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NEW DISEASE-MODIFYING THERAPIES IN ALZHEIMER'S DISEASE: A CLINICAL REVIEW OF LECANEMAB AND DONANEMAB

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ABSTRACT

It has been widely suggested that monoclonal antibodies targeting amyloid-β represent a potentially disease-modifying therapeutic approach for Alzheimer's disease (AD), offering an alternative to purely symptomatic treatments. In recent years, considerable research attention has focused on anti-amyloid strategies aimed at modifying the underlying pathophysiology of early symptomatic AD. Among the agents currently under investigation, lecanemab and donanemab have demonstrated consistent amyloid plaque reduction and statistically significant slowing of cognitive and functional decline in patients with mild cognitive impairment or mild dementia due to AD.

The present review aims to critically evaluate evidence from pivotal clinical trials of both therapies, with particular emphasis on efficacy outcomes, safety profiles, pharmacological characteristics, and regulatory approval status. Special attention is given to treatment-related risks, including amyloid-related imaging abnormalities (ARIA), as well as factors influencing patient eligibility, treatment initiation, and monitoring strategies in clinical practice.

Taken together, the available evidence suggests that amyloid-targeting monoclonal antibodies may provide a modest yet clinically meaningful benefit in carefully selected patients, while simultaneously highlighting ongoing challenges related to safety, implementation, and long-term therapeutic effectiveness.

KEYWORDS

Lecanemab, Donanemab, Alzheimer's Disease, ARIA

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1. Introduction

Alzheimer's disease (AD) is widely recognized as a progressive neurodegenerative disorder and the most common cause of dementia, accounting for a substantial and increasing global health burden. The disease is typically characterized by a gradual decline in memory, cognition, and functional abilities, ultimately resulting in loss of independence. With aging populations worldwide, it is anticipated that the prevalence of AD will rise markedly in the coming decades, thereby underscoring the urgent need for effective therapeutic strategies.

From a neuropathological perspective, AD is defined by the accumulation of extracellular amyloid-β plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. It has been shown that these pathological processes begin years before the onset of clinical symptoms, thus providing a critical window for early intervention. Recent advances in biomarker technologies, including cerebrospinal fluid analysis and positron emission tomography (PET), have enabled in vivo detection of AD pathology and have facilitated the development of targeted therapeutic approaches.

Historically, treatment options for AD have been largely limited to symptomatic therapies that do not alter disease progression. More recently, monoclonal antibodies directed against aggregated amyloid-β have emerged as potential disease-modifying therapies, particularly in the early stages of the disease. Clinical trials have demonstrated substantial reductions in cerebral amyloid burden, leading to regulatory approvals and renewed interest in biologically driven treatment strategies.

Despite these advances, several challenges remain, including safety concerns, patient selection, and the requirement for intensive monitoring. Furthermore, differences in trial design, outcome measures, and risk profiles complicate the interpretation and comparison of available evidence.

The aim of this work is to review and synthesize current clinical evidence on lecanemab and donanemab, with particular emphasis on their mechanisms of action, efficacy, safety, and practical considerations for clinical use in early Alzheimer's disease.

2. Methods

This narrative literature review evaluates lecanemab and donanemab as emerging disease-modifying therapies for Alzheimer's disease. A focused literature search was conducted using PubMed and Google Scholar to identify key clinical trials, observational studies, systematic reviews, and regulatory reports relevant to the efficacy, safety, and clinical implementation of these agents. Priority was given to large randomized controlled trials and high-impact publications. The included studies were critically assessed in a qualitative manner with attention to study design, sample size, outcome measures, and potential limitations, in order to provide a balanced and clinically relevant synthesis of the current evidence.

3. Alzheimer's Disease – Overview

Definition and Clinical Manifestation

Alzheimer's disease (AD) is widely recognized as the most common cause of dementia, accounting for approximately 50%–75% of all cases, and is predominantly regarded as a disorder of older age. Epidemiological evidence indicates that its prevalence increases exponentially, nearly doubling every five years after the age of 65 (Lane et al., 2018). Alzheimer's disease is typically characterized by a progressive decline in cognitive, functional, and behavioral abilities, with symptom onset most commonly manifesting as impairment in memory for recent events (Zhang et al., 2021). From a pathological standpoint, Alzheimer's disease is most commonly associated with the accumulation of amyloid-β (Aβ) plaques, tau-containing neurofibrillary tangles, and widespread neurodegeneration, which collectively contribute to synaptic dysfunction and progressive brain atrophy.

Although the majority of Alzheimer's disease cases are considered to be sporadic in nature, it has been well established that mutations in three genes: amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2), are responsible for a rare (<0.5%) familial form of the disease, commonly referred to as autosomal-dominant Alzheimer's disease (ADAD). This inherited form is characterized by a markedly earlier age of onset compared with sporadic AD, with clinical symptoms typically manifesting between 30 and 50 years of age (Bateman et al., 2011).

The clinical presentation of Alzheimer's disease is widely understood to follow a continuous disease trajectory that unfolds over an extended period of time, typically spanning 15–25 years, beginning with cognitively intact individuals and progressing through mild cognitive impairment to overt dementia (Scheltens et al., 2021).

The most commonly reported clinical manifestations include memory impairment that interferes with activities of daily living, difficulties with planning or problem-solving, and challenges in completing familiar tasks. Patients may also experience disorientation with respect to time or place, as well as newly emerging language difficulties affecting speech or writing. In addition, impairments in visual information processing and spatial relationships may occur, along with frequent misplacement of objects and an inability to retrace steps. Furthermore, alterations in mood, personality, or behavior, together with withdrawal from occupational or social activities, are frequently observed.

As the disease progresses, individuals with Alzheimer's disease increasingly require assistance from caregivers to meet their daily care needs („2022 Alzheimer's Disease Facts and Figures", 2022).

Epidemiology and risk factors

According to recent global estimates, as reported in the 2018 World Alzheimer Report, the global population living with dementia is estimated to be approximately 50 million and is projected to increase to 152 million by 2050, with a disproportionate burden expected to fall on low- and middle-income countries, where nearly two-thirds of affected individuals reside (International & Patterson, 2018). Similarly, recent projections indicate that Europe will experience an almost twofold increase in dementia cases by 2050, reaching an estimated 18,846,286 individuals (*2019 Alzheimer Europe Yearbook*, 2025). In the United States, epidemiological forecasts suggest that the number of individuals aged 65 years and older living with Alzheimer's disease will rise substantially, from 5.8 million to 13.8 million by 2050 („2020 Alzheimer's Disease Facts and Figures", 2020).

