

# Aducanumab in the Treatment of Alzheimer's Disease

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THE NEW WONDER DRUG OR A FIGMENT OF OUR  
IMAGINATION?

Cathy Li, BSc(Pharm), ACPR  
Clinical Pharmacist  
Geriatric Specialty Services  
Island Health – South Island

# Presenter disclosure

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Presenter's Name: Cathy Li

I have no current or past relationships with commercial entities

Speaking Fees for current program:

- I have received a speaker's honorarium from CSHP-BC for this learning activity

# Commercial support disclosure

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This learning activity has received no financial or in kind support from any commercial or other organization

# Learning objectives

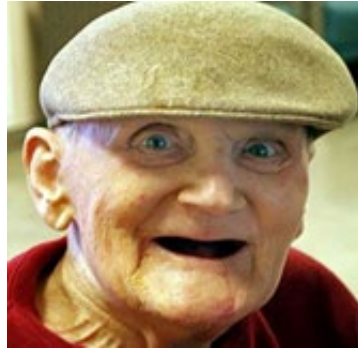
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By the end of this session, the learner will be able to:

Describe the amyloid cascade hypothesis

Describe the mechanism of action of aducanumab

Discuss the efficacy and safety of aducanumab in the treatment of Alzheimer's disease and the controversial FDA approval



# Case: Meet Bob

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# Case

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ID	83 year old male
CC	Declining cognition – “my memory is slipping!”
HPI	Insidious and progressive cognitive dysfunction over 2 years - Forgets what he has done the day before - Forgets where items are in the home - Forgot the steps to make turkey soup - Gets irritated when his memory issues are pointed out
Allergies	None known
Family Hx	Mother had Alzheimer’s disease dementia. Father had cognitive impairment (unclear etiology)
Social Hx	Lives with supportive wife; non-drinker; non-smoker
Compliance	Uses dosette and sets alarms to remind him to take his medications

# Case

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Past Medical history	Medications
Hypertension	Trandolapril 2mg PO daily
Dyslipidemia	Atorvastatin 20mg PO daily
Coronary artery disease	ASA 81mg PO daily
Vitamin B12 deficiency	Vitamin B12 1000mcg SL daily
Lumbar spinal stenosis – 3 back surgeries 1995, 1998, 2005	
Total hip arthroplasty - 2009	

# Case

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Physical Ax	<ul style="list-style-type: none"><li>- BP = 140/76 (HR=77)</li><li>- Chronic numbness and weakness in lower extremities</li><li>- No other significant findings on review of systems</li></ul>
Cognitive Ax	<ul style="list-style-type: none"><li>- MOCA = 25/30 (4 points lost on recall and 1 point on trails B)</li><li>- No major functional loss – continues to grocery shop, cook, clean, drive and handles the finances</li></ul>
Medical Imaging	CT head shows “Deep white matter is homogeneous. Prominent dilation of the temporal horns in keeping with the presence of hippocampal atrophy. Mild generalized atrophy elsewhere with deep white matter ischemic changes”
Diagnosis	Mild Neurocognitive disorder – probable mixed Alzheimer’s and vascular etiology of mild severity

# Bob asks:

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“WHAT CAN I DO OR TAKE TO PREVENT MY  
MEMORY AND THINKING FROM GETTING  
WORSE??”

# Neurocognitive Disorders(NCD)

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ALZHEIMER'S DISEASE



# Neurocognitive Disorders

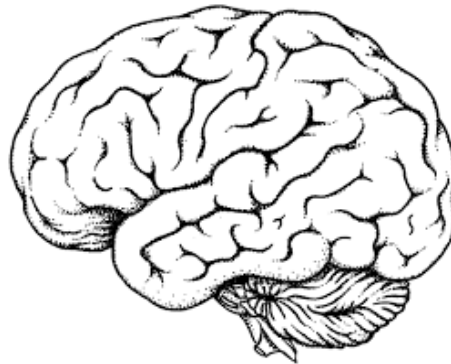
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Clinical syndrome of cognitive and functional decline

- Frequently associated with behavior or personality changes

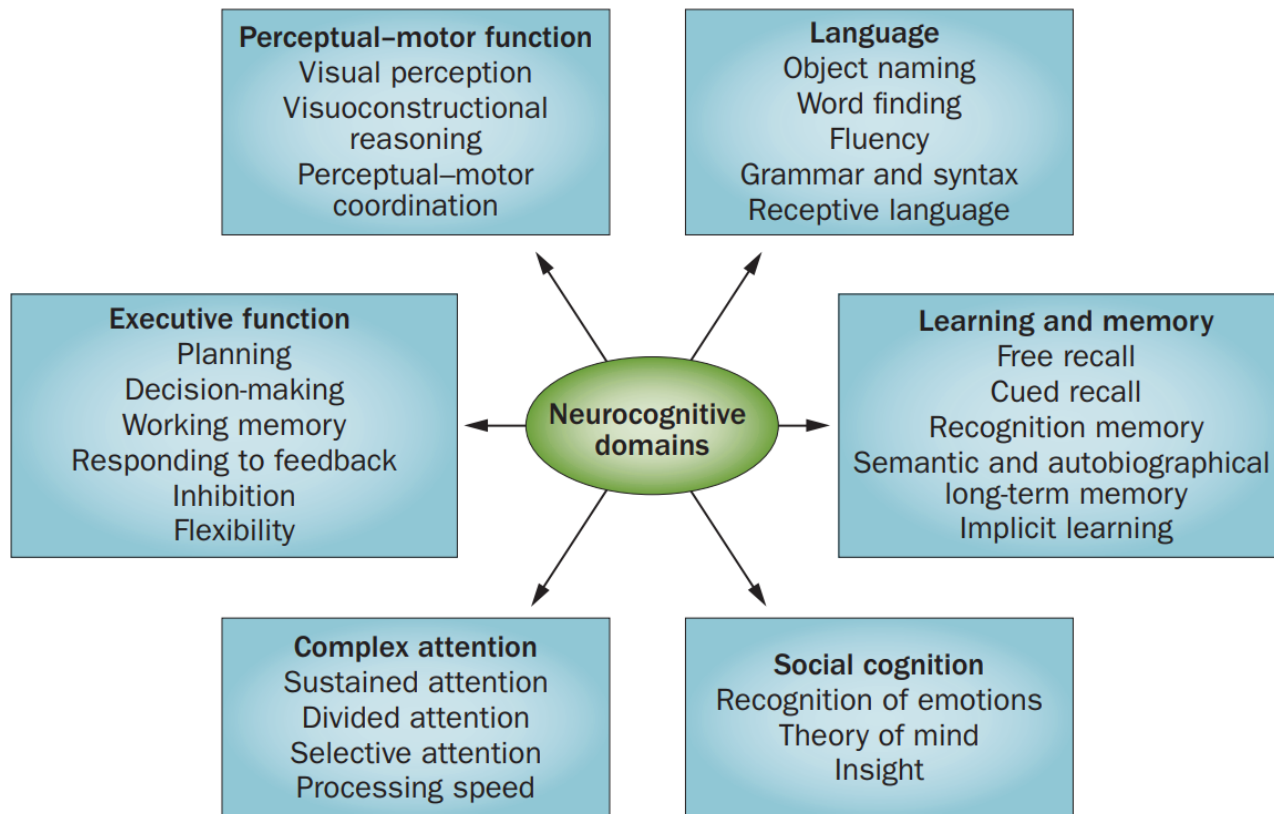
Clinical diagnosis that can't be replaced by any laboratory or imaging test

