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SCIENCE MEDICINES HEALTH

Introduction on Alzheimer´s Disease and current therapies

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Disclaimer

- As a member of a NCA and government employee, I have **no Conflicts of Interest** to declare.
- **All information** presented here **is publicly available**.
- The content of this talk is my own and does not necessarily reflect the official views of the Federal Institute of Drugs and Medical Devices (BfArM) or the European Medicines Agency (EMA).

Content

- Background including Epidemiology of Alzheimer´s Disease and unmet medical need
- Available Therapies with a focus on amyloid antibodies
- Knowledge Gaps
- How Registries/Real world data may help

Background

Increasing societal burden of dementia

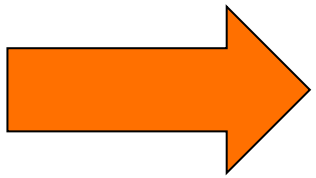
- In 2021, **57 million people worldwide** had dementia
- **~8 million people in the EU** with dementia, **60-80% Alzheimer´s disease**
- The numbers of people with dementia in Europe will almost **double by 2050** increasing to **~14,3 million** in the European Union and **18,8 million** in the wider European region.
- In 2019, dementia cost economies globally **US$ 1.3 trillion**, approximately 50% of these costs are attributable to care provided by informal carers
- Women are disproportionally affected

https://www.alzheimer-europe.org/dementia;
https://www.oecd.org/en/publications/health-at-a-glance-europe-2024_b3704e14-en.html
(2025), 2025 Alzheimer's disease facts and figures. Alzheimer's Dement., 21: e70235. https://doi.org/10.1002/alz.70235

EMA is dedicated to expedite development in AD

- November 2024: EMA **Horizon Scanning report** (EMA/5408572024); https://www.ema.europa.eu/en/documents/report/alzheimers-disease-eu-horizon-scanning-report_en.pdf
- February 2018 „Guideline on the clinical investigation of medicines for the treatment of Alzheimer´s disease“ (CPMP/EWP/553/95 Rev.2)
- 06 August 2025: **Concept paper on the need for revision of the Alzheimer´s Disease Guideline** (EMA/231314/2025) released for public consultation
- Drafting Group for **Revision of the AD Guideline** has started working
- Multiple **Scientific Advice** procedures
- **Qualification Procedures**

- **Licensing of Leqembi and Kisunla**



AD Patient Registry Workshop

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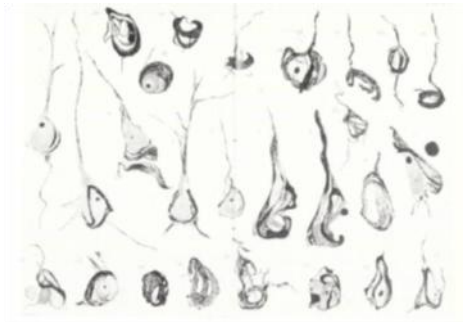
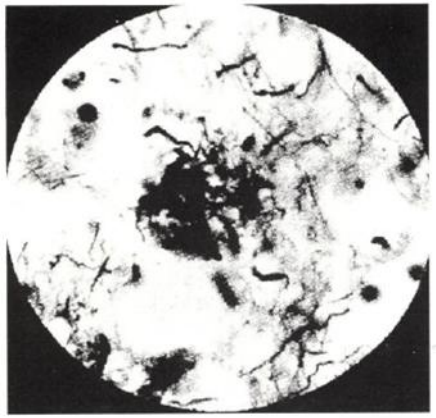
Alzheimer´s disease

Auguste Deter
1850-1906

Alois Alzheimer
1864-1915

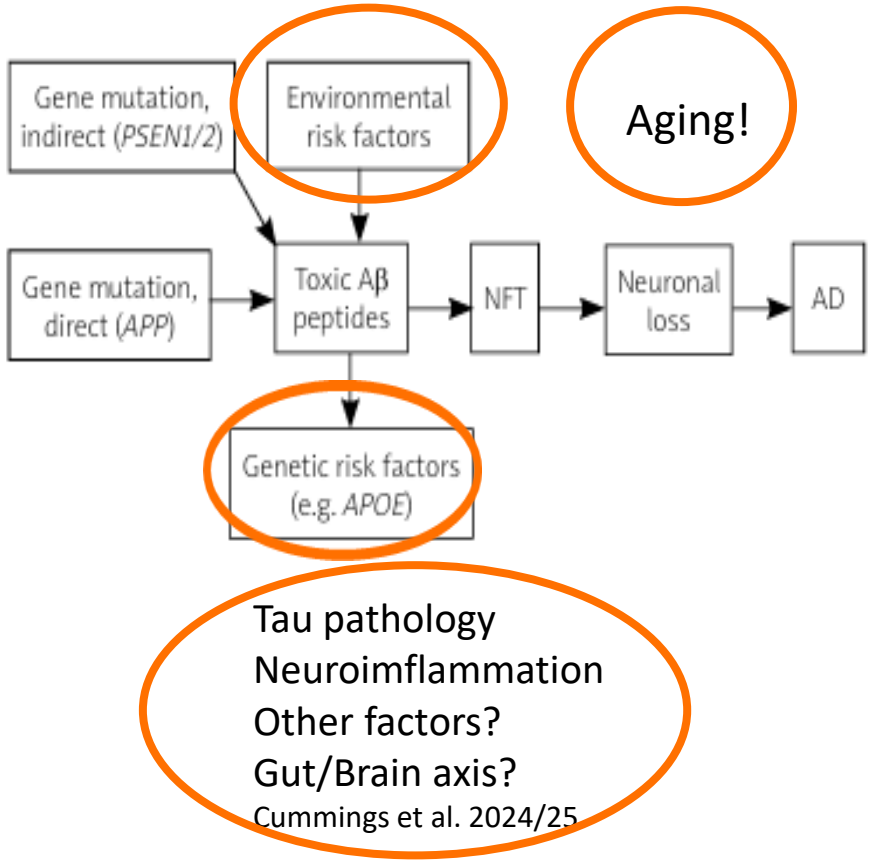




Alzheimer A. *Über eine eigenartige Erkrankung der Hirnrinde.*
Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin 1907;64:146-8.

