy around aducanumab, which targets the cause rather than the symptoms.  
1 day ago




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BIG deal, first AD therapy to be approved in nearly 20 years since memantine (Namenda) in 2003

Tacrine was approved by the US Food and Drug Administration (FDA) in 1993, now discontinued due to toxicity.


Then donepezil in 1996, rivastigmine in 1998, galantamine in 2001, and memantine in 2003 (made available in the United States in 2004).


## Aducanumab (Aduhelm™) Controversy

 **Biogen CEO says \$56,000 annually for Alzheimer's drug is 'fair,' promises not to hike price for at least 4 years**


Biogen CEO Michel Vounatsos told CNBC that the list price of \$56,000 per year for the company's FDA-approved Alzheimer's disease drug...


1 day ago



 **Alzheimer's Drug Is Bonanza for Biogen, Most Likely at Taxpayer Expense**

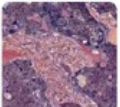
Despite scant evidence that it works, the drug, Aduhelm, is predicted to generate billions of dollars in revenue, much of it from Medicare.




 **Landmark Alzheimer's drug approval confounds research community**

Many scientists say there is not enough evidence that Biogen's aducanumab is an effective therapy for the disease.


1 day ago



 **Editor's Corner—The FDA's decision on aducanumab will drag down innovation for years to come**

The amyloid theory just won't die. In fact, by approving Biogen's new Alzheimer's disease drug, the FDA has just resurrected it for a long and...

3 hours ago



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Controversy!!!

High Cost

Lack of Evidence poor Efficacy

Alzheimer's Disease  
and  
the Amyloid Hypothesis

**Alzheimer's disease is a public health crisis!**

MORE THAN **6 MILLION** AMERICANS ARE LIVING WITH ALZHEIMER'S. BY 2050, THIS NUMBER IS PROJECTED TO RISE TO NEARLY 13 MILLION.  
*1 in 9 people > 65yo*

MORE THAN **11 MILLION** AMERICANS PROVIDE UNPAID CARE FOR PEOPLE WITH ALZHEIMER'S OR OTHER DEMENTIAS.

IN 2021, ALZHEIMER'S AND OTHER DEMENTIAS WILL COST THE NATION **\$355 BILLION**. BY 2050, THESE COSTS COULD RISE AS HIGH AS \$1.1 TRILLION.  
*\$59k per patient*

IN 2020, THESE CAREGIVERS PROVIDED AN ESTIMATED **15.3 BILLION** HOURS OF CARE VALUED AT NEARLY \$257 BILLION.

Source: Alzheimer's Association, www.alz.org

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National Health Expenditure 2019:

\$3.8 trillion, \$11.5k per person, 17.7% GDP

Medicare \$799 billion

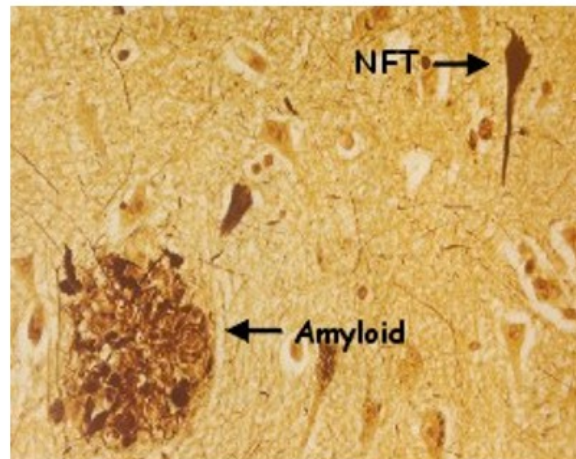
Medicaid \$613 billion

## Alzheimer's Disease

- » Progressive neurodegenerative condition that is ultimately fatal
- » Clinical diagnosis, confirmed by post-mortem autopsy
- » Estimated to be responsible for ~60-80% of clinical dementia
- » Classically associated with CNS pathology of ***beta-amyloid*** and ***tau-neurofibrillary tangles***
- » **NO CURE**
- » Minimal clinical benefit with currently available pharmacotherapy, mainly in delaying further disease progression

## Etiology of Alzheimer's Disease

» In 1906, Alois Alzheimer report the first senile plaques and intracellular neuro-fibrillary tangles in the brain of 51 yo F who died from advanced dementia.

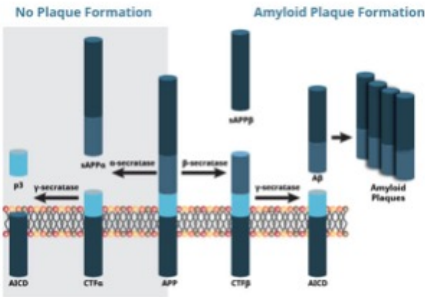


Alois Alzheimer, 1906

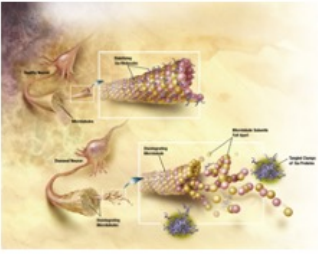
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Then, no significant advances occurred until about 40 years ago, both plaques and tangles were biochemically and genetically characterized.

**Senile plaques consist of amyloid A $\beta$  deposits** BBRC, 120: 885-90. **1984**



**Neurofibrillary tangles consist of tau aggregates** Science 232: 648-50 **1986**



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But it wasn't until 1984, with the availability of modern biochemistry and cell biology tools, that amyloid plaques and neurofibrillary tangles were analyzed and their main components described.

The first ones to fall were amyloid plaques, which were reported to consist mainly of amyloid ab deposits.

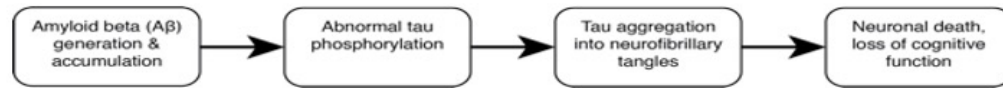
In 1986, the main component of NFTs was also identified. It was the microtubule binding protein tau. In a healthy neuron, tau regulates microtubule dynamics through its phosphorylation, thereby contributing to appropriate axonal transport. In an AD neuron, tau is abnormally phosphorylated, and this pattern of phosphorylation leads to its aggregation and to microtubule disruption. Because microtubules are central to axonal transport, and axonal transport is key to neuronal function, tau aggregation into NFTs lead eventually to cellular dysfunction and cell death



## Amyloid Hypothesis of AD Pathogenesis

### » The Amyloid Hypothesis

- The dominating hypothesis of AD pathogenesis since its proposal by Hardy and Higgins in 1992



Science 256: 184-5 1992

Prediction is: Reverse amyloid accumulation = reverse/delay AD

**Nearly 30 years of active research and 400+ clinical trials later:**

**No amyloid targeting therapy has been shown to provide clinical benefit**

Ageing Res Rev 2012 12: 282

BMC Neurology 2014 14: 169

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400+ trials between 2002-2012 alone (at the “peak” of AD research funding)

In 2021, there are 126 therapies in 152 treatments

## Not all “Alzheimer’s” are the same!

### » Familial Alzheimer’s disease (FAD, before age 65):

- Also known as “early onset Alzheimer’s”, **est. < 5% of AD**
- Mutations in *APP*, *PSEN1*, and *PSEN2* (Mendelian dominant inheritance)

### » Alzheimer’s disease associated with T21 Down Syndrome:

- Chr. 21 contains the *APP* gene (Amyloid Precursor Protein), thus DS patients have 3 copies of the *APP* gene and accelerated amyloid deposits in the brain, and the onset and progression of AD-like dementia
- DS patients develop early onset AD ~age 40

### » Sporadic Alzheimer’s disease (SAD, after age 65):

- **THE MAJORITY of AD (>90%)**
- Still estimated to be largely heritable ( ~79%) but not associated with genetic mutations directly related to Amyloid biology
- Etiologically heterogeneous

Robert C. Barber, "The Genetics of Alzheimer's Disease", *Scientifica*, vol. 2012, Article ID 246210, 14 pages, 2012. <https://doi.org/10.6064/2012/246210>

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Maybe it is more intuitive for us clinicians

When there is a syndrome, a culmination of symptoms, it is very likely that there are different subtypes

In the case of AD, there is at least 3 distinct subtypes!

The reason I want to make these clinical distinctions is because in the realm of basic science research for AD, under the amyloid hypothesis, they clump all of these three into one AD and every therapeutic attempt has been geared towards.

