XVIII Convegno

I CENTRI PER I DISTURBI COGNITIVI E LE DEMENZE E LA GESTIONE INTEGRATA DELLA DEMENZA

27 – 28 novembre 2025

Aula Pocchiari, Istituto Superiore di Sanità
Viale Regina Elena 299, Roma

Osservatorio Demenze
ISTITUTO SUPERIORE DI SANITÀ

organizzato da
ISTITUTO SUPERIORE DI SANITÀ
Centro Nazionale Prevenzione delle Malattie e Promozione della Salute (CNaPPS)
Reparto Promozione e Valutazione delle Politiche di Prevenzione delle Malattie Croniche

ANALISI PER RESPONDER

NICOLA VANACORE

Osservatorio Demenze
ISTITUTO SUPERIORE DI SANITÀ

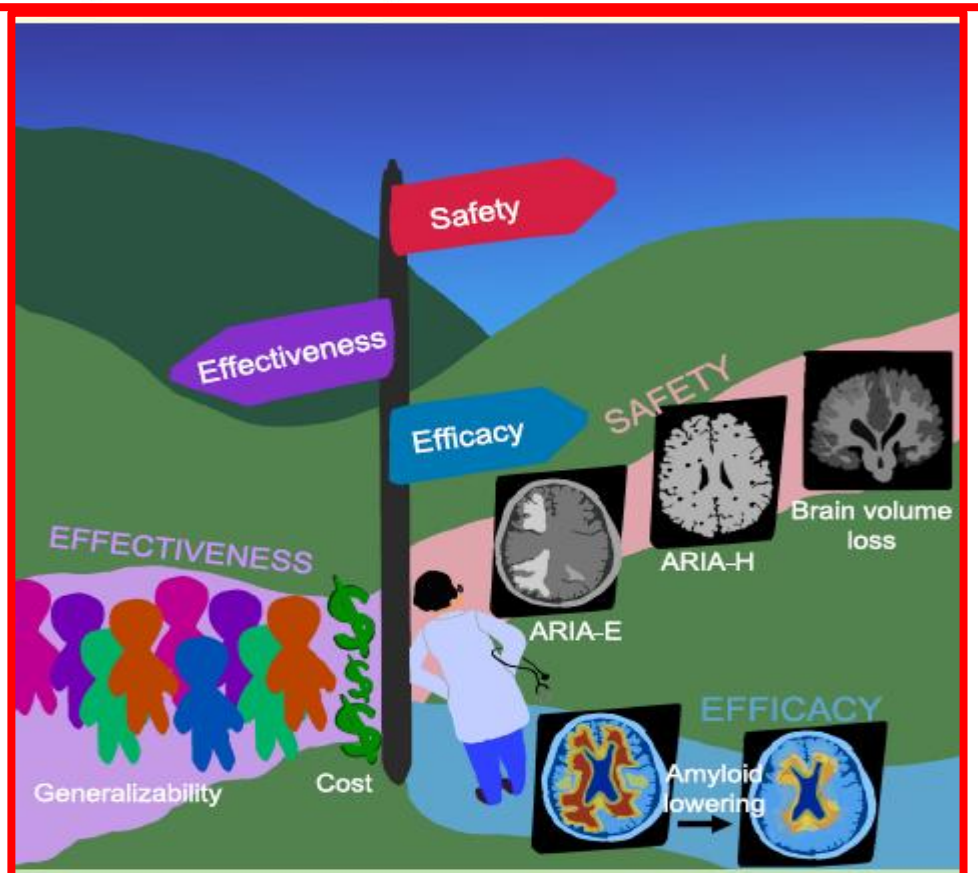
https://doi.org/10.1093/braincomms/fcad175 BRAIN COMMUNICATIONS 2023: Page 1 of 10 | 1

BRAIN COMMUNICATIONS

REVIEW ARTICLE

Key questions for the evaluation of anti-amyloid immunotherapies for Alzheimer's disease

Kathy Y. Liu,[1] Nicolas Villain,[2,3] Scott Ayton,[4] Sarah F. Ackley,[5] Vincent Planche,[6,7] Robert Howard[1] and Madhav Thambisetty[8]



Graphical abstract key
ARIA-E: Amyloid-related imaging abnormalities with cerebral edema or effusion; **ARIA-H**: Amyloid-related imaging abnormalities with microhemorrhages or hemosiderosis.
Picture credit: Batool Rizvi, University of California, Irvine

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1. EVIDENZE DI EFFICACIA

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Lecanemab in Early Alzheimer's Disease

N Engl J Med 2023;388:9-21.

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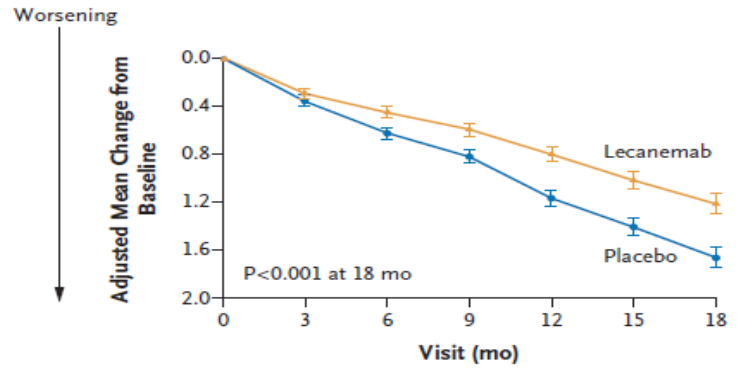
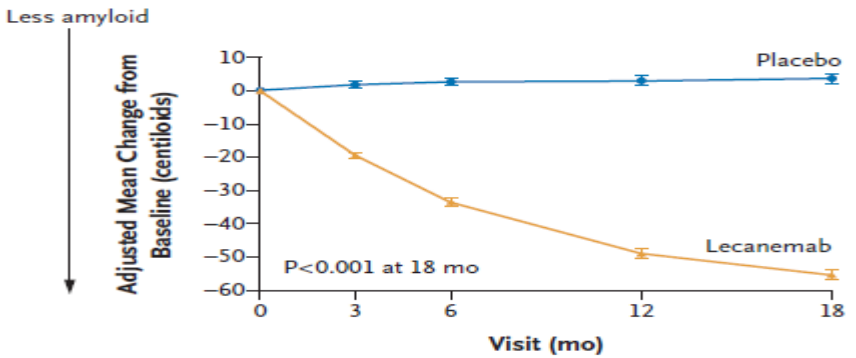
A CDR-SB Score



No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

B Amyloid Burden on PET



No. of Participants

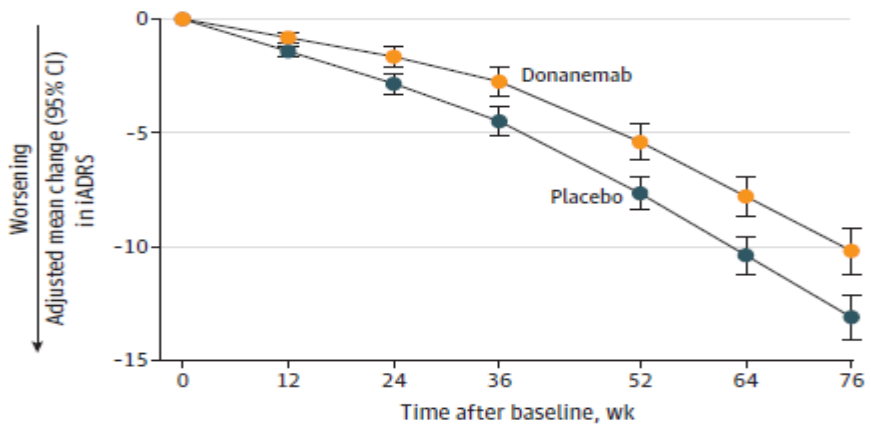
Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

Donanemab in Early Symptomatic Alzheimer Disease

The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

JAMA | Original Investigation

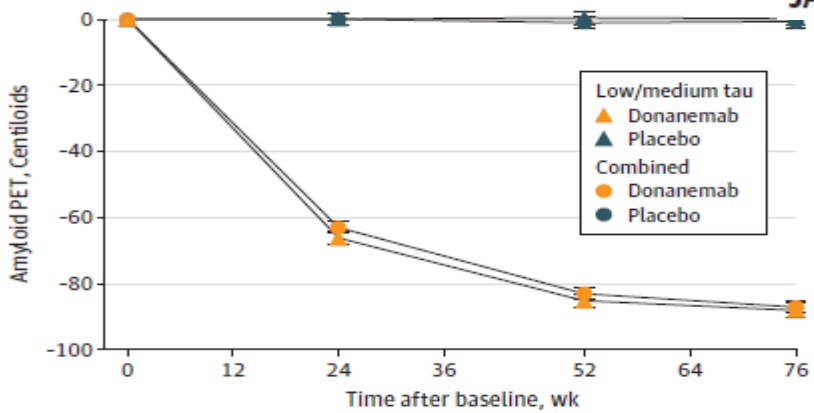
B iADRS in combined population



No. of participants

Placebo	824	805	767	738	693	651	653
Donanemab	775	752	712	665	636	579	583

A Adjusted mean change (95% CI) in amyloid PET



No. of participants					76-wk value, Centiloids	Difference from baseline %
Low/medium tau						
Donanemab	525	521	463	433	-88.0	-85.5
Placebo	556	552	498	470	0.2	0.2
Combined						
Donanemab	765	760	670	614	-87.0	-83.7
Placebo	812	805	729	690	-0.7	-0.7

	Aducanumab		Lecanemab	Donanemab
Name RCT	**EMERGE**	**ENGAGE**	**CLARITY AD**	**TRAILBLAZER-ALZ 2**
Clinical and sociodemographic characteristics				
Number of patients	543 (low-dose)	547 (low-dose)	859 (active group)	860 (active group)
	547 (high-dose)	555 (high-dose)	875 (placebo)	876 (placebo)
	548 (placebo)	545 (placebo)		
Clinical Forms (%)				
MCI due to AD	1336 (81.6%)	1325 (80.4%)	1072 (61.8%)	283 (16.3%)
Mild AD	302 (18.4%)	322 (19.6%)	662 (38.2%)	1451 (83.6%)
Moderate AD	-	-	-	1 (0.1%)
AChEI/memantine use (%)	848 (51.7%)	929 (56.4%)	915 (52.8%)	1059 (61.0%)
ApoE ε4 status – Carrier (%)	1095 (66.8%)	1145 (69.5%)	1192 (68.7%)	1219 (70.2%)

