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*Review Article in Medicine and Health*

# Approved and Late Clinical Trial Monoclonal Antibodies for the Treatment of Alzheimer's Disease

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**Abstract**: Alzheimer's disease is a major type of dementia characterized by progressive neurodegeneration that leads to cognitive decline and brain atrophy. The progression of the disease is marked by the accumulation of amyloid β plaques and tau tangles that are proposed to be the driver of subsequent neural death and atrophy. Targeting these hallmarks with monoclonal antibodies has become a promising approach to treating Alzheimer's disease. As of 2021, the FDA approved the amyloid β targeting monoclonal antibody aducanumab as the first approved treatment for Alzheimer's disease. Since this landmark, significant work has been done to develop monoclonal antibodies to treat Alzheimer's disease. In this review, we discuss the development of FDA-approved monoclonal antibodies aducanumab, lecanemab, and donanemab, as well as the monoclonal antibodies remternetug and E2814 that are currently in late-phase clinical trials.

**Keywords**: Alzheimer's disease; monoclonal antibody; amyloid beta; tau

## 1. Introduction

Alzheimer's disease (AD) is the most common type of dementia, affecting 50 million patients worldwide, with an expected increase to 152 million patients by 2050 (De-Paula et al., 2012; Livingston et al., 2020). These patients, their families, and the economy are affected by the burden of AD, with an estimated annual global cost of US$1 trillion. (Alzheimer's Disease International & Patterson, n.d.) AD is distinguished by slow progressive neurodegeneration by the presence of neuritic plaques and neurofibrillary tangles. It has various pathogenic mechanisms, including Aβ aggregation, tau tangle formation, neuronal inflammation, and oxidative stress (Breijyeh & Karaman, 2020). AD progress and symptoms are linked to two types of neuropathological changes: the positive lesions caused by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, cerebral amyloid angiopathy (CAA), among other lesions found in the brains of AD patients, and the negative lesions due to the significant atrophy caused by neural, neuropil, and synaptic loss. Other factors may also cause neurodegeneration, such as neuroinflammation, oxidative stress, and injury of cholinergic neurons (Serrano-Pozo et al., 2011), (Spires-Jones & Hyman, 2014). Amyloid-β protein (Aβ) extracellular deposits, known as senile plaques, are a hallmark of AD and are proposed to be the driver of AD progression in accordance with the Aβ hypothesis (Karran & De Strooper, 2022). The source of these Aβ plaques is the transmembrane amyloid precursor protein (APP), formed by proteolytic cleavage enzymes β-secretase and γ-secretase (Cras et al., 1991), (Cras et al., 1991). There are several forms of Aβ monomers, including large and insoluble amyloid fibrils that can clump into amyloid plaques or soluble oligomers

that can expand throughout the brain. Because Aβ is related to neurotoxicity and neural function, the buildup of denser plaques in the amygdala, cerebral cortex, and hippocampus can result in stimulation of astrocytes and microglia, damaged axons, dendrites, and cognitive impairments, as well as loss of synapses (Chen et al., 2017).

Tau proteins support the internal skeleton of neurons. In healthy neurons, tau binds to the microtubules to stabilize the structural proteins. In contrast, abnormal tau can detach from microtubules and complex with other tau proteins, forming tangles in the neuron (*What Happens to the Brain in Alzheimer's Disease?*, n.d.). Such tangles are proposed to disrupt neurons from sending signals properly. These tau tangles are found to be hyperphosphorylated (p-tau) and can be found in the cerebrospinal fluid (CSF) depending on AD and tau pathology severity. People with abnormal p-tau baselines have higher rates of AD progression (Gonzalez-Ortiz et al., 2023).