The amyloid cascade hypothesis

Hardy JA, Higgins GA 1992;
Armstrong RA 2019



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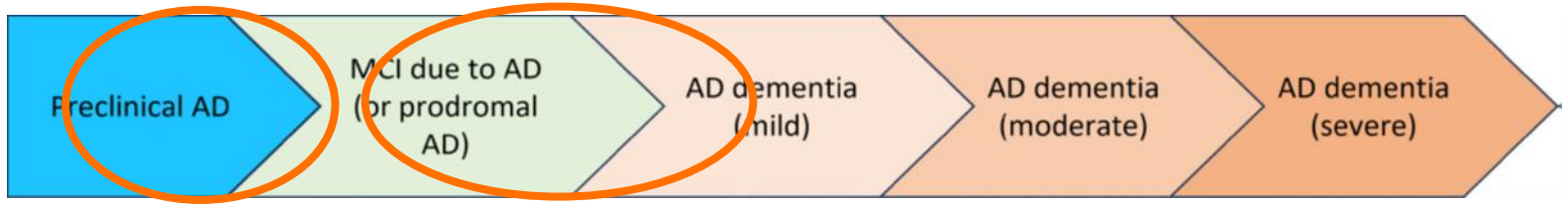
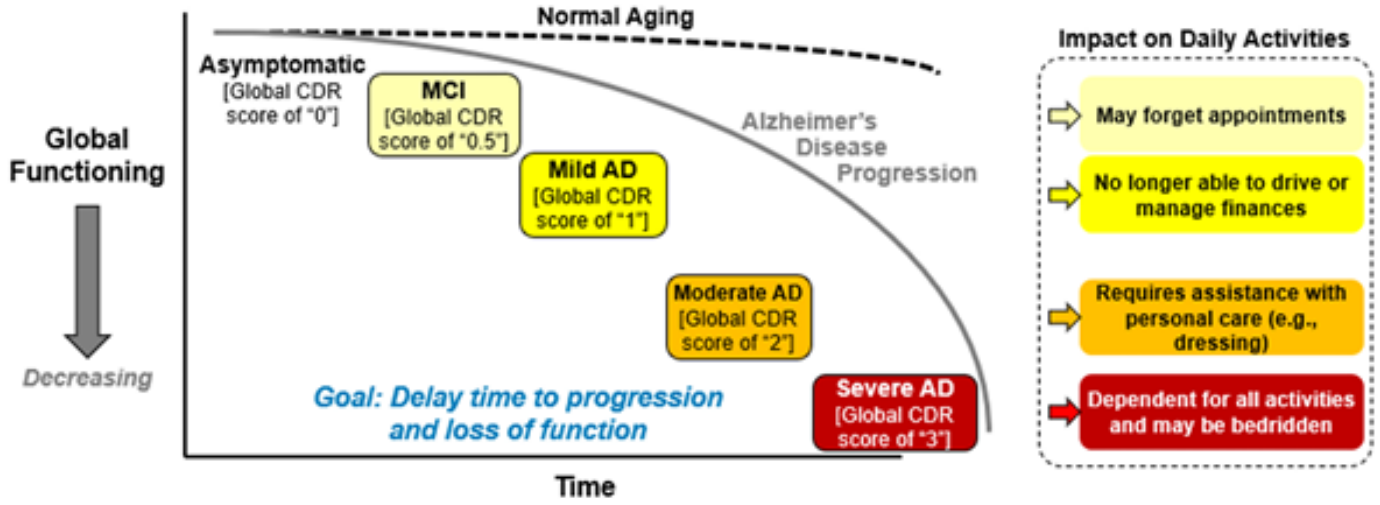
AD decline across the continuum versus normal aging





AD = Alzheimer´s disease, CDR = Clinical Dementia Rating, MCI = mild cognitive impairment

Source Sperling et al., 2011 (adapted)

Biological Definition of Alzheimer´s Disease and Biomarker profiles

Biomarker profiles and categories

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

A= Amyloid
T= Tau
N= Neurodegeneration

Jack et al.,Alz & Dem, 2018

Biological versus Clinical-biological definition

Definition and possible implications	AA 2024	IWG 2024
Definition of Alzheimer disease	Biological ("AD should be defined biologically not based on a clinical syndrome")	Clinical-biological ("AD is a clinical-biological construct")
Possible implications for the diagnosis in clinical setting	Presence of any abnormal core 1 AD biomarker (ie, fluid Aβ42/40, p-tau, etc) is sufficient.	Presence of objective cognitive deficits and AD biomarkers is needed.
	A biomarker-positive cognitively normal person can be diagnosed with AD.	A biomarker-positive cognitively normal person cannot be diagnosed with AD.[a]
Possible implications in diagnostic disclosure of individual's status	Cognitively normal persons with 1 positive core 1 AD biomarker can be told they have AD.	Cognitively normal persons with positive AD biomarker can be told they are at risk for AD.[a]
Possible implications for phase 3 preventive clinical trials	Biomarkers could be primary endpoints in clinical trials.	Biomarkers cannot be primary end points in clinical trials.
	Demonstration of efficacy on clinical parameters may not be necessary.	Demonstration of efficacy on clinical parameters is necessary.

Abbreviations: AA, Alzheimer Association; Aβ42/40, amyloid β 42/40; BM, biomarker; IWG, International Working Group; p-tau, phosphorylated tau.

[a] Except in the cases fulfilling the requirements for presymptomatic AD.