## Not all “Alzheimer’s” are the same!

**SNP variants associated with sporadic-AD are mostly located in or near genes involved in cholesterol metabolism, immune response, and endocytosis**

» GENE	LOCATION	SNP	OddsRatio	Pop-attrib-frac %
» <b>APOE4</b>	19q13.32	rs429358	3.93/11.71	30
» ABCA7	19p13.3	rs3764650	1.23	2.8
» <b>CR1</b>	1q32.2	rs6656401	1.21	3.5
» <b>BIN1</b>	2q14.3	rs744373	1.15	8.2
» FERMT2	14q22.1	rs17125944	1.14	1.2
» CD2AP	6p12.3	rs9349407	1.12	2.6
» HLA-DRB5/1	6p21.32	rs9271192	1.11	3.0
» PTK2B	8p21.2	rs28834970	1.10	3.6
» CELF1	11p11.2	rs10838725	1.08	2.5
» INPP5D	2q37.1	rs35349669	1.08	3.8
» MEF2C	5q14.3	rs190982	0.93	2.8
» NME8 locus	7p14.1	rs2718058	0.93	2.5
» CD33	19q13.41	rs3865444	0.91	1.8
» EPHA1	7q35	rs11771145	0.91	3.3
» MS4A6A locus	11q12.2	rs983392	0.91	3.8
» SLC24A4/RIN3	14q32.12	rs10498633	0.91	1.9
» ZCWPW1	7q22.1	rs1476679	0.91	2.5
» CASS4	20q13.31	rs7274581	0.88	1.0
» <b>PICALM</b>	11q14.2	rs3851179	0.86	4.5
» <b>CLU</b>	8p21.1	rs11136000	0.85	5.1
» SORL1	11q24.1	rs11218343	0.77	0.91

Lancet Neurol. 2015, 14: 814; Genet Med. 2016 18: 421; Handb Clin Neurol. 2018 148: 395

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So the first problem is to identify early causative factors of AD. And what we know, in the absence of suitable animal models, comes from populations studies. And it looks as if cholesterol, inflammation and lifestyle outcomes are strongly linked to the risk of AD

\*\*\* additional genetic data in AD:

In these studies, which were published back to back in *Nature Genetics* [56, 57], Lambert et al. and Harold and colleagues described associations between late onset Alzheimer’s disease and genetic markers in three genes in addition to *APOE*: clusterin (*CLU*), complement receptor 1 (*CR1*), and phosphatidylinositol binding clathrin assembly protein (*PICALM*).

J. C. Lambert, S. Heath, G. Even et al., “Genome-wide association study identifies variants at *CLU* and *CR1* associated with Alzheimer’s disease,” *Nature Genetics*, vol. 41, no. 10, pp. 1094–1099, 2009.

D. Harold, R. Abraham, P. Hollingworth et al., “Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer’s disease,” *Nature Genetics*, vol. 41, no. 10, pp. 1088–1093, 2009.

**Beta-amyloid has been shown to possess a wide array of neuroprotective functions**

Ab40 vs Ab42	Biological model	Physiological effect	Ref.
Neuronal viability	Ab <sub>1-28</sub>	Rat hippocampal neurons Ab <sub>1-28</sub> (10-100 mg/ml) enhances cell survival	[1] Science 1989, 243:1488
	Ab <sub>42</sub>	Rat hippocampal neurons Hormetic curve short-to-long-term of low mM treatment – No neurotoxicity at 0.2nM	[2] Science 1990, 250: 279
	Ab <sub>42</sub> & Ab <sub>42</sub>	Rat cortical neurons pM amyloid enhances neuronal viability	[10] J Neurosci. 2003, 23: 5531
Oxidative damage	Ab <sub>42</sub>	Rat cerebral cortex nM Ab <sub>42</sub> reduces iron-induced toxicity	[11] J Neurosci Res, 2003, 73: 316
	Ab <sub>42</sub>	Rat cortical neurons pM monomeric Ab <sub>42</sub> prevents cell death caused by metal-induced oxidative damage	[8] J Neurosci, 2002, 22: 4833
	Ab <sub>42</sub>	Human CSF & plasma nM Ab <sub>42</sub> inhibits auto-oxidation of CSF lipoproteins and plasma LDL	[5] Free Radic Biol Med, 2001, 30: 119
	Ab <sub>42</sub> & Ab <sub>42</sub>	Human CSF CSF oxidative resistance directly correlates with CSF I Ab <sub>42</sub> & Ab <sub>42</sub> levels	[6] Free Radic Res, 2001, 35: 507
Synaptic plasticity, LTP & memory retention	Ab <sub>42</sub> & Ab <sub>42</sub>	Human autopsy brain Ab excess coincides with less oxidative damage – more significant in ApoE <sub>4</sub> carriers and in the presence of NFTs	[7] J Neuropathol Exp Neurol, 2001, 60: 759
	Ab <sub>42</sub>	Rat hippocampus nM Ab <sub>42</sub> enhances NMDA-R mediated synaptic currents	[3] Neuroreport, 1995, 6: 2409
	Ab <sub>42</sub>	Rat hippocampus nM Ab <sub>42</sub> enhances LTP	[4] Eur J Pharmacol, 1995, 286: R1-3
	Ab <sub>42</sub>	Rat hippocampus nM Ab <sub>42</sub> promotes cholesterol-dependent LTP	[9] Neurobiol Lipids, 2003, 1: 45
	Ab <sub>42</sub>	Rat hippocampus Ab <sub>42</sub> depletion disrupts memory retention, pM Ab <sub>42</sub> enhances memory retention	[13] Learn Mem, 2009, 16: 267
	Ab <sub>42</sub>	Mouse primary neurons & hippocampus pM Ab <sub>42</sub> : Short-term (min) enhances LTP & memory; long-term (h) decreases both (hormesis)	[20] Sci Rep 2016, 6: 32553
	Ab <sub>42</sub> , Ab <sub>42</sub> , Ab <sub>1-42</sub>	Human (intracerebral microdialysis) Ab increases with neurological improvement and decreases with neurological decline	[15] Science 2008, 321: 1221
	Ab <sub>42</sub>	Mouse hippocampus Ab depletion reduces LTP and memory. Phenotype rescued by pM Ab <sub>42</sub>	[16] Ann Neurol, 2011, 69: 819
	Ab <sub>42</sub>	Mouse hippocampus Hormetic curve of LTP and memory response to Ab <sub>42</sub> [pM to mM range]	[18] Neurobiol Aging 2012, 33: 1484
	Ab <sub>42</sub> & Ab <sub>42</sub>	Rat hippocampus Endogenous Ab positively modulates release probability via hormetic mechanism in hippocampal synapses	[14] Nat Neurosci, 2009, 12: p. 1567
Acetylcholine receptors	Ab <sub>42</sub>	Mouse hippocampus pM Ab <sub>42</sub> enhances LTP and memory via α7 acetylcholine receptors	[12] J Neurosci 2008, 28: 14537
	Ab <sub>1-42</sub>	Mouse primary neurons & hippocampus Ab <sub>1-42</sub> enhances LTP and memory via acetylcholine receptors	[19] J Neurosci, 2014, 34: 14210
	Ab <sub>42</sub> & Ab <sub>42</sub>	Rat primary neurons pM Ab increases synaptic vesicle recycling via α7 acetylcholine receptors	[21] Front Mol Neurosci 2017, 10: 221
	Intraneuronal Ab	Human autopsy brain Intraneuronal Ab is present from infancy to old age in the general population	[17] Curr Alzheimer Res 2014, 11: 317

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So where do we fit amyloid in the pathogenic cascade of AD? The AH sees it as a toxic byproduct of the APP. But the reality is much more complex than that. Amyloid at low concentrations, between picomolar and low micromolar in in vitro systems, or at endogenous concentrations in the healthy brain, is in fact a physiological molecule, it plays a role in memory formation and initiates an adaptive protective responses against a variety of stress stimuli that are relevant to AD, such as cholesterol dysregulation, microbial infection and oxidative stress, and it does so through a hormetic mechanism.

Baruch-Suchodolsky R, Fischer B. Abeta40, either soluble or aggregated, is a remarkably potent antioxidant in cell-free oxidative systems. Biochemistry. 2009;48(20):4354-70.

**Beta-amyloid peptide possesses potent anti-microbial activity**

Organism	MIC (µg/ml)					
	Aβ42	Aβ40	roAβ42	LL-37	reAβ42	scAβ42
<i>Candida albicans</i>	0.78	0.78	0.78	6.25	>25	>50
<i>Escherichia coli</i>	1.56	1.56	3.13	1.56	>50	>50
<i>Staphylococcus epidermidis</i>	3.13	50	3.13	25	>50	>50
<i>Streptococcus pneumoniae</i>	6.25	12.5	6.25	1.56	50	>50
<i>Staphylococcus aureus</i>	6.25	25	12.5	6.25	>50	>50
<i>Listeria monocytogenes</i>	6.25	25	6.25	25	>50	50
<i>Enterococcus faecalis</i>	6.25	50	3.13	6.25	50	>50
<i>Streptococcus agalactiae</i>	12.5	50	>50	12.5	>50	>50
<i>Pseudomonas aeruginosa</i>	>50	>50	>50	6.25	>50	>50
<i>Streptococcus pyogenes</i>	>50	>50	>50	6.25	>50	>50
<i>Streptococcus mitis</i>	>50	50	>50	6.25	>50	>50
<i>Streptococcus salivarius</i>	>50	>50	>50	50	>50	>50

