

EFFICACY AND SAFETY OF ANTI-AMYLOID ANTIBODIES IN EARLY ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW OF LECANEMAB AND DONANEMAB

PAULO HENRIQUE LUIS DA SILVA JÚNIOR¹, YANLEY LÚCIO NOGUEIRA²

1. Graduando em Medicina na Universidade Federal de Goiás (UFG), Goiânia/GO, Brasil.

2. Médico Psiquiatra no Médico Psiquiatra no Hospital das Clínicas da UFG (HC-UFG), Goiânia/GO, Brasil.

ABSTRACT

Alzheimer's disease has historically been treated with symptomatic drugs, without consistent modification of its biological course. The recent approval of anti-amyloid monoclonal antibodies has changed this landscape, especially for patients with mild cognitive impairment or mild dementia associated with amyloid pathology. This systematic review without meta-analysis assessed evidence on the efficacy and safety of lecanemab and donanemab in early Alzheimer's disease. Randomized, double-blind, placebo-controlled clinical trials evaluating these drugs in biomarker-confirmed Alzheimer's disease were included. The synthesis followed PRISMA 2020 and SWiM recommendations, grouping findings by drug, trial phase, cognitive-functional outcomes, biomarkers, and adverse events. Four clinical trials met eligibility criteria. Lecanemab and donanemab reduced amyloid burden and slowed cognitive-functional decline in phase 3 studies, although the absolute magnitude of benefit was moderate. The main adverse events were amyloid-related imaging abnormalities, infusion-related reactions, and rare hemorrhagic events, with higher risk among ApoE $\epsilon 4$ carriers. The findings suggest a real but limited therapeutic advance, restricted to carefully selected patients and dependent on biomarker confirmation, serial magnetic resonance imaging, and healthcare infrastructure able to recognize and manage treatment-related adverse events.

Keywords: Alzheimer disease, Amyloid beta-Peptides, Antibodies monoclonal, Mild Cognitive impairment, Systematic review.

INTRODUCTION

Alzheimer's disease remains one of the neurological conditions with the greatest clinical and social impact. Its relevance is not limited to how frequently it occurs among dementias. The burden of the disease also lies in the way it progressively transforms memory, language, autonomy, family caregiving, and the organization of healthcare services. For decades, pharmacological treatment was restricted to symptomatic interventions, such as acetylcholinesterase inhibitors and memantine, which are useful in certain contexts but are unable to demonstrably modify the central neuropathological processes of the disease. This gap between clinical impact and therapeutic limitations has made the search for disease-modifying treatments one of the most persistent areas of research in neurology.

In recent years, the very definition of Alzheimer's disease has shifted. Diagnosis is no longer based solely on the syndromic recognition of an amnestic dementia and has increasingly incorporated amyloid, tau, and neurodegeneration biomarkers. The AT(N) model, proposed in the NIA-AA Research Framework, organized the disease according to measurable biological processes, separating the clinical syndrome from the neuropathological etiology.¹ More recent criteria from the Alzheimer's Association reinforced this direction by stating that core biomarkers, including amyloid PET, approved cerebrospinal fluid markers, and accurate plasma biomarkers, can establish the biological diagnosis of the disease in appropriate contexts.² This change is not merely conceptual. It has become a practical requirement for prescribing beta-amyloid-targeted therapies.

Lecanemab and donanemab have emerged in this context. Both are anti-amyloid monoclonal antibodies, but they are not identical. Lecanemab is a humanized IgG1 antibody with greater affinity for soluble beta-amyloid aggregates, particularly protofibrils.³ Donanemab recognizes an N-terminally truncated and pyroglutamylated form of beta-amyloid, found predominantly in established plaques.⁴ This distinction is relevant because the two drugs differ not only in epitope but also in clinical development design, biomarker selection, dosing regimen, and monitoring strategy.

Phase 3 clinical trials produced statistically favorable results. Clarity AD demonstrated that lecanemab reduced amyloid markers and resulted in less decline on the Clinical Dementia Rating Scale Sum of Boxes in patients with early Alzheimer's disease.⁵ TRAILBLAZER-ALZ 2 showed that donanemab slowed clinical progression in patients with early symptomatic Alzheimer's disease, positive amyloid status, and different levels of tau pathology.⁶ These findings represented a turning point compared with previous attempts at anti-amyloid therapies, many of which were marked by negative or controversial clinical results.

