ALZHEIMER'S DISEASE UPDATE ON CURRENT RESEARCH

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DISCLOSURES

Consultant: Eisai, Miller Communications

Recent Research Funding: Abbvie, Axovant, Biogen, Bristol-Myer Squibb, Eisai, Eli Lilly, Genentech, Roche, TauRx

Share Holder: none

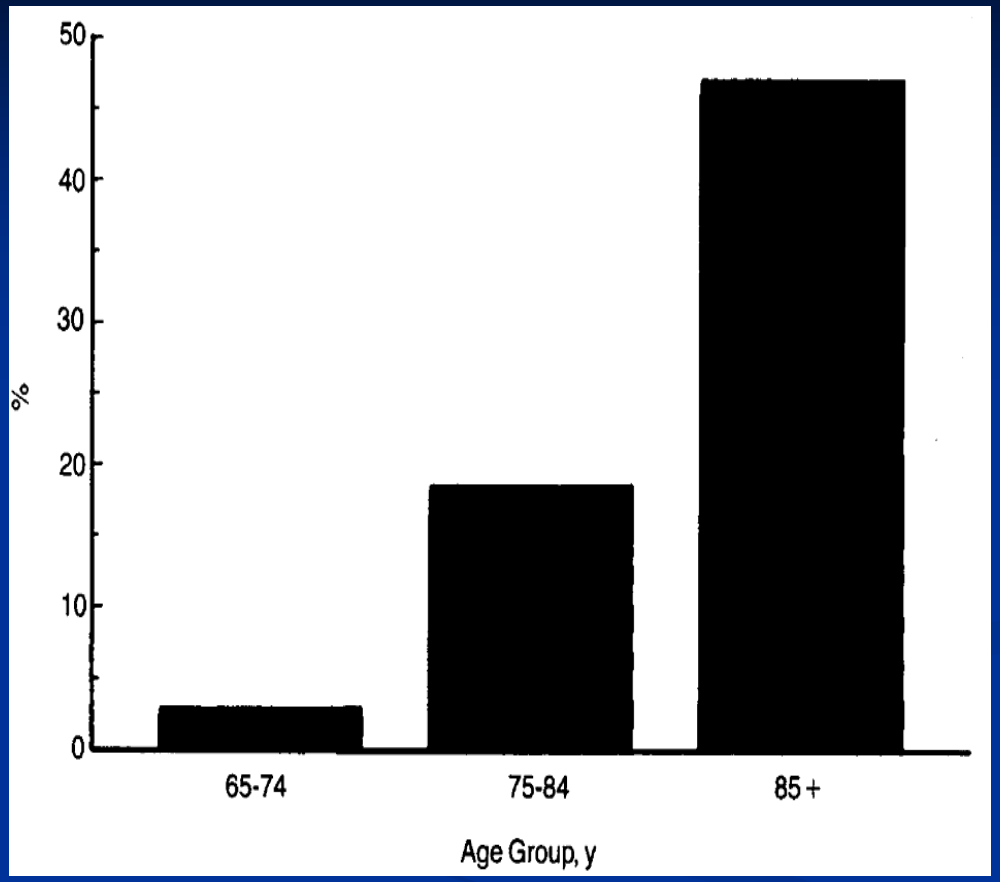
I will discuss investigational drugs, and off-label usage of drugs.

ALZHEIMER'S DISEASE

Research in Epidemiology

ALZHEIMER'S RISK FACTORS

- AGE
- Education
- Gender
  - Head Trauma?
  - Diet?
  - Exercise?
  - Hypertension?
  - Hyperlipidemia?
  - Diabetes?
  - Cardiovascular or Cerebrovascular Disease?
- GENETICS



Evans DA JAMA 1989; 262:2551-6

ALZHEIMER'S GENETIC FACTORS

- **Early-onset autosomal dominant disorders**
  - APP, PS1, PS2 : (<0.1% of patients)
- **Late-onset risk factors**
  - APOE-e4

AD Neuropathology Change (ADNC)	% e4neg	%e4pos	N
Low ADNC	73%	27%	367
Intermediate ADNC	57%	43%	429
High ADNC	39%	61%	1097

  - SORL1, CLU, CR1, BIN1, PICALM, EXOC3L2, ABCA7, CD2AP, EPHA1, TREM2 + >20 others!
- **Late onset protective factors**
  - APP Icelandic mutation (A673T)

ALZHEIMER'S DISEASE

Research in Diagnostics

EXAMINATION: General, Neurological, Cognitive, Lab, MRI

Consciousness

Attention and concentration

Language: expression, comprehension, naming, repetition

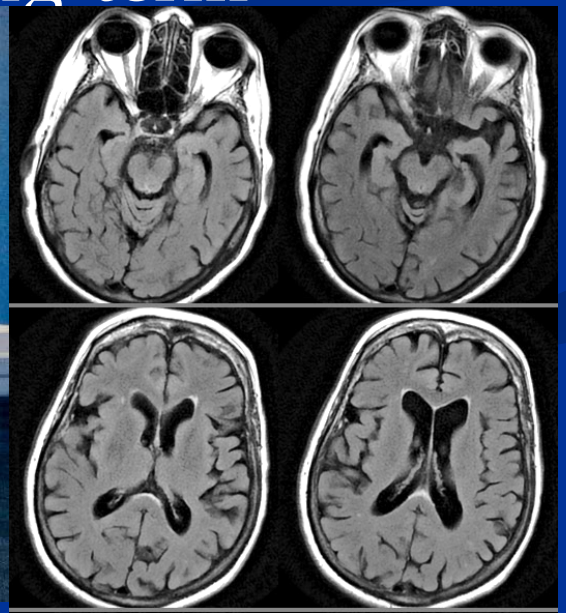
Orientation to time, place, and person

Memory functions: immediate, short-term, long-term

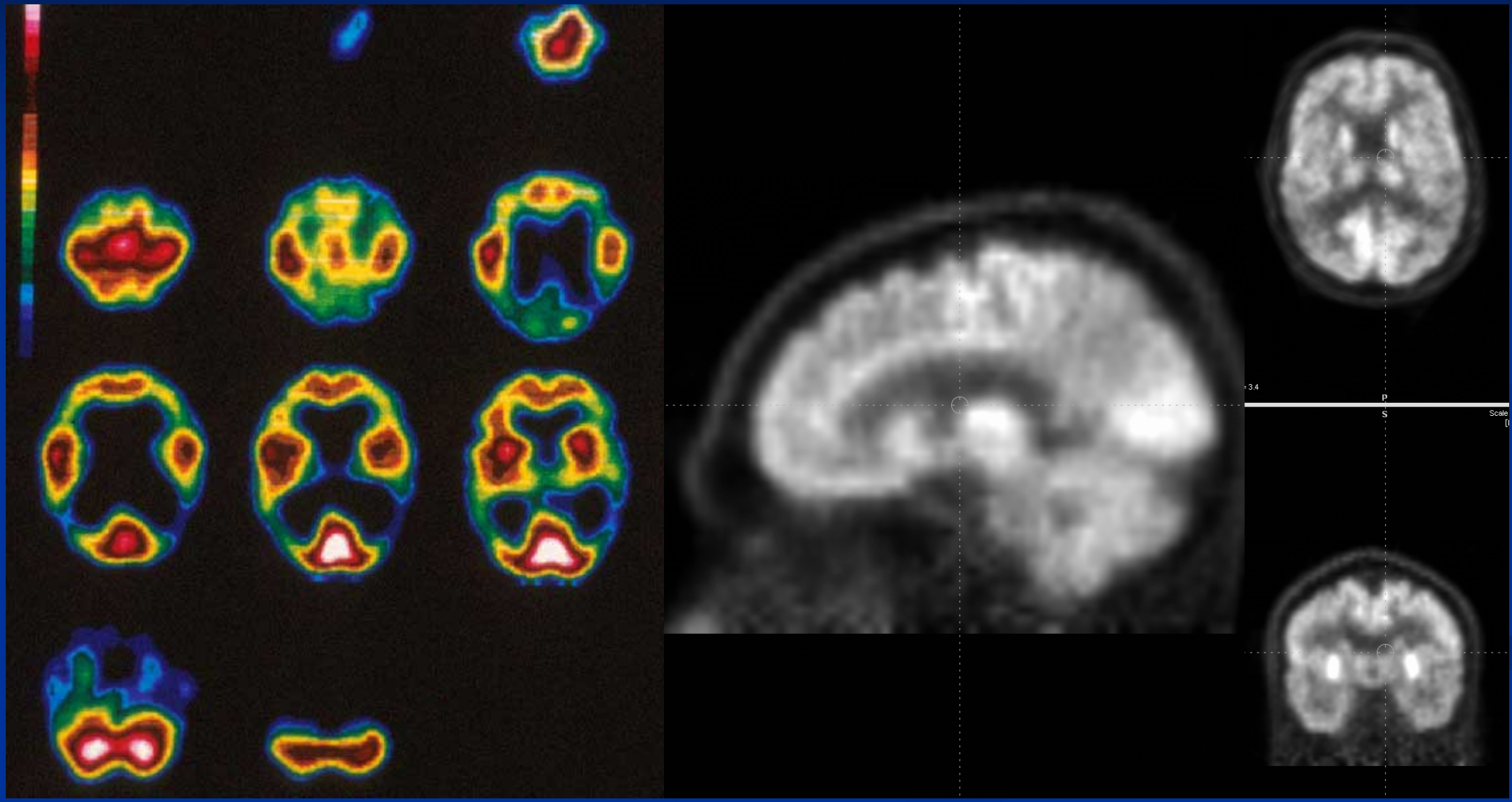
Visuospatial abilities: drawing

Analytic abilities

Judgment and Insight



Positron Emission Tomography-FDG



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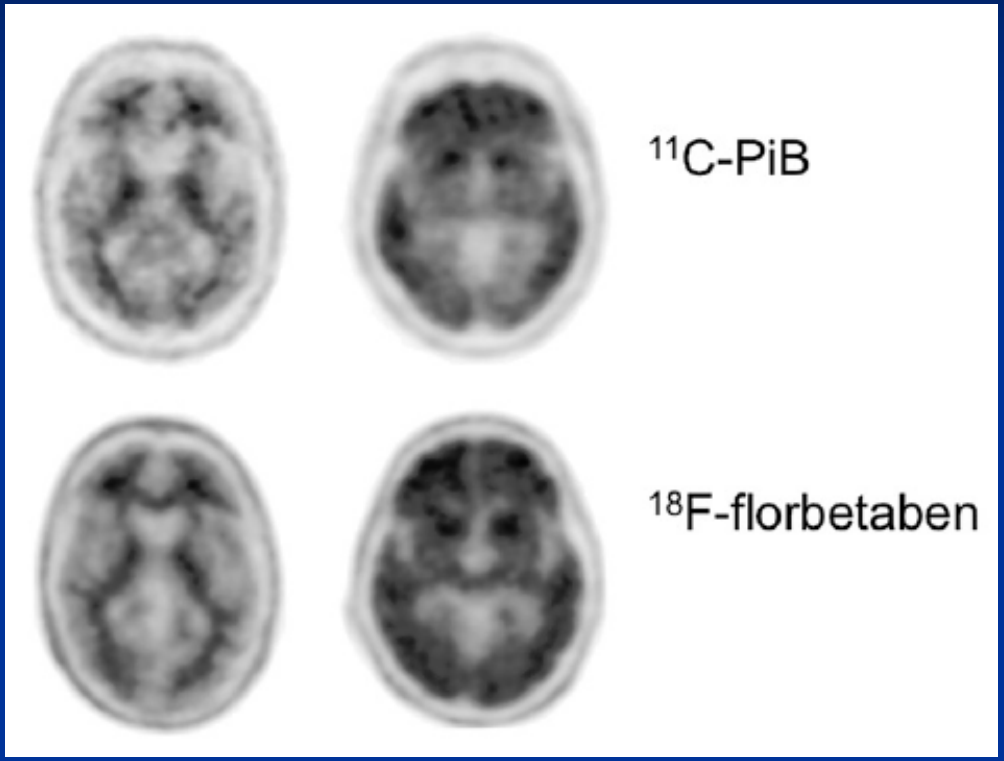
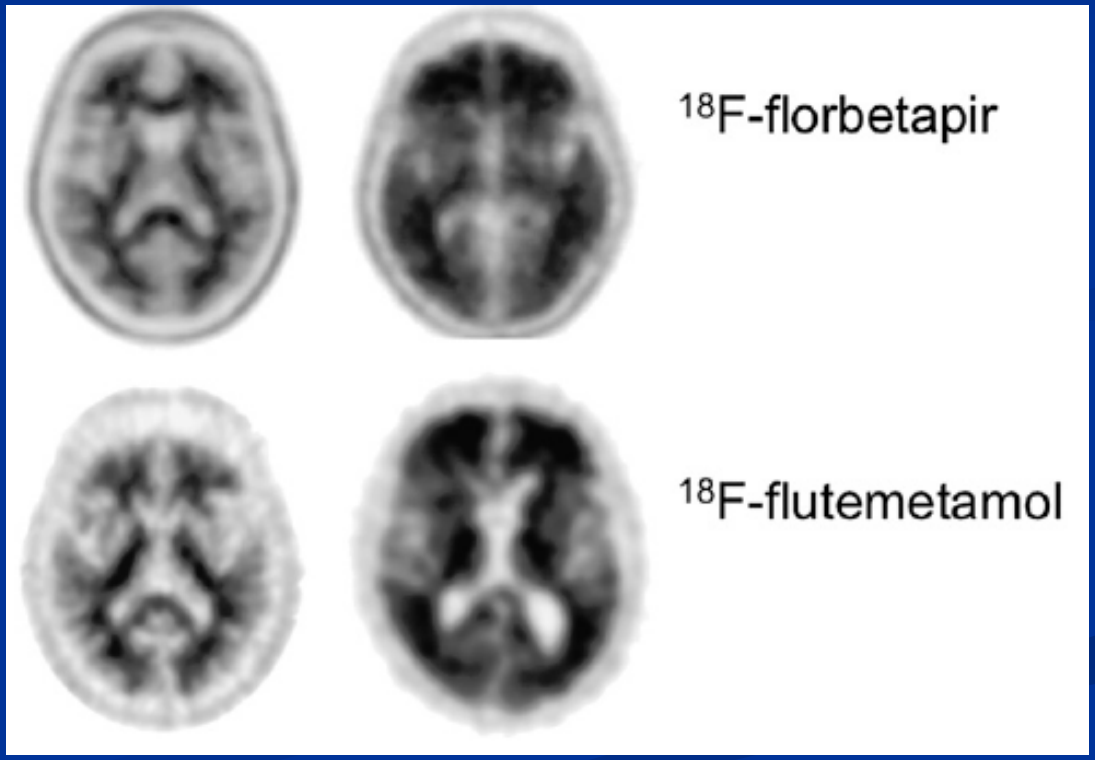
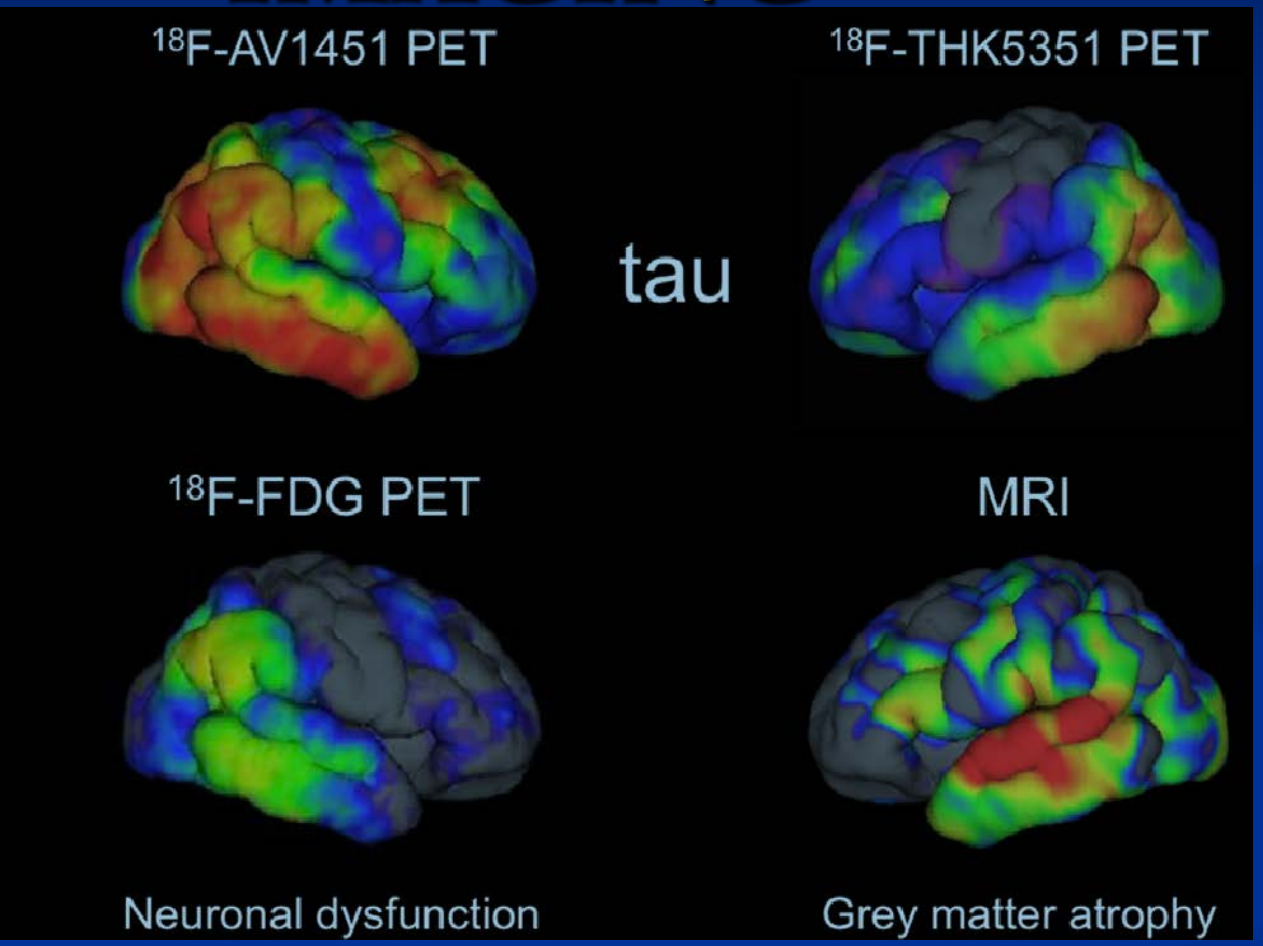