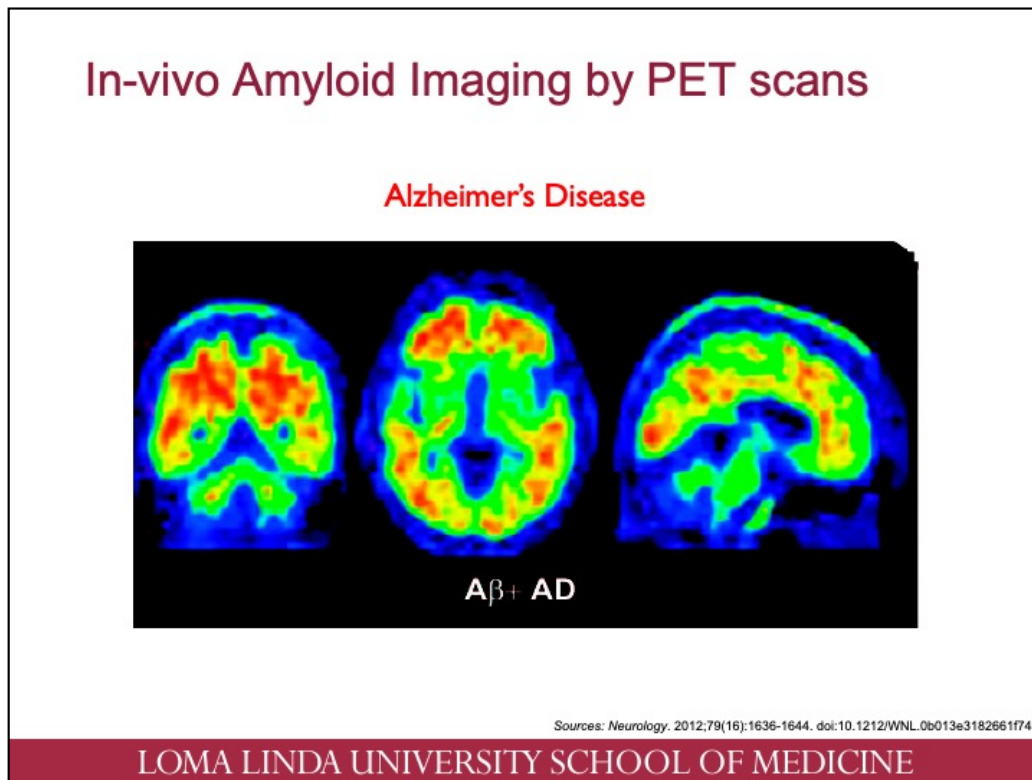
The antimicrobial activity of synthetic Aβ1-42 (Aβ42), Aβ1-40 (Aβ40), LL-37 (LL-37), reverse Aβ42-1 (rAβ42), or scrambled Aβ42 (scAβ42) peptides were determined as minimal inhibitory concentrations (MIC) against 12 microorganisms. Antimicrobial activity was assayed by broth microdilution susceptibility test on 96-well plates with microbial growth in wells determined by visual inspection following an overnight incubation. Inhibition of growth in plate wells was confirmed by alamar blue cell viability assay and by surface plating of incubants on agar and counting CFU. Inoculums contained mid-logarithmic phase cells. Consistent with antimicrobial activity specific to the Aβ sequence, inhibition was not observed for reverse and scrambled peptides. doi:10.1371/journal.pone.0009505.t001

PLoS One. 2010;5(3):e9505

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If the normal function of Aβ is to function as an AMP, then an absence of the peptide may result in increased vulnerability to infection.

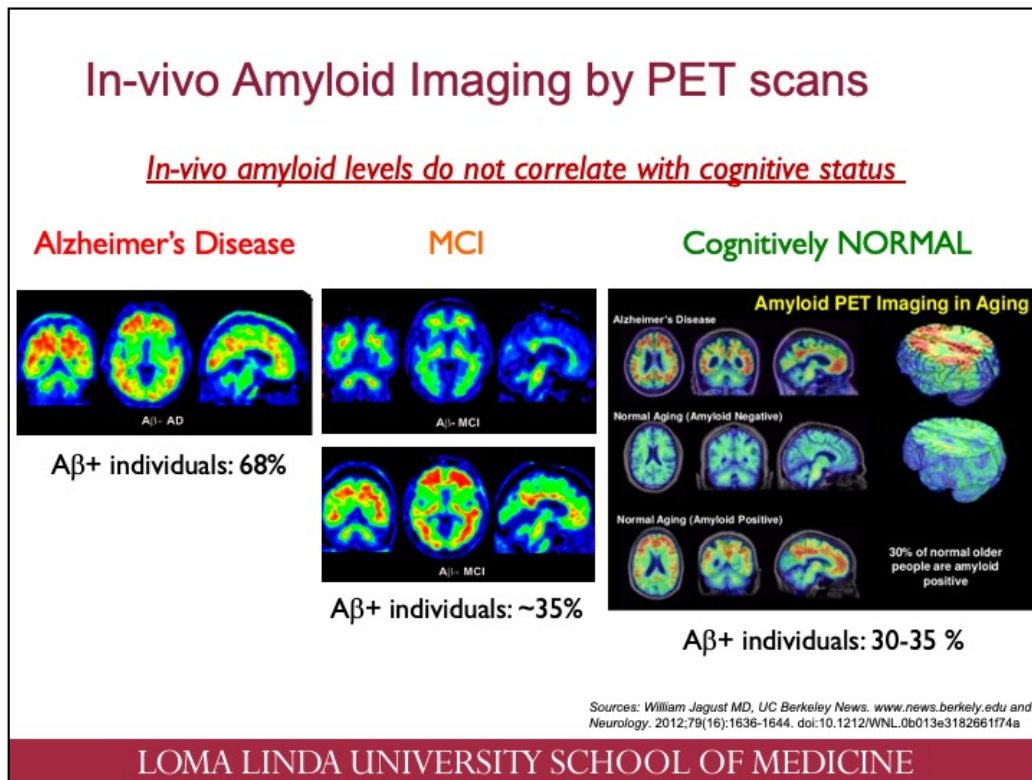
And it's also important to note that amyloid generation is only part of a broader mechanism, which is the processing of the amyloid precursor protein.



When in-vivo imaging for amyloid plaques became available in the early 2000s, it was a BIG deal. There was so much hope for this technology as an accurate diagnostic modality since we had to rely on post-mortem autopsy to confirm amyloid plaques in AD patients.

PET images using florbetapir dye to highlight beta-amyloid plaques show (A), a cognitively normal subject; (B) an amyloid-positive patient with Alzheimer's disease; (C) a patient with mild cognitive impairment; and (D) a patient with mild cognitive impairment who progressed to dementia during the study. Credit: Slide courtesy of the journal *Neurology*.

<https://radiology.ucsf.edu/patient-care/services/specialty-imaging/alzheimer#:~:text=Since%202003%2C%20UCSF%20Imaging%20has,of%20plaques%20in%20living%20people.>



However, when studies were carried out using this modality, we found that not all AD patients had amyloid plaques!!!

32% of AD patients did not have amyloid plaques

~65% of patients with mild cognitive decline did not have amyloid plaques

How do you explain this if amyloid accumulation is supposed to happen years, if not decades, before AD symptoms begin?

AND up to 35% of patients with normal cognitive function had significant amyloid plaques!!

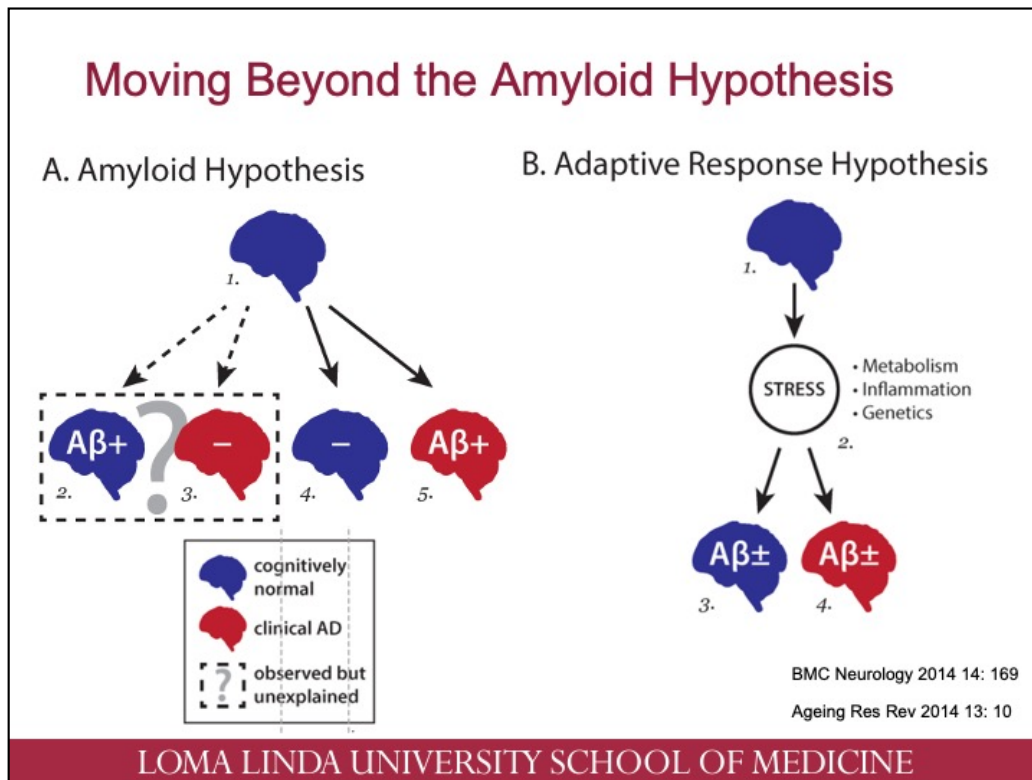
--how are these individuals able to function cognitively if their brain is laden with amyloid?!!

BTW due to this clinical discrepancy, amyloid PET imaging was not adapted to regular clinical practice of AD care.

