Le evidenze dai Trial Clinici

Alessandro Padovani
Università degli Studi di Brescia

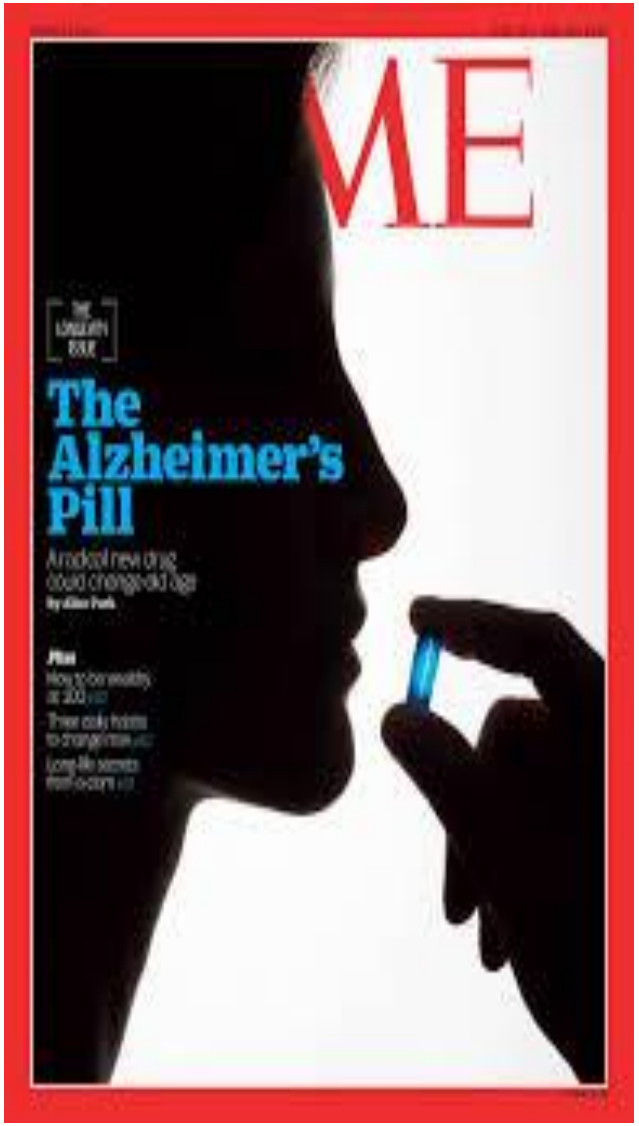
Disclosure

In the last two years

Member of National/International Advisory Board: Actelion, Eli-Lilly, Lundbeck, Novartis, GE-Health, ROCHE, BIOGEN, NEURAXPHARMA

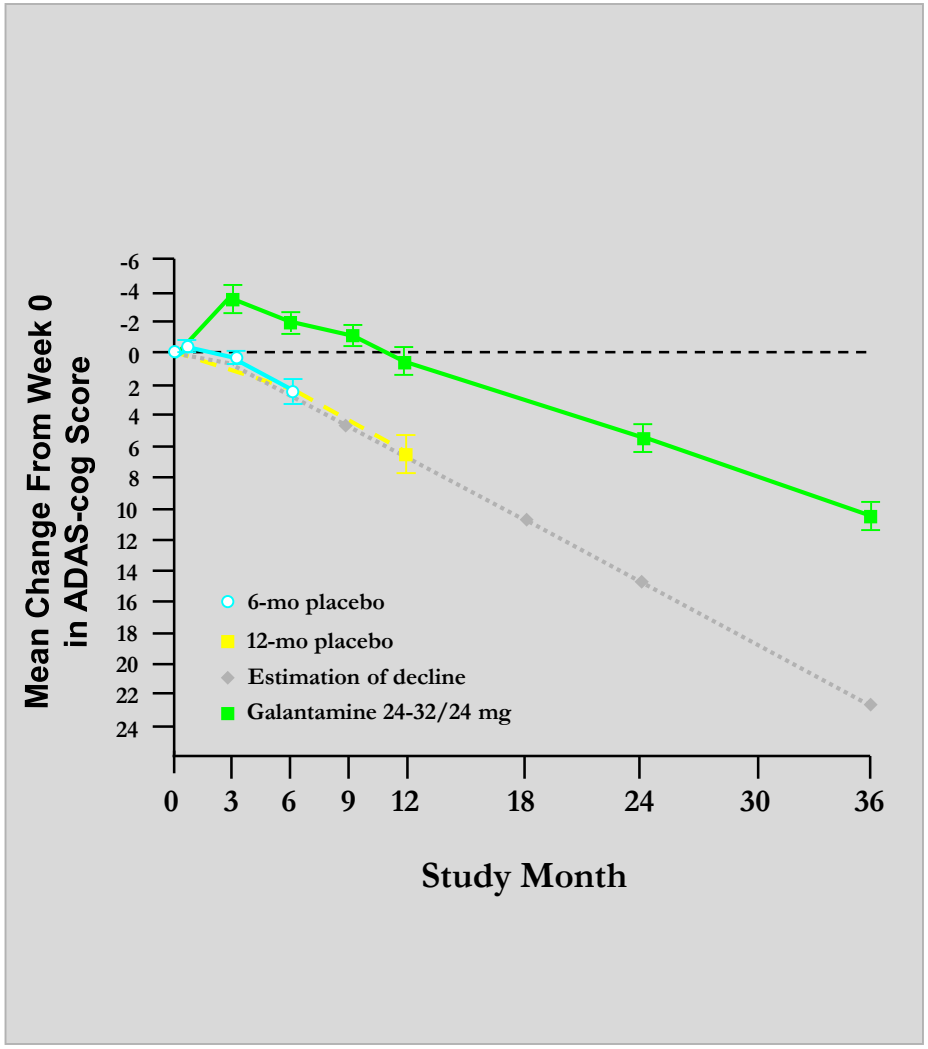
Investigator of Clinical Trial: Roche, UCB, Lundbeck, FORUM, AVID, GE-Health, Boehringer, Biogen

Neverending story

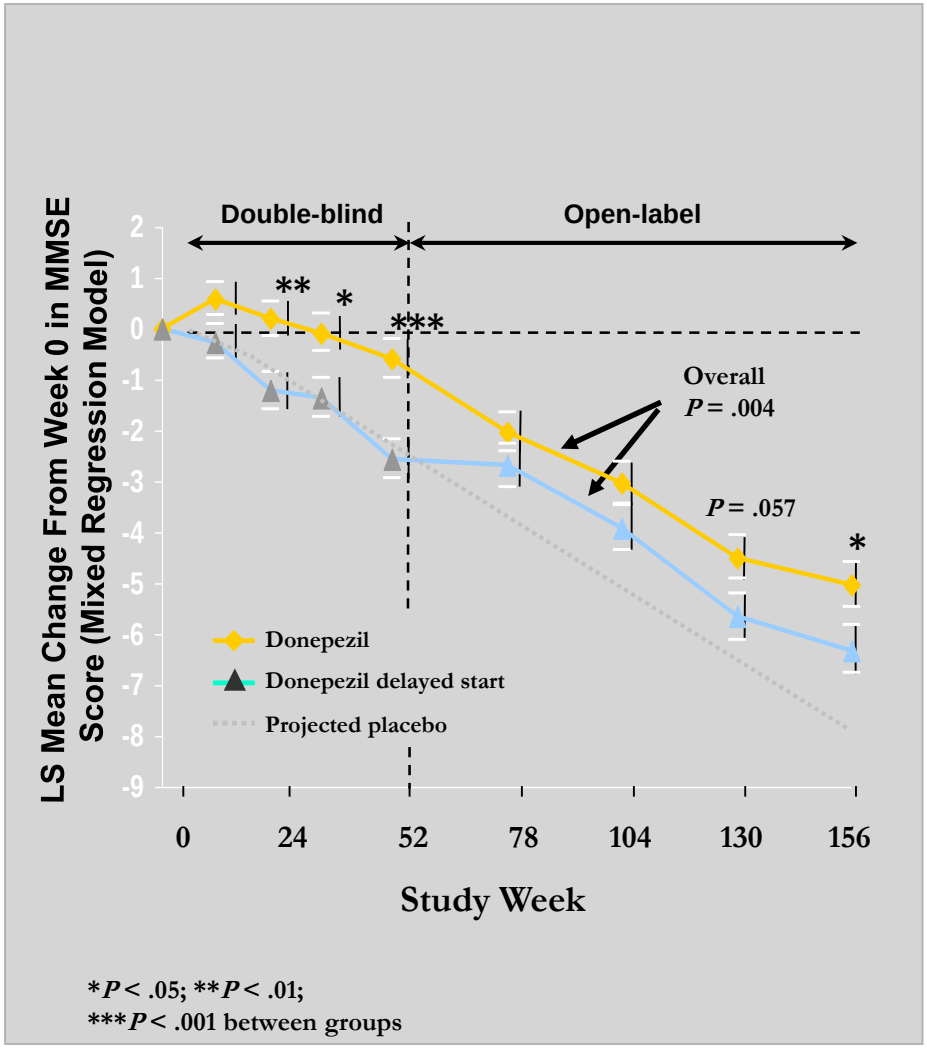


DA DOVE VENIAMO

Treatment with cholinesterase inhibitors Over 3 Years

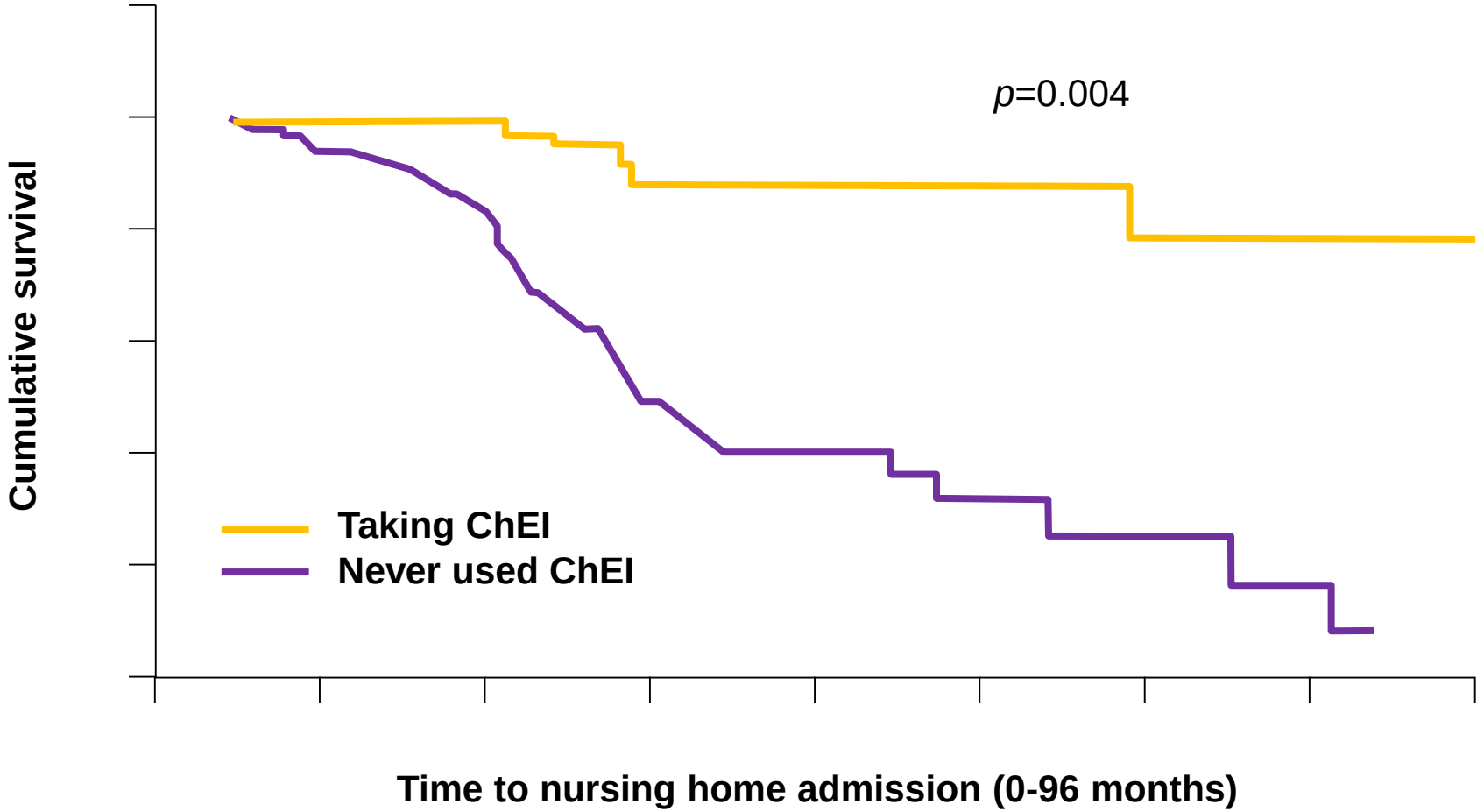


Raskind MA, et al. *Arch Neurol*. 2004.



Winblad B, et al. *Dement Geriatr Cogn Disord*. 2006

Significant delay to nursing home admission



Lopez OL, et al. J Neurol Neurosurg Psychiatry 2002;72:310-314

Donepezil decreases annual rate of hippocampal atrophy in suspected prodromal Alzheimer's disease

Bruno Dubois[a,b,c,*], Marie Chupin[b], Harald Hampel[a,b,c], Simone Lista[a,b], Enrica Cavedo[a,b], Bernard Croisile[d], Guy Louis Tisserand[d], Jacques Touchon[e], Alain Bonafe[e], Pierre Jean Ousset[f], Amir Ait Ameur[g], Olivier Rouaud[h], Fréderic Ricolfi[h], Alain Vighetto[d], Florence Pasquier[i], Christine Delmaire[j], Mathieu Ceccaldi[k], Nadine Girard[k], Carole Dufouil[l], Stéphane Lehericy[b,c,m], Isabelle Tonelli[n], Françoise Duveau[n], Olivier Colliot[b], Line Garnero[b], Marie Sarazin[a,b,c], Didier Dormont[b,c,o], and the "Hippocampus Study Group"

APC in volumetric measures (%) in per protocol population

	Placebo (n = 92)	Donepezil (n = 82)	Treatment difference (95% CI)	*P*-value
APC of total hippocampal volume			−1.58 (−2.51, −0.65)	$P < .001$
n/N	92/92	82/82		
Mean (SE)	−3.47 (0.32)	−1.89 (0.34)		
APC of left hippocampal volume			−1.83 (−2.94, −0.71)	$P = .001$
n/N	92/92	82/82		
Mean (SE)	−3.64 (0.39)	−1.81 (0.41)		
APC of right hippocampal volume			−1.43 (−2.47, −0.38)	$P = .008$
n/N	92/92	82/82		
Mean (SE)	−3.45 (0.36)	−2.02 (0.39)		
APC of global cerebral volume			−0.30 (−0.51, −0.09)	$P = .005$
n/N	92/92	80/82		
Mean (SE)	−0.71 (0.07)	−0.41 (0.08)		
APC of ventricular volume			1.71 (0.75, 2.67)	$P < .001$
n/N	92/92	80/82		
Mean (SE)	4.87 (0.33)	3.16 (0.35)		

Abbreviations: APC, annualized percentage change; SE, standard error.

NOTE. *P*-value denotes a significant difference at analysis of variance.

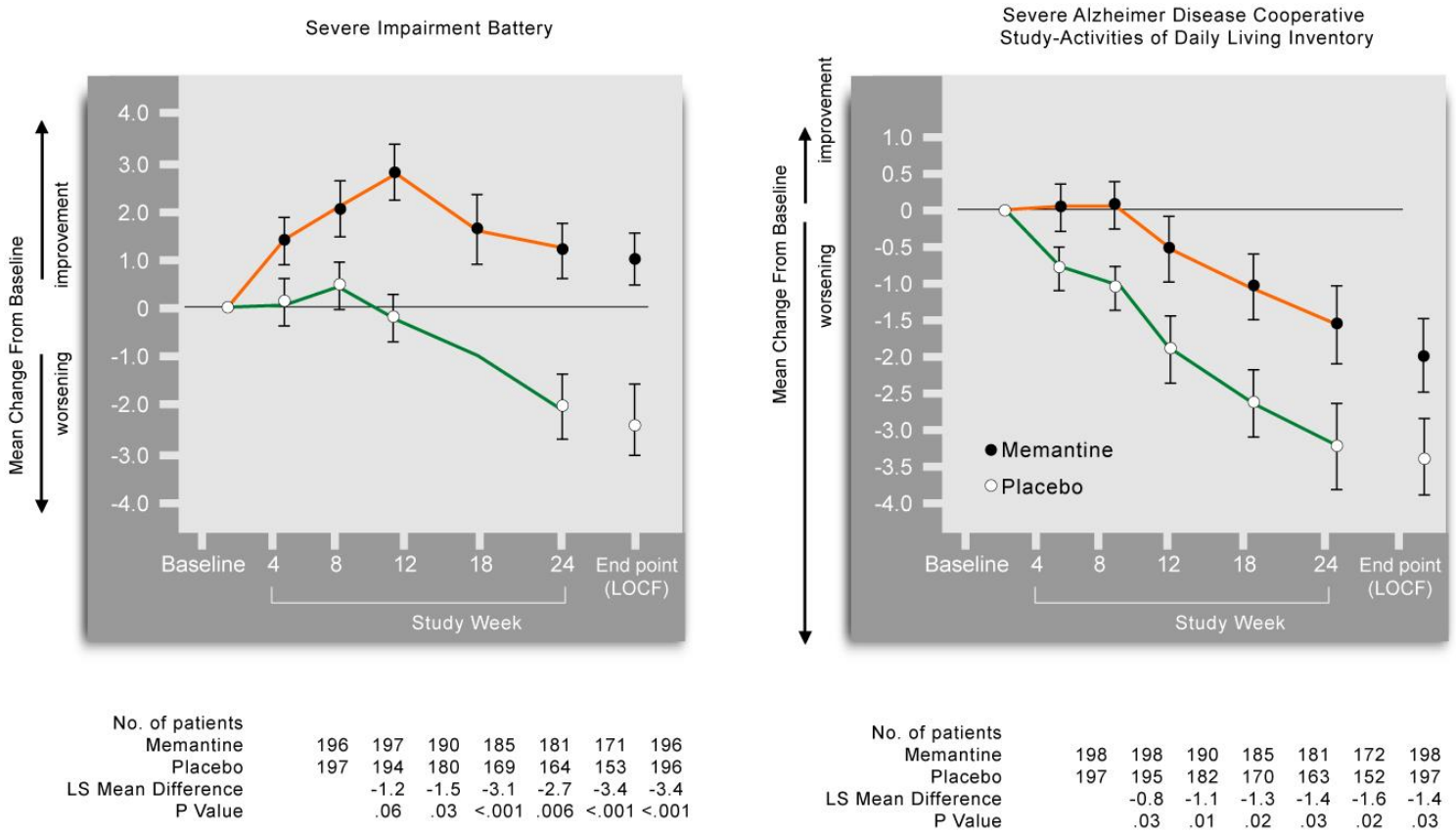
Alzheimer's & Dementia 11 (2015) 1041-1049

JAMA

2004;291:317-324.