However, interpretation of these studies requires caution. Relative percentages of slowing, such as 27%, 29%, or 35%, may suggest a more substantial effect than that observed in absolute units on clinical scales. Contemporary discussion regarding clinically meaningful differences in Alzheimer's disease shows that statistical significance and clinical perception by the patient or caregiver are not equivalent.⁷ In addition, amyloid removal should not automatically be treated as synonymous with sufficient functional benefit. The field of anti-amyloid therapy itself has been built around the tension between biomarker improvement, mean clinical effect, and applicability outside the controlled environment of clinical trials.

Safety also occupies a central position. Lecanemab and donanemab are associated with amyloid-related imaging abnormalities, known by the acronym ARIA. These abnormalities include edema or effusion, classified as ARIA-E, and hemorrhagic changes, such as microhemorrhages and superficial siderosis, classified as ARIA-H. Most events in the trials were asymptomatic, but symptomatic, severe, and rarely fatal cases have been described.^{8,9} The risk is higher in ApoE ϵ 4 carriers, especially homozygotes, and is also related to pre-existing findings of cerebral amyloid angiopathy, microhemorrhages, anticoagulation, and the need for thrombolysis in situations of suspected stroke.

The arrival of these drugs in the Brazilian debate makes the issue even more complex. The position paper of the Scientific Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology states that anti-amyloid antibodies provide modest clinical benefits, relevant risks, and important challenges related to diagnostic access, cost-effectiveness, safety, and population representativeness.¹⁰ The Brazilian Health Regulatory Agency approved donanemab in 2025 and lecanemab in 2025 for adult patients in the early stage of the disease, with restriction to ApoE ϵ 4 non-carriers or heterozygotes.^{11,12} Even so, regulatory approval alone does not resolve clinical

implementation. Treatment depends on early diagnosis, biomarker confirmation, serial magnetic resonance imaging, an infusion center, and a team capable of managing ARIA.

Given this scenario, the relevant question is not merely whether anti-amyloid antibodies work. The more precise question is in which patients, with what magnitude of benefit, under what level of risk, and under what implementation conditions they may be considered. This systematic review analyzes the efficacy and safety of lecanemab and donanemab in early Alzheimer's disease, using a structured narrative synthesis without meta-analysis.

OBJECTIVES

The general objective of this study was to systematically analyze the available evidence on the efficacy and safety of lecanemab and donanemab in the treatment of early Alzheimer's disease.

The specific objectives were to describe the characteristics of the randomized clinical trials that evaluated these drugs; synthesize the main cognitive and functional outcomes, including the Clinical Dementia Rating Scale Sum of Boxes, Integrated Alzheimer's Disease Rating Scale, Alzheimer's Disease Assessment Scale Cognitive Subscale, and measures of activities of daily living; analyze the effects on amyloid and tau biomarkers, when available; identify the frequency and clinical relevance of adverse events, with emphasis on ARIA-E, ARIA-H, infusion-related reactions, serious adverse events, and treatment discontinuation; and discuss the clinical applicability of the findings in light of the need for biomarker-based selection, ApoE stratification, serial magnetic resonance imaging, and healthcare infrastructure.

METHODS

A systematic literature review without meta-analysis was conducted, using a structured narrative synthesis. The reporting followed the PRISMA 2020 recommendations for systematic reviews and incorporated SWiM principles for synthesis without meta-analysis, since the included studies differed substantially in terms of drug, development phase, primary scale, biomarker criteria, follow-up duration, and outcome reporting.^{13,14} The protocol was not prospectively registered.

The research question was formulated according to the PICO strategy. The population included adults with early Alzheimer's disease, defined as mild cognitive impairment or mild dementia associated with Alzheimer's disease, with biomarker confirmation of amyloid pathology. The interventions were lecanemab or donanemab. The comparator was placebo. Outcomes included cognitive-functional decline, biomarker changes, ARIA-E, ARIA-H, infusion-related reactions, serious adverse events, treatment-related deaths, and discontinuation.

Publications from January 2020 to June 2026 were considered, a period selected to encompass the consolidation of phase 2 and phase 3 clinical trials of the studied drugs, as well as regulatory publications and appropriate-use recommendations. The databases searched were PubMed/MEDLINE, the Virtual Health Library, Cochrane Library, SciELO, and Google Scholar as a complementary source. Reference lists of the included articles and regulatory or clinical guidance documents directly related to implementation of the drugs were also reviewed.