Instead, it is only used in research as a tool to assess a drug's ability to

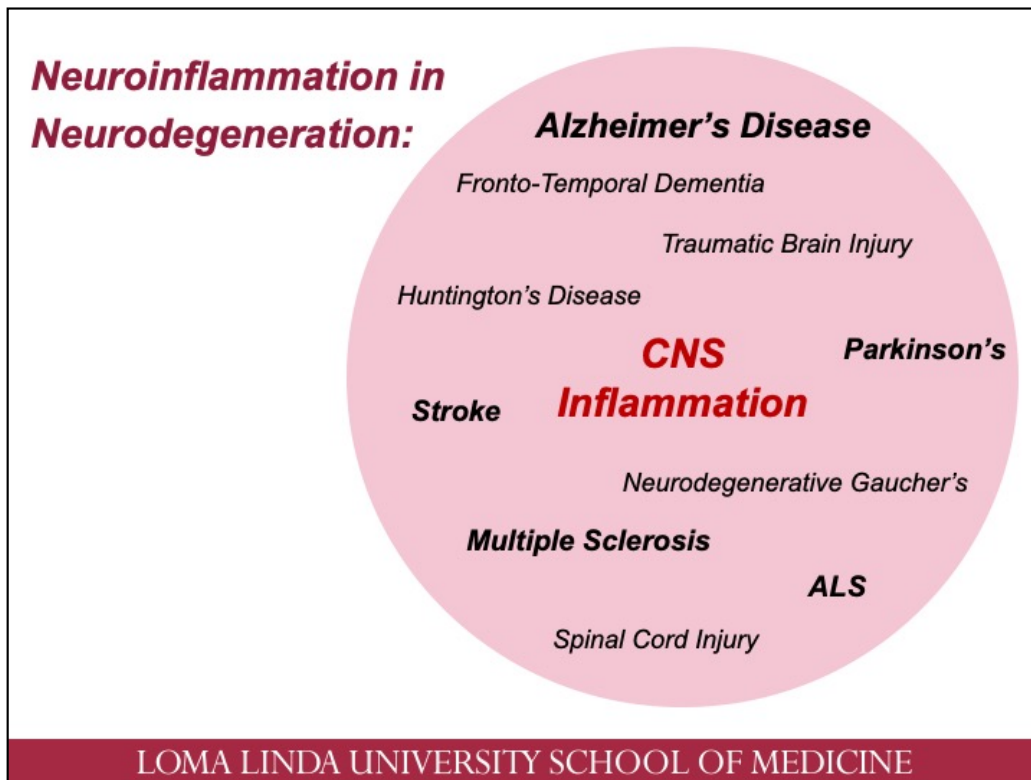
clear amyloid from AD brains... (except full blown AD patients without positive amyloid PET have been excluded from studies!)





Amyloid hypothesis cannot explain the PET imaging findings of amyloid-free AD nor amyloid laden brains that are cognitively normal

Rather, a more nuanced and comprehensive approach will place amyloid as a downstream marker of stress that may or may not affect cognitive function based on individual patient's adaptive response to various sources of stress (including amyloid itself)



Uncontrolled inflammation is emerging as a common denominator of many neurodegenerative conditions, as well as many psychiatric conditions.

# Aducanumab (Aduhelm™) for Alzheimer's Disease

Drug Facts

MOA

Indication

Route of Administration

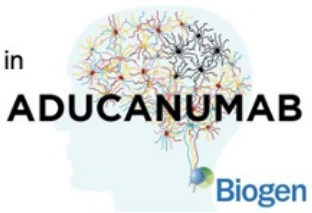
Efficacy

Adverse Effects

Take home points for Patient Education

## Aducanumab (Aduhelm™)

- » Produced by Biogen Inc.
- » First new FDA approved drug for Alzheimer's disease in nearly 20 years



**ADUCANUMAB**  
Biogen

**Current FDA approved pharmacotherapies for AD**

- » Mild-moderate AD: Central acetylcholine esterase inhibitors:
  - Donepezil (Aricept), 1996
  - Rivastigmine (Exelon), 1998
  - **Galantamine (Razadyne), 2001**
- » Moderate-severe AD: NMDA-R antagonist
  - **Memantine (Namenda), 2003**

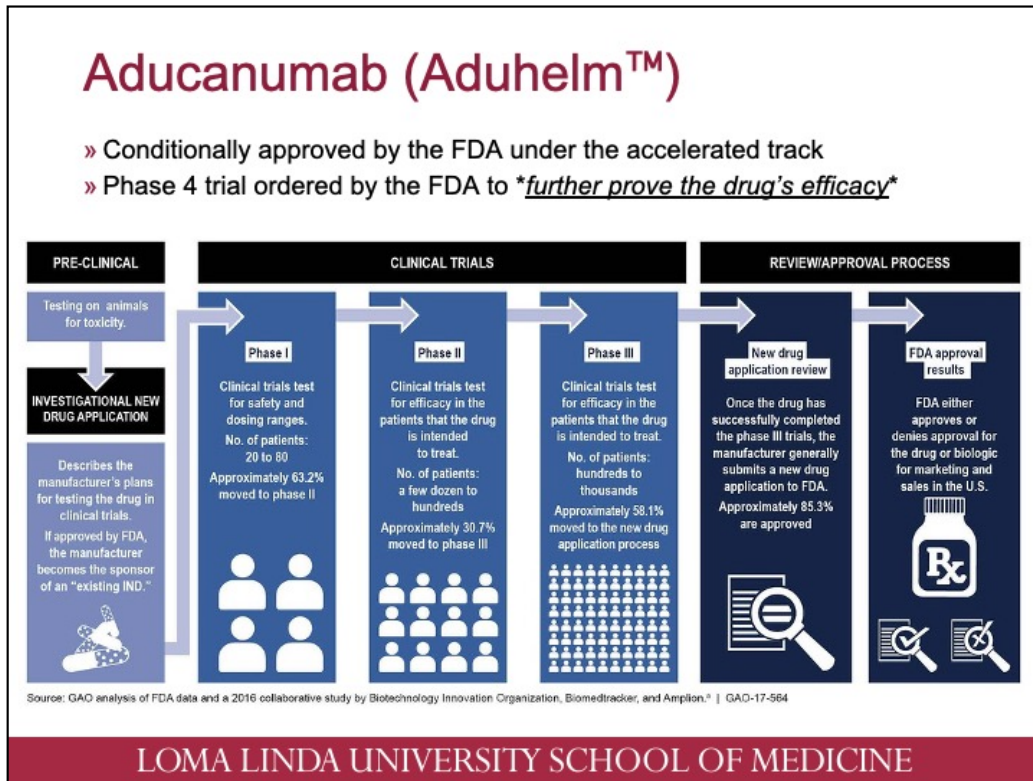
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US Government Accountability Office

Memantine (Nmenda) 2003 – NMDA-R antagonist for mod-sev ALZD

BIG deal, first in nearly 20 years since memantine (Namenda) in 2003, Galatamine CNS-AchE inh 2001

Tacrine was approved by the US Food and Drug Administration (FDA) in 1993, donepezil in 1996, rivastigmine in 1998, galantamine in 2001, and memantine in 2003 (made available in the United States in 2004).



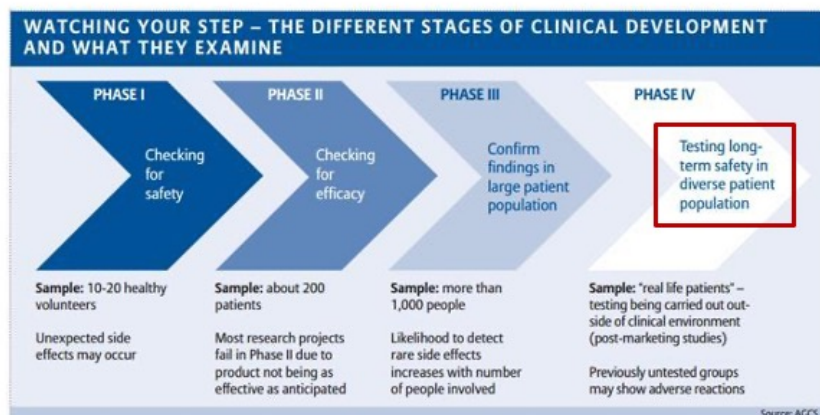
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## Aducanumab (Aduhelm™)



- » FDA approved aducanumab against the FDA's own Peripheral and Central Nervous System Drug Advisory Committee.
  - 0/11 voting members voted "yes" to whether the phase III trials of Aducanumab have proven sufficient clinical efficacy.

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**VOTE:** In light of the understanding provided by the exploratory analyses of Study 301 and Study 302, along with the results of Study 103 and evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology, is it reasonable to consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease? YES/NO/UNCERTAIN

**Vote Results: Yes: 0 No: 10 Uncertain: 1**

**Committee Discussion:** *Almost all of the committee members voted "No", agreeing that it is not reasonable to consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease. These members were not persuaded by the analyses provided and expressed their reluctance to suggest approval of aducanumab for the treatment of Alzheimer's disease due to the insubstantial evidence shown. In addition, these members expressed the difficulty for them to draw a conclusion on the information provided due to un-addressed criticisms provided by the statistical analysis of the studies. The one member who was uncertain on this question noted that Study 302 is positive, and Study 103 provided some additional evidence along with the evidence shown by the biomarkers. Please see the transcript for details of the Committee's discussion.*

## FDA Advisory Committee



### About Advisory Committees

The FDA uses committees and panels to obtain independent expert advice on scientific, technical, and policy matters. FDA seeks to include the views of women and men, members of all racial and ethnic groups, and individuals with and without disabilities on its advisory committees and, therefore, encourages nominations of appropriately qualified candidates from these groups.