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	Aducanumab		Lecanemab	Donanemab
Name RCT	**EMERGE**	**ENGAGE**	**CLARITY AD**	**TRAILBLAZER-ALZ 2**
Clinical findings				
Primary Outcome	**CDR-SB** (low-dose): difference, −0.26 (95% CI,−0.57, 0.04) at 17.9 months; p = 0.09	**CDR-SB** (low-dose): difference, −0.18 (95% CI,−0.47, 0.11) at 17.9 months; p = 0.225	**CDR-SB**: difference, −0.45 (95% CI, −0.67, −0.23) at 18 months; **p<0.001**	**iADRS** (low/medium tau population): difference, 3.25 (95%CI, 1.88, 4.62) at 17.5 months; **p < 0.001**
	CDR-SB (high dose): difference, −0.39 (95% CI, −0.69, −0.09) at 18 months; **p = 0.012**	**CDR-SB** (high dose): difference, −0.03 (95% CI,−0.26, 0.33) at 18 months; p = 0.833	-	**iADRS** (combined population): difference, 2.92 (95%CI, 1.51, 4.33) at 17.5 months; **p < 0.001**

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Lecanemab in Early Alzheimer's Disease

N Engl J Med 2023;388:9-21.

Protocol

Protocol for: van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med 2023;388:9-21. DOI: 10.1056/NEJMoa2212948

This trial protocol has been provided by the authors to give readers additional information about the work.

Time to worsening of global CDR scores by 18 months

Time to worsening of global CDR scores by 18 months will be analyzed on the FAS and FAS+ using Cox regression model for treatment effect adjusting for stratification variables on the FAS and FAS+. Time to worsening of a global CDR score is defined as time from randomization to worsening of the global CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose global CDR scores have not worsened by the end of study, the time to worsening of the global CDR score will be censored at the date of last CDR assessment for these subjects. Median, 1st quartile, 3rd quartile of time to worsening of global CDR scores and proportion of subjects with worsening of global CDR scores at 3, 6, 9, 12, 15, and 18 months will be estimated using Kaplan-Meier method. (revised per Amendments 08 and 09)

Table 1. Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Lecanemab (N=859)	Placebo (N=875)
Global CDR score — no. (%)‡		
0.5	694 (80.8)	706 (80.7)
1	165 (19.2)	169 (19.3)

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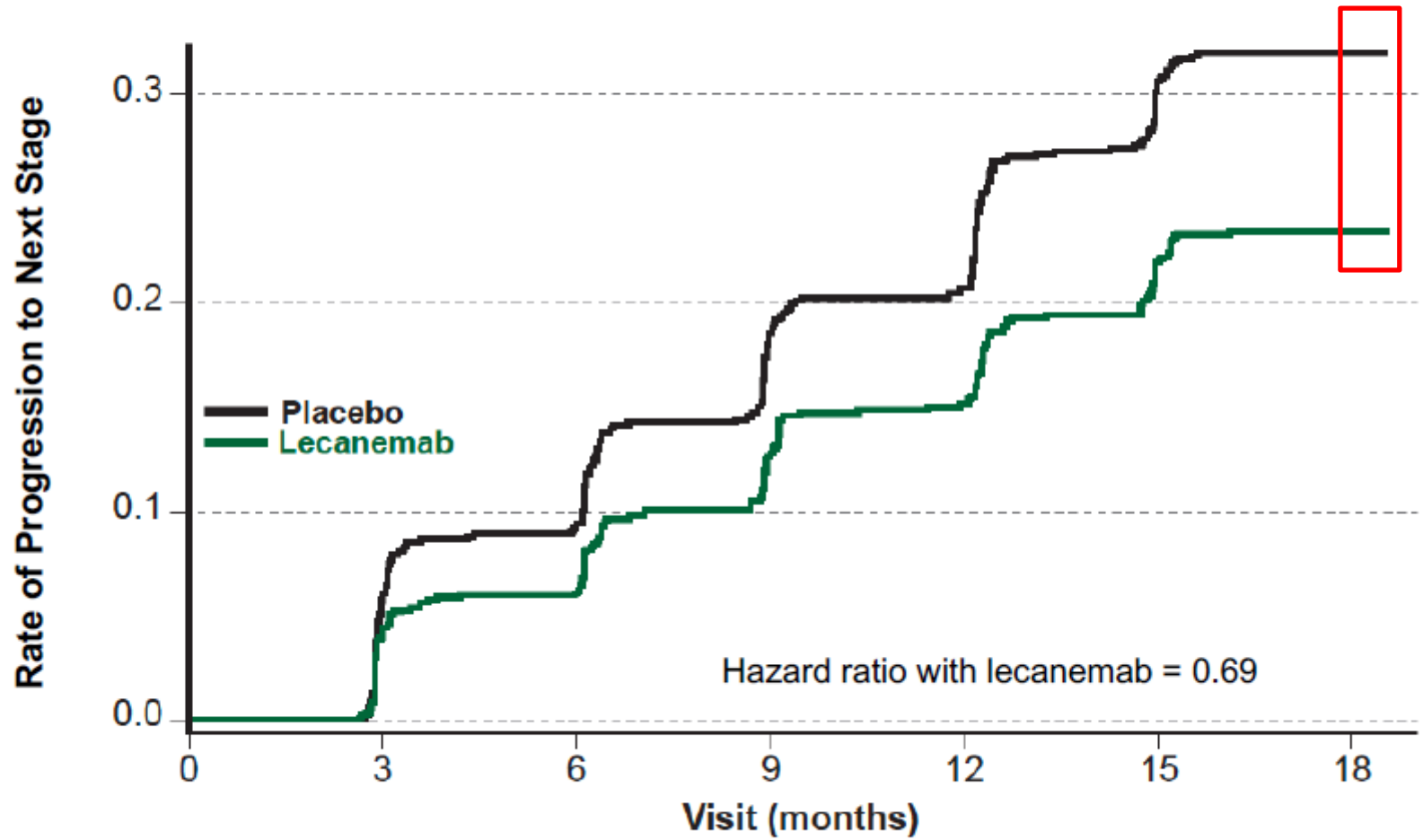
Figure S6. Time to Worsening of Global CDR Score



(N) Placebo:	875	792	757	649	603	524	265
(N) Lecanemab:	859	801	765	677	642	554	299

JAMA | Original Investigation

Donanemab in Early Symptomatic Alzheimer Disease
The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

I5T-MC-AACI Statistical Analysis Plan

4.5. Tertiary/Exploratory Endpoints Analysis

4.5.3. Analysis of Time to Substantial Decline

For this analysis, the change in CDR scores, both CDR global and CDR-SB, and iADRS as described below will be considered as meeting the criteria of time to substantial decline (MCID, Andrews et al. 2019; Wessels et al. 2022; Lansdall et al. 2023):

1. Any increase in CDR-global score from baseline.
2. 1 point or more increase in CDR-SB from baseline for participants with baseline clinical status as mild cognitive impairment (MCI), or 2 points increase from baseline for participants with baseline clinical status as mild AD.
3. 5 points decrease in iADRS from baseline for participants with baseline clinical status as MCI, or 9 points decrease from baseline for participants with baseline clinical status as mild AD.

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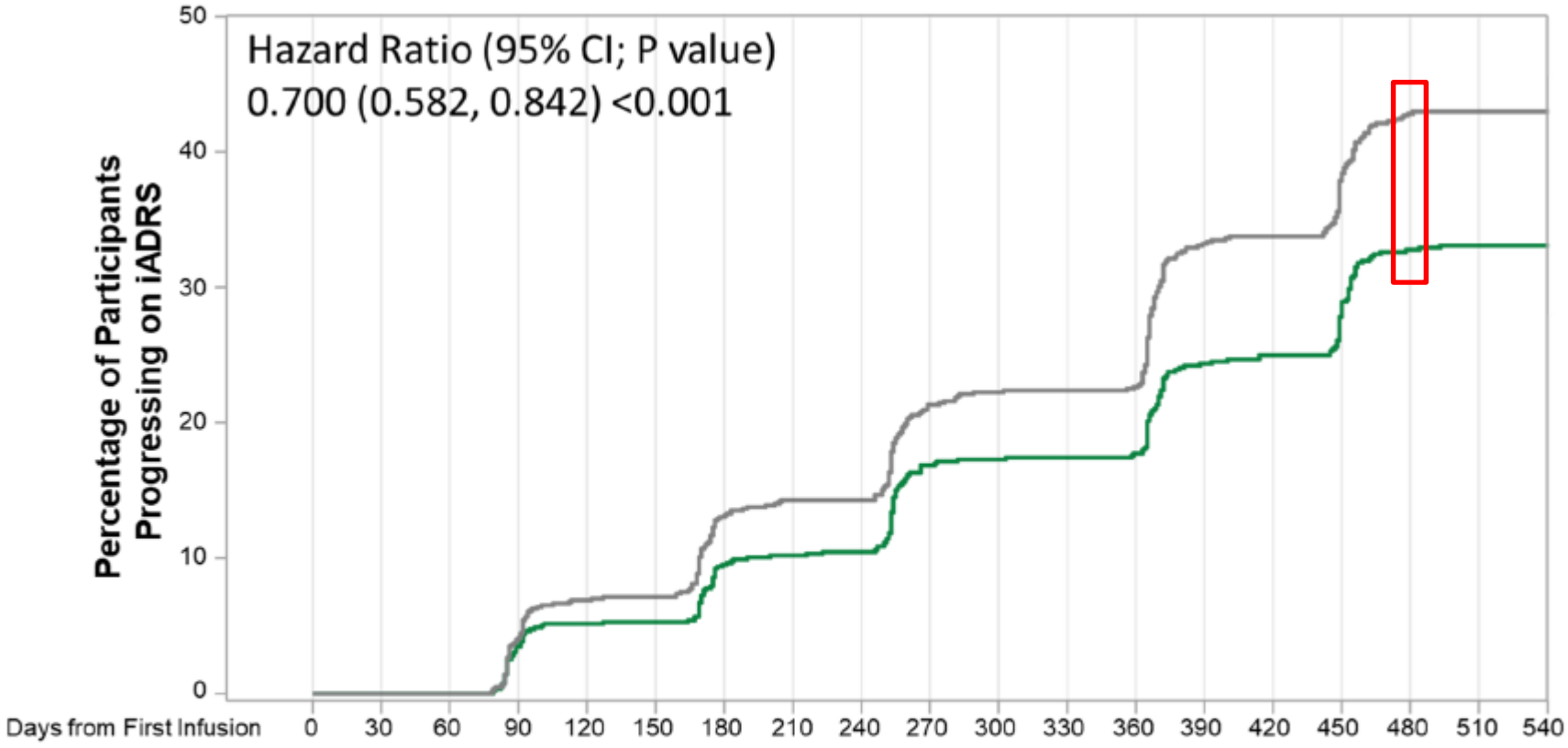
B)