Clear decline from a previous level of functioning in one or more of a key cognitive domain



# Neurocognitive domains

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# Mild vs major NCD

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Difference between mild and major NCD is the severity of cognitive deficits and functional impairment

Mild NCD = 'Mild Cognitive Impairment' (MCI)

- Modest decline in cognition from a previous level of performance in one or more cognitive domains
- Do not interfere with the capacity for independence in everyday activities

Major NCD = 'Dementia'

- Significant cognitive decline from previous level of performance in one or more cognitive domain
- Cognitive deficits interfere with independence in everyday activities

# Main types of NCD

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Alzheimer's Disease (AD)

Vascular Disease

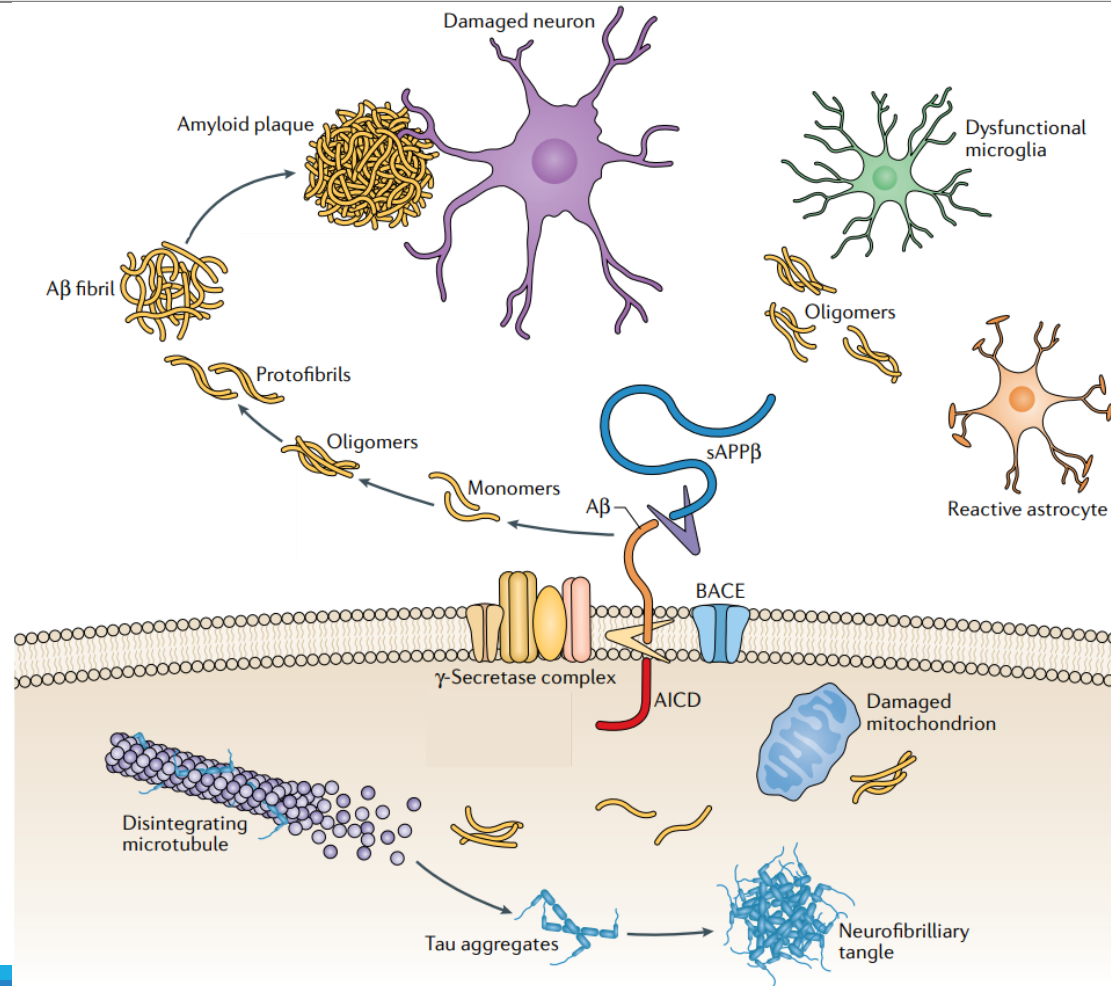
Lewy Body Disease

Parkinson's Disease

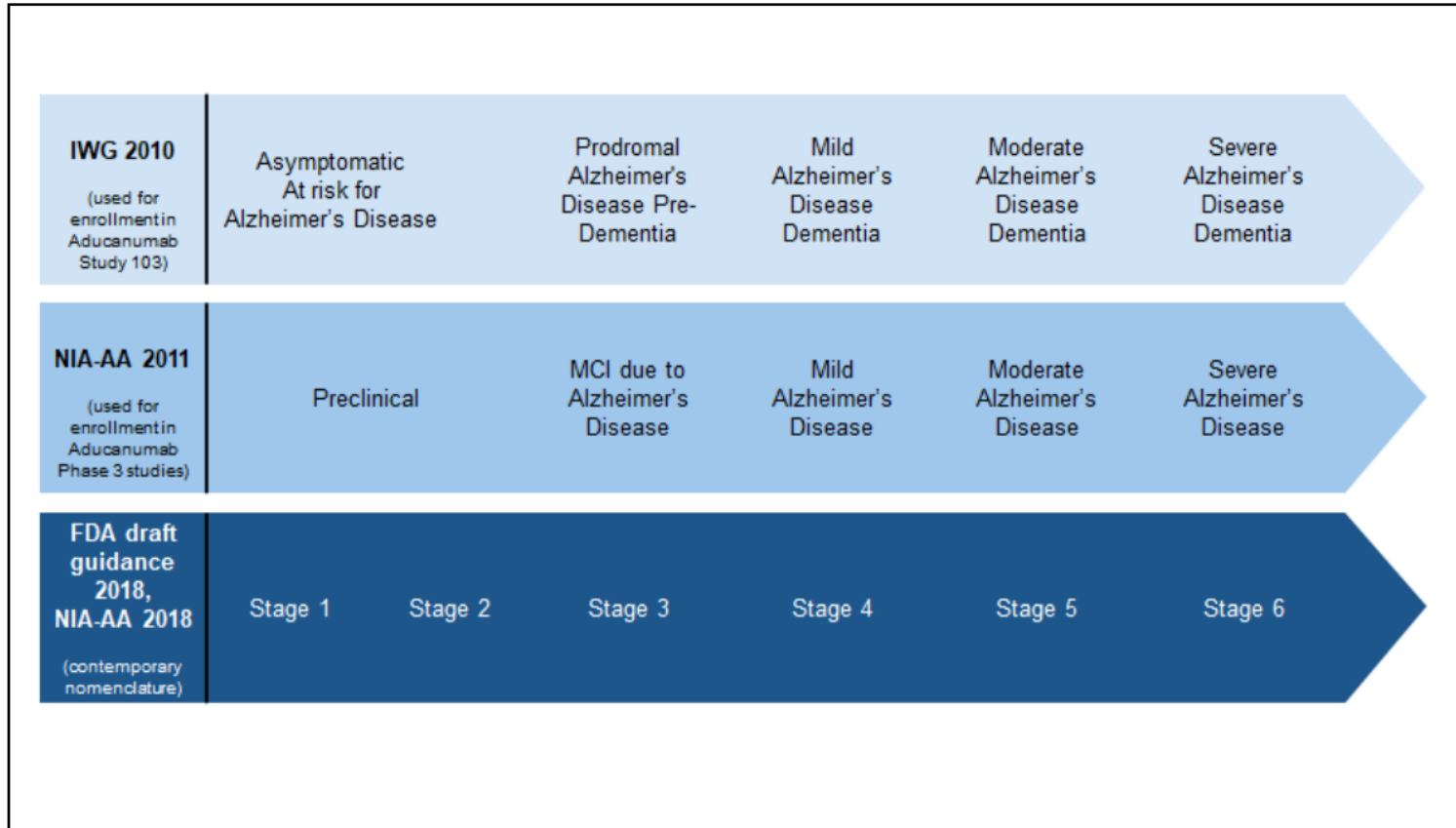
Frontotemporal lobar degeneration