Monoclonal antibodies (mAbs) are lab-made clones of an antibody designed to bind an antigen of choice (*Monoclonal Antibodies*, n.d.). The mAb utilized the innate immune system to destroy the antigen. This use of the immune system to degrade the antigen target has successfully proved the therapeutic response of mAbs, as shown by their use in treating conditions such as cancer, osteoporosis, nervous system disorders, and infections. The mechanism of Aβ plaque reduction by mAbs is hypothesized to involve endosomal/lysosomal system degradation and microglia activation through fibrillar Aβ phagocytosis (Cummings et al., 2024). Anti-amyloid mAbs reduced the β-amyloid plaque in the brain and slowed the clinical decline measured by Clinical Dementia Rating-Sum of Boxes (CDR-SB). In this review, monoclonal antibodies to treat AD that are FDA-approved or in late clinical trials are discussed.

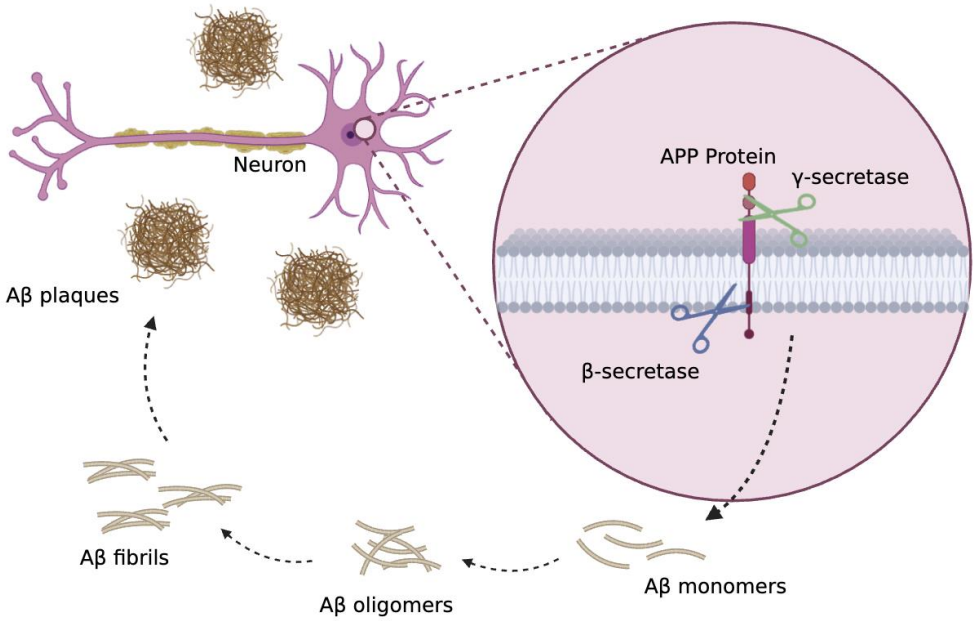


Figure 1. β-secretase and γ-secretase cleave APP protein located in neuron membrane, forming Aβ monomers that develop into Aβ plaques.

## 2. Measuring the Success of mAb Alzheimer's Treatments

Throughout clinical trials, positron emission tomography (PET) measurement of Aβ biomarkers serves multiple purposes, such as acting as an inclusion criterion to show the presence of the therapeutic target, measuring the pharmacodynamic response to anti-amyloid mABb treatment, and offering supportive evidence of disease modification. Moreover, magnetic resonance imaging (MRI) plays an important role in measuring AD progression. MRI is used to detect asymptomatic amyloid-related imaging abnormalities (ARIA) caused by an increased vascular permeability and inflammatory response resulting in the accumulation of extravasation proteinaceous fluid and blood products in the brain. There are two classifications of ARIAs, marked by edema and/or effusion (ARIA-E) or hemorrhaging (ARIA-H). Although usually asymptomatic ARIA and self-resolving, they can be associated with headaches, confusion, nausea, dizziness, or seizures and, in rare cases, can be fatal (Agarwal et al., 2023).