Memantine Treatment in Patients With Moderate to Severe Alzheimer Disease Already Receiving Donepezil A Randomized Controlled Trial

Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I,; for the Memantine Study Group

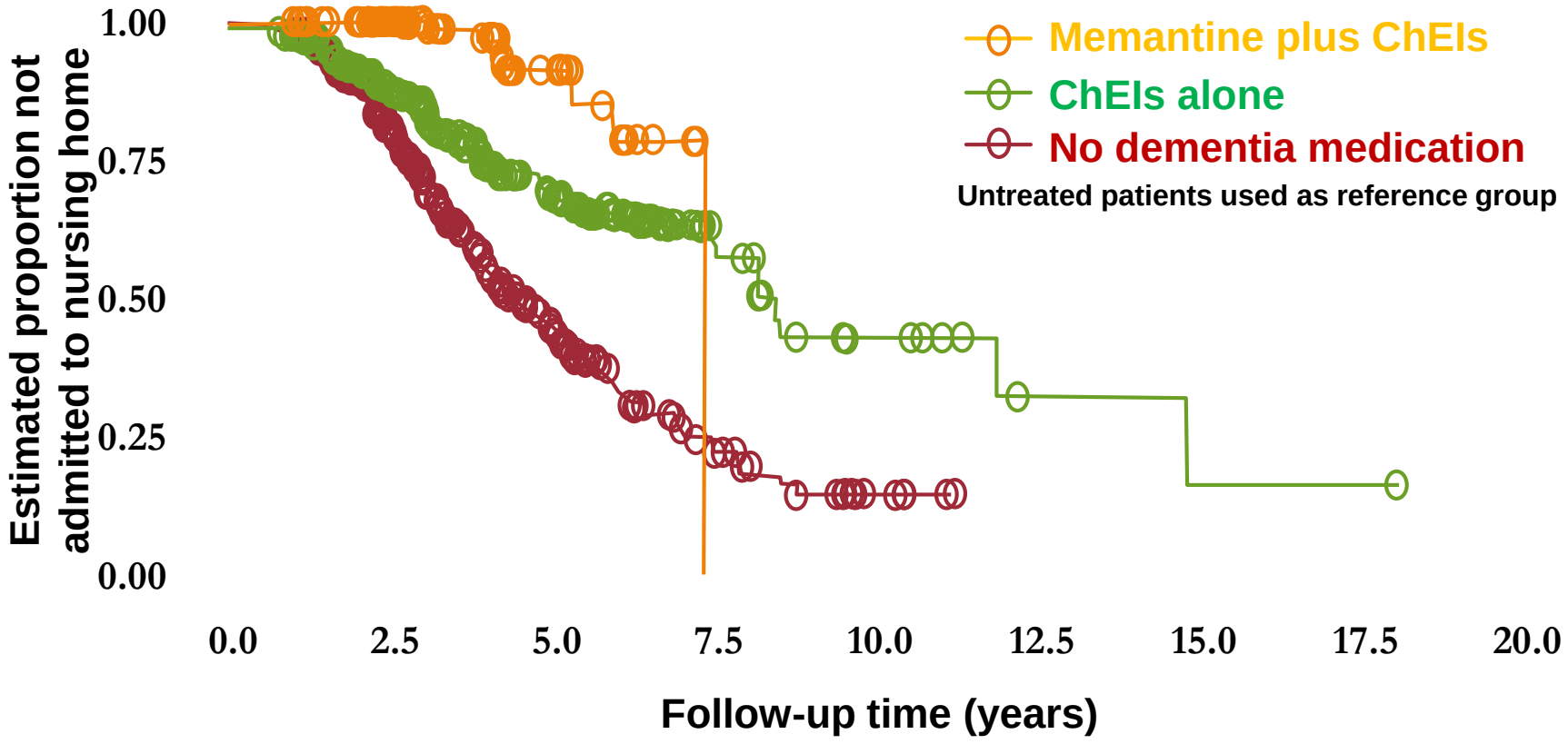


No. of patients							
Memantine	196	197	190	185	181	171	196
Placebo	197	194	180	169	164	153	196
LS Mean Difference		-1.2	-1.5	-3.1	-2.7	-3.4	-3.4
P Value		.06	.03	<.001	.006	<.001	<.001

No. of patients							
Memantine	198	198	190	185	181	172	198
Placebo	197	195	182	170	163	152	197
LS Mean Difference		-0.8	-1.1	-1.3	-1.4	-1.6	-1.4
P Value		.03	.01	.02	.03	.02	.03

SIB and ADCS-ADL19 by Visit (Observed Case) and at End Point (LOCF)

Memantine in combination with Cholinesterase inhibitors delays nursing home admission (Cohort 1) (N= 943 Probable AD Patients)



Lopez et al. J Neurol Neurosurg Psychiatry 2009; 80: 600–607

DOVE SIAMO

J Neuroimmune Pharmacol (2017) 12:194–203
DOI 10.1007/s11481-016-9722-5

BRIEF REPORT

Safety and Efficacy of Anti-Amyloid-β Immunotherapy in Alzheimer's Disease: A Systematic Review and Meta-Analysis

Ross Penninkilampi[1] · **Holly M. Brothers**[2] · **Guy D. Eslick**[1]

Outcome	n	Studies Included	Effect		Heterogeneity	
			Difference in Means (95% CI)	*p*-value	I^2	*p*-value
ADAS-cog	4628	4 (Doody et al. 2014; Gilman et al. 2005; Salloway et al. 2014)	-0.30 (−1.13 to 0.53)	0.47	99.58	<0.001
MMSE	3588	3 (Doody et al. 2014; Gilman et al. 2005; Salloway et al. 2014)	0.44 (0.07 to 0.81)	0.02	99.49	<0.001
ADCS-ADL	2052	2 (Doody et al. 2014)	0.60 (−1.36 to 2.56)	0.55	99.77	<0.001
CDR-sb	4628	4 (Doody et al. 2014; Gilman et al. 2005; Salloway et al. 2014)	-0.02 (−0.23 to 0.18)	0.82	99.59	<0.001

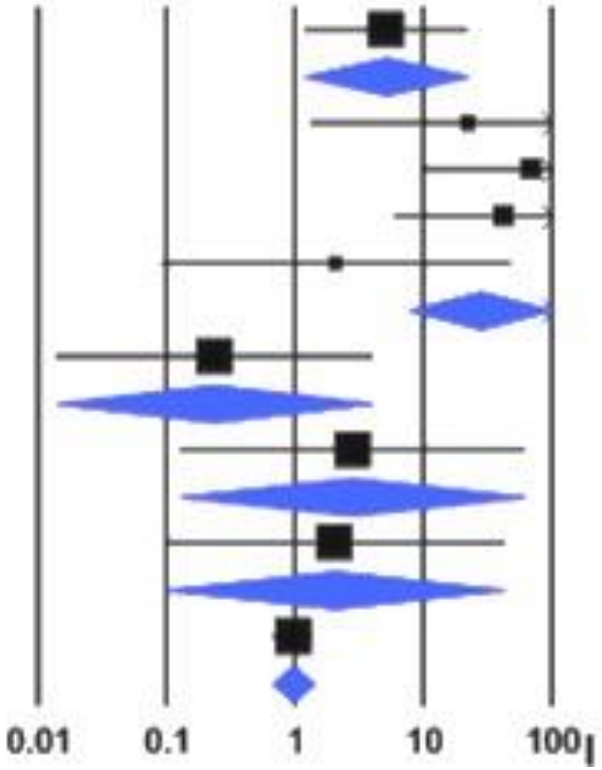
J Neuroimmune Pharmacol (2017) 12:194–203
DOI 10.1007/s11481-016-9722-5

BRIEF REPORT

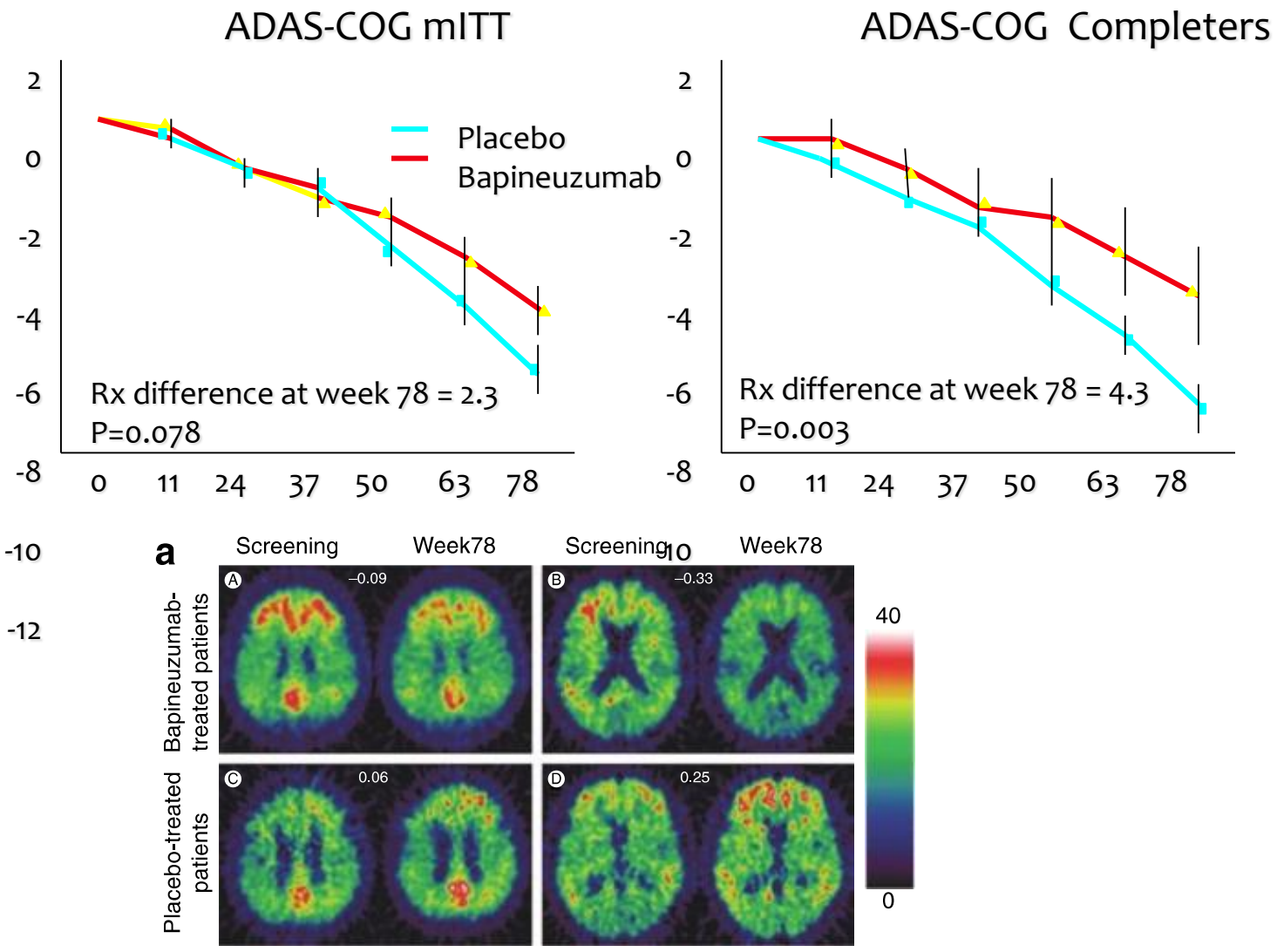
Safety and Efficacy of Anti-Amyloid-β Immunotherapy in Alzheimer's Disease: A Systematic Review and Meta-Analysis

Ross Penninkilampi[1] · Holly M. Brothers[2] · Guy D. Eslick[1]

Group by Drug	Study name	Odds ratio	Lower limit	Upper limit	p-Value
Adu	Sevigny et al. (2016)	5.12	1.17	22.32	0.03
Adu		5.12	1.17	22.32	0.03
Bapi	Salloway et al. (2009)	22.19	1.30	379.13	0.03
Bapi	Salloway et al. (2014)	68.56	9.53	493.17	0.00
Bapi	Salloway et al. (2014) a	42.21	5.84	305.09	0.00
Bapi	Rinne et al. (2010)	2.07	0.09	47.89	0.65
Bapi		27.83	7.60	101.93	0.00
CAD106	Farlow et al. (2015)	0.23	0.01	4.04	0.32
CAD106		0.23	0.01	4.04	0.32
Gant	Ostrowitzki et al. (2012)	2.79	0.12	62.45	0.52
Gant		2.79	0.12	62.45	0.52
Pon	Landen et al. (2012)	2.04	0.10	43.16	0.65
Pon		2.04	0.10	43.16	0.65
Sol	Doody et al. (2014)	0.97	0.67	1.40	0.85
Sol		0.97	0.67	1.40	0.85



Estimated Mean Change from Baseline on ADAS-COG



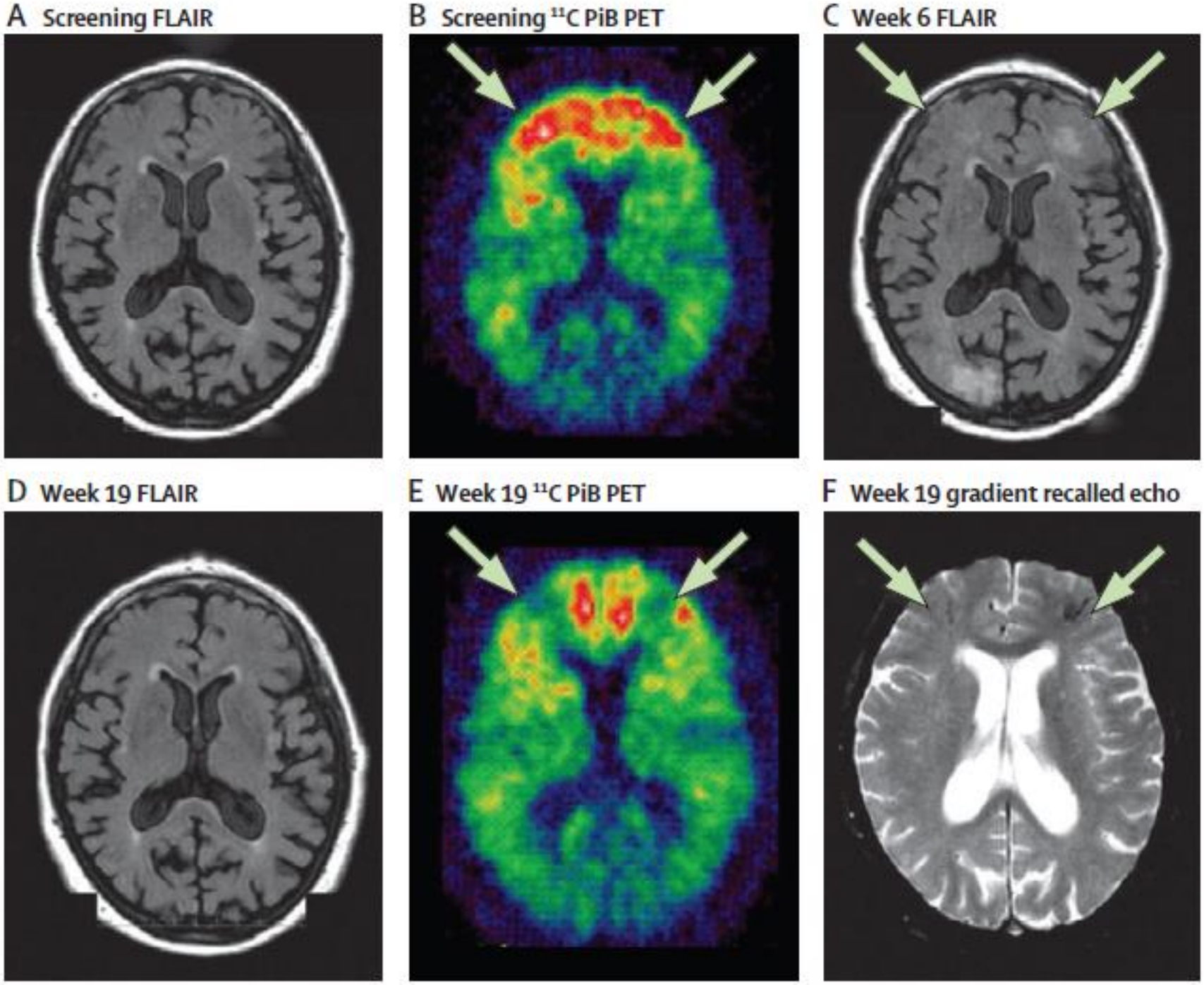
Salloway S, et al. Neurology 2009; 73:2061-2070

Amyloid-related imaging abnormalities AIRA

ARIA represents a spectrum of changes including sulcal effusion and parenchymal edema (ARIA-E), and haemosiderin deposition (ARIA-H).

Animal models indicate that anti-amyloid β treatment removes vascular amyloid with a corresponding compromise of the integrity of the vascular wall and leakage of blood resulting in microhaemorrhages and

haemosiderin deposition

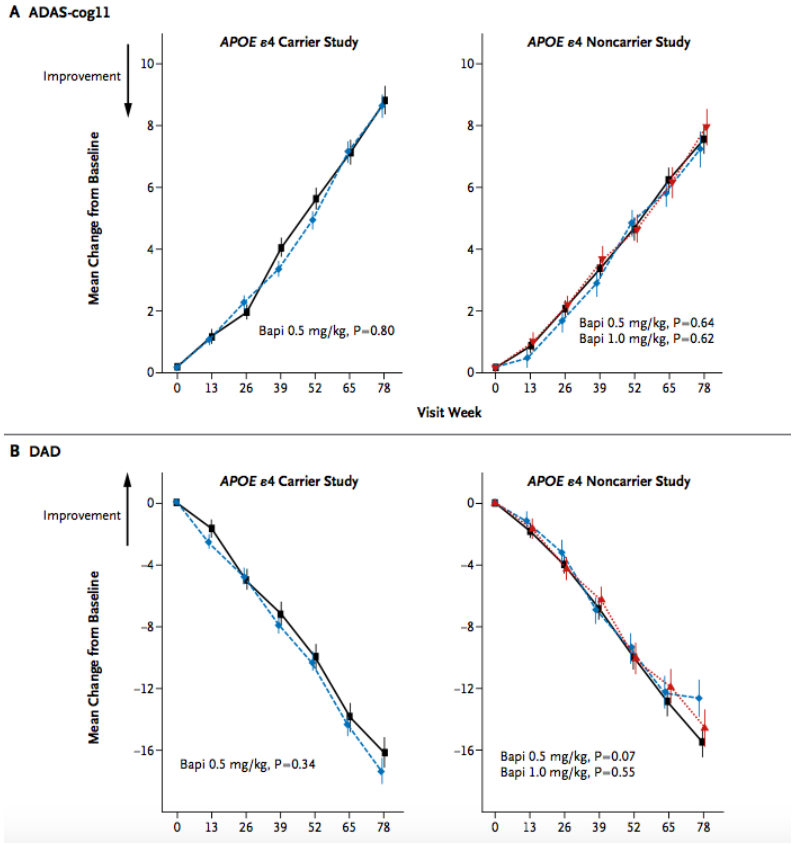

A Screening FLAIR
B Screening ^{11}C PiB PET
C Week 6 FLAIR
D Week 19 FLAIR
E Week 19 ^{11}C PiB PET
F Week 19 gradient recalled echo

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

Stephen Salloway, M.D., Reisa Sperling, M.D., Nick C. Fox, M.D., Kaj Blennow, M.D., William Klunk, M.D., Murray Raskind, M.D., Marwan Sabbagh, M.D., Lawrence S. Honig, M.D., Ph.D., Anton P. Porsteinsson, M.D., Steven Ferris, Ph.D., Marcel Reichert, M.D., Nzeera Ketter, M.D., Bijan Nejadnik, M.D., Volkmar Guenzler, M.D., Maja Miloslavsky, Ph.D., Daniel Wang, Ph.D., Yuan Lu, M.S., Julia Lull, M.A., Iulia Cristina Tudor, Ph.D., Enchi Liu, Ph.D., Michael Grundman, M.D., M.P.H., Eric Yuen, M.D., Ronald Black, M.D., and H. Robert Brashear, M.D., for the Bapineuzumab 301 and 302 Clinical Trial Investigators*



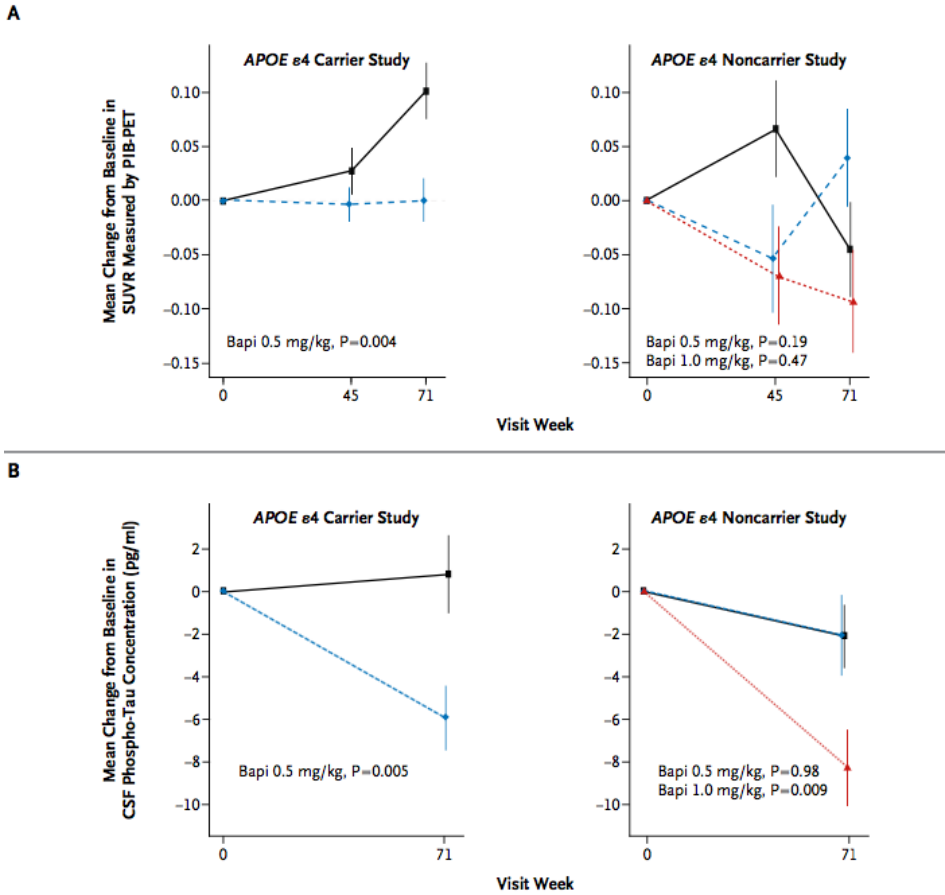


Table 2. Changes in Clinical End Points from Baseline to Week 78.*

End Point	Placebo	Bapineuzumab, 0.5 mg/kg			Bapineuzumab, 1.0 mg/kg		
	Change	Change	Least Squares Mean Difference from Placebo (95% CI)	P Value	Change	Least Squares Mean Difference from Placebo (95% CI)	P Value
Carrier study†							
ADAS-cog11 total score	8.7±0.5	8.5±0.4	−0.2 (−1.4 to 1.0)	0.80			
DAD total score	−16.2±1.0	−17.4±0.8	−1.2 (−3.8 to 1.3)	0.34			
Clinical Dementia Rating Scale–Sum of Boxes total score‡	3.0±0.2	3.3±0.1	0.2 (−0.2 to 0.6)	0.25			
Neuropsychological Test Battery total score§	−0.204±0.029	−0.213±0.024	−0.009 (−0.082 to 0.065)	0.82			
MMSE total score	−4.5±0.2	−4.7±0.2	−0.2 (−0.9 to 0.4)	0.50			
Dependence Scale¶	1.4±0.1	1.6±0.1	0.2 (−0.1 to 0.5)	0.30			
Noncarrier study‖							
ADAS-cog11 total score	7.4±0.5	7.1±0.6	−0.3 (−1.8 to 1.1)	0.64	7.8±0.6	0.4 (−1.1 to 1.8)	0.62
DAD total score	−15.5±1.0	−12.7±1.2	2.8 (−0.2 to 5.8)	0.07	−14.6±1.2	0.9 (−2.1 to 4.0)	0.55
Clinical Dementia Rating Scale–Sum of Boxes total score‡	2.6±0.2	2.6±0.2	0.0 (−0.5 to 0.5)	0.97	2.8±0.2	0.2 (−0.3 to 0.7)	0.42
Neuropsychological Test Battery total score§	−0.111±0.025	−0.143±0.031	−0.032 (−0.109 to 0.045)	0.42	−0.069±0.032	0.042 (−0.036 to 0.121)	0.29
MMSE total score	−3.9±0.2	−3.5±0.3	0.4 (−0.3 to 1.2)	0.29	−3.7±0.3	0.2 (−0.6 to 0.9)	0.66
Dependence Scale¶	1.4±0.1	1.3±0.1	−0.1 (−0.4 to 0.3)	0.74	1.5±0.2	0.1 (−0.2 to 0.5)	0.46

