Morbus Alzheimer – Therapy

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Disclosure Slide

- I received honoraria for lecture from Pfizer, Lundbeck, Merz Pharmaceuticals Austria, Janssen, Novartis, Takeda
- I am currently on the advisory board of Axon Pharmaceuticals and Avraham

Learning Objective

- Information about current direction of drug development in Alzheimer´s
- Current concepts of dealing with the enormously high failure rate in previous studies
- Presentation of promising ongoing studies which were sucessful in phase II
- Overview of Tau-directed therapy. First in man first in kind Tau-vaccination study results

Key Messages

- ChE Inhibitors und Memantine have consistent but small effects on cognition and global functioning
- New GRADE guideline of the European Academy of Neurology recommends combination therapy
- Diagnosis of pre-dementia states of AD is one way to prevent future failures, but the definitions are heterogeneous and not yet fully validated
- New targets are also in the focus of research
- Aducanumab, a human monoclonal antibody selective for aggregated form of beta-amyloid shows promising results, but there are several other interesting compounds in phase III with promising phase II results
- The first in man Tau-vaccination was tested in phase I and showed no safety signals of concern and a robust immune response

CURRENT THERAPY AND FUTURE APPROACHES FOR AD

Symptomatic

Neurotransmitter manipulation
- AChEI
- Spec. M1- Agonists
- Nicotinic Agonists
- Memantine

Non-specific cognitive enhancement
- nootropics

Memory consolidation
- AMPA-glutamate receptors modulators
- 5-HT- Antagonists
- PDE- Inhibitors

Cognitive training

Hypothetically disease modifying

Mechanism-based
- modulation of Aβ-metabolism
- interventions on tau-pathology
- stimulation of neurotrophic signaling
- stem cells

Other postulated pathogenic events
- antioxidants
- anti-inflammatory
- HRT

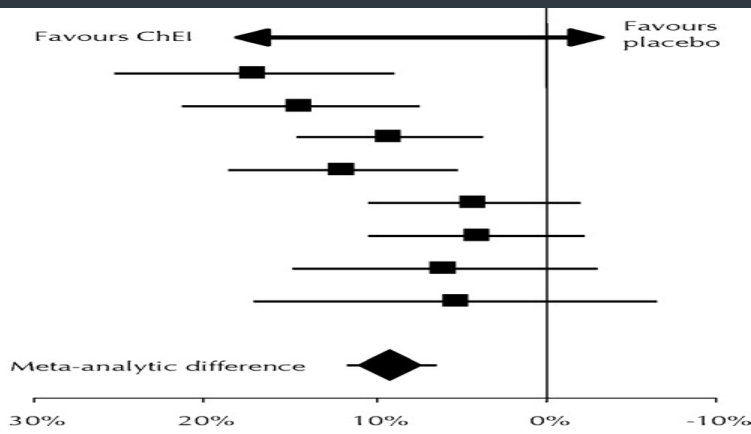
Modification of risk factors
- antihypertensive treatment
- cholesterol-lowering strategies
- homocysteine levels

Conclusions on Standard Therapy

- ChE Inhibitors und Memantine have consistent effects on cognition and global functioning
- Effect size is small
- 3 comparative studies show no significant difference in cognition and behavior

Realistic expecations

Study	Cholinesterase inhibitor	ChEI responders	Placebo responders	Total subjects
Rogers,[11] 1998a	Donepezil	107/305	27/150	455
Rogers,[10] 1998b	Donepezil	76/298	17/152	450
Burns,[12] 1999	Donepezil	125/544	38/274	818
Rösler,[18] 1999	Rivastigmine	149/467	44/220	687
Raskind,[20] 2000	Galantamine	64/357	27/196	553
Wilcock,[21] 2000	Galantamine	84/414	33/203	617
Rockwood,[24] 2001	Galantamine	61/240	24/123	363
Wilkinson,[23] 2001	Galantamine	59/179	23/83	262



Overall 22%

Outcome	No. of subjects, total (ChEI, placebo)	Mean difference in proportions, % (and 95% CI)	Heterogeneity: χ^2 (and *p* value)	No. needed to treat/harm (and 95% CI)
Global response*	4205 (2804, 1401)	9 (6, 12)	12.2 (0.10)	12 (9, 16)
Cognitive response†	2419 (1606, 813)	10 (4, 17)	12.7 (0.01)	10 (8, 15)
Adverse events	6784 (4381, 2403)	8 (5, 12)	26.8 (0.01)	12 (10, 18)
Dropout	7691 (5022, 2669)	8 (5, 11)	40.4 (< 0.001)	13 (11, 17)
Dropout due to adverse events	7952 (5154, 2798)	7 (3, 10)	104.3 (< 0.001)	16 (13, 19)

*Minimal or greater improvement on a standardized global scale, such as the CIBIS+ or the CGIC, in a predominantly Caucasian population.
†Improvement of 4 or more points on the ADAS-cog.

For Stabilisation or improvement in global clinical impression the between group difference is 15%, p< 0.0001; NNT = 7.

When treating 7 patients one remains stable or improves above the rate expected in placebo Plazeborate

For strong improvements „Halleluja-Effect“ the difference is 2 %, p=0.04; NNT = 42

CMAJ · JAMC

EFNS-ENS/EAN GUIDELINE

EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease

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Keywords:
Alzheimer's disease, cholinesterase inhibitors, dementia, EFNS/ENS Guidelines, Grading of Recommendations Assessment, Development and Evaluation, memantine, meta-analysis, treatment

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Background and purpose: Previous studies have indicated clinical benefits of a combination of cholinesterase inhibitors (ChEI) and memantine over ChEI monotherapy in Alzheimer's disease (AD). Our objective was the development of guidelines on the question of whether combined ChEI/memantine treatment rather than ChEI alone should be used in patients with moderate to severe AD to improve global clinical impression (GCI), cognition, behaviour and activities of daily living (ADL).