With respect to disease prognosis, data from a European memory-clinic cohort have demonstrated that the median survival following a diagnosis of Alzheimer's disease dementia is approximately six years (median 6.2 years, range 6.0–6.5) (Rhodius-Meester et al., 2019).

A number of risk factors have been identified as being strongly associated with the development of Alzheimer's disease, most notably advanced age, the presence of at least one apolipoprotein E (APOE) ε4 allele, and a positive family history of the disease (Lautenschlager et al., 1996; van der Lee et al., 2018).

Among these, age is widely regarded as the most influential determinant of risk. Epidemiological data indicate that the prevalence of Alzheimer's dementia increases sharply with advancing age, affecting 3.0% of individuals aged 65–74 years, 17.6% of those aged 75–84 years, and 32.3% of individuals aged 85 years and older (Hebert et al., 2013). Nevertheless, it is important to emphasize that Alzheimer's dementia should not be considered a normal consequence of aging, and advanced age alone is insufficient to cause the disorder (Nelson et al., 2011).

From a genetic perspective, among more than 40 alleles implicated in Alzheimer's disease susceptibility, APOE ε4 is widely recognized as the strongest genetic risk factor for both early- and late-onset forms of the disease, conferring an estimated three- to fifteen-fold increase in risk (Jansen et al., 2019; Scheltens et al., 2021). Evidence from meta-analyses has shown that, in Caucasian populations, carriage of a single ε4 allele (ε2/ε4, OR 2.6; ε3/ε4, OR 3.2) is associated with an increased risk compared with the ε3/ε3 genotype, with a markedly elevated risk observed in ε4/ε4 homozygous individuals (OR 14.9) (Liu et al., 2013).

Although Alzheimer's disease may occur in the absence of a family history, numerous studies have demonstrated that the risk is significantly higher among individuals with an affected first-degree relative. Specifically, the cumulative risk of dementia by 85 years of age has been estimated to increase by a factor of 2.6 (95% CI, 1.3–4.4) in White populations and 2.4 (95% CI, 2.1–3.2) in African American populations (Green et al., 2002). Furthermore, evidence suggests that individuals with multiple affected first-degree relatives face an even greater risk; for example, offspring of conjugal Alzheimer's disease couples have been shown to exhibit an approximately fivefold increased risk compared with individuals whose parents are unaffected (Lautenschlager et al., 1996).

Pathophysiology of Alzheimer's Disease

The pathophysiology of Alzheimer's disease is widely regarded as multifactorial and remains incompletely understood; however, several hallmark biological processes have been consistently linked to disease onset and progression (Bloom, 2014). Current evidence indicates that AD pathology is primarily driven by abnormal protein aggregation, progressive synaptic dysfunction, chronic neuroinflammation, and neuronal loss (Jain et al.).

A central and early pathological event in AD is thought to be the extracellular accumulation of amyloid-β (Aβ) peptides, which are generated through the sequential cleavage of amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase. In contrast, it has been demonstrated that α-secretase processing of APP produces soluble APPα, a neuroprotective fragment that precludes Aβ formation. Aβ peptides may accumulate in monomeric, oligomeric, or fibrillar forms, with growing evidence suggesting that soluble oligomers represent the most synaptotoxic species (Jain et al., 2024).Excessive aggregation of Aβ ultimately leads to the formation of amyloid plaques, which interfere with neuronal communication and synaptic plasticity („2022 Alzheimer's Disease Facts and Figures", 2022; Jain et al., 2024).

Tau pathology represents a second major molecular abnormality associated with AD. Under pathological conditions, hyperphosphorylated tau dissociates from microtubules and aggregates into neurofibrillary tangles (NFTs), thereby disrupting intracellular transport and promoting neuronal dysfunction. Accumulating evidence suggests that Aβ deposition may precede and facilitate tau pathology, thereby accelerating downstream neurodegenerative processes („2022 Alzheimer's Disease Facts and Figures", 2022; Jain et al., 2024; Kamatham et al., 2024).

As a consequence of Aβ- and tau-mediated toxicity, synaptic loss occurs and is widely considered to be a key correlate of cognitive impairment, memory failure, and behavioral changes characteristic of AD („2022 Alzheimer's Disease Facts and Figures", 2022; Jain et al., 2024). In parallel, AD-affected brains exhibit a marked reduction in acetylcholine (ACh), a neurotransmitter essential for memory and learning. This decline has been attributed, at least in part, to disrupted cholinergic signaling, increased acetylcholinesterase activity, and degeneration of cholinergic neurons. At the same time, dysregulation of N-methyl-D-aspartate (NMDA) receptors results in excitotoxicity, as excessive calcium influx further exacerbates neuronal injury (Ju & Tam, 2021).

Oxidative stress has also been identified as a critical contributor to AD progression. Elevated levels of reactive oxygen species (ROS) damage cellular proteins, lipids, and DNA, while simultaneously activating inflammatory signaling pathways, thereby creating a self-perpetuating cycle of neuronal injury (Kumar & Singh, 2015). Notably, ROS overproduction has been observed both in the central nervous system and in peripheral tissues of AD patients and appears to precede the onset of clinical symptoms. Furthermore, oxidative stress has been shown to enhance Aβ production by stimulating β- and γ-secretase activity, thereby exacerbating amyloid-related pathology (Tamagno et al., 2008; Wright et al., 2013).

Neuroinflammation represents another key pathological component of AD. In response to Aβ accumulation and oxidative stress, microglia and astrocytes become activated. Although this response may initially serve a protective function, prolonged activation results in sustained release of pro-inflammatory cytokines, impaired clearance of toxic proteins, and acceleration of neuronal damage (Di Benedetto et al., 2022).

Overactivation of microglia has further been shown to promote additional Aβ and tau accumulation, thereby perpetuating inflammatory and neurodegenerative cycles (Jain et al., 2024).