ORIGINAL ARTICLE

Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease

Rachelle S. Doody, M.D., Ph.D., Ronald G. Thomas, Ph.D., Martin Farlow, M.D., Takeshi Iwatsubo, M.D., Ph.D., Bruno Vellas, M.D., Steven Joffe, M.D., M.P.H., Karl Kieburtz, M.D., M.P.H., Rema Raman, Ph.D., Xiaoying Sun, M.S., and Paul S. Aisen, M.D., for the Alzheimer's Disease Cooperative Study Steering Committee; and Eric Siemers, M.D., Hong Liu-Seifert, Ph.D., and Richard Mohs, Ph.D., for the Solanezumab Study Group

Table 2. Primary and Secondary Outcomes in EXPEDITION 1, 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†	4.5 (3.3 to 5.8)	3.8 (2.5 to 5.0)	−0.8 (−2.1 to 0.5)	0.24
ADAS-cog14 score‡	5.8 (4.3 to 7.3)	4.5 (2.9 to 6.0)	−1.4 (−2.9 to 0.2)	0.09
ADCS-ADL score†	−8.7 (−10.4 to −7.0)	−9.1 (−10.9 to −7.4)	−0.4 (−2.3 to 1.4)	0.64
CDR-SB score§	1.8 (1.3 to 2.3)	2.0 (1.5 to 2.4)	0.1 (−0.3 to 0.6)	0.51
NPI score¶	0.6 (−1.5 to 2.6)	−0.3 (−2.4 to 1.7)	−0.9 (−2.6 to 0.8)	0.29
MMSE score	−2.0 (−2.8 to −1.2)	−1.4 (−2.2 to −0.6)	0.6 (0.0 to 1.2)	0.06
Free $A\beta_{40}$ in CSF — pg/ml	80.9 (−2100.5 to 2262.3)	−1127.3 (−3272.4 to 1017.9)	−1208.2 (−2132.4 to −283.9)	0.01
Free $A\beta_{42}$ in CSF — pg/ml	−28.5 (−160.0 to 102.9)	−54.4 (−186.7 to 77.9)	−25.8 (−88.3 to 36.6)	0.41
Total $A\beta_{40}$ in CSF — pg/ml	−1902.1 (−6660.1 to 2855.8)	1325.4 (−3162.0 to 5812.9)	3227.6 (1253.6 to 5201.5)	0.002
Total $A\beta_{42}$ in CSF — pg/ml	−242.3 (−1144.4 to 659.7)	471.4 (−436.0 to 1378.8)	713.7 (309.1 to 1118.4)	<0.001

ORIGINAL ARTICLE

Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease

Rachelle S. Doody, M.D., Ph.D., Ronald G. Thomas, Ph.D., Martin Farlow, M.D., Takeshi Iwatsubo, M.D., Ph.D., Bruno Vellas, M.D., Steven Joffe, M.D., M.P.H., Karl Kieburtz, M.D., M.P.H., Rema Raman, Ph.D., Xiaoying Sun, M.S., and Paul S. Aisen, M.D., for the Alzheimer's Disease Cooperative Study Steering Committee; and Eric Siemers, M.D., Hong Liu-Seifert, Ph.D., and Richard Mohs, Ph.D., for the Solanezumab Study Group

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

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 25, 2018 VOL. 378 NO. 4

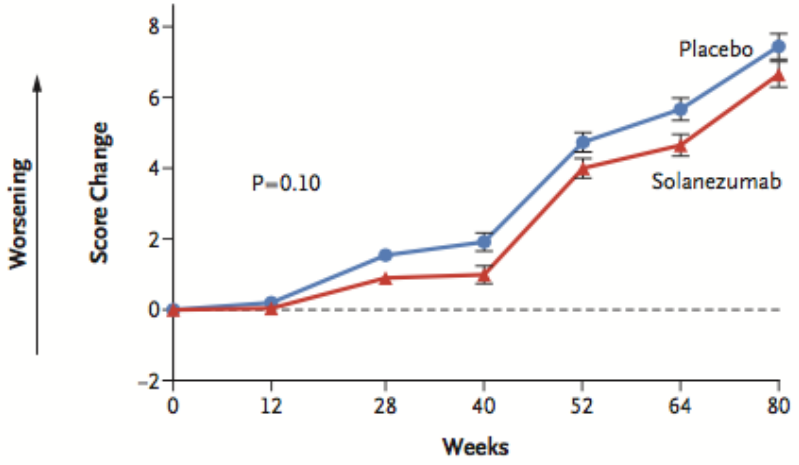
Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease

Lawrence S. Honig, M.D., Ph.D., Bruno Vellas, M.D., Michael Woodward, M.D., Mercè Boada, M.D., Ph.D., Roger Bullock, M.D., Michael Borrie, M.B., Ch.B., Klaus Hager, M.D., Niels Andreasen, M.D., Ph.D., Elio Scarpini, M.D., Hong Liu-Seifert, Ph.D., Michael Case, M.S., Robert A. Dean, M.D., Ph.D., Ann Hake, M.D., Karen Sundell, B.S., Vicki Poole Hoffmann, Pharm.D., Christopher Carlson, Ph.D., Rashna Khanna, M.D., Mark Mintun, M.D., Ronald DeMattos, Ph.D., Katherine J. Selzler, Ph.D., and Eric Siemers, M.D.

Table 1. Characteristics of the Patients at Baseline.*

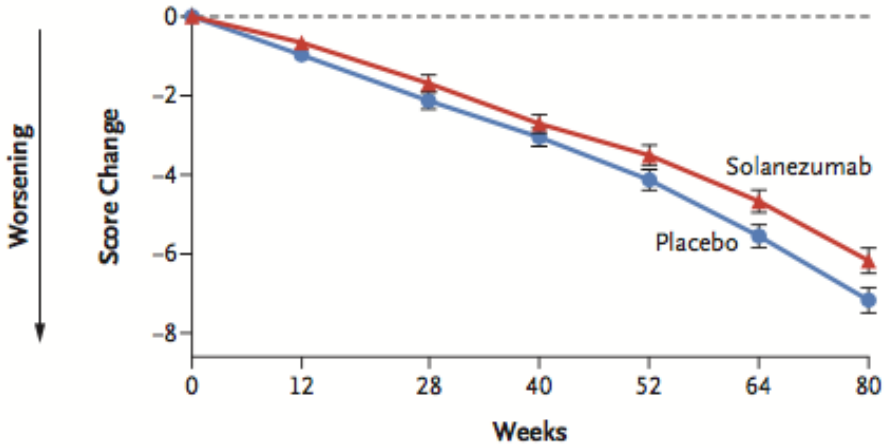
Characteristic	Placebo (N=1072)	Solanezumab (N=1057)	P Value
Age — yr	73.3±8.0	72.7±7.8	0.07
Female sex — no. (%)	631 (58.9)	600 (56.8)	0.34
Race — no./total no. (%)†			0.76
White	894/986 (90.7)	878/970 (90.5)	
Black	19/986 (1.9)	14/970 (1.4)	
Asian	71/986 (7.2)	75/970 (7.7)	
Multiple or other	2/986 (0.2)	3/970 (0.3)	
APOE ε4 allele — no./total no. (%)	685/1033 (66.3)	712/1027 (69.3)	0.14
Education — yr	13.7±3.8	13.7±3.7	0.91
Duration since symptom onset — yr	4.3±2.6	4.2±2.5	0.41
Duration since diagnosis — yr	1.6±1.7	1.5±1.6	0.13
Acetylcholinesterase inhibitor or memantine use — no. (%)	856 (79.9)	822 (77.8)	0.24
ADAS-cog14 score‡	29.7±8.5	28.9±8.3	0.02
ADCS-iADL score§	45.4±8.1	45.6±7.9	0.44
MMSE score¶	22.6±2.9	22.8±2.8	0.12
FAQ score‖	10.6±7.1	10.3±6.8	0.36
CDR-SB score**	3.9±2.0	3.9±1.9	0.54

A Change in Alzheimer's Disease Assessment Scale–Cognitive Subscale Score



No. at Risk							
Placebo	1067	—	—	—	—	—	893
Solanezumab	1053	—	—	—	—	—	908

B Change in Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Subscale Score



No. at Risk							
Solanezumab	1053	—	—	—	—	—	908
Placebo	1063	—	—	—	—	—	896

A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease

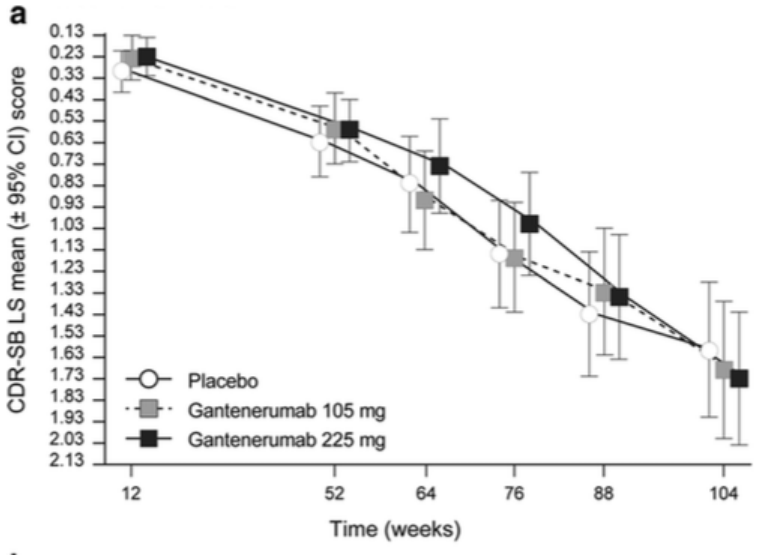
Susanne Ostrowitzki[1], Robert A. Lasser[2], Ernest Dorflinger[3], Philip Scheltens[4], Frederik Barkhof[4,5,6], Tania Nikolcheva[6], Elizabeth Ashford[7], Sylvie Retout[8], Carsten Hofmann[8], Paul Delmar[9], Gregory Klein[6], Mirjana Andjelkovic[8], Bruno Dubois[10], Mercè Boada[11], Kaj Blennow[12], Luca Santarelli[13], Paulo Fontoura[9*] and for the SCarlet RoAD Investigators

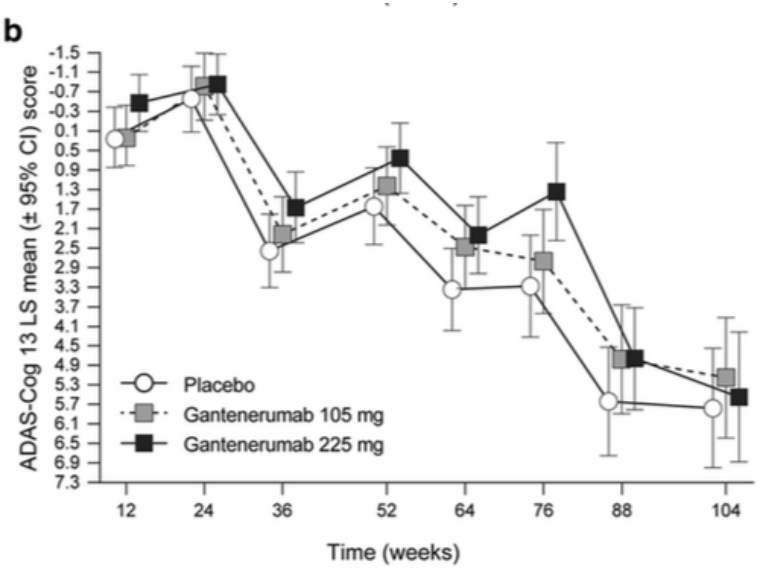
Table 1 Baseline characteristics of patients in the SCarlet RoAD study

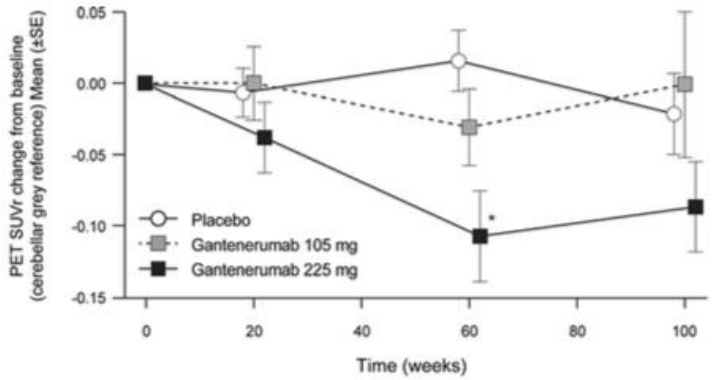
Variable	Intention-to-treat population ($n = 797$)		
	Placebo ($n = 266$)	Gantenerumab 105 mg ($n = 271$)	Gantenerumab 225 mg ($n = 260$)
Age, years, mean (SD)	69.5 (7.5)	70.3 (7.0)	71.3 (7.1)
Education, years, mean (SD)	89.8%	93.0%	91.9%
Weight, kg, mean (SD)	12.6 (4.3)	12.9 (4.8)	12.1 (4.5)
APOE ε4 genotype, %[a]	69.8 (12.9)	70.5 (13.6)	70.1 (12.5)
0ε4	29.7%	21.0%	38.5%
1ε4	50.4%	41.0%	61.5%
2ε4	19.9%	38.0%	–
Clinical scores			
CDR-SB, mean score (SD)	2.1 (1.0)	2.2 (1.0)	2.0 (0.9)
ADAS-Cog 13, mean score (SD)	23.5 (7.2)	23.1 (6.9)	23.0 (6.2)
FAQ, mean score (SD)	4.9 (4.3)	4.6 (3.9)	4.8 (4.3)
FCSRT-Total Recall, mean score (SD)	29.3 (10.8)	28.3 (10.8)	30.5 (10.4)
MMSE, mean score (SD)	25.7 (2.1)	25.7 (2.3)	25.7 (2.2)
CSF biomarkers			
$A\beta_{42}$, pg/ml, mean (SD)	487.8 (170.4)	475.3 (142.2)	511.8 (172.0)
t-tau, pg/ml, mean (SD)	556.3 (203.8)	563.2 (239.1)	544.5 (220.5)
p-tau, pg/ml, mean (SD)	84.0 (31.4)	86.3 (39.5)	82.5 (34.2)
Neurogranin, pg/ml, mean (SD)	474.8 (260.7)	500.5 (270.0)	484.9 (293.9)

Abbreviations: ADAS-Cog Alzheimer's Disease Assessment Scale–Cognitive subscale, *APOE* Apolipoprotein E, *CDR-SB* Clinical Dementia Rating Sum of Boxes, *CSF* Cerebrospinal fluid, *FAQ* Functional Activities Questionnaire, *FCSRT* Free and Cued Selective Reminding Test, *MMSE* Mini Mental State Examination

[a]By design, there were no *APOE* 2ε4 patients in the gantenerumab 225 mg arm







	Placebo			Gantenerumab 105 mg			Gantenerumab 225 mg		
	n	Change from baseline (SD)	% Change from baseline	n	Change from baseline (SD)	% Change from baseline	vs. placebo p-value	n	Change from baseline (SD)	% Change from baseline	vs. placebo p-value
Week 20	35	-0.01 (0.10)	-0.28	32	0.00 (0.15)	0.53	0.70	30	-0.04 (0.14)	-1.83	0.27
Week 60	30	0.02 (0.12)	1.00	25	-0.03 (0.13)	-1.15	0.26	26	-0.11 (0.16)	-5.79	0.002
Week 100	21	-0.02 (0.13)	-1.09	15	0.00 (0.20)	0.72	0.64	19	-0.09 (0.14)	-4.82	0.10

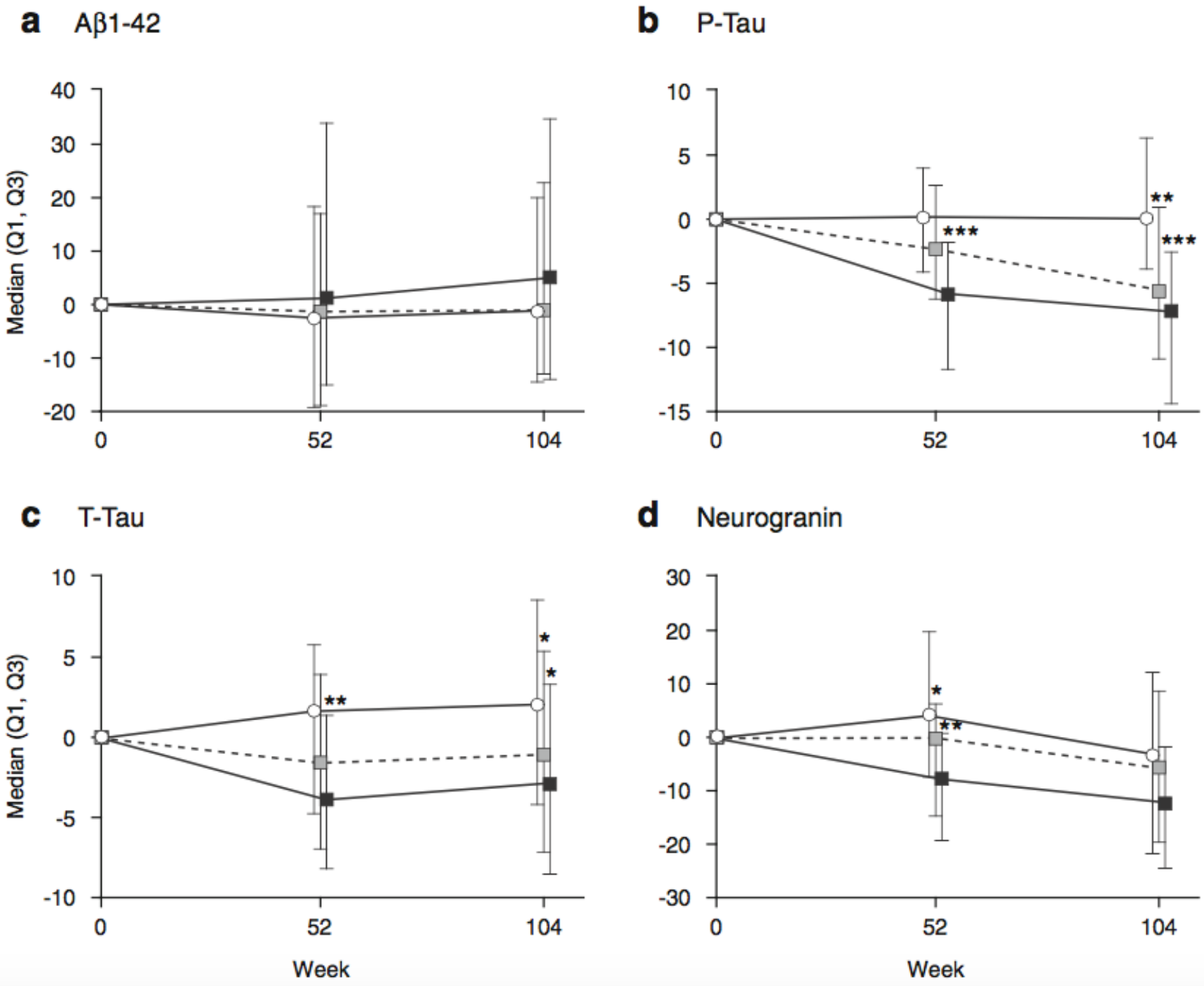

a Aβ1-42
b P-Tau
c T-Tau
d Neurogranin
Median (Q1, Q3)
Week
0
52
104
40
30
20
10
0
-10
-20
5
-5
-15
-30
*
**
***

Table 4 Fast and slow progressors in the SCarlet RoAD population

Variable, median score (Q1; Q3)	Change from baseline at week 104 ($n = 310$[a])					
	Slow progressors ($n = 202$)			Fast progressors ($n = 108$)		
	Placebo ($n = 70$)	Gantenerumab 105 mg ($n = 57$)	Gantenerumab 225 mg ($n = 75$)	Placebo ($n = 35$)	Gantenerumab 105 mg ($n = 47$)	Gantenerumab 225 mg ($n = 26$)
Primary endpoint						
CDR-SB	0.5 (0, 1.5)	0.5 (0, 2)	1.0 (0, 1.5)	1.5 (0.5, 3)	1.0 (0, 2.75)	2.0 (1, 2.88)
Secondary endpoints						
ADAS-Cog 13	3.34 (−1.41, 8.41)	3.5 (−2.5, 6.25)	3.33 (−0.34, 8.67)	6.0 (2.34, 12.17)	4.84 (1.5, 7.92)	2.66 (0.67, 7.5)
CANTAB	−1.43 (−2.52, −0.31)	−1.14 (−3, 0.97)	−0.99 (−3.22, 0.56)	−2.42 (−4.09, 0.07)	−1.31 (−3.27, 0.25)	−0.81 (−1.98, 0.69)
FAQ	1 (0, 5)	1 (0, 7)	2 (0, 6)	5 (2.5, 8)	6 (2, 8.5)	4 (1, 9)
MMSE	−1 (−4, 0)	−1 (−4, 0.25)	−2 (−3, 0)	−3.5 (−4.75, −2)	−3 (−4.5, 0)	−2 (−4, 0)

Abbreviations: ADAS-Cog 13 Alzheimer's Disease Assessment Scale–Cognitive subscale, *CANTAB* Cambridge Neuropsychological Test Automated Battery, *CDR-SB* Clinical Dementia Rating Sum of Boxes, *FAQ* Functional Activities Questionnaire, *MMSE* Mini Mental State Examination

[a]Six patients completing study drug treatment had missing efficacy assessment at the week 104 visit time window

A phase 2 randomized trial of crenezumab in mild to moderate Alzheimer disease

Jeffrey L. Cummings, MD, ScD, Sharon Cohen, MD, Christopher H. van Dyck, MD, Mark Brody, MD, Craig Curtis, MD, William Cho, MD, Michael Ward, PhD, Michel Friesenhahn, MA, Christina Rabe, PhD, Flavia Brunstein, MD, PhD, Angelica Quartino, PhD, Lee A. Honigberg, PhD, Reina N. Fuji, VMD, PhD, David Clayton, PhD, Deborah Mortensen, PhD, Carole Ho, MD, and Robert Paul, MD