# AD pathophysiology: Amyloid cascade hypothesis



# 6 stages of AD



Abbreviations: IWG = International Working Group; MCI = mild cognitive impairment; NIA-AA = National Institute on Aging and the Alzheimer's Association.

# Cognitive enhancers

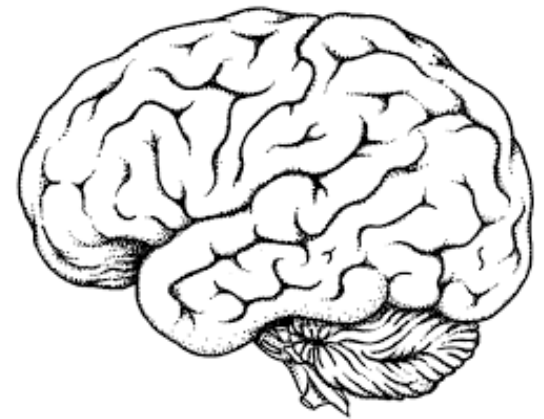
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## Acetylcholinesterase Inhibitors

- Donepezil
- Galantamine ER
- Rivastigmine
- Rivastigmine patch

## NMDA Receptor Antagonist

- Memantine



# June 7, 2021

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EXCITING NEWS IN THE AD WORLD.....



FDA NEWS RELEASE

# FDA Grants Accelerated Approval for Alzheimer's Drug

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**For Immediate Release:** June 07, 2021

Today, the U.S. Food and Drug Administration approved (aducanumab) for the treatment of Alzheimer's, a debilitating disease affecting 6.2 million Americans. ADU 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 the**

Content current as of:  
06/07/2021

Regulated Product(s)  
Drugs

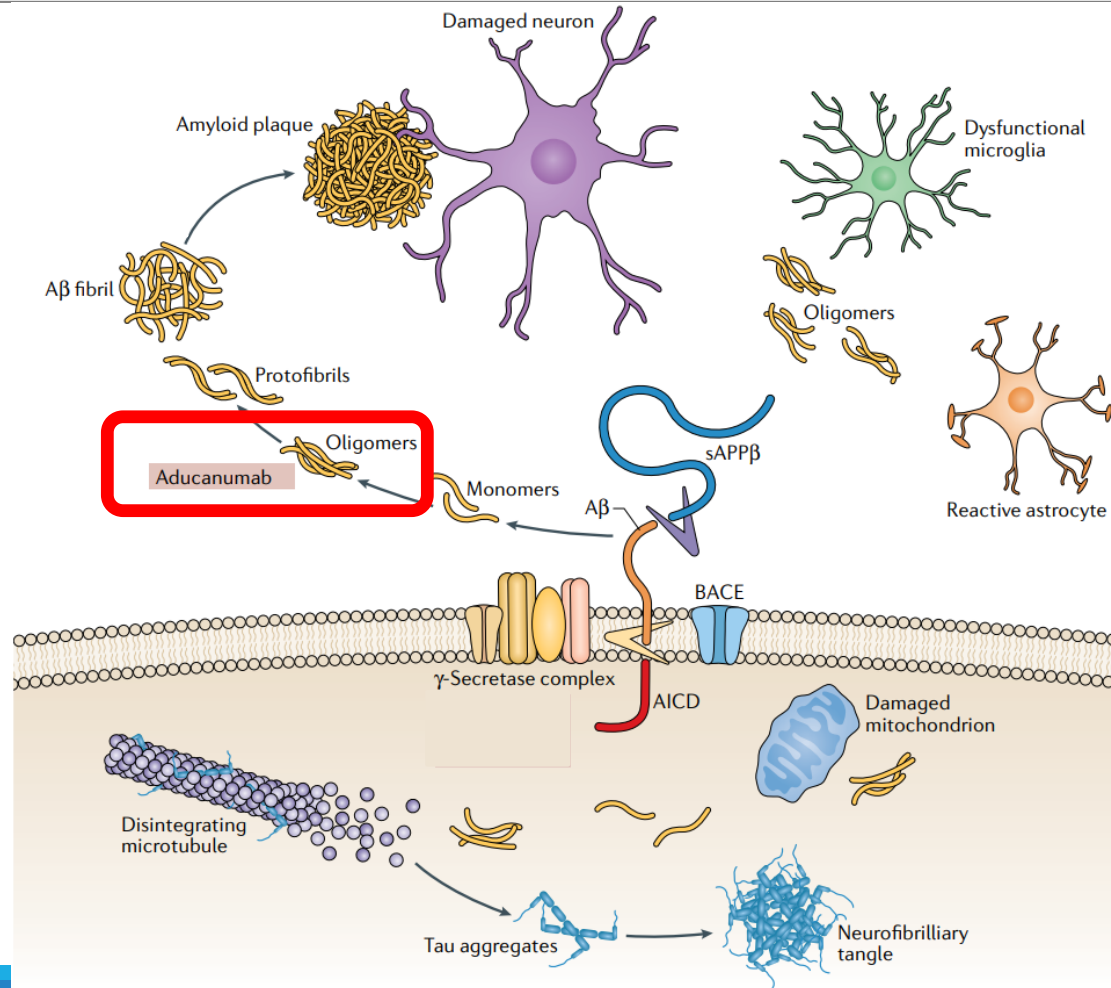
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# Aducanumab (ADU)

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THE NEW WONDER DRUG?