Apolipoprotein E ε4 (*APOE4*) gene is linked to AD risk, with patients possessing one copy of the gene showing a 2 to 3 times increased likelihood of getting Alzheimer's disease. Furthermore, some patients have two copies of *APOE4*, one from each parent, which results in an even greater risk of getting AD (Corder et al., 1993; Serrano-Pozo et al., 2021). The genotyping of APOE in anti-amyloid MAB trials shows valuable data. ARIAs occur more frequently among *APOE4* carriers during anti-amyloid MAB treatments. Most ARIAs show no associated symptoms, but some result in severe inflammation and even death. Considering these risks of ARIA, APOE genotyping is recommended before treatment (Cummings et al., 2022). *APOE4* gene genotyping may impact the patient's family members, as they may carry the familial genes with an increased risk of AD.

Measuring biomarkers in the CSF has shown evidence of anti-amyloid mAb treatment. Biomarker changes in CSF vary from trial to trial, measuring total tau, p-tau, and neurogranin decreases relative to the placebo group (Ostrowitzki et al., 2017; Pontecorvo et al., 2022). These biomarkers serve as indicators of pharmacodynamics and offer proof in favor of illness change. They align with the consequences suggested in the amyloid hypothesis. People with brain amyloid accumulation are more likely to have phosphorylated plasma tau at threonine 217 or 181. The peri-plaque environment may generate tau-related neuritic changes, which could be reflected in the elevations of p-tau. This p-tau declined with amyloid plaque in the treatment group compared to the placebo group in several trials.

## 3. Monoclonal Antibodies Targeting Amyloid Plaques

### 3.1 Aducanumab

Aducanumab, marketed as Aduhelm, is a monoclonal antibody targeting Aβ plaques, developed by Biogen and Eisai, and was the first AD treatment approved by the FDA. While it was a landmark for the disease, there was controversy over the treatment's evidence of efficacy. Over three separate studies, a total of 3,482 patients with Alzheimer's disease showed a significant dose-and time-dependent reduction of Aβ plaque when patients received aducanumab, compared to placebo (Office of the Commissioner, 2021). PET imaging measured plaques in brain regions heavily impacted by AD compared to regions that are likely unaffected. Unfortunately, aducanumab has been shown to cause ARIAs, most likely from temporary swelling, resulting in headaches, confusion, dizziness, vision changes, or nausea. Aducanumab also carries warnings for hypersensitivity reactions such as angioedema and urticaria. Adding to the controversy, aducanumab was tested in two nearly identical trials but showed different results. In the ENGAGE trial, aducanumab did not display significant efficacy over placebo, but in the EMERGE trial, it showed a significant benefit at a higher dose (Budd Haeberlein et al., 2022). Both trials were stopped prematurely when interim analysis of the first 50% of participants indicated they would not meet their endpoints. However, a reanalysis of the data revealed some cognitive benefits in high-dosage EMERGE study participants. These results, along with a measurable reduction in Aβ plaque of patients

receiving aducanumab, backed the controversial fast-track approval despite convincing proof of efficacy to some of the reviewers. About one-third of the participants developed ARIAs. While offering similar benefits, lecanemab, Biogen and Eisai's other monoclonal antibody targeting Aβ has around a third of the ARIA frequency of aducanumab. Nonetheless, on Jan 31, 2024, Biogen announced that they would prioritize developing Leqembi (lecanemab), and discontinue the development and commercialization of Aduhelm (aducanumab)(*Biogen to Realign Resources for Alzheimer's Disease Franchise*, n.d.).

| mAb | Company | Target | Indication | ARIA | Clinical Status |
|---|---|---|---|---|---|
| Aducanumab | Eisai, Biogen | Aβ | Mild AD | 33% | FDA approved |
| Lecanemab | Eisai, Biogen | Aβ | Mild AD/Cognitive Impairment | 11% | FDA approved |
| Donanemab | Eli Lilly | pyroglutamate Aβ | Early symptomatic AD | 25% | FDA approved |
| Remternetug | Eli Lilly | pyroglutamate Aβ | Early AD | 25% | Phase 3 |
| E2814 | Eisai | tau | Mild AD | 24% | Phase 2/3 |

**Table 1**. Approved and late clinical trial monoclonal antibodies to treat Alzheimer's disease. ARIA's are shown as a percentage of participants showing ARIA in phase 3 clinical trials.