CC Rowe & VL Villemagne. J Nuc Med 2011; 52:1733-1740

TAU IMAGING



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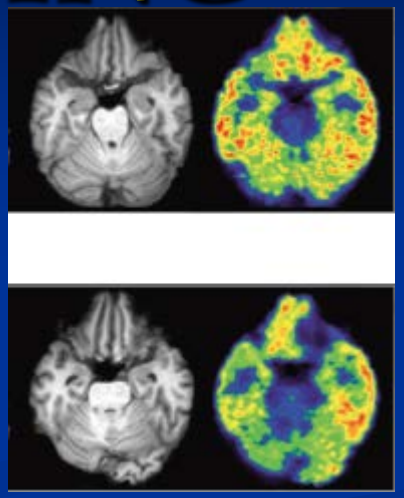
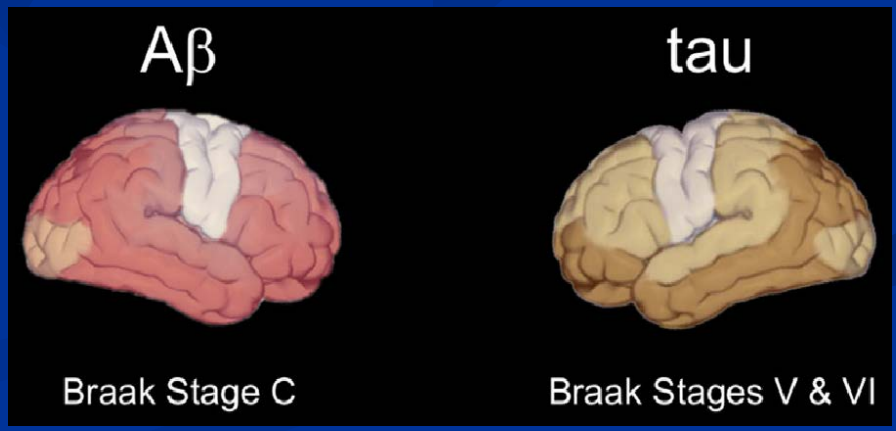


UCB1017
Chen et al. JAMA Neurol 2018



Villemagne VL et al. Sem Nuc Med 2017;47:75-88

CEREBROSPINAL FLUID

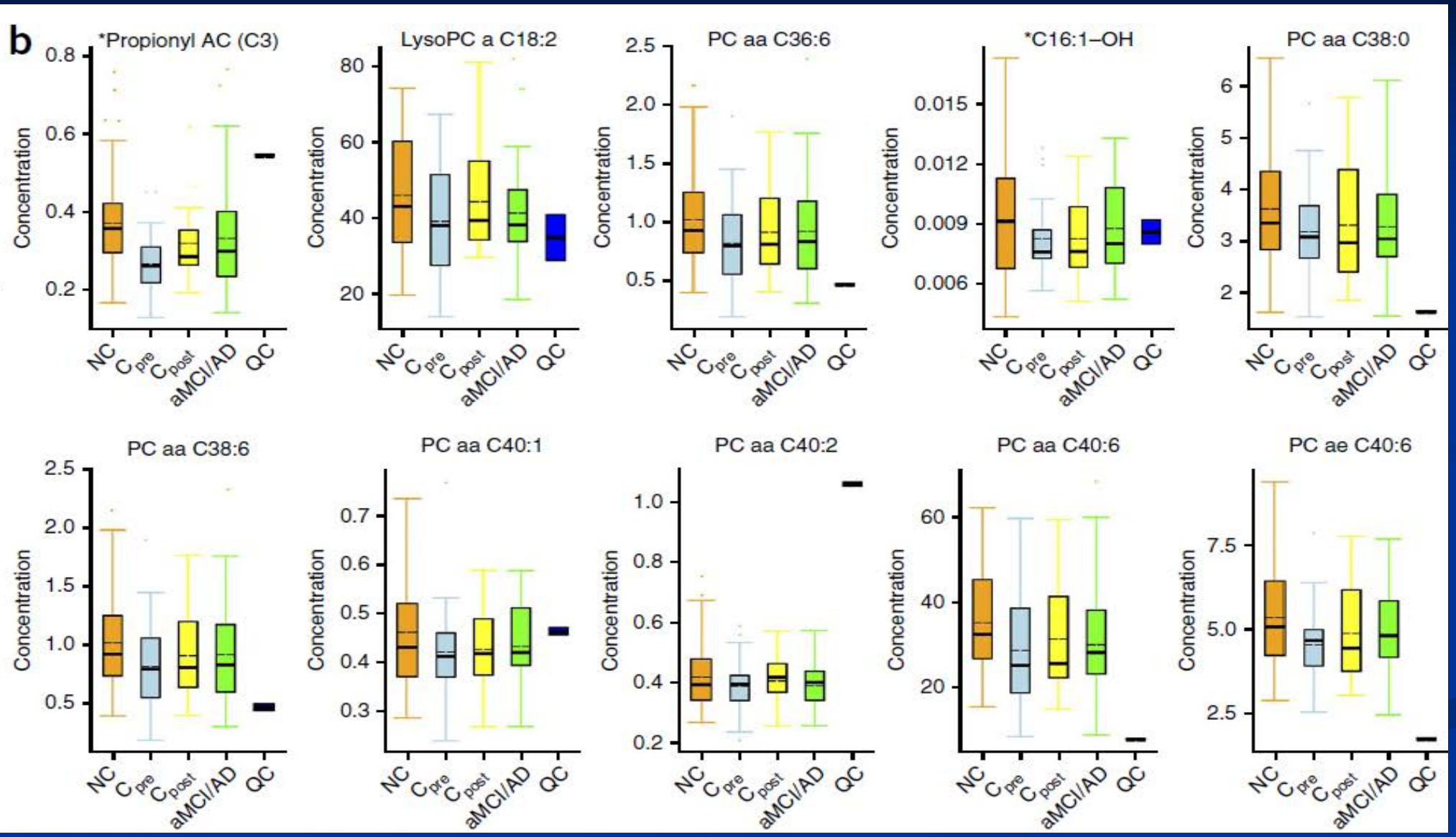
Table 1. Biomarker changes in different cognitive disorders

Cognitive disorder	$A\beta_{42}$	T-tau	P-tau	ATI*
Alzheimer's disease	↓	↑	↑	↓
Mild cognitive impairment	↓	↑	↑	↓
Healthy aging	↔	↔	↔	↔
Depression	↔	↔	↔	↔
Frontotemporal dementia	↔ or ↓	↔ or ↑	↔	↓ or ↑
Dementia with Lewy bodies	↔ or ↓	↔ or ↑	↔ or ↑	↔ or ↓
Vascular dementia	↔ or ↓	↔ or ↑	↔	↔ or ↓
Creutzfeldt-Jakob disease	↔ or ↓	↑↑↑	↔ or ↑	↓↓

*ATI is an index created by Athena Diagnostics for combined assessment of $A\beta_{42}$ and tau ($A\beta_{42}$/(240 + 1.18*T-tau); ATI < 1.0 is considered suggestive of Alzheimer's disease, except when tau is extremely high (eg, due to Creutzfeldt-Jakob disease, stroke, or encephalitis).
↔—normal levels; ↓—decreased levels (eg, $A\beta_{42}$ < 700 ng/mL); ↑—increased levels (eg, T-tau > 500; P-tau > 60); Aβ—beta-amyloid; P-tau—phospo-tau; T-tau—total tau.

JR Steinerman & LS Honig. Curr Neurol and Neurosci Rep 2007; 7: 381-387

PLASMA BIOMARKERS



M Mapstone et al. Nat Med 2014; 20: 415-418

ALZHEIMER'S DISEASE

Research in Therapeutics

AD Timeline & Drug Development

Auguste D. evaluation–1901
Krapelin named disease–1910
Katzman NEJM editorial–1976
McKhann ADRDA/NINDS crit–1984
Glenner & Wong β-amyloid–1984
Iqbal identifies P-tau–1986
Roses identifies APOE–1993
Games 1st Tg mouse PDAPP–1995
St. George Hyslop PS1–1995
Schellenberg PS2–1995
Schenk mouse vaccine–1999

1977–hydergine
1993–tacrine
1996–donepezil
2000–rivastigmine
2001–galantamine
2003–memantine

2002–AN1792
2009–flurbi
2013–sema, ava
2014–bapi, sola
2016–IVIG
2017–sola
2018–veru, lana
cren,adu,gant,elen

CLINICAL DRUG TRIALS

Preclinical – screening /PD /PK /ADME /Toxicity

In silico ⟹ biochemistry ⟹ cell culture

rodent (mouse) ⟹ small animal (dog) ⟹ primate (rhesus)

Phase 0	"expIND" – subpharm/therap (PD/PK)
Phase 1	"FiH" - safety – SAD ~~M~~AD
Phase 2	"PoC" - dose-finding safety and efficacy
Phase 3	"PoE" - efficacy
Phase 4	post-approval - safety/usage considerations

CLNICAL DRUG TRIALS REQUIREMENTS

- IND, Protocol, ICF, Regulatory/Contractual Approvals
- Research Pharmacy
- Research Nurses / Drug delivery team
- Large Team of raters/testers: Npsych, Clinical, Functional
- Fluid Biomarkers – blood, urine, cerebrospinal fluid
- Structural Imaging Biomarkers – MRI
- Functional Imaging Biomarkers – FDGPET
- Molecular Imaging Biomarkers – amyloid PET, tau PET
- Other Biomarkers – EEG, EMG, ECG, Echo, etc.

Treatments of Neurological Diseases

- Multiple Sclerosis
- Immune-mediated Encephalitides
- Inflammatory Neuro/myopathies
  - Alzheimer's Disease, FTD, LBD, HD
  - Degenerative Neuro/myopathies
  - Stroke
  - Traumatic Brain Injury

ALZHEIMER THERAPIES

- THERAPY FOR NON-SPECIFIC DISEASE SYMPTOMS
- THERAPY FOR DISEASE-SPECIFIC DYSFUNCTION
  - Targeted: neurotransmitter-based (cholinergic, glutamatergic, etc.)
  - Generalized: (nootropes, stimulants, vasoactive drugs, etc.)
- TREATMENT OF PRIMARY DISEASE PROCESS
  - Decrease amyloid production (e.g. secretase inhibitors, SALA)
  - Increase amyloid clearance by active immunization (e.g. vanutide)
  - Increase amyloid clearance by passive immunization (e.g. BAN-2401, gantenerumab, crenezumab, aducanumab, solanezumab, bapineuzumab)
  - Decrease amyloid fibrillization (e.g. scyllo-inositol, tramiprosate)
  - Decrease amyloid-induced injury (e.g. RAGE inh., PPAR-γ antagonist)
  - Decrease downstream nerve cell damage (e.g. tau-disrupters)
  - Anti-inflammatory agents (e.g. NSAIDS, etc.)
  - Neuroprotective agents (e.g. antioxidants, growth factors, etc.)