Dubois et al., JAMA Neurology, 2024

Amyloid and tauPET-positive cognitively unimpaired individuals are at high risk for future cognitive decline

Ossenkoppele et al., Nat Med 2022

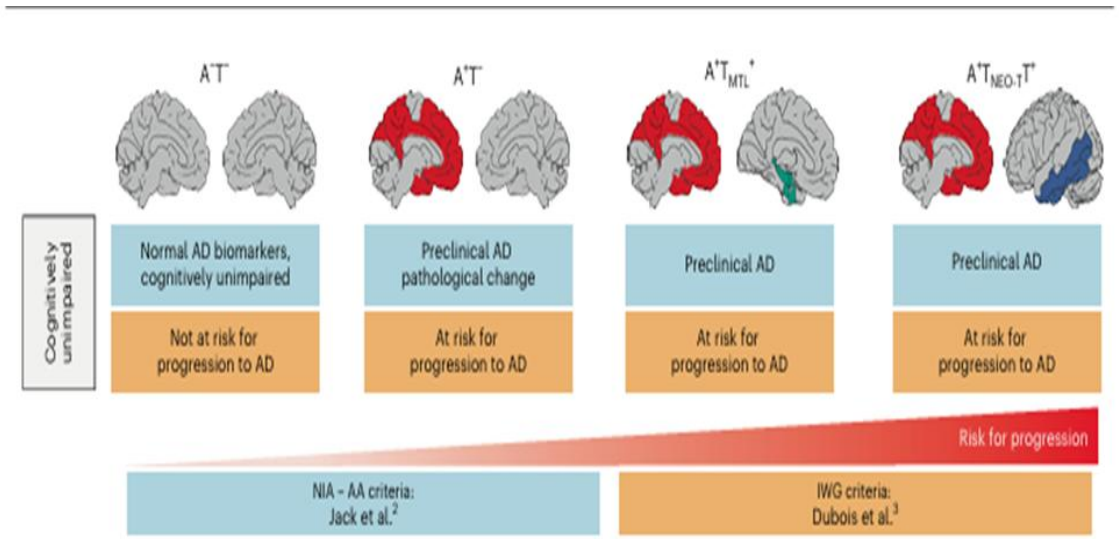
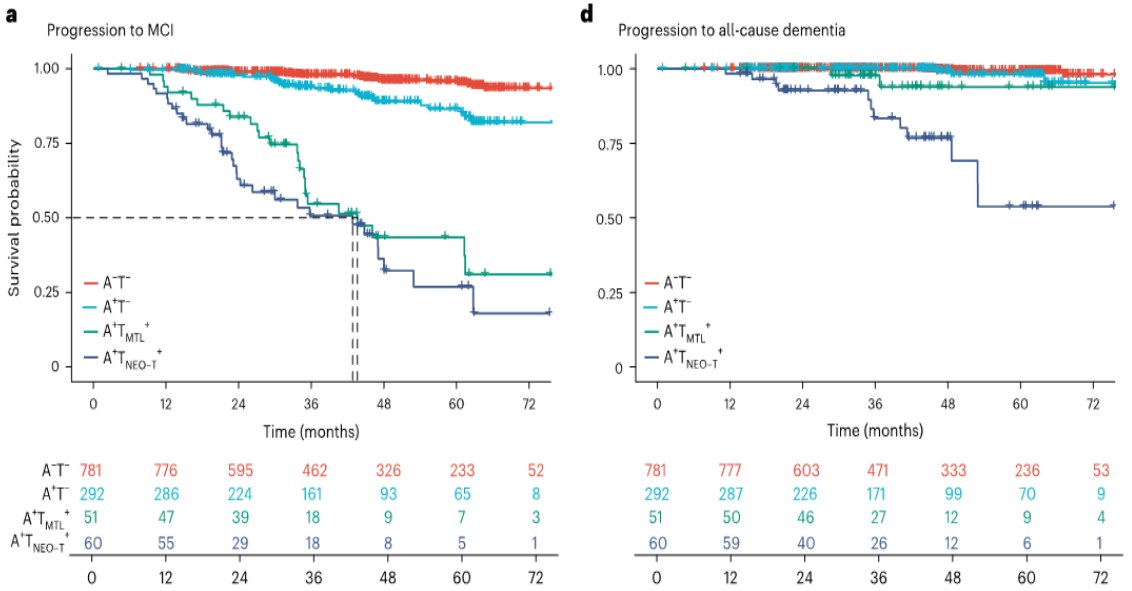


Fig. 1 | NIA-AA versus IWG criteria. Differences in the nomenclature of cognitively unimpaired individuals with (+) or without (−) in vivo biomarker evidence of Aβ (A) and tau (T) pathology in the NIA-AA versus IWG criteria for AD. Note that for the IWG criteria, the presumed 'risk for progression' level rises when both A and T biomarkers are positive.



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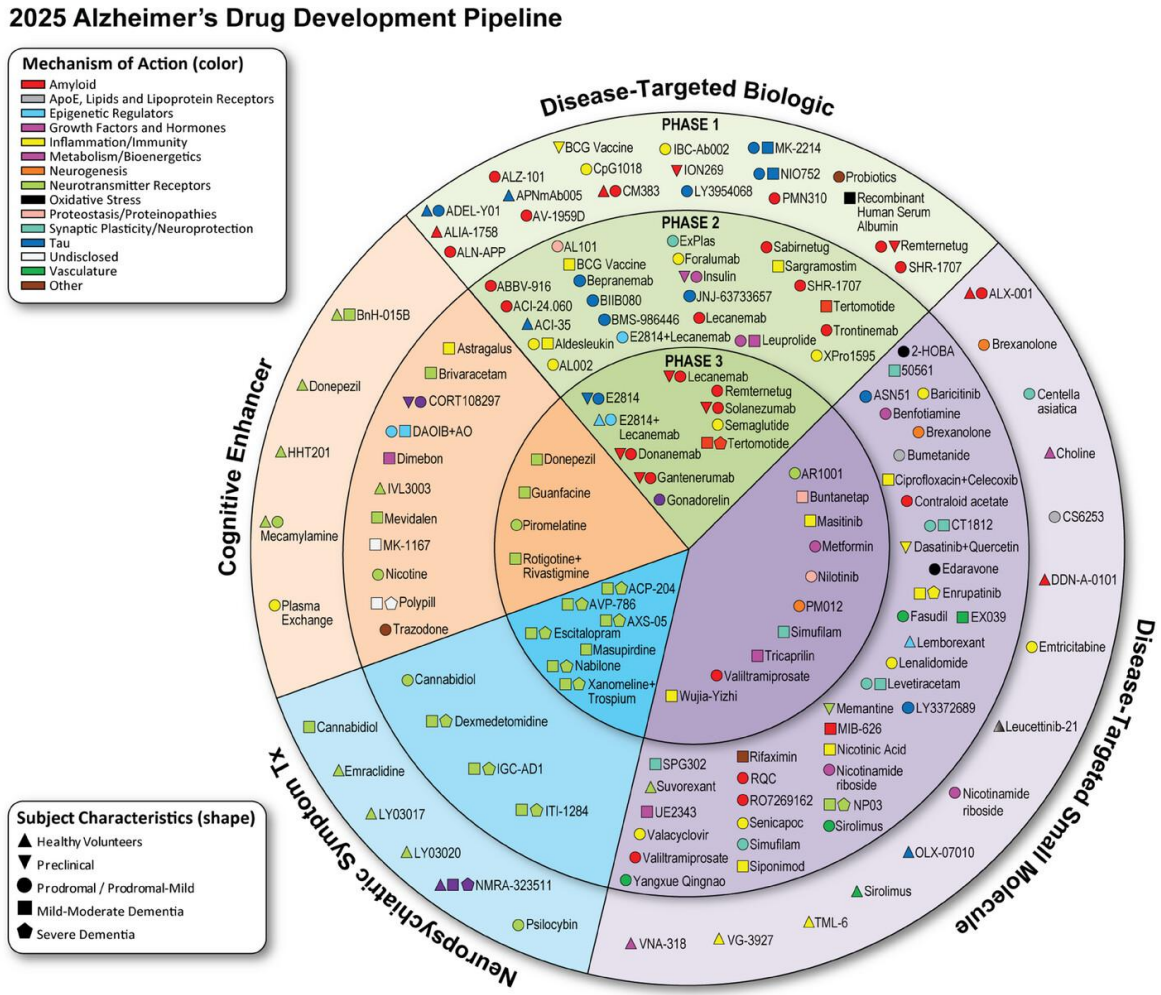
Available therapies