3.2 Lecanemab

In 2023, the humanized IgG1 monoclonal antibody, lecanemab, received full approval to treat early AD (Office of the Commissioner, 2023). The biologic was developed by Eisai and Biogen to bind soluble Aβ protofibrils with a high degree of affinity. Lecandemab showed efficacy in an 18-month, multicenter, double-blind, phase 3 trial (van Dyck Christopher H. et al., 2023). The participants, ages 50 to 90 years, had mild cognitive impairment or mild dementia and showed evidence of amyloid on PET or CSF testing, with 898 of 1795 participants receiving lecanemab and 897 receiving a placebo. The Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment) score change from baseline at 18 months was the primary endpoint. Lecanemab significantly reduced the amount of amyloid in the brain compared to placebo (-59.1 centiloids) in a substudy involving 698 participants. Secondary endpoints of the study were the change in the amyloid burden on PET, the Alzheimer's Disease Composite Score (ADCOMS), the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL), and the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14). Lecanemab caused ARIA-E in 12.6% of the participants and infusion-related responses in 26.4% of the participants. Lecanemab was associated with side effects but also decreased amyloid markers in early AD and showed modest retention of cognition and function compared to the placebo.

3.3 Donanemab

Donanemab, or N3pG, is a humanized IgG1 monoclonal antibody derived from mouse mE8-IgG2a that targets Aβ(p3-42), a pyroglutamate type of Aβ found in amyloid plaques. Most Aβ antibodies in therapeutic development bind to diverse soluble or insoluble species but have little affinity for amyloid plaques. The principle of donanemab is that targeting deposited plaque is required to eliminate the brain's current amyloid burden rather than simply preventing future plaque deposition or growth (Demattos et al., 2012). The Phase 3 head-to-head trial TRAILBLAZER-ALZ 4 is an open-label comparison

of amyloid plaque clearance by donanemab that was initiated in November 2021 (Salloway et al., 2023). Donanemab cleared four times more plaque than aducanumab in the first six months of treatment, showing 38% reduction in Aβ plaques below the amyloid-positive threshold, compared to 2% for aducanumab. Additionally, donanemab reduced plasma p-tau217 by 25%, while aducanumab showed no reduction. ARIA-E was prevalent in both groups, affecting 24% of the donanemab group versus 35% of those taking aducanumab. Moreover, 78% of donanemab recipients became amyloid-negative, while only 43% of aducanumab patients showed the same result (*ClinicalTrials.Gov*, n.d.-a). In August 2022, Lilly launched TRAILBLAZER-ALZ 5, a Phase 3 trial for early symptomatic Alzheimer's patients, enrolling 1,500 participants across multiple countries (*ClinicalTrials.Gov*, n.d.-b).

In 2023, results from the Phase 3 study TRAILBLAZER-ALZ2 showed that donanemab slowed patients' cognitive decline by 40% (Sims et al., 2023). Those who became amyloid-negative continued to have a slower rate of decline after stopping the antibody. People with mild cognitive impairment benefited the most, showing 60% slowing on iADRS. Moreover, donanemab decreased blood p-tau biomarkers, but it did not affect the tangle load measured by tau PET. Of the participants, 25% developed ARIA, 6% showed symptoms, and 2% had severe symptoms. The FDA rejected donanemab's accelerated approval due to insufficient safety data in January 2023. However, four months later, positive results from TRAILBLAZER-ALZ 2 prompted Lilly to seek traditional FDA approval. On July 2, 2024, the FDA approved donanemab, now marketed as Kisunla (Center for Drug Evaluation & Research, 2024).