# Mechanism of action



# Failed anti-amyloid-beta therapies in AD

Drug	Mechanism of action	Patient population	Trial phase	Main reasons for failure	Remarks
2002					
AN-1792 (REF. <sup>203</sup> )	A $\beta$ antigen	Mild to moderate AD	II	Toxicity and lack of efficacy	–
2007					
Tramiprosate <sup>204</sup>	A $\beta$ aggregation inhibitor	Mild to moderate AD	III	Lack of efficacy	–
2009					
Tarenflurbit <sup>205</sup>	$\gamma$ -Secretase modulator	Mild AD	III	Lack of efficacy	Worsens global status
Scyllo-inositol <sup>206</sup>	A $\beta$ aggregation inhibitor	Mild to moderate AD	II	Toxicity and lack of efficacy	* Increases mortality * Inactivates A $\beta$ oligomers
2010					
Begacestat <sup>207</sup>	$\gamma$ -Secretase inhibitor	Mild to moderate AD	II	Toxicity and lack of efficacy	–
2011					
Ponezumab <sup>208</sup>	Anti-A $\beta$ monoclonal antibody	Mild to moderate AD	II	Lack of efficacy	–
Semagacestat <sup>209</sup>	$\gamma$ -Secretase inhibitor	Mild to moderate AD	III	Toxicity and lack of efficacy	Worsens cognition
2012					
Bapineuzumab <sup>210</sup>	Anti-A $\beta$ monoclonal antibody	Mild to moderate AD	III	Lack of efficacy	–
Avagacestat <sup>211</sup>	$\gamma$ -Secretase inhibitor	Mild to moderate AD	II	Toxicity and lack of efficacy	Worsens cognition
Avagacestat <sup>212</sup>	$\gamma$ -Secretase inhibitor	Prodromal AD	II	Toxicity and lack of efficacy	Worsens cognition
2013					
Solanezumab <sup>49</sup>	Anti-A $\beta$ monoclonal antibody	Mild to moderate AD	III	Lack of efficacy	–
Vanutide <sup>56</sup>	A $\beta$ antigen	Mild to moderate AD	II	Lack of efficacy	–
Immunoglobulin <sup>221</sup>	Anti-A $\beta$ polyclonal antibody	Mild to moderate AD	III	Lack of efficacy	–
LY2886721 (REF. <sup>214</sup> )	$\beta$ -Secretase inhibitor	Mild to moderate AD	II	Toxicity	–
AZD3839 (REF. <sup>215</sup> )	$\beta$ -Secretase inhibitor	Healthy volunteers	I	Toxicity	–
2014					
Affitope AD02 (REF. <sup>216</sup> )	A $\beta$ antigen	Early AD	II	Lack of efficacy	Worsens cognition
CAD106 (REF. <sup>46</sup> )	A $\beta$ antigen	Mild AD	II	Lack of efficacy	Worsens cognition
PBT2 (REF. <sup>217</sup> )	A $\beta$ aggregation inhibitor	Prodromal AD	II	Lack of efficacy	–
Crenezumab <sup>65</sup>	Anti-A $\beta$ monoclonal antibody	Mild to moderate AD	II	Lack of efficacy	Binds oligomeric A $\beta$
Gantenerumab <sup>57</sup>	Anti-A $\beta$ monoclonal antibody	Prodromal AD	II	Lack of efficacy	Binds oligomeric A $\beta$
Gantenerumab <sup>59</sup>	Anti-A $\beta$ monoclonal antibody	Mild AD	II	Lack of efficacy	Binds oligomeric A $\beta$
2016					
Solanezumab <sup>58</sup>	Anti-A $\beta$ monoclonal antibody	Mild AD	III	Lack of efficacy	–
Solanezumab <sup>218</sup>	Anti-A $\beta$ monoclonal antibody	Prodromal AD	III	Strategic	–
Verubecestat <sup>59</sup>	BACE inhibitor	Mild to moderate AD	III	Lack of efficacy	* Increases mortality * Worsens cognition
2018					
Verubecestat <sup>62</sup>	BACE inhibitor	Prodromal AD	III	Lack of efficacy	Worsens cognition
Atabecestat <sup>66</sup>	BACE inhibitor	Asymptomatic at risk of AD	III	Toxicity	Worsens cognition
Lanabecestat <sup>68</sup>	BACE inhibitor	Early AD	III	Lack of efficacy	Worsens cognition
Lanabecestat <sup>68</sup>	BACE inhibitor	Mild AD	III	Lack of efficacy	Worsens cognition

Studies are grouped by year of publication of the main results. A $\beta$ , amyloid- $\beta$ ; AD, Alzheimer disease; BACE,  $\beta$ -secretase.

# PRIME: Phase 1b Trial

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(STUDY 103)

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# The antibody aducanumab reduces A $\beta$ plaques in Alzheimer's disease

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

**Alzheimer's disease (AD) is characterized by deposition of amyloid- $\beta$  (A $\beta$ ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against A $\beta$  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 A $\beta$ . In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal A $\beta$ , and reduce soluble and insoluble A $\beta$  in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain A $\beta$  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.**

# EMERGE and ENGAGE: Phase 3 Clinical Trials

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(STUDIES 302 AND 301)



# EMERGE and ENGAGE

Author & Year of Publication (Trial)	Study Design & Duration of Follow-Up
EMERGE (302) <sup>25</sup>	<p>Two Phase III Global, Double-Blind, Placebo-Controlled, RCTs</p> <p>18-month DB PC treatment period followed by dose-blinded LTE</p> <p><b>Randomization stratified by Apolipoprotein E (APOE) e4</b></p> <p><b>Inclusion:</b></p> <ul style="list-style-type: none"> <li>- MMSE 24-30</li> <li>- +ve amyloid PET scan</li> <li>- Stable meds x 8 weeks</li> </ul> <p><b>Exclusion:</b></p> <ul style="list-style-type: none"> <li>- Any unstable cardiac or psychiatric conditions</li> <li>- Any medical conditions that may contribute to cognitive impairment</li> </ul>
ENGAGE (301) <sup>25</sup>	<ul style="list-style-type: none"> <li>- Any bleeding disorders, brain hemorrhage, or CV disorders</li> <li>- Any blood thinners (except ASA ≤ 325mg)</li> </ul>

# Protocol amendments

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Version 1: Issued April 9, 2015

Version 2: No patients were consented

Version 3: Issued July 21, 2016

- Modified dosing in relation to amyloid related imaging abnormalities (ARIA) management