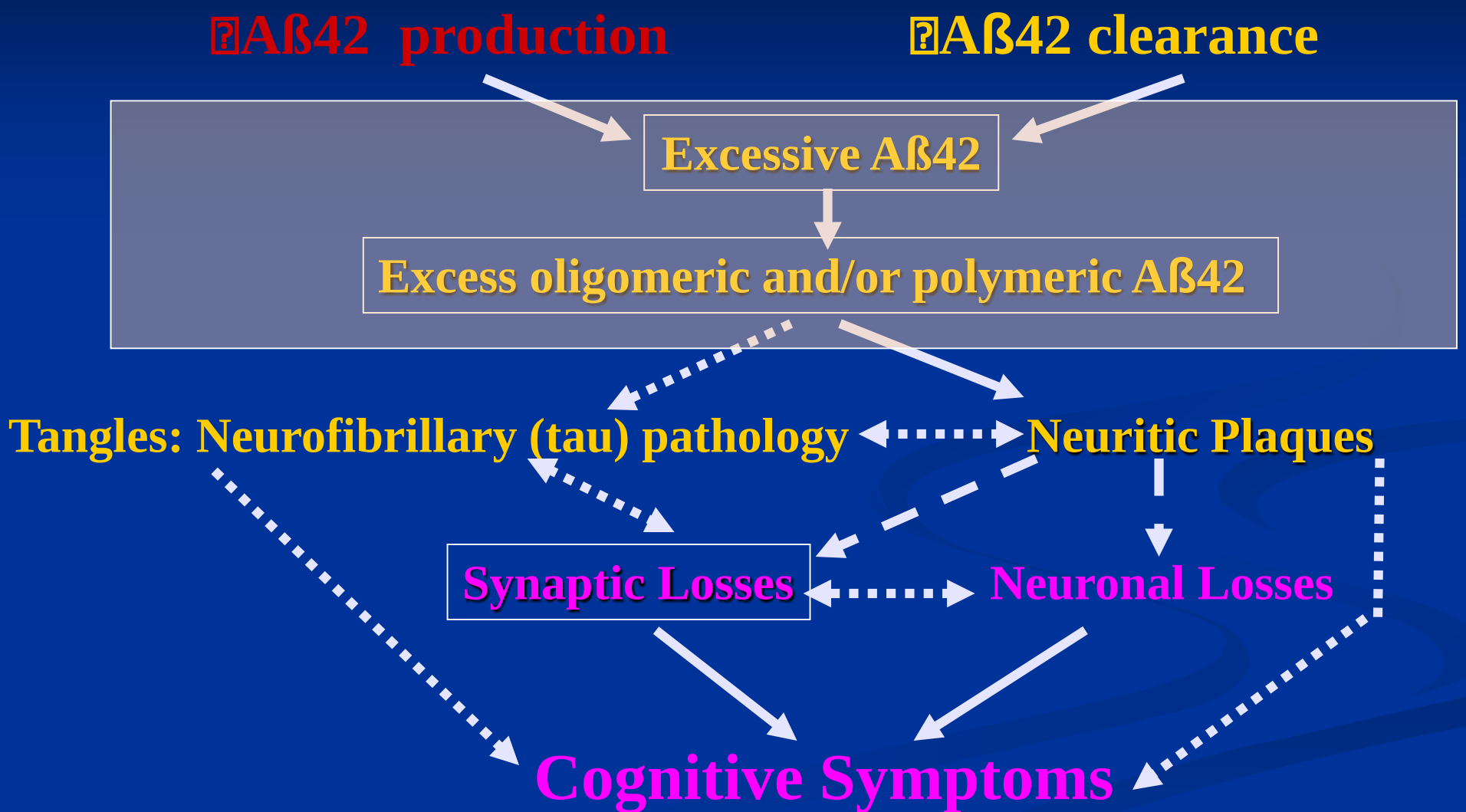
TREATING DISEASE-SPECIFIC DYSFUNCTION

- *Inhibition of brain acetylcholinesterase*
  - tacrine hydrochloride (Cognex®)
  - donepezil hydrochloride (Aricept®)
  - rivastigmine tartrate (Exelon®)
  - galantamine hydrobromide (Razadyne® ER)
- *Inhibition of brain NMDA glutamate receptor*
  - memantine hydrochloride (Namenda®)

Drug Targets from AD Pathology

- NEURITIC PLAQUES
- NEUROFIBRILLARY TANGLES
- NEURONAL LOSSES
- SYNAPTIC LOSSES
- NEUROTRANSMITTER CHANGES
- OTHER BIOCHEMICAL/CELL CHANGES

PATHOGENETIC CASCADE IN AD



Aβ IMMUNIZATION IN MICE

THE NEW YORK TIMES NATIONAL THURSDAY, JULY 8, 1999 A16

Vaccine in Mice Fights Brain Changes Tied to Alzheimer's

By LAWRENCE M. FISHER

Scientists working with mice have developed a vaccine that has proved highly effective in both preventing and reversing one of the primary brain abnormalities associated with Alzheimer's disease.

It remains to be seen if the compound will produce the same effects in people. Indeed, it remains to be seen if it improves cognition even in mice, which is difficult to measure. It is also unknown if the abnormality is a cause of the ailment's devastation in the brain or simply one of its symptoms.

But the researchers' report of their work, being published today in the journal Nature, is being hailed by scientists as a landmark achievement in the battle against Alzheimer's, the fourth largest cause of death in the United States.

The vaccine was developed by researchers at Elan Pharmaceuticals of South San Francisco, a subsidiary of the Elan Corporation of Dublin. The company's researchers worked with mice that the researchers had genetically altered so that they developed the plaque-like deposits commonly found in the brains of Alzheimer's patients. These deposits, amyloid plaques, are believed to cause cell death in the brain.

When the scientists vaccinated healthy young mice, the mice grew up without developing the plaques, the researchers said. In diseased mice, they said, the treatment eradicated the plaques, improved the condition of damaged neurons and reduced inflammation in surrounding tissues as well.

Elan officials said they would seek permission from the Food and Drug Administration to begin safety trials in humans within the year. They said preliminary discussions with the agency had been encouraging. Anticipating a flood of calls about the development, both Elan and the Alzheimer's Association have set up toll-free telephone numbers. Elan is at (800) 894-7303; the association is at (800) 272-3900.

Alzheimer's, characterized by progressive dementia and incapacitation, affects four million Americans and costs the nation $100 billion a year, according to the Alzheimer's Association. The longer people live, the more likely they are to develop symptoms of Alzheimer's.

Only a handful of drugs have been approved to treat Alzheimer's and none provide more than slight, temporary relief of symptoms. For many patients the drugs are ineffective.

This is the first time anyone has demonstrated the ability to either totally prevent plaque deposition, or

Questions and plaudits after a major advance against Alzheimer's.

to make the deposits remove themselves," said Dr. Steven DeKosky, chairman of the scientific and medical advisory board of the Alzheimer's Association and head of the Alzheimer's disease research center at the University of Pittsburgh.

"This finding is really exciting on a couple of levels," Dr. DeKosky said. "The biggest issue is the use of immunization. It's very clever to have tried that."

This is the first time the association has expressed optimism about any pharmaceutical development in treating or preventing the disease.

"It is a radical innovation, a creative approach," said Roger Rosenberg, a professor of neurology at the University of Texas Southwest Medical Center in Dallas, and past president of the American Academy of Neurology. "I don't remember anyone proceeding with an immunization."

The Elan scientists said they had been concerned that an immunization might prompt inflammation in the brain, giving rise to conditions like encephalitis or multiple sclerosis, but that no such symptoms had been observed in the mice. To their surprise, they said, not only did the immune system mount antibodies against the amyloid protein, but scavenger cells also appeared to clear the accumulated plaque from the brains of the diseased mice.

"It's better than anything we had hoped for," said Dr. Dale Schenk, Elan's vice president of neurobiology. "We actually think the vaccine is stimulating the immune system to come in and take up the plaque."

Dr. Ivan M. Lieberburg, senior vice president of research at Elan Pharmaceuticals, said the company was "moving forward to clinical trials aggressively."

The Elan researchers immunized the mice with a synthetic form of the beta-amyloid peptide, which is the predominant compound found in the plaques in patients' brains. They linked the peptide to an immune system stimulus, or adjuvant, that is commonly used in mouse studies. The adjuvant prompts the immune system to attack the amyloid plaques it would otherwise ignore.

The adjuvant used in the mice is not tolerated by people, though the researchers said that designing one that was tolerated was not regarded as a major hurdle.

The mice had been implanted with a mutated human gene that prompts the overproduction of amyloid, but that mutation is only found in a minority of actual Alzheimer's patients, those with so-called familial Alzheimer's, rather than the more common sporadic form. People with sporadic Alzheimer's do not overproduce amyloid, but instead seem to have a problem clearing it from the body. The only way to determine whether the vaccine is effective for them would be through clinical trials.

Moreover, some scientists believe that the amyloid plaques are a symptom rather than a cause of Alzheimer's and that the primary pathology of the disease is actually manifested in twisted proteins inside the brain cells of Alzheimer's patients that look like tangled wire. The mice do not develop such tangles so there is no way of gauging their relative significance from this experiment. Nor is it possible to assess accurately memory loss or cognitive ability in the mice.

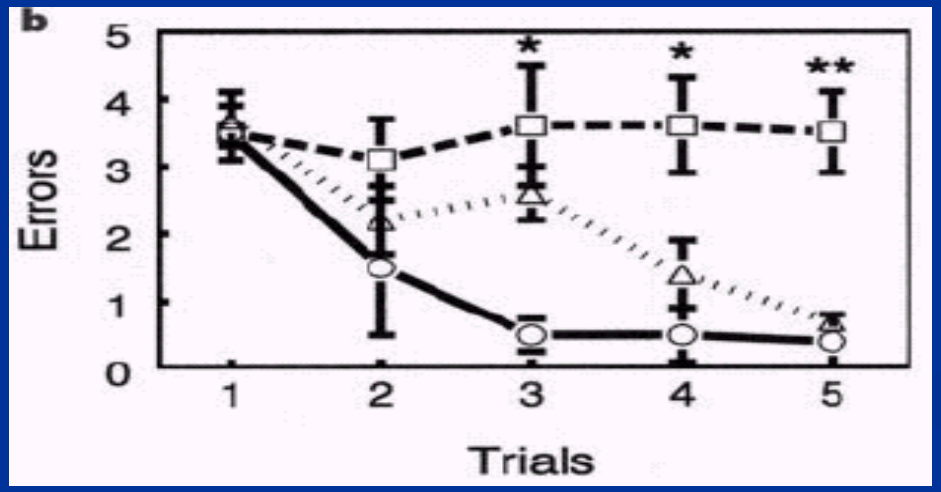
If a human form of the vaccine can be developed and proved safe, further studies should answer these questions.

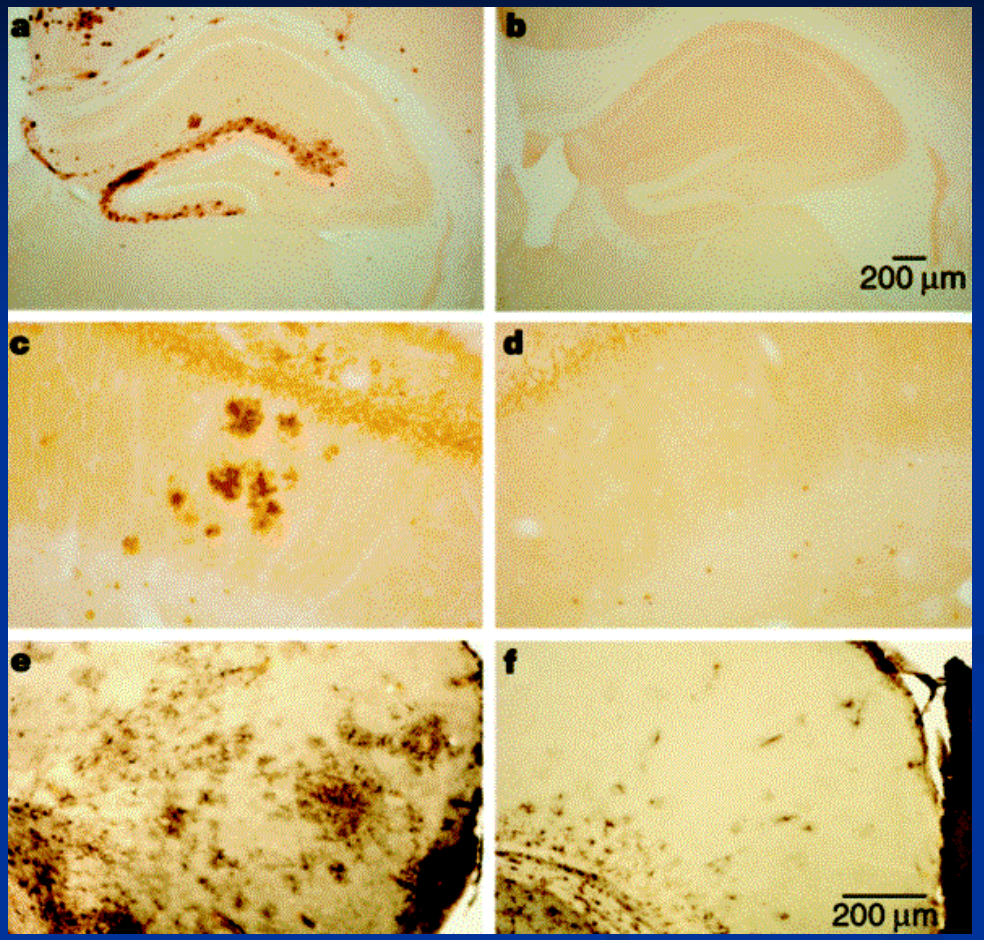
"If this cannot be commercially developed in humans without untoward effects, I think we may have our first crack at treating people," said Dr. Leon Thal, an Alzheimer's specialist at the Veterans' Administration Medical Center at the University of California at San Diego. Dr. Thal has been an adviser to Elan on other studies.

The Elan laboratory in South San Francisco is part of Athena Neurosciences, a small biotech company acquired by the Elan Corporation in 1995. Founded in 1987, Athena first achieved scientific renown in 1995 with the development of the transgenic mouse, the first laboratory animal for the study of Alzheimer's. Athena and Elan have also been pioneers in the development of screening tests using genes or proteins that can help diagnose or show a familial predilection for Alzheimer's.

Using these tests, together with commonly used observation techniques, Elan plans to recruit a small group of elderly Alzheimer's patients for safety trials, most likely beginning early next year. Should the vaccine prove safe, it would be subject to at least two phases of clinical trials with larger groups of patients before it could be submitted to the F.D.A. for approval, which is about a five-year process. Tests on healthy patients whose genetic makeup shows a strong likelihood of Alzheimer's would follow.

THE FRESH AIR FUND: MOUNTAINS, LAKES AND STREAMS





D Schenk et al. *Nature* 1999; **400:** 173-177

D Morgan et al. Nature 2000; 408: 982-985

IMMUNIZATION THERAPY

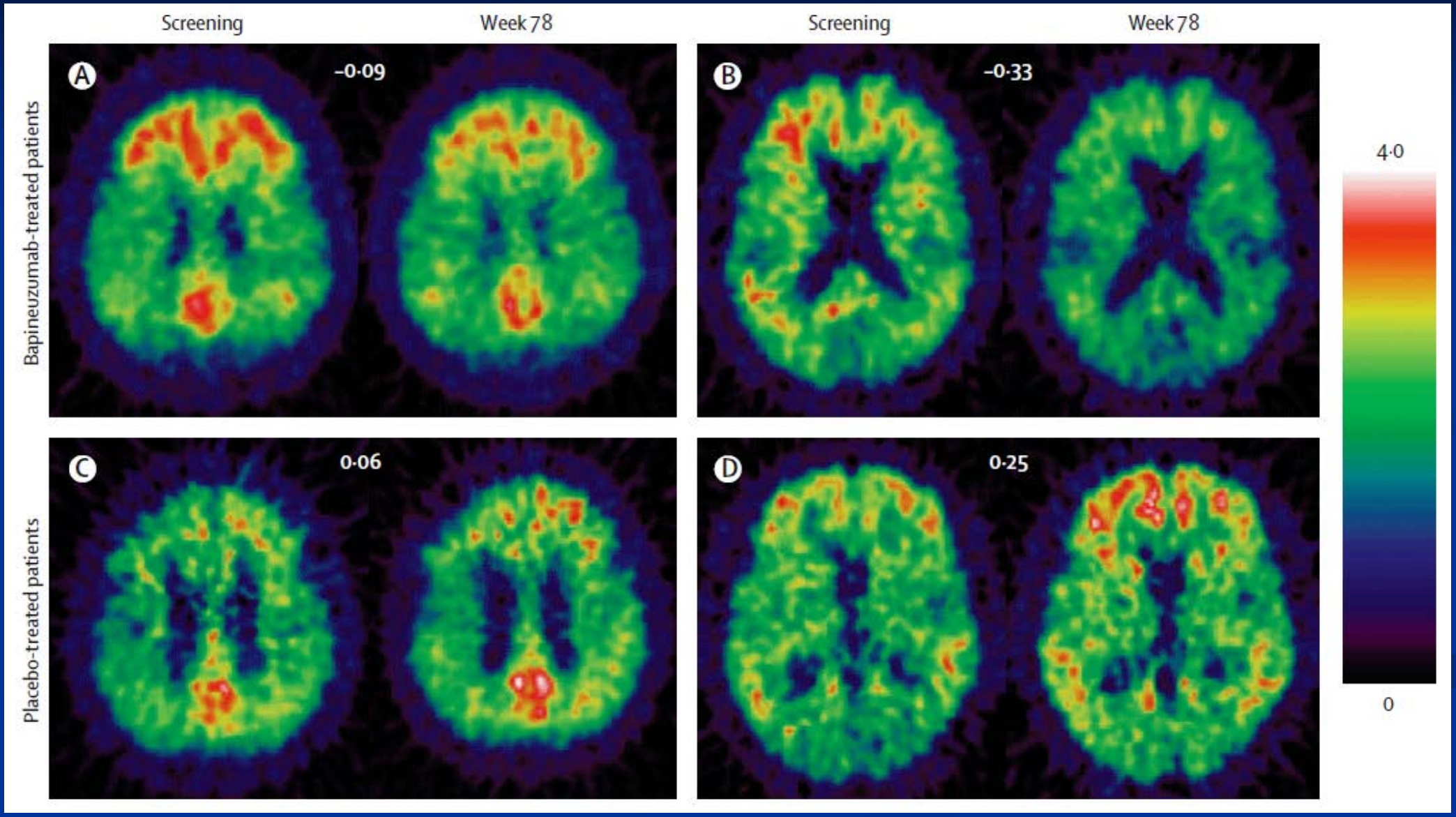
Active Immunization:

- purified Aß by intramuscular injection (Elan/Wyeth AN-1792 = AIP-001)
  - **Phase 0** (1999-2000)**: Preclinical Studies in PDAPP mice:** subcutaneous, intranasal, behavioral
  - **Phase 1** (2000): 101 US & 103 European pts (single & multiple doses w/o adv. effects)
  - **Phase 2A** (9/2001-1/2002): 375 pts,11 sites; stopped due to inflammatory encephalitis in ~6 % pts
- purified Aß carrier protein/QS21 adj(Pfizer/Janssen vanutide crid ACC-001)
- purified N-terminal Aß (Novartis/Cytos Immunodrug® = CAD106)
- Other Aß with immunostimulant (Merck V950)

Passive Immunization:

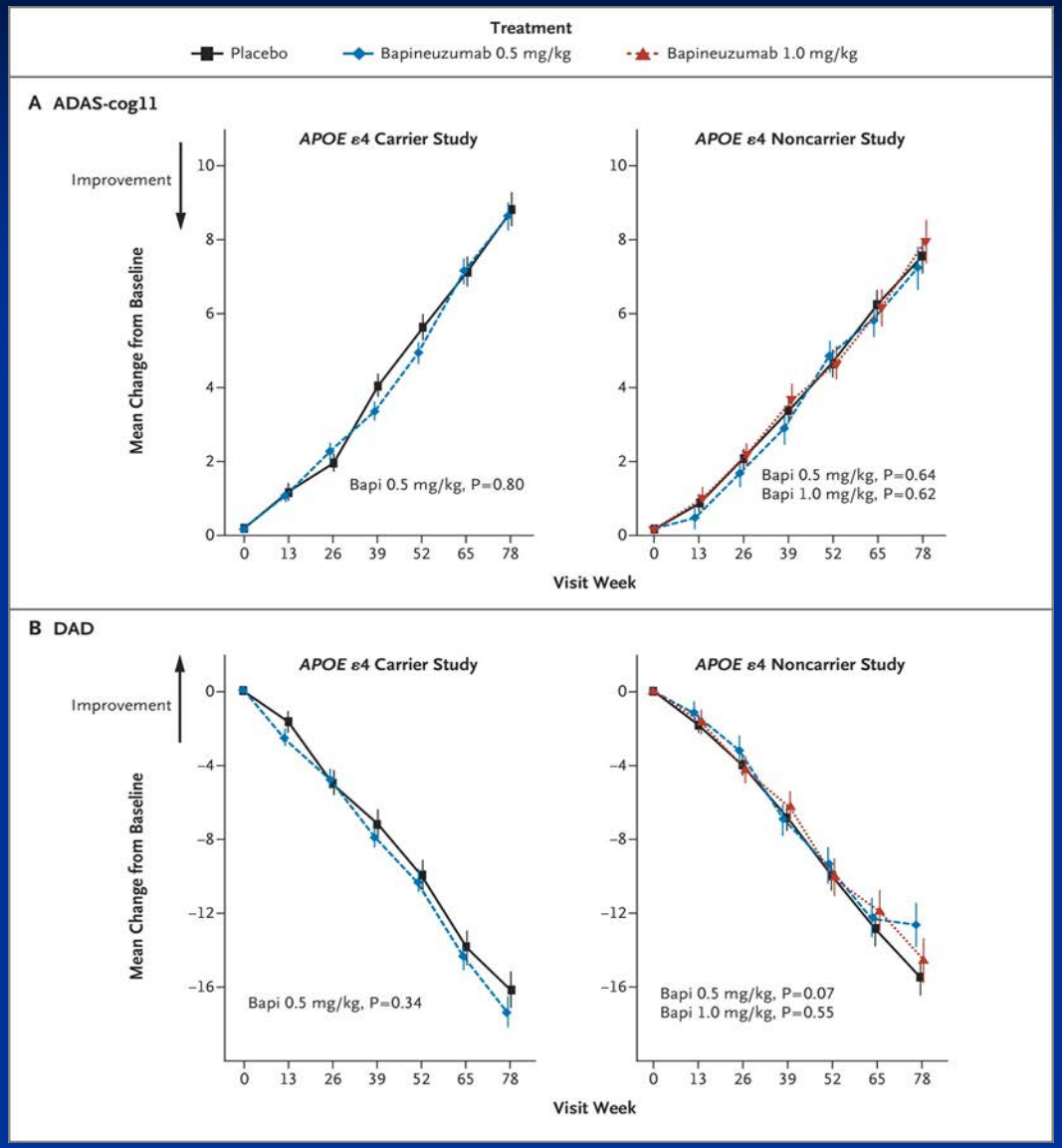
- Bapineuzumab: humanized mouse mAb to N-terminal Aß42 (Elan/Wyeth -> Janssen(J&J)/Pfizer AAB-001 = ELN115727)
- Solanezumab: humanized mAb to mid-region Aß42 (Lilly LY2062430)
- Crenezumab: humanized IgG4 mAb midAß42 (Genentech MABT5102A)
- Gantenerumab: fully human mAb to aggreg Aß42 (Roche RO4909832)
- Aducanamab: humanized IgG1 mAb to aggreg Aß42 (Neurimmune/Biogen)
- BAN-2401: humanized IgG1 mAb to Aß42 fibrils (BioArctic/Eisai/Biogen)

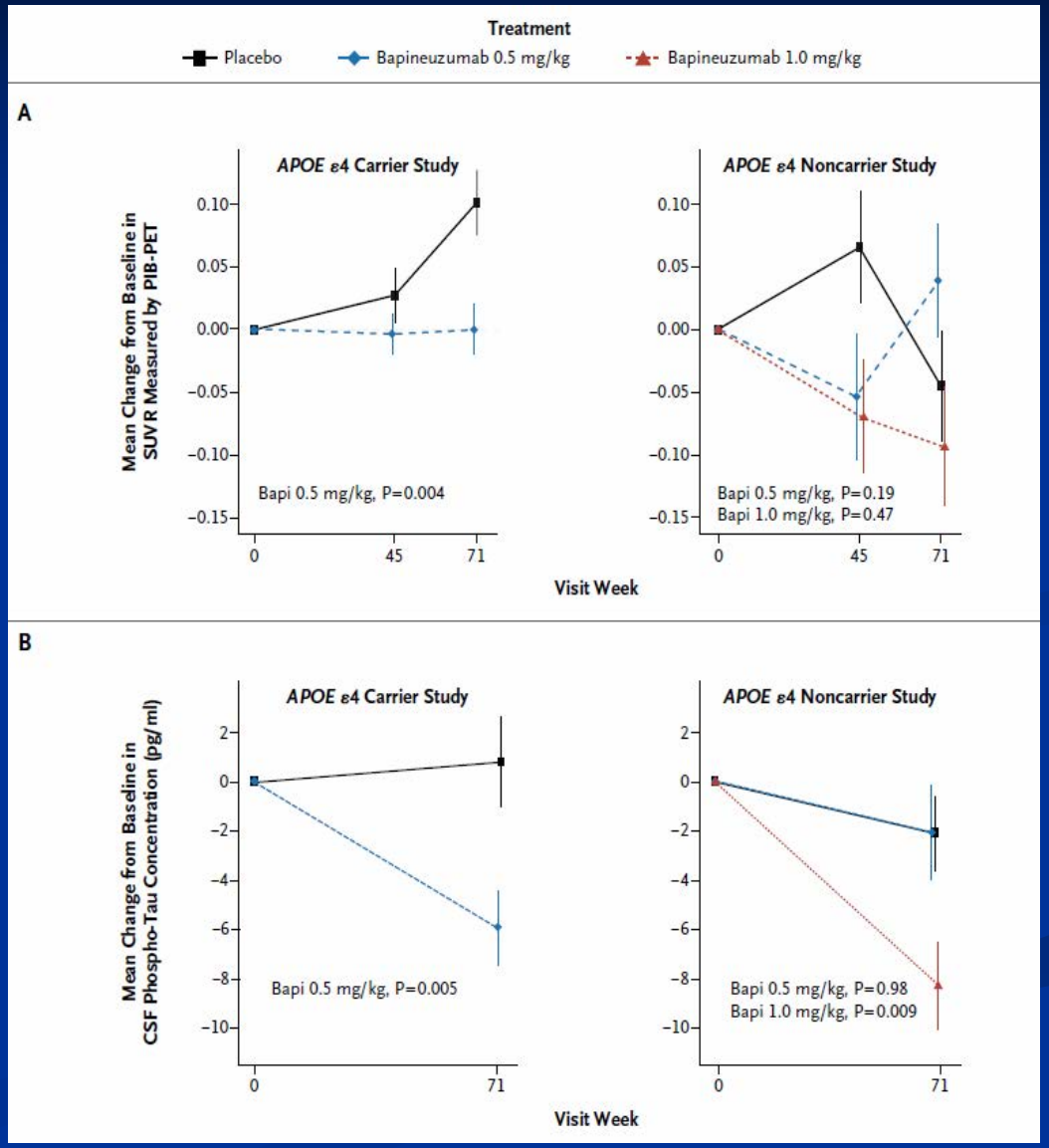
PIB PET: BAPINEUZUMAB PH2



JO Rinne et al. Lancet Neurology 2010; 9: 363-372

Bapineuzumab anti-A-beta42





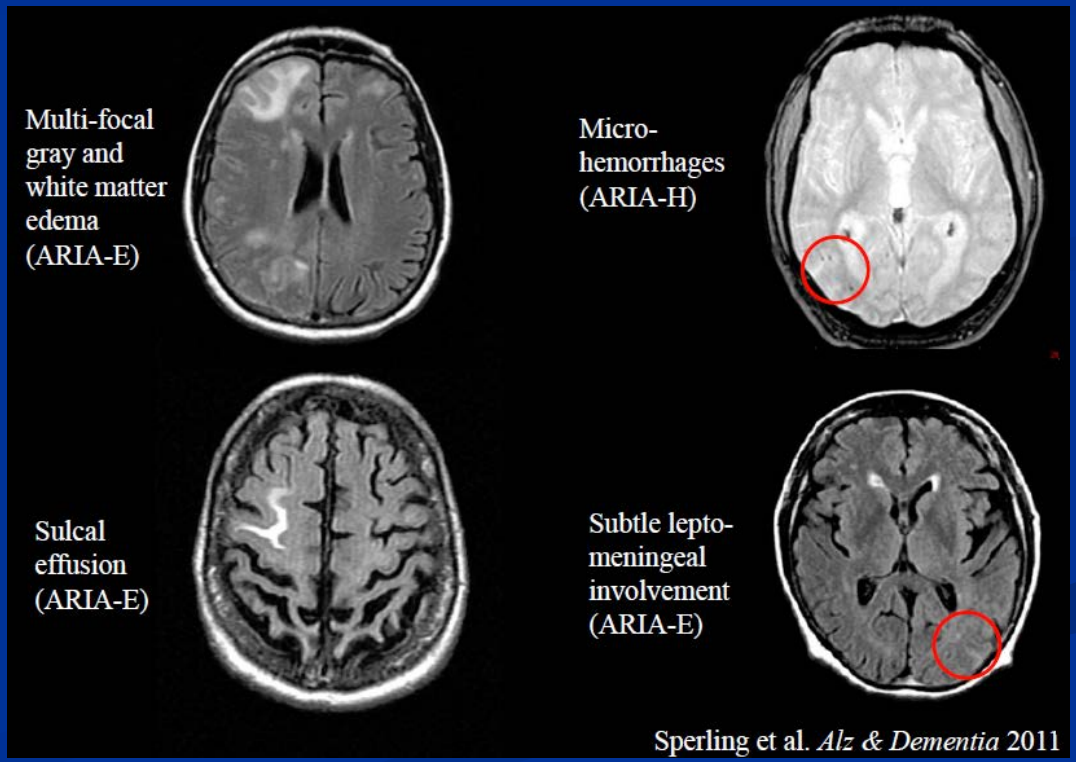
Salloway S et al. N Engl J Med 2014;370:322-333

Bapineuzumab Ph3

Table 3. Adverse Events.*

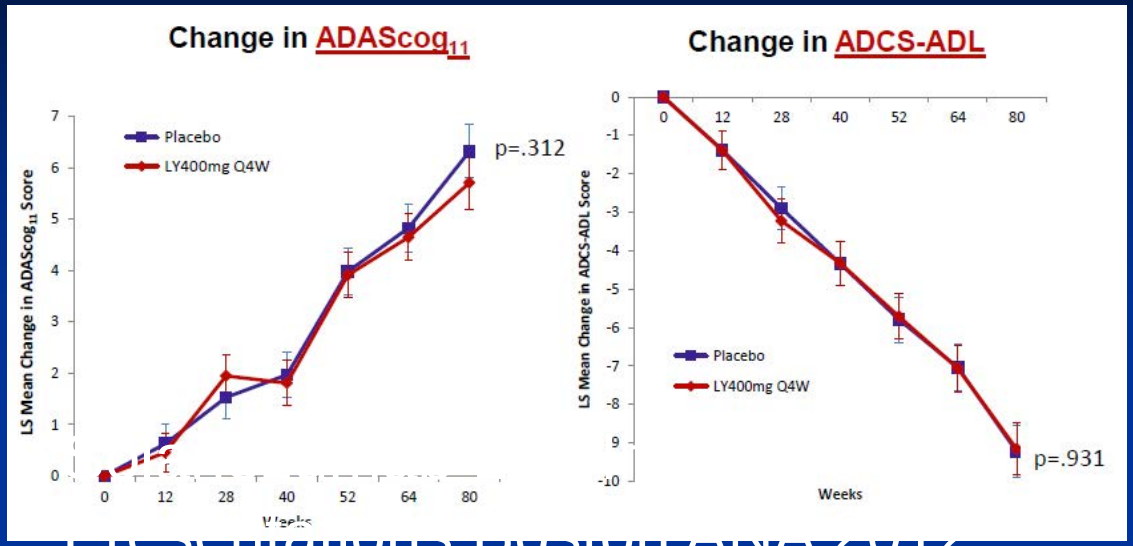
Adverse Event	Placebo	Bapineuzumab, 0.5 mg/kg	Bapineuzumab, 1.0 mg/kg	Bapineuzumab, 2.0 mg/kg
	number of patients (percent)			
Carrier study†				
Amyloid-related imaging abnormalities with edema	1 (0.2)	103 (15.3)		
Fall	64 (14.3)	100 (14.9)		
Headache	48 (10.7)	78 (11.6)		
Noncarrier study‡				
Amyloid-related imaging abnormalities with edema	1 (0.2)	14 (4.2)	31 (9.4)	20 (14.2)
Fall	73 (13.9)	43 (12.8)	43 (13.1)	23 (16.3)
Urinary tract infection	59 (11.3)	40 (11.9)	42 (12.8)	15 (10.6)
Anxiety	43 (8.2)	19 (5.6)	39 (11.9)	11 (7.8)
Headache	49 (9.4)	30 (8.9)	34 (10.3)	16 (11.3)
Agitation	37 (7.1)	26 (7.7)	15 (4.6)	16 (11.3)

