

Monoclonal antibodies for early Alzheimer disease: a long road to discovery and marketing approval, a short timeline for health systems to organise services

Annachiara Cagnin¹  · Alberto Benussi^{2,3} · Camillo Marra^{4,5} · Laura Bonanni⁶ · Marco Bozzali⁷ · The SINdem Group

© Fondazione Società Italiana di Neurologia 2025

Disease-modifying drugs are now available for the treatment of early Alzheimer disease (AD). These agents belong to the class of monoclonal antibodies (mAbs) and target amyloid- β_{1-42} in different molecular epitopes and aggregation states [1]. In the United States, two anti-amyloid drugs are available on the market following approval by the Food and Drug Administration (FDA): lecanemab, approved in 2023, and donanemab, approved in 2024. Earlier, in 2022, another mAb, aducanumab, was available in the US before being withdrawn in 2024. Since then, other countries have aligned with the FDA's decision and licensed these anti-amyloid mAbs for clinical use in patients with mild cognitive impairment and mild dementia due to AD.

After extensive debate at the European Medicine Agency (EMA), lecanemab was eventually approved by the European Commission on 15 April 2025. Donanemab received

a positive recommendation in July 2025 and marketing authorisation on 25 September 2025.

The main concerns of the regulatory authorities relate to the modest clinical benefit demonstrated in clinical trials and the risk of side effects, notably amyloid related imaging abnormalities (ARIA), which can present as asymptomatic or symptomatic brain oedema/effusion (ARIA-E) and haemorrhages (ARIA-H) on magnetic resonance imaging (MRI). Both lecanemab and donanemab showed similar effect size in slowing disease progression (a reduction in disease progression on the CDR-SB scale of 27% with lecanemab and 29% with donanemab) [2, 3]. In the donanemab trial, a greater response (35% change) was observed in patients with low/medium tau-related neuropathological changes [3]. A 30% reduction in the slope trajectory translates in approximately a 5-month delay in expected cognitive and functional decline.

In clinical trials, ARIA-related side effects were detected in 21.5% of patients treated with lecanemab (vs. 9.5% with placebo) and 36.8% of those treated with donanemab (vs. 14.9% with placebo), and these were mostly asymptomatic [2, 3]. However, more recent data using a modified dose titration regimen for donanemab, with a lower starting dose, have shown a significant reduction in ARIA events, even in *APOE* $\epsilon 4$ carriers who are at higher risk of ARIA [4].

Following the EMA approval of the first anti-amyloid mAb, the Italian Drug Regulatory Agency (AIFA) will need to develop recommendations for patient inclusion criteria, protocols for drug administration and side effects monitoring, and the overall patient journey. Additionally, AIFA will need to define standards for the reorganization of dedicated healthcare services. Guidelines for appropriate use recommendations (AUR) are already available in the literature for both lecanemab [5, 6] and donanemab [7], and can serve as a baseline framework to be adapted to the context of the Italian healthcare system.

✉ Annachiara Cagnin
annachiara.cagnin@unipd.it

¹ Department of Neuroscience (DNS) and Padua Neuroscience Centre (PNC), University of Padova, Padova, Italy

² Neurology Unit, Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy

³ Neurology Unit, Hospital Care Department of Medicine, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy

⁴ Department of Psychology, Catholic University of the Sacred Heart, Milan, Italy

⁵ Memory Clinic, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy

⁶ Department of Medicine and Aging Sciences, "G. d'Annunzio" University of Chieti-Pescara, Pescara, Italy

⁷ Department of Neurosciences "Rita Levi Montalcini", University of Turin, Neurology 2 Unit, A.O.U. Città della Salute e Della Scienza di Torino, Turin, Italy

The work of the Italian Authorities should be guided by the optimization of the risk/benefit ratio, aiming to maximize clinical benefit and minimize the risk of ARIA. To maximize clinical benefit, accurate selection of patients with a higher probability of response to treatment is needed, i.e., those at an early disease stage and with biological evidence of AD pathology and absent or minimal co-pathology such as small vessel disease or Lewy body disease. To minimize the risk of side effects, a careful assessment of clinical, neuroimaging, and genetic factors predisposing to ARIA should be performed before treatment. After initiation, patients should be closely monitored clinically and radiologically for early detection of ARIA and prompt dosing modification (Fig. 1).