The search strategy combined terms in English and Portuguese related to early Alzheimer's disease, lecanemab, donanemab, anti-amyloid antibodies, efficacy, safety, and ARIA. In PubMed/MEDLINE, the main strategy was: ("Alzheimer Disease" OR "early Alzheimer's disease" OR "mild cognitive impairment" OR "mild dementia") AND (lecanemab OR donanemab OR "anti-amyloid monoclonal antibody") AND (efficacy

OR safety OR "amyloid-related imaging abnormalities" OR ARIA OR "CDR-SB" OR iADRS). In the VHL and SciELO, equivalent terms in Portuguese were used: ("Doença de Alzheimer" OR "comprometimento cognitivo leve" OR "demência leve") AND (lecanemabe OR donanemabe OR "anticorpos monoclonais anti-amiloide") AND (eficácia OR segurança OR ARIA OR "anormalidades de imagem relacionadas ao amiloide").

Randomized, double-blind, placebo-controlled clinical trials evaluating lecanemab or donanemab in patients with early Alzheimer's disease and biomarker confirmation of amyloid pathology were included. Phase 2 and phase 3 studies were eligible provided that they reported clinical efficacy and safety data. Preclinical studies, animal studies, case reports, editorials, commentaries, conference abstracts without full text, studies of other anti-amyloid antibodies without separate analysis of lecanemab or donanemab, studies in moderate or severe Alzheimer's disease, and publications without clinical outcomes, biomarkers, or safety data were excluded.

Records were initially screened by title and abstract. Potentially eligible full-text articles were then reviewed. Data extraction included author, year, drug, study phase, design, number of participants, age, clinical stage, biomarker criteria, intervention, comparator, duration, primary outcome, main secondary outcomes, biomarker changes, ARIA-E, ARIA-H, infusion-related reactions, serious adverse events, treatment-related deaths, and methodological limitations.

Risk of bias assessment for the clinical trials was planned according to the domains of the Cochrane RoB 2 tool, considering the randomization process, deviations from intended interventions, missing data, outcome measurement, and selection of reported results. As this was a literature review based on secondary data and public documents, submission to a Research Ethics Committee was not required.

Regulatory documents, appropriate-use recommendations, diagnostic guidelines, reviews on ARIA, national position statements, and health technology assessments were not treated as clinical trials included in the main synthesis. These texts were used as complementary references to interpret safety, eligibility, monitoring, and applicability. This separation was adopted to preserve the methodological coherence of the systematic review and to avoid synthesizing documents of different natures as if they represented the same level of evidence.

RESULTS AND DISCUSSION

The search and full-text review identified four randomized clinical trials eligible for the main synthesis: one phase 2b study of lecanemab, Clarity AD, TRAILBLAZER-ALZ phase 2, and TRAILBLAZER-ALZ 2.3-6 Complementary documents included appropriate-use recommendations for lecanemab and donanemab, the Brazilian position statement of the Brazilian Academy of Neurology, diagnostic guidelines, publications on ARIA, documents from the Brazilian Health Regulatory Agency, an assessment by the National Institute for Health and Care Excellence, and a recent Cochrane review on anti-amyloid antibodies.^{1,2,7-12,15-21}

Table 1: Main Characteristics of the Included Clinical Trials.

Study	Drug	Phase	Participants	Population	Entry Biomarkers	Primary Outcome	Duration
BAN2401-G 000-2013	Lecanemab	2b	854 treated	Early Alzheimer's disease	Amyloid positive	ADCOMS at 12 months	18 months
Clarity AD5	Lecanemab	3	1.795	Mild cognitive impairment or mild dementia due to Alzheimer's disease	Amyloid by PET or cerebrospinal fluid	CDR-SB at 18 months	18 months
TRAILBLAZER-ALZ4	Donanemab	2	257	Early symptomatic Alzheimer's disease	Amyloid and tau by PET	iADRS at 76 weeks	76 weeks
TRAILBLAZER-ALZ 26	Donanemab	3	1.736	Mild cognitive impairment or mild dementia due to Alzheimer's disease	Amyloid and tau by PET	iADRS at 76 weeks	76 weeks

Source: Authors' own elaboration, 2026.

The development pathway of these drugs shows that the positive phase 3 results did not emerge in a linear manner. In the phase 2b study of lecanemab, the primary Bayesian objective at 12 months was not met. The 10 mg/kg dose administered every two weeks had a 64% probability of being superior to placebo by at least 25% on the Alzheimer's Disease Composite Score, below the prespecified threshold of 80%.³ At 18 months, however, the same dose showed amyloid reduction and favorable signals on the Alzheimer's Disease Composite Score, Alzheimer's Disease Assessment Scale Cognitive Subscale, and Clinical Dementia Rating Scale Sum of Boxes.³ This result should not be interpreted as either a simple failure or an unequivocal success. It shows that the clinical effect of these antibodies may depend on treatment duration, dose selection, choice of scale, and the relationship between biomarker and functional outcome.