 The New York Times

### Three F.D.A. Advisers Resign Over Approval of Alzheimer's Drug

He said the agency's approval of the drug, aducanumab, which is ... Alzheimer's experts — objected to two major aspects of the F.D.A.'s approval decision. ... In November, F.D.A. officials told the advisory committee members  
16 hours ago



Sources: FDA; [www.fda.gov](http://www.fda.gov); [www.nytimes.com](http://www.nytimes.com)

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## Aducanumab (Aduhelm™)

- » Aducanumab was previously announced “futile” by Biogen’s futility analysis of phase III trials.
- » Biogen later “reanalyzed” the data, provided justification for poor outcomes and moved forward with Biologics License Application in 2020

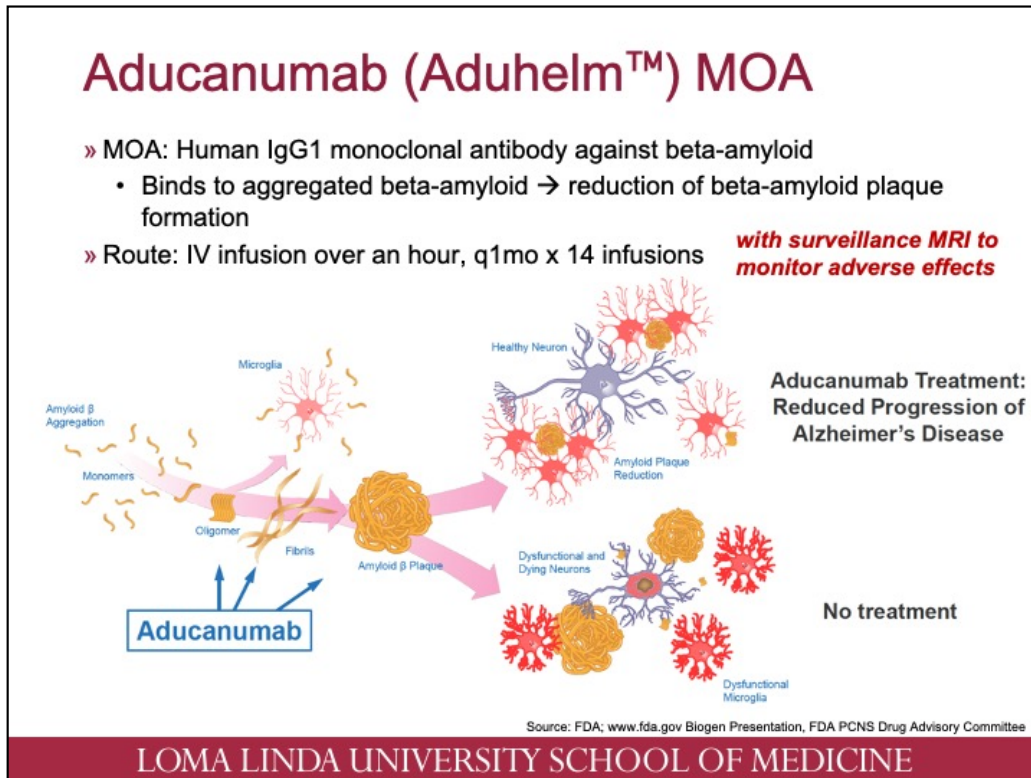
### Aducanumab US Regulatory History



Source: FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

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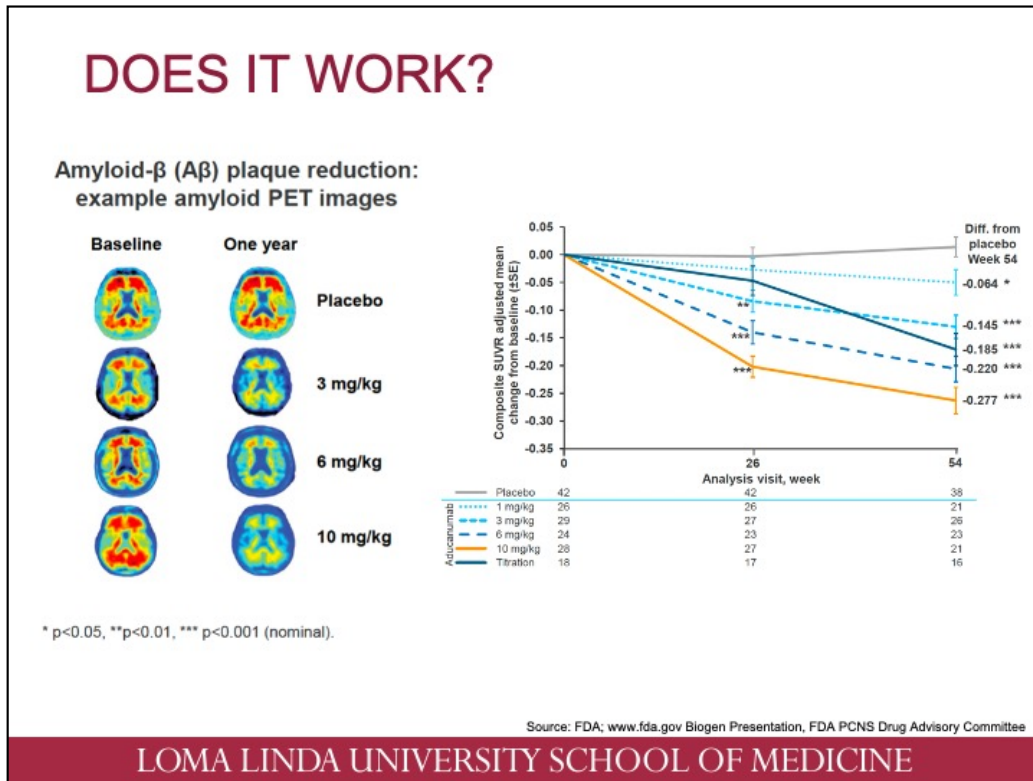


Other similar drugs:

Eli Lilly and Company: solanezumab, failed phase III trial 2015

Pfizer and J&J bapinezumab, failed in 2012 after 2,400 people

Roche – gantenerumab, halted after 3,000 pt



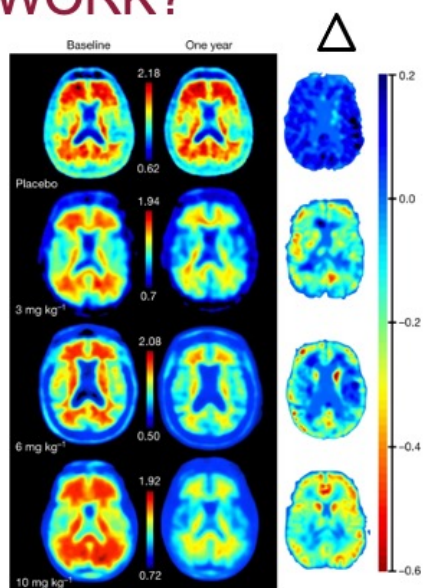
The answer is, it depends!

There is two parts to this

The first part is “does it remove amyloid” = YES

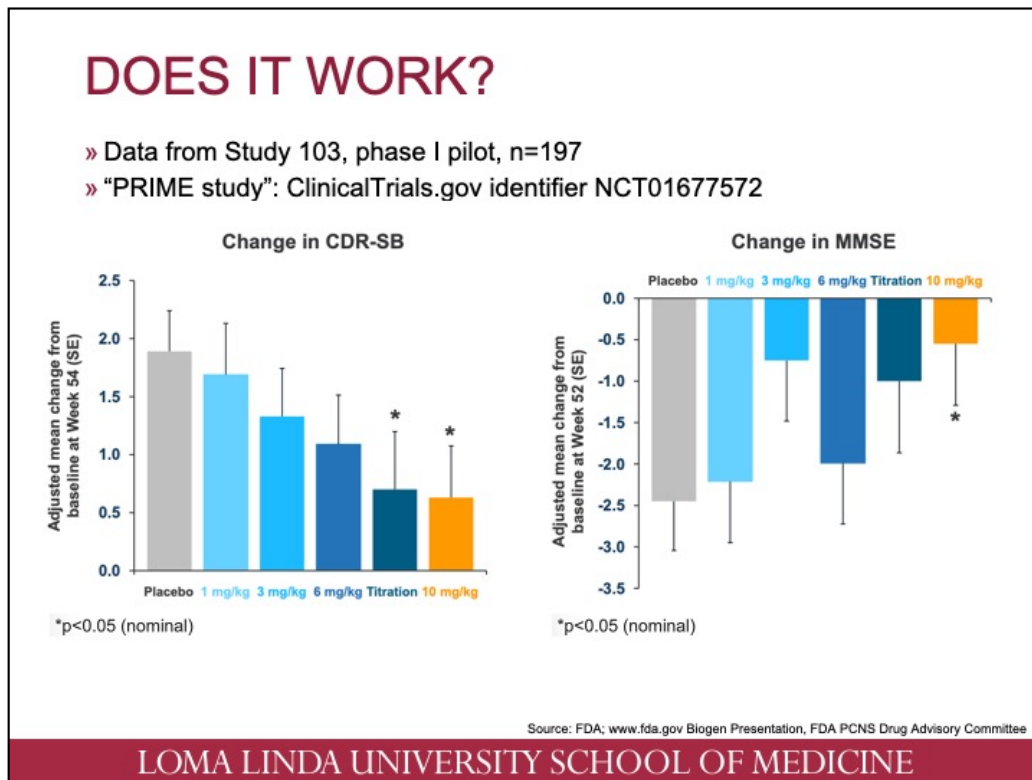
The second part is “does it improve function” = NOOOOO

## DOES IT WORK?



Sevigny, J., Chiao, P., Bussière, T. *et al.* Addendum: The antibody aducanumab reduces A $\beta$  plaques in Alzheimer's disease. *Nature* **546**, 564 (2017). <https://doi.org/10.1038/nature22809>

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The second part of the question in “does it work” is “does it provide clinical benefit?”