Alzheimer´s Drug development Pipeline

- The 2025 Alzheimer's disease drug development pipeline hosts 182 trials and 138 novel drugs.
- The 2025 Alzheimer's disease drug development pipeline is diverse, with agents that address 15 basic disease processes.
- The 2025 Alzheimer's disease drug development pipeline has more trials and more drugs than the 2024 pipeline.
- Biomarkers play an important role in current trials to determine trial eligibility and as outcomes of trials.
- Repurposed agents comprise approximately one-third of the agents and trials in the 2025 Alzheimer's disease drug development pipeline.

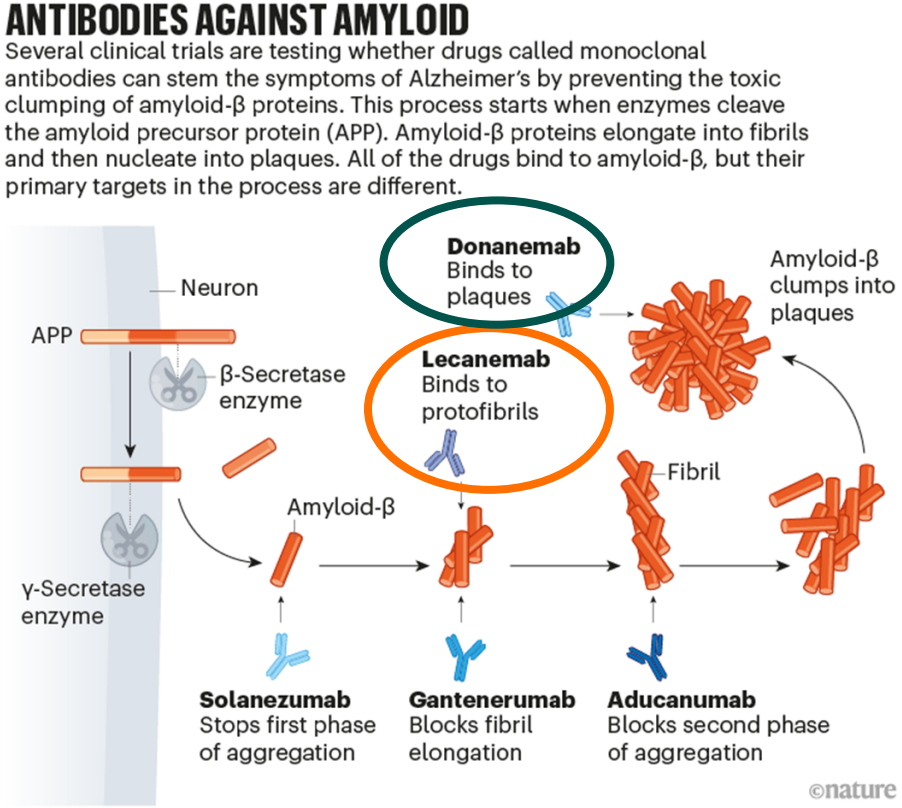


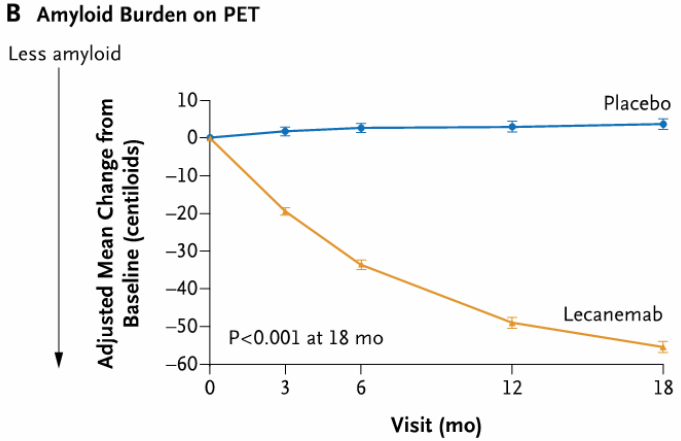
Cummings et al. 2025
https://doi.org/10.1002/trc2.70098

Available Treatments

Treatment	Asymptomatic	Mild cognitive impairment	Mild dementia	Moderate dementia	Severe Dementia
1997 **Donepezil** Cholinesterase-Inhibitor			■	■	
1997 **Galantamin** Cholinesterase-Inhibitor			■	■	
1998 **Rivastigmin** Cholinesterase-Inhibitor			■	■	
2002 **Memantine** NMDA receptor antagonist				■	■
2025 Lecanemab		■	■		
2025 Donanemab		■	■		