Version 4: Issued March 24, 2017

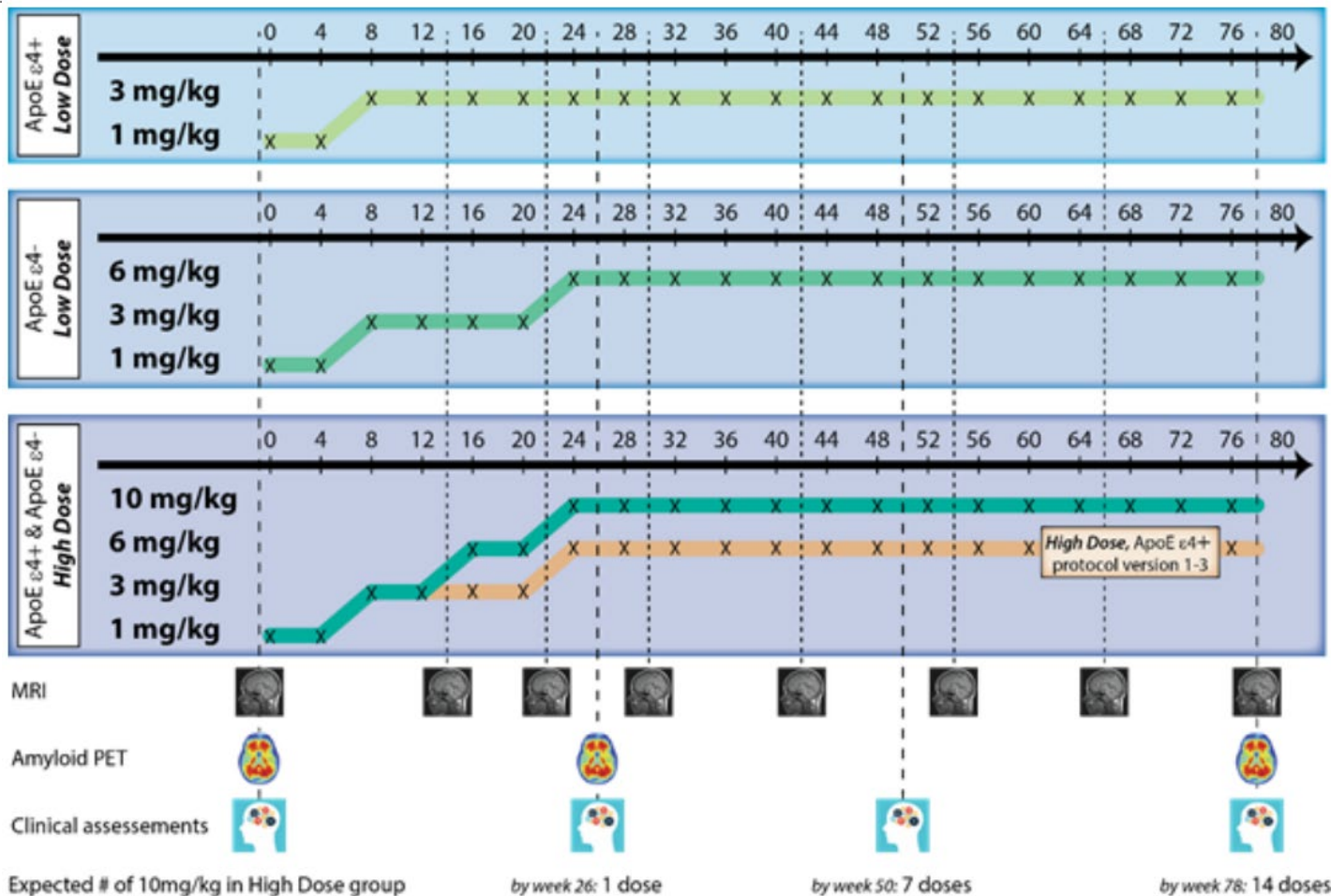
- Allowed ApoE  $\epsilon$ 4 carriers randomized to ADU high dose to receive the same ADU dose received by ApoE  $\epsilon$ 4 non-carriers (titrate to 10mg/kg)

Version 5: ?

Version 6: Issued June 28, 2018

- Updated sample size from 450 to 535 per treatment group following blinded sample size re-estimation

# Dose regimen



# Statistics

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Statistical analysis plan finalized on September 11, 2018

Mixed model repeated measures model to analyze primary endpoint change from baseline CDR-SB

Multiplicity adjustments to control Type I error rate

Analysis of pre-defined subgroups

Interim analysis— blinded sample size reassessment

# Statistics

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## Interim analysis– futility assessment

- Planned to occur after ~50% of patients had completed week 78 visit
- Conducted by an independent, unblinded statistician
- Futility criteria based on conditional power
  - Defined as the chance that the primary efficacy endpoint analysis would be statistically significant in favor of aducanumab at the planned final analysis, given the data at the futility analysis
  - Studies considered futile if both studies had conditional power for the primary efficacy analysis that was less than 20% in both the high-dose and low-dose treatment groups

# Baseline characteristics

Study Arms	EMERGE (302) <sup>75,25</sup>				ENGAGE (301) <sup>75,25</sup>				
	Placebo	Low Dose	High Dose	Overall	Placebo	Low Dose	High Dose	Overall	
<b>N</b>	<b>548</b>	<b>543</b>	<b>547</b>	<b>1638</b>	<b>545</b>	<b>547</b>	<b>555</b>	<b>1647</b>	
<b>Age, Mean (SD)</b>	70.8 (7.40)	70.6 (7.45)	70.6 (7.47)	70.7 (7.43)	69.8 (7.72)	70.4 (6.96)	70.0 (7.65)	70.1 (7.45)	
<b>Female, n (%)</b>	290 (52.9)	269 (49.5)	284 (51.9)	843 (51.5)	287 (52.7)	284 (51.9)	292 (52.6)	863 (52.4)	
<b>Race, n (%)</b>	Asian	77 (14.1)	89 (16.4)	72 (13.1)	128 (7.8)	55 (10.1)	55 (10.1)	125 (10.6)	
	White	431 (78.6)	432 (79.6)	422 (77.1)	1285 (78.4)	413 (75.8)	412 (75.3)	413 (74.4)	1238 (75.2)
<b>Education Years, Mean (SD)</b>	14.5 (3.68)	14.5 (3.63)	14.5 (3.60)	14.5 (3.63)	14.7 (3.66)	14.6 (3.77)	14.6 (3.72)	14.6 (3.71)	
<b>AD Medications Used, n (%)</b>	282 (51.5)	281 (51.7)	285 (52.1)	848 (51.8)	299 (54.9)	317 (58.0)	313 (56.4)	929 (56.4)	
<b>APOE ε4 Status, n (%)</b>	Carrier	368 (67.2)	362 (66.7)	365 (66.7)	1095 (66.8)	376 (69.0)	391 (71.5)	378 (68.1)	1145 (69.5)
	Non-Carrier	178 (32.5)	178 (32.8)	181 (33.1)	537 (32.8)	167 (30.6)	156 (28.5)	176 (31.7)	499 (30.3)
<b>Clinical Stage, n (%)</b>	MCI due to AD	446 (81.4)	452 (83.2)	438 (80.1)	1336 (81.6)	443 (81.3)	440 (80.4)	442 (79.6)	1325 (80.4)
	Mild AD	102 (18.6)	91 (16.8)	109 (19.9)	302 (18.4)	102 (18.7)	107 (19.6)	113 (20.4)	322 (19.6)
<b>Amyloid PET SUVR, Mean Composite (SD), n (Sub-Study – Not Full Population)</b>	1.38 (0.17), 159	1.40 (0.18), 159	1.38 (0.18), 170	1.38 (0.18), 488	1.38 (0.20), 204	1.39 (0.19), 198	1.41 (0.18), 183	1.39 (0.19), 585	
<b>RBANS Delayed Memory Score, Mean (SD)</b>	60.5 (14.23)	60.0 (14.02)	60.7 (14.15)	NR	60.0 (13.65)	59.5 (14.16)	60.6 (14.09)	NR	
<b>MMSE Score, Mean (SD)</b>	26.4 (1.78)	26.3 (1.72)	26.3 (1.68)	26.3 (1.73)	26.4 (1.73)	26.4 (1.78)	26.4 (1.77)	26.4 (1.76)	
<b>CDR Global Score</b>	0.5	544 (99.3)	543 (100)	546 (99.8)	NR	544 (99.8)	546 (99.8)	554 (99.8)	NR
	1	3 (0.5)	0 (0)	1 (0.2)	NR	1 (0.2)	1 (0.2)	0 (0)	NR
<b>CDR-SB Score, Mean (SD)</b>	2.47 (1.00)	2.46 (1.01)	2.51 (1.05)	2.48 (1.02)	2.40 (1.01)	2.43 (1.01)	2.40 (1.01)	2.41 (1.01)	
<b>ADAS-Cog 13 Score, Mean (SD)</b>	21.9 (6.7)	22.5 (6.8)	22.2 (7.1)	22.2 (6.9)	22.5 (6.6)	22.5 (6.3)	22.4 (6.5)	22.5 (6.5)	
<b>ADCS-ADL-MCI Score, Mean (SD)</b>	42.6 (5.7)	42.8 (5.5)	42.5 (5.2)	42.6 (5.7)	43.0 (5.6)	42.9 (5.7)	42.9 (5.7)	42.9 (5.7)	