Clarity AD was the confirmatory study of lecanemab. In this trial, 1,795 patients with early Alzheimer's disease received lecanemab 10 mg/kg every two weeks or placebo. The primary outcome was the change in the Clinical Dementia Rating Scale Sum of Boxes at 18 months. The lecanemab group worsened by 1.21 points, whereas the placebo group worsened by 1.66 points, a difference of -0.45 points, corresponding to a 27% relative slowing.⁵ Secondary outcomes also favored lecanemab, including the Alzheimer's Disease Assessment Scale Cognitive Subscale, Alzheimer's Disease Composite Score, and Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for Mild Cognitive Impairment.⁵ Appropriate interpretation of this result requires clarity about what it represents. Lecanemab did not improve patients' cognition. It reduced the mean rate of decline in a selected population followed under clinical trial conditions.

The phase 2 study of donanemab, TRAILBLAZER-ALZ, included 257 patients with early symptomatic Alzheimer's disease and amyloid and tau positivity on PET. Donanemab was administered every four weeks, at 700 mg for the first three doses and 1,400 mg thereafter. The primary outcome was the change in the Integrated Alzheimer's Disease Rating Scale at 76 weeks. The change was -6.86 points with donanemab and -10.06 with placebo, a difference of 3.20 points.⁴ Although the primary endpoint favored the drug, most secondary outcomes did not show substantial differences.⁴ This finding is important because it prevents an overly homogeneous interpretation. Donanemab showed a clinical signal and

marked amyloid reduction, but clinical consistency still needed to be tested in a larger sample.

TRAILBLAZER-ALZ 2 expanded this evidence. The study included 1,736 participants with early symptomatic Alzheimer's disease, amyloid positivity, and low/medium or high tau pathology. Donanemab was compared with placebo for 76 weeks. In the low/medium tau population, the change in the Integrated Alzheimer's Disease Rating Scale was -6.02 in the donanemab group and -9.27 in the placebo group, a difference of 3.25 points. In the combined population, the difference was 2.92 points. On the Clinical Dementia Rating Scale Sum of Boxes, the difference was -0.67 in the low/medium tau population and -0.70 in the combined population.⁶ The study therefore demonstrated a statistically significant slowing of progression. At the same time, the need for stratification by tau and amyloid reinforces that the observed effect applies to a biologically selected population.

Table 2: Main Clinical Efficacy Results.

Study	Primary Scale	Main Result	Interpretation
Swanson, Zhang, Dhadda, Wang, Kaplow, Lai, Lannfelt, Bradley, Rabe, Koyama, Reyderman, Berry, Gordon, Kramer e Cummings ³	ADCOMS	Primary endpoint at 12 months not met; favorable signals at 18 months	Study provided the rationale for dose selection and phase 3, with an initially negative primary result
van Dyck, Swanson, Aisen, Bateman, Chen, Gee, Kanekiyo, Li, Reyderman, Cohen, Froelich, Katayama, Sabbagh, Vellas, Watson, Dhadda, Inzarray, Kramer e Iwatsubo ⁷	CDR-SB	Difference of -0.45 points at 18 months	Statistically significant slowing, with modest absolute magnitude
Mintun, Lo, Evans, Wessels, Ardayio, Andersen, Shcherbinin, Sparks, Sims, Brys, Apostolova, Salloway e Skovronsky ⁶	iADRS	Difference of 3.20 points at 76 weeks	Favorable primary outcome, with mixed secondary outcomes
Sims, Zimmer, Evans, Lu, Ardayio, Sparks, Wessels, Shcherbinin, Wang, Monkul Nerv, Collins, Solomon, Salloway, Apostolova, Hansson, Ritchie, Brooks, Mintun e Skovronsky ⁶	iADRS	Difference of 3.25 points in the low/medium tau group and 2.92 in the combined population	Statistically significant slowing in a phase 3 study

Source: Authors' own elaboration, 2026.