In recent years, neurofilament light chain (NfL) has emerged as a biomarker of axonal injury and neurodegeneration, with levels in cerebrospinal fluid and blood correlating with cognitive decline (Alagaratnam et al., 2021; Gonzales et al., 2021). Importantly, increasing NfL concentrations may be detectable decades before symptom onset in genetically determined AD, highlighting the prolonged preclinical phase of the disease („2022 Alzheimer's Disease Facts and Figures", 2022).

These molecular and cellular alterations are accompanied by structural and metabolic brain changes. Progressive brain atrophy, particularly affecting the hippocampus and cortical regions, reflects ongoing neuronal loss, while impaired cerebral glucose metabolism, detectable long before clinical manifestation, further compromises neuronal energy homeostasis (Quiroz et al., 2020).Advances in biomarker technologies, including cerebrospinal fluid assays and amyloid- and tau-specific PET imaging, now allow early detection and monitoring of these pathological processes („2022 Alzheimer's Disease Facts and Figures", 2022; Kamatham et al., 2024).

Taken together, these interacting mechanisms collectively drive the progressive neurodegeneration characteristic of Alzheimer's disease and underscore the existence of multiple potential targets for therapeutic intervention.

4. Current Therapeutic Landscape

Symptomatic Treatments

Current standard therapy for Alzheimer's disease is largely based on symptomatic treatments that provide modest and transient benefits in cognitive and functional domains, without altering the underlying neurodegenerative process. The principal pharmacological agents currently used in routine clinical practice include acetylcholinesterase inhibitors (AChEIs), namely donepezil, rivastigmine, and galantamine, which are indicated for patients with mild to moderate stages of the disease. These agents act primarily by enhancing central cholinergic neurotransmission through increased availability of acetylcholine (ACh) in the synaptic cleft, thereby supporting cognitive performance and activities of daily living (Massoud & Léger, 2011).

For patients with more advanced disease, particularly those with moderate to severe AD, the N-methyl-D-aspartate (NMDA) receptor antagonist memantine is commonly prescribed. Memantine exerts its effects by modulating glutamatergic neurotransmission and is thought to reduce excitotoxic neuronal injury, resulting in modest improvements in cognition, behavior, and functional outcomes (Kavirajan, 2009). Despite their widespread clinical use, the overall therapeutic effects of these agents remain limited, with no convincing evidence demonstrating a sustained impact on disease progression or long-term neurodegeneration (Fox et al., 2025).

Rationale for Disease-Modifying Therapies

The limited efficacy of existing symptomatic treatments has underscored the urgent need for disease-modifying therapies (DMTs) that target the core pathophysiological mechanisms underlying Alzheimer's disease (Cummings et al., 2019). A growing body of evidence from genetic, biomarker, and neuropathological studies supports the central role of amyloid-β (Aβ) accumulation as an early and upstream event in the disease cascade, preceding tau pathology, synaptic dysfunction, and neuronal loss (Long & Holtzman, 2019).

Recent advances in biomarker-based diagnostic approaches, together with a paradigm shift toward earlier therapeutic intervention, have renewed interest in anti-amyloid strategies aimed at slowing or potentially halting disease progression rather than merely alleviating symptoms (Cummings et al., 2019). In this context, monoclonal antibodies targeting aggregated Aβ species, such as lecanemab and donanemab, have emerged as a paradigm shift in AD therapeutics, offering the potential to modify the disease course in carefully selected patient populations at early stages of Alzheimer's disease (Soni et al., 2025).

5. Lecanemab

Mechanism of Action

Lecanemab (BAN2401) is a humanized IgG1 monoclonal antibody that has been specifically developed to target multiple aggregated forms of amyloid-β (Aβ), including soluble oligomers, protofibrils, and insoluble fibrillar deposits, with particular emphasis placed on Aβ protofibrils, which are widely regarded as among the most neurotoxic Aβ assemblies (Cummings et al., 2023; Lord et al., 2009). Its molecular design is derived from the murine antibody mAb158, which is characterized by high affinity for protofibrillar Aβ and minimal binding to monomeric Aβ species (Rizoska et al., 2024). As a result, lecanemab demonstrates more than a 1,000-fold selectivity for protofibrillar Aβ compared with monomers, while retaining the capacity to bind insoluble fibrillar deposits that constitute a major structural component of cerebral amyloid (Johannesson et al., 2024; Rizoska et al., 2024).

Preclinical evidence has demonstrated that administration of the murine analog mAb158 results in efficient removal of Aβ protofibrils, significant reduction of amyloid deposition in APP transgenic mouse models, and prevention of initial amyloid accumulation in ArcSwe models. These findings provide strong support for lecanemab's ability to enhance Fcγ receptor-mediated uptake and clearance of protofibrillar Aβ by microglia, thereby suggesting a potential mitigation of neuronal toxicity in vivo (Tucker et al., 2015).

Following target engagement, lecanemab facilitates the elimination of protofibrillar Aβ via Fcγ receptor-mediated microglial uptake, thereby promoting amyloid clearance (van Olst et al., 2025).

In addition to its direct amyloid-clearing effects, lecanemab has been shown to interfere with a vascular toxicity pathway by blocking the interaction between Aβ protofibrils and fibrinogen. This mechanism prevents protofibril-induced clot abnormalities, delayed fibrinolysis, and reduces synaptotoxicity in organotypic hippocampal cultures (Singh et al., b.d.).

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic profile of lecanemab has been extensively evaluated in single ascending dose (SAD) and multiple ascending dose (MAD) studies. In SAD studies, lecanemab exhibited dose-proportional pharmacokinetics with first-order elimination, with median time to maximum concentration (tmax) occurring approximately 1.8–2.2 hours post-infusion. Both peak plasma concentration (Cmax) and area under the curve (AUC) increased proportionally across the 0.3–15 mg/kg dose range, while the mean serum half-life at higher doses ranged from 165 to 174 hours (~7 days) (Logovinsky et al., 2016). In MAD studies, steady-state concentrations were achieved after approximately six weeks of 10 mg/kg administered biweekly, with a modest systemic accumulation of 1.4-fold (U.S. Food and Drug Administration, 2023).