Salloway S et al. N Engl J Med 2014;370:322-333



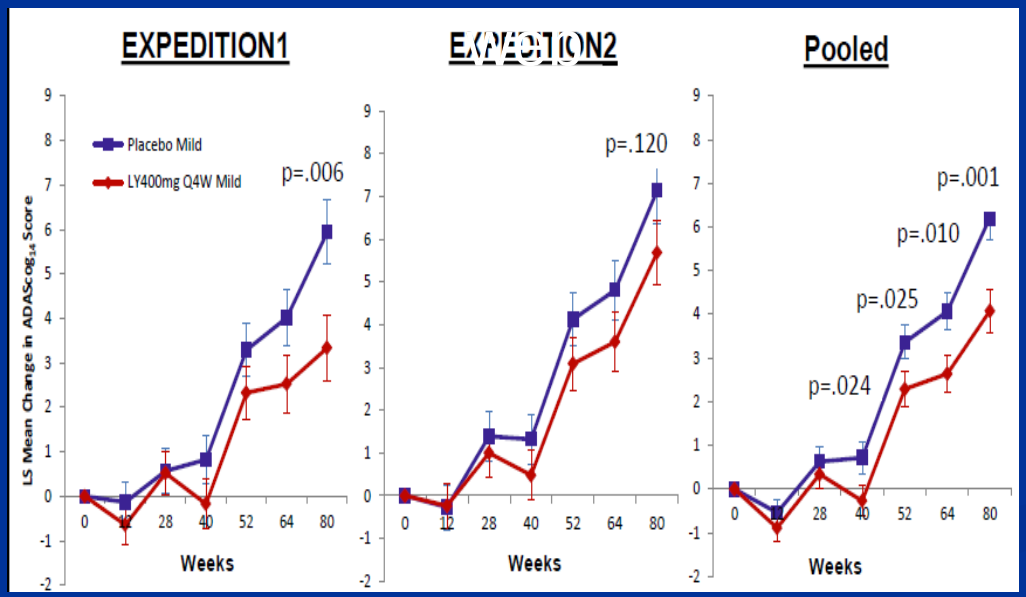
Solanezumab anti-A-beta42 EXP1&2

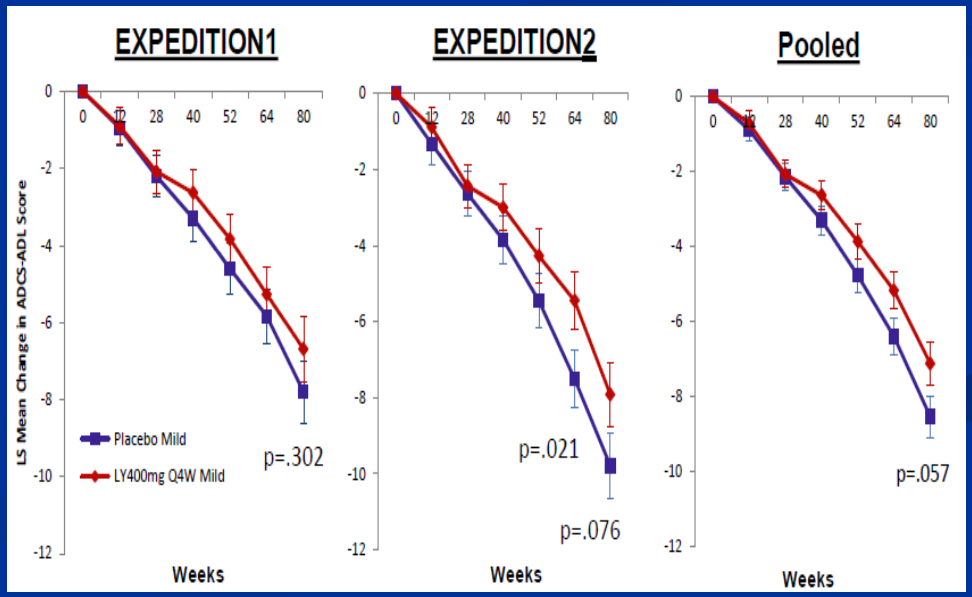
OVERALL



Presentations Boston ANA 2012

MILD ONLY





Siemers ER et al. Alz & Dem 2016;12:110-20 & ANA2012

Solanezumab anti-A-beta42 EXP3

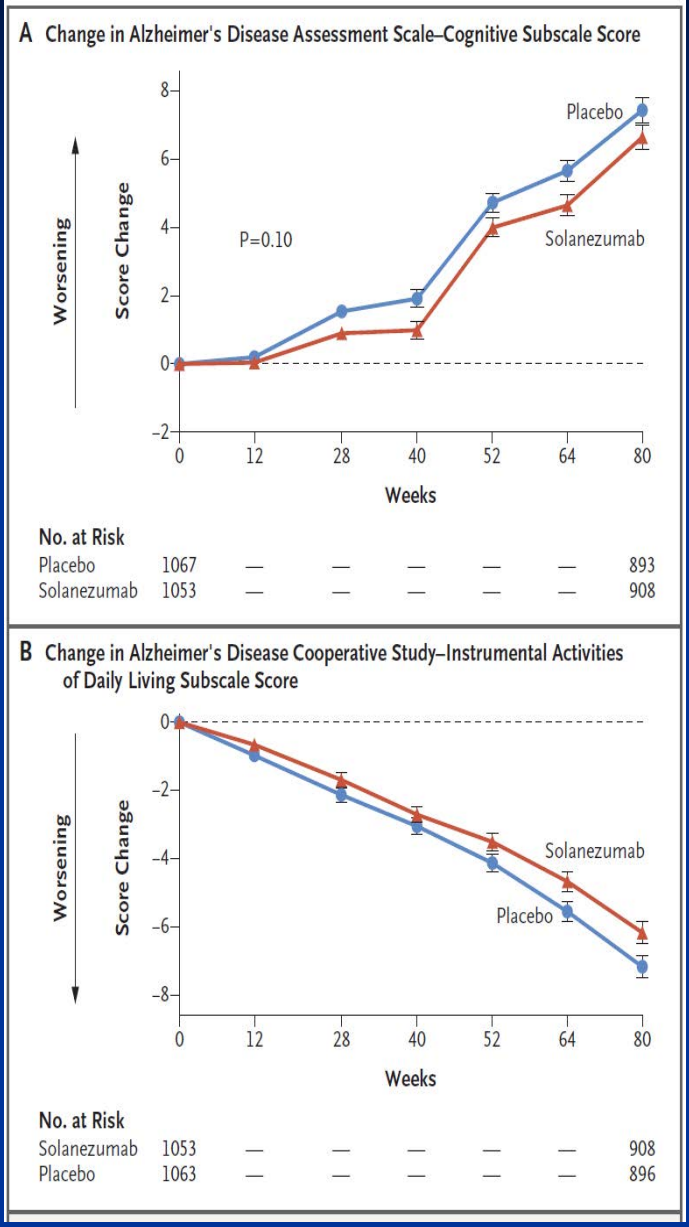
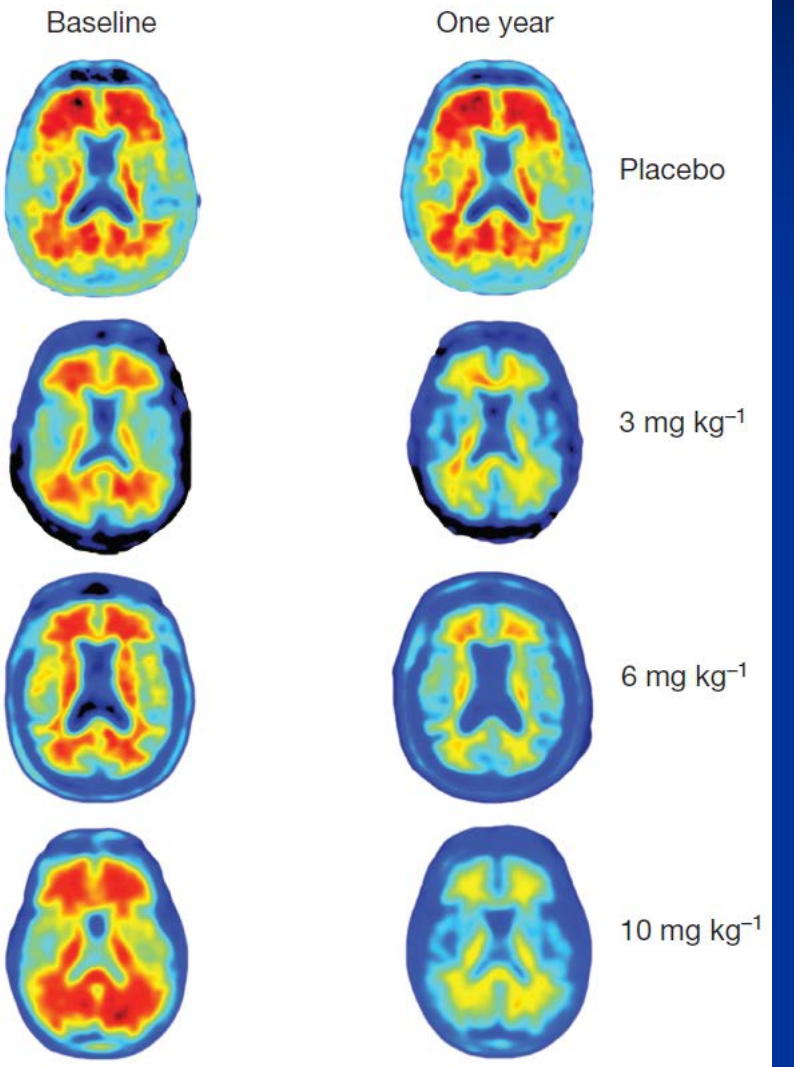


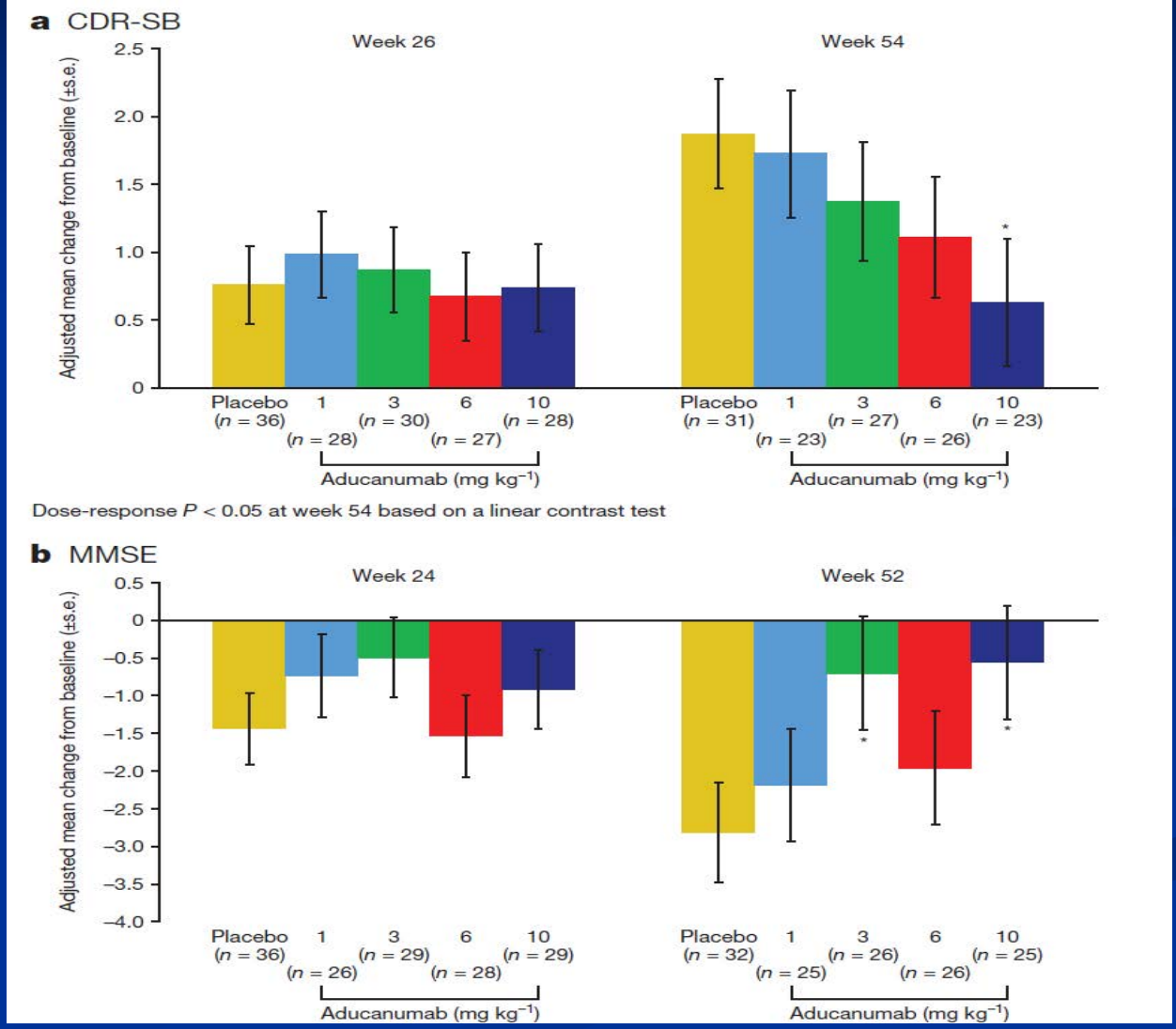
Table 2. Primary and Key Secondary Outcomes.*

Outcome	Raw Score at Baseline		Raw Score at 80 Wk		Least-Squares Mean Change at 80 Wk		Estimated Difference at 80 Wk (95% CI)	P Value†
	Placebo	Solanezumab	Placebo	Solanezumab	Placebo	Solanezumab		
Primary outcome: ADAS-cog14 score	29.70±8.50	28.87±8.26	36.11±14.27	35.09±13.28	7.44±0.36	6.65±0.36	−0.80 (−1.73 to 0.14)	0.10
Secondary outcomes								
MMSE score	22.62±2.89	22.81±2.77	19.09±5.56	19.62±5.30	−3.66±0.16	−3.17±0.15	0.49 (0.10 to 0.88)	—
ADCS-iADL score	45.37±8.14	45.60±7.93	39.01±11.86	39.83±11.41	−7.17±0.32	−6.17±0.32	1.00 (0.17 to 1.83)	—
ADCS-ADL score‡	66.69±9.15	67.02±8.67	59.00±14.61	60.20±13.52	−8.77±0.39	−7.42±0.39	1.35 (0.33 to 2.37)	—
FAQ score	10.60±7.11	10.31±6.81	15.73±8.10	15.35±8.24	5.57±0.21	5.17±0.21	−0.40 (−0.93 to 0.13)	—
CDR-SB score	3.93±1.95	3.88±1.90	6.02±3.38	5.72±3.18	2.21±0.11	1.87±0.10	−0.34 (−0.57 to −0.11)	—
iADRS score§	105.70±13.95	106.73±13.47	93.04±23.71	94.81±22.15	−14.59±0.54	−12.92±0.53	1.68 (0.29 to 3.06)	—