In this context, several issues require in-depth consideration and are not fully addressed in the published guidelines [5–7]. A panel of dementia experts affiliated with SIndem (The Italian Neurological Society for Dementia) has identified crucial themes in the patient journey and the need for health service reorganization to ensure efficient care for patients eligible for these treatments.

To optimize the diagnostic process, several clinical issues deserve consideration.

Inclusion/exclusion criteria:

- What is the minimum dataset (i.e., type of cognitive assessment; blood-based biomarkers; MRI;) that should be

used for case finding of suitable candidates, and which specialist should be primarily involved?

- Should a chronological upper age limit be established, and patient's frailty be considered an integrative variable?
- In the evaluation of patients with MCI due to AD, risk factors algorithm of progression should influence the clinician's decision-making process?
- Apart from patients with typical hippocampal amnesic syndrome, should other atypical AD variants be considered (e.g., those with a high probability of AD-related neuropathology as the primary cause, such as posterior cortical atrophy and logopenic aphasia, or nonfluent aphasia and corticobasal syndrome)?
- Which medical conditions and medications (in addition to anticoagulants) should constitute exclusion criteria for anti-amyloid mAbs?

Establishing a biological diagnosis:

- Which is the most cost-effective investigational pathway for a biological diagnosis?
- If CSF is considered the first-line investigation and amyloid-PET a second choice, how would this sequence be implemented in memory clinics without expertise or access to personnel who can perform lumbar punctures?

Eligible Subjects: Precise Selection

Reduced Prognostic Risk Factors For ARIA

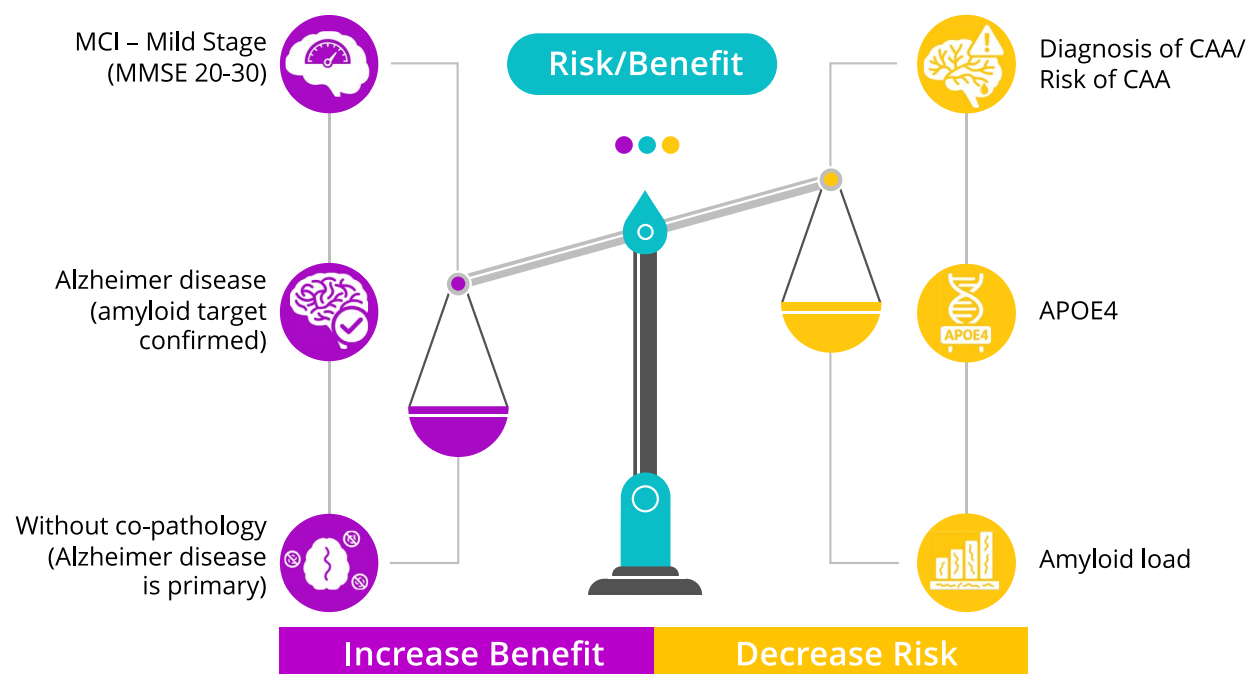


Fig. 1 The image shows the conditions related to the improvement of benefit (list on the left) and decrease of the risks (list on the right) to optimize the risk/benefit balance with the use of anti-amyloid monoclonal antibodies for mild Alzheimer disease

- When amyloid PET is used, will quantification of brain amyloid burden using centiloids or other metrics be necessary for a biological diagnosis, other than monitoring of response to therapy, or will visual assessment with validated criteria be sufficient?
- Should approved blood-based biomarkers (e.g., pTau₂₁₇/Aβ_{1–42} ratio) be considered as first-line screening if approved by EMA/AIFA, as recently suggested by the FDA?