AD: Alzheimer's disease, ADAS-Cog 13: Alzheimer's Disease Assessment Scale-Cognitive 13-Item Scale, ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment, APOE ε4: apolipoprotein Eε4, CDR: Clinical Dementia Rating scale, CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes, MCI: mild cognitive impairment, mg/kg: milligram per kilogram, MMSE: Mini-Mental State Examination, n: number, N: total number, NR: not reported, PET: positron emission tomography, RBANS: Repeatable Battery for the Assessment of Neuropsychological Status, SD: standard deviation, SUVR: standard uptake value ratio

# March 21, 2019

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FUTILITY ASSESSMENT - OH NO.....

# Futility assessment

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Estimated conditional power values, based on pooled data for CDR-SB in high dose group:

- EMERGE (302): 12%
- ENGAGE (301): 0%

# October 22, 2019

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BUT, WAIT....

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# Review of futility results

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Using pre-specified analysis methods, CDR-SB showed:

- EMERGE (302): Treatment difference favoring high dose ADU of -18%
- ENGAGE (301): Treatment difference favoring placebo of 15%

Results violated assumption that the estimation of conditional power would be similar

Conditional power reestimated for individual studies:

- EMERGE (302): 59%
- ENGAGE (301): 0%

Results violated assumption that treatment effect would not change over time

# FDA conclusion

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“Based on the data presented....the pre-specified plan for the futility analysis in the meeting minutes [is] flawed, and....would have been more appropriate if futility had not been declared for those studies.”

# EMERGE and ENGAGE: Results Post-futility Assessment

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(STUDIES 302 AND 301)



# Primary outcome

	ENGAGE (301)			EMERGE (302)		
	Placebo (n=545)	ADU Low Dose (n=547)	ADU High Dose (n=555)	Placebo (548)	ADU Low Dose (543)	ADU High Dose (547)
<b>Baseline CDR-SB, Mean</b>	2.40	2.43	2.40	2.47	2.46	2.51
<b>Adjusted Mean Change From Baseline at Week 78 (95% CI)</b>	1.56 (1.23, 1.77)	1.38 (1.16, 1.59)	1.59 (1.37, 1.81)	1.74 (1.51, 1.96)	1.47 (1.25, 1.70)	1.35 (1.12, 1.57)
<b>Difference vs. Placebo (95% CI)</b>	--	-0.18 (-0.47, 0.11)	0.03 (-0.26, 0.33)	--	-0.26 (-0.57, 0.04)	-0.39* (-0.69, -0.09)
<b>% Difference vs. Placebo</b>	--	-12%	2%	--	-15%	-22%
<b>p-value (vs. Placebo)</b>	--	0.2250	0.8330	--	0.0901	0.0120

ADU: aducanumab, CDR-SB: Clinical Dementia Rating-Sum of Boxes, CI: confidence interval, ITT: intention-to-treat

\*p<0.05.

# Secondary outcomes

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	ENGAGE (301)			EMERGE (302)		
	Placebo Decline	Difference vs. Placebo (p-value)		Placebo Decline	Difference vs. Placebo (p-value)	
		Low Dose	High Dose		Low Dose	High Dose
<b>MMSE*</b>	-3.5	0.2 (0.48)	-0.1 (0.81)	-3.3	-0.1 (0.76)	0.6 (0.05)
<b>ADAS-Cog 13†</b>	5.14	-0.58 (0.25)	-0.59 (0.26)	5.16	-0.7 (0.20)	-1.4 (0.01)
<b>ADCS-ADL-MCI‡</b>	-3.8	0.7 (0.12)	0.7 (0.15)	-4.3	0.7 (0.15)	1.7 (0.0006)