Methods: A systematic review and meta-analysis of randomized controlled trials based on a literature search in ALOIS, the register of the Cochrane Dementia and Cognitive Improvement Group, was carried out with subsequent guideline development according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Results: Pooled data from four trials including 1549 AD patients in the moderate to severe disease stage demonstrated significant beneficial effects of combination therapy compared to ChEI monotherapy for GCI [standardized mean difference (SMD) −0.20; 95% confidence interval (CI) −0.31; −0.09], cognitive functioning (SMD −0.27, 95% CI −0.37; −0.17) and behaviour (SMD −0.19; 95% CI −0.31; −0.07). The quality of evidence was high for behaviour, moderate for cognitive function and GCI and low for ADL. Agreement of panellists was reached after the second round of the consensus finding procedure. The desirable effects of combined ChEI and memantine treatment were considered to outweigh undesirable effects. The evidence was weak for cognition, GCI and ADL so that the general recommendation for using combination therapy was weak.

Conclusions: We suggest the use of a combination of ChEI plus memantine rather than ChEI alone in patients with moderate to severe AD. The strength

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The GRADE evidence profile.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AChEI + memantine	AChEI monotherapy	Relative (95% CI)	Absolute		
Activities of daily living (follow-up 24 -30 weeks[1]; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	728	713	-	SMD 0.08 lower (0.18 lower to 0.02 higher)	⊕⊕OO LOW	CRITICAL
Behaviour (follow-up 24-30 weeks[1]; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	710	698	-	SMD 0.19 lower (0.31 to 0.07 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Cognitive functioning (follow-up 24-30 weeks[1]; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	726	709	-	SMD 0.27 lower (0.37 to 0.17 lower)	⊕⊕⊕O MODERATE	CRITICAL
Frequency of serious adverse events (follow-up 24-30 weeks[1])												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	94/769 (12.2%)	109/757 (14.4%)	Risk Difference -0.02 (-0.06 to 0.02)	2 fewer per 100 (from 6 fewer to 2 more)	⊕⊕OO LOW	CRITICAL
Global clinical impression (follow-up 24 weeks; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	666	649	-	SMD 0.20 lower (0.31 to 0.09 lower)	⊕⊕⊕O MODERATE	CRITICAL

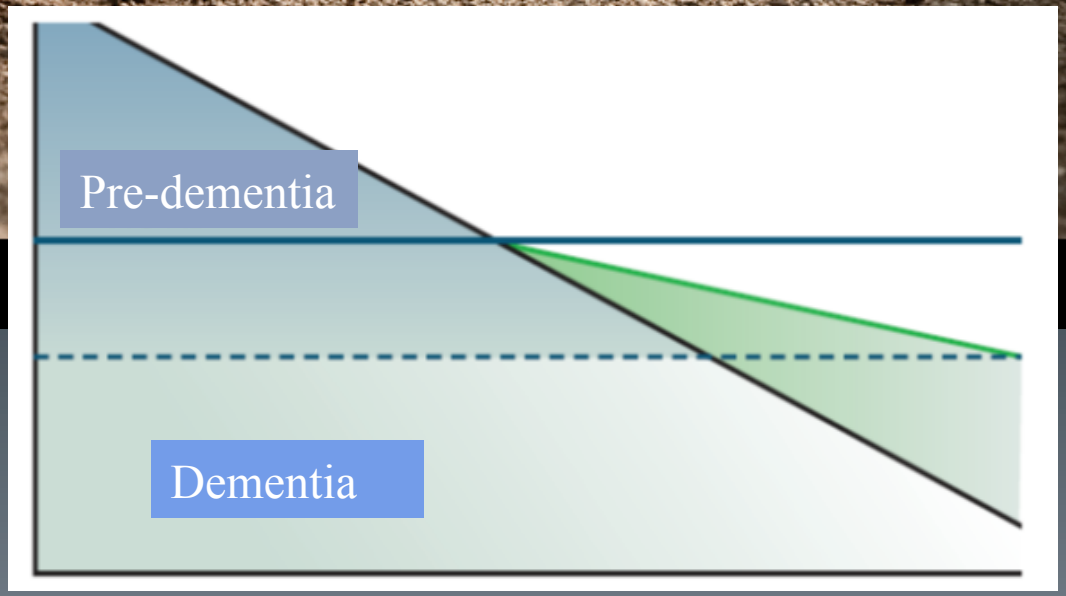
[1] Tariot2004, Porsteinsson2008 und Grossberg2008: 24 weeks, Howard2012: 30 weeks
[2] Metaanalysis confidence interval contains positive and negative values
[3] Howard2012: wide confidence interval
[4] Wide confidence intervals in individual studies