Honig L.S. et al. N Engl J Med 2018;378:321-330

Aducanumab Phase 1b Study





Sevigny et al. Nature 1 Sep 2016

IGIV

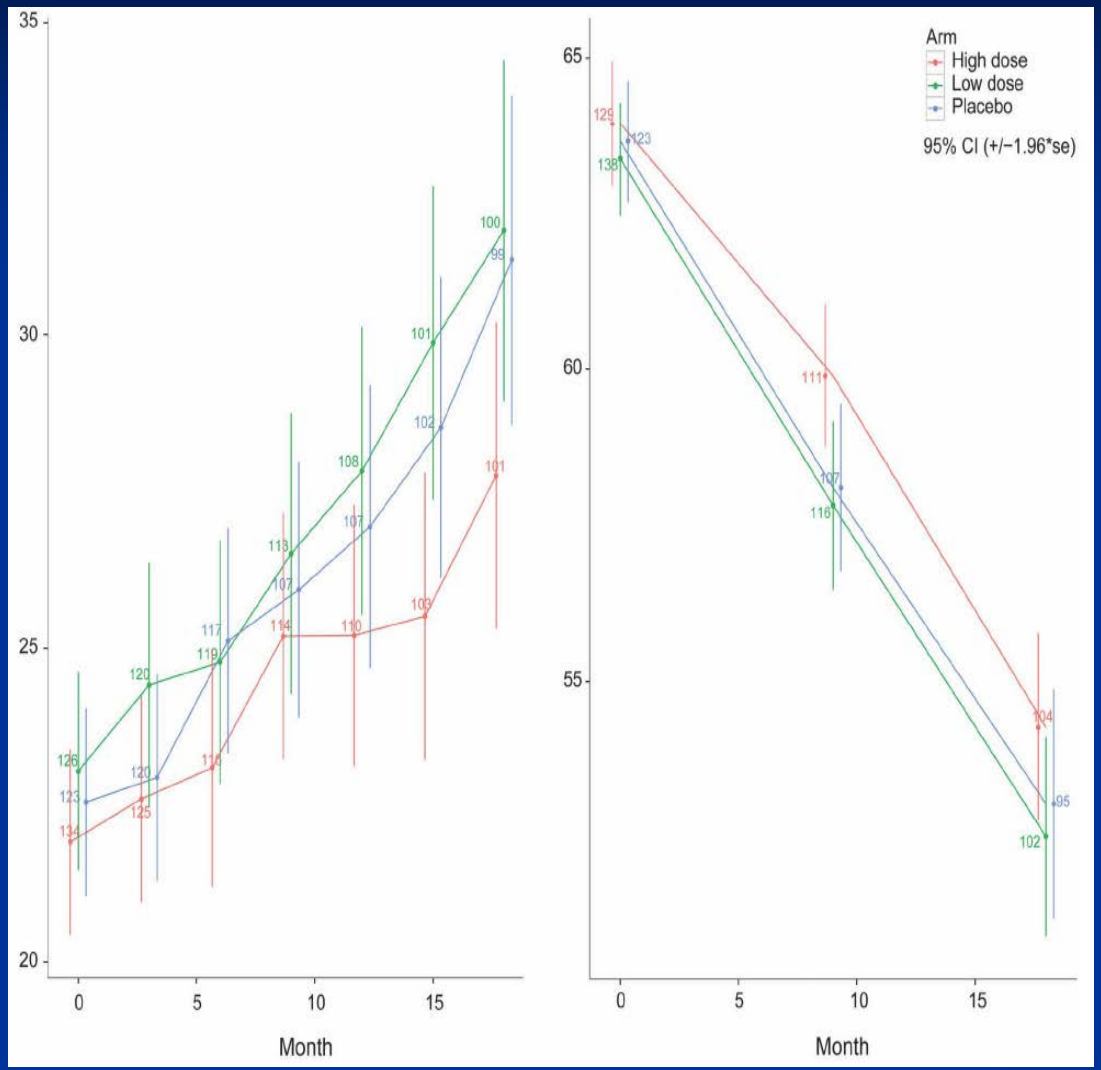


Table 2 Results of secondary clinical outcome analyses in the modified intent-to-treat population

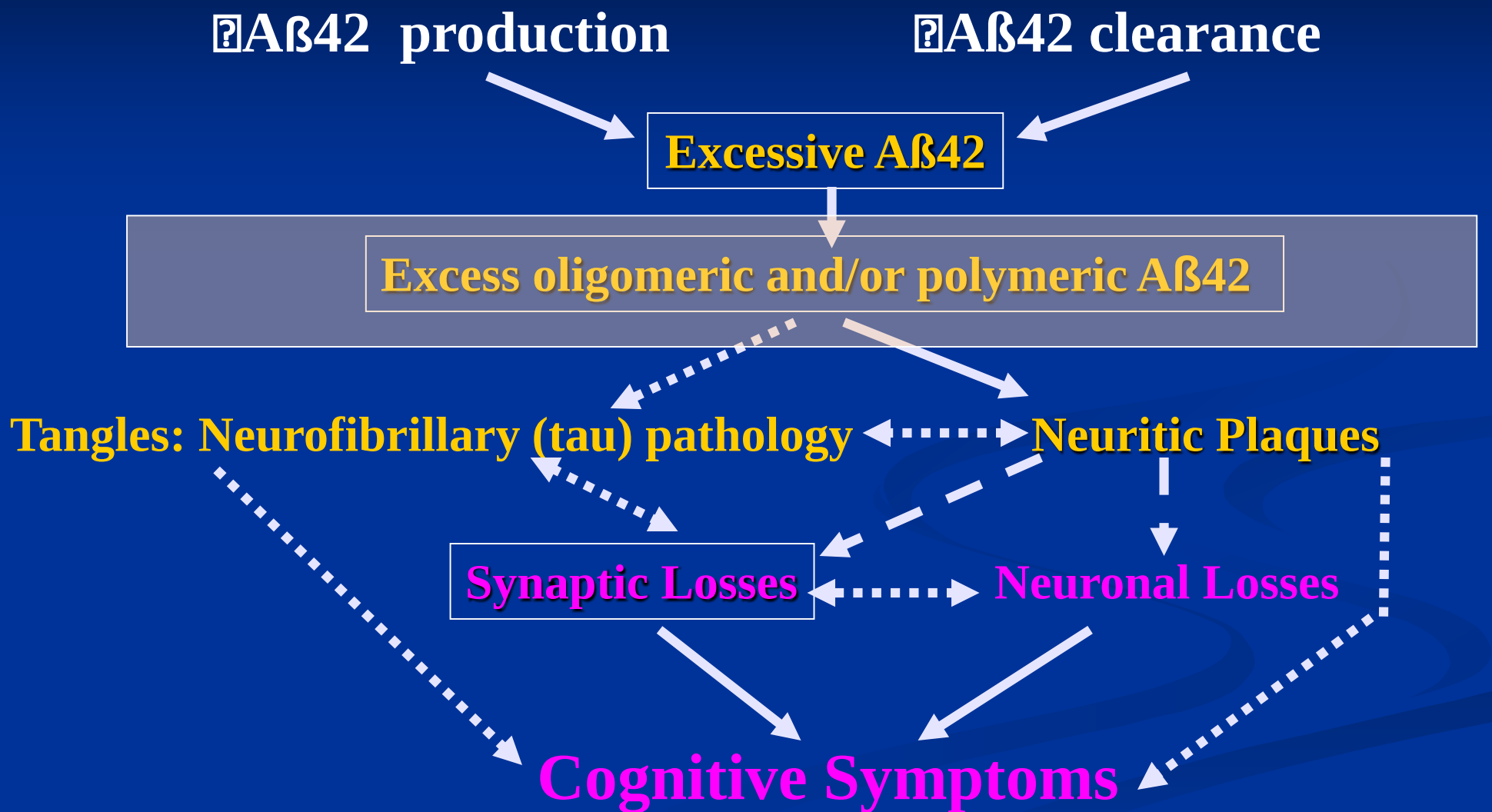
Study assessment	Change from baseline (95% CI) 0.4 g/kg (n = 129)	0.2 g/kg (n = 138)	Placebo (n = 123)	Difference in LSM change 0.4 g/kg vs placebo	Difference in LSM change 0.2 g/kg vs placebo
Change at month 9 in ADAS-Cog (LSM)	3.1 (1.9 to 4.3)	4.6 (3.4 to 5.8)	3.6 (2.4 to 4.9)	−0.5 (−2.2 to 1.2), p = 0.586	1.0 (−0.7 to 2.7), p = 0.237
Change at month 9 in ADCS-ADL (LSM)	−5.4 (−7.2 to −3.6)	−5.7 (−7.6 to −3.9)	−5.6 (−7.5 to −3.7)	0.2 (−2.4 to 2.8), p = 0.878	−0.1 (−2.7 to 2.4), p = 0.912
ADCS-CGIC (LSM)	5.2 (5.0 to 5.3)	5.3 (5.1 to 5.4)	5.2 (5.0 to 5.4)	−0.1 (−0.3 to 0.2), p = 0.660	0.0 (−0.2 to 0.3), p = 0.766
NPI (mean)	3.7 (1.2 to 6.3)	4.9 (2.3 to 7.5)	2.4 (0.2 to 4.6)	0.7 (−2.1 to 3.4), p = 0.640	2.5 (−0.3 to 5.3), p = 0.075
Logsdon QOL-AD (subject) (mean)	−0.5 (−1.5 to 0.6)	−0.7 (−1.6 to 0.2)	−1.5 (−2.6 to −0.4)	1.1 (−0.2 to 2.3), p = 0.093	1.1 (−0.2 to 2.3), p = 0.094
Logsdon QOL-AD (caregiver) (mean)	−3.0 (−4.0 to −2.0)	−2.5 (−3.5 to −1.5)	−1.6 (−2.7 to −0.6)	−1.1 (−2.3 to 0.2), p = 0.096	−1.0 (−2.2 to 0.3), p = 0.123

Table 3 Serious adverse events

Event	IVIg 0.4 g/kg (n = 127), n (%)	IVIg 0.2 g/kg (n = 135), n (%)	Placebo (n = 121), n (%)
Deaths during or after treatment	1 (0.8)	3 (2.2)	2 (1.7)
Hospitalization due to an adverse event	19 (15.0)	26 (19.3)	24 (19.8)
Rash requiring therapy	19 (15.0)	16 (11.9)	8 (6.6)
Renal failure	2 (1.6)	1 (0.7)	2 (1.7)
Venous thromboembolic events	2 (1.6)	3 (2.2)	6 (5.0)
Arterial thrombosis (myocardial infarction, stroke)	1 (0.8)	0 (0.0)	1 (0.8)
Upper respiratory infections	16 (12.6)	24 (17.8)	28 (23.1)

Relkin NR et al. Neurology 2017; 88:1768-75

PATHOGENETIC CASCADE IN AD

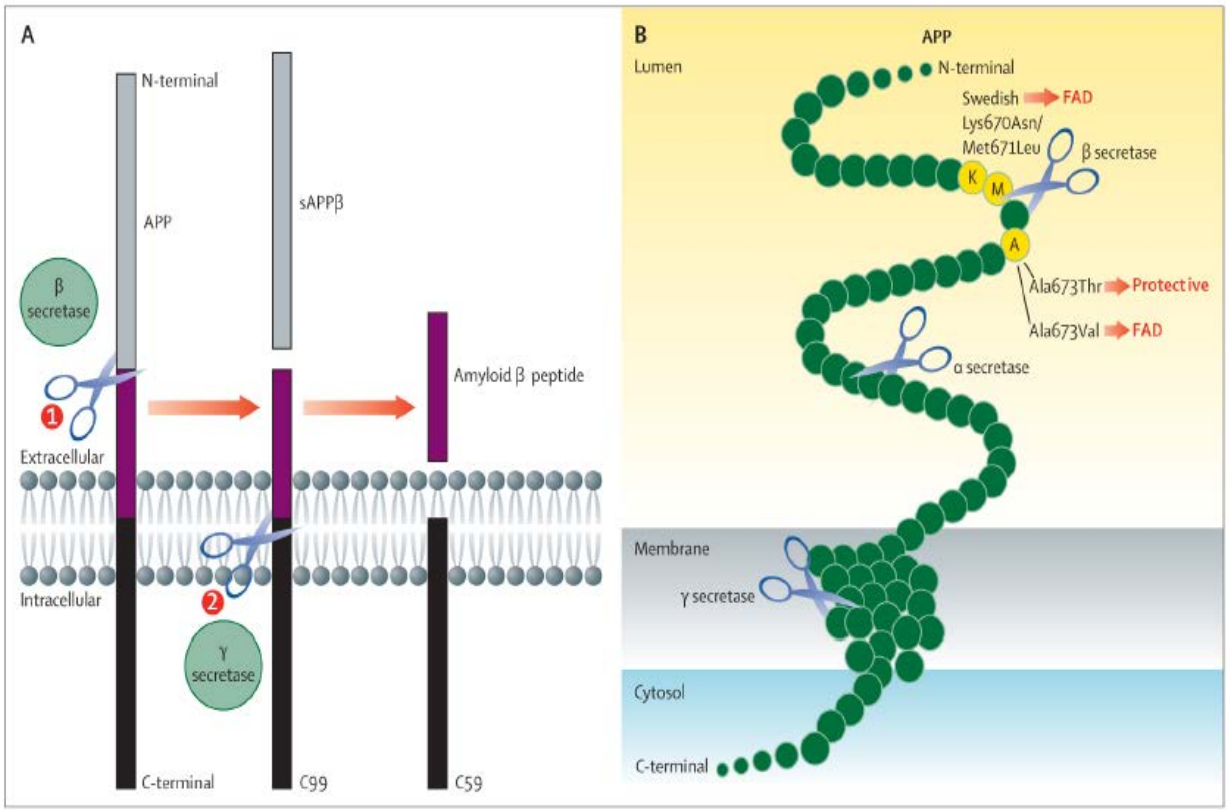


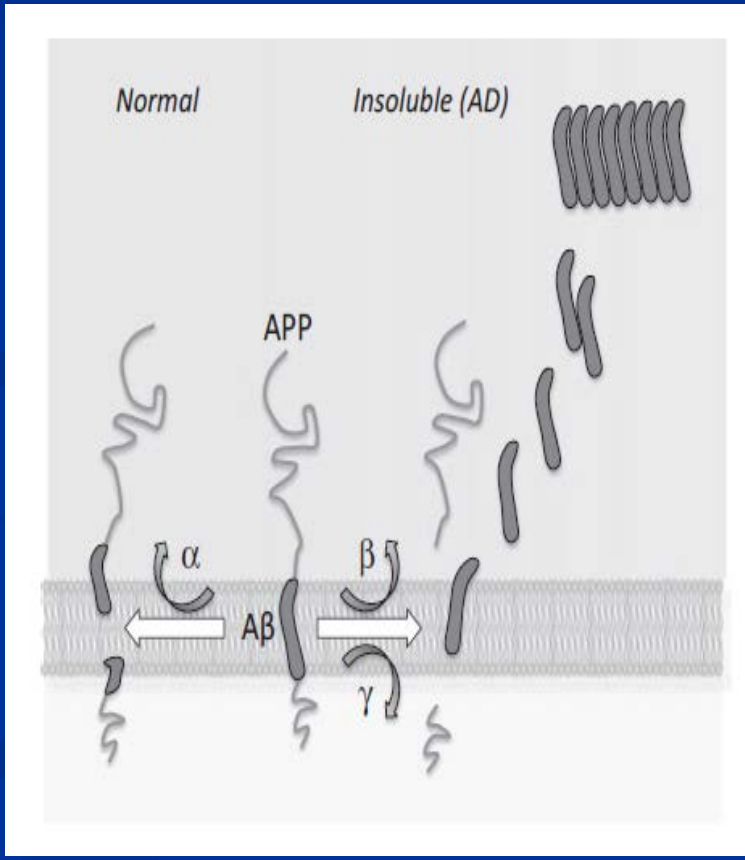
ANTI-FIBRILLAR AGENTS

- Tramiprosate (Alzhemed™)
- "Aβ antagonist" GAG mimetic (2-amino-1-propanesulfonate)
- Mild-to-mod AD: 2 RDBPCT Phase 3: North Amer & Europe
- Duration: 18 mos. +12 mos. open label extension 150 mg bid
- Three arms: Placebo, Alzhemed 100 mg BID, 150 mg BID
- North American Trial: 67 sites - 50 in USA & 17 in Canada
  - 1052 pts enrolled: Completed 2/07, Results 8/07
  - Adverse Events: nausea, vomiting, diarrhea, wgt loss, dizziness, falls
  - NO EFFICACY PRIMARY ENDPOINTS (drug development ceased)
- Elan D-005 scyllo-inositol
  - Impedes amyloid aggregation; improves memory in mice
  - Phase 2 completed: no clear efficacy – no planned phase 3

SECRETASE INHIBITION

- ß- and γ-secretase inhibitors decrease Aß production
- Protease inhibitors are useful in hypertension & HIV