Correspondence
Dr. Cummings
cumminj@ccf.org

Neurology® 2018;0:e1-e9. doi:10.1212/WNL.0000000000005550

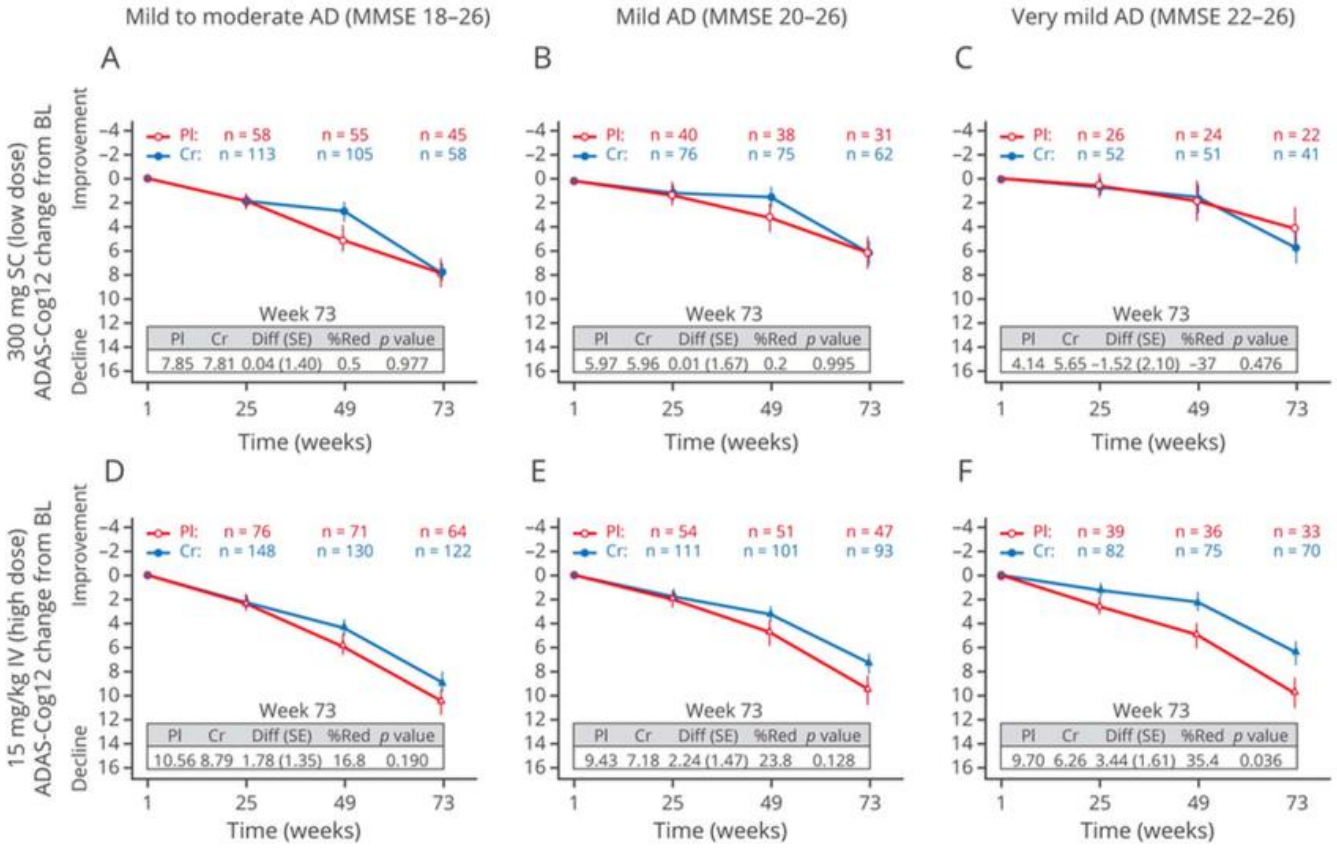
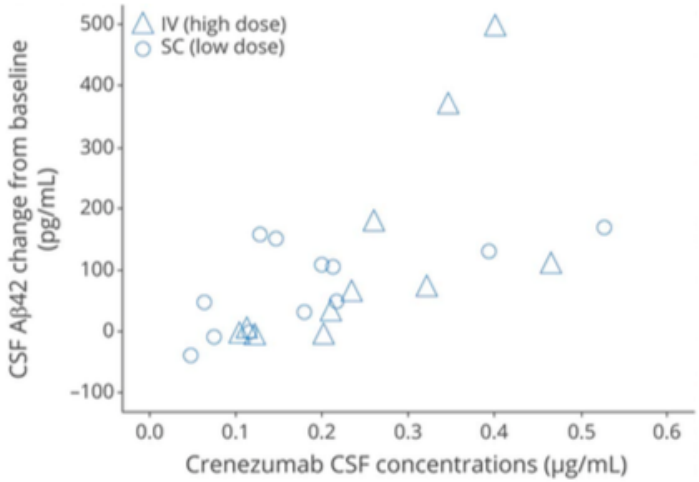
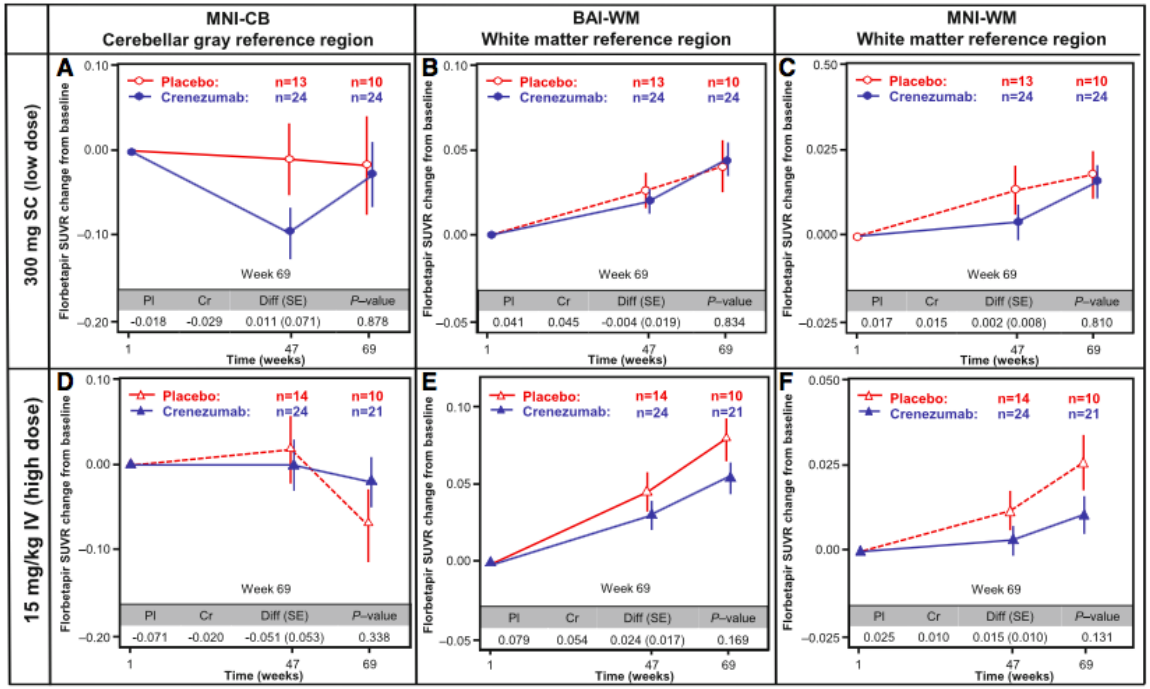


Figure 2 CSF $A\beta_{1-42}$ and crenezumab correlation analysis



Correlation analysis of change in CSF $A\beta_{1-42}$ from baseline and crenezumab concentrations in patients receiving low-dose 300 mg SC (circles) and those receiving high-dose 15 mg/kg IV (triangles). Aβ = β-amyloid.



The NEW ENGLAND JOURNAL of MEDICINE

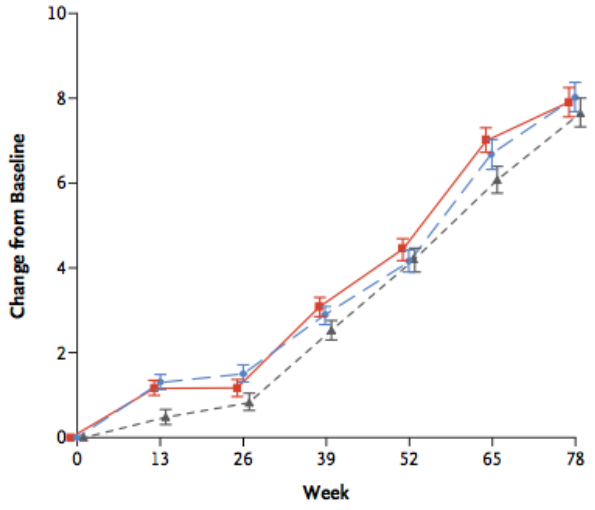
ORIGINAL ARTICLE

Randomized Trial of Verubecestat for Mild-to-Moderate Alzheimer's Disease

Michael F. Egan, M.D., James Kost, Ph.D., Pierre N. Tariot, M.D., Paul S. Aisen, M.D., Jeffrey L. Cummings, M.D., Sc.D., Bruno Vellas, M.D., Ph.D., Cyrille Sur, Ph.D., Yuki Mukai, M.D., Tiffini Voss, M.D., Christine Furtek, B.S., Erin Mahoney, B.A., Lyn Harper Mozley, Ph.D., Rik Vandenberghe, M.D., Ph.D., Yi Mo, Ph.D., and David Michelson, M.D.

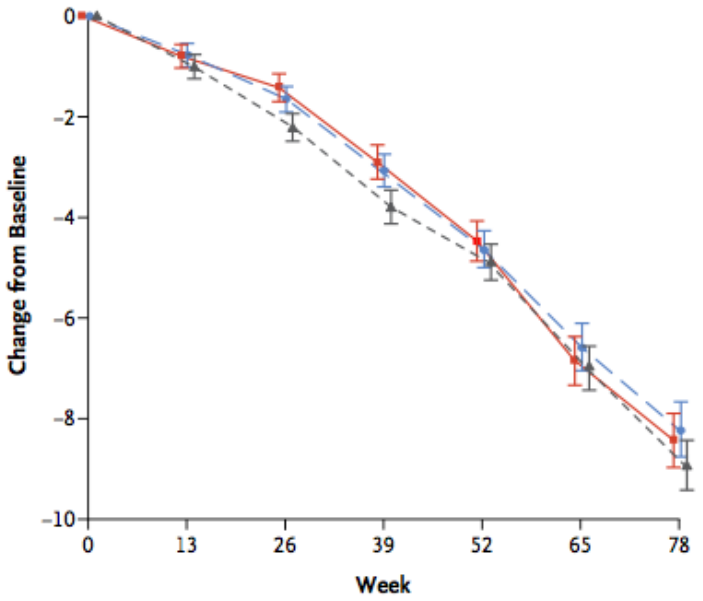
n engl j med 378;18 nejm.org May 3, 2018

A Worsening Score on ADAS-cog



No. of Patients							
12-mg group	629	619	607	577	559	519	448
40-mg group	621	616	591	565	545	519	432
Placebo group	639	628	616	597	576	539	463

B Worsening Score on ADCS-ADL



No. of Patients							
12-mg group	625	605	601	572	557	517	443
40-mg group	617	601	584	561	541	521	436
Placebo group	631	606	608	593	570	531	453

Adverse events, including rash, falls and injuries, sleep disturbance, suicidal ideation, weight loss, and hair-color change, were more common in the verubecestat groups than in the placebo group.

Failure of AD Candidate Therapeutics in the Clinic

Phase III randomized, placebo controlled , double-blind clinical trials

Agent	Target/Mechanism	Outcome
Atorvastatin	HMG CoA reductase	Negative
Dimebon	Mitochondrial function	Negative
LY450139	Gamma secretase	Negative
NSAIDs	Inflammation	Negative
Phenserine	Cholinesterase/Amyloid	Negative
Rosiglitazone	PPAR gamma agonist	Negative
Simvastatin	HMG CoA reductase	Negative
Tarenflurbil	Gamma secretase	Negative
Xaliproden	Serotonin antagonist	Negative

The most common reasons for Phase III failure: *lack of efficacy and toxicity.*

LE POSSIBILI RAGIONI DEI RISULTATI NEGATIVI

Reasons for failure to show a drug-placebo difference at the end of a clinical trial of a disease-modifying agent. AD, Alzheimer's disease

Drug-related
• Lack of efficacy of the agent
• Inappropriately low dosing of an effective agent
• Excessive toxicity or lack of tolerability leading to high discontinuation rates in the active treatment arms
• Excessive toxicity or lack of tolerability leading to early termination of the trial
Trial-related
• Lack of decline in the placebo group
• Recruitment of non-AD patients into trials requiring an AD substrate for drug benefit to occur
• Excessive measurement variability
• Lack of measurable effect of active comparator drugs (if available)

Other alternative explanations for clinical trial failures

(1) the possibility that the amyloid hypothesis is wrong;

(2) the possibility that treatments aimed at a single pathologic process will be ineffective;

(3) the possibility that the amyloid hypothesis may be correct, but that the compounds that have been taken into clinic are ineffective and do not represent a true test of the amyloid hypothesis in symptomatic patients.

The third explanation leads to at least two potential root causes:

(1) the preclinical models currently used to test compounds are not appropriate and are systematically biased toward “false positive” results;

(2) compounds are being pushed into pivotal trials despite a lack of robust signals of “drug-like behavior” at earlier stages of development.

Reasons for mismatch with experimental models

A lot of the data in mice is from young animals, and their immune system is quite different from an aged individual; the mouse models, therefore, might best reflect the early stages of Alzheimer's disease, including the period before a patient's diagnosis.

If that were the case, clinical trials of drugs that target amyloid-β could be failing because people are treated too late to halt the death of brain cells.

Most of the animal work has seen mice treated at the beginning of plaque build-up, which is more a prevention than treatment paradigm

Person-Specific Contribution of Neuropathologies to Cognitive Loss in Old Age

Patricia A. Boyle, PhD,[1,2] Lei Yu, PhD,[1,3] Robert S. Wilson, PhD,[1,2,3] Sue E. Leurgans, PhD,[1,3] Julie A. Schneider, MD, MS,[1,3,4] and David A. Bennett, MD[1,3]

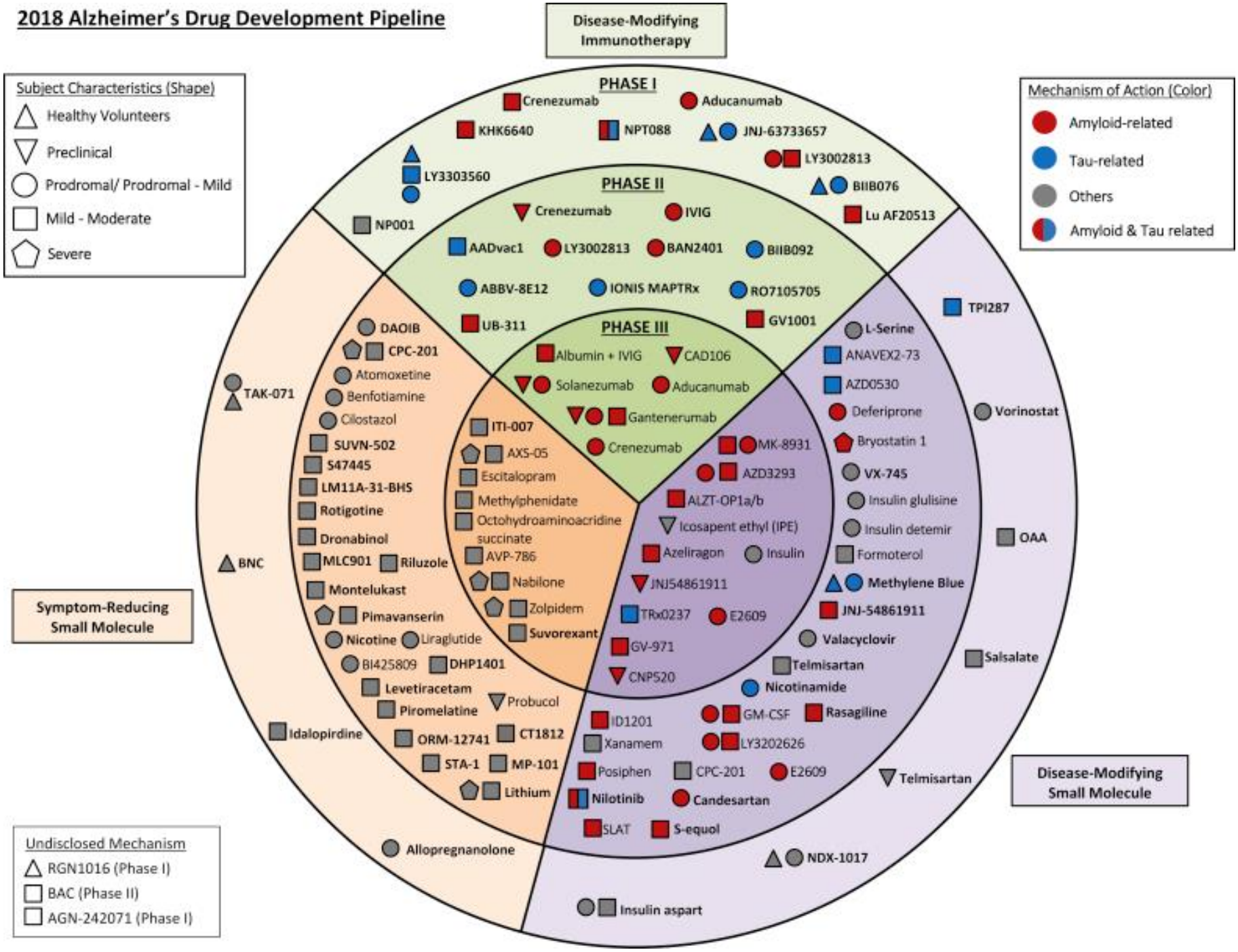
ANN NEUROL 2018;83:74–83

TABLE 2. Association of Demographics and Common Neuropathologies with Late Life Cognitive Decline

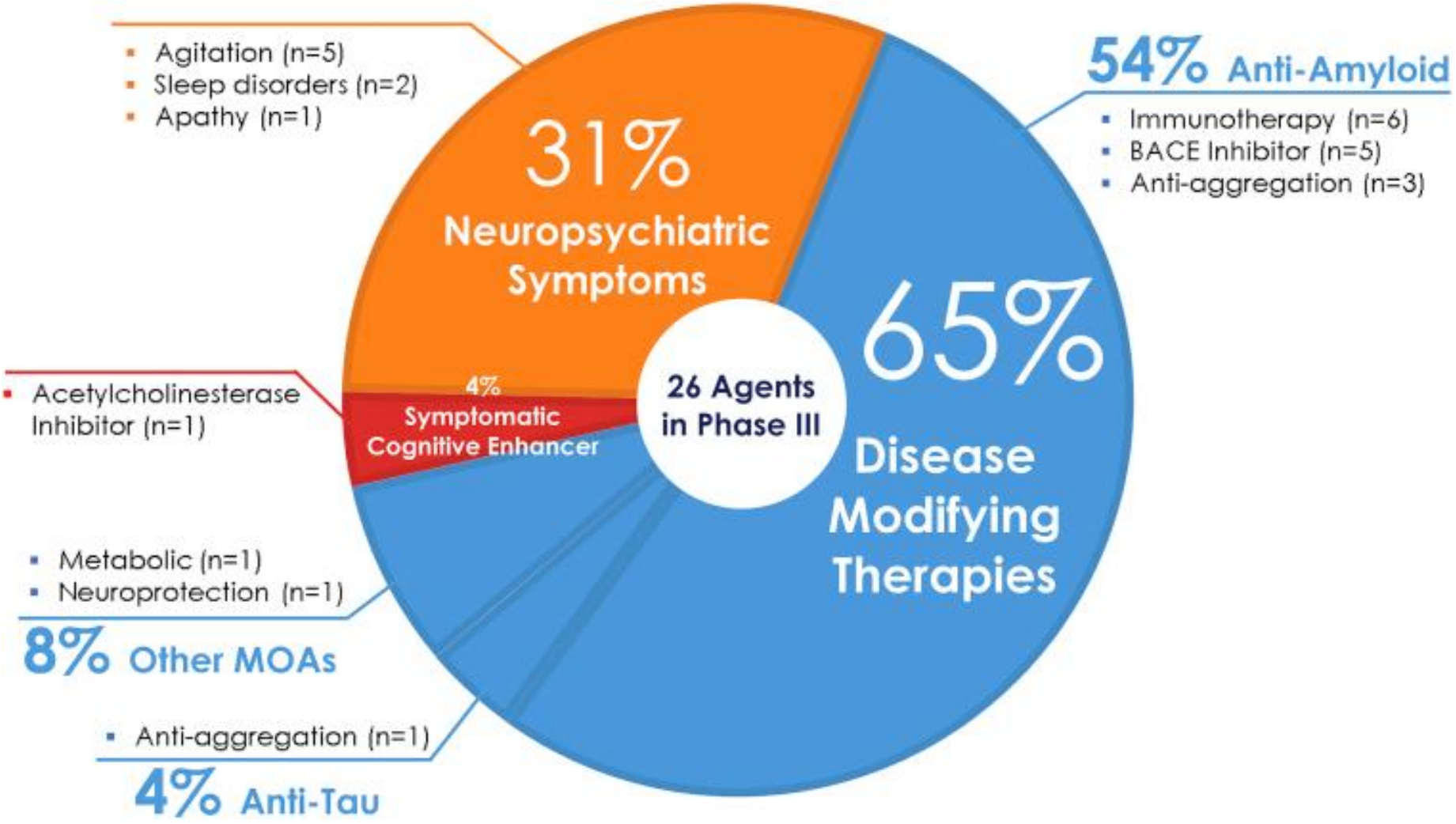
Variable	Cognitive Level[a]	Rate of Cognitive Decline
Age at death	0.003 (0.005), 0.526	0.002 (0.0005), <0.001
Female sex	0.111 (0.070), 0.112	0.015 (0.007), 0.018
Education	0.037 (0.009), <0.001	0.001 (0.0008), 0.111
AD	−0.679 (0.070), <0.001	−0.062 (0.006), <0.001
Macroscopic infarcts	−0.280 (0.069), <0.001	−0.025 (0.006), <0.001
Cerebral amyloid angiopathy	−0.265 (0.068), <0.001	−0.018 (0.006), 0.005
TDP-43	−0.347 (0.072), <0.001	−0.032 (0.007), <0.001
Atherosclerosis	−0.281 (0.070), <0.001	−0.021 (0.007), 0.001
Arteriolosclerosis	−0.240 (0.071), <0.001	−0.024 (0.007), <0.001
Microinfarcts	−0.032 (0.070), 0.647	0.006 (0.006), 0.366
Cortical Lewy bodies	−0.592 (0.094), <0.001	−0.062 (0.009), <0.001
Hippocampal sclerosis	−0.685 (0.110), <0.001	−0.038 (0.010), <0.001

Statistics are presented are estimate (standard error), p value.
[a]Level proximate to death.
AD = Alzheimer disease.