Exposure parameters remained dose-proportional, and elimination kinetics continued to follow a first-order process. At steady state, the mean terminal half-life in the highest MAD cohort was approximately 127 hours, with a central volume of distribution of ~3.22 L and clearance of ~0.434 L/day (U.S. Food and Drug Administration, 2023).

Cerebrospinal fluid (CSF) penetration was limited, with CSF-to-serum ratios ranging from 0.04–0.08% at 24 hours in lower-dose cohorts. In the 10 mg/kg biweekly cohort, CSF-to-serum ratios increased from 0.13% at 24 hours to 0.29% at 14 days, reflecting systemic accumulation (Logovinsky et al., 2016). From a pharmacodynamic perspective, small, dose-dependent increases in plasma Aβ(1–40) were observed shortly after dosing, whereas no significant early changes were detected in CSF Aβ(1–42), total tau, or phosphorylated tau relative to placebo. Subsequent analyses from the CLARITY-AD trial indicated that modest reductions in plasma and CSF phosphorylated tau species emerged over 18 months, suggesting that downstream tau modulation may require prolonged treatment exposure (Dyck et al., 2023).

Key Clinical Trials

Lecanemab has advanced through several pivotal clinical trial phases, including the phase 2b Study 201 and the phase 3 CLARITY-AD trial, which together provide critical evidence regarding its efficacy, safety, and disease-modifying potential in early Alzheimer's disease.

Phase 2b - "Study 201"

Phase 2b Study 201 was designed as a multicenter, randomized, double-blind, placebo-controlled trial employing a Bayesian adaptive design. The study evaluated multiple dosing regimens of lecanemab (2.5, 5, or 10 mg/kg administered monthly or biweekly) in patients with early Alzheimer's disease and biomarker-confirmed amyloid pathology (Swanson et al., 2021). The primary endpoint was change in the Alzheimer's Disease Composite Score (ADCOMS), with the aim of identifying the ED90 dose, defined as the lowest dose achieving ≥90% of the maximal treatment effect using Bayesian probability. ADCOMS is a composite measure sensitive to early cognitive and functional decline, incorporating selected items from ADAS-Cog14 (

Alzheimer's Disease Assessment Scale – Cognitive Subscale), CDR-SB (Clinical Dementia Rating–Sum of Boxes), and activities of daily living scales. Key secondary outcomes included CDR-SB and ADAS-Cog14, which assess global cognition, functional performance, and core cognitive domains (Berry et al., 2023; Swanson et al., 2021).

After 18 months, the 10 mg/kg biweekly regimen was associated with a marked reduction in cerebral amyloid burden (~−0.306 standardized uptake value ratio [SUVR] on amyloid PET) and a slower rate of clinical decline across ADCOMS, CDR-SB, and ADAS-Cog14 compared with placebo (Swanson et al.).The safety profile was considered acceptable, with ARIA-E occurring in <10% of patients, predominantly asymptomatic or mild, and more frequent among APOE-ε4 homozygotes. The adaptive Bayesian design enabled efficient identification of the most effective dose, improving statistical power and precision of treatment effect estimates (Honig et al., 2023; Satlin et al., 2016).

Phase 3 - CLARITY-AD

Based on the optimal dose identified in Study 201, the 10 mg/kg biweekly regimen was advanced to the phase 3 CLARITY-AD trial. This was a global, randomized, double-blind, placebo-controlled study enrolling 1,795 participants with early Alzheimer's disease and confirmed amyloid pathology (Honig et al., 2023; U.S. Food and Drug Administration, 2023). Participants were randomized 1:1 to lecanemab 10 mg/kg IV every 2 weeks or placebo. The primary endpoint was change in CDR-SB at 18 months (Dyck et al., 2023). Treatment with lecanemab was associated with a statistically significant slowing of clinical decline, as evidenced by a smaller worsening in the CDR-SB score compared with placebo. Specifically, CDR-SB worsened by 1.21 points in the lecanemab group versus 1.66 points in the placebo group (difference −0.45; 95% CI −0.67 to −0.23; $P < 0.001$), corresponding to an approximate 27% relative reduction in disease progression (Dyck et al., 2023).

Secondary outcome measures included ADCOMS, ADAS-Cog14, amyloid positron emission tomography (PET), cerebrospinal fluid (CSF) biomarkers, and hippocampal volume assessed by magnetic resonance imaging (MRI) (U.S. Food and Drug Administration, 2023). Consistent with its proposed mechanism of action, treatment with lecanemab resulted in a mean amyloid PET reduction of approximately 59 centiloids, thereby confirming robust and sustained amyloid clearance (Dyck et al., 2023). Modest reductions in plasma and CSF phosphorylated tau species were observed over 18 months, although these effects emerged later and were smaller than amyloid-lowering responses (Dyck et al., 2023; U.S. Food and Drug Administration, 2023).

Additional clinical benefits were observed across ADCOMS, ADAS-Cog14, and ADCS-MCI-ADL scores, indicating consistent effects on cognition and functional abilities (Dyck et al., 2023). With regard to safety, amyloid-related imaging abnormalities occurred in 12.6% (ARIA-E) and 16% (ARIA-H) of treated participants, with the majority of cases being asymptomatic or mild. Infusion-related reactions were also reported, typically during the first infusion and generally mild to moderate in severity (Honig et al., 2023; U.S. Food and Drug Administration, 2023).

Taken together, these findings provide compelling evidence that lecanemab exerts clinically meaningful disease-modifying effects in early Alzheimer's disease, while simultaneously underscoring the importance of careful patient selection and structured MRI monitoring to mitigate treatment-related risks (Honig et al., 2023; U.S. Food and Drug Administration, 2023).

Safety Profile

In clinical trials evaluating lecanemab, the most clinically relevant safety concern has been the occurrence of amyloid-related imaging abnormalities (ARIA), which encompass ARIA-E (edema or sulcal effusions) and ARIA-H (micro- or macrohemorrhages and superficial siderosis) (Honig et al., 2023; Sperling et al., 2012). Although the precise mechanisms underlying ARIA remain incompletely elucidated, current evidence suggests that these events may arise from transient increases in blood–brain barrier permeability and the mobilization of amyloid deposits from cerebral vessel walls, processes that are closely associated with underlying cerebral amyloid angiopathy (CAA) (Honig et al., 2023).