			Time, % (SE) n at risk					
Treatment	N	Event	60 days	120 days	180 days	240 days	360 days	480 days
Placebo	831	329	0.0 (0.00) 827	6.9 (0.88) 766	13.2 (1.18) 702	14.3 (1.22) 673	22.6 (1.48) 576	42.8 (1.81) 403
Donanemab	788	232	0.0 (0.00) 783	5.1 (0.79) 731	9.5 (1.06) 675	10.5 (1.11) 650	17.7 (1.40) 549	32.8 (1.80) 416

Quanti ?
MCI due AD
Mild AD

2. IL COSTRUTTO DEL MINIMAL CLINICAL IMPORTANT DIFFERENCE (MCID)

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CLINICAL RELEVANCE ON ALZHEIMER'S DISEASE ENDPOINTS
C Sampaio
The Journal of Nutrition, Health & Aging; Jul/Aug 2007; 11, 4; ProQuest Medical Library
pg. 316

The Journal of Nutrition, Health & Aging©
Volume 11, Number 4, 2007

CLINICAL RELEVANCE ON ALZHEIMER'S DISEASE ENDPOINTS

C. SAMPAIO

Minimal Clinical Important Change (MCIC) also called Minimal Clinical Important Difference (MCID) for any given measurement is the smallest difference between two assessments that have a perceived impact in disability and/or handicap. It has been also defined as the smallest treatment effect that would result in a change in patient management,

CDR-SUM OF BOX

Published in final edited form as:
Arch Neurol. 2008 August ; 65(8): 1091–1095. doi:10.1001/archneur.65.8.1091.

Staging Dementia Using Clinical Dementia Rating Scale Sum of Boxes Scores:

A Texas Alzheimer's Research Consortium Study

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RANGE 0-18

Sum of Boxes Staging Category

CDR Sum of Boxes Range	Staging Category
0	Normal
0.5–4.0	Questionable cognitive impairment
0.5–2.5	Questionable impairment
3.0–4.0	Very mild dementia
4.5–9.0	Mild dementia
9.5–15.5	Moderate dementia
16.0–18.0	Severe dementia

The need to show minimum clinically important differences in Alzheimer's disease trials

Kathy Y Liu, Lon S Schneider, Robert Howard

	Alzheimer's disease population	Endpoint (weeks)	CDR-SB	MMSE	ADAS-Cog11	ADAS-Cog13	ADAS-Cog14
MCID[16]	MCI	..	-0·98	1·26	..	..	..
MCID[16,17]	Mild	..	-1·63	2·32	-3	..	..
MCID[16]	Moderate-severe	..	-2·30	3·22	..	..	..

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Received: 21 February 2022 | Revised: 22 April 2022 | Accepted: 4 May 2022 | Published online: 5 June 2022

DOI: 10.1002/trc2.12312

RESEARCH ARTICLE

Alzheimer's & Dementia
Translational Research & Clinical Interventions

Integrated Alzheimer's Disease Rating Scale: Clinically meaningful change estimates

Alette M. Wessels[1] | Dorene M. Rentz[2,3] | Michael Case[1] | Steve Lauzon[1] | John R. Sims[1]

iADRS

The iADRS (score range, 0–144) is a linear combination of its two components, the ADAS-Cog$_{13}$ (range, 0–85; higher scores indicating greater deficit of global cognition) [23] and the ADCS-Iadl (instrumental items of the ADCS-ADL scale [items 6a and 7–23]; range, 0–59; lower scores indicating greater impairment) [24, 25].

Results: All three anchors met criteria for "sufficiently associated" (|r| = 0.4–0.7). Cumulatively, results from anchor-based and distribution-based results converged to suggest an iADRS MCID of 5 points for MCI due to AD and 9 points for AD with mild dementia. Regression analyses and CDF plots supported these values.

Discussion: These findings suggest the iADRS can be used in clinical trials to detect a clinically meaningful outcome of AD progression.

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3. ANALISI PER RESPONDER CON GLI INIBITORI DELLE COLINESTERASI

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Movement disorders

RESEARCH PAPER

What is the clinically relevant change on the ADAS-Cog?

Anette Schrag,[1] Jonathan M Schott,[2] Alzheimer's Disease Neuroimaging Initiative

J Neurol Neurosurg Psychiatry 2012;**83**:171–173. doi:10.1136/jnnp-2011-300881

Results 181 patients (baseline ADAS-Cog score 18.5±6.4) had ADAS-Cog data at 0 and 6 months. Those undergoing clinically significant worsening on any of the four anchor questions (n=41–47) had an average ADAS-Cog change of 3.1–3.8 points. Similar results were found for the 177 patients with 6–12-month data. The average 1/2 SD for the baseline ADAS-Cog score was 3.2, and the SEM was 3.7.

UNA VARIAZIONE DI 4 PUNTI ALL'ADAS-COG SONO CLINICAMENTE RILEVANTI

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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ARICEPT 5 mg film coated tablets

DONEPEZIL

Patients who fulfilled the criteria listed below were considered treatment responders.

Response = Improvement of ADAS-Cog of at least 4 points
No deterioration of CIBIC +
No Deterioration of Activities of Daily Living Subscale of the Clinical Dementia Rating Scale

	% Response	
	Intent to Treat Population n=365	Evaluable Population n=352
Placebo Group	10%	10%
ARICEPT tablets 5-mg Group	18%*	18%*
ARICEPT tablets 10-mg Group	21%*	22%**

* $p<0.05$
** $p<0.01$

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

RIVASTIGMINA

Table 4

	Patients with Clinically Significant Response (%)			
	Intent to Treat		Last Observation Carried Forward	
Response Measure	**Rivastigmine 6–12 mg N=473**	**Placebo N=472**	**Rivastigmine 6–12 mg N=379**	**Placebo N=444**
ADAS-Cog: improvement of at least 4 points	21***	12	25***	12
CIBIC-Plus: improvement	29***	18	32***	19
PDS: improvement of at least 10%	26***	17	30***	18
At least 4 points improvement on ADAS-Cog with no worsening on CIBIC-Plus and PDS	10*	6	12**	6

*p<0.05, **p<0.01, ***p<0.001

In addition, a post-hoc definition of response is provided in the same table. The secondary definition of response required a 4-point or greater improvement on the ADAS-Cog, no worsening on the CIBIC-Plus, and no worsening on the PDS. The mean actual daily dose for responders in the 6–12 mg group, corresponding to this definition, was 9.3 mg. It is important to note that the scales used in this indication vary and direct comparisons of results for different therapeutic agents are not valid.

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European Medicines Agency

London, 19 July 2007

-The proportion of patients who achieve a clinically meaningful benefit (response) should be reported.

-Responders (in patient populations with AD, PDD or DLB) may be defined at 6 months as improved to a relevant pre-specified degree in the cognitive endpoint and at least not worsened in the two other domains.

-Functional and global domains as primary endpoints may be more appropriate to establish clinically relevant symptomatic improvement in the more advanced forms of the disease

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RISPOSTA ALLA TERAPIA CON INIBITORI DELLE COLINESTERASI

TIPOLOGIA 1 - L'efficacia degli AchI è limitata ed essenzialmente sintomatica. Nei principali trial di fase III il miglioramento osservato (sulla scala ADAS-cog) nei pazienti trattati per sei mesi è pari a 2–3 punti rispetto al placebo.

TIPOLOGIA 2 – Effetto sintomatico nella progressione della patologia (nessun peggioramento al MMSE o ADAS-cog)

TIPOLOGIA 3 - FDA: almeno 4 punti nella scala ADAS-cog. responder: 24-36% dei pazienti trattati a 6 mesi rispetto al 15-21% nei gruppi placebo. (2 punti MMSE = 5 punti ADAS-cog)

TIPOLOGIA 4 - EMEA: almeno 4 punti nella scala ADAS-cog + non peggioramento in una scala sulle attività di vita quotidiana responder: 10-21% dei pazienti trattati a 6 mesi rispetto al 6-10% nei gruppi placebo.