The efficacy synthesis allows an initial conclusion: both drugs showed a favorable clinical effect in phase 3 studies. The question that remains concerns the clinical magnitude of this effect. The rapid review by Muir, Hill, Black, and Smith identified previously published thresholds for clinically important differences in scales used in Alzheimer's disease trials. For mild cognitive impairment, approximately +1 point on the Clinical Dementia Rating Scale Sum of Boxes, -5 points on the Integrated Alzheimer's Disease Rating Scale, +2 to +3 points on the Alzheimer's Disease Assessment Scale Cognitive Subscale, and -1 to -2 points on the Mini-Mental State Examination were considered meaningful. For mild Alzheimer's disease, the thresholds were even higher.⁷ The mean differences observed in the lecanemab and donanemab studies fall below some of these thresholds. This does not invalidate the trials, but it requires a distinction between mean population effect, clinically perceptible difference, and possible individual benefit.

The difficulty lies in translating a group mean into the life of an individual patient. In neurodegenerative diseases, slowing decline may be relevant even when the change on a scale is small. Preserving a few months of autonomy may have value for the patient and family. However, this argument does not justify overstating the result. The scientific text must hold both ideas together. There is statistical and biological benefit. There is also uncertainty regarding the clinical perception of its magnitude.

Biomarkers showed a more robust response than clinical scales. The phase 2b lecanemab study demonstrated amyloid reduction on PET with the 10 mg/kg every-two-weeks regimen.³ Clarity AD confirmed a reduction in amyloid burden and favorable changes in disease-related biomarkers.⁵ In the phase 2 donanemab study, there was a marked reduction in amyloid plaques, with a difference of 85.06 centiloids compared with placebo.⁴ TRAILBLAZER-ALZ 2 also demonstrated amyloid reduction and supported the strategy of discontinuing treatment when amyloid burden reached low levels, a particular feature of donanemab.⁶

This relative dissociation between biomarker effect and clinical magnitude is one of the central issues of the review. Lecanemab and donanemab alter the biological target they are intended to affect. The question is not whether they remove amyloid, but how much that removal translates into measurable and clinically valued functional benefit. The 2026 Cochrane review, evaluating anti-amyloid monoclonal antibodies as a class, concluded that mean effects on cognition and function were small or trivial, while events such as cerebral edema and microhemorrhages increased.²¹ This conclusion should be interpreted with caution because it groups older and newer drugs with distinct mechanisms and performance. Even so, it serves as a necessary methodological counterpoint to an excessively optimistic interpretation of amyloid removal.

Table 3: Safety in the Main Clinical Trials.

Study	Most Relevant Safety Event	Main Finding
Swanson, Zhang, Dhadda, Wang, Kaplow, Lai, Lannfelt, Bradley, Rabe, Koyama, Reyderman, Berry, Berry, Gordon, Kramer e Cummings ³	ARIA-E	Incidence of 9.9% with the 10 mg/kg every-two-weeks regimen
van Dyck, Swanson, Aisen, Bateman, Chen, Gee, Kanekiyo, Li, Reyderman, Cohen, Froelich, Katayama, Sabbagh, Vellas, Watson, Dhadda, Irizarry, Kramer e Iwatsubo ⁵	ARIA e reações infusionais	ARIA-E in 12.6% and infusion-related reactions in 26.4%
Mintun, Lo, Evans, Wessels, Ardayfio, Andersen, Shcherbinin, Sparks, Sims, Brys, Apostolova, Salloway e Skovronsky ⁴	ARIA-E e descontinuação	Amyloid-related edema or effusion occurred with donanemab and was generally asymptomatic
Sims, Zimmer, Evans, Lu, Ardayfio, Sparks, Wessels, Shcherbinin, Wang, Monkul Nery, Collins, Solomon, Salloway, Apostolova, Hansson, Ritchie, Brooks, Mintun e Skovronsky ⁶	ARIA-E e eventos graves	ARIA-E in 24.0%; 52 symptomatic cases; three deaths in the donanemab group and one in the placebo group considered treatment-related

Source: Authors' own elaboration, 2026.

Safety is the area in which clinical interpretation becomes most concrete. In Clarity AD, ARIA-E occurred in 12.6% of participants treated with lecanemab, and infusion-related reactions occurred in 26.4%.⁵ In TRAILBLAZER-ALZ 2, ARIA-E occurred in 24.0% of patients treated with donanemab, with 52 symptomatic cases.⁶ These events cannot be treated as footnotes. They reshape the way treatment must be prescribed, monitored, and discontinued.