Antibodies targeting amyloid

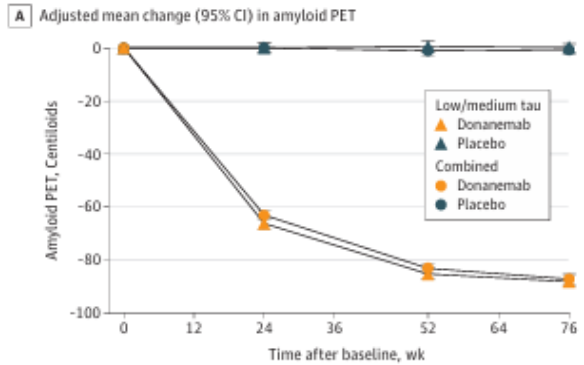




No. of Participants

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

Van Dyck et al., NEJM, 2023



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

Sims et al., JAMA, 2023

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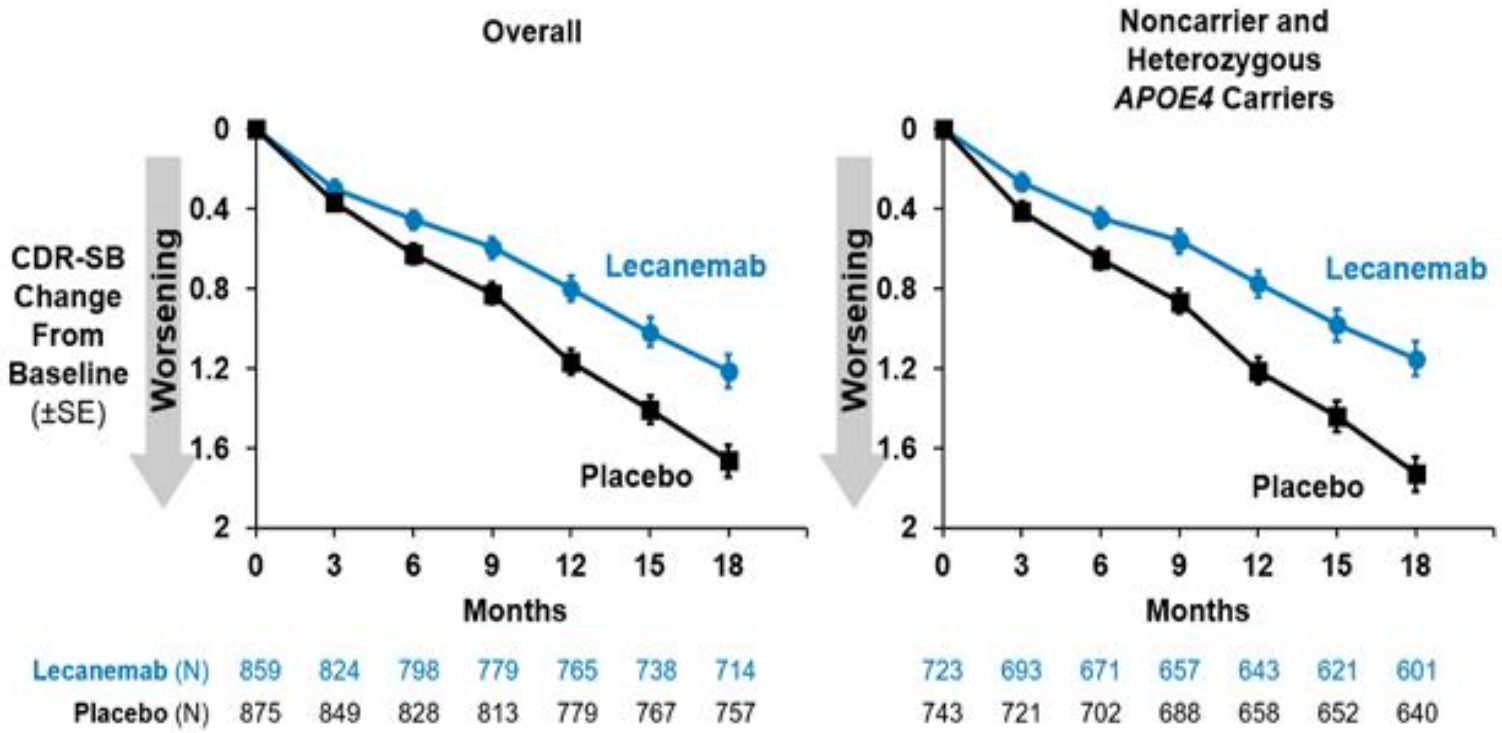
Lecanemab – Clarity study (n=1795)

Van Dyck et al., NEJM, 2023



Adjusted mean change from baseline in CDR-SB-study 301 core
https://www.ema.europa.eu/en/documents/assessment-report/leqembi-epar-public-assessment-report_en.pdf