Across clinical development programs, ARIA-E was observed in a dose-dependent manner and occurred more frequently among carriers of the APOE-ε4 allele. In the phase 2b Study 201, ARIA-E occurred in approximately 9.9% of participants receiving lecanemab at a dose of 10 mg/kg biweekly, with a higher incidence of approximately 14% among APOE-ε4 carriers (Swanson et al., 2021). Consistent with these findings, the pivotal phase 3 CLARITY-AD trial reported ARIA-E in 12.6% of lecanemab-treated patients compared with 1.7% in the placebo group, while ARIA-H occurred in 16.0% versus 8.9%, respectively. Notably, the majority of ARIA events were asymptomatic or mild in severity, with symptomatic ARIA-E

occurring in only 2.8% of patients. Most ARIA-E events resolved within four months, and radiographically severe cases were rare (Honig et al., 2023; U.S. Food and Drug Administration, 2023).

Further supportive evidence is provided by data from FDA Study 301. Among 898 patients treated with lecanemab, 12.6% experienced ARIA-E, with a pronounced genotype-dependent gradient, including 32.6% in homozygous APOE-ε4 carriers, 10.9% in heterozygous carriers, and 5.4% in noncarriers. Isolated ARIA-H occurred in 8.9% of treated patients and demonstrated timing and risk profiles similar to placebo, whereas concurrent ARIA-E and ARIA-H were observed in 8.2% of participants. Severe ARIA-H events were uncommon (3.6%), and the majority remained clinically silent. Importantly, the use of antithrombotic therapy did not appear to increase the risk of ARIA (U.S. Food and Drug Administration, 2023). Beyond imaging abnormalities, infusion-related reactions were more frequently reported with lecanemab than placebo (26.3% vs. 7.1%), typically occurring during the first infusion and generally classified as mild to moderate in severity. Treatment discontinuation due to adverse events was infrequent (6.9%), and most patients were able to continue therapy despite mild ARIA or infusion reactions. Overall mortality rates were comparable between groups (0.7% lecanemab vs. 0.8% placebo), with few deaths attributable to intracerebral hemorrhage (U.S. Food and Drug Administration, 2023).

Taken together, these findings highlight the critical importance of careful patient selection, APOE genotyping, dose optimization, and structured MRI monitoring to mitigate treatment-associated risks in patients receiving lecanemab. Reassuringly, immunogenicity was low, and the presence of anti-drug antibodies did not adversely affect either safety or efficacy outcomes (U.S. Food and Drug Administration, 2023).

Regulatory and Clinical Use

Lecanemab (Leqembi) was granted accelerated approval by the U.S. Food and Drug Administration (FDA) in January 2023 for the treatment of early Alzheimer's disease, specifically in individuals with mild cognitive impairment or mild dementia due to Alzheimer's disease and biomarker-confirmed amyloid pathology. This regulatory decision was primarily based on robust amyloid-lowering effects demonstrated in randomized clinical trials, with continued approval contingent upon confirmation of clinical benefit in ongoing and post-marketing studies (U.S. Food and Drug Administration, 2023).

In routine clinical practice, the use of lecanemab necessitates careful patient selection, particularly with respect to APOE-ε4 carrier status, as homozygous carriers exhibit a substantially increased susceptibility to treatment-emergent adverse events. Accordingly, patients with a history of intracerebral hemorrhage, significant small-vessel cerebrovascular disease, or coagulopathy may be considered unsuitable candidates for therapy (Honig et al., 2024; U.S. Food and Drug Administration, 2023).

The recommended dosing regimen consists of 10 mg/kg administered intravenously every two weeks. Prior to treatment initiation, a baseline magnetic resonance imaging (MRI) scan is required, with follow-up imaging recommended during the early phase of treatment (typically after the third and seventh infusions) and at regular intervals thereafter. In the event of symptomatic or radiographically severe safety events, temporary treatment interruption or permanent discontinuation is advised in accordance with established safety guidelines (Dyck et al., 2023; U.S. Food and Drug Administration, 2023).

Efficacy

With respect to clinical efficacy, the observed 27% relative reduction in cognitive and functional decline on the CDR-SB in the CLARITY-AD trial provides evidence supporting lecanemab's role as a promising disease-modifying therapy in early Alzheimer's disease (Dyck et al., 2023; Honig et al., 2024). However, effective implementation in clinical settings requires individualized risk–benefit assessment, APOE genotyping, structured MRI surveillance, and strict adherence to approved dosing and monitoring protocols.

6. Donanemab

Mechanism of Action

Donanemab (LY3002813) is a humanized IgG1 monoclonal antibody that has been specifically engineered to target amyloid plaques, exhibiting high selectivity for a pyroglutamate-modified, N-terminally truncated amyloid-β species, pGlu3-Aβ (also referred to as AβpE3 or N3pG) (Bayer, 2022; Lowe et al., 2021).

This epitope is exclusively detected within cerebral amyloid plaques and is regarded as a defining neuropathological feature of Alzheimer's disease, rather than a component of physiological amyloid processing (Lowe et al., 2021).

By selectively binding to this plaque-restricted Aβ species, donanemab targets a molecular signature strongly associated with plaque maturation, stability, and chronic deposition. Upon engagement with pGlu3-Aβ within amyloid plaques, the Fc domain of donanemab interacts with Fcγ receptors expressed on microglia,

thereby triggering microglial activation, phagocytosis, and subsequent clearance of plaque material (DeMattos et al., 2012).

Notably, pGlu3-Aβ is not generated during normal neuronal metabolism but instead arises through post-translational modification within established plaques, underscoring its disease-specific nature.

From a therapeutic perspective, this high degree of pathological selectivity is of particular relevance, as targeting pGlu3-Aβ is unlikely to interfere with physiological amyloid-β species. It has therefore been hypothesized that such specificity may reduce off-target effects and potentially lower the risk of ARIA, a frequent adverse event associated with less selective amyloid-directed immunotherapies (Alawode et al., 2021).