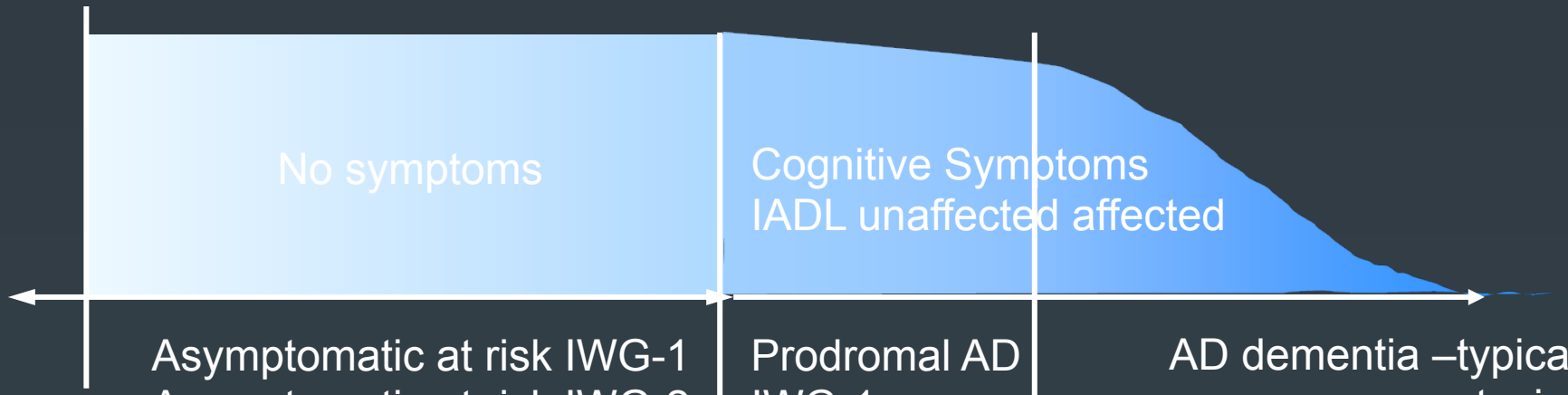
Conclusion

- We suggest that the use of a combination of ChEI plus memantine rather than ChEI alone provides useful benefits in patients with moderate to severe AD.
- The overall strength of recommendation is weak as it is for global clinical impression, cognitive functioning, and ADL.
- We give a strong recommendation for the use of combination therapy in patients with moderately severe AD who have behavioral symptoms.

Amyloid with Bio-markers

Other targets





Asymptomatic at risk IWG-1
Asymptomatic at risk IWG-2

Presymptomatic AD

Preclinical AD

Stage1 Stage 2 Stage3

SNAP

SCD
SCD plus

Prodromal AD
IWG-1
IWG2
MCI-IWG
MCI due to AD
MCI due to SNAP

AD dementia –typical
atypical

AD dementia –increased certainty

-decreased certainty

Symptomatic Alzheimer Disease

Mild Neurocognitive Disorder DSM-5

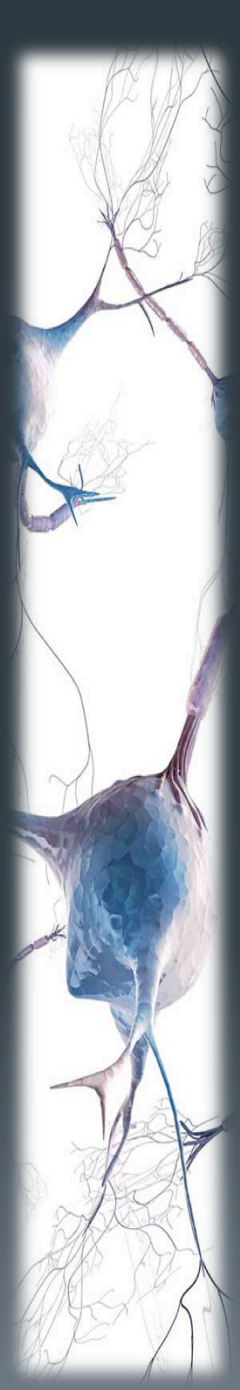
Major Neurocognitive Disorder DSM-5

Table 3. Primary and Secondary Outcomes in EXPEDITION 2, Intention-to-Treat Population.*

Variable	Mean Change from Baseline to Wk 80 (95% CI)		Mean Difference (95% CI)	P Value
	Placebo	Solanezumab		
ADAS-cog11 score†	6.6 (5.2 to 7.9)	5.3 (4.0 to 6.7)	−1.3 (−2.5 to 0.3)	0.06
ADAS-cog14 score†	7.5 (5.8 to 9.1)	5.9 (4.3 to 7.5)	−1.6 (−3.1 to 0.1)	0.04
ADCS-ADL score†	−10.9 (−12.7 to −9.1)	−9.3 (−11.2 to −7.5)	1.6 (−0.2 to 3.3)	0.08
CDR-SB score	1.9 (1.4 to 2.4)	1.6 (1.2 to 2.1)	−0.3 (−0.7 to 0.2)	0.17
NPI score	3.0 (0.8 to 5.1)	2.8 (0.7 to 5.0)	−0.2 (−1.8 to 1.5)	0.85
MMSE score	−2.8 (−3.6 to −2.0)	−2.1 (−2.8 to −1.3)	0.8 (0.2 to 1.4)	0.01
Free $A\beta_{40}$ in CSF — pg/ml	−649.0 (−2139.5 to 841.5)	−1258.1 (−2695.8 to 179.7)	−609.1 (−1228.4 to 10.2)	0.05
Free $A\beta_{42}$ in CSF — pg/ml	−35.1 (−129.5 to 59.3)	1.0 (−94.1 to 96.2)	36.1 (−1.0 to 73.3)	0.06
Total $A\beta_{40}$ in CSF — pg/ml	−876.4 (−4342.5 to 2589.8)	2156.8 (−1211.9 to 5525.4)	3033.1 (1628.4 to 4437.9)	<0.001
Total $A\beta_{42}$ in CSF — pg/ml	323.8 (86.2 to 561.5)	726.6 (489.4 to 963.9)	402.8 (307.7 to 497.8)	<0.001

Table 4. Outcomes in Patients with Mild Alzheimer's Disease and in Those with Moderate Alzheimer's Disease at Enrollment in EXPEDITION 2, Intention-to-Treat Population.*

Variable	Mild Alzheimer's Disease				Moderate Alzheimer's Disease				Test for Heterogeneity
	Mean Change from Baseline to Wk 80		Mean Difference (95% CI)	P Value†	Mean Change from Baseline to Wk 80		Mean Difference (95% CI)	P Value†	P Value‡
	placebo	*solanezumab*			*placebo*	*solanezumab*			
ADAS-cog11 score	5.1	3.6	−1.5 (−3.0 to 0.0)	0.05	10.9	10.0	−0.9 (−3.1 to 1.3)	0.43	0.65
ADAS-cog14 score	5.8	4.1	−1.7 (−3.5 to 0.1)	0.06	12.7	11.3	−1.5 (−4.1 to 1.1)	0.26	0.88
ADCS-ADL score	−8.9	−6.6	2.3 (0.2 to 4.4)	0.04	−16.3	−15.8	0.5 (−2.6 to 3.5)	0.77	0.34
CDR-SB score	1.6	1.3	−0.3 (−0.8 to 0.2)	0.22	3.4	3.2	−0.3 (−0.9 to 0.4)	0.44	0.95
NPI score	1.5	1.0	−0.5 (−2.4 to 1.3)	0.58	8.0	8.4	0.4 (−2.5 to 3.4)	0.78	0.60
MMSE score	−2.4	−1.8	0.7 (−0.1 to 1.4)	0.10	−5.8	−4.8	1.0 (0.0 to 1.9)	0.04	0.60