To minimize risk of ARIA, the following issues should be considered.

Evaluation of ARIA risk:

- To what extent does detection of cortical siderosis and microbleeds differ between GE and SWI sequences, or between 1.5 T and 3 T MRI scanners?
- Should specific centres be selected for centralised MRI evaluation to align with the new Boston criteria for cerebral amyloid angiopathy and vascular burden assessment?
- Do patients who meet eligibility MRI criteria have an increased risk of ARIA (and how much) even if they have a low burden of CAA or cerebrovascular disease and (e.g., 1–3 microbleeds or a Fazekas scale score of 2)?
- Could an ARIA risk card, including clinical, radiological, and genetic features (e.g., *APOE* ε4 heterozygosity, arterial hypertension, cerebrovascular load, number of microbleeds, and amyloid load), be helpful in the management of treatment infusion?
- If patients with *APOE* ε4 heterozygosity are eligible, should the schedule of monitoring and follow-up be adjusted for these patients (e.g., the use of 3 T MRI scanners and SWI sequences to increase sensitivity to ARIA)?

How to manage ARIA side effects and mimickers:

- Given the higher risk of acute symptoms due to ARIA in patients on anti-amyloid drugs, is it necessary to implement a dedicated neuroimaging protocol to assess patients presenting at ER services with sudden focal onset symptoms, and if so, should those patients be referred directly to a hub centre of the stroke network?
- What is the best acute management treatment for stroke in these patients?
- What should be done if oral anticoagulation is suddenly required?

The greatest challenge will be adapting the organization of current memory services to the changes required by this

new paradigm of diagnostic and monitoring workup, scaling from a large number of potential candidates to the small percentage of patients (around 10%) expected to be eligible for this treatment. For case finding and first-level screening, a major game-changer could be the use of blood-based biomarkers to identify or exclude candidates for further investigations to reach a biological diagnosis. In May 2025, a diagnostic test based on detection of plasma pTau₂₁₇ and Aβ_{1–42} received FDA approval as an aid for AD diagnosis. Most validation studies suggest their use as screening tools, with two cut-offs providing an effective strategy to reduce the number of patients requiring CSF or amyloid PET assessment [8]. Moreover, the informative value of biological staging extends to the prognostic likelihood of rate of progression in symptomatic patients with AD [9]. This information, in association with clinical-demographic variables [10], can inform the clinician's decision making when evaluating the risk/benefit ratio in the real-world scenario of the memory clinics. In addition to this point, there is also a timely need for novel biomarkers to predict ARIA and to overcome the current limitations of MRI markers.

In the near future, the organization of dementia services would benefit from improved networking among health-care professionals and from the contribution of different specialists (clinicians, neuroradiologists, nuclear medicine physicians, biologists, geneticists, neuropsychologists). The application of virtual consultations could facilitate more efficient interactions. Interdisciplinary case discussion meetings will be essential for collective decisions about eligibility and patient management. Tele-consulting for neuro-image assessment could strengthen collaborations between local neuroradiologists and specialists at infusion centres, enabling a rapid exchange of information in cases of acute or subacute ARIA-like symptoms. There is a significant risk of inequity and limited access to treatments for certain subpopulations or regions, making it essential to implement a network to optimise referrals. The use of remote cognitive assessment may be useful to mitigate the negative impact of limited access to early diagnosis.

After two years of experience in the US and in other few Countries, recent published data on the use of anti-amyloid mAbs in real-world settings may inform clinicians on the best approach to management of these treatments and regulatory Authorities on the needs for the organization of dedicated health services [11]. A reorganization of health services for dementia is therefore mandatory in the context of a publicly-funded health system, such as the one available in Italy. There are urgent needs to be addressed before the widespread commercialization of mAbs. These include: 1) defining and preparing services capable of drug delivery to selected eligible patients; 2) implementing new modes of interdisciplinary streamlined communication; 3)

establishing a Pharmacovigilance Risk Assessment Committee to implement a patient register as well as post-authorization studies of safety and efficacy.