The review by Jeong, Suh, Kim, Lemere, Lim, and Lee helps clarify the clinical and radiological nature of ARIA. The phenomenon is described as resulting from alterations in vascular integrity and permeability, leading to edema or effusion in ARIA-E and deposition of blood products in ARIA-H.⁸ The minimum recommended MRI sequences for evaluation are T2-FLAIR, T2* gradient

echo or susceptibility-weighted imaging, and diffusion-weighted imaging.⁸ FLAIR is essential for ARIA-E, T2* or susceptibility-weighted imaging for ARIA-H, and diffusion-weighted imaging helps differentiate ARIA from acute or subacute ischemia.⁸

The recommendations of the American Society of Neuroradiology reinforce this point in operational terms. ARIA occurs in approximately 10% to 30% of participants treated with anti-amyloid immunotherapies, and most cases are asymptomatic and detected on surveillance MRI.⁹ When symptomatic, it may present with headache, confusion, dizziness, visual disturbances, apraxia, or focal deficits.⁹ Its resemblance to stroke is a practical concern. Treating ARIA as acute ischemia and administering thrombolytic therapy may result in severe intracranial hemorrhage.⁹

Risk is not the same for all patients. Appropriate-use recommendations for lecanemab state that candidates should have mild cognitive impairment or mild dementia due to Alzheimer's disease, confirmation of amyloid pathology by PET or cerebrospinal fluid, a cognitive range compatible with early-stage disease, and no major risk factors for bleeding.¹⁵ They also recommend ApoE genotyping to inform ARIA risk and considerable caution in patients requiring anticoagulation.¹⁵ For donanemab, appropriate-use recommendations indicate patients in clinical stages 3 to 4, Mini-Mental State Examination scores between 20 and 30 or an equivalent assessment, confirmation of Alzheimer's disease pathology by PET or cerebrospinal fluid, and recent pretreatment MRI.¹⁶ Tau PET is not required for clinical eligibility, although it may help estimate individual benefit.¹⁶

This point highlights a difference between trials and practice. TRAILBLAZER-ALZ 2 used tau PET for stratification, whereas real-world use acknowledges that this examination may not be available.^{6,16} The transition from research to clinical practice requires simplification, but each simplification may alter the treated population. If eligibility becomes broader than in the trials, uncertainty regarding efficacy and safety increases. If it remains as restrictive as in the trials, treatment becomes accessible to only a small fraction of patients.

In Brazil, this tension is even more evident. The Brazilian position paper highlights four main concerns: the modest magnitude of benefit, real-world eligibility, high cost, and the risk of indiscriminate use in ineligible patients, such as asymptomatic individuals or people with moderate to severe dementia.¹⁰ The Brazilian Health Regulatory Agency approved donanemab for mild cognitive impairment and mild dementia associated with Alzheimer's disease in adults who are either ApoE $\epsilon 4$ heterozygotes or non-carriers.¹¹ Lecanemab was approved for early-stage Alzheimer's disease with confirmed amyloid pathology and the same restriction regarding ApoE $\epsilon 4$.¹² These regulatory indications already show that, in Brazil, treatment is introduced as a selective therapy.

The comparison between regulatory approval and health-system incorporation is also relevant. In 2025, the National Institute for Health and Care Excellence concluded that the benefits of lecanemab and donanemab remained too small to justify the additional costs to the National Health Service, including acquisition, administration, and monitoring.²⁰ This decision does not invalidate the clinical trials. It addresses a different question. While a regulatory agency asks whether a drug has an acceptable benefit-risk relationship for a given indication, a healthcare system must ask whether it can deliver that treatment safely, equitably, and at a justifiable cost.

The discussion of blood-based biomarkers fits into this context. The 2025 Alzheimer's Association guideline proposed that blood tests with sensitivity of at least 90% and specificity of at least 75% may be used for triage in specialized services, and that tests with both sensitivity and specificity of at least 90% may replace amyloid PET or cerebrospinal fluid testing in certain contexts.¹⁷ At the

same time, the guideline emphasizes that many available tests do not meet these thresholds and that blood biomarkers do not replace a complete clinical assessment.¹⁷ For Brazil, this suggests a possible pathway toward broader diagnostic access, but not an immediate solution.

The review also highlights methodological limitations of the included studies. The trials were randomized, double-blind, and placebo-controlled, strengthening internal validity. However, they were conducted in highly selected populations, with biomarker confirmation, strict MRI criteria, exclusion of patients at high hemorrhagic risk, and intensive follow-up.^{3,6} External validity is therefore limited. Real-world patients tend to be older, have more comorbidities, use more medications, and access less coordinated services than research-center populations.¹⁶

Another issue is funding. The main trials were sponsored by the companies developing the drugs, with sponsor involvement in study design, conduct, analysis, or interpretation of the data.⁶ This does not invalidate the findings, but it should be recognized as an element of critical appraisal. In a field marked by strong public expectations and commercial interest, independent real-world studies will be decisive in defining the place of these drugs in clinical practice.