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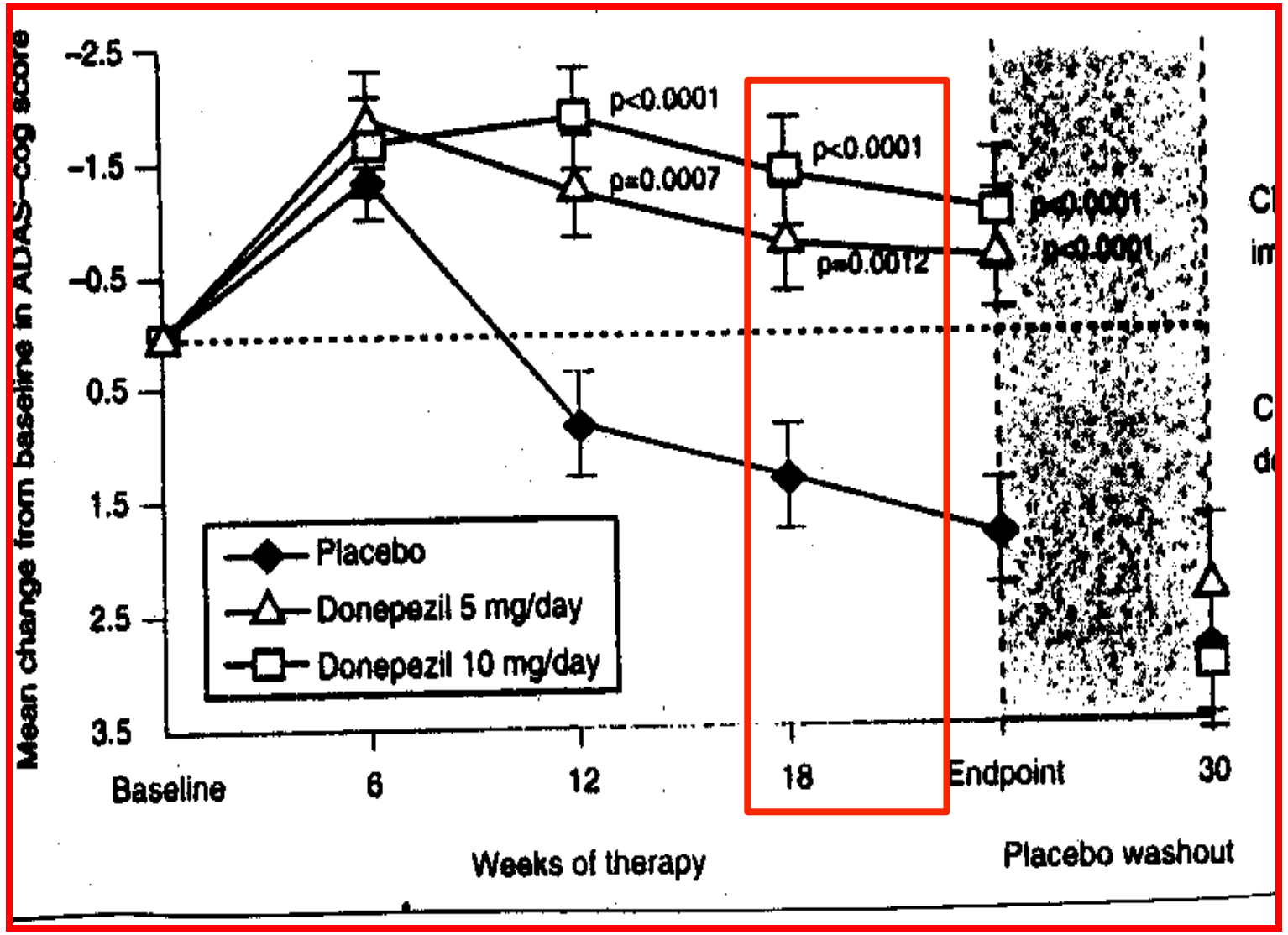
TIPOLOGIA 1



Rogers '98

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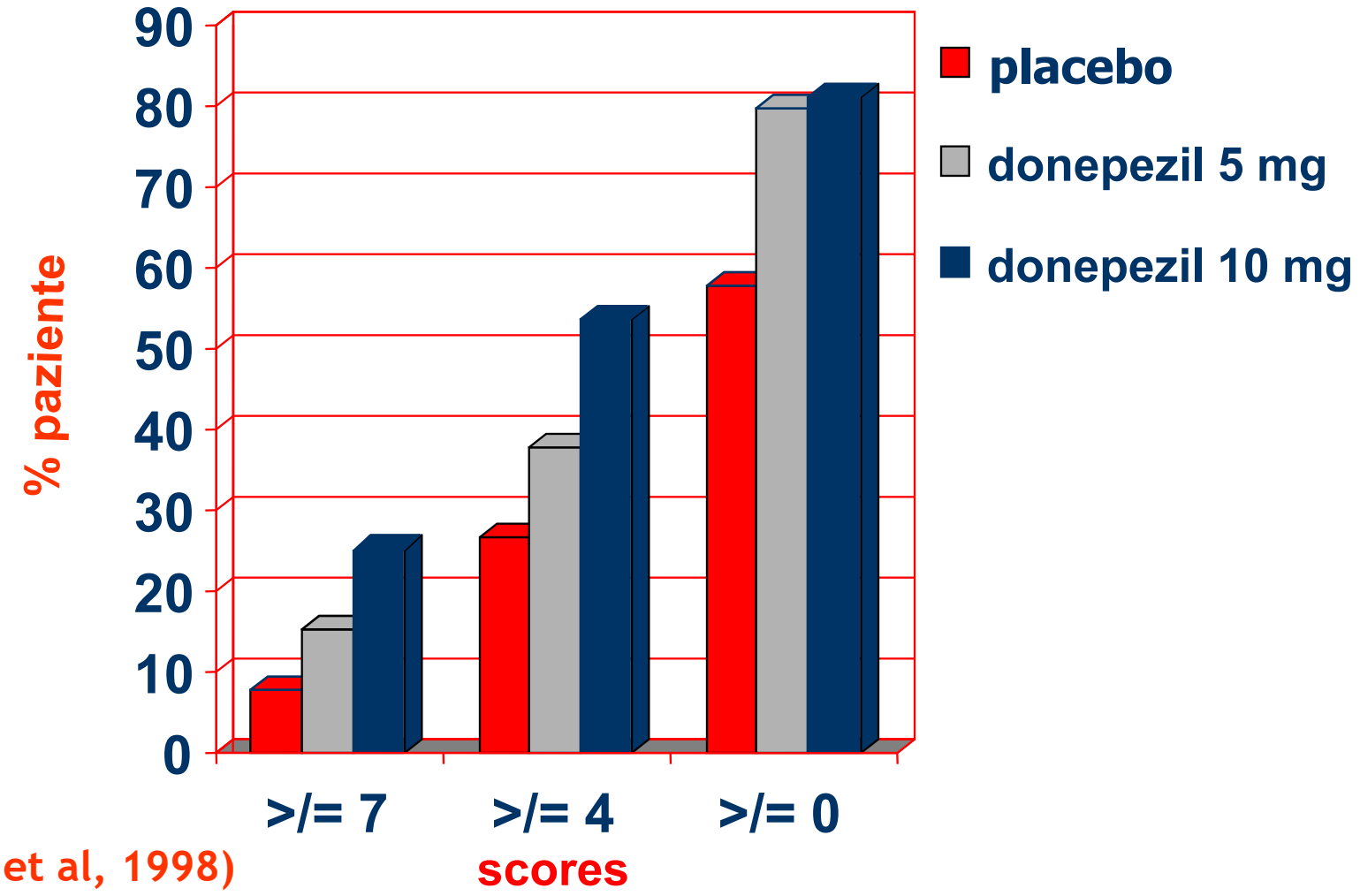
CHANGE IN ADAS-cogn SCORE VERSUS BASELINE (TIPOLOGIA 2 –3)(ANALISI LOCF)



(Rogers SL et al, 1998)

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PAZIENTI CON RISPOSTA CLINICAMENTE SIGNIFICATIVA (RESPONDERS) AGLI INIBITORI DELLE COLINESTERASI (intention-to-treat)(TIPOLOGIA 4)

Donepezil (n=365)	Resp.	Diff. plac
placebo	10%	
5 mg	18%	8%
10 mg	21%	11%
Rivastigmina		
placebo (n=444)	6%	
6-12mg (n=379)	12%	6%
Galantamina		
placebo (n=273)	6.6%	
16 mg (n=266)	14.7%	8.1%
24 mg (n =262)	15.3%	8.7%

Almeno 4 punti alla ADAS-cog senza peggioramento alla CIBIC e alle scale PDS (rivastigmina), ADCS/ADL (galantamina) e ADL della CRDS (donepezil)

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DONEPEZIL

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ARICEPT 5 mg film coated tablets

RIVASTIGMINA

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Exelon 1.5 mg hard capsules
Exelon 3.0 mg hard capsules
Exelon 4.5 mg hard capsules
Exelon 6.0 mg hard capsules

?

LECANEMAB

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LEQEMBI 100 mg/mL concentrate for solution for infusion

DONANEMAB

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kisunla 350 mg concentrate for solution for infusion

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4. PERCHE' E' IMPORTANTE IN TERMINI DI SANITA' PUBBLICA L'ANALISI PER RESPONDER ?