In conclusion, the availability of monoclonal antibodies marks a significant advance in the treatment of early Alzheimer's disease. While the introduction of these therapies poses important challenges for the Italian healthcare system, we believe that, with careful patient selection, rigorous monitoring, and appropriate organizational changes, these treatments can be implemented safely and effectively. The SINDem group strongly endorses the timely and responsible adoption of anti-amyloid monoclonal antibodies for eligible patients with Alzheimer's disease in Italy, and supports the development of clear, evidence-based protocols to ensure equitable access and optimal patient outcomes.

Acknowledgements

Co- Authors of the SINDem group

1. Federica Agosta
Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy
Center for Alzheimer's disease and related disorders (CARD), IRCCS Ospedale San Raffaele, Milan, Italy
Vita-Salute San Raffaele University, Milan, Italy
Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy
Neurotech Hub, Vita-Salute San Raffaele University, Milan, Italy
agosta.federica@hsr.it
2. Andrea Arighi
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
andrea.arighi@policlinico.mi.it
3. Giuseppe Bellelli
School of Medicine and Surgery, Milano Bicocca University and Acute Geriatric Unit, IRCCS Foundation San Gerardo dei Tintori, Monza, Italy
giuseppe.bellelli@unimib.it
4. Valentina Bessi
University of Florence, Department of NEUROFARBA (Neuroscience, Psychology, Drug Research and Child Health)
valentina.bessi@unifi.it
5. Giuseppe Bruno
Dept. of Human Neuroscience, Sapienza, University of Rome
giuseppe.bruno@uniroma1.it
6. Paolo Caffarra
Member of permanent committee of the Italian Ministry of Health on dementia
paolo.caffarra@unipr.it
7. Stefano F Cappa
Scuola Universitaria di Studi Superiori IUSS di Pavia, Pavia, Italy.
IRCCS Istituto Auxologico, Milan, Italy.
8. Chiara Cerami
Scuola Universitaria di Studi Superiori IUSS di Pavia, IUSS Cognitive Neuroscience (ICoN) Center, Pavia, Italy Istituti Clinici Scientifici Maugeri IRCCS, Brain e-Health Aging (BeA) Laboratory, Department of Neurorehabilitation, Milan, Italy
chiara.cerami@iusspavia.it
9. Carlo Ferrarese
Department of Medicine and Surgery and Milan Center for Neuroscience ((NeuroMI), University of Milano-Bicocca, Milan, Italy.
Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy.
10. Biancamaria Guarnieri
Center of Sleep Medicine, Department of Neurology, Villa Serena

Hospital, Città Sant'Angelo, Pescara, Italy and Fondazione Villaserena per la ricerca, Villaserena Hospital, Città Sant'Angelo, Pescara, Italy
bmariaguarnieri@villaserena.it

11. Alessandro Iavarone
UOC Neurologia Ospedale CTO AO Specialistica "Ospedali dei Colli" Napoli

aleiavarone@gmail.com

12. Antonina Luca

Department of Medical and Surgical Sciences and Advanced Technologies, "GF Ingrassia", University of Catania, Catania, Italy
antolucaster@gmail.com

13. Simona Luzzi

SOS Unità di Neurologia Cognitiva e Comportamentale, Clinica Neurologica, Università Politecnica delle Marche
Azienda Ospedaliero Universitaria delle Marche
s.luzzi@univpm.it

14. Roberto Monastero

Memory and Parkinson's disease Center Policlinico "Paolo Giaccone", Palermo, and Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.), University of Palermo, Italy
roberto.monastero@unipa.it

15. Silvia Daniela Morbelli

Department of Medical Sciences, University of Turin, Turin, Italy
Nuclear Medicine Unit, Città della Salute e della Scienza di Torino, Turin, Italy

silviadaniela.morbelli@unito.it

16. Benedetta Nacmias

Department of Neuroscience, Psychology, Drug Research and Child Health University of Florence, Florence, Italy
IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy

benedetta.nacmias@unifi.it

17. Leonardo Pantoni

Neuroscience Research Center, Department of Biomedical and Clinical Sciences, University of Milan

Department of Neurorehabilitation Sciences, Casa di Cura Igea, Milan, Italy.

leonardo.pantoni@unimi.it

18. Fabrizio Piazza

CAA and AD Translational Research and Biomarkers Lab, School of Medicine, iCA β International Network, University of Milano-Bicocca, Monza, Italy.

fabrizio.piazza@unimib.it

19. Andrea Pilotto

Department of Clinical and Experimental Sciences, University of Brescia, Italy.