CDR-SB = decrease by ~1 pt on CDR-SB with large Ses (0-18, 0 is normal 18 is severe dementia)

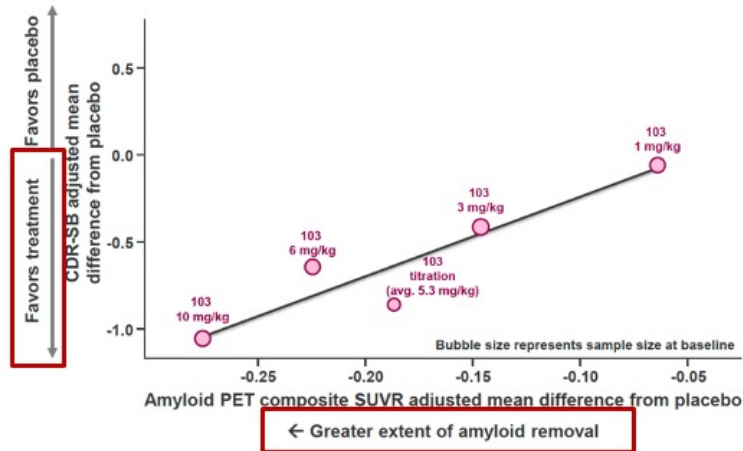
MMSE = improvement by ~2 pts with large Ses (scored 0-30, >25 normal, <10 is severe dementia)

Clinical dementia rating – sum of boxes

Mini-mental status exam = created to trend clinical progression of AD symptoms

## DOES IT WORK?

- » Study 103, pilot proof of concept, n=197
- » "PRIME": **Multiple Dose Study of Aducanumab (BIIB037)**, ClinicalTrials.gov identifier **NCT01677572**



FDA; www.fda.gov, Biogen Presentation, FDA PCNS Drug Advisory Committee, Sevigny, J., Chiao, P., Bussière, T. et al. The antibody aducanumab reduces A $\beta$  plaques in Alzheimer's disease. *Nature* 537, 50–56 (2016).

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## DOES IT WORK?

» CDR-SB: Clinical Dementia Rating-Sum of Boxes

- Six areas: Memory, Orientation, Judgement and Problem Solving, Community Affairs, Home and Hobbies, Personal Care

No memory loss or slight inconsistent forgetfulness (0)	Fully oriented (0)	Solves everyday problems well; judgment good in relation to past performance (0)
Mild consistent forgetfulness; partial recollection of events; "benign" forgetfulness (0.5)	Fully oriented except for slight difficulty with time relationships (0.5)	Slight impairment in solving problems, similarities, and differences (0.5)
Moderate memory loss; more marked for recent events; interferes with everyday activities (1)	Moderate difficulty with time relationships; oriented for place and person at examination but may have geographic disorientation (1)	Moderate difficulty in handling complex problems; social judgment usually maintained (1)
Severe memory loss; only highly learned material retained; new material rapidly lost (2)	Severe difficulty with time relationships; usually disoriented to time, often to place (2)	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired (2)
Severe memory loss; only fragments remain (3)	Oriented to person only (3)	Unable to make judgments or solve problems (3)

Source: <https://www.mdcalc.com/clinical-dementia-rating-cdr-scale>

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Biogen’s aducanumab, AT BEST, improves CDR-SB by ~1 point in the successful group 302 EMERGE.

This was used as a “scientific evidence” to support its approval....

In reality, the 1 point improvement in CDR-SB is vague and minimal

## DOES IT WORK?

» CDR-SB: Clinical Dementia Rating-Sum of Boxes

- Six areas: Memory, Orientation, Judgement and Problem Solving, Community Affairs, Home and Hobbies, Personal Care

Independent function at usual level in job, shopping, business, and financial affairs, volunteer and social groups (0)	Life at home, hobbies, and intellectual interests well maintained (0)	Fully capable of self-care (0)
Slight impairment in these activities (0.5)	Life at home, hobbies, and intellectual interests slightly impaired (0.5)	Needs prompting (1)
Unable to function independently at these activities although may still be engaged in some; <u>appears normal to casual inspection</u> (1)	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned (1)	Requires assistance in dressing, hygiene, keeping of personal effects (2)
No pretense of independent function outside home; <u>appears well enough to be taken to functions outside a family home</u> (2)	Only simple chores preserved; very restricted interests, poorly maintained (2)	Requires much help with personal care; frequent incontinence (3)
No pretense of independent function outside home; appears too ill to be taken to functions outside a family home (3)	No significant function in home (3)	

Source: <https://www.mdcalc.com/clinical-dementia-rating-cdr-scale>

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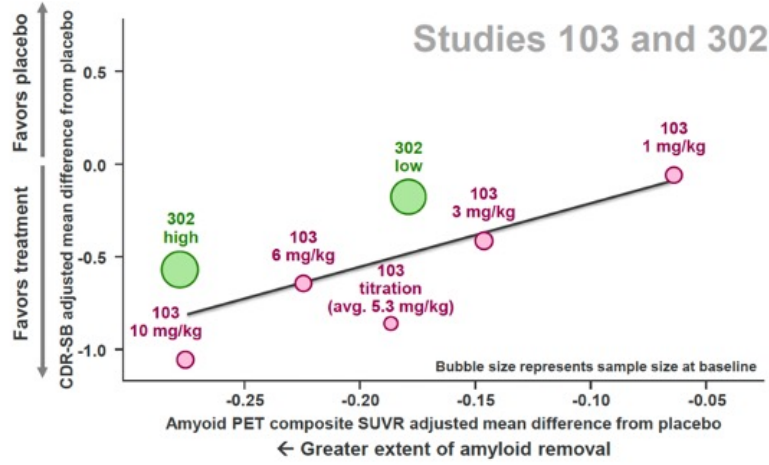
Biogen’s aducanumab, AT BEST, improves CDR-SB by ~1 point in the successful group 302 EMERGE.

This was used as a “scientific evidence” to support its approval....

In reality, the 1 point improvement in CDR-SB is vague and minimal

## DOES IT WORK?

- » Study 302, Phase III, n=1643, ~50% completed
- » "EMERGE": 221AD302 (BIB037), ClinicalTrials.gov identifier **NCT02484547**



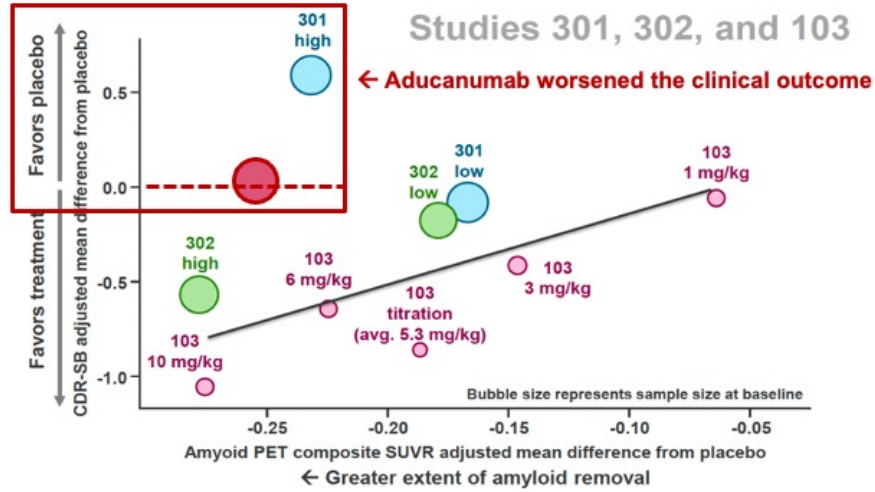
FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

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# DOES IT WORK?

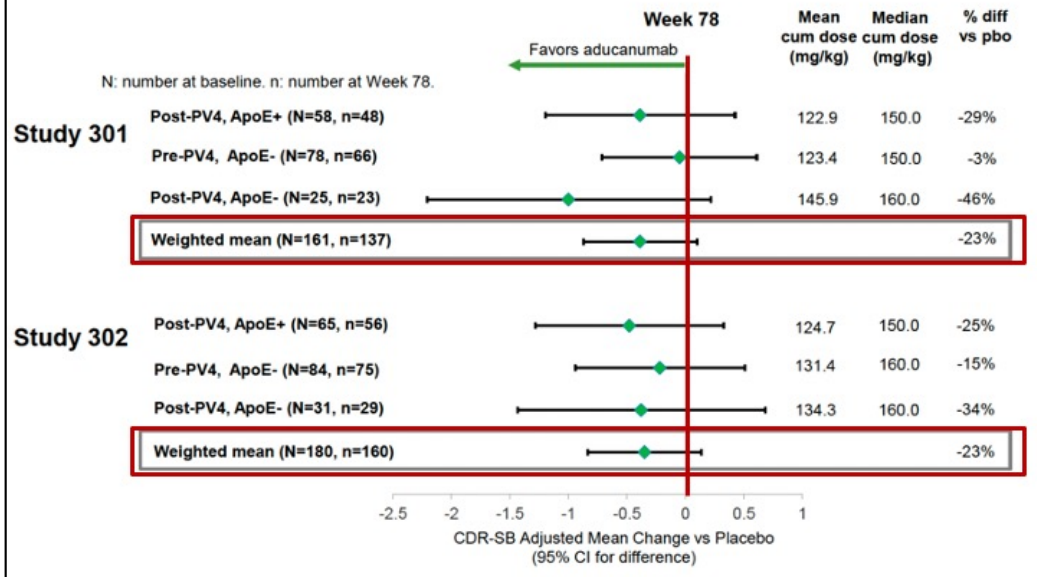
- » Study 301, Phase III, n=1653, ~60% completed
- » "ENGAGE": 221AD301 (BIIB037), ClinicalTrials.gov identifier NCT02477800



FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

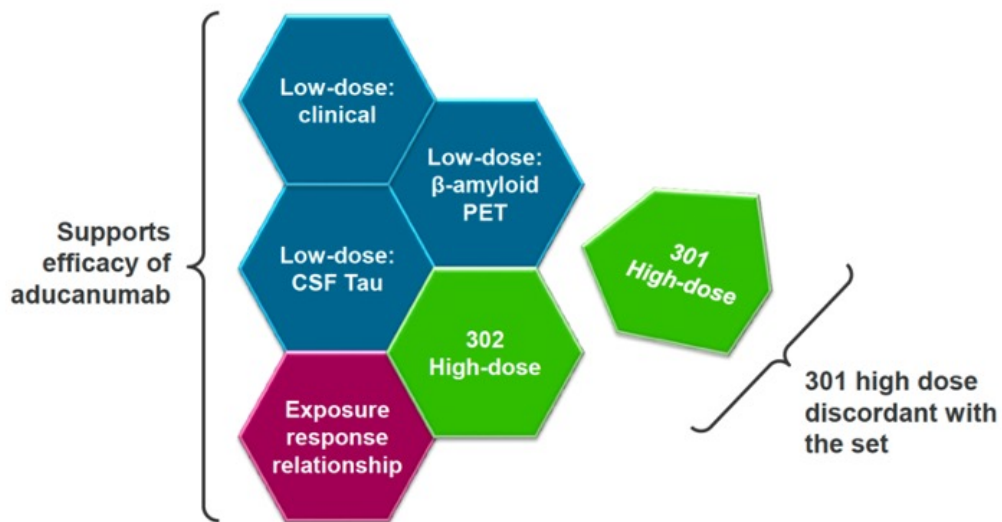
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### Biogen's Rationale for failed 301 high dose group



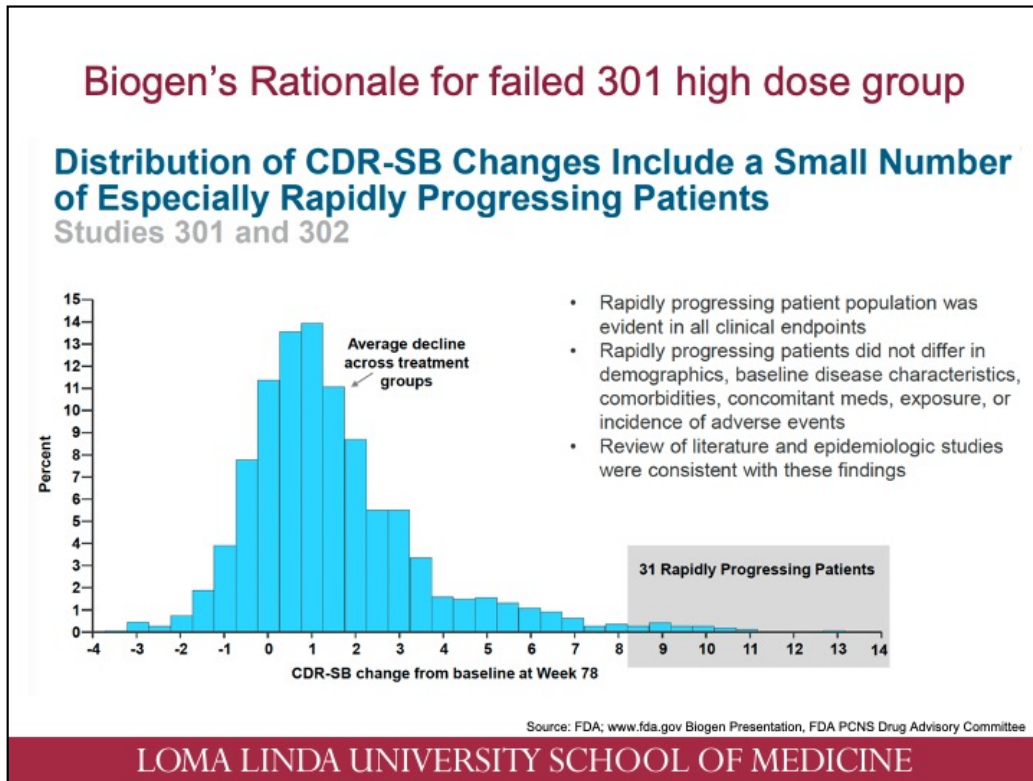
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## Biogen's Rationale for 301 high dose

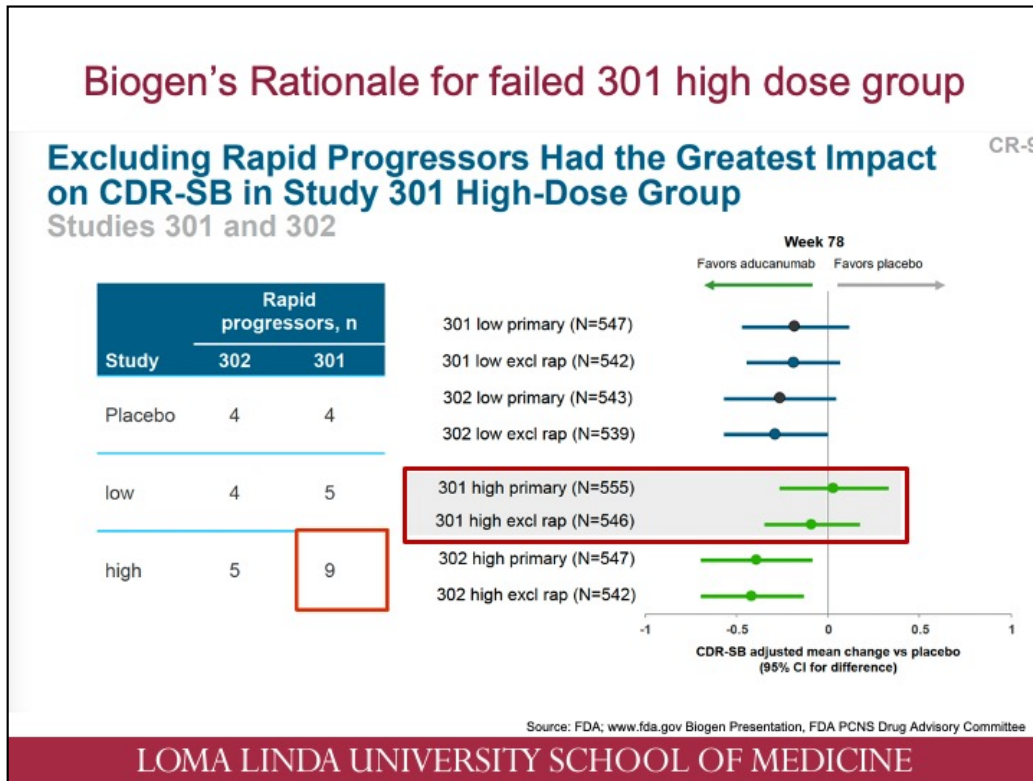


Source: FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

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Basically claiming Sample Bias, claiming there were higher number of rapidly progressing outliers in the 301 high dose group which threw off the whole study



Basically claiming Sample Bias, claiming there were higher number of rapidly progressing outliers in the 301 high dose group which threw off the whole study

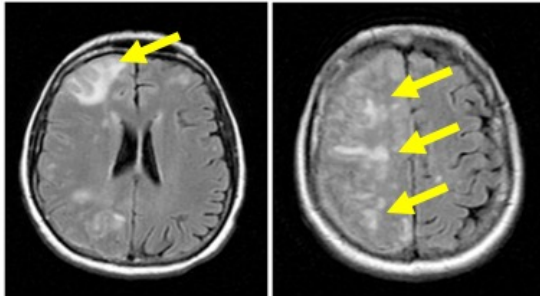
## Adverse Effects: Aducanumab (Aduhelm™)

### Amyloid-Related Imaging Abnormalities (ARIA)

Source: FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

ARIA refers to radiographic abnormalities observed with anti-A $\beta$  antibodies

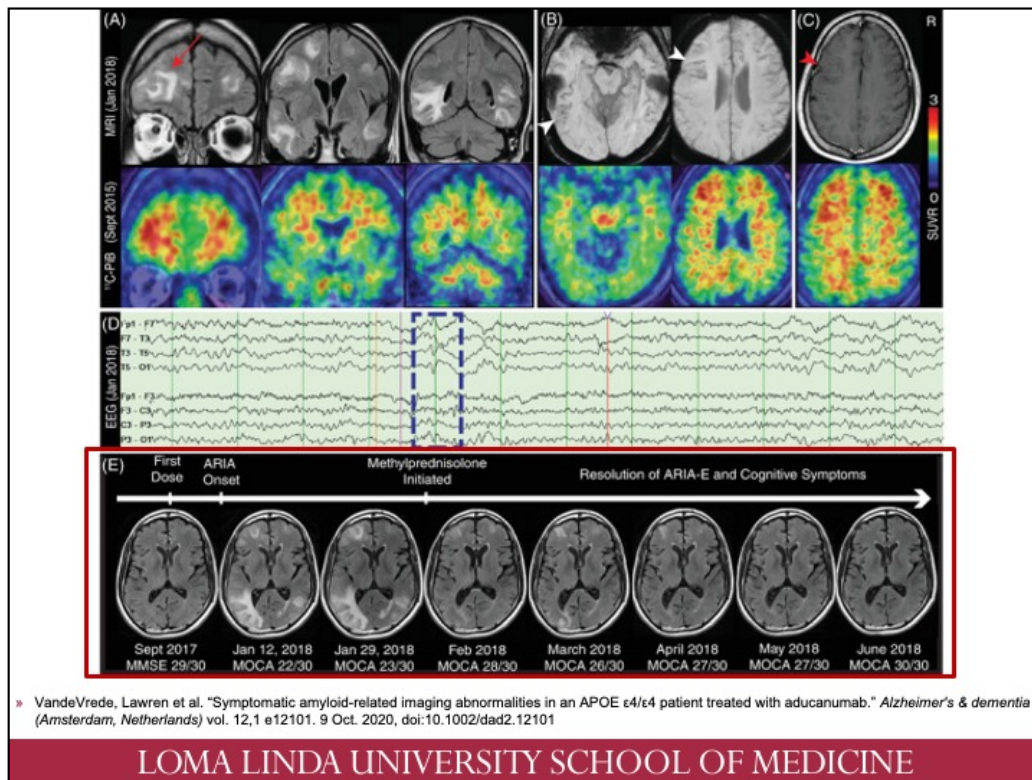
- ARIA-Edema (ARIA-E): vasogenic edema or sulcal effusion
- ARIA-Hemorrhage (ARIA-H): brain microhemorrhages or localized superficial siderosis
- May result from increased cerebrovascular permeability as a consequence of antibody binding to deposited amyloid-beta