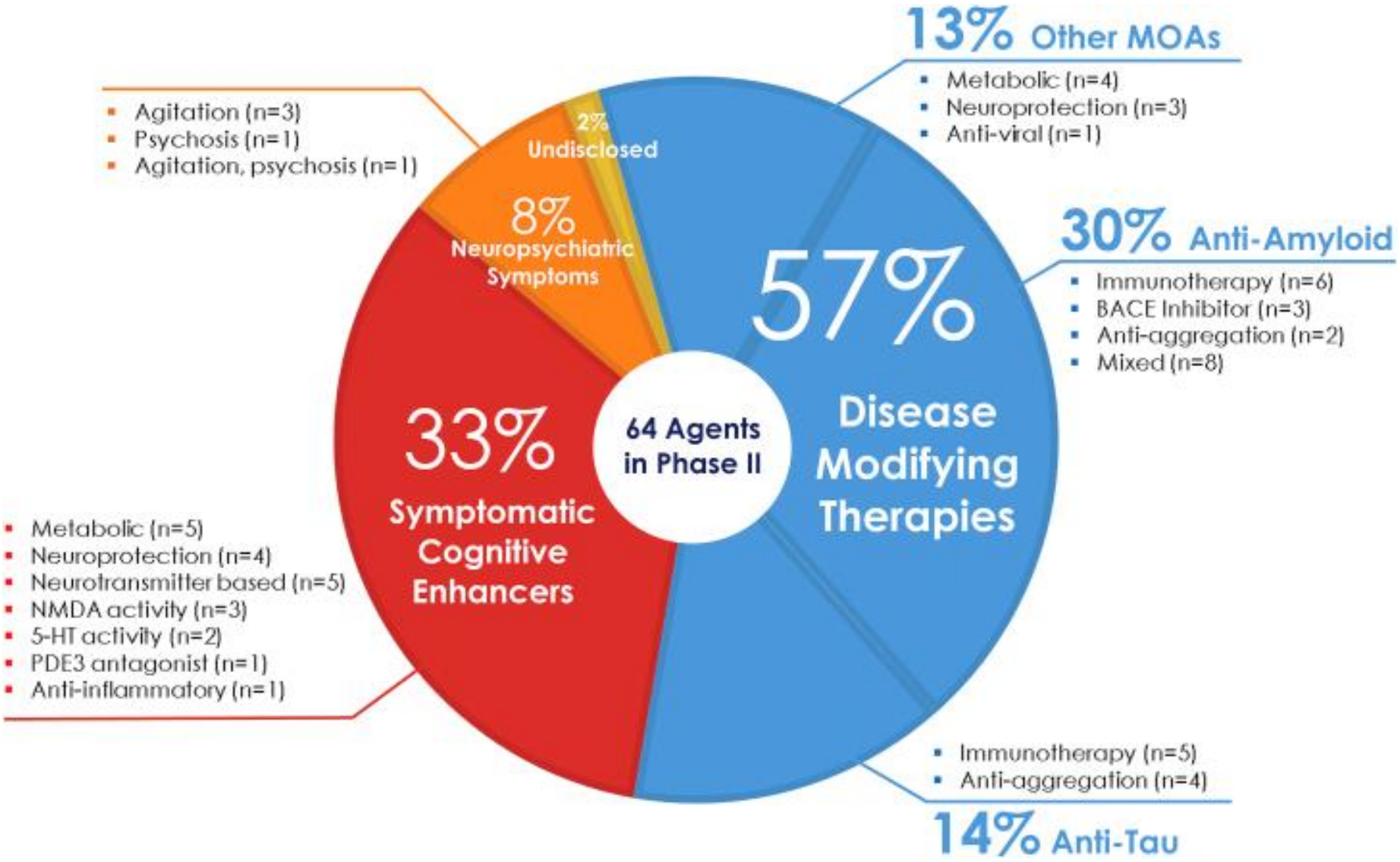
2018 Alzheimer's Drug Development Pipeline



Mechanisms of action of agents in phase III.



Mechanisms of action of agents in phase II.



The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

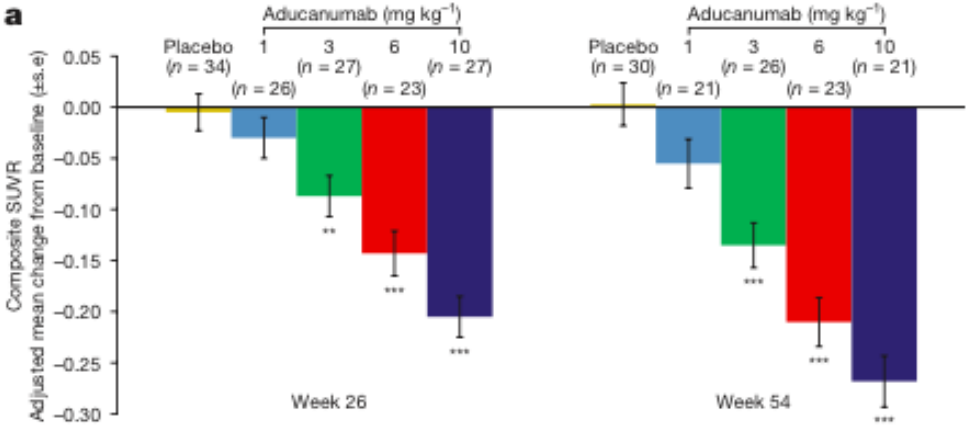
Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1],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

Characteristic		Placebo ($n=40$)	Aducanumab 1 mg kg^{-1} ($n=31$)	Aducanumab 3 mg kg^{-1} ($n=32$)	Aducanumab 6 mg kg^{-1} ($n=30$)	Aducanumab 10 mg kg^{-1} ($n=32$)	Total ($n=165$)*
Years of age (mean ± s.d.)		72.8 ± 7.2	72.6 ± 7.8	70.5 ± 8.2	73.3 ± 9.3	73.7 ± 8.3	72.6 ± 8.1
Female sex (*n* (%))		23 (58)	13 (42)	17 (53)	15 (50)	15 (47)	83 (50)
ApoE ε4 (*n* (%))	Carriers	26 (65)	19 (61)	21 (66)	21 (70)	20 (63)	107 (65)
	Non-carriers	14 (35)	12 (39)	11 (34)	9 (30)	12 (38)	58 (35)
Clinical stage (*n* (%))	Prodromal	19 (48)	10 (32)	14 (44)	12 (40)	13 (41)	68 (41)
	Mild	21 (53)	21 (68)	18 (56)	18 (60)	19 (59)	97 (59)
MMSE (mean ± s.d.)		24.7 ± 3.6	23.6 ± 3.3	23.2 ± 4.2	24.4 ± 2.9	24.8 ± 3.1	24.2 ± 3.5
Global CDR (*n* (%))	0.5	34 (85)	22 (71)	22 (69)	25 (83)	24 (75)	127 (77)
	1	6 (15)	9 (29)	10 (31)	5 (17)	8 (25)	38 (23)
CDR-SB (mean ± s.d.)		2.66 ± 1.50	3.40 ± 1.76	3.50 ± 2.06	3.32 ± 1.54	3.14 ± 1.71	3.18 ± 1.72
FCSRT sum of free recall score (mean ± s.d.)		15.2 ± 8.5	13.2 ± 9.0	13.8 ± 8.0	14.4 ± 8.3	14.6 ± 8.3	14.3 ± 8.3
PET SUVR composite score (mean ± s.d.)		1.44 ± 0.17	1.44 ± 0.15	1.46 ± 0.15	1.43 ± 0.20	1.44 ± 0.19	1.44 ± 0.17
AD medications use† (*n* (%))		24 (60)	19 (61)	28 (88)	20 (67)	17 (53)	108 (65)

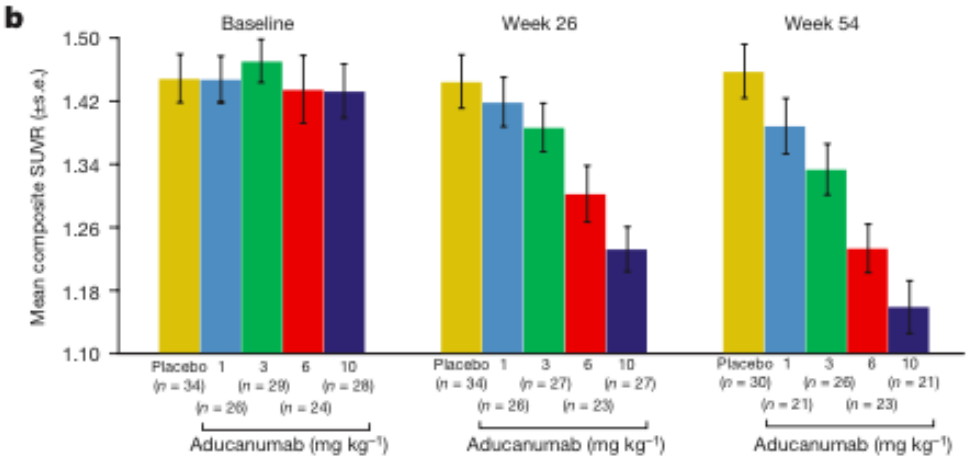
Percentages are rounded to the nearest integer. AD, Alzheimer's disease; ApoE ε4, apolipoprotein E ε4 allele; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating—Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SD, standard deviation; SUVR, standard uptake value ratio.

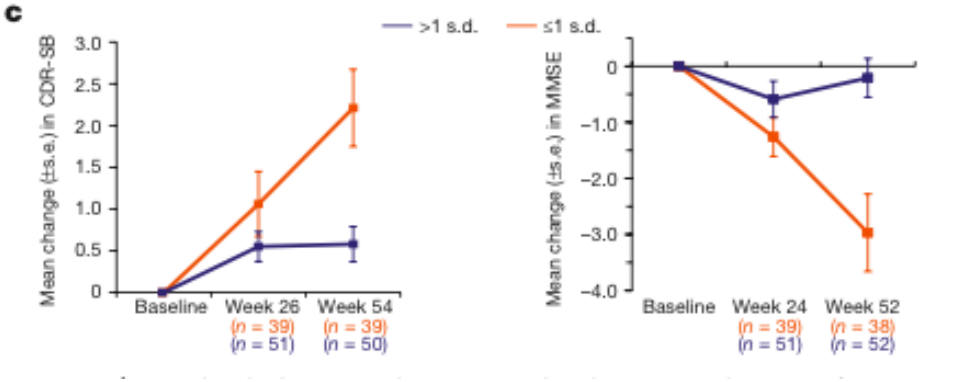
*Number of patients dosed.

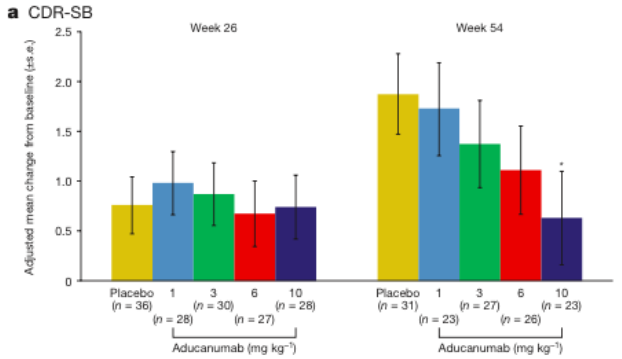
†Cholinesterase inhibitors and/or memantine.



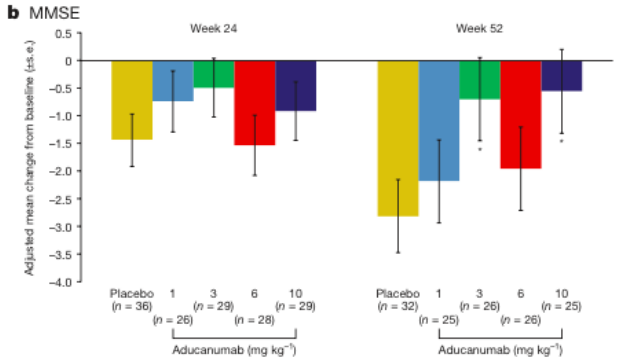
Dose-response $P < 0.001$ at weeks 26 and 54 based on a linear contrast test

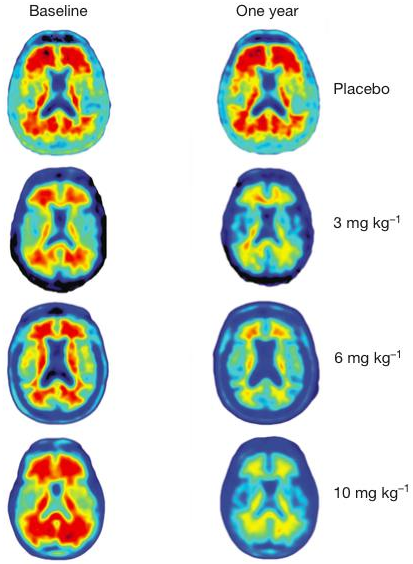




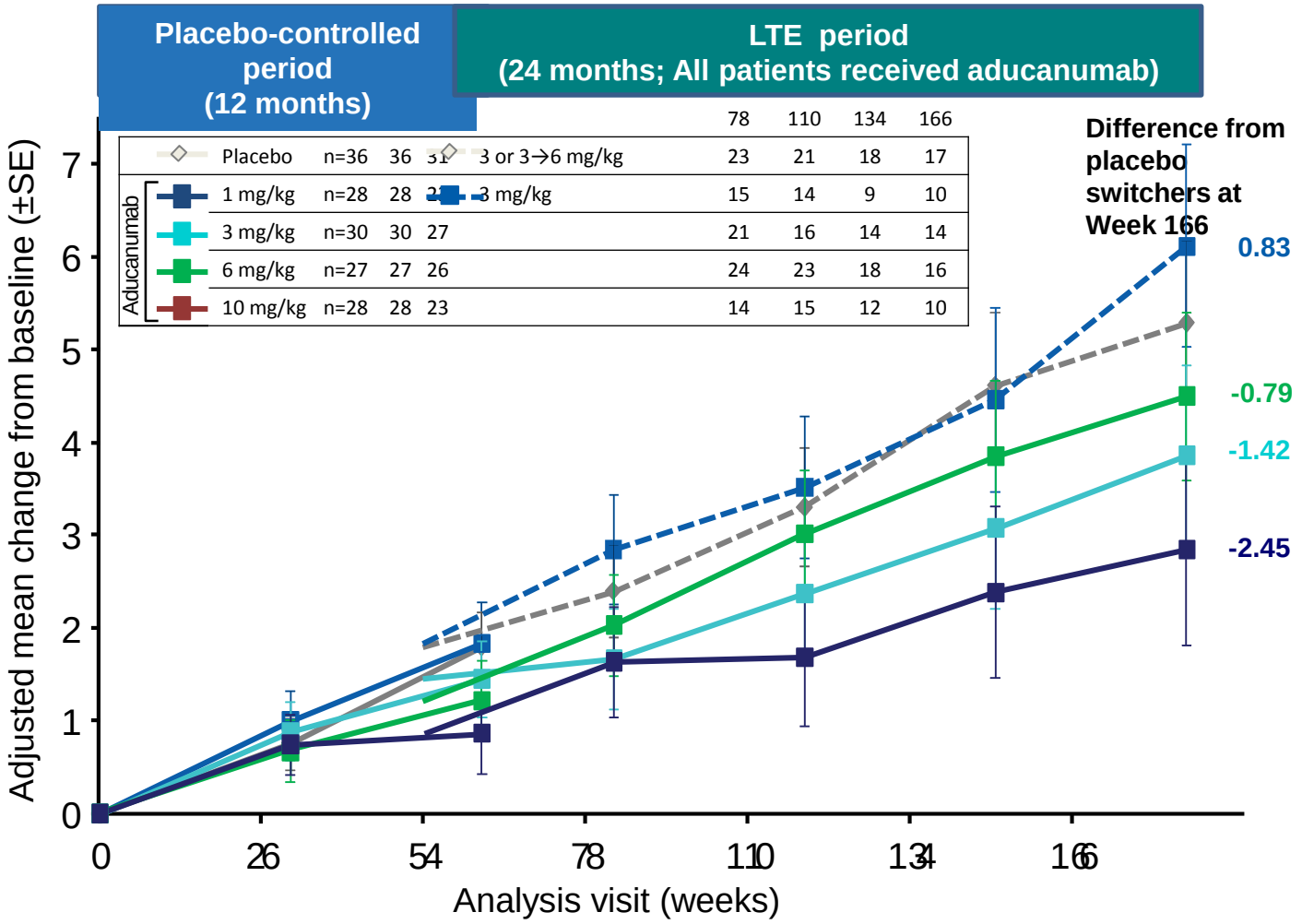


Dose-response $P < 0.05$ at week 54 based on a linear contrast test



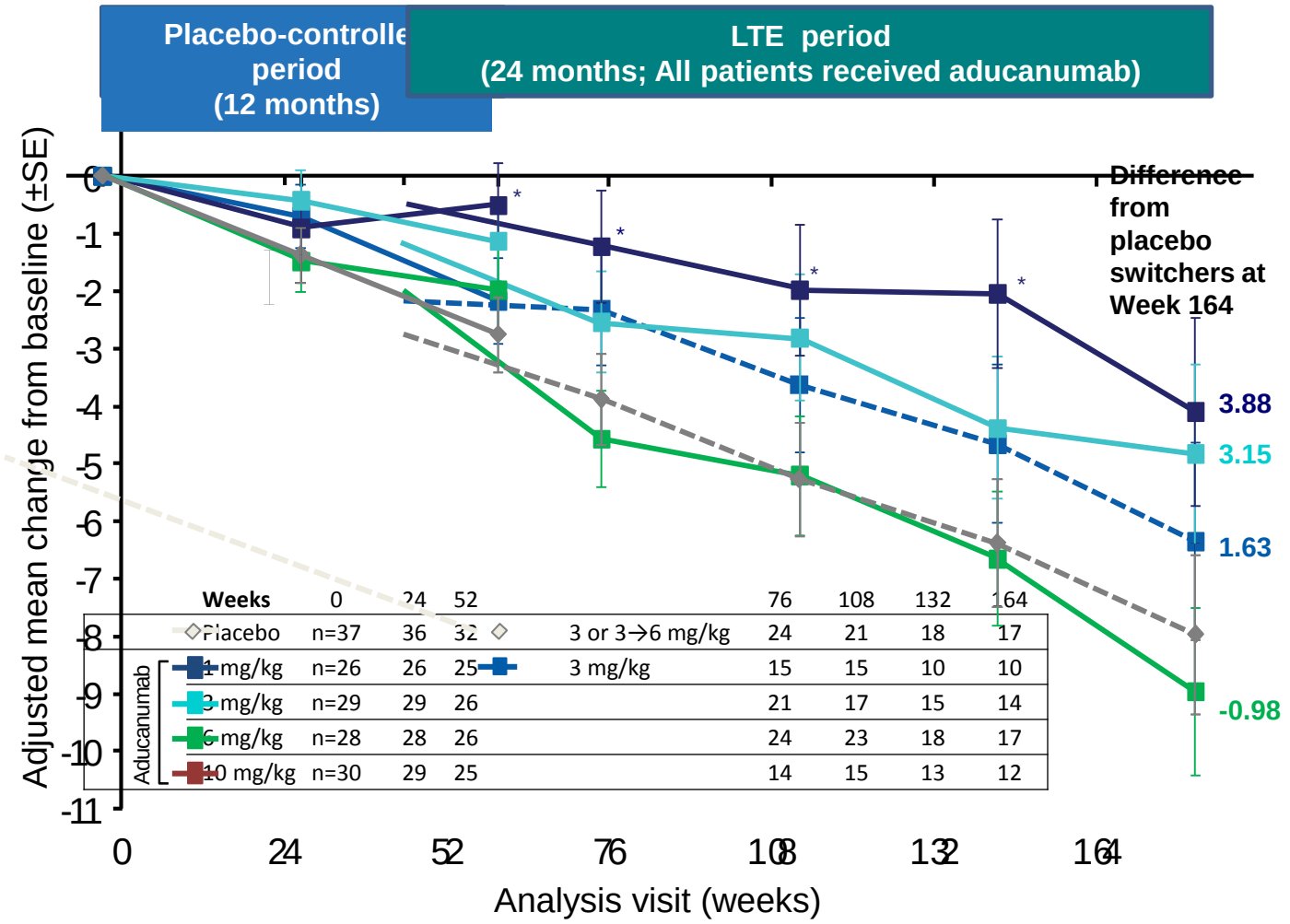


Effect of Aducanumab on Clinical Decline as Measured by CDR-SB (Exploratory Endpoint)



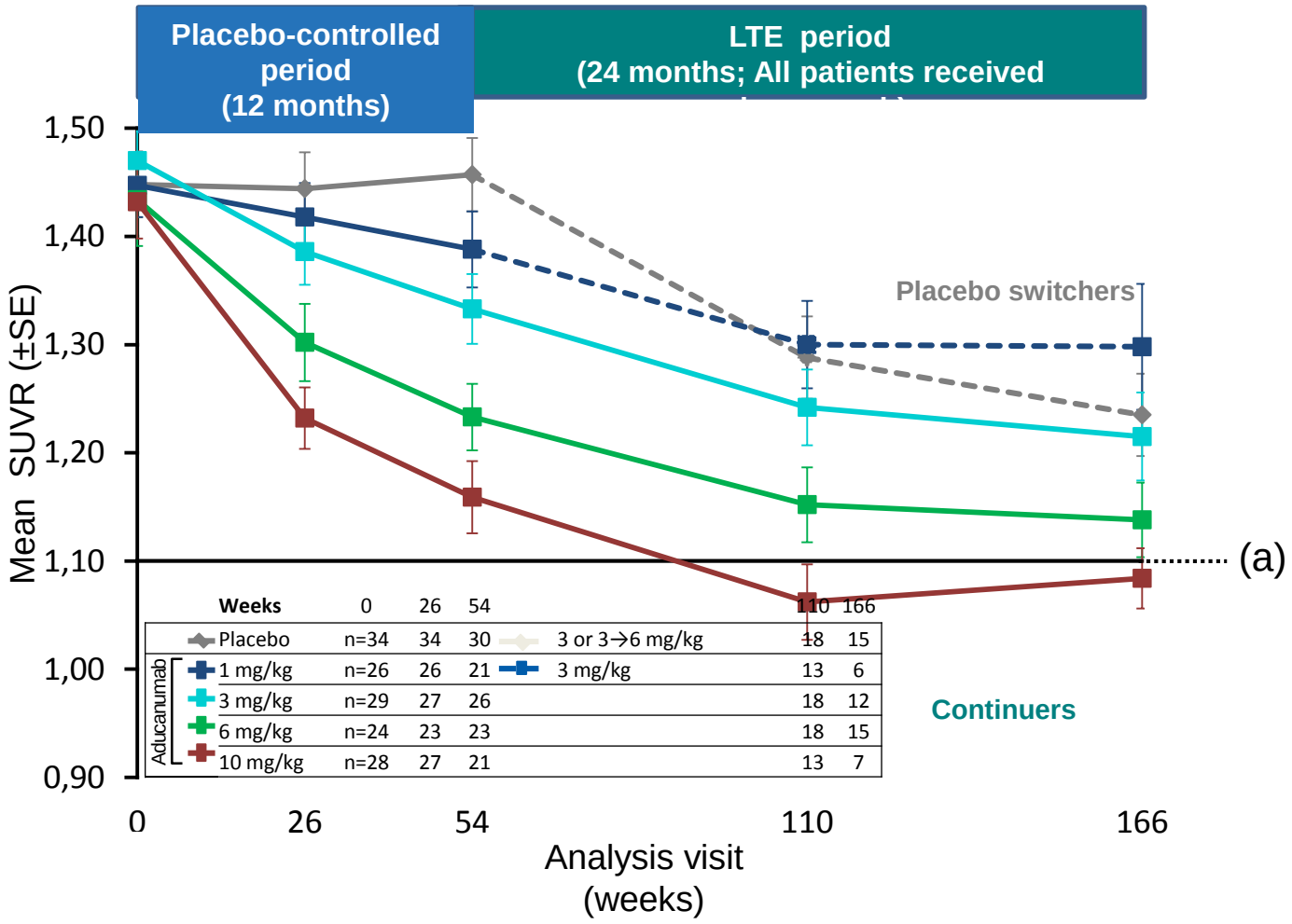
CDR-SB is an exploratory endpoint. Results based on MMRM, fitted with change from baseline as a dependent variable, and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction, continuous baseline value, and laboratory ApoE ε4 status (carrier and non-carrier). CDR-SB, Clinical Dementia Rating–Sum of Boxes; LTE, long-term extension; MMRM, mixed model for repeated measures; SE, standard error.