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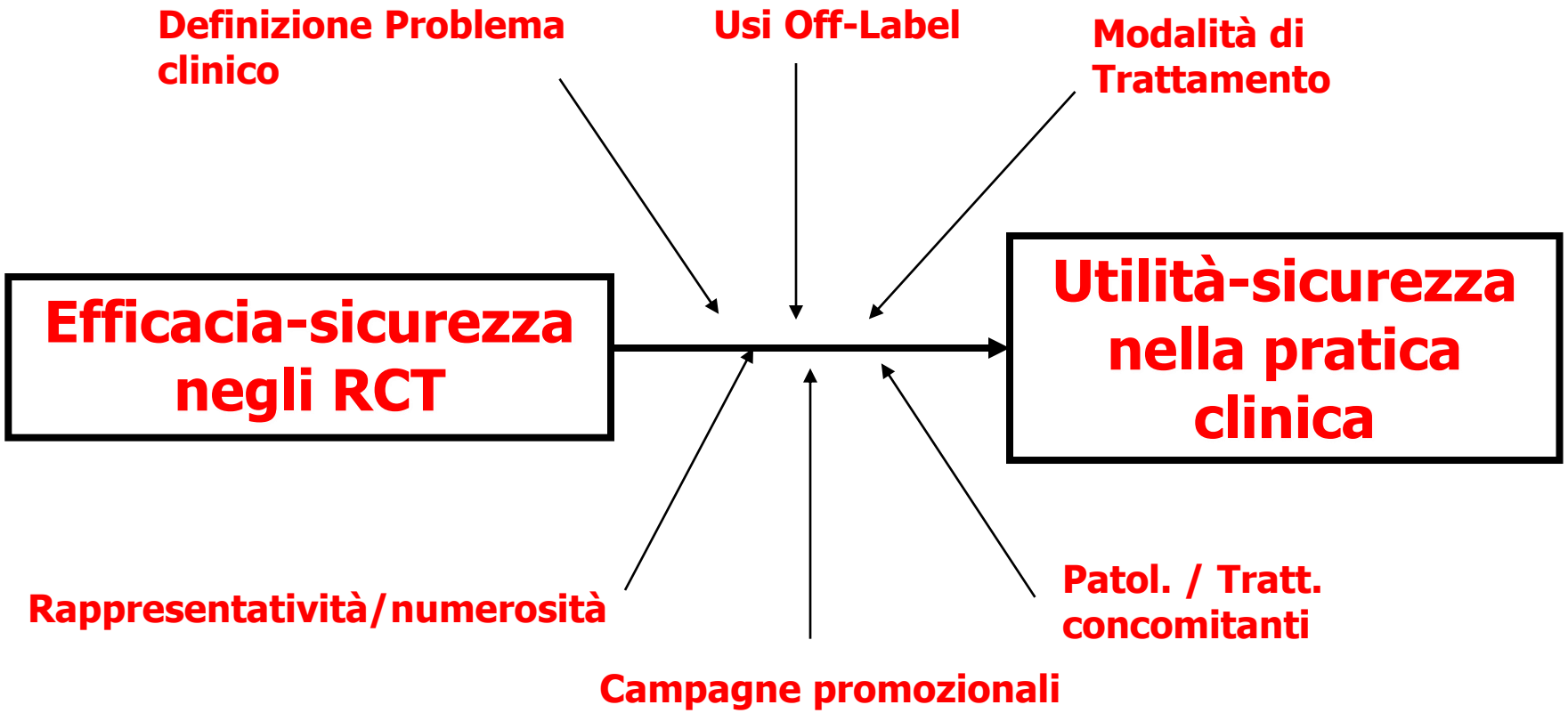
IL PROFILO COMPLESSIVO DI EFFICACIA E SICUREZZA DI UN FARMACO



VALIDITA' INTERNA - VALIDITA' ESTERNA

Can it work? Does it work? Is it worth it?

The testing of healthcare interventions is evolving

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Cochrane Library

Cochrane Database of Systematic Reviews

Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials: a meta-epidemiological study (Review)

Toews I, Anglemyer A, Nyirenda JLZ, Alsaid D, Balduzzi S, Grummich K, Schwingshackl L, Bero L

Can it work? Does it work? Is it worth it?

The testing of healthcare interventions is evolving

Faraoni and Schaefer *BMC Anesthesiology* (2016) 16:102
DOI 10.1186/s12871-016-0265-3

BMC Anesthesiology

COMMENTARY Open Access

Randomized controlled trials vs. observational studies: why not just live together?

David Faraoni[1] and Simon Thomas Schaefer[2*]

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ESITO clinico CATEGORICO (analisi per responder)

Riduzione assoluta del rischio	$ARR = I_c - I_t$
Rischio relativo	$RR = I_t / I_c$
Riduzione relativa del rischio	$RRR = [(I_c - I_t) / I_c] \times 100$
Numero di soggetti da trattare per evitare un evento	$NNT = 1/ARR$

Ic

Incidenza di risposta nei controlli

It

Incidenza di risposta nei trattati

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STUDI OSSERVAZIONALI DEL MONDO REALE

Short Communication

Reducing ARIA risk in Alzheimer's disease: Real-world impact of *APOE* genotype-guided slow titration with aducanumab and lecanemab

Journal of Alzheimer's Disease
2025, Vol. 107(4) 1400–1403
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DOI: 10.1177/13872877251366657
journals.sagepub.com/home/alz
Sage | IOS Press

Nicholas Mervosh[1], Nadir Bilici[1], Thomas Wisniewski[2,3,4] and Gayatri Devi[1,5]

Xing et al. Alzheimer's Research & Therapy (2025) 17:15
https://doi.org/10.1186/s13195-024-01669-4
Alzheimer's Research & Therapy

RESEARCH Open Access

Post-marketing safety concerns with lecanemab: a pharmacovigilance study based on the FDA Adverse Event Reporting System database

Xiaoxuan Xing[1†], Xiaotong Zhang[1†], Ke Wang[1], Zhizhou Wang[1], Yingnan Feng[1], Xiaoxi Li[1], Yiming Hua[1], Lan Zhang[1*] and Xianzhe Dong[1*]

Journal of Neurology (2025) 272:394
https://doi.org/10.1007/s00415-025-13142-9

ORIGINAL COMMUNICATION

Monoclonal antibody administration in an academic institution and private neurological practice: a tale of two clinics

Michael Rosenbloom[1,2,3] · Andrea Schnee[1] · Saanvi Nimma[4] · Helen Lutz[4] · Dan Gzesh[4] · David Weisman[4]

Received: 30 June 2025 | Revised: 1 September 2025 | Accepted: 2 September 2025
DOI: 10.1002/alz.70750

RESEARCH ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Lecanemab treatment for Alzheimer's Disease of varying severities and associated plasma biomarkers monitoring: A multi-center real-world study in China

Sihui Chen[1] | Ruwei Ou[1] | Qianqian Wei[1] | Chunyu Li[1] | Wei Song[1] | Bi Zhao[1] | Jing Yang[1] | Jiajia Fu[1] | Yuanzheng Ma[1] | Jiyong Liu[1] | Xiangming Wang[2] | Dengfu Fang[3] | Tao Hu[4] | Li Xiao[5] | Shushan Zhang[6] | Rui Huang[7] | Xiaoyan Guo[8] | Fei Feng[9] | Xueping Chen[1] | Huifang Shang[1]

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Original Article

Safety and effectiveness of lecanemab in Chinese patients with early Alzheimer's disease: Evidence from a multidimensional real-world study

Wenyan Kang[1,2], Chao Gao[1], Xiaoyan Li[2], Xiaoxue Wang[3], Huizhu Zhong[2], Qiao Wei[2], Yonghua Tang[4,5], Peijian Huang[1,2], Ruinan Shen[1], Lingyun Chen[6], Jing Zhang[4], Rong Fang[1], Wei Wei[7], Fengjuan Zhang[7], Gaiyan Zhou[7], Weihong Yuan[8], Xi Chen[8], Zhao Yang[1], Ying Wu[3], Wenli Xu[9], Shuo Zhu[3], Liwen Zhang[10], Naying He[4], Weihuan Fang[4], Miao Zhang[11], Yu Zhang[11], Huijun Ju[11], Yaya Bai[11], Jun Liu[1]

Safety and short-term outcomes of lecanemab for Alzheimer's disease in China: a multicentre study

Ling-Ling Li,[1,†] Rong-Ze Wang,[1,2,†] Zhen Wang,[3,†] Hua Hu,[4,†], Wei Xu,[5,†] Lin Zhu,[6,†] Yan Sun,[7,†] Ke-Liang Chen,[1,†] Shu-Fen Chen,[1,†] Xiao-Yu He,[1] Ming-Yang Yuan,[1] Yu-Yuan Huang,[1] Xiaoyan Liu,[7] Ping Liu,[7] Qin-Yong Ye,[2] Jie Wang,[1] Zi-Zhao Ju,[8] Wei Zhang,[9] Bin Hu,[10] Yu Guo,[1] Xiao-Yun Cao,[11] Yu-Xin Li,[10] Chuan-Tao Zuo,[8] Wei Cheng,[9] Teng Jiang,[6] Lan Tan,[5] Xiao-Chun Chen,[2] Qian-Hua Zhao,[1] Mei Cui,[1] Guo-Ping Peng,[7] Jia-Wei Xin[2] and Jin-Tai Yu[1]

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THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Lecanemab treatment for Alzheimer's Disease of varying severities and associated plasma biomarkers monitoring: A multi-center real-world study in China

Sihui Chen[1] | Ruwei Ou[1] | Qianqian Wei[1] | Chunyu Li[1] | Wei Song[1] | Bi Zhao[1] | Jing Yang[1] | Jiajia Fu[1] | Yuanzheng Ma[1] | Jiyong Liu[1] | Xiangming Wang[2] | Dengfu Fang[3] | Tao Hu[4] | Li Xiao[5] | Shushan Zhang[6] | Rui Huang[7] | Xiaoyan Guo[8] | Fei Feng[9] | Xueping Chen[1] | Huifang Shang[1]

In patients with AD-MCI and mild dementia (CDR ≤ 1), ADAS-cog14 scores significantly declined at V1(-2.88; 95% CI: −4.43 to −1.34; $p < 0.001$) and V2 (-5.19; 95% CI: −7.33 to −3.04; $p < 0.001$, Table S8),

Table S8. Comparison of cognitive function and plasma biomarkers in *non-APOE4* carriers

Variables	V0 (n=27)	V1 (n=24)	P-value (n=24)	V2 (n=17)	P-value (n=17)
ADAS-cog14[a]	36.64 ± 17.64	34.87 ± 22.32	**0.036**	31.07 ± 20.41	**0.045**