Department of continuity of care and frailty, Neurology Unit, ASST Spedali Civili Hospital, Brescia, Italy.

Neurobiorepository and Laboratory of Advanced Biological Markers, University of Brescia and ASST Spedali Civili Hospital, Brescia, Italy.
Center for Alzheimer Research, Division of Clinical Geriatrics Department of Neurobiology, Care Sciences and Society (NVS) Karolinska Institutet, Stockholm, Sweden.

pilottoandreae@gmail.com

20. Davide Quaranta

Neurology Unit, Foundation Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

davidequaranta@hotmail.it

21. Pietro Tiraboschi

Neurologia e Neuropatologia, Istituto Neurologico Carlo Besta, Milano, Italia

pietro.tiraboschi@istituto-besta.it

22. Enza Maria Valente

Department of Molecular Medicine, University of Pavia, Pavia, Italy
Neurogenetics Research Centre, IRCCS Mondino Foundation, Pavia, Italy

enzamaria.valente@unipv.it

23. Annalena Venneri

Department of Medicine and Surgery, University of Parma, Parma, Italy

Department of Neuroscience, University of Sheffield, UK

annalena.venneri@unipr.it

24. Gianluigi Zanusso

Section of Neurology, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona

gianluigi.zanusso@univr.it

Authors' contribution All main Authors contributed to study concept, preparations of materials and drafting the manuscript. The Authors within the SINDem group participated in revision of the manuscript.

Funding No funds, grants, or other support was received.

Data availability not applicable.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. The research does not involve data or materials from human participants and ethic approval or consent were not needed as confirmed by the Hospital Ethic Committee of Gemelli Hospital.

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Informed consent Human materials are not used and expert views do not need informed consent.

References

- Heneka MT, Morgan D, Jessen F (2024) Passive anti-amyloid β immunotherapy in Alzheimer's disease—opportunities and challenges. *Lancet* 404:2198–2208
- van Dyck CH, Swanson CJ, Aisen P et al (2023) Lecanemab in early Alzheimer's disease. *N Engl J Med* 388:9–21. <https://doi.org/10.1056/NEJMoa2212948>
- Sims JR, Zimmer JA, Evans CD et al (2023) Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA* 330:512–527. <https://doi.org/10.1001/jama.2023.13239>
- Wang H, SerapMonkul Nery E, Ardayfio P et al (2025) Modified titration of donanemab reduces ARIA risk and maintains amyloid reduction. *Alzheimers Dement*. <https://doi.org/10.1002/alz.70062>
- Cummings J, Apostolova L, Rabinovici GD (2023) Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis* 10:362–377
- Villain N, Planche V, Lilamand M et al (2025) Lecanemab for early Alzheimer's disease: appropriate use recommendations from the French federation of memory clinics. *J Prev Alzheimers Dis* 12:100094
- Rabinovici GD, Selkoe DJ, Schindler SE (2025) Donanemab: appropriate use recommendations. *J Prev Alzheimers Dis* 12:100150. <https://doi.org/10.1016/j.tjpad.2025.100150>
- Palmqvist S, Warmenhoven N, Anastasi F (2025) Plasma phospho-tau217 for Alzheimer's disease diagnosis in primary and secondary care using a fully automated platform. *Nat Med*. <https://doi.org/10.1038/s41591-025-03622-w>
- Johnson DR, Wiste HJ, Lowe V et al (2025) Staging Alzheimer's disease through amyloid and tau PET. *Brain*. <https://doi.org/10.1093/brain/awaf346>. Online ahead of print
- Carrarini C, Caraglia N, Quaranta D et al (2025) Risk factors of dementia in a cohort of individuals with mild cognitive impairment in the Italian Interceptor project. *Eur J Neurol*. <https://doi.org/10.1111/ene.16591>
- Paczynski M, Hofmann A, Posey Z (2025) Lecanemab treatment in a specialty memory clinic. *JAMA Neurol* 12:e251232. <https://doi.org/10.1001/jamaneurol.2025.1232>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.