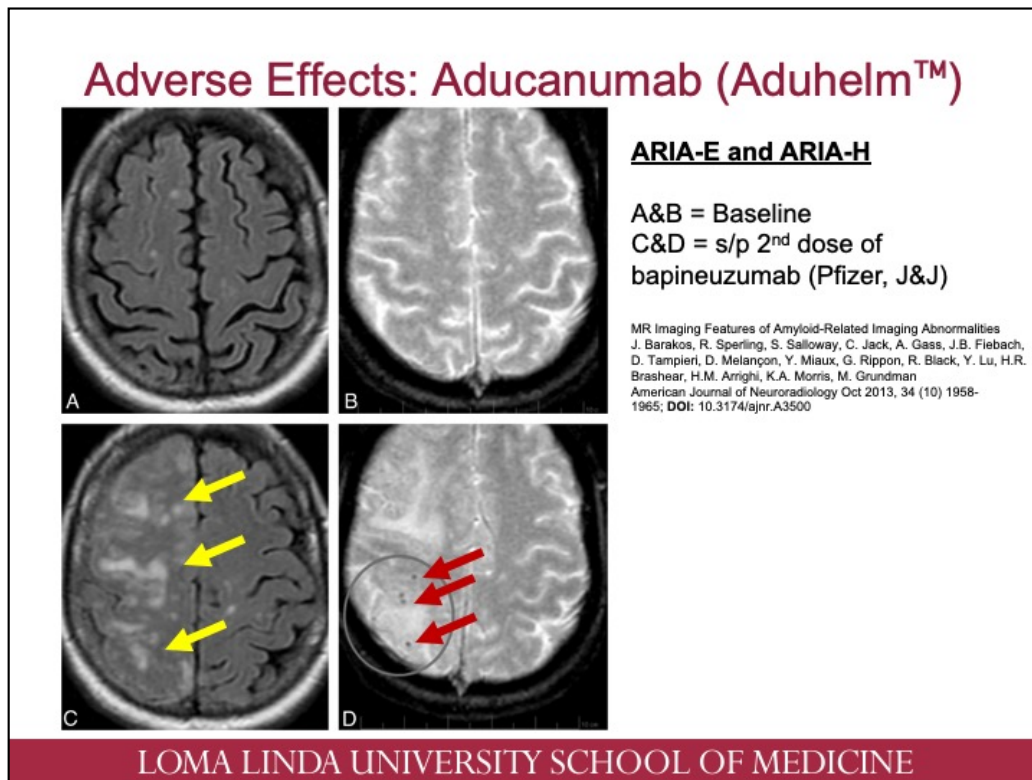
**ARIA-E detected on MR FLAIR**  
Vasogenic Edema appears white

Sperling, Reisa A et al. "Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup." *Alzheimer's & dementia : the journal of the Alzheimer's Association* vol. 7,4 (2011): 367-85. doi:10.1016/j.jalz.2011.05.2351

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**FIGURE 2** Amyloid-related imaging abnormalities (ARIA) after treatment with aducanumab. A, T2 fluid-attenuated inversion recovery (FLAIR) sequences (top) demonstrating ARIA-E after treatment with aducanumab, compared to 2015 <sup>11</sup>C-Pittsburgh Compound B (<sup>11</sup>C-PiB) positron emission tomography (PET; bottom); red arrow highlights edema in area of high amyloid signal in left frontal pole. B, Susceptibility weighted imaging sequence demonstrating ARIA-H (top), compared to 2015 <sup>11</sup>C-PiB PET (bottom); white arrowheads indicate microhemorrhages in left frontal and temporal lobes. C, Post-contrast T1 sequence (top), compared to 2015 <sup>11</sup>C-PiB PET (bottom); red arrowhead indicates nodular enhancement in left frontal lobe. D, Electroencephalogram with left temporal sharps and after-going slow waves (dotted blue box), maximal electronegativity at T3 with field to T1, F7, T5, and O1. E, Sequential T2 FLAIR at the level of maximal edema, with subsequent resolution after treatment with intravenous steroids, with cognitive assessment showing resolution in parallel with ARIA-E



**Fig 4.**ARIA-E (edema) with incident ARIA-H (microhemorrhages). FLAIR and corresponding gradient recalled-echo/T2\* sequences of the same patient, at baseline (A and B) and week 19 (C and D). By week 19 (6 weeks after the second dose of bapineuzumab), significant right-hemispheric edema has developed. As is characteristic of ARIA-E, despite the extensive parenchymal changes, DWI and ADC findings remained normal (not shown), confirming these findings as reflecting vasogenic as opposed to cytotoxic edema. On the corresponding gradient recalled-echo/T2\* images, there is concomitant development of several punctate microhemorrhages in the right parietal region (*circle*). On subsequent imaging, the cerebral edema resolved while the microhemorrhages remained stable (not shown). In general, the severity of ARIA changes was associated with both *Apolipoprotein ε4* allele status and drug dosage. As such, this patient was an *Apolipoprotein ε4* homozygote and in the highest drug-dose arm.



## Adverse Effects: Aducanumab (Aduhelm™)

	Patients, n (%)				Total (all doses combined) N=2198
	Placebo N=1087	Aducanumab			
		3 mg/kg N=760	6 mg/kg N=405	10 mg/kg N=1033	
Adverse events	945 (86.9)	700 (92.1)	347 (85.7)	946 (91.6)	1993 (90.7)
ARIA-E	29 (2.7)	223 (29.3)	83 (20.5)	362 (35.0)	668 (30.4)
Serious adverse events	151 (13.9)	105 (13.8)	54 (13.3)	141 (13.6)	300 (13.6)
Serious ARIA-E	1 (<0.1)	6 (0.8)	3 (0.7)	13 (1.3)	22 (1.0)
Fatal adverse events	5 (0.5)	3 (0.4)	0	8 (0.8)	11 (0.5)

Source: FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

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20-35% of patients experienced ARIA-E

~6% of patients across three doses had to stop the TX due to ARIA

## Adverse Effects: Aducanumab (Aduhelm™)

### ARIA-E Incidence

Studies 301 and 302 Placebo-Controlled Period

	Patients, <sup>a</sup> n (%)	
	Placebo N=1076	Aducanumab 10 mg/kg N=1029
ARIA-E	29 (2.7)	362 (35.2)
ApoE ε4 carriers	16/742 (2.2)	290/674 (43.0)
ApoE ε4 non-carriers	13/334 (3.9)	72/355 (20.3)

Source: FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

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ApoE e4 carriers have significantly higher risk of AD... and this most genetically vulnerable AD patients are the ones who suffer the most adverse effects!

## Adverse Effects: Aducanumab (Aduhelm™)

	Patients, n (%)	
	Placebo N=1087	Aducanumab 10 mg/kg N=1033
<b>Adverse events</b>	<b>945 (86.9)</b>	<b>946 (91.6)</b>
ARIA-E	29 (2.7)	362 (35.0)
Headache	165 (15.2)	212 (20.5)
ARIA-H Brain microhemorrhage	71 (6.5)	197 (19.1)
Fall	128 (11.8)	155 (15.0)
ARIA-H Superficial siderosis	24 (2.2)	151 (14.6)
Diarrhea	74 (6.8)	92 (8.9)

Source: FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

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## Take Home Points for Patient Education

- » Aducanumab is a biologic, a human IgG1 antibody against CNS beta-amyloid plaques
- » Aducanumab is administered intravenously at an infusion center q1mo.
  
- » Aducanumab was approved by the FDA against FDA's independent expert panel
  - None of the 11 voting members voted "yes" to the drug's efficacy
- » Aducanumab's clinical efficacy is questionable with two conflicting phase III trials that were abruptly stopped due to futility analysis
  - Under the best scenario, Aducanumab appears to improve CDR-SB by ~1 pt s/p 1+ year of therapy
  
- » Aducanumab is associated with significant adverse effects of ARIA-E and ARIA-H which can be fatal
  - ~35% patients will develop ARIA-E, ~45% if ApoE e4 carrier
  - **\*\*\*Pt with amyloid-plaques (Cerebral Amyloid Angiopathy) are already at increased risk of hemorrhage. Aducanumab appears to increase this risk\*\*\***
  - Therefore, aducanumab requires surveillance MRIs to monitor adverse effects.
  
- » Aducanumab costs \$56,000 per year + infusion cost + surveillance MRI cost + radiology + ARIA treatment

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Question: Would you prescribe Aducanumab for AD?

Any questions?