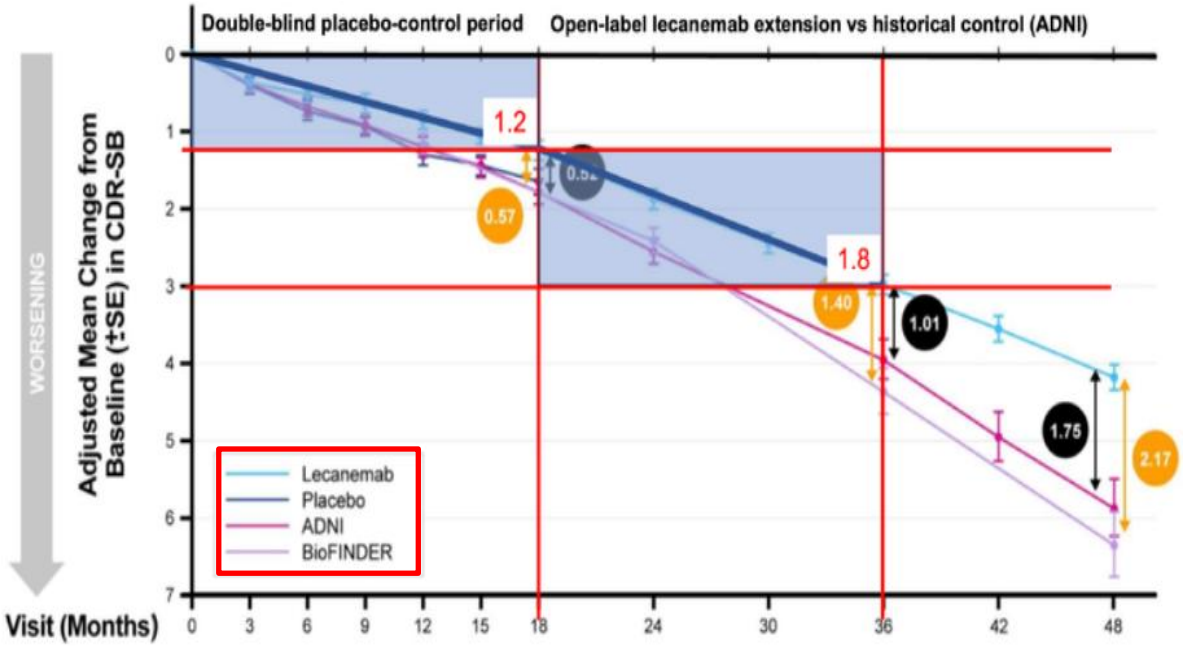
A reduction of ≥4 points in the ADAS-cog14 score was considered to represent the minimal clinically important difference (MCID), indicating an improvement thatwould be perceived as clinically meaningful

Benefit" in Alzheimer's Antibody Trials

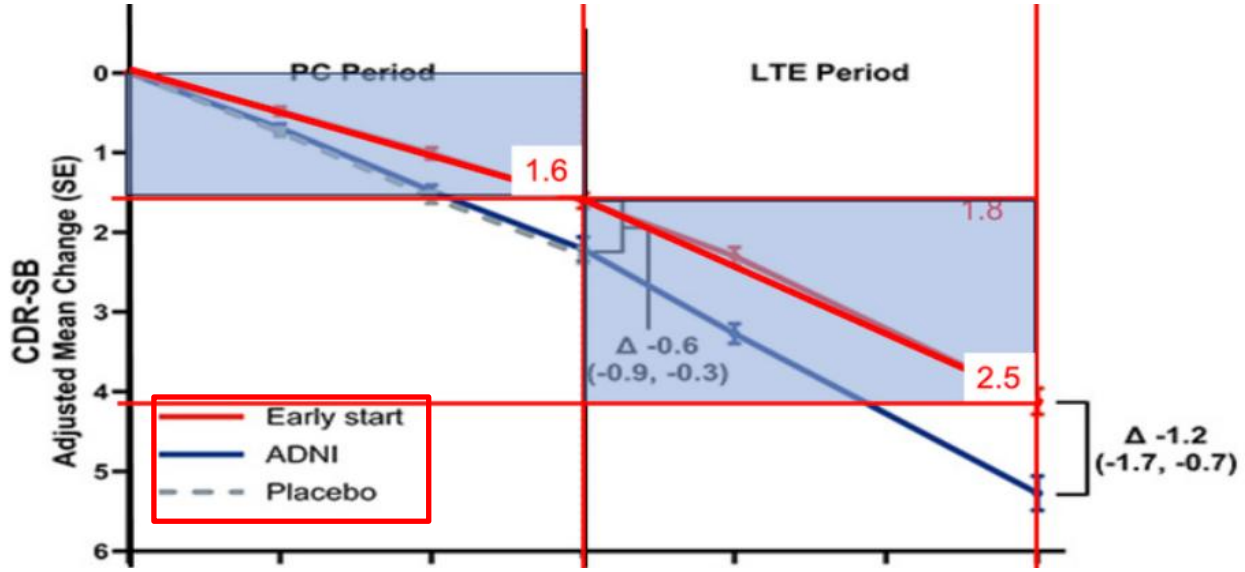
Estensione open label vs coorti storiche

Alberto Espay
Data pubblicazione: 28 ago 2025

For lecanemab, in the 18 double-blind months, the CDR-SB score lowered (worsened) by 1.2 (vs. 1.7 in placebo); in the subsequent 18 open-label months, the CDR-SB lowered by 1.8 (3 -1.2) –a **50% faster decline** (1.8 -1.2 /1.2 * 100).



For donanemab, in the 18 double-blind months, the CDR-SB score lowered by 1.6 (vs. 2.2 in placebo); in the subsequent 18 open-label months, the CDR-SB lowered 2.5 (4.1-1.6) –**a 56% faster decline** (2.5 -1.6 /1.6 * 100).



The treatment arms were not compared with concurrent placebo groups, but with an **external historical cohort (ADNI)**. This introduces major sources of bias:

When compared with the extrapolated placebo slope from the original trial, the drug–placebo gap actually narrows over time:

Osservatorio Demenze
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L'IMPORTANZA DEI REGISTRI

Correspondence

https://doi.org/10.1038/s43587-025-00980-5

A Japanese registry for optimizing the safe use of anti-amyloid therapies for Alzheimer's disease in Japan

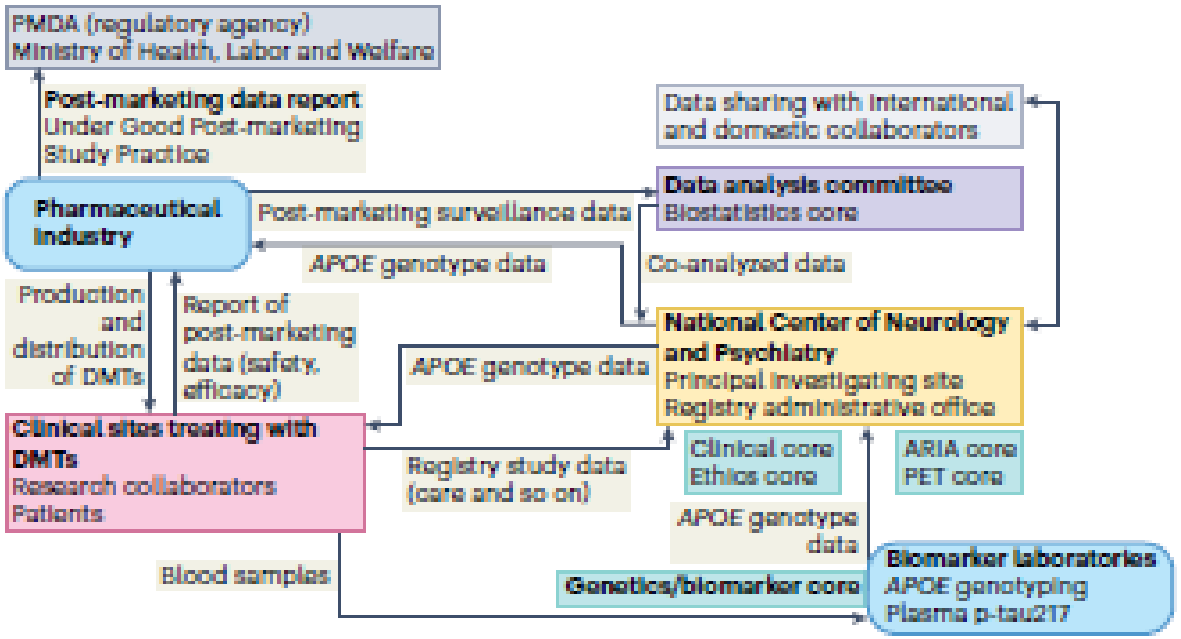

Fig. 1 | Research structure for the Japanese Registry for Alzheimer's Disease-Modifying Therapies. Post-marketing surveillance data collected by the pharmaceutical industry under the Good Post-marketing Study Practice guidelines will be shared directly with the data analysis committee (including the biostatisti core; purple), which is separate from the pharmaceutical industry and academic members with potential conflicts of interest.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Patient Registry workshop on Alzheimer's disease

15 December 2025
In-person at the EMA building, Amsterdam + virtual enabled

AIFA
AGENZIA ITALIANA DEL FARMACO

Ufficio Registri di monitoraggio

Analisi registri di monitoraggio

L'AIFA pubblica in questa sezione i report con i dati dei registri dei farmaci sottoposti a monitoraggio.

INFORMAZIONI SUL PROFILO DEL RESPONDER IN TERMINI DI SICUREZZA

Table 1. Prescribing information descriptions from the included regulatory authorities

	FDA Prescribing information	PMDA Deliberation of results	MHRA Prescribing information	EMA Prescribing information
Country or Region	United States	Japan	United Kingdom	European Union
Regulatory approval pathway	Accelerated approval followed by traditional approval	Priority review	Traditional approval	Traditional approval
Discontinuation criteria	n/r	Treatment discontinuation if clinically ineffective (assessed every 6 months) or if disease progresses to a moderate/severe stage.	Progression to moderate AD	• Progression to moderate AD; • If the clinical course suggests that lecanemab has not demonstrated effectiveness (cognitive symptoms should be assessed every 6 months)

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Eur J Clin Pharmacol (2005) 61: 361–368
DOI 10.1007/s00228-005-0946-1

CLINICAL TRIALS

Roberto Raschetti · Marina Maggini
Giacoma Carla Sorrentino · Nello Martini
Bruno Caffari · Nicola Vanacore

A cohort study of effectiveness of acetylcholinesterase inhibitors in Alzheimer's disease

Methods: From September 2000 to December 2001, a total of 5,462 patients diagnosed with mild to moderate Alzheimer's disease were enrolled at the time of their first prescription of the study drugs and followed up for an average of 10.5 months. Responders were defined as patients with a mini-mental state examination (MMSE) score improvement of 2 or more points from baseline after 9 months of therapy.