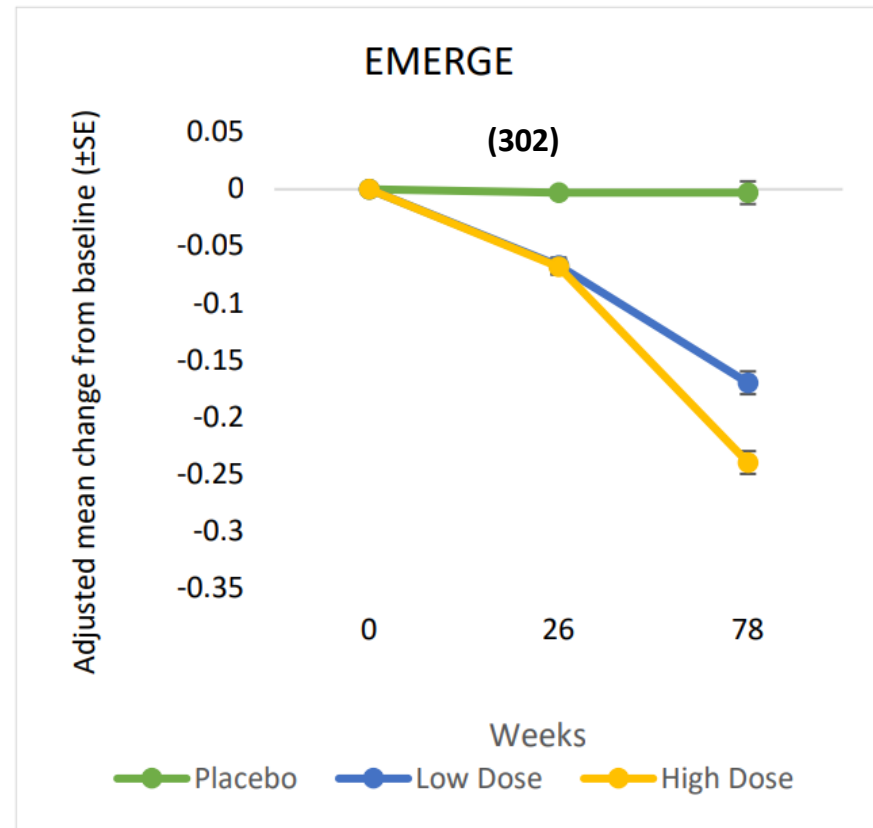
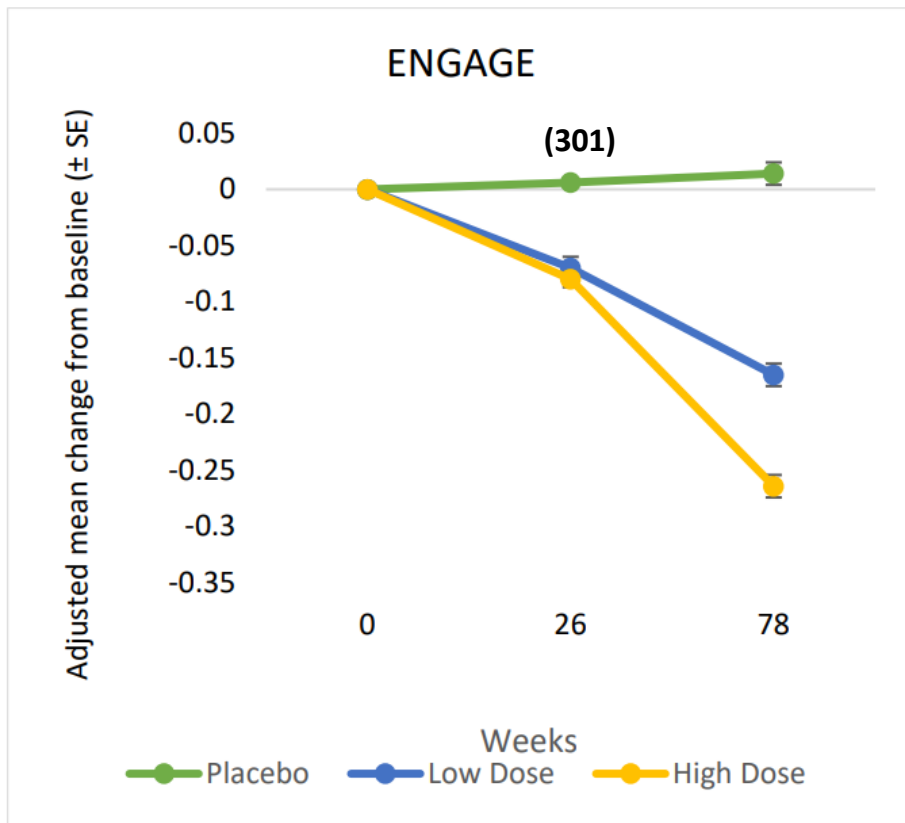
ADAS-Cog 13: Alzheimer's Disease Assessment Scale-Cognitive Subscale, ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study Scale for Activities of Daily Living in Mild Cognitive Impairment, MMSE: Mini-Mental State Exam,

\*MMSE scores range from 0 to 30, with higher scores indicating less cognitive impairment.

†ADAS-Cog 13 scores range from 0 to 85, with higher scores indicating more cognitive impairment.

‡ADCS-ADL-MCI scores range from 0 to 53, with higher scores indicating less deterioration.

# Change from baseline in beta-amyloid PET SUVR



PET: positron emission tomography, SE: standard error, SUVR: standardized uptake value ratio

# Pooled adverse events

		Patients, n (%)				Total for ADU Arms (N=2198)
		Placebo (N=1087)	ADU 3 mg/kg (N=760)	ADU 6 mg/kg (N=405)	ADU 10 mg/kg (N=1033)	
<b>AE</b>		845 (86.9)	700 (92.1)	247 (85.7)	846 (91.6)	1992 (90.7)
<b>Study Drug-Related AE</b>		273 (25.1)	373 (49.1)	148 (36.5)	530 (51.3)	1051 (47.8)
<b>Serious AE</b>		151 (13.9)	105 (13.8)	54 (13.3)	141 (13.6)	300 (13.6)
<b>Serious Study Drug-Related AE</b>		8 (0.7)	9 (1.2)	7 (1.7)	21 (2.0)	37 (1.7)
<b>Deaths</b>		5 (0.5)	3 (0.4)	0 (0)	8 (0.8)	11 (0.5)
<b>AE Severity</b>	<b>Mild</b>	445 (40.9)	252 (33.2)	122 (30.1)	331 (32.0)	705 (32.1)
	<b>Moderate</b>	408 (37.5)	328 (43.2)	177 (43.7)	465 (45.0)	970 (44.1)
	<b>Severe</b>	92 (8.5)	120 (15.8)	48 (11.9)	150 (14.5)	318 (14.5)
<b>AE Leading to Study Drug Discontinuation</b>		45 (4.1)	65 (8.6)	45 (11.1)	91 (8.8)	201 (9.1)
<b>AE Leading to Study Discontinuation</b>		31 (2.9)	32 (4.2)	27 (6.7)	38 (3.7)	97 (4.4)
<b>AE Leading to Study Drug Discontinuation Due to ARIA</b>		6 (0.6)	47 (6.2)	21 (5.4)	64 (6.2)	132 (6.1)
<b>Headache</b>		165 (15.2)	161 (21.2)	58 (14.3)	212 (20.5)	431 (19.6)
<b>Fall</b>		128 (11.8)	105 (13.8)	50 (12.3)	155 (15.0)	310 (14.1)
<b>Diarrhea</b>		74 (6.8)	62 (8.2)	27 (6.7)	92 (8.9)	181 (8.2)

ADU: aducanumab, AE: adverse event, ARIA: amyloid-related imaging abnormalities, mg/kg: milligram per kilogram, n: number, N: total number

# Pooled ARIA data

	Patients, n (%)					
	Placebo (N=1076)	ADU 3 mg/kg (N=756)	ADU 6 mg/kg (N=292)	ADU 10 mg/kg (N=1029)	Total for ADU Arms (N=2177)	
ARIA-E or ARIA-H	444 (40.3)	274 (36.2)	194 (66.5)	425 (41.2)	893 (36.0)	
ARIA-E	29 (2.7)	223 (29.3)	83 (20.5)	362 (35.0)	668 (30.4)	
Serious ARIA-E	1 (<0.1)	6 (0.8)	3 (0.7)	13 (1.3)	22 (1.0)	
ARIA-E, n/N (%)	APOE ε4 Carrier	16/742 (2.2)	NR	NR	299/674 (42.0)	NR
	APOE ε4 Non-Carrier	13/334 (3.9)	NR	NR	72/355 (20.3)	NR
ARIA-E by Symptomatic Status, n/N (%)	Asymptomatic	26/29 (89.7%)	NR	NR	268/362 (74.0)	NR
	Symptomatic	3/29 (10.3)	NR	NR	94/362 (26.0)	NR
ARIA-H	94 (8.7)	193 (25.5)	63 (16.1)	291 (28.3)	547 (25.1)	
ARIA-H Microhemorrhage	71 (6.6)	141 (18.6)	50 (12.3)	197 (19.1)	388 (17.7)	
ARIA-H Macrohemorrhage	4 (0.4)	1 (0.1)	3 (0.8)	3 (0.3)	7 (0.3)	
ARIA-H Superficial Siderosis of CNS	24 (2.2)	91 (12.0)	22 (5.9)	151 (14.7)	265 (12.2)	
AE Leading to Study Drug Discontinuation Due to ARIA	6 (0.6)	47 (6.2)	21 (5.4)	64 (6.2)	132 (6.1)	