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic profile of donanemab has been extensively characterized using population pharmacokinetic modeling, incorporating single- and multiple-dose data from 2,131 patients with Alzheimer's disease. Across every-4-week dosing regimens, drug accumulation was minimal (<1.3-fold), and steady-state concentrations were effectively achieved after the initial dose, with comparable systemic exposure observed across dosing schedules. Serum Cmax and AUC increased proportionally following single doses ranging from 350 to 2,800 mg (up to approximately twice the approved 1,400 mg dose) and multiple doses between 350 and 1,400 mg. The estimated central volume of distribution (3.36 L) and clearance (0.0255 L/h) support predictable and consistent systemic exposure with standard dosing (Gueorguieva et al., 2023; U.S. Food and Drug Administration (FDA), 2024).

Donanemab demonstrated a dose-dependent half-life, with shorter elimination at lower doses. Following single-dose administration of 0.1–3.0 mg/kg, mean terminal half-life was ~4 days, increasing to ~10 days (243 hours) at 10 mg/kg (Lowe et al., 2021).

Although interindividual variability related to body weight and anti-drug antibody titers influenced systemic exposure, these factors did not appear to meaningfully affect pharmacodynamic responses. Amyloid plaque reduction was observed once serum donanemab concentrations exceeded 4.43 μg/mL. Importantly, the time required to achieve plaque clearance was influenced by baseline amyloid burden, with higher initial plaque levels associated with slower clearance kinetics. Nevertheless, by week 52, the majority of treated participants achieved amyloid plaque clearance, indicating robust target engagement and sustained pharmacodynamic activity (Gueorguieva et al., 2023).

Key Clinical Trials

Donanemab has advanced through key clinical development stages, including the Phase 2 TRAILBLAZER-ALZ trial and the Phase 3 TRAILBLAZER-ALZ 2 study, which together provide evidence regarding its efficacy, safety, and potential disease-modifying effects in early Alzheimer's disease.

Phase 2 study: TRAILBLAZER-ALZ

The Phase 2 TRAILBLAZER-ALZ study was a multicenter, randomized, double-blind, placebo-controlled trial enrolling individuals with early symptomatic Alzheimer's disease and intermediate levels of tau deposition. Participants received intravenous donanemab at 700 mg every four weeks for the first three doses, followed by 1,400 mg every four weeks for up to 72 weeks. Treatment with donanemab was associated with a statistically significant slowing of cognitive and functional decline compared with placebo (Shcherbinin et al., 2022).

Phase 3 studies: TRAILBLAZER-ALZ 2

TRAILBLAZER-ALZ 2 was an 18-month, randomized, double-blind, placebo-controlled phase 3 trial evaluating the safety and efficacy of donanemab in 1,736 individuals with early symptomatic Alzheimer's disease, including mild cognitive impairment and mild dementia. All participants were amyloid-positive and exhibited low, intermediate, or high tau pathology on PET imaging. The primary outcome, assessed using the Integrated Alzheimer's Disease Rating Scale (iADRS), demonstrated a 35.1% reduction in the rate of clinical decline compared with placebo ($p < 0.0001$).

Consistent effects were observed across key secondary endpoints, with the CDR-SB showing a 36% slowing of clinical decline over 18 months ($p < 0.0001$). Prespecified secondary analyses indicated that 47% of donanemab-treated participants exhibited no deterioration on CDR-SB at one year, compared with 29% in the placebo group ($p < 0.001$). By 18 months, 72% of participants in the donanemab group had completed treatment, largely due to achieving amyloid plaque clearance, with 52% reaching this threshold by one year. Treatment was also associated with a 40% reduction in functional decline, as measured by the ADCS-iADL ($p < 0.0001$), and a 39% lower risk of progression to a more severe clinical stage (CDR-Global Score; hazard ratio 0.61; $p < 0.001$) (Sims, Zimmer, Evans, Lu, Ardayfio, et al., 2023).

TRAILBLAZER-ALZ 3

The ongoing TRAILBLAZER-ALZ 3 trial is designed to evaluate whether donanemab can delay or prevent the onset of Alzheimer's disease in cognitively unimpaired individuals with biomarker-confirmed amyloid pathology. This study focuses on therapeutic intervention during the preclinical stage of Alzheimer's disease, aiming to assess the efficacy of amyloid-targeting therapy prior to symptom emergence. The results are expected to provide critical insights into the potential role of donanemab in early disease interception, with implications for biomarker-based risk stratification and preventive treatment strategies (Yaari et al., 2025).

TRAILBLAZER-ALZ 4

TRAILBLAZER-ALZ 4 is a phase 3 randomized trial comparing donanemab with aducanumab in achieving amyloid plaque clearance (≤24.1 Centiloids) at six months in patients with early symptomatic Alzheimer's disease. Amyloid clearance was achieved in 37.9% of donanemab-treated participants, compared with 1.6% of those receiving aducanumab ($p < 0.001$). Among participants with intermediate tau levels, clearance was observed in 38.5% of the donanemab group versus 3.8% in the aducanumab group ($p = 0.008$). These findings suggest superior amyloid-lowering efficacy of donanemab compared with aducanumab, with potential implications for downstream clinical outcomes (Salloway et al., 2023).

TRAILBLAZER-ALZ 5

TRAILBLAZER-ALZ 5 is a phase 3 study evaluating the efficacy and safety of donanemab in individuals with early symptomatic Alzheimer's disease, including prodromal and mild dementia stages, who exhibit cerebral tau pathology. Eligible participants are aged 60–85 years, have experienced gradual progressive memory decline for at least six months, have a Mini-Mental State Examination (MMSE) score between 20 and 28, and demonstrate tau pathology on neuroimaging. The primary objective is to assess the effect of donanemab on cognitive and functional decline, as measured by the iADRS, while secondary objectives include safety outcomes, biomarker changes, and additional cognitive and functional measures (Dickson et al., 2023; *TRAILBLAZER-ALZ 5*, b.d.).

TRAILBLAZER-ALZ 6

TRAILBLAZER-ALZ 6 was a phase 3b study designed to evaluate the impact of different donanemab dosing strategies on the incidence and severity of amyloid-related imaging abnormalities with edema (ARIA-E) in individuals with early symptomatic Alzheimer's disease, including prodromal and mild dementia stages. Interim analyses demonstrated that a modified titration dosing regimen significantly reduced the incidence of ARIA-E compared with the standard dosing schedule, corresponding to a 41% relative risk reduction. Overall safety profiles were comparable between dosing groups, with no new safety signals identified. The frequency of infusion-related reactions in the modified titration group was similar to that observed with standard dosing. These findings suggest that dose titration may improve tolerability by mitigating ARIA-E risk while preserving therapeutic efficacy (Wang et al., 2025).