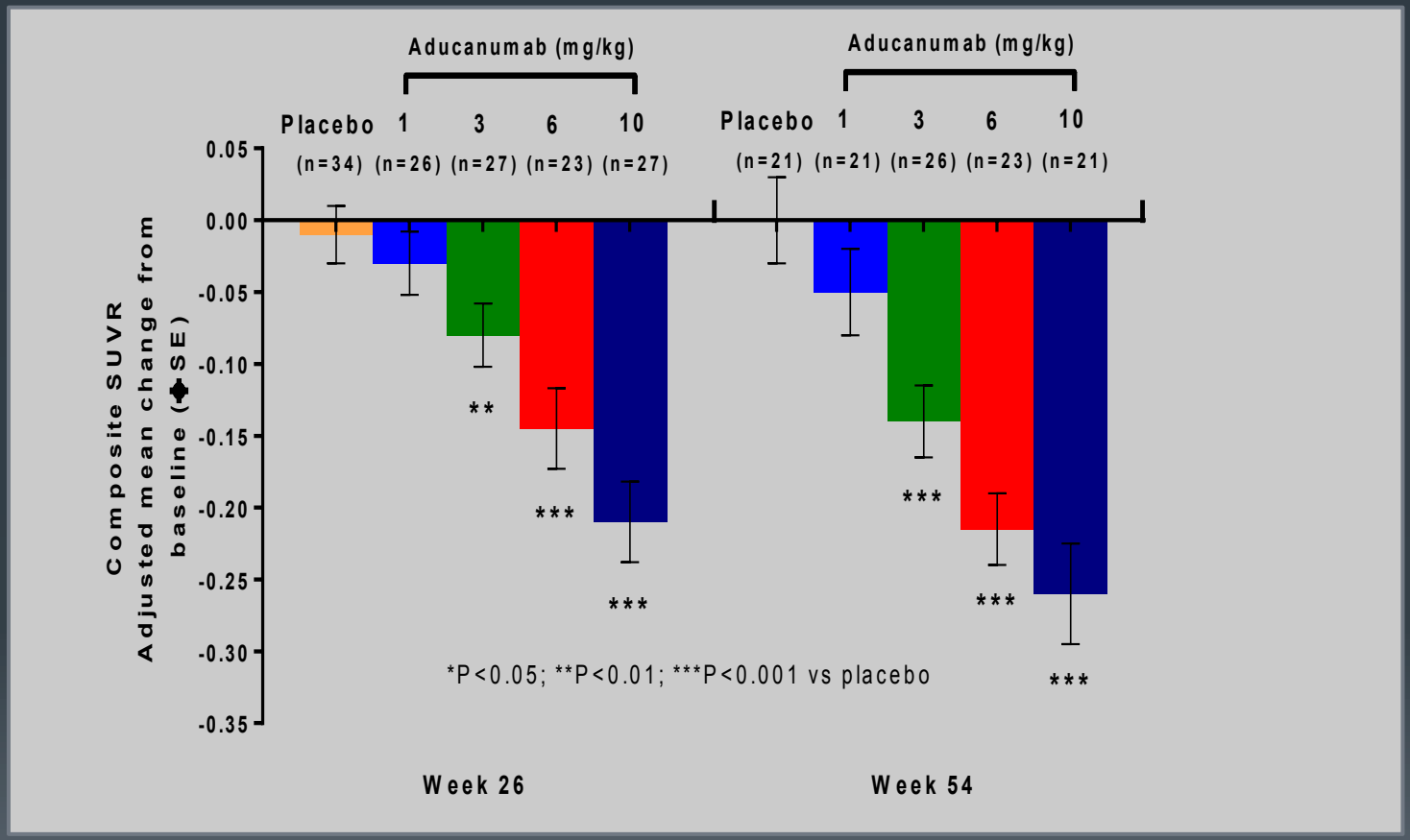
Aducanumab Background

- Human monoclonal antibody selective for aggregated form of beta-amyloid, including soluble oligomers and insoluble fibrils
- In Tg2576 mouse model of AD:[1]
  - Dose dependent reduction of Aβ with chronic dosing[1]
  - Microglia –mediated phagocytosis of amyloid plaques[2]
- A single ascending dose study[3] of Aducanumab demonstrated acceptable safety and tolerability in mild to moderate AD subjects at doses up to 30 mg/kg.

1: Bussiere et al. ADPD 2013; 2: Nitsch et al. Geneva/Springfield symposium 2014; 3 Sevigny et al. AD/PD 2013