ADU: aducanumab, AE: adverse event, APOE ε4: apolipoprotein E ε4, ARIA: amyloid-related imaging abnormalities, ARIA-E: amyloid-related imaging abnormalities-edema/effusion, ARIA-H: amyloid-related imaging abnormalities-hemorrhage or superficial siderosis, CNS: central nervous system, mg/kg: milligram per kilogram, n: number, N: total number, NR: not reported

# Patient disposition

Randomized	EMERGE (302) (n = 1643)			ENGAGE (301) (n = 1653)		
	Placebo n = 548	Low dose n = 543	High dose n = 547	Placebo n = 545	Low dose n = 547	High dose n = 555
Dosed	n = 1638			n = 1647		
<b>DC Tx, n(%)</b>	82 (15.0)	108 (19.9)	121 (13.9)	96 (17.6)	104 (19.2)	148 (26.7)
Adverse Event	16 (2.9)	41 (7.6)	26 (4.8)	26 (5.4)	43 (7.9)	64 (26.7)
<b>WD study, n(%)</b>	39 (7.1)	54 (9.9)	66 (12.1)	58 (10.6)	60 (11.0)	78 (14.1)
Adverse Event	10 (1.8)	11 (2.0)	18 (3.3)	16 (2.9)	23 (4.2)	26 (4.7)

\*DC = Discontinued, Tx = Treatment, WD = Withdrew

And the  
conclusion is...

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## FDA's Decision to Approve New Treatment for Alzheimer's Disease

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### News & Events for Human Drugs

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From Our Perspective

Spotlight on CDER Science

By Dr. Patrizia Cavazzoni, Director, FDA Center for Drug Evaluation and Research

Today FDA approved [\(aducanumab\)](#) to treat patients with Alzheimer's disease using the [Accelerated Approval](#) pathway, under which the FDA approves a drug for a serious or life-threatening illness that may provide meaningful therapeutic benefit over existing treatments when the drug is shown to have an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients and there remains some uncertainty about the drug's clinical benefit.

This approval is significant in many ways. ADU is the first novel therapy approved for Alzheimer's disease since 2003. Perhaps more significantly, ADU is the first treatment directed at the underlying pathophysiology of Alzheimer's disease, the presence of amyloid beta plaques in the brain. The clinical trials for ADU were the first to show that a reduction in these plaques—a hallmark finding in the brain of patients with Alzheimer's—is expected to lead to a reduction in the clinical decline of this devastating form of dementia.

We are well-aware of the attention surrounding this approval. We understand that ADU has garnered the attention of the press, the Alzheimer's patient community, our elected officials, and other interested stakeholders. With a treatment for a serious, life-threatening disease in the balance, it makes sense that so many people were following the

Content current as of:  
06/07/2021

Regulated Product(s)  
Drugs

# Institute for Clinical and Economic Review

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“ The need for disease-modifying treatment for patients with AD is great, however, it is unclear that treatment with aducanumab provides net health benefits to patients. Given the certainty that harms can occur in patients treated with aducanumab and uncertainty about benefits, we rate the evidence to be *insufficient* to determine the net health benefit of aducanumab in patients with MCI or mild AD”

# Critical Appraisal

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# Evidence - strengths

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Randomized

Double blind

Placebo-controlled

Multicentre

# Evidence - limitations

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Data not published in a peer reviewed journal

Numerous protocol adjustments during trial

Changes in statistical analysis of data during trial

Trial was stopped for futility

Post-hoc analysis after futility assessment is exploratory

Potential functional unblinding with adverse effects – ARIA

Higher dose had larger proportion of patients discontinuing treatment

Not using intention-to-treat population

# Evidence - limitations

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CDR-SB showed statistical significance, but not clinical significance

Use of surrogate markers to evaluate efficacy

- Amyloid PET scans showed amyloid reduction
- Similar reduction in both trials on surrogate marker, but ?clinical benefit in EMERGE, but not ENGAGE

Drug approved on accelerated pathway

Close collaboration between the drug company and the FDA on trial design and data analysis

Use of phase 1b trial to provide a second positive trial

# Clinical limitations

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Excluded patients who were on blood thinners

Lack of ethnic diversity (~75% white)

PET scan to confirm beta-amyloid present in brain

Frequent MRIs to monitor for ARIA performed in clinical trials is not required by FDA labeling

ARIA occurred in 1/3 of patients

- 6% discontinued due to serious symptoms
- 15-20% develop ARIA-E within 6 months
- Long term impact of ARIA unknown

Cost of \$56,000 USD per year

Not approved or available in Canada

# Aducanumab in the Treatment of Alzheimer's Disease

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THE NEW WONDER DRUG OR A FIGMENT OF OUR  
IMAGINATION?

# Clinical application

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Given numerous limitations to the efficacy data, lack of clear clinical benefit, significant potential adverse effects, and need for close monitoring, it is difficult to apply these results to any specific patient population group with cognitive impairment

These trials can help re-define future clinical trial designs of other anti-beta amyloid monoclonal antibodies



Back to the case  
of Bob.....

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# Bob asks:

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“WHAT CAN I DO OR TAKE TO PREVENT MY  
MEMORY AND THINKING FROM GETTING  
WORSE??”

# Drug therapy problem

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Bob is experiencing mild cognitive impairment and would benefit from a review of the available treatment options

# Therapeutic options

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~~Aducanumab 10mg/kg IV Q4weeks~~

~~Acetylcholinesterase inhibitor~~

~~◦ Donepezil titrated up to 10mg PO daily~~

~~◦ Galantamine ER titrated up to 24mg PO daily~~

~~◦ Rivastigmine titrated up to 12mg PO BID~~

~~◦ Rivastigmine patch titrated up to 13.3mg (15) TOP daily~~

~~Memantine titrated up to 10mg PO BID~~

Lifestyle measures

- Optimization of medical conditions
- Exercise
- Diet
- Social engagement
- Intellectual stimulation

# Recommendation

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## Lifestyle measures

### Optimization of medical conditions

- Manage vascular risk factors

### Exercise

- Moderate level of exercise of 30 minutes 4x/week

### Diet

- Mediterranean diet

### Social engagement

### Intellectual stimulation

# Monitoring plan & follow-up

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Cognitive and functional assessment annually

Screening blood work annually

Blood pressure check at each healthcare visit

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# Questions?

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