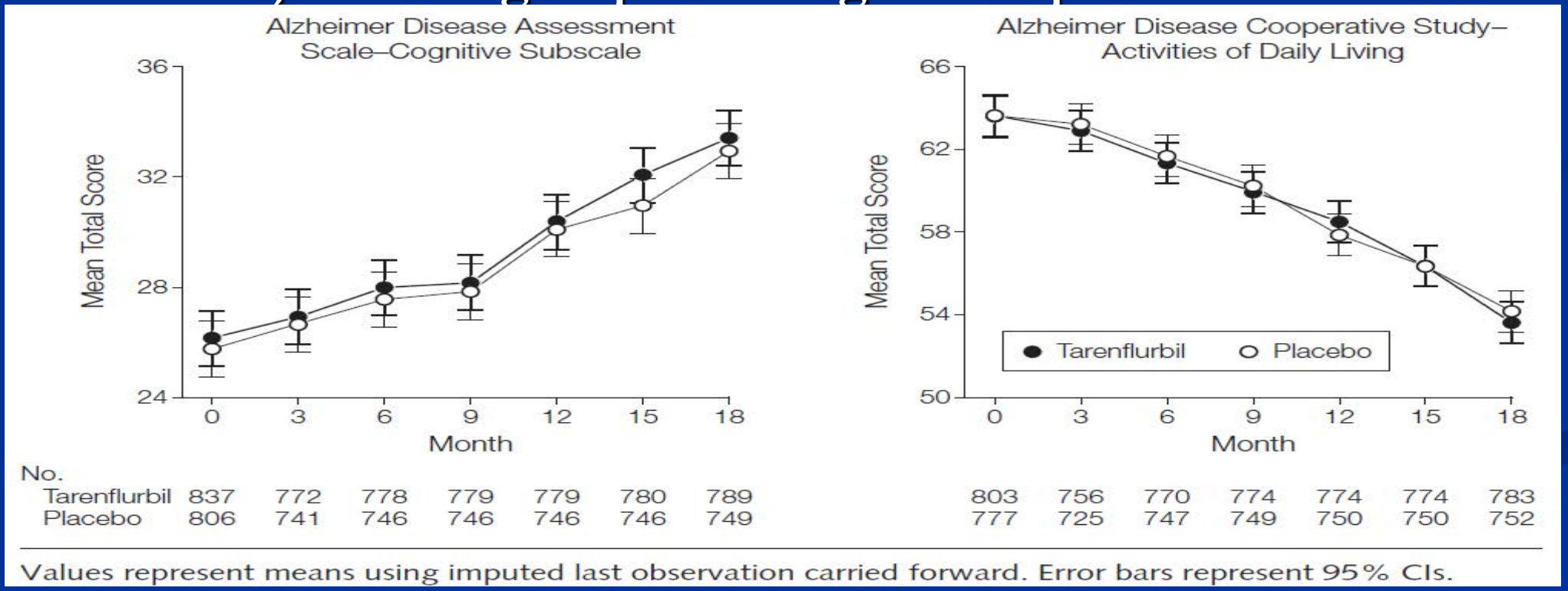
Yan & Vassar. Lancet Neurol 2014; 13:319

Mikulca et al. JClinPharTher 2014; 39:25

γ-Secretase Modulator: Tarenflurbil

- Selective Aβ42-lowering agent *in vitro* and *in vivo*
- Allosteric modulation of γ-secretase

- Phase 3: age>55; MMSE 20-26; 133 sites: 18 mo+1 mo washout
- 1649 subjects in 2 groups: 800 mg BID *vs* placebo BID



R Green et al. & the Tarenflurbil Study Group. *JAMA. 2009; 302: 2557-2564*

γ-Secretase Inhibitor: Semagacestat

Table 2. Estimated Mean Change from Baseline for the Coprimary and Secondary Outcomes, According to a Mixed-Model Repeated-Measures Analysis.*

Outcome	Placebo	Semagacestat, 100 mg	Semagacestat, 140 mg	P Values	
				Semagacestat, 100 mg, vs. Placebo	Semagacestat, 140 mg, vs. Placebo
ADAS-cog score				0.15	0.07
No. of participants with results	486	483	497		
Mean change in score (95% CI)	6.4 (5.48 to 7.40)	7.5 (6.44 to 8.53)	7.8 (6.72 to 8.85)		
ADCS–ADL†				0.14	<0.001
No. of participants with results	480	481	490		
Mean change in score (95% CI)	−9.0 (−10.37 to −7.67)	−10.5 (−11.94 to −9.07)	−12.6 (−14.1 to −11.2)		
CDR-SB‡				0.06	<0.01
No. of participants with results	485	480	494		
Mean change in score (95% CI)	2.4 (2.06 to 2.67)	2.8 (2.47 to 3.13)	3.1 (2.73 to 3.41)		
NPI§				0.28	0.05
No. of participants with results	473	463	472		
Mean change in score (95% CI)	1.9 (0.69 to 3.12)	2.9 (1.58 to 4.21)	3.7 (2.36 to 5.08)		
MMSE				0.23	0.03
No. of participants with results	400	328	303		
Mean change in score (95% CI)	−3.4 (−3.95 to −2.86)	−3.9 (−4.51 to −3.30)	−4.3 (−4.99 to −3.68)		

Table 3. Summary of Adverse Events Occurring during the Study Treatment, According to the MedDRA System or Organ Class and Preferred Term.*

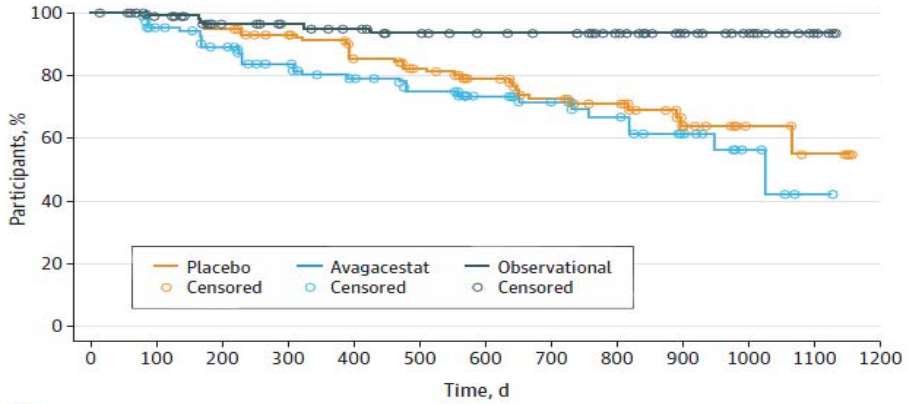
Event	Placebo (N=501)	Semagacestat			Total (N=1534)
		100 mg (N=506)	140 mg (N=527)	Combined (N=1033)	
	percent of participants				
System or organ class					
Neoplasms — benign, malignant, or unspecified	5	15	16	15	12
Skin or subcutaneous-tissue disorders	21	45	52	48	39
Preferred term					
Alopecia	0	1	5	3	2
Basal-cell carcinoma	1	3	5	4	3
Decreased appetite	3	7	11	9	7
Epistaxis	1	3	3	3	2
Eyelash discoloration	0	2	5	3	2
Hair-color changes	1	13	19	16	11
Nausea	5	11	12	11	9
Pruritus	2	3	4	3	3
Rash					
Erythematous	2	5	5	5	4
Macular	4	7	8	8	6
Maculopapular	1	3	5	4	3
Papular	1	3	4	4	3
Skin lesion	1	3	3	3	2
Squamous-cell carcinoma of skin	1	6	5	5	4
Syncope	1	3	3	3	3
Vomiting	4	10	9	9	7
Weight decrease	3	5	9	7	6

* The listed adverse events are those with an incidence of at least 2% in any one group and a rate in the combined semagacestat groups that was at least two times as high as the rate in the placebo group. MedDRA denotes *Medical*

Doody RS et al. NEJM 2013; 369: 341-350

γ-Secretase Inhibitor: Avagacestat

Figure 2. Cerebrospinal Fluid (CSF) Biomarker Entry Criteria on Time to Adjudicated Progression to Dementia



No. of Participants at Risk

Placebo	124	117	108	101	87	78	64	54	41	22	8	5	0
Avagacestat	117	97	85	73	61	53	43	37	26	16	5	1	0
Observed	91	85	75	67	62	57	53	49	43	26	16	4	0

Table 3. Mean Changes From Baseline to Weeks 24, 56, and 104 in Cognitive and Functional Outcomes[a]

	Placebo (n = 131)			Avagacestat (n = 132)		
Characteristic	Week 24	Week 56	Week 104	Week 24	Week 56	Week 104
ADAS-Cog score						
No. of patients	114	102	66	100	77	45
Mean change (SE)	1.02 (0.38)	1.15 (0.46)	2.52 (0.72)	1.14 (0.41)	1.52 (0.52)	3.15 (0.83)
Difference vs placebo				0.12	−0.36	−0.63
P value				.83	.59	.57
ADCS ADL-MCI score						
No. of patients	107	101	64	98	75	45
Mean change (SE)	0.09 (0.42)	−1.36 (0.52)	−3.57 (0.83)	−1.28 (0.45)	−2.10 (0.57)	−4.41 (0.97)
Difference vs placebo				−1.28	−0.74	−0.84
P value				.02	.33	.51
CDR-SB						
No. of patients	111	103	66	100	76	45
Mean change (SE)	0.13 (0.12)	0.76 (0.13)	1.65 (0.25)	0.35 (0.13)	0.74 (0.15)	1.12 (0.29)
Difference vs placebo				0.24	−0.02	−0.20
P value				.20	.90	.16
MMSE score						
No. of patients	114	103	67	99	77	46
Mean change (SE)	−1.20 (0.23)	−1.48 (0.32)	−2.24 (0.42)	−1.60 (0.25)	−2.39 (0.36)	−2.95 (0.49)
Difference vs placebo				−0.39	−0.83	−0.71
P value				.23	.08	.27

Table 2. Summary of AEs

Characteristic	Placebo (n = 131)	Avagacestat (n = 132)
Any SAE, No. (%)	31 (23.7)	49 (37.1)
Cardiac disorders	1 (0.8)	3 (2.3)
GI tract disorders	1 (0.8)	6 (3.5)
Neoplasms	12 (9.2)	23 (17.4)
Injury, poisoning, and procedural complications	4 (3.1)	7 (5.3)
Any AE leading to treatment discontinuation, No. (%)	13 (9.9)	46 (34.8)
Any GI tract AE	3 (2.3)	19 (14.4)
Any skin AE	1 (0.8)	7 (5.3)
Any nervous system disorder	2 (1.5)	8 (6.1)
Any AE, No. (%)	110 (84.0)	126 (95.5)
Any GI tract AE	48 (36.6)	87 (65.9)
Diarrhea	24 (18.3)	41 (31.1)
Nausea	4 (3.1)	35 (26.5)
Vomiting	2 (1.5)	14 (10.6)
Any skin AE	50 (38.2)	72 (54.5)
Rash	8 (6.1)	27 (20.5)
Any neoplasms	20 (15.3)	25 (18.9)
BCC	5 (3.8)	8 (6.1)
SCC skin	1 (0.8)	8 (6.1)
SCC	0	8 (6.1)
Malignant melanoma	1 (0.8)	0
Other AEs		
Fatigue	9 (6.8)	24 (18.2)
Weight decreased	2 (1.5)	14 (10.6)
Appetite decreased	3 (2.3)	14 (10.6)
Dizziness	13 (9.9)	20 (15.2)
Depression	11 (8.4)	7 (5.3)
Anxiety	12 (9.2)	4 (3.0)
Cerebral microbleed	2 (1.5)	4 (3.0)
Vasogenic edema	1 (0.8)	3 (2.3)

Coric V et al. JAMA Neurol 2015; 72:1324-33

β-Secretase Inhibitor: verebecestat

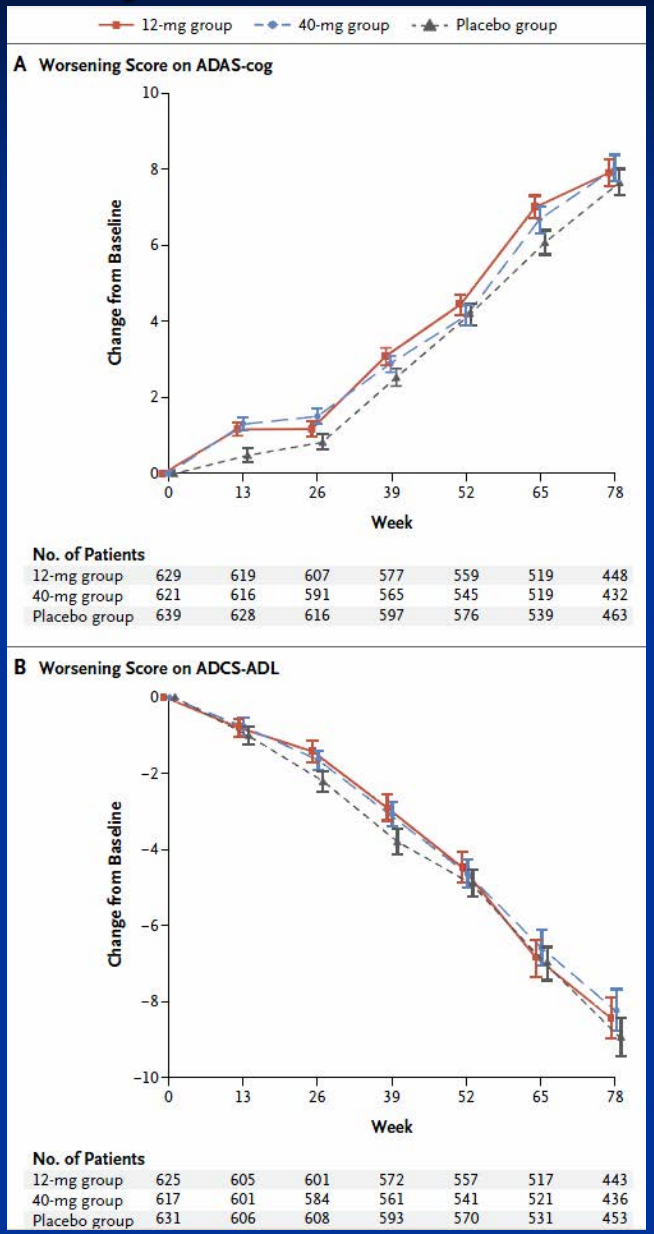
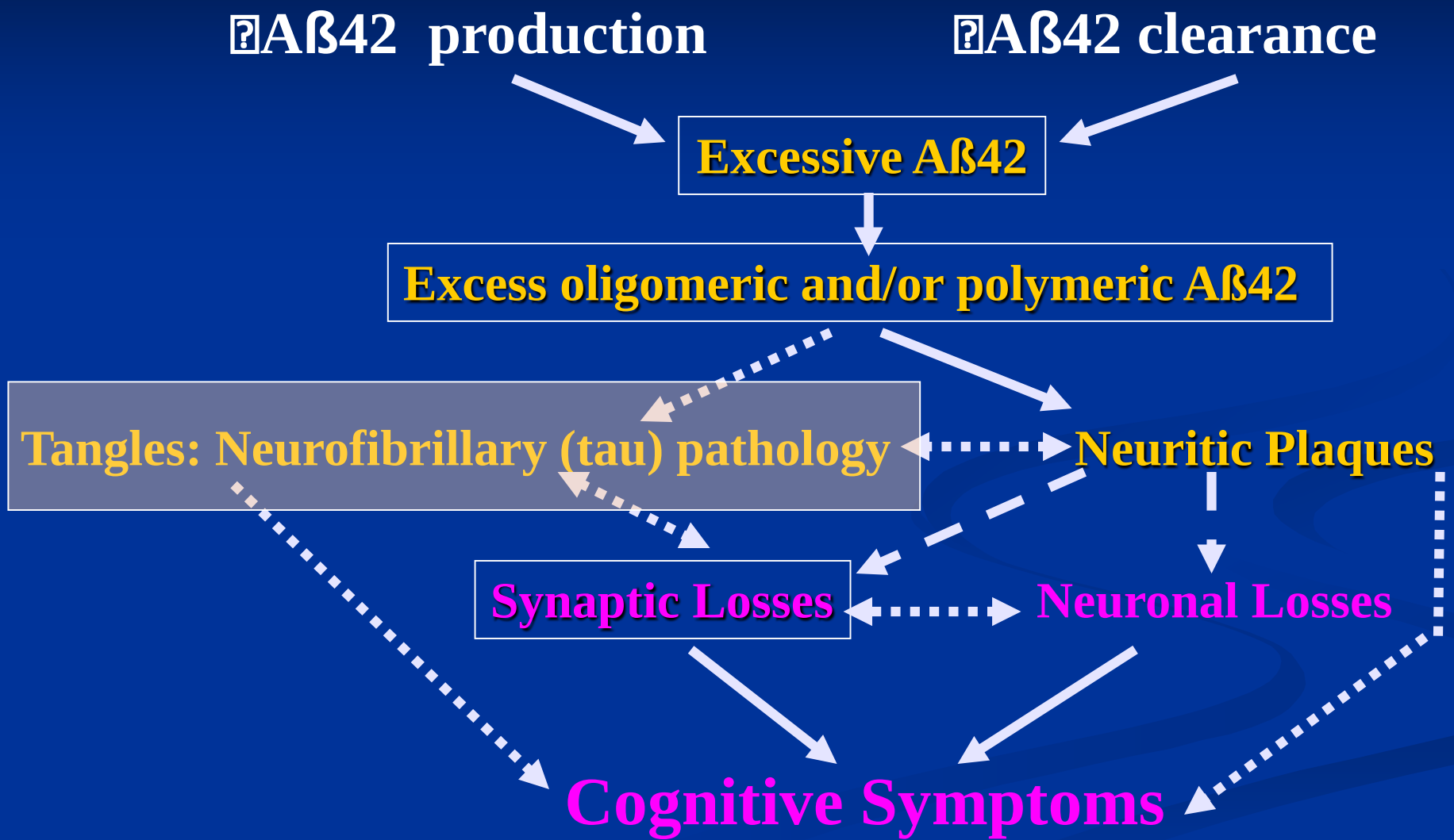