Effect of Aducanumab on Clinical Decline as Measured by MMSE (Exploratory Endpoint)



Nominal *P<0.05 vs placebo in the placebo-controlled period and vs placebo switchers in the LTE period. MMSE is an exploratory endpoint. Results based on MMRM, fitted with change from baseline as a dependent variable, and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction, continuous baseline value, and laboratory ApoE ε4 status (carrier and non-carrier). LTE, long-term extension; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Exam; SE, standard error.

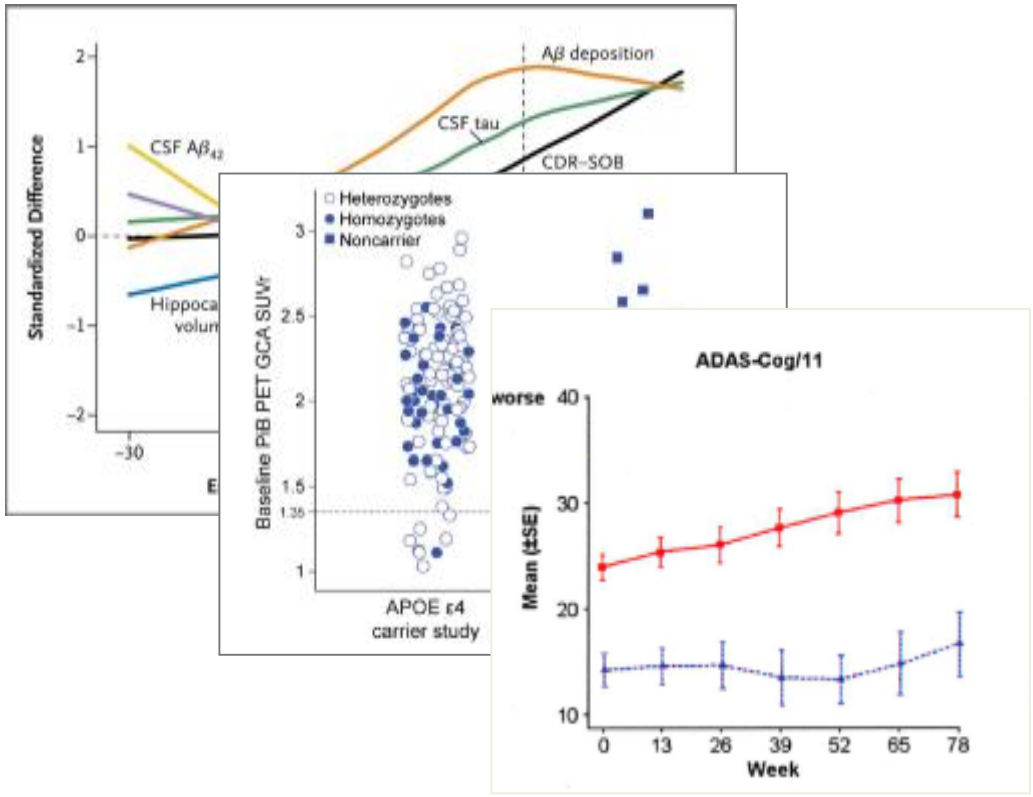
Effect of Aducanumab on Amyloid Plaque Levels



[a]The value of 1.10 has been used as a quantitative cut-point that discriminates between positive and negative scans[1,2]

1. Landau SM, et al. Ann Neurol. 2012;72:578–586; 2. Joshi A et al. J Nucl Med. 2012; 53:378–384. LTE, long-term extension; SUVR, standardized uptake value ratio.

What have we learnt from clinical trial about Alzheimer disease?

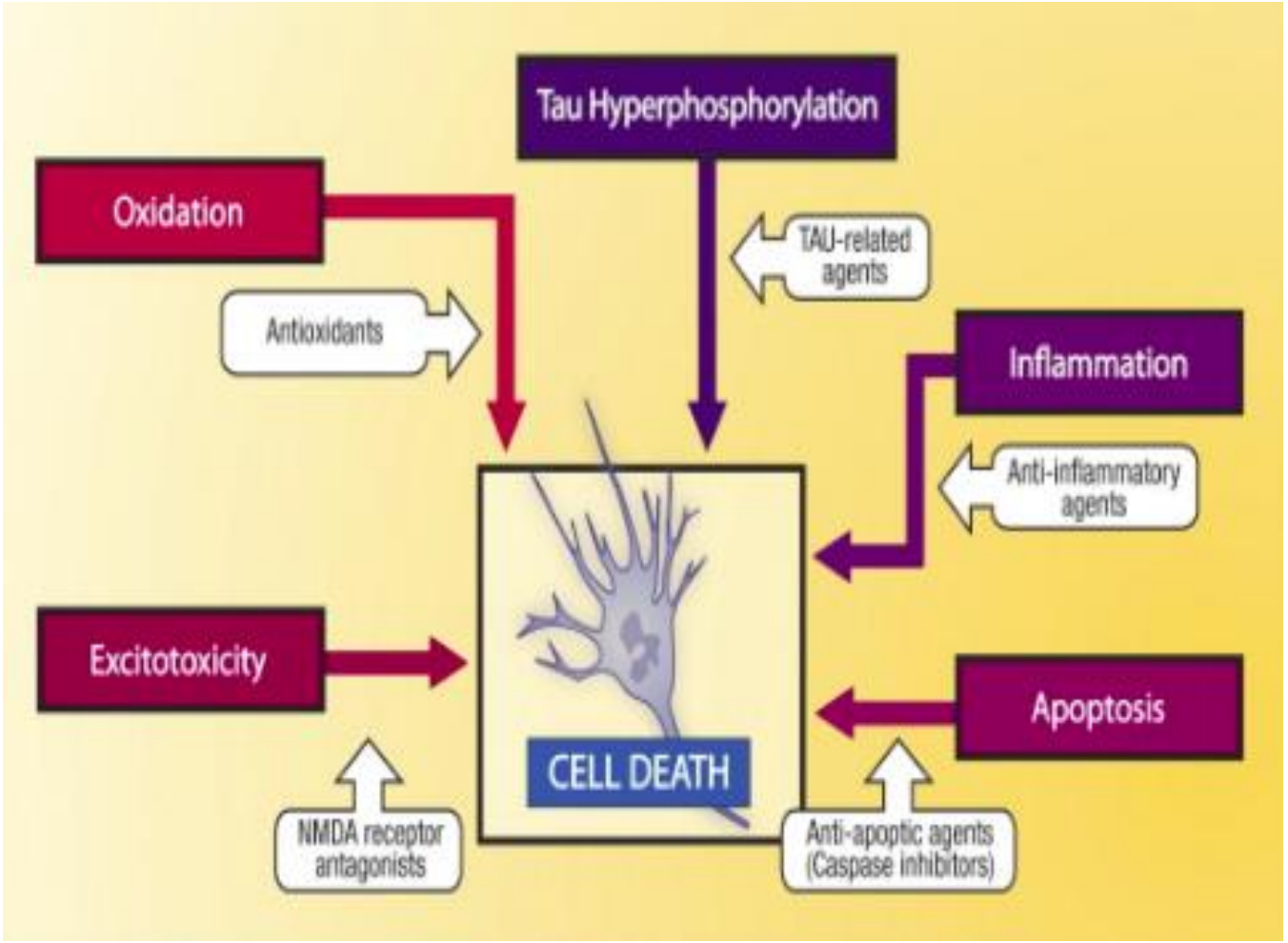


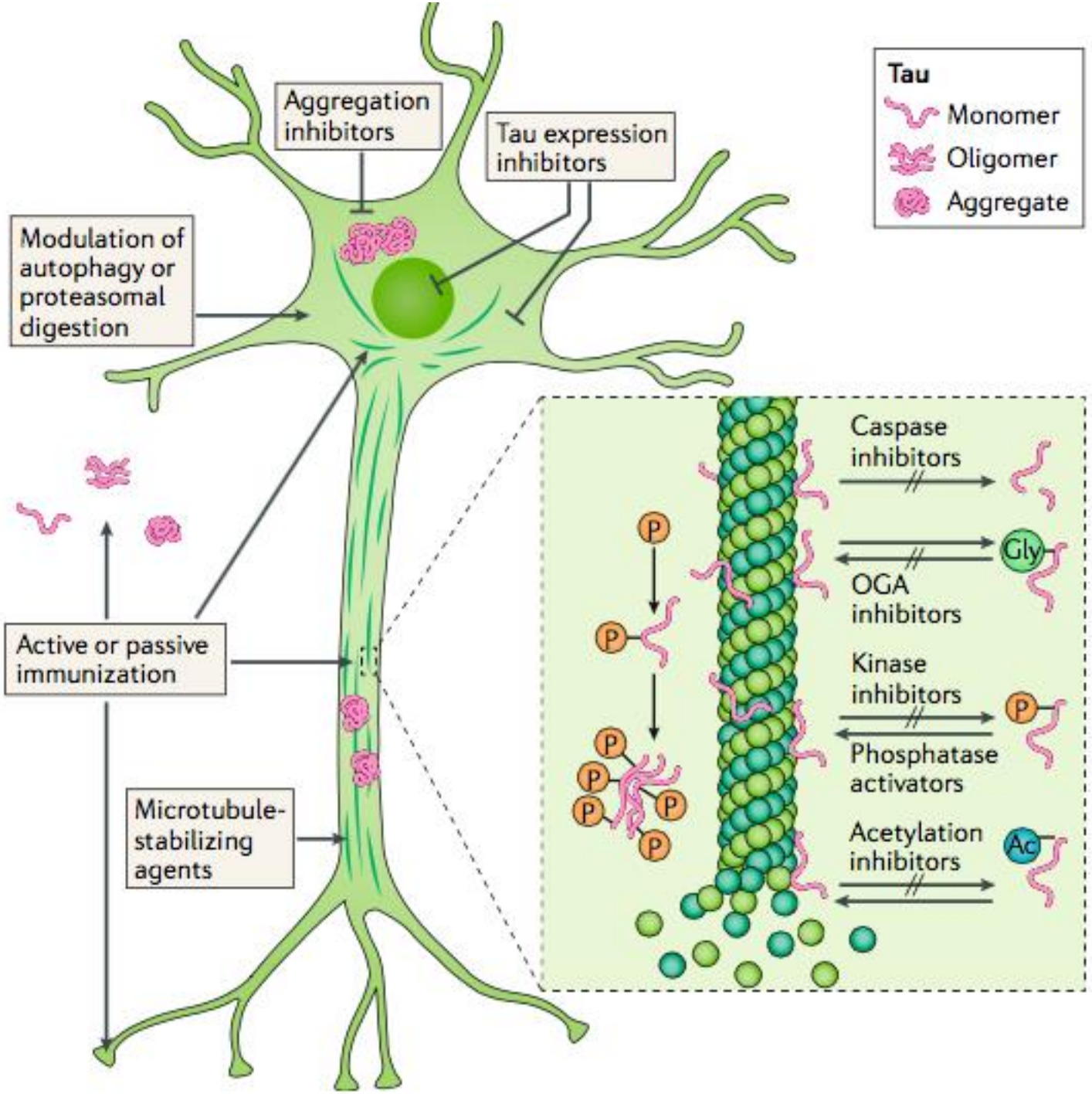
- Biomarkers tell us that Alzheimer's starts many years prior to the appearance of symptoms
- In previous Phase 3 studies, patients were enrolled without evidence of amyloid pathology (Alzheimer's pathogenesis)
- The presence of pathology defines different baseline scores and trajectories for cognitive and functional decline in Ab+ and Ab- subjects.

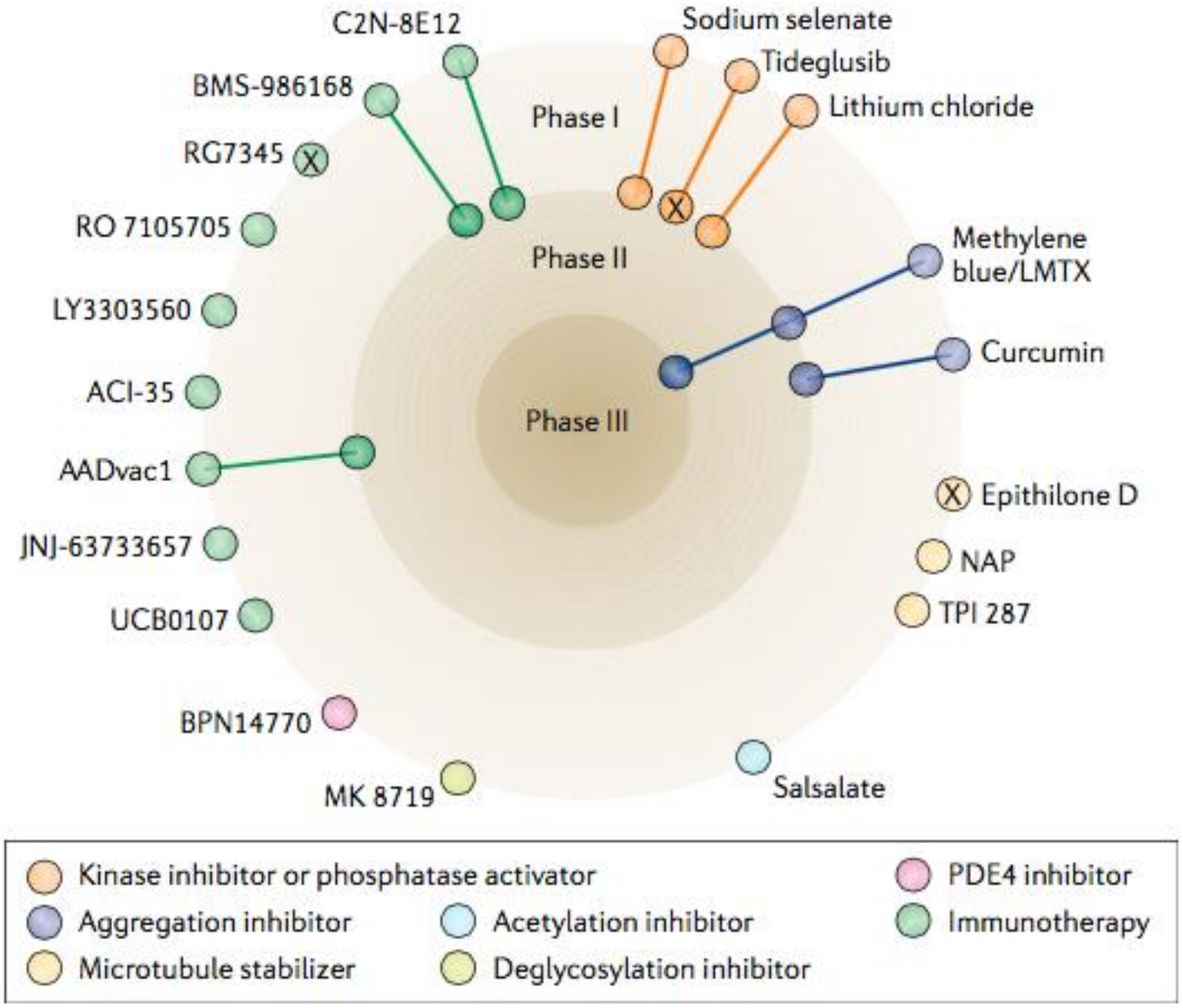
Bateman B et al NEJM 2012;367(9):795–804, Liu E et al Neurology 2015;85(8):692–700; Salloway S et al. Alzheimers Dement 2013;9(4):P888–P889

DOVE STIAMO ANDANDO?

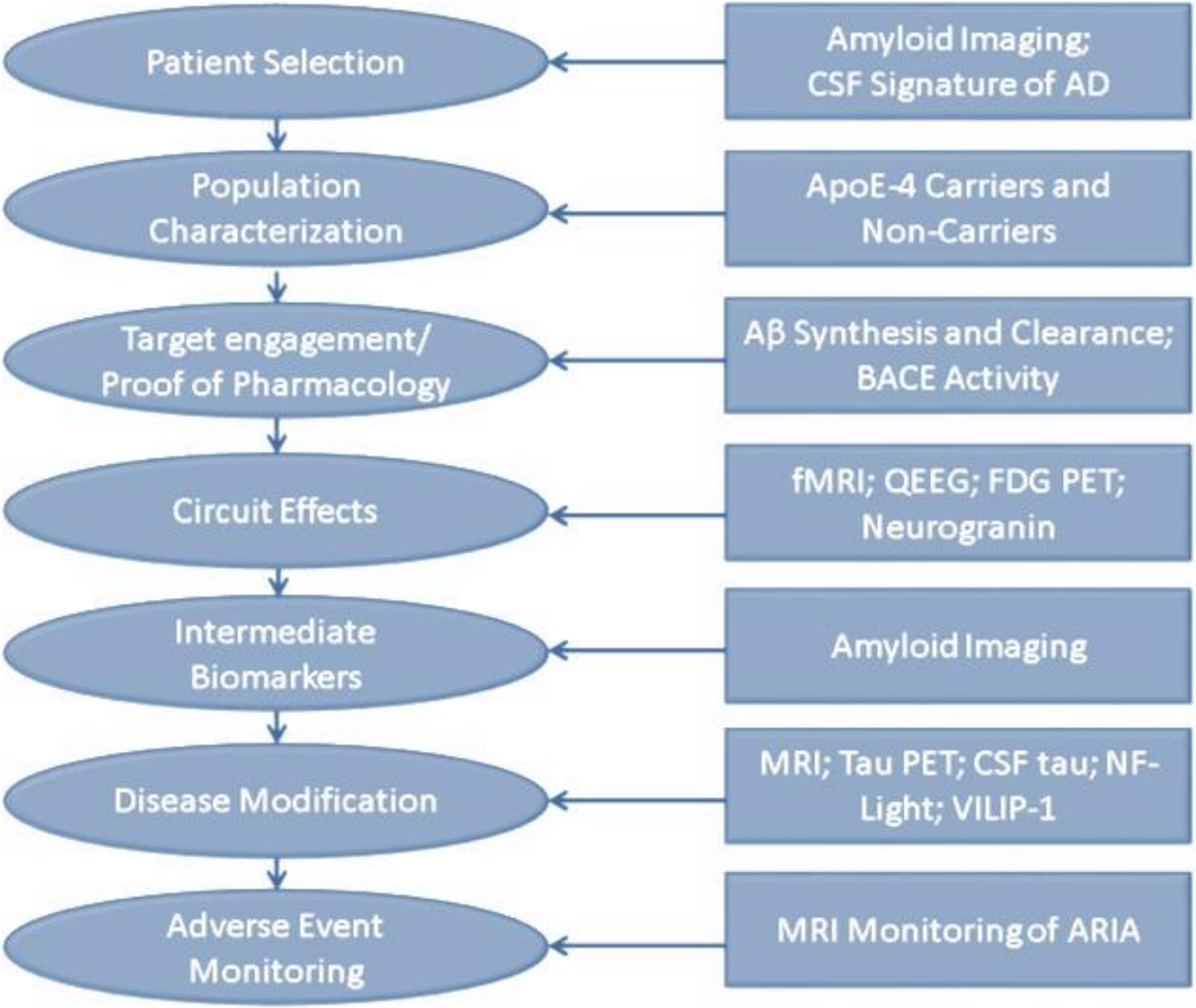
NUOVI FARMACI PER APPROCCI COMBINATI


Tau Hyperphosphorylation
Oxidation
TAU-related agents
Antioxidants
Inflammation
Anti-inflammatory agents
Excitotoxicity
Apoptosis
CELL DEATH
NMDA receptor antagonists
Anti-apoptic agents (Caspase inhibitors)