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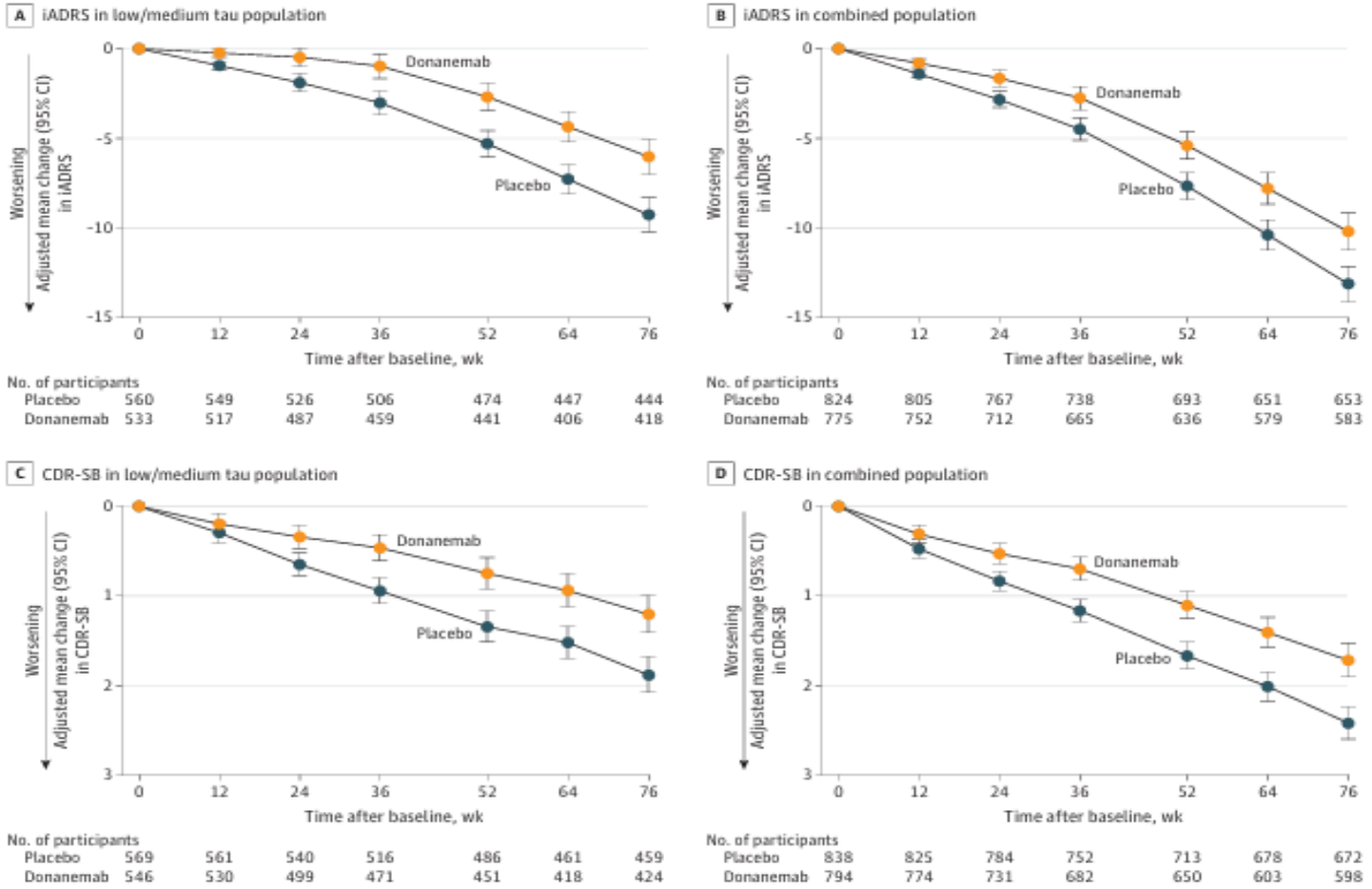
Donanemab: Trailblazer-ALZ 2 study (n=1736)

Sims et al., JAMA, 2023

Figure 2. Integrated Alzheimer Disease Rating Scale (iADRS) and Sum of Boxes of the Clinical Dementia Rating Scale (CDR-SB) From Baseline to 76 Weeks



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Efficacy has been demonstrated

The magnitude of the effects is robust using different imputation methods.

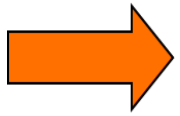
Leqembi and Kisunla are licensed after Re-Examination for the following indications:

- **Leqembi** is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early Alzheimer's disease) **who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes** with confirmed amyloid pathology.

- **Donanemab** is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early symptomatic Alzheimer's disease) **who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers** with confirmed amyloid pathology.

Safety – Focus on amyloid-related imaging abnormalities (ARIA): haemorrhages (ARIA-H) and oedema (ARIA-E)

- Brain parenchymal Aβ plaques are associated with gradual loss of cerebral vascular integrity and reduced perivascular clearance.
- In patients with pre-existing Aβ vascular pathology, anti-Aβ immunization may temporarily increase vascular vulnerability due to breakdown of plaques in response to immunisation.
- The incidence of ARIA (including the incidence of severe and fatal cases) correlated with the presence and number of ApoE4 alleles.



Treatment of early AD in patients who are not homozygotes for *APOE4*.

Safety comparison – ARIA

Table: Incidence of ARIA with 3rd generation anti-amyloid immunotherapies.
Data from EMERGE, TRAILBLAZER-ALZ, and Clarity AD trials (from Yadollahikhales and Rojas, 2023)

	Aducanumab		*Donanemab*		*Lecanemab*	
	Most effective dose	Placebo	Most effective dose	Placebo	Most effective dose	Placebo
All ARIA	41.3%	10.3%	38.9%	8%	26.6%	9.4%
ARIA-E	35.2%	2.7%	26.7%	0.8%	12.6%	1.7%
ARIA-H	19.1%	6.6%	30.5%	7.2%	14.0%	7.7%
Discontinuation	6.2%	0.6%	15%	4.8%	6.9%	2.9%
Death	1%	0.9%	0.8%	1.6%	0.7%	0.8%

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Risk minimisation measures (Leqembi and Kisunla)

- Both medicines are subject to **Controlled Access Programmes**

can only be prescribed when all RMMs are in place (distribution to preselected centers with multidisciplinary teams).

- **Contraindications** (beyond those in clinical development programmes)
  - Pre-treatment MRI findings of prior intracerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema, or other findings, which are suggestive of cerebral amyloid angiopathy (CAA).
  - Patients with bleeding disorders that are not under adequate control.
  - Treatment should not be initiated in patients receiving ongoing anticoagulant therapy.
  - /…/

- **Mandatory** regular **MRI** monitoring
- Healthcare Professional Guide and Checklist
- Patient Alert Card
- In case of Kisunla a modified titration regimen
- **PASS studies**

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Knowledge gaps

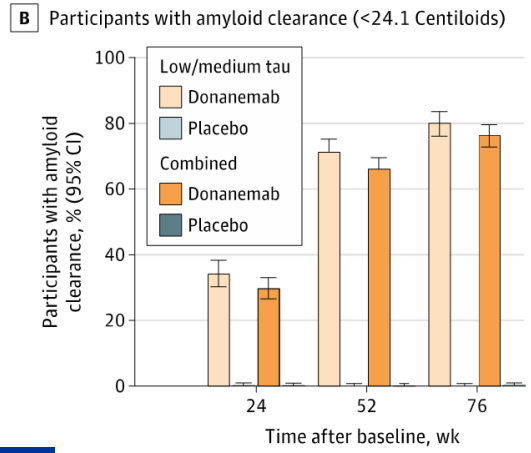
Knowledge gaps and what should be addressed in registries/ by real- world data

- Safety and risk minimisation measures, especially long-term consequences of ARIA – effects on cognition; brain atrophy

How long should be treated?