Amyloid Plaque Reduction

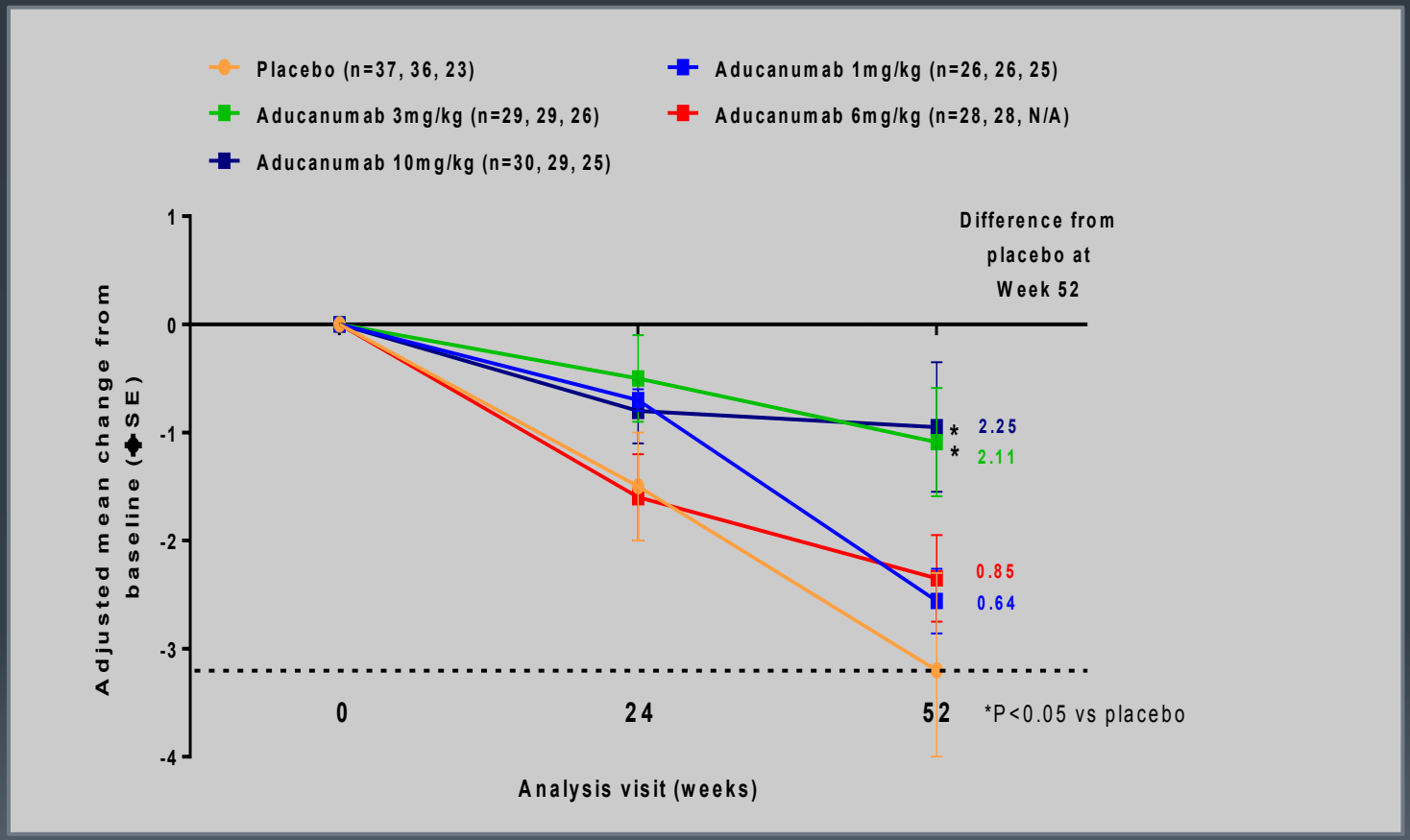
with Aducanumab



Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status, (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized subjects who received at least one dose of study medication and had at least 1 post-baseline assessment of the parameter.

Aducanumab Effect

on MMSE



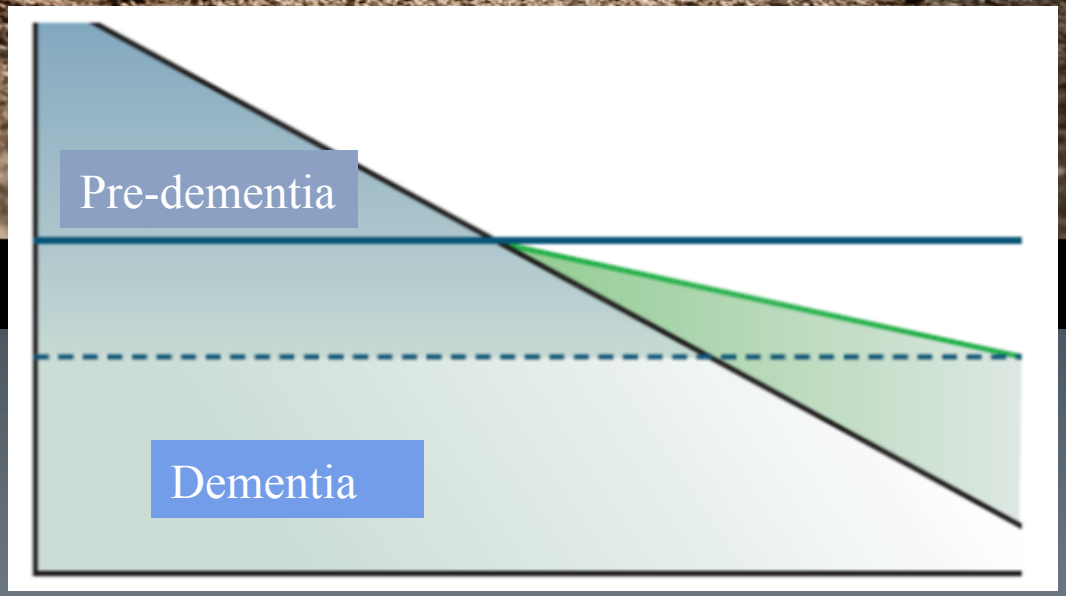
MMSE as exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status, (carrier and non-carrier), and baseline MMSE. Efficacy analysis population is defined as all randomized subjects who received at least one dose of study medication and had at least 1 post-baseline assessment of the parameter.