The absence of meta-analysis in this review reflects a methodological choice. Lecanemab and donanemab have not been compared directly. The studies differ in primary scale, entry criteria, tau burden, dosing, discontinuation strategy, and outcome reporting. Pooling these findings into a single quantitative effect could create an appearance of precision beyond what the evidence supports. A structured narrative synthesis better preserves the differences between the drugs and avoids inappropriate indirect comparison.

An integrated reading of the studies supports an intermediate conclusion. Lecanemab and donanemab are not merely new versions of symptomatic treatments. They reduce amyloid and, on average, slow cognitive-functional decline in patients with early Alzheimer's disease. At the same time, they do not represent a cure, clinical reversal, or a broadly applicable intervention for anyone with dementia. Rational use requires biological diagnosis, stage selection, genetic and hemorrhagic risk assessment, serial MRI, and shared decision-making with the patient and caregiver.

This conclusion may appear less compelling than the idea of a therapeutic breakthrough. Even so, it is the interpretation most faithful to the data. The real advance represented by these antibodies may lie less in solving Alzheimer's disease and more in inaugurating a new way of treating it, in which prescribing depends on the convergence of biology, imaging, cognition, vascular risk, cost, and institutional capacity. This new model may open relevant avenues. It may also increase inequalities if implemented without planning.

CONCLUSION

Lecanemab and donanemab demonstrated reductions in amyloid burden and slowing of cognitive-functional decline in patients with early Alzheimer's disease, particularly in populations with biomarker confirmation and structured follow-up. Phase 3 trials support a statistically significant benefit, but the absolute magnitude of the effect was moderate, with no evidence of disease reversal or actual cognitive improvement.

Safety remains a central limitation. ARIA-E, ARIA-H, infusion-related reactions, and rare hemorrhagic events require rigorous patient selection, ApoE genotyping when available, baseline and serial magnetic resonance imaging, and a team prepared to recognize symptoms that may mimic stroke. Thus, the efficacy of these drugs cannot be separated from the practical conditions required for their safe use.

In Brazil, clinical implementation is likely to be particularly complex. Access to biomarker-based diagnosis, cognitive specialists, serial magnetic resonance imaging, infusion centers, and ARIA management is uneven. Therefore, lecanemab and donanemab should be understood as therapies representing genuine but

conditional progress. Their place in clinical practice will depend on long-term follow-up data, real-world studies, cost-effectiveness assessment, and the organization of care pathways capable of delivering treatment to the appropriate patients, with acceptable risk and realistic clinical expectations.