Tau
Monomer
Oligomer
Aggregate
Aggregation inhibitors
Tau expression inhibitors
Modulation of autophagy or proteasomal digestion
Active or passive immunization
Microtubule-stabilizing agents
Caspase inhibitors
Gly
OGA inhibitors
Kinase inhibitors
Phosphatase activators
Acetylation inhibitors
Ac
P


C2N-8E12
BMS-986168
RG7345
RO 7105705
LY3303560
ACI-35
AADvac1
JNJ-63733657
UCB0107
BPN14770
MK 8719
Sodium selenate
Tideglusib
Lithium chloride
Phase I
Phase II
Phase III
Methylene blue/LMTX
Curcumin
Epithilone D
NAP
TPI 287
Salsalate
Kinase inhibitor or phosphatase activator
Aggregation inhibitor
Microtubule stabilizer
Acetylation inhibitor
Deglycosylation inhibitor
PDE4 inhibitor
Immunotherapy

NUOVI MARCATORI PER SELEZIONARE E MONITORARE L'IMPATTO DELLE TERAPIE


Patient Selection
Amyloid Imaging; CSF Signature of AD
Population Characterization
ApoE-4 Carriers and Non-Carriers
Target engagement/ Proof of Pharmacology
Aβ Synthesis and Clearance; BACE Activity
Circuit Effects
fMRI; QEEG; FDG PET; Neurogranin
Intermediate Biomarkers
Amyloid Imaging
Disease Modification
MRI; Tau PET; CSF tau; NF-Light; VILIP-1
Adverse Event Monitoring
MRI Monitoring of ARIA

Biomarkers as outcome measures in phase II and phase III trials for agents in the Alzheimer's disease drug development pipeline (clinicaltrials.gov; 6/5/2017)

Biomarker	N of trials (%)	
	Phase III	Phase II
CSF amyloid	12 (28.6)	17 (25.0)
CSF tau	13 (31.0)	16 (23.5)
FDG-PET	5 (11.9)	10 (14.7)
vMRI	9 (21.4)	6 (8.8)
Plasma amyloid	4 (9.5)	5 (7.4)
Plasma tau	0	1 (1.5)
Amyloid PET	13 (31.0)	6 (8.8)
Tau PET	1 (2.4)	0

INTERVENTI PRECOCI

Cognitively Normal	Episodic Memory Impairment	Dementia
Functionally Normal	Functionally Normal	Functionally Impaired
+ Amyloid Imaging; AD CSF Signature	+ Amyloid Imaging; AD CSF Signature	+ Amyloid Imaging; AD CSF Signature
MRI Normal	MRI Atrophy	MRI Marked Atrophy
Prevent/Delay Cognitive Decline	Prevent Progression to AD Dementia	Slow Progression of AD Dementia

Outcome tools used for the progressive phases of Alzheimer's disease [39, 40, 63–70]

Feature	Preclinical AD	Prodromal AD	AD Dementia
Cognition	Preclinical Alzheimer Cognitive Composite (PACC); Alzheimer Prevention Initiative Cognitive Composite (APCC) Test	Clinical Dementia Rating- Sum of Boxes (CDR-sb); AD Composite Score (ADCOMS); Integrated AD Rating Scale (iADRS)	Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog); Severe Impairment Battery (SIB); Neuropsychological Test Battery (NTB)
Function	None	Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS ADL) Scale, Mild Cognitive Impairment (MCI)	Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS ADL) Scale; Disability Assessment for Dementia (DAD)
Trial Outcome	Drug-placebo difference in biomarker considered reasonably likely to predict clinical benefit; Reduction in cognitive decline compared to placebo	Drug-placebo difference in a composite outcome plus biomarker outcomes supportive of disease modification (composite differences between drug and placebo should not be due exclusively to cognitive benefits of therapy)	Drug-placebo difference in dual cognitive and functional or global outcomes plus biomarker outcomes supportive of disease modification

CARATTERIZZAZIONE DEL MALATO

ALZHEIMER'S DISEASE

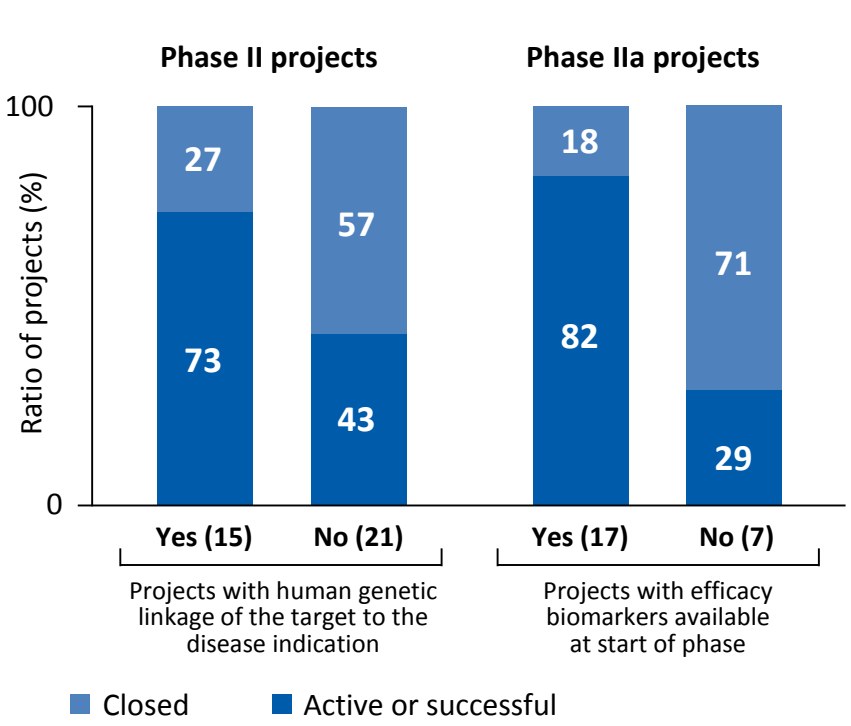
Testing the Right Target and Right Drug at the Right Stage

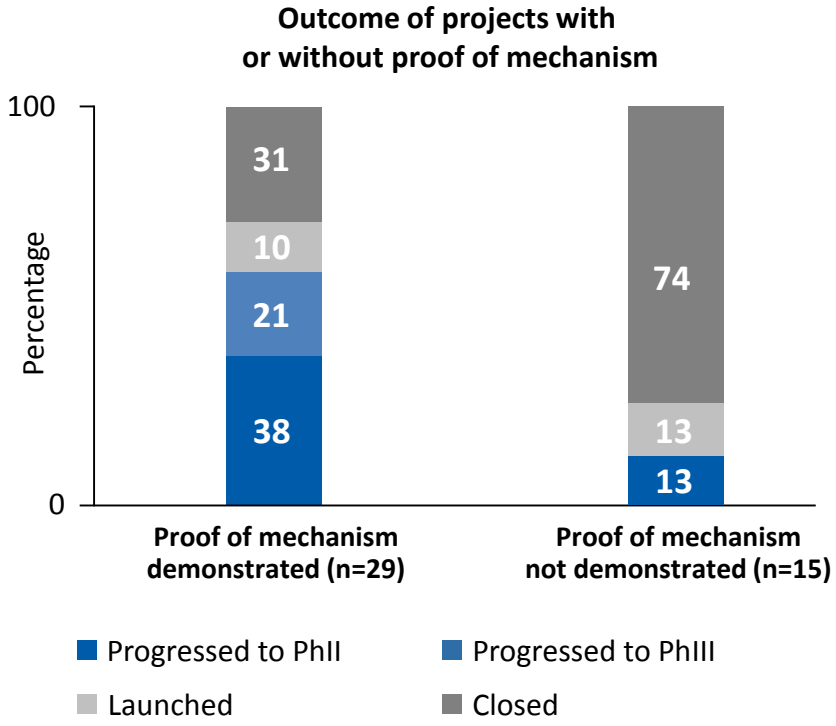
Reisa A. Sperling,[1*] Clifford R. Jack Jr.,[2] Paul S. Aisen[3]

Alzheimer's disease (AD) is the only leading cause of death for which no disease-modifying therapy is currently available. Recent disappointing trial results at the dementia stage of AD have raised multiple questions about our current approaches to the development of disease-modifying agents. Converging evidence suggests that the pathophysiological process of AD begins many years before the onset of dementia. So why do we keep testing drugs aimed at the initial stages of the disease process in patients at the end-stage of the illness?

Key factors important to project progression in clinical phase

- Human genetic data is more common in projects that succeed vs fail in PhII
- Successful projects are more likely to have biomarkers (82 vs 30%)[1]
- Proof of Mechanism – quantifiable target engagement has a positive impact on progression to PhII (38%), PhIII (21%) or launch (10%)[2]





1. Cook et al 2014 Nat Rev Drug Disc; 2. Morgan P et al. Nat Rev Drug Disc 2018;17:167–181

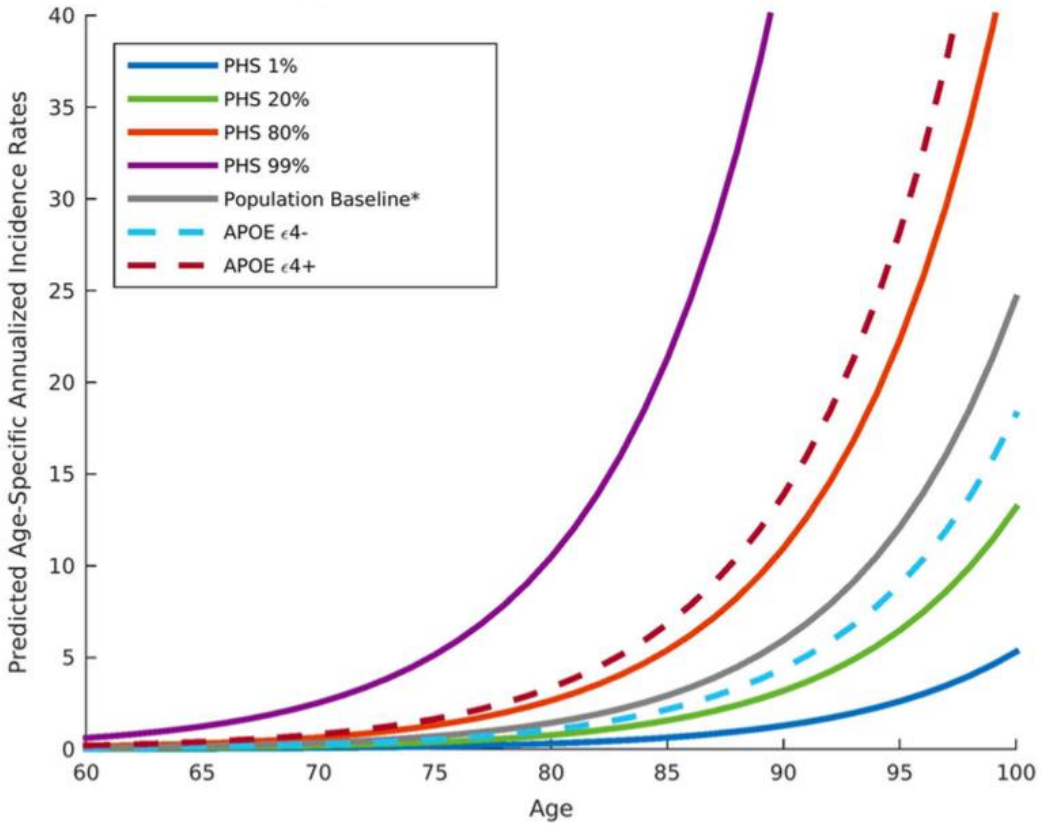
AD-ITA-0016
Date of preparation: March 2018

RESEARCH ARTICLE

Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score

PLOS Medicine | DOI:10.1371/journal.pmed.1002258

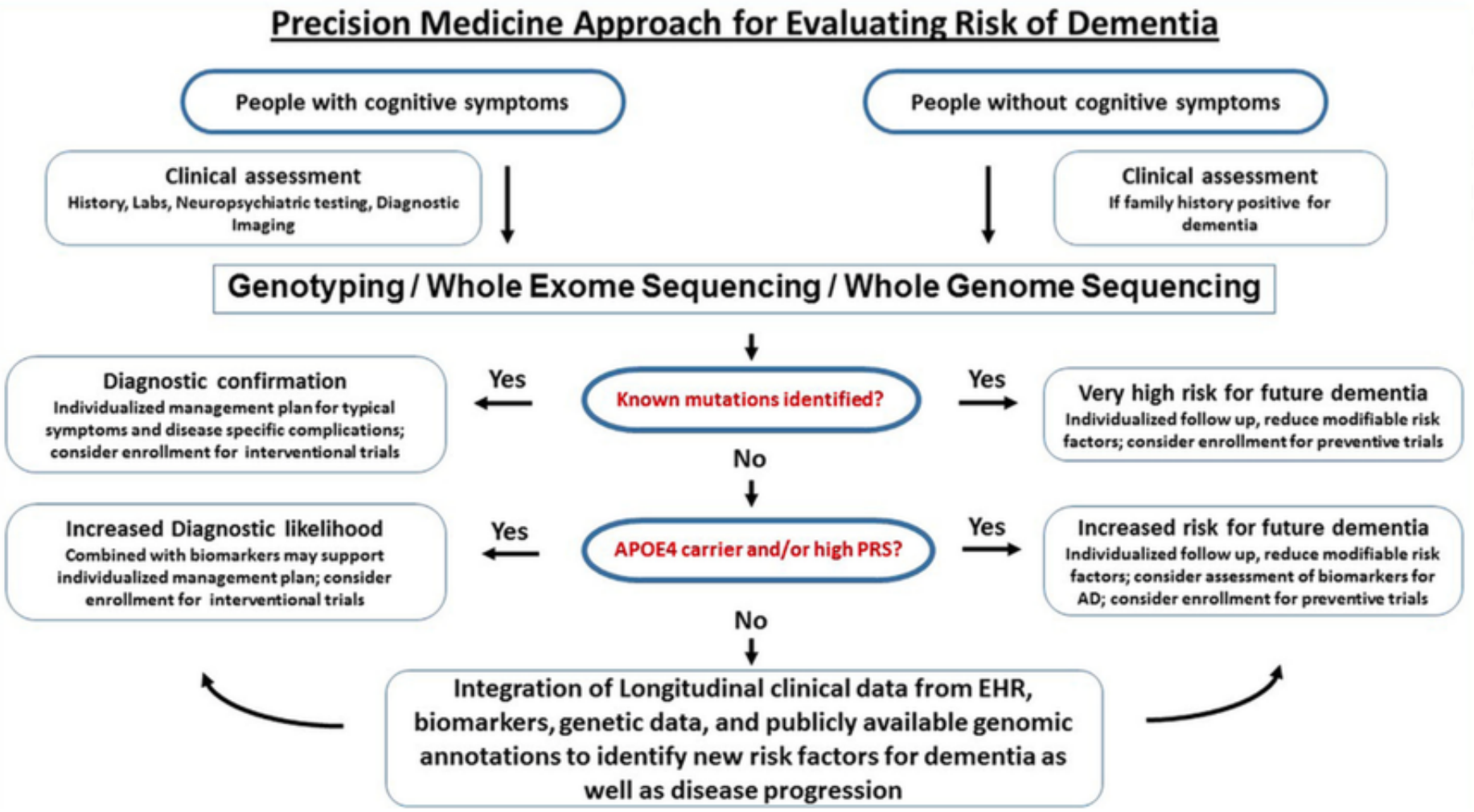
March 21, 2017



The Role of Genetics in Advancing Precision Medicine for Alzheimer's Disease—A Narrative Review

Yun Freudenberg-Hua[1,2], Wentian Li[3] and Peter Davies[1]*

[1] Litwin-Zucker Center for the study of Alzheimer's Disease, The Feinstein Institute for Medical Research, Northwell Health, Manhasset, NY, United States, [2] Division of Geriatric Psychiatry, Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, United States, [3] Robert S Boas Center for Genomics and Human Genetics, The Feinstein Institute for Medical Research, Northwell Health, Manhasset, NY, United States



The BIOCARD Index

A Summary Measure to Predict Onset of Mild Cognitive Impairment

Ned Sacktor, MD, Anja Soldan, PhD,* Maura Grega, RN,† Leonie Farrington, RN,* Qing Cai, BS,‡ Mei-Cheng Wang, PhD,‡ Rebecca F. Gottesman, MD, PhD,* Raymond S. Turner, MD,§ Marilyn Albert, PhD,* and the BIOCARD Research Team*

Alzheimer Dis Assoc Disord 2017;31:114–119

BIOCARD Index

Patient		
Have you notice changes with your memory recently?	Yes	0
	No	1
Do you feel sad or depressed	Yes	0
	No	1
Age	≥ 90	0
	80-89	1
	70-79	2
	60-69	3
	≤ 59	4
Education	<High School	0
	High School	1
	>High School	2
History of Hypertension	Yes	0
	No	1
History of Diabetes	Yes	0
	No	1
History of Hypercholesterolemia	Yes	0
	No	1
History of Heart disease	Yes	0
	No	1
History of Stroke or Transient Ischemic Attack (TIA)	Yes-Stroke	0
	Yes-TIA	1
	No	2
Have you smoked in the past 30 days?	Yes	0
	No	1
Any traumatic brain injury with a chronic deficit?	Yes	0
	No	1
Any family member with dementia?	Yes	0
	No	1
Mini-Mental Status Exam (MMSE) score	≤ 22	0
	23	1
	24	2
	25	3
	26	4
	27	5
	28	6
	29	7
	30	8
Informant		
Have you noticed changes with memory in the patient?	Yes	0
	No	1
Any changes in the patient's ability to perform finances?	Yes	0
	No	1
Any changes in the patient's ability to perform shopping tasks	Yes	0
	No	1
Any changes in the patient's ability to remember appointments, holidays, or medications?	Yes	0
	No	1
BIOCARD Index Total Score		= _____
		(Range 0-29)

TABLE 2. Participant Characteristics at Baseline Stratified by Trial Outcome

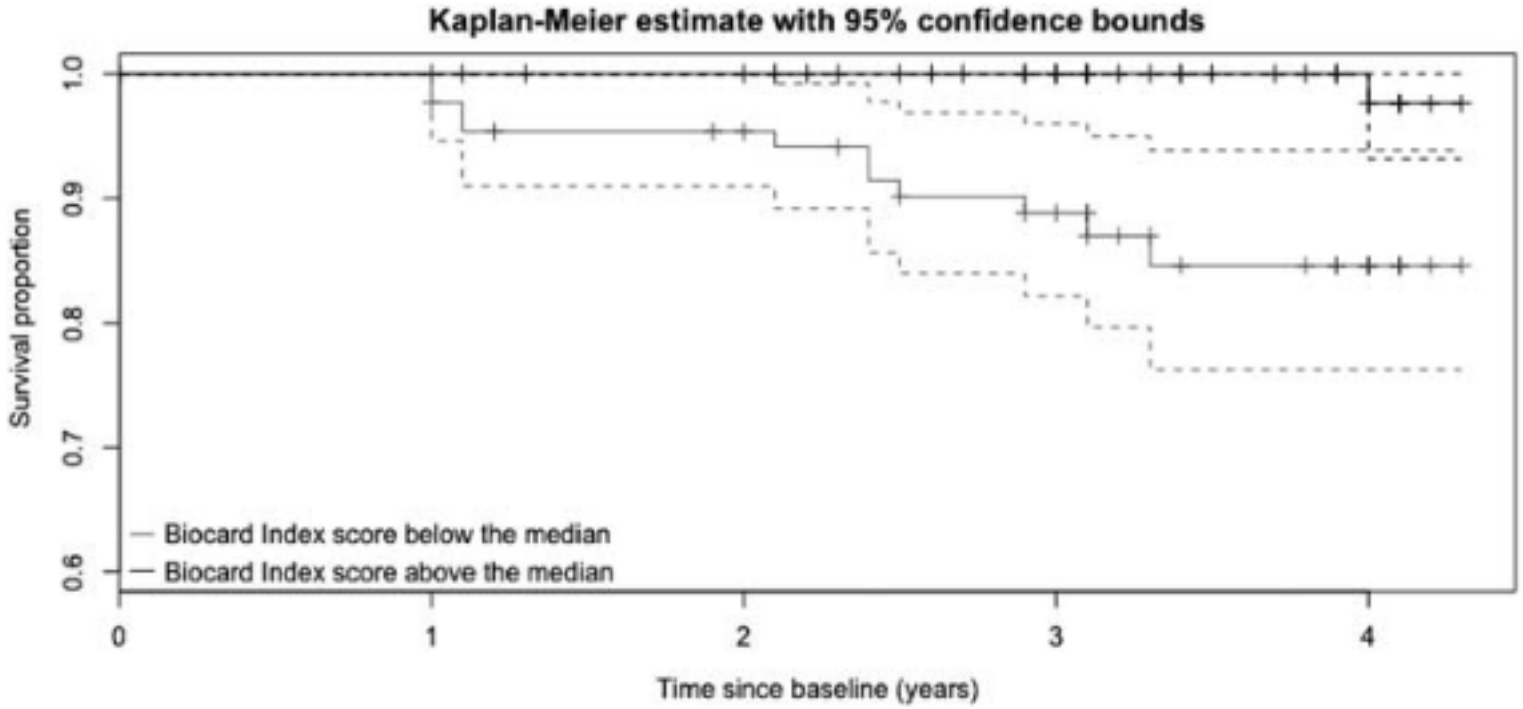
	Remained Normal (n = 210)	Progressed to MCI (n = 12)
Age (y) [mean (SD)]	63.6 (9.5)	75.0 (5.9)**
Education (y) [mean (SD)]	17.3 (2.2)	15.8 (3.1)
Sex, female (%)	62.9	33.3*
Ethnicity, white (%)	99.0	100.0
Hypertension (%)	35.2	58.3
Diabetes (%)	7.1	33.3**
Hypercholesterolemia (%)	49.5	66.7
Heart disease (%)	10.0	41.7**
Stroke or TIA (%)	5.7	16.7
Smoking (%)	4.8	0
Traumatic brain injury (%)	22.4	0
APOE4 carriers (%)	31.9	16.7
MMSE [mean (SD)]	29.3 (1.0)	28.3 (1.7)
BIOCARD Index score [mean (SD)]	24.8 (2.3)	20.3 (2.9)

Significant differences between the group who remained normal and the group who progressed are indicated by asterisks.