Safety Profile

Across clinical trials, donanemab treatment was associated with a higher incidence of amyloid-related imaging abnormalities compared with placebo. ARIA-E occurred in 24% of treated participants versus 2% in the placebo group, while ARIA-H with microhemorrhages was observed in 25% versus 11%, respectively. ARIA-H presenting as superficial siderosis was reported in 15% of donanemab-treated individuals compared with 3% of those receiving placebo. The incidence of amyloid-related imaging abnormalities increased with the number of APOE ε4 alleles carried. Accordingly, enhanced monitoring strategies, including scheduled and unscheduled MRI assessments, particularly in APOE ε4 homozygotes and individuals with additional risk factors, are recommended to mitigate ARIA risk (U.S. Food and Drug Administration (FDA), 2024; Vukmir, 2024).

Infusion-related reactions were more frequent in the donanemab group (9%) than in the placebo group (0.5%), with the majority (70%, 52/74) occurring within the first four infusions. Common clinical manifestations included chills, erythema, nausea and vomiting, dyspnea, diaphoresis, hypotension, headache, and chest pain (Khartabil & Awaness, 2025; U.S. Food and Drug Administration (FDA), 2024).

Hypersensitivity reactions, including anaphylaxis and angioedema, have also been reported. Infusion should be discontinued immediately at the first signs of hypersensitivity, and appropriate medical management should be initiated without delay. Donanemab is contraindicated in patients with a known history of severe hypersensitivity to donanemab-azbt or any of its excipients (U.S. Food and Drug Administration (FDA), 2024).

Regulatory and Clinical Use

Donanemab (Kisunla) received approval from the U.S. Food and Drug Administration (FDA) in July 2024 for the treatment of early symptomatic Alzheimer's disease, including patients with mild cognitive impairment or mild dementia. This regulatory decision was based primarily on evidence from the phase 3 TRAILBLAZER-ALZ 2 trial, which demonstrated substantial reductions in cerebral amyloid plaque burden on positron emission tomography (PET), together with a statistically significant slowing of clinical decline (Sims, Zimmer, Evans, Lu, Zboch, et al., 2023, s. 2; U.S. Food and Drug Administration (FDA), 2024).

Appropriate clinical use requires careful patient selection, including confirmation of amyloid-β pathology prior to treatment initiation and assessment of APOE-ε4 genotype, as homozygous carriers exhibit a markedly increased risk of treatment-related adverse events. Patients with a history of intracerebral hemorrhage, advanced small-vessel cerebrovascular disease, or underlying coagulopathies may be unsuitable candidates for donanemab therapy (U.S. Food and Drug Administration (FDA), 2024).

The recommended dosing regimen consists of intravenous administration of 700 mg every four weeks for the initial three doses, followed by 1,400 mg every four weeks thereafter. Infusions require dilution prior to administration and are delivered over approximately 30 minutes. A baseline magnetic resonance imaging (MRI) scan is mandatory before treatment initiation and should be repeated prior to the second, third, fourth, and seventh infusions. Patients presenting with symptoms suggestive of amyloid-related imaging abnormalities should undergo prompt clinical assessment, including MRI where indicated. In cases of symptomatic or severe safety events, temporary interruption or discontinuation of treatment should be considered (Sims, Zimmer, Evans, Lu, Zboch, et al., 2023; U.S. Food and Drug Administration (FDA), 2024).

Efficacy

After 28 weeks, treatment with donanemab at 10 mg/kg resulted in a statistically significant reduction in cerebral amyloid burden, as measured by PET, compared with placebo ($p < 0.0002$). Patients receiving three to five doses of 10 mg/kg demonstrated consistent cortical amyloid reductions, with mean changes of −0.26 SUVR (SD 0.12) and −44.4 centiloids (SD 14.2), corresponding to an estimated 40–50% decrease in amyloid burden. In contrast, minimal changes were observed in the placebo group, and lower donanemab doses (0.3–3 mg/kg) did not produce significant amyloid reduction (Lowe et al., 2021).

In the subsequent phase 3 trial employing the currently recommended dosing regimen, donanemab demonstrated a clinically meaningful effect on disease progression. Tau PET imaging with flortaucipir showed a statistically significant slowing of clinical decline on the Integrated Alzheimer's Disease Rating Scale (iADRS) at Week 76, both in the overall study population (difference 2.92; $p < 0.0001$) and in the low-to-intermediate tau subgroup (difference 3.25; $p < 0.0001$). Consistent treatment effects were also observed on the CDR-SB, with reduced clinical decline relative to placebo at Week 76 (−0.70; $p < 0.0001$) (U.S. Food and Drug Administration (FDA), 2024).

7. Comparative Analysis: Lecanemab vs Donanemab

Efficacy

Across pivotal trials, both lecanemab and donanemab demonstrated clinically meaningful efficacy in slowing cognitive and functional decline. Lecanemab reduced CDR-SB worsening at 18 months by 0.45 points compared with placebo, corresponding to a 27% relative slowing of disease progression (Dyck et al. 2023). Donanemab produced a comparable effect at 76 weeks, with a 0.70-point difference versus placebo and an estimated 29% relative slowing of progression (*Patient Dosing & Monitoring | Kisunla™ (Donanemab-Azbt)*, b.d.; U.S. Food and Drug Administration (FDA), 2024).

Safety

Both donanemab and lecanemab were associated with higher rates of amyloid-related imaging abnormalities than placebo. A systematic review by Terao et al. reported ARIA-E incidences of 12.6% and 9.9% in lecanemab-treated patients, compared with 26.7% and 24% in donanemab-treated patients. ARIA-H occurred in 17.3% and 6.8% of lecanemab recipients, and in 22.1% and 19.7% of those receiving donanemab, respectively (Terao & Kodama, 2024).