REFERENCES

1. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, Phelps C, Rankin KP, Rowe CC, Scheltens P, Siemers E, Snyder HM, Sperling R. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562.
2. Jack CR Jr, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, Hansson O, Ho C, Jagust W, McDade E, Molinuevo JL, Okonkwo OC, Pani L, Rafii MS, Scheltens P, Siemers E, Snyder HM, Sperling R, Teunissen CE, Carrillo MC. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. 2024;20(8):5143-5169.
3. Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RYK, Lannfelt L, Bradley H, Rabe M, Koyama A, Reyderman L, Berry DA, Berry S, Gordon R, Kramer LD, Cummings JL. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-A β protofibril antibody. *Alzheimers Res Ther*. 2021;13(1):80.
4. Mintun MA, Lo AC, Evans CD, Wessels AM, Ardayfio PA, Andersen SW, Shcherbinin S, Sparks J, Sims JR, Brys M, Apostolova LG, Salloway SP, Skovronsky DM. Donanemab in early Alzheimer's disease. *N Engl J Med*. 2021;384(18):1691-1704.
5. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388(1):9-21.
6. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, Wessels AM, Shcherbinin S, Wang H, Monkul Nery ES, Collins EC, Solomon P, Salloway S, Apostolova LG, Hansson O, Ritchie C, Brooks DA, Mintun M, Skovronsky DM. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330(6):512-527.
7. Muir RT, Hill MD, Black SE, Smith EE. Minimal clinically important difference in Alzheimer's disease: rapid review. *Alzheimers Dement*. 2024;20(5):3352-3363.
8. Jeong SY, Suh CH, Kim SJ, Lemere CA, Lim JS, Lee JH. Amyloid-related imaging abnormalities in the era of anti-amyloid beta monoclonal antibodies for Alzheimer's disease: recent updates on clinical and imaging features and MRI monitoring. *Korean J Radiol*. 2024;25(8):726-741.
9. Cogswell PM, Andrews TJ, Barakos JA, Barkhof F, Bash S, Benayoun MD, Chiang GC, Franceschi AM, Jack CR Jr, Pillai JJ, Poussaint TY, Raji CA, Ramanan VK, Tanabe J, Tanenbaum L, Whitlow CT, Yu FF, Zaharchuk G, Zeinab M, Benzinger TS. Alzheimer disease anti-amyloid immunotherapies: imaging recommendations and practice considerations for monitoring of amyloid-related imaging abnormalities. *AJNR Am J Neuroradiol*. 2025.
10. Barbosa BJAP, Resende EPF, Castilhos RM, Borelli WV, Frota NAF, Balthazar MLF, Amato Filho ACS, Smid J, Barbosa MT, Coutinho AM, Souza LC, Schilling LP, Silva MNM, Fernandes GBP, Bertolucci PHF, Nitrini R, Engelhardt E, Forlenza OV, Caramelli P, Brucki SMD, Studart-Neto A. Use of anti-amyloid therapies for Alzheimer's disease in Brazil: a position paper from the Scientific Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology. *Dement Neuropsychol*. 2024;18:e2024C002.
11. Agência Nacional de Vigilância Sanitária. Kisunla (donanemabe): novo registro. Brasília: Anvisa; 2025.
12. Agência Nacional de Vigilância Sanitária. Leqembi (lecanemabe): novo registro. Brasília: Anvisa; 2025.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
14. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, Hartmann-Boyce J, Ryan R, Shepperd S, Thomas J, Welch V, Thomson H. Synthesis without meta-analysis in systematic reviews: reporting guideline. *BMJ*. 2020;368:l6890.
15. Cummings J, Apostolova L, Rabinovici GD, Atri A, Aisen P, Greenberg S, Hendrix S, Selkoe D, Weiner M, Petersen RC, Salloway S. Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis*. 2023;10(3):362-377.
16. Rabinovici GD, Selkoe DJ, Schindler SE, Aisen P, Apostolova LG, Atri A, Greenberg SM, Hendrix SB, Petersen RC, Weiner M, Salloway S, Cummings J. Donanemab: appropriate use recommendations. *J Prev Alzheimers Dis*. 2025;12:100150.
17. Palmqvist S, Whitson HE, Allen LA, Suarez-Calvet M, Galasko D, Karikari TK, Okrahvi H, Paczynski M, Schindler SE, Teunissen CE, Zetterberg H, Carrillo MC, Edelmayer RM, Mahinrad S, McAteer MB, Kahale LA, Pahlke S, Tampi MP. Alzheimer's Association clinical practice guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings. *Alzheimers Dement*. 2025;21:e70535.

18. Food and Drug Administration. Leqembi (lecanemab-irmb) prescribing information. Silver Spring: FDA; 2025.
19. Food and Drug Administration. Kisunla (donanemab-azbt) prescribing information. Silver Spring: FDA; 2025.
20. National Institute for Health and Care Excellence. Final draft guidance finds benefits of 2 Alzheimer's treatments remain too small to justify the additional cost to the NHS. London: NICE; 2025.
21. Cochrane Central Editorial Service. Amyloid-beta-targeting monoclonal antibodies for people with mild cognitive impairment or dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2026;4:CD0162.

MAILING ADDRESS

PAULO HENRIQUE LUIS DA SILVA JÚNIOR

Rua Rio de Janeiro, s/n, Quadra 27, Lote 18, Vale das Goiabeiras, Inhumas/GO, Brazil.

E-mail: paulo.junior@discente.ufg.br

EDITORIAL AND REVIEW

Chief editors:

Waldemar Naves do Amaral - <http://lattes.cnpq.br/4092560599116579> - <https://orcid.org/0000-0002-0824-1138>

Nílzio Antônio da Silva - <http://lattes.cnpq.br/1780564621664455> - <https://orcid.org/0000-0002-6133-0498>

Authors:

Paulo Henrique Luis da Silva Júnior - <http://lattes.cnpq.br/1532039100593458> - <https://orcid.org/0009-0004-2846-762X>

Yanley Lúcio Nogueira - <http://lattes.cnpq.br/1045762578931468> - <https://orcid.org/0000-0003-1682-2714>

Library Review: Izabella Goulart

Spell Check: Dario Alvares

Translation: Soledad Montalbetti

Received: 24/08/26. Accepted: 27/08/26. Published in: 29/09/2026.