APOE4 indicates Apolipoprotein E4; MCI, mild cognitive impairment; MMSE, Mini-Mental State examination.

*$P < 0.05$.

**$P < 0.01$.


Kaplan-Meier estimate with 95% confidence bounds
Survival proportion
1.0
0.9
0.8
0.7
0.6
Biocard Index score below the median
Biocard Index score above the median
0
1
2
3
4
Time since baseline (years)

Original Investigation

Predicting Aggressive Decline in Mild Cognitive Impairment
The Importance of White Matter Hyperintensities

Giuseppe Tosto, MD; Molly E. Zimmerman, PhD; Owen T. Carmichael, PhD; Adam M. Brickman, PhD; for the Alzheimer's Disease Neuroimaging Initiative

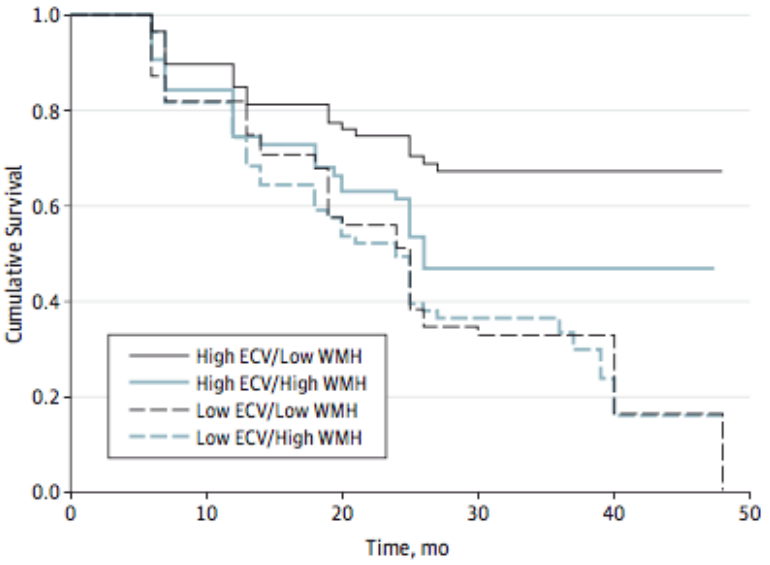
JAMA Neurol. 2014;71(7):872-877.

Table 1. Patient Demographics

Demographic	ADNI Patients With MCI (N = 332)
Male/Female, No.	219/118
Age at baseline, mean (SD), y	74.6 (7.4)
Education, mean (SD), y	15.6 (3)
Any APOE ε4, %	52.5
White matter hyperintensity (log10 transformed), mean (SD)	−0.56 (0.67)
Entorhinal cortex volume, mean (SD), mm^3	1650.46 (385)
Patients matching rapid progression definition, %	49

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein E; MCI, mild cognitive impairment.

Figure 2. Cumulative Survival of Individuals With High and Low White Matter Hyperintensity (WMH) as a Function of Entorhinal Cortex Volume (ECV)



The figure contrasts the 4 groups. Groups were defined by median split. The clinical event was defined as a decline of 3 points over 6 months or 6 points over 1 year on the Mini-Mental State Examination. Both WMH and ECV were related to clinical outcome; the 2 predictors interacted such that individuals with high ECV and low WMH were at particularly low likelihood of decline.

Table 5. Comparison of Classic Alzheimer Disease (AD) and Rapidly Progressive AD

Variable	Rapidly Progressive AD	Classic AD
Survival	Few (2-3 y)	8-10 y
Age at onset	Unclear, approximately age 73 y in the study by Schmidt et al[8]	Approximately age 65 y (<65 y is early onset, ≥65 y is late onset)
Rate of cognitive decline	>6 MMSE points per year (ie, fast)	Approximately 3-6 MMSE points per year (ie, slow)
Focal neurologic signs	Occurring in early stages, multiple (especially extrapyramidal signs)	Occurring in late stages
CSF biomarkers	Very high total tau and ptau levels, very low Aβ1-42 level, 14-3-3 protein sometimes present (exact values unclear)	High total tau and ptau levels, low Aβ1-42 level, 14-3-3 protein usually absent
APOE ε4 genotype	Controversial: see Table 4 for its influence on decline; sometimes absent in rapid cases[8]	Established as a risk factor

Short Report

Consensus-based recommendations for the management of rapid cognitive decline due to Alzheimer's disease

Jianping Jia[a,*], Serge Gauthier[b,**], Sarah Pallotta[c], Yong Ji[d], Wenshi Wei[e], Shifu Xiao[f], Dantao Peng[g], Qihao Guo[h], Liyong Wu[a], Shengdi Chen[i], Weihong Kuang[j], Junjian Zhang[k], Cuibai Wei[a], Yi Tang[a]

J. Jia et al. / Alzheimer's & Dementia 13 (2017) 592-597

Proposed rapid decline risk score in patients with dementia due to AD

Risk factor	Relative weight based on current evidence
MMSE score <20 at onset of treatment	3
Vascular risk factors	2
Early appearance of hallucinations and psychosis	2
Early appearance of extrapyramidal symptoms	2
Higher education	1
Younger than 70 years at onset of symptoms	1

Abbreviations: AD, Alzheimer's disease; MMSE, Mini-Mental State Examination.

PREPARING THE SYSTEM

Ritchie *et al. Alzheimer's Research & Therapy* (2017) 9:85
DOI 10.1186/s13195-017-0312-4

Alzheimer's
Research & Therapy

COMMENTARY Open Access

The Edinburgh Consensus: preparing for the advent of disease-modifying therapies for Alzheimer's disease

Craig W. Ritchie[1,2*†], Tom C. Russ[1,2,3,4†], Sube Banerjee[5], Bob Barber[6], Andrew Boaden[7], Nick C. Fox[8], Clive Holmes[9], Jeremy D. Isaacs[10], Ira Leroi[11], Simon Lovestone[12], Matt Norton[13], John O'Brien[14], Jim Pearson[15], Richard Perry[16], James Pickett[7], Adam D. Waldman[18], Wai Lup Wong[17], Martin N. Rossor[8†] and Alistair Burns[11†]

Consensus conclusions

- Healthcare systems will need to **identify and engage with prodromal and preclinical populations** who might benefit from such interventions. These people may not be in contact with health services or, if they are, this will not be because of Alzheimer's disease.

- Diagnosis, eligibility, and perhaps IOT monitoring of treatment efficacy will require diagnostics to demonstrate **evidence of cerebral amyloidosis** as an example of precision medicine.

- **Realistic planning is needed now to direct the evolution of services to optimise appropriate patient access and prepare protocols for phase IV testing of these treatments to inform real world practice and commissioning decisions**.

18 CENTRI

CHIARI, ESINE, LENO, PALAZZOLO, POLIAMBULANZA, SALO‘, SANT'ANNA, SPEDALI CIVILI (Brescia)
NEUROLOGIA, SAN CAMILLO,SOSPIRO (Cremona)
MAUGERI, MAZZALI (Mantova)
GAVAZZENI, GAZZANIGA, SAN FRANCESCO, VERTOVA (Bergamo)

Caratteristiche socio demografiche di un campione di 1201 soggetti afferiti presso CDCD Lombardia orientale nel mese di ottobre.

	Media	DS	N (%)
Età (anni)	80,5	6,8	
Sesso (f)			769 (64%)
Scolarità anni	6,3	3,0	
MMSE (0-30)	18,6	6,9	
IADL mantenute (0-8)	2,9	2,9	
BADL mantenute (0-6)	4,0	2,1	
GDS (0-15)	3,8	3,7	
NPI totale (0-144)	12,8	12,2	

Caratteristiche socio demografiche di un campione di 289 soggetti afferiti per I Visita presso CDCD Lombardia orientale nel mese di ottobre.

	Media	DS	N (%)
Età (anni)	79,7	7,8	
Sesso (f)			169 (64%)
Scolarità anni	6,8	3,3	
MMSE (0-30)	20,9	6,4	
IADL mantenute (0-8)	4	2,9	
BADL mantenute (0-6)	4,4	1,8	
GDS (0-15)	4,15	4,3	
NPI totale (0-144)	12,8	12,2	

Gravità di malattia (CDR 0-5) di un campione di 289 soggetti afferiti presso CDCD Lombardia orientale

CDR	Frequenza	Percentuale
0	27	9.3
0,5	85	29,4
1	77	26.6
2	66	22.8
3	27	9.3
4	6	2,1
5	1	0,3

Prevalenza di pazienti (240) con sintomatologia depressiva valutata con la GDS (GDS ≥5 indica depressione).

	Frequenza	Percentuale
Non depressi	147	61
Depressi	93	43

GRAZIE PER L’ATTENZIONE

Study duration for each subject participating in the placebo-controlled period only will be approximately 102 weeks (up to an 8-week screening period, 76 weeks of placebo or MoABdosing, and 18 weeks of follow-up [FU]).

For subjects who enter the optional LTE period, the total study duration will be approximately 206 weeks or 47 months (up to an 8-week screening period, 76 weeks of placebo or aducanumab dosing, and 4 weeks of FU, plus an optional LTE period including 100 weeks of dose-blind aducanumab dosing and 18 weeks of FU).

Inclusion Criteria

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance
with national and local subject privacy regulations.

2. Aged 50 to 85 years old, inclusive, at the time of informed consent.

3. All women of childbearing potential and all men must practice highly effective contraception during the study and for 24 weeks after their last dose of study treatment.

4. Must have at least 6 years of education or work experience to exclude mental deficits other than MCI or mild AD.

5. Must have a positive amyloid PET scan. Previously obtained PET scan (within 12 months of Screening) is permissible for subjects not participating in the amyloid PET
substudy. Previous PET scan images must be submitted to the central imaging vendor to confirm study inclusion criteria are met.

6. Must meet all of the following clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria [Albert 2011; McKhann 2011], and must have:
- A CDR global score of 0.5.
- An RBANS score of 85 or lower indicative of objective cognitive impairment (based upon the Delayed Memory Index score).
- An MMSE score between 24 and 30 (inclusive).

7. Apart from a clinical diagnosis of early AD, the subject must be in good health as determined by the Investigator, based on medical history and screening assessments.

8. Must consent to ApoE genotyping.

9. Has one informant/care partner who, in the Investigator's opinion, has frequent and sufficient contact with the subject as to be able to provide accurate information about the subject's cognitive and functional abilities. The informant/care partner must minimally be available by phone to provide information to the Investigator and study staff about the subject and agrees to attend in person clinic visits that require partner input for scale completion. An informant/care partner should be available for the duration of the study, and the use of the same informant/care partner for the duration of the study is encouraged.

Exclusion Criteria

Medical History

1. Any uncontrolled medical or neurological/neurodegenerative condition (other than AD) that, in the opinion of the Investigator, might be a contributing cause of the subject's
cognitive impairment (e.g., substance abuse, vitamin B12 deficiency, abnormal thyroid function, stroke or other cerebrovascular condition, Lewy body dementia, fronto-temporal dementia, head trauma).

2. Clinically significant unstable psychiatric illness (e.g., uncontrolled major depression, uncontrolled schizophrenia, uncontrolled bipolar affective disorder) within 6 months
prior to Screening.

3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening.

4. Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following:
-Acute or sub-acute hemorrhage.
- Prior macrohemorrhage (defined as □1 cm in diameter on T2* sequence) or prior subarachnoid hemorrhage unless it can be documented that the finding is not due to an underlying structural or vascular abnormality (i.e., finding does not suggest subject is at risk of recurrent hemorrhage).
- Greater than 4 microhemorrhages (defined as □1 cm in diameter on T2* sequence).
- Cortical infarct (defined as >1.5 cm in diameter).
- 1 lacunar infarct (defined as □1.5 cm in diameter).
- Superficial siderosis.
- History of diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scale [Wahlund 2001].
- Any finding that, in the opinion of the Investigator, might be a contributing cause of subject's dementia, might pose a risk to the subject, or might prevent a satisfactory MRI assessment for safety monitoring.

5. History of bleeding disorder or predisposing conditions, blood clotting or clinically significant abnormal results on coagulation profile at Screening, as determined by the
Investigator.

6. Presence of diabetes mellitus that, in the judgment of the Investigator, cannot be controlled or adequately managed.

7. History of unstable angina, myocardial infarction, chronic heart failure (New York Heart Association Class III or IV), or clinically significant conduction abnormalities (e.g.,
unstable atrial fibrillation) within 1 year prior to Screening.

8. Clinically significant 12-lead ECG abnormalities, as determined by the Investigator.

9. Uncontrolled hypertension defined as: average of 3 systolic blood pressure [SBP]/diastolic blood pressure [DBP] readings >165 mmHg and/or >100 mmHg at Screening (blood pressure measurements exceeding these limits may be repeated as warranted by the Investigator, but values must be within the specified limits for the subject to be eligible for the study), or persistent SBP/DBP readings >180 mmHg and/or >100 mmHg 3 months prior to randomization (Day 1) that, in the opinion of the Investigator, are indicative of chronic uncontrolled hypertension.

Exclusion Criteria

10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:

- Subjects with cancers in remission more than 5 years prior to Screening.
- Subjects with a history of excised or treated basal cell or squamous carcinoma of the skin.
- Subjects with localized prostate cancer with treatment cycles that completed at least 6 months prior to Screening.

11. History of seizure within 10 years prior to Screening.

12. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≥ 2 × the upper limit of normal).

13. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.

14. Recent history (within 1 year of Screening) of alcohol or substance abuse as determined by the Investigator, a positive urine drug (due to non-prescription drug) or alcohol test at Screening, or use of cannabinoids (prescription or recreational).

15. Clinically significant systemic illness or serious infection (e.g., pneumonia, septicemia) within 30 days prior to or during Screening.

16. History of or known seropositivity for human immunodeficiency virus (HIV).

17. History of or positive test result at Screening for hepatitis C virus antibody or hepatitis B virus (defined as positive for both hepatitis B surface antigen AND hepatitis B core antibody).

18. History of severe allergic or anaphylactic reactions, or history of hypersensitivity to any of the inactive ingredients in the drug product (refer to the IB for information on the clinical formulation).

19. Any other medical conditions (e.g., renal disease) that are not stable or controlled, or, which in the opinion of the Investigator, could affect the subject’s safety or interfere with the study assessments.

Exclusion Criteria

20. Any medications that, in the opinion of the Investigator, may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to
perform cognitive testing or complete study procedures.

21. Use of allowed chronic medications at doses that have not been stable for at least 4 weeks prior to Screening Visit 1 or use of AD medications (including but not limited to donepezil, rivastigmine, galantamine, tacrine, and memantine) at doses that have not been stable for at least 8 weeks prior to Screening Visit 1.

22. Use of medications with platelet anti-aggregant or anti-coagulant properties (the use of aspirin at a prophylactic dose [≤ 325 mg daily] is allowed).

23. Use of illicit narcotic medication.

24. Vaccinations within 10 days prior to randomization (Day 1).

25. Participation in any active immunotherapy study targeting Aβ unless documentation of receipt of placebo is available.

26. Participation in any passive immunotherapy study targeting Aβ within 12 months of Screening unless documentation of receipt of placebo is available.

27. Participation in any study with purported disease-modifying effect in AD within 12 months prior to Screening unless documentation of receipt of placebo is available.
Subjects who developed ARIA-E during a previous disease-modifying trial should be excluded.

28. Participation in a previous study with aducanumab (subject is eligible if he/she did not receive active aducanumab).

Study Procedures
29. Contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia that cannot be medically managed).

30. Contraindication to having a PET scan (e.g., inability to lie flat or still for the duration of the scan) or intolerance to previous PET scans (i.e., previous hypersensitivity reactions to any PET ligand or imaging agent, failure to participate in and comply with previous PET scans).

31. A negative PET scan result with any amyloid-targeting ligand within 6 months prior to

Exclusion Criteria

Screening.

32. Have had or plan exposure to experimental radiation within 12 months prior to Screening such that radiodosimetry limits would be exceeded by participating in this study.

33. For subjects who consent to LP, any contraindications to having a LP (e.g., platelet count < 100,000/μL, lumbar spine deformity). Any symptoms caused by or related to the optional LP during Screening must be resolved prior to randomization. Subjects may still participate in the overall study even if participation in the optional LP portion is contraindicated.

Others

34. Female subjects who are pregnant or currently breastfeeding.

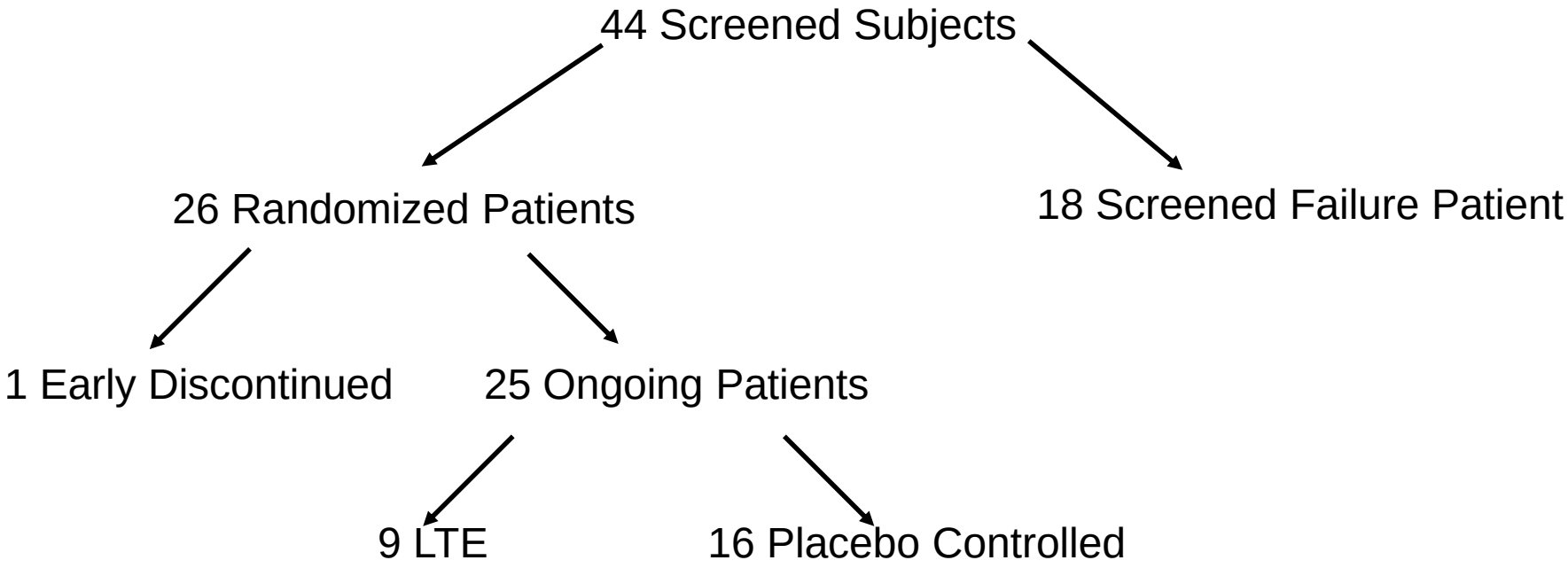
35. Previous participation in this study. Subjects who fail Screening will be permitted to be rescreened once at the Sponsor's discretion, except those who fail due to PET, MMSE, CDR global score >0.5, hepatitis B or C, or abnormal MRI findings. (Subjects who fail Screening due to a CDR global score of 0 may be rescreened; such subjects will be allowed to repeat the screening CDR assessment after 6 months.)

36. Subject currently living in an organized care facility with extensive intervention and/or support of daily living activities.
37. Blood donation (≥ 1 unit) within 1 month prior to Screening.
38. Inability to comply with study requirements.
39. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

Table 3: Brain MRI, ARIA Management, and Follow-Up Phone Call Schedule During the Placebo-Controlled Period

Study Week	Screening (≤ 60 days before Day 1)[1]			Placebo-Controlled Period													Unscheduled Visit/ MRI for ARIA[4]	FU[2]
				1	2	6	10	14	18	22	26	30	42	54	66	78/ EOT[3]		94 (or 18 weeks after final dose for subjects who discontinue treatment early)
Study Day	V1	V2	V3	1	15 ± 3	43 ± 3	71 ± 3	99 ± 3	127 ± 3	155 ± 3	183 ± 3	211 ± 3	295 ± 3	379 ± 3	463± 3	547 ± 3		659 ± 7
Follow-Up Phone Call[5]					X	X	X	X	X	X	X	X						
Brain MRI[6]		X						X		X		X	X	X	X	X	X	X
Aducanumab Concentration[7]										X		X		X			X	X
MOCA				X													X	
RNA, Serum, and Plasma for Biomarkers[8]																	X	
PBMC collection[8]																	X	

ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormality-edema; ARIA-H = amyloid-related imaging abnormality-hemorrhage or superficial siderosis; EOT = End of Treatment; FU = Follow-Up; LTE = long-term extension; MOCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; RNA = ribonucleic acid; V1, V2, V3 = Screening Visit 1, Screening Visit 2, and Screening Visit 3.


44 Screened Subjects
26 Randomized Patients
18 Screened Failure Patient
1 Early Discontinued
25 Ongoing Patients
9 LTE
16 Placebo Controlled

SCREENING FAILURE

4 Pazienti Failure - 3 per Emorragia in numero superiore a 4 e 1 per lesione espansiva

1 Paziente Screening Failure per NPS

2 Pazienti per HBV non nota

6 Pazienti per PET negativa

ARIA

7 ARIA

3 ARIA E risolti

2 ARIA E ripetuti

1 ARIA E in corso

1 ARIA E e H in corso (forse ED)