Table 3. Adverse Events That Occurred within 14 Days after the Last Dose over the Course of 78 Weeks.*

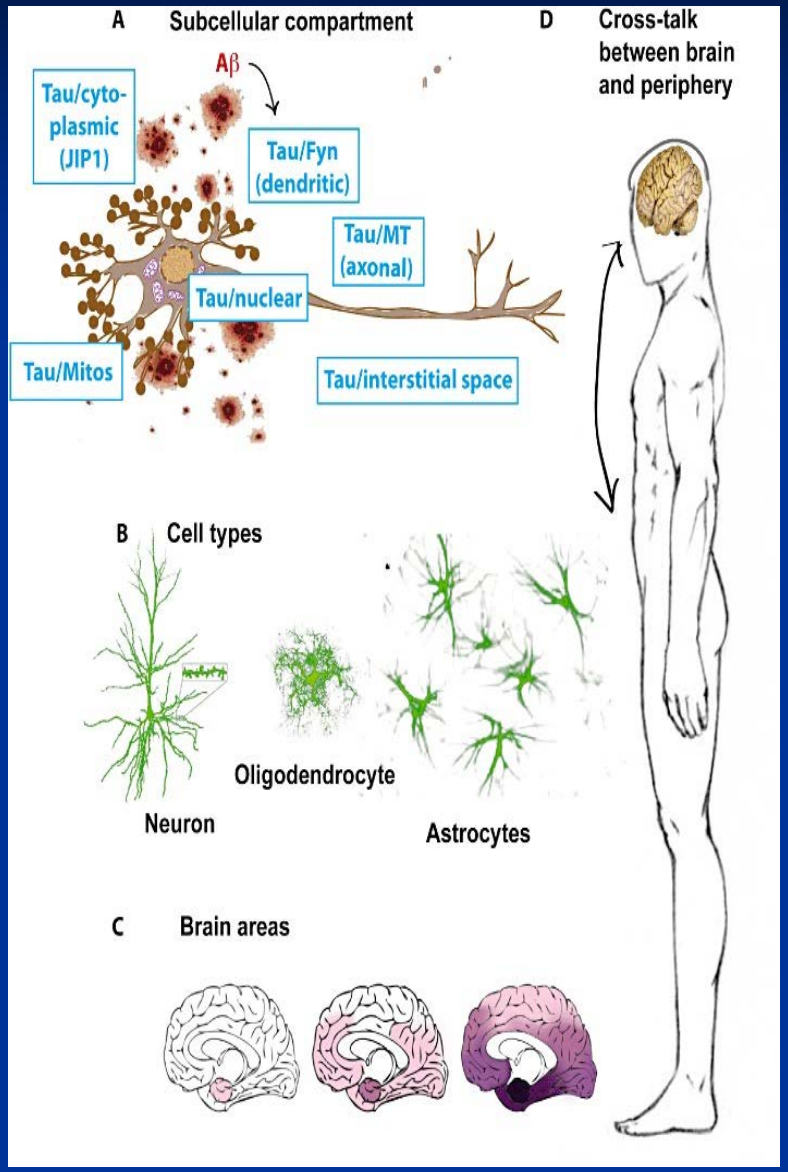
Event	Verubecestat 12-mg Group (N=652)	Verubecestat 40-mg Group (N=652)	Placebo Group (N=653)	Absolute Difference between 12-mg Group and Placebo Group	Absolute Difference between 40-mg Group and Placebo Group
	number of patients (percent)			*percentage points (95% CI)*	
Any adverse event	582 (89.3)	601 (92.2)	533 (81.6)	7.64 (3.84 to 11.48)	10.55 (6.96 to 14.23)
Any serious adverse event	128 (19.6)	148 (22.7)	117 (17.9)	1.71 (–2.53 to 5.96)	4.78 (0.42 to 9.15)
Adverse event that resulted in discontinuation of assigned trial regimen	54 (8.3)	61 (9.4)	38 (5.8)	2.46 (–0.32 to 5.31)	3.54 (0.67 to 6.48)
Death	9 (1.4)	12 (1.8)	5 (0.8)	0.61 (–0.57 to 1.93)	1.07 (–0.17 to 2.51)
Prespecified adverse events of clinical interest					
Amyloid-related imaging abnormalities of microhemorrhage, superficial siderosis, or macrohemorrhage	8/312 (2.6)	14/341 (4.1)	13/331 (3.9)	–1.36 (–4.36 to 1.52)	0.18 (–2.97 to 3.31)
Amyloid-related imaging abnormalities of incident vasogenic edema	0/312	0/341	1/331 (0.3)	–0.30 (–1.69 to 0.92)	0.30 (–1.69 to 0.82)
Delirium	5 (0.8)	12 (1.8)	6 (0.9)	–0.15 (–1.32 to 0.98)	0.92 (–0.38 to 2.38)
Rash†	30 (4.6)	28 (4.3)	8 (1.2)	3.38 (1.63 to 5.39)	3.07 (1.36 to 5.04)
Specific adverse events with incidence >5.0% in a verubecestat group and with greater incidence in a verubecestat group than in the placebo group‡					
Falls and injuries§	132 (20.2)	151 (23.2)	103 (15.8)	4.47 (0.30 to 8.65)	7.39 (3.10 to 11.68)
Rash, dermatitis, or urticaria§	79 (12.1)	66 (10.1)	38 (5.8)	6.30 (3.24 to 9.47)	4.30 (1.38 to 7.32)
Sleep disturbance§	67 (10.3)	55 (8.4)	31 (4.7)	5.53 (2.71 to 8.48)	3.69 (1.01 to 6.47)
Diarrhea	53 (8.1)	57 (8.7)	38 (5.8)	2.31 (–0.46 to 5.14)	2.92 (0.10 to 5.81)
Weight decrease	42 (6.4)	42 (6.4)	20 (3.1)	3.38 (1.10 to 5.81)	3.38 (1.10 to 5.81)
Suicidal ideation	39 (6.0)	38 (5.8)	21 (3.2)	2.77 (0.51 to 5.15)	2.61 (0.37 to 4.98)
Anxiety	39 (6.0)	46 (7.1)	24 (3.7)	2.31 (–0.02 to 4.73)	3.38 (0.96 to 5.93)
Dizziness	31 (4.8)	53 (8.1)	32 (4.9)	–0.15 (–2.53 to 2.23)	3.23 (0.56 to 5.99)
Psychotic symptoms§	30 (4.6)	36 (5.5)	20 (3.1)	1.54 (–0.56 to 3.73)	2.46 (0.27 to 4.77)
Other adverse events of interest¶					
Hair-color change	12 (1.8)	16 (2.5)	0	1.84 (1.06 to 3.19)	2.45 (1.52 to 3.95)
Syncope-like events§	26 (4.0)	27 (4.1)	17 (2.6)	1.38 (–0.58 to 3.44)	1.54 (–0.44 to 3.62)

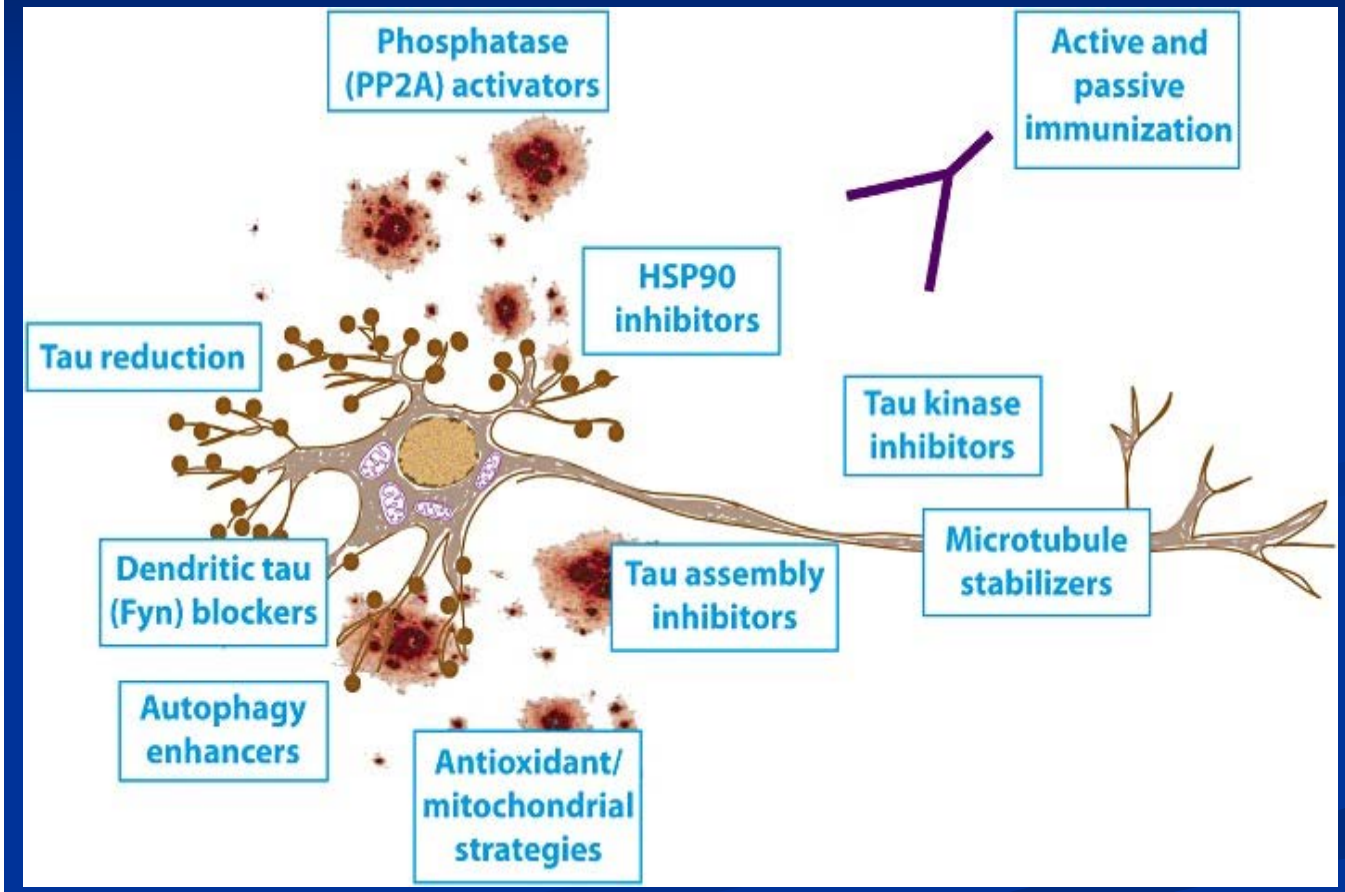
Egan M et al. NEJM 2018; 378:1691-703

PATHOGENETIC CASCADE IN AD



Tau Drugs





J Gotz et al. Brit J Pharm 2012

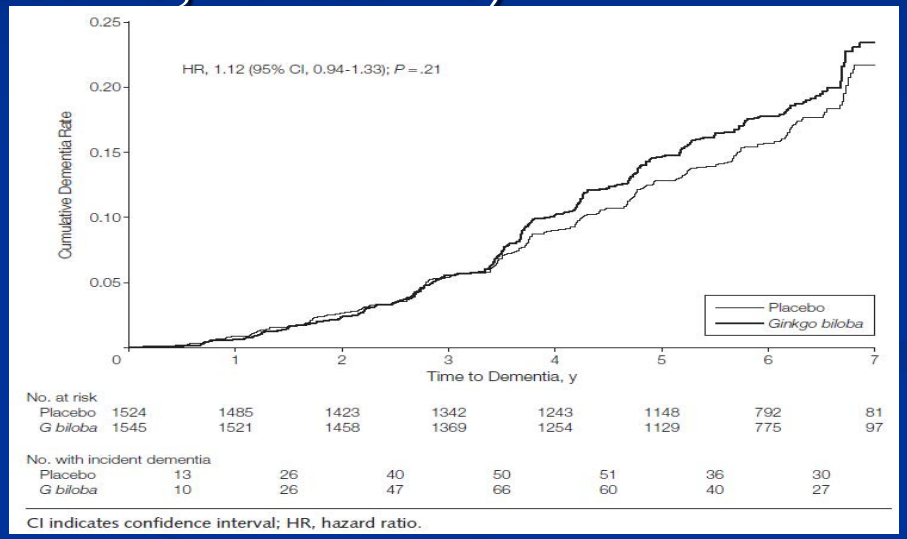
DRUGS for TAU

- Methylthioninium Cl, MTC, LMTX
- Decreases hyperphosphorylated tau in vitro
- Phase 3 studies failed in AD and FTD

- Anti-Tau Antibodies
- ABBV-8E12, BMS986168/BIIB092, UCB0107
- Bind to extracellular tau preventing propagation of tau across synapses from neuron to neuron

NON-NOVEL & "OVER-THE-COUNTER" THERAPIES

- phosphatidyl serine, α-tocopherol (vitamin E), statins
- NSAIDS (ibuprofen, naproxen, celecoxib, rofecoxib)
- Estrogens or DHEA
- Gingko biloba
- Huperzine A
- CSF shunting therapies
- Plasma replacement therapies
- Medical foods: Souvenaid® and MCT (Axona®)
- Fish oil (EPA / DHA), Coconut oil, Aqueporin, etc.



S Dekosky et al & GEM. JAMA 2008; 300: 2253-22

Status Summary

- **Epidemiology –**

  genetic factors are likely paramount

- **Diagnosis –**

  new imaging is helpful in research, spinal fluid analysis is an important clinical tool

- **Therapeutics –**
  - biological basis of disease allows informed clinical trials
  - incrementally moving towards disease modifying therapies

Center of Excellence for Alzheimer's Disease (CEAD)

For patient referral/ educational programing contact:

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Alzheimercenter@cumc.Columbia.edu

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