PROGETTO CRONOS

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PROGETTO CRONOS

Regressione logistica sulla risposta		OR*	IC 95%
Età	*≥80*	*1*	
	74-79	1,2	0,9-1,5
	<74	1,1	1,0-1,5
Sesso	*Donne*	*1*	
	Uomini	1,0	0,8-1,2
MMSE	*10-15*	*1*	
	16-19	1,2	1,0-1,5
	20-26	1,0	0,8-1,3
Mal concomitanti	No	2,1	1,5-2,9
Altri farmaci	No	1,4	0,9-2,2
Farmaci	*Donepezil*	*1*	
	Rivastigmina	0,9	0,8-1,1
	Galantamina	*0,8*	0,5-1,2
Risposta a tre mesi	Si	20,6	17,2-24,6

* aggiustato per dose

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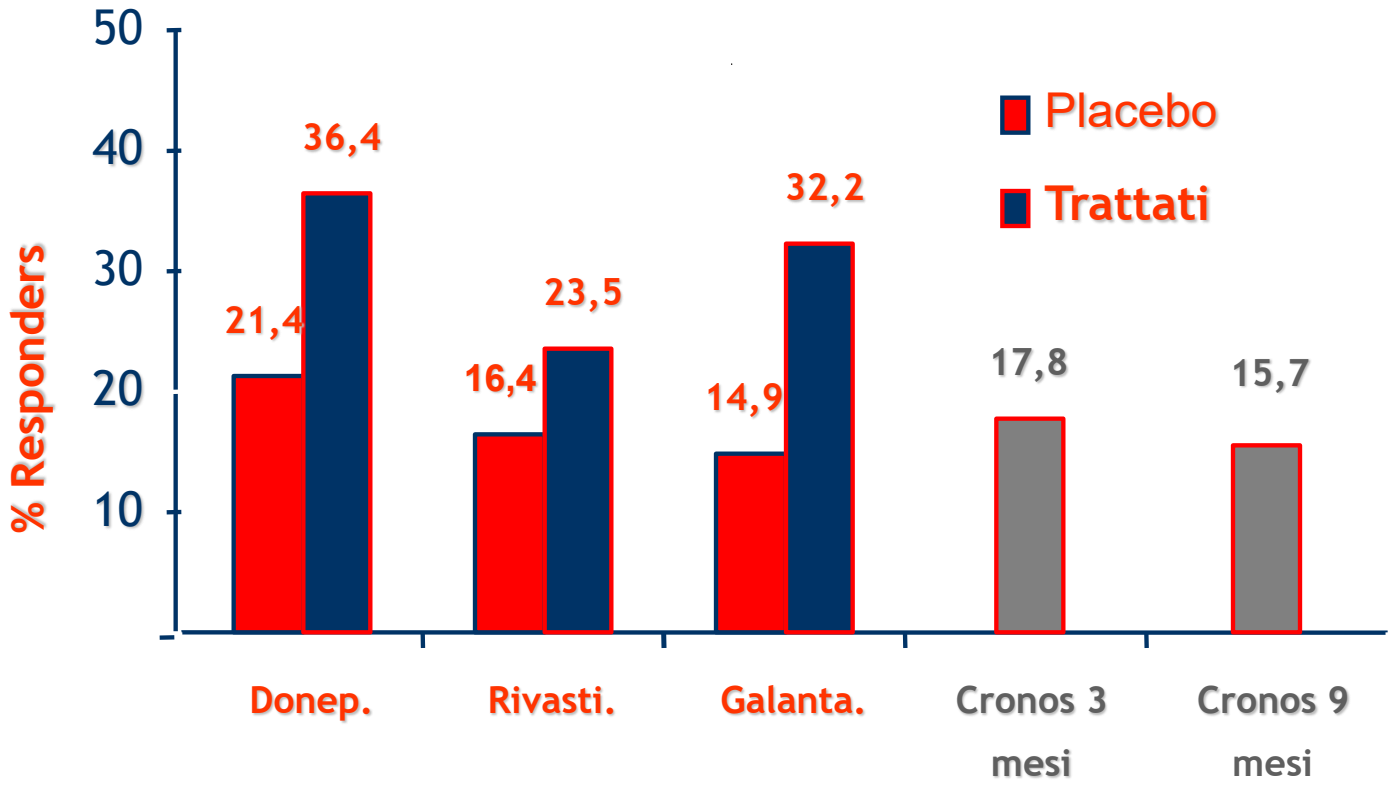
FREQUENZA DI RISPOSTA AD ALMENO 4 PUNTI ALLA SCALA ADAS-cog (tipologia 3)



2 punti di MMSE equivalgono a 5 punti dell'ADAS-cog

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https://doi.org/10.1093/braincomms/fcad276 BRAIN COMMUNICATIONS 2023: Page 1 of 2 | 1

BRAIN COMMUNICATIONS

LETTER TO THE EDITOR

Responder analyses for anti-amyloid immunotherapies for Alzheimer's disease: a paradigm shift by regulatory authorities is urgently needed

Simone Salemme,[1] Antonio Ancidoni[2,3] and Nicola Vanacore[2]

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Articles

Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial

AD2000 Collaborative Group*

Findings Cognition averaged 0·8 MMSE (mini-mental state examination) points better (95% CI 0·5–1·2; p<0·0001) and functionality 1·0 BADLS points better (0·5–1·6; p<0·0001) with donepezil over the first 2 years. No significant benefits were seen with donepezil compared with placebo in institutionalisation (42% *vs* 44% at 3 years; p=0·4) or progression of disability (58% *vs* 59% at 3 years; p=0·4). The relative risk of entering institutional care in the donepezil group compared with placebo was 0·97 (95% CI 0·72–1·30; p=0·8); the relative risk of progression of disability or entering institutional care was 0·96 (95% CI 0·74–1·24; p=0·7).

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2005 VOL. 352 NO. 23

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D., Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D., Christopher H. van Dyck, M.D., and Leon J. Thal, M.D., for the Alzheimer's Disease Cooperative Study Group*

A total of 769 subjects were enrolled, and possible or probable Alzheimer's disease developed in 212. The overall rate of progression from mild cognitive impairment to Alzheimer's disease was 16 percent per year. As compared with the placebo group, there were no significant differences in the probability of progression to Alzheimer's disease in the vitamin E group (hazard ratio, 1.02; 95 percent confidence interval, 0.74 to 1.41; P=0.91) or the donepezil group (hazard ratio, 0.80; 95 percent confidence interval, 0.57 to 1.13; P=0.42) during the three years of treatment. Prespecified analyses of the treat-

LA CONFUSIONE SUI CRITERI CLINICI DA ADOTTARE E LA DEFINIZIONE BIOLOGICA PER L'ASSUNZIONE DEI FARMACI

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DOI: 10.1002/alz.13859

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RESEARCH ARTICLE

Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup

Clifford R. Jack Jr.[1] | J. Scott Andrews[2] | Thomas G. Beach[3] | Teresa Buracchio[4] | Billy Dunn[5] | Ana Graf[6] | Oskar Hansson[7,8] | Carole Ho[9] | William Jagust[10] | Eric McDade[11] | Jose Luis Molinuevo[12] | Ozioma C. Okonkwo[13] | Luca Pani[14] | Michael S. Rafii[15] | Philip Scheltens[16] | Eric Siemers[17] | Heather M. Snyder[18] | Reisa Sperling[19] | Charlotte E. Teunissen[20] | Maria C. Carrillo[18]

CRITERI AMERICANI

Clinical Review & Education

JAMA Neurology | Special Communication

Alzheimer Disease as a Clinical-Biological Construct—An International Working Group Recommendation

Bruno Dubois, MD, MSc; Nicolas Villain, MD, PhD; Lon Schneider, MD, MSc; Nick Fox, MD, MA; Noll Campbell, PharmD, MSc; Douglas Galasko, MD, MSc; Mila Kivipelto, MD, PhD; Frank Jessen, MD; Bernard Hanseeuw, MD, PhD; Mercè Boada, MD, PhD; Frederik Barkhof, MD, PhD; Agneta Nordberg, MD, PhD; Lutz Froelich, MD, PhD; Gunhild Waldemar, MD, DMSc; Kristian Steen Frederiksen, MD, PhD; Alessandro Padovani, MD, PhD; Vincent Planche, MD, PhD; Christopher Rowe, MD; Alexandre Bejanin, PhD; Agustin Ibanez, PhD; Stefano Cappa, MD; Paulo Caramelli, MD, PhD; Ricardo Nitrini, MD, PhD; Ricardo Allegri, MD, PhD; Andrea Slachevsky, MD, PhD; Leonardo Cruz de Souza, MD, PhD; Andrea Bozoki, MD; Eric Widera, MD; Kaj Blennow, MD, PhD; Craig Ritchie, MD, PhD; Marc Agronin, MD; Francisco Lopera, MD; Lisa Delano-Wood, PhD; Stéphanie Bombois, MD, PhD; Richard Levy, MD, PhD; Madhav Thambisetty, MD, DPhil; Jean Georges, BA; David T. Jones, MD; Helen Lavretsky, MD, MSc; Jonathan Schott, MD, BSc; Jennifer Gatchel, MD, PhD; Sandra Swantek, MD; Paul Newhouse, MD; Howard H. Feldman, MD; Giovanni B. Frisoni, MD

CRITERI EUROPEI

Lg LINEA GUIDA

Diagnosi e trattamento di demenza e *Mild Cognitive Impairment*

CRITERI NIA-AA NELLA LG INCLUSA NEL SNLG

ELSEVIER

Alzheimer's & Dementia 7 (2011) 270–279

Alzheimer's & Dementia

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Marilyn S. Albert[a,*], Steven T. DeKosky[b,c], Dennis Dickson[d], Bruno Dubois[e], Howard H. Feldman[f], Nick C. Fox[g], Anthony Gamst[h], David M. Holtzman[i,j], William J. Jagust[k], Ronald C. Petersen[l], Peter J. Snyder[m,n], Maria C. Carrillo[o], Bill Thies[o], Creighton H. Phelps[p]

ELSEVIER

Alzheimer's & Dementia 7 (2011) 263–269

Alzheimer's & Dementia

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Guy M. McKhann[a,b,*], David S. Knopman[c], Howard Chertkow[d,e], Bradley T. Hyman[f], Clifford R. Jack, Jr.[g], Claudia H. Kawas[h,i,j], William E. Klunk[k], Walter J. Koroshetz[l], Jennifer J. Manly[m,n,o], Richard Mayeux[m,n,o], Richard C. Mohs[p], John C. Morris[q], Martin N. Rossor[r], Philip Scheltens[s], Maria C. Carrillo[t], Bill Thies[t], Sandra Weintraub[u,v], Creighton H. Phelps[w]