Lecanemab:
Treatment should be discontinued **once the patient progresses to moderate Alzheimer´s disease**

Donanemab:
Treatment should be maintained **until amyloid plaques are cleared** (e.g. at 6 or 12 months, see section 5.1) as confirmed using a validated method. The maximum treatment duration is 18 months which should not be exceeded even if plaque clearance is not confirmed. The benefit-risk of treatment should be reassessed at regular intervals on an individual basis and considering the rate of disease progression. Consideration should be given to discontinuing treatment before the end of the 18 months maximum treatment **if patients progress to moderate AD**.



Proportion of "amyloid-free" patients, in whom treatment with donanemab can be stopped:

- *After 6 months: 20-40%*
- *After 12 months: 60-70%*
- *After 18 months: 70-80%*

Sims et al., JAMA, 2023

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Knowledge gaps and what should be addressed in registries/ by real-world data

- Safety and risk minimisation measures, especially long-term consequences of ARIA – effects on cognition; brain atrophy

- Long-term treatment strategy (including criteria for discontinuation and retreatment), e.g. based on data of amyloid re-accumulation

Prevention strategies

Recommendation from the EU-IN Horizon Scanning Report on Alzheimer´s Disease:
"In line with the CNS WP workplan ("Develop consistent principles for feasible, efficient and robust data generation in the asymptomatic phase of neurodegenerative disorders. With an ageing population in the EU, and the observed progress in scientific research on the topic that could potentially allow prevention of symptomatic diseases, **a consistent approach to studying the asymptomatic phases of neurodegenerative disorders is highly needed"**), engaging discussions on how to investigate pre-clinical, asymptomatic AD in order to allow the development of a preventive approach."

- A4 (Anti-Amyloid treatment in Asymptomatic Alzheimer´s disease) study failed to show significant cognitive benefits in 4.5 years for Solanezumab in Preclinical Alzheimer´s Disease (Sperling et al; 2023)
- AHEAD study of Lecanemab in preclinial AD (Rafi et al. 2023) *ongoing*
- Trailblazer-ALZ 3 study of Donanmab in preclinical AD *ongoing*
- FINGER studies: A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial (Ngandu et al. 2015); https://fbhi.se/the-finger-study/

Dementia prevention in memory clinics: recommendations from the European task force for brain health services

Giovanni B. Frisoni,[a,*] Daniele Altomare,[a] Federica Ribaldi,[a] Nicolas Villain,[b,c] Carol Brayne,[d] Naaheed Mukadam,[e] Marc Abramowicz,[f] Frederik Barkhof,[g,h] Marcelo Berthier,[i] Melanie Bieler-Aeschlimann,[j,k] Kaj Blennow,[l] Andrea Brioschi Guevara,[j,m] Emmanuel Carrera,[n] Gaël Chételat,[o] Chantal Csajka,[p] Jean-François Demonet,[j,q] Alessandra Dodich,[r] Valentina Garibotto,[s] Jean Georges,[t] Samia Hurst,[u] Frank Jessen,[v,w,x] Miia Kivipelto,[y,z,aa,ab] David J. Llewellyn,[ac,ad] Laura McWhirter,[ae] Richard Milne,[d,af] Carolina Minguillón,[ag,ah,ai] Carlo Miniussi,[r,aj] José Luis Molinuevo,[ag,ak] Peter M. Nilsson,[al,am] Alastair Noyce,[an] Janice M. Ranson,[ac] Oriol Grau-Rivera,[ag] Jonathan M. Schott,[ao] Alina Solomon,[ap,aq,ab] Ruth Stephen,[ap] Wiesje van der Flier,[ar,as,at] Cornelia van Duijn,[au,av] Bruno Vellas,[aw] Leonie N. C. Visser,[y,ax] Jeffrey L. Cummings,[ay] Philip Scheltens,[ar,az] Craig Ritchie,[ba] and Bruno Dubois[b,c]

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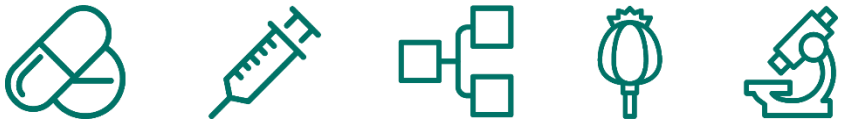
Lancet Regional Health Europe, 2023

Knowledge gaps and what should be addressed in registries/ by real-world data

- Safety and risk minimisation measures, especially long-term consequences of ARIA – effects on cognition; brain atrophy
- Long-term treatment strategy (including criteria for discontinuation and retreatment), e.g. based on data of amyloid re-accumulation
- Prevention of symptomatic AD (including in patients with subtle detectable abnormalities but no functional impairment)

Question:
How can we include asymptomatic individuals in registries if they are not identified unless they have one of the autosomal dominant/genetic forms or are included in studies with secondary prevention objectives?

Thank you very much for your attention!



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Zertifikat seit 2010
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Back-up slides

Clinical endpoints with robust effect sizes

Endpoint*	Leqembi (Lecanemab)	Kisunla (Donemab)
CDR-SB**	**-0.535 (95% CI:-0.778, -0.293)**	-0.69 (-0.95, -0.43)
i-ADRS***		**-2.65 (-1.04, -4.26)**
Cognition	ADAS-Cog14: -1.512 (-2.486, -0.538)	ADAS-Cog 13: -1.35 (-2.19. – 0.51)
Function	ADCS MCI-ADL: 1.936 (1.029, 2.844)	ADCS-ADL: 1.46 (.050, 2.42)
EQ-5DL	49% less decline	
QoL-AD	56% less decline	
ZBI	38% reduction	

* J2R for Missing Data Due to Death or Severe, Symptomatic, or Serious ARIA Events, and CIR for Other Reaseons
** Primary endpoint in Clarity study
*** Primary endpoint in Trailblazer AD2 study