Incidence of ARIA

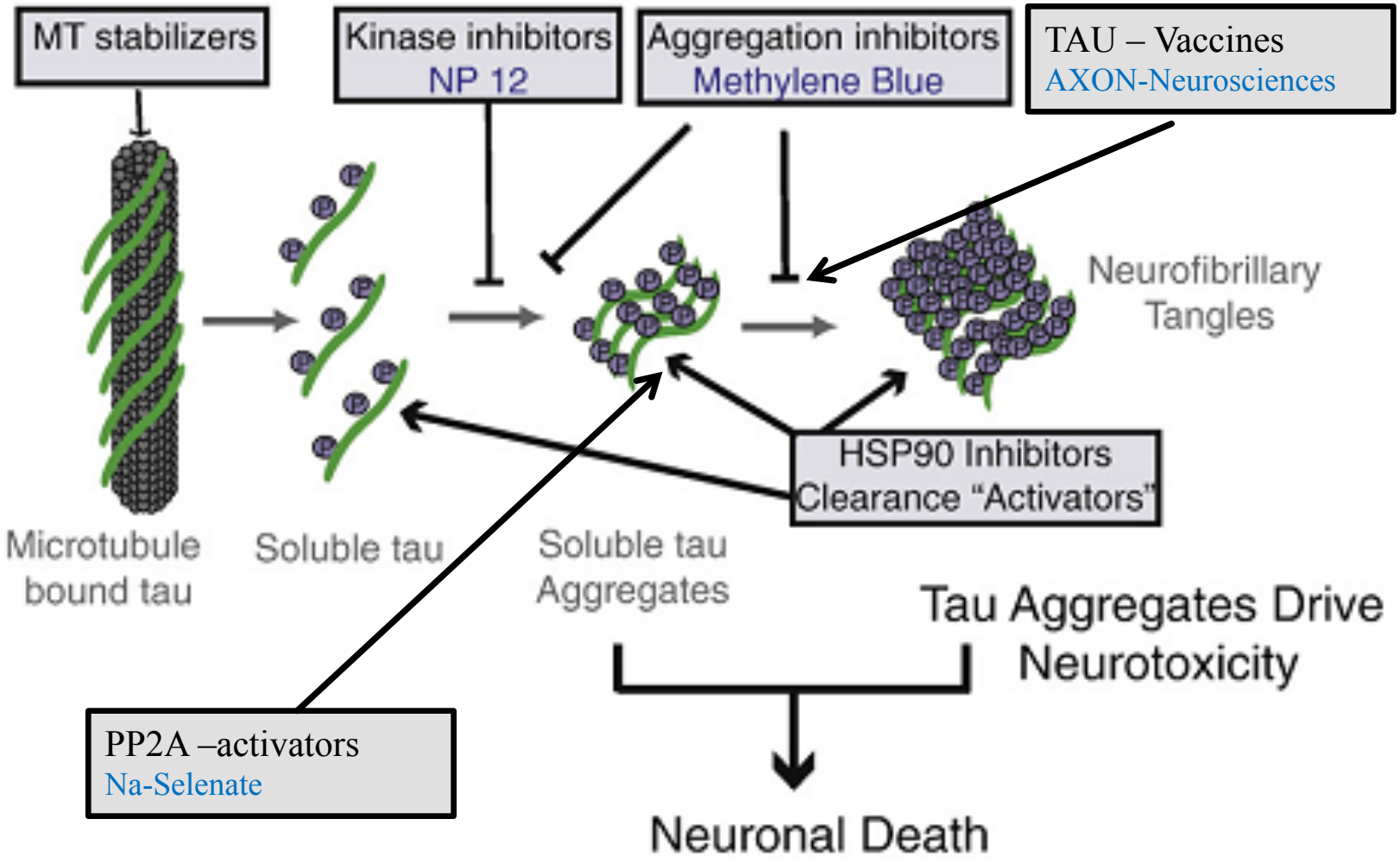
		Aducanumab			
	Placebo (n=40)	1 mg/kg (n=31)	3 mg/kg (n=32)	6 mg/kg (n=30)	10 mg/kg (n=32)
Subjects with at least 1 MRI	38	31	32	30	32
ARIA-E n (%)	0/38	1/31 (3)	2/32 (6)	11/30 (37)	13/32 (41)
ApoE ε4 carrier	0/24	1/19 (5)	1/21 (5)	9/21 (43)	11/20 (55)
ApoE ε4 non-carrier	0/14	0/12	1/11 (9)	2/9 (22)	2/12 (17)
Isolated ARIA-H, n (%)	2/38 (5)	2/31 (6)	3/32 (9)	0/30	2/32 (6)