Table 1. Comparison of donanemab and lecanemab (*Donanemab for Treatment of Early Alzheimer's | Alz.Org*, b.d.; *Lecanemab Approved for Treatment of Early Alzheimer's | Alz.Org*, b.d.; *Patient Dosing & Monitoring | Kisunla™ (Donanemab-Azbt)*, b.d.; Dyck et al., 2023).

Drug Name	Mechanism of Action	Dosage	Administration	Frequency	Price
Donanemab-azbt (Kisunla)	Humanized monoclonal antibody targeting insoluble N-truncated pyroglutamate amyloid beta	700 mg every 4 weeks for 3 doses. Then 1400 mg every 4 weeks	IV infusion over 30 min	Once every 4 weeks	$32,000/year
Lecanemab (Leqembi)	Humanized monoclonal antibody binding to soluble and insoluble toxic amyloid-beta protofibrils	10 mg/kg body weight	IV infusion over 1 h	Once every 2 weeks	$26,500/year

Efficacy-Safety Trade-offs Between Treatments

While both agents demonstrate a statistically significant slowing of disease progression, donanemab may offer a greater efficacy signal, as reflected by a larger absolute reduction in CDR-SB decline. However, this apparent advantage is accompanied by a higher incidence of amyloid-related imaging abnormalities (ARIA). In contrast, lecanemab exhibits a more favorable safety profile and a broader base of clinical experience, which may enhance its feasibility and long-term utility in real-world clinical practice.

8. Future Directions

Combination therapies targeting amyloid and tau pathology

Anti-amyloid monoclonal antibodies, including lecanemab and donanemab, represent a major advance in disease-modifying therapy for Alzheimer's disease; however, their clinical benefits remain modest and do not fully arrest neurodegeneration (Dyck et al., 2023; Sims, Zimmer, Evans, Lu, Zboch, et al., 2023). These limitations have driven increasing interest in combination therapeutic strategies that simultaneously target multiple pathogenic mechanisms. Given the temporal and mechanistic link between amyloid deposition and downstream tau pathology, the combination of anti-amyloid and anti-tau approaches is widely regarded as a rational next step in therapeutic development (Angioni et al., 2025).

Preclinical and translational studies suggest that amyloid reduction alone may be insufficient once tau pathology is established, whereas early amyloid clearance may enhance the effectiveness of tau-directed interventions (Hanseeuw et al., 2019). Accordingly, future clinical trials are expected to explore both sequential and combination treatment paradigms, including monoclonal antibodies, tau aggregation inhibitors, and antisense oligonucleotides aimed at modulating tau expression (Long & Holtzman, 2019). The successful design of such studies will require careful consideration of safety (particularly ARIA risk) as well as the selection of sensitive biomarker endpoints capable of detecting additive or synergistic treatment effects (Angioni et al., 2025).

Blood biomarkers and earlier diagnosis

The clinical implementation of disease-modifying therapies highlights the need for accessible and scalable diagnostic tools capable of identifying eligible patients at the earliest possible disease stages. In this context, blood-based biomarkers have emerged as particularly promising (Angioni et al., 2025). Plasma phosphorylated tau species (p-tau181, p-tau217, p-tau231), the amyloid-β42/40 ratio, neurofilament light chain, and glial fibrillary acidic protein have demonstrated high diagnostic and prognostic accuracy for Alzheimer's disease pathology and cognitive decline (Jack et al., 2024). In routine clinical practice, blood biomarkers may serve as first-line screening tools, guiding targeted referral for confirmatory cerebrospinal fluid analysis or

amyloid PET imaging (Grande et al., 2025; Karikari et al., 2022). Such a stepwise diagnostic approach has the potential to reduce costs, improve access to treatment, and facilitate longitudinal monitoring of therapeutic response. Moreover, the inclusion of plasma biomarkers as secondary endpoints in lecanemab and donanemab trials may further elucidate the relationship between biomarker dynamics and clinical outcomes (Dyck et al., 2023; Karikari et al., 2022; Sims, Zimmer, Evans, Lu, Zboch, et al., 2023).

Access, cost, and ethical and practical challenges

Despite their therapeutic promise, anti-amyloid monoclonal antibodies raise substantial challenges related to cost, infrastructure, and health system capacity. High acquisition costs, the requirement for regular intravenous infusions, and repeated MRI monitoring for amyloid-related imaging abnormalities place considerable demands on healthcare systems. Economic modeling suggests that widespread adoption in the absence of strict eligibility criteria could lead to unsustainable budgetary impact, prompting payers to consider restrictive reimbursement policies or coverage-with-evidence-development frameworks (Jönsson et al., 2023).

Ethical and practical challenges also warrant careful consideration. Early or preclinical biomarker-based diagnosis introduces complex issues related to risk disclosure, patient autonomy, and informed consent, particularly as cognitive impairment evolves (Karlawish, 2011; Whitehouse, 2019). While clinicians frequently emphasize the modest magnitude of benefit and potential safety risks, patients and the general public tend to prioritize affordability, access, and willingness to pay for treatment (Kinchin et al., 2024). SSocioeconomic disparities may further exacerbate inequities in access to care. Addressing these challenges through transparent communication, shared decision-making, and equitable allocation of healthcare resources is essential for the responsible clinical implementation of disease-modifying therapies (Karlawish, 2011; Kinchin et al., 2024; Whitehouse, 2019).

9. Conclusions

Amyloid-targeting monoclonal antibodies represent a significant therapeutic advance in the management of early Alzheimer's disease. Evidence from randomized clinical trials indicates that both lecanemab and donanemab effectively reduce cerebral amyloid burden and achieve a modest but clinically meaningful slowing of cognitive and functional decline in appropriately selected patients. Differences in pharmacological properties, dosing strategies, and safety profiles distinguish these agents and carry important implications for clinical decision-making.

The risk of amyloid-related imaging abnormalities remains a central limitation of both therapies, necessitating careful patient selection, biomarker confirmation of amyloid pathology, and structured safety monitoring, particularly in individuals carrying APOE ε4 alleles. While current evidence supports the use of lecanemab and donanemab in early symptomatic Alzheimer's disease, further research is required to define their long-term effectiveness, optimal sequencing, and integration into routine clinical practice. Together, these therapies represent an important step toward disease-modifying treatment strategies in Alzheimer's disease.

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