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Leqembi

	All patients on PBO (N=897) % (n)	All patients on LEC (N=898) % (n)	APOE4 Noncarrier: PBO (N=286) % (n)	APOE4 Noncarrier: LEC (N=278) % (n)	APOE4 Carrier: PBO (N=611) % (n)	APOE4 Carrier: LEC (N=620) % (n)	APOE4 Heterozygous: PBO (N=478) % (n)	APOE4 Heterozygous: LEC (N=479) % (n)	APOE4 Non-Carrier and Heterozygous APOE4 carriers - PBO % (n)	APOE4 Non-Carrier and Heterozygous APOE4 carriers - LEC % (n)	APOE4 Homozygous: PBO (N=133) % (n)	APOE4 Homozygous: LEC (N=141) % (n)
ARIA-E	1.7 (15/897)	12.6 (113/898)	0.3 (1/286)	5.4 (15/278)	2.3 (14/611)	15.8 (98/620)	1.9 (9/478)	10.9 (52/479)	1.3 (10/764)	8.9 (67/757)	3.8 (5/133)	32.6 (46/141)
Symptomatic ARIA-E	-	2.8 (25/898)	-	1.4 (4/278)	-	3.4 (21/620)	-	1.7 (8/479)	-	1.6 (12/757)	-	9.2 (13/141)
ARIA-E SAEs	-	0.8 (7/898)	-	0.7 (2/278)	-	0.8 (5/620)	-	0.4 (2/479)	-	0.5 (4/757)	-	2.1 (3/141)
Recurrent ARIA-E events	0.1 (1/897)	3.1 (28/898)	0 (0)	0.4 (1/278)			0 (0)	1.5 (7/479)			0.8 (1/133)	14.2 (20/141)
Total ARIA-H (concurrent and isolated)	8.9 (80/897)	16.9 (152/898)	3.8 (11/286)	11.5 (32/278)	11.3 (69/611)	19.4 (120/620)	8.6 (41/478)	13.8 (66/479)	6.8 (52/764)	12.9(98/757)	22.1 (28/133)	39 (55/141)
Symptomatic ARIA-H*	0.2 (2/897)	1.2 11/898)	-	0.7 (2/278)	0.3 (2/611)	1.5 (9/620)	0.2 (1/478)	0.8 (4/479)	0.1 (1/764)	0.8 (6/757)	0.8 (1/133)	3.5 (5/141)
ARIA-H SAEs	-	0.2 (2/898)	-	0.4 (1/278)	-	0.5 (1/620)	-	-	-	0.1 (1/757)	-	0.7 (1/141)
Recurrent ARIA-H events	2.7 (24/897)	6.8 (61/898)	0.3 (1/286)	2.2 (6/278)			2.3 (11/478)	5.2 (25/479)			9 (12/133)	22 (31/141)
ICH[2] (incl. non TEAE)	0.2 (2/897)[1]	0.7 (6/898)[1]	0.3 (1/286)	0.4 (1/278)	0.2 (1/611)[1]	0.8 (5/620)[1]	0.2 (1/478)[1]	0.6 (3/479)[1]	0.3 (2/764)	0.5 (4/757)	-	1.4 (2/141)
Isolated ARIA-H[3]	7.7 (69/897)	8.7 (78/898)	3.5 (10/286)	7.9 (22/278)	9.7 (59/611)	9 (56/620)	7.3 (35/478)	8.1 (39/479)	5.9 (45/764)	8.1 (61/757)	18 (24/133)	12.1 (17/141)
Symptomatic isolated ARIA-H	0.2 (2/897)	0.2 (2/898)	-	-	0.3 (2/611)	0.3 (2/620)	0.2 (1/478)	0.4 (2/479)	0.1 (1/764)	0.3 (2/757)	0.8 (1/133)	-

*1. Includes one non-treatment emergent adverse event (non-TEAE) case in each treatment group: event occurred during study but > 30 days after discontinuing study medication; 2. ICH -Intracerebral haemorrhage (>1cm) or macrohaemorrhage; 3. ARIA-H in subjects who did not also experience ARIA-E at any time. *Overall and isolated*

Safety: Relative risks for ARIA/ ICH events – DON/ PBO vs. LEC/ PBO

Relative risk of ARIA and ICH>1cm in the Restricted Indicated Population in Study AACI-PC (DON) and Clarity-AD

	Heterozygotes + Noncarriers Study AACI-PC		Relative risk DON/ PBO [95% CI]	Heterozygotes + Noncarriers Legembi Clarity AD (301 core)		Relative risk LEC/ PBO [95% CI]
	PBO (N = 728) n (%)	Dona (N = 710) n (%)		PBO (N = 764) n (%)	LEC (N = 757) n (%)	
ARIA-E	13 (1.8)	146 (20.6)	11.5 [6.6, 20.1]	10 (1.3)	67 (8.9)	6.8 [3.5,13.0]
Symptomatic ARIA-E	0	40 (5.6)	NA	0	12 (1.6)	NA
SAE of ARIA-E	0	9 (1.3)	NA	0	4 (0.5)	NA
Recurrent ARIA-E	0	35 (4.9)	NA	NA	NA	NA
ARIA-H	89 (12.2)	196 (27.6)	2.3 [1.8,2.8]	52 (6.8)	98 (12.9)	1.9 [1.4, 2.6]
Symptomatic ARIA-H	2 (0.3)	8 (1.1)	4.1 [0.9,19.2]	1 (0.1)	6 (0.8)	6.1 [0.7,50.2]
Isolated ARIA-H	84 (11.5)	88 (12.4)	1.1 [0.8,1.4]	45 (5.9)	61 (8.1)	1.4 [0.9,2.0]
Concurrent ARIA-H (with ARIA-E)[ab]	3 (0.4)	90 (12.7)	31.8	NA	NA	NA
SAE of ARIA-H	0	2 (0.3)	NA	0	1 (0.1)	NA
Recurrent ARIA-H	24 (3.3)	70 (9.9)	3.0	NA	NA	NA
ICH>1cm	2 (0.3)	3 (0.4)	1.5 [0.3,9.2]	2 (0.3)	4 (0.5)	2.0 [0.4,11.0]
SAE of ICH>1cm	1 (0.1)	1 (0.1)	1	NA	NA	NA