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STUDI LONGITUDINALI DI PAZIENTI CON MCI E POSITIVI ALL'AMILOIDE

Autori	Setting	N. MCI positivi età media (SD)	Criteri clinici MCI	Metodo positività amiloide	Conversione a demenza/totale	1-3 anni	3-5 anni	> 5 anni
Jack 2010	ADNI	165 75 anni	Petersen 2010	PiB-PET (≥ 1.5), CSF (xMAPLuminex platform	81/165 = 49.1% DSM-IV	2 anni		
Villain 2012	Melbourne Healthy Ageing Study	31 74,4 anni	Petersen 1999	PiB-PET cut-off 0.71	13/20 = 65% NINCDS-ADRDA	20 mesi		
Parnetti 2012	Memory clinic	38 66-67 anni (SD 8-9)	Petersen 2004	CSF Ab42/p-tau cut-off: <1372	31/38 = 81% declino cognitivo con MMSE < 24	Entro 1 anno 22/38 (58%)	Entro 4 anni 31/38 = 81%	
Da 2014	ADNI	84 75 (SD 7)	Petersen, 2001	CSF MAPLuminex platform ≤ 192 pg/mL.	48/84= 57% ADNI/NIA-AA	Entro 18 mesi		
Iaccarino 2017	Clinical setting	20 63 (SD 7)	Petersen, 2014	PiB-PET Cut-off non riportato	14 /20 =70% NIA-AA	21-34 mesi		
Moon 2017	ADNI	186 72-73 (SD 6-7)	Petersen 2004	amyloid-PET florbetapir positività SUVR ≥1.10	47/186 = 25.3% NR	Entro 2 anni		
Wolk 2018	ADNI	97 71 (SD 8-9)	Petersen and Morris criteria	Amyloid-PET Flutemetamol cut-off: scheda vizamyl	52/97 = 53.6% NINCDS-ADRDA	Entro 3 anni		
Villamagne 2018	Memory clinic	45 73 (SD 8)	Petersen, 1999	PiB-PET Positività: SUVR > 1.5	30/45 = 66.7% NINCDS-ADRDA	Entro 20 mesi		
Roberts 2018	MSCA	110 80 (SD 7)	Petersen 2004	Amyloid PET Positivity: SUVR > 1.42	36/110 = 33% NINCDS-ADRDA, NIA-AA, DSM-IV		3.2 (2) anni	
Ye, 2018	Setting clinico	31 70 (SD 9)	Petersen, 1999	PiB-PET SUVR ≥ 1.5	22/31 = 71% DSM-IV		Entro 3,6 anni	
Jiménez-Bonilla 2019	University of Cantabria	9 69 (SD 4)	Petersen 2004	PiB-PET Cut-off non riportato	7/9 = 78% Diagnosi clinica		5 anni	
Eckerström 2019	Gothenburg study	131 (MCI+ SCI) 63-70 (SD 6-8)	GDS*-3	CSF Ab42 (INNOTEST) A+: Aβ42 ≤482 ng/L	72/131 = 54.9% NINCDS-ADRDA	Entro 3 anni 48/131 = 36.6%	Dopo 3 anni 24/83 = 29%	
Kim 2023	ADNI	158 71-75 (SD 7-8)	ADNI criteria	BP-PET (SUVR>1.11)	69/158 = 44% deterioramento alla CDR		(>3 anni)	
Rossini (submitted) INTERCEPTOR	CDCD	178	NIA-AA 2011	Aβ1-42 /p-Tau ≤11.8 o Aβ1-42/1–40 ≤ 0.068	60/178 = 33.3%	2.3 anni (0.5-4.2 anni)		

5. LA RIMOZIONE DELLE PLACCHE AMILOIDEE SONO ASSOCIATE A UN BENEFICIO CLINICO RILEVANTE ? (Validazione dell'end-point surrogato)

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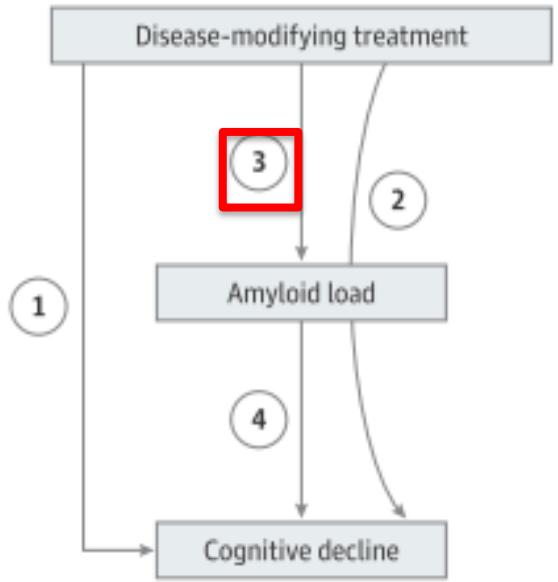
VIEWPOINT

US Food and Drug Administration Approval of Aducanumab—Is Amyloid Load a Valid Surrogate End Point for Alzheimer Disease Clinical Trials?

Vincent Planche, MD, PhD
University of Bordeaux, CNRS, IMN, UMR 5293, Bordeaux, France; and Centre Mémoire Ressources Recherches, Pôle de Neurosciences Cliniques, CHU de Bordeaux, Bordeaux, France.

Nicolas Villain, MD, PhD
AP-HP Sorbonne Université, Hôpital Pitié-Salpêtrière, Department of Neurology, Institute of Memory and Alzheimer's Disease, Paris, France; and Institut du Cerveau - ICM, Sorbonne Université, INSERM U1127, CNRS 7225, Paris, France.

Figure. Graphical Representation of the Criteria Demonstrating Surrogacy (Prentice Criteria)



(1) The treatment must have an effect on the clinical outcome; (2) the treatment effect on the clinical outcome must be captured by the surrogate (demonstration of the lack of statistical relationship between the treatment and the clinical outcome when taking into account the surrogate); (3) the treatment must have an effect on the potential surrogate marker; and (4) the surrogate must be associated with the clinical outcome. Currently, only the third criterion is unarguably fulfilled to support amyloid load as a valid surrogate end point for antiamyloid clinical trials in individuals with Alzheimer disease.

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APPROCCIO STATISTICO ALLA VALIDAZIONE END-POINT SURROGATO

Received: 14 December 2018 | Revised: 10 September 2019 | Accepted: 13 December 2019
DOI: 10.1002/sim.8465

RESEARCH ARTICLE

Statistics in Medicine WILEY

Bayesian hierarchical meta-analytic methods for modeling surrogate relationships that vary across treatment classes using aggregate data

Tasos Papanikos[1] | John R. Thompson[2] | Keith R. Abrams[1] | Nicolas Städler[3] | Oriana Ciani[4,5] | Rod Taylor[4,6] | Sylwia Bujkiewicz[1]

Received: 5 May 2023 | Revised: 14 August 2023 | Accepted: 18 August 2023
DOI: 10.1002/alz.13470

RESEARCH ARTICLE

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Estimated effects of amyloid reduction on cognitive change: A Bayesian update across a range of priors

Sarah F. Ackley[1] | Jingxuan Wang[2] | Ruijia Chen[1] | Melinda C. Power[3] | Isabel Elaine Allen[2] | M. Maria Glymour[1]

RESEARCH

Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis

Sarah F Ackley,[1] Scott C Zimmerman,[1] Willa D Brenowitz,[1,2] Eric J Tchetgen Tchetgen,[3] Audra L Gold,[1] Jennifer J Manly,[4] Elizabeth Rose Mayeda,[5] Teresa J Filshtein,[6] Melinda C Power,[7] Fanny M Elahi,[8] Adam M Brickman,[4] M Maria Glymour[1]

Evaluating amyloid-beta as a surrogate endpoint in trials of anti-amyloid drugs in Alzheimer's disease: a Bayesian meta-analysis

Sa Ren[1], Janharpreet Singh[2], Sandro Gsteiger[3], Christopher Cogley[2], Ben Reed[2], Keith R Abrams[4], Dalia Dawoud[5], Rhiannon K Owen[6], Paul Tappenden[1], Terrence J Quinn[7], Sylwia Bujkiewicz[2]

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2.2 *Statistical analyses*

We adopted a Bayesian bivariate meta-analysis model (allowing for the incorporation of multi-arm trials) to perform trial-level evaluation of Aβ as a surrogate endpoint for clinical function, following the method of Daniels & Hughes [24]. The surrogate relationship between the treatment effects on Aβ level and on the clinical function was described in the form of a regression equation. The strength of the association was evaluated based on the criteria set out by Daniels & Hughes, who consider a perfect surrogate relationship when: (i) the intercept is zero, meaning that a null effect on the surrogate endpoint should imply a null effect on the final clinical outcome; (ii) slope is non-zero, which signified evidence of an association between effects on the surrogate endpoint and the final outcome, and (iii) the variance (of the treatment effect on the clinical outcome conditional on the effect on the surrogate endpoint) is zero, implying that the treatment effect on the final outcome could be predicted perfectly from the effect on the surrogate endpoint.

Aducanumab (marketed as Aduhelm) Information

Postmarket Drug Safety Information for Patients and Providers

Index to Drug-Specific Information

Aduhelm is an amyloid beta-directed antibody indicated to treat Alzheimer's disease. Aduhelm is approved under the accelerated approval pathway, which provides patients with a serious disease earlier access to drugs when there is an expectation of clinical benefit despite some uncertainty about the clinical benefit.

Accelerated approval is based upon the drug's effect on a surrogate endpoint — an endpoint that reflects the effect of the drug on an important aspect of the disease — where the drug's effect on the surrogate endpoint is expected, but not established, to predict clinical benefit. In the case of Aduhelm, the surrogate endpoint is the reduction of amyloid beta plaque. The accelerated approval pathway requires the company to verify clinical benefit in a post-approval trial. If the sponsor cannot verify clinical benefit, FDA may initiate proceedings to withdraw approval of the drug.