Amyloid with Bio-markers

Other targets



Strategies against NF - Pathology

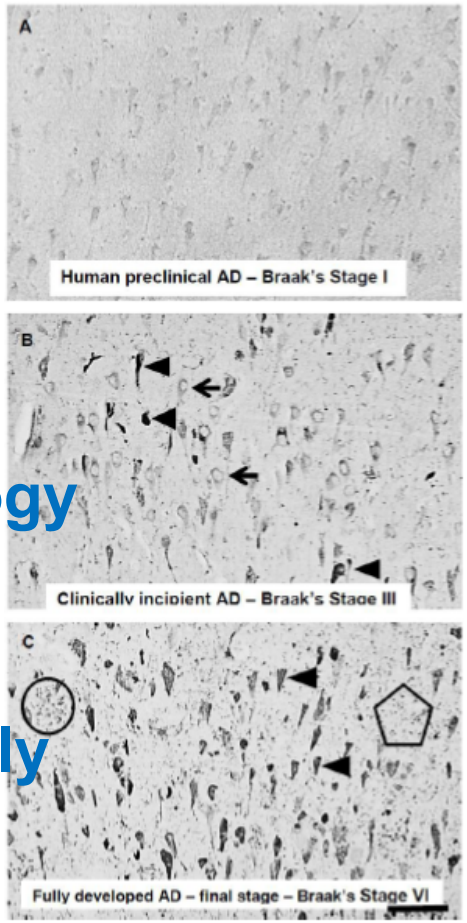


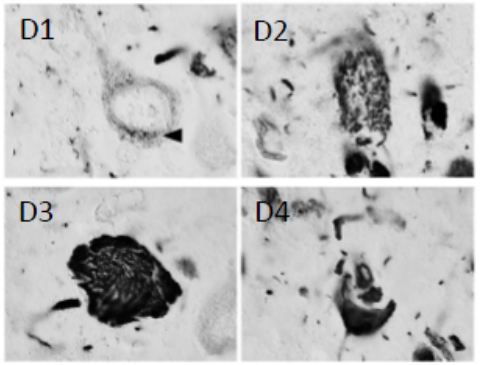
AADvac1 – safety by design

DC8E8 is selective and specific for tau pathology

DC8E8 detects all stages of tau pathology

AADvac1 is made to raise antibodies highly similar to DC8E8



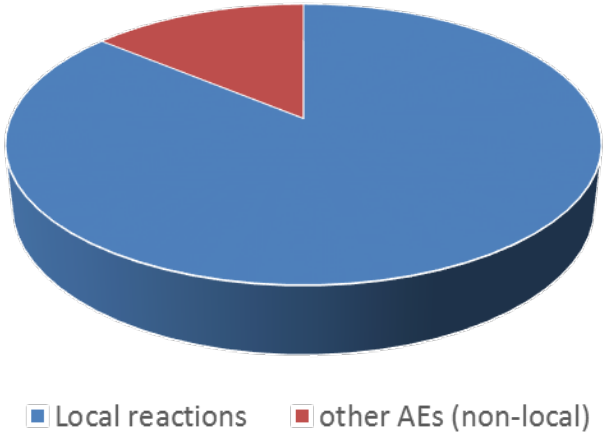


Monoclonal antibody DC8E8 discriminates between preclinical AD, clinically incipient AD and fully developed final stage AD.

DC8E8 recognizes all pathological misfolded tau proteins in human Alzheimer's disease brains. DC8E8 displays staining of early stages (tau monomers, dimers) of pathological tau in human preclinical AD – Braak's Stage I. (A). The antibody recognizes the stage of pathological tau oligomers (arrows) and the stage of pathological tau polymers (tangles) (arrowhead) (B). In fully developed Alzheimer's disease (final stage – Braak's Stage VI), DC8E8 recognizes mainly pathological tau polymers in forms of the neurofibrillary tangles (arrowhead), neuritic plaques (inside the circle) and neuritic threads (inside the pentagon) (C). Scale bar: 100µm. Monoclonal antibody DC8E8 recognizes all developmental stages of tangle formation in Alzheimer's disease (D). DC8E8 recognizes early developmental stages of tangle formation – monomeric, dimeric and early oligomeric stage (D1), and late oligomeric, pre- tangle stage (D2), as well as late developmental stages of pathological tau polymers – intracellular (D3) and extracellular neurofibrillary tangles (D4).

Overall adverse events

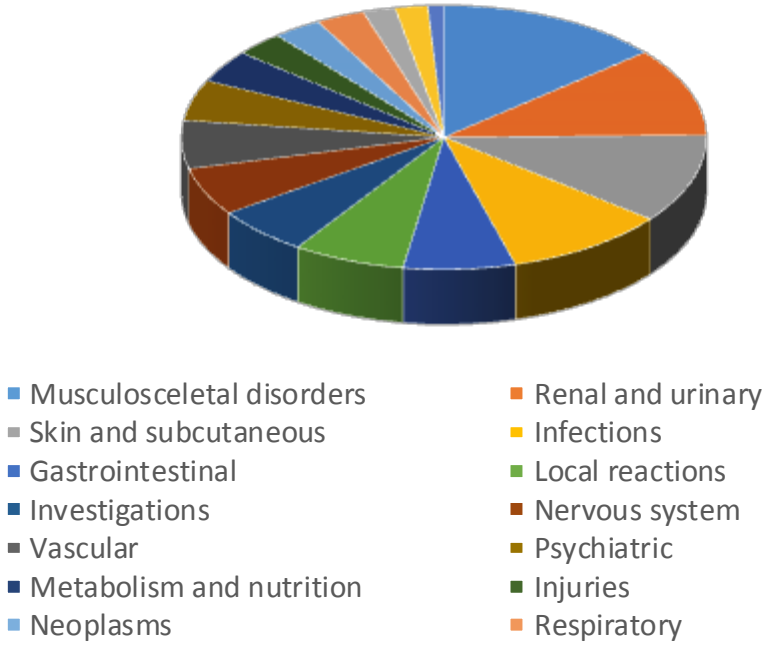
Possibly related AEs (n=101)



A vast majority of AEs were expected **local vaccination reactions** and not toxicologically relevant

The rest of AEs is distributed across SOC and gives **no safety signal**

Non related AEs (n=101)



Consistent with background incidence

No safety signal

Immunogenicity

Robust immune response

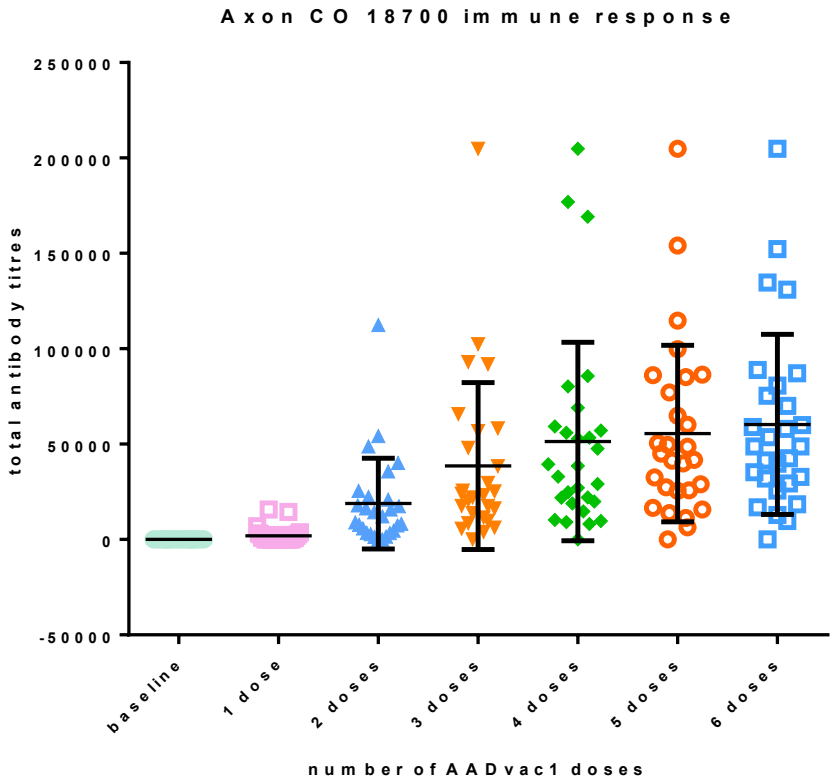
Data at V8:

Number of AADvac1 treated patients with immune response:
29/30

Geometric mean (95% CI of the mean):
33,097 (14,286 – 76,674)

Aritmetic mean (95% CI of the mean):
60,341 (42,065 – 78,617)

Median (interquartile range):
48,745 (30,067 – 79,299)



Conclusions from Encenicline Phase 2

- Significant improvement of cognition (ADAS, COWAT)
- Significant improvement of global function (CDR)
- Effects in drug naive patients and subjects on AChE treatment – Amplification of ACh Neurotransmission!
- Well tolerated

September 16th www.Alzforum.org

- **Rare but Severe Side Effects Sideline Some Phase 3 Encenicline Trials**
- Three international Phase 3 trials ongoing at multiple sites in the US, Europe, Australia, Mexico, Japan and other countries, designed to test the effectiveness of EVP-6124 against cognitive decline in mild to moderate AD A total of 875 patients so far enrolled
- The patients were randomized to receive daily oral doses of 2 mg or 3 mg of EVP-6124, or placebo, for 26 weeks.
- Primary outcome measures included changes in scores on the ADAS-Cog13 and CDR-Sum of Boxes
- The trials were slated to run until January 2017.
- **The FDA has put all of them on hold.**

alzheimer's association®

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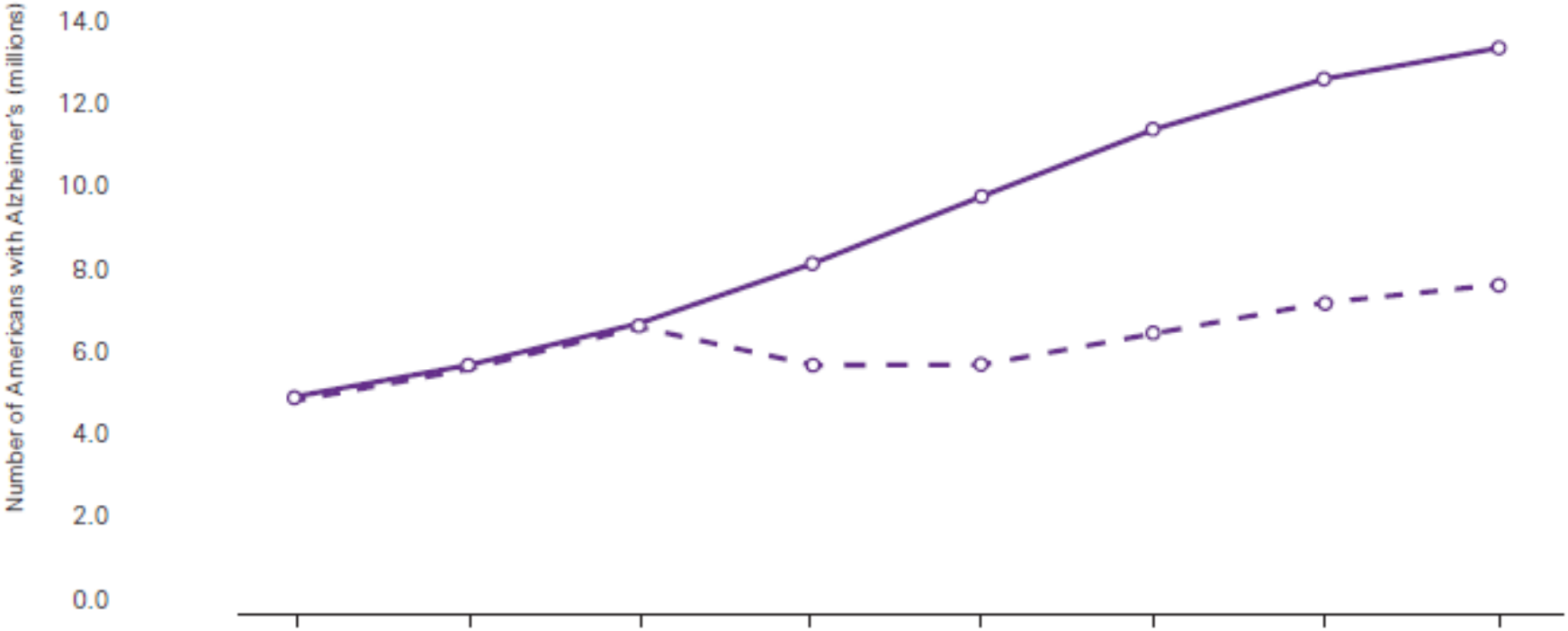
Impact of a Treatment That Delays Onset by Five Years on the Number of Americans Age 65 and Older Living with Alzheimer's Disease, 2015-2050



	2015	2020	2025	2030	2035	2040	2045	2050
Current trajectory	5.1	5.8	6.8	8.2	9.9	11.6	12.8	13.5
Delayed onset	5.1	5.8	6.8	5.8	5.9	6.6	7.3	7.8
Decrease	0.0	0.0	0.0	2.5	4.0	5.0	5.5	5.7

*Totals may not add due to rounding.