### 3.4 Remternetug

Remternetug is another investigational monoclonal antibody, N3pG-Aβ mAb, being developed by Lilly that targets pyroglutamate Aβ aggregates (*Remternetug*, n.d.). Following up on donanemab's success, remternetug is currently in Phase 3 trials. In the Phase 1 study of remternetug (41 participants received 250 - 2800 mg monthly for 6 months), all participants fell below the amyloid positivity threshold after 3 months on 2800 mg (*ClinicalTrials.Gov*, n.d.-c). There were 10 ARIA-E in *APOE4* carriers and 7 ARIA-H instances, but there was no clear association with the dosage. A Phase 3 trial called TRAILRUNNER-ALZ1 started in August 2022 and is expected to be completed in October 2025 (*ClinicalTrials.Gov*, n.d.-d). Its primary outcome is the percentage of patients whose amyloid plaques are removed at the end of the treatment. Secondary outcomes assess anti-drug antibodies, pharmacokinetics, and amyloid clearance in further detail. Remternetug will be tested in the Knight Family DIAN-TU Primary Prevention Trial (*The Knight Family DIAN-TU Primary Prevention Trial Announcement*, n.d.). This four-year trial will enroll 220 individuals as young as 18 years old who have familial AD mutations but little or no brain amyloid to receive remternetug treatment. The primary outcomes of the trial will look at Aβ accumulation with an additional four-year open-label extension to look at the primary endpoint of odds of lower disease progression based on CSF and MRI biomarkers.

## 4. Monoclonal Antibodies Targeting Tau

### 4.1 E2814

E2814 is a monoclonal antibody that targets the microtubule-binding region (MTBR) of tau with the hopes of preventing tau tangle seeds from proliferating in the brain (Roberts et al., 2020). The antibody was discovered during a collaboration between Eisai and University College London. In August 2020, E2814 completed Phase 1 clinical trials, showing no notable drug-related clinical changes or dose-limiting cases (Horie et al., 2019). Additionally, serum and CSF pharmacokinetics were proportional to the dosage and comparable to other antibodies. By 4 months, anti-E2814 antibodies were found in 2 participants. The increase in antibody-tau association was found to be dose-related and lasted for at least

a month. The study showed that 60% of tau mid-domain fragments were complexed with the antibody when dosed at 30 mg/kg.

Following these positive results, E2814 was announced to be tested in the DIAN-TU prevention trial in March 2021, with participants who had pathogenic APP and presenilin mutations (*ClinicalTrials.Gov*, n.d.-e). During 12 weeks, 8 participants with mild to moderate dementia received antibody infusions. The change from baseline in CSF free, bound, and total tau MTBR fragments was used to measure target engagement. The second phase of the trial continued for 96 weeks to measure endpoints of adverse events, laboratory value changes, vital signs alterations, and electrocardiogram findings. Upon approval of lecanemab, the DIAN-TU study was changed in November 2021, and for the first 24 weeks, participants with mild cognitive impairment or dementia will receive open-label intravenous lecanemab (*ClinicalTrials.Gov*, n.d.-e). Then, they will be randomized to receive intravenous E2814 or a placebo with lecanemab. Tau spread during E2814 treatment, measured by tau PET in the symptomatic participants, is the primary endpoint. Secondary endpoints in the same group are amyloid PET, CSF neurofilament light chain, and cognitive composite changes. In the asymptomatic participants, the endpoint is the changes in the ratio of CSF p-tau217 to total tau. Eisai announced in July 2023 that both the AD and healthy cohorts found E2814 safe and well-tolerated up to the maximum dosage of 4500 mg (*CSF MTBR-Tau-243 Tracks Tangles, Plummets in Response to Antibody*, n.d.). E2814's dose-dependent binding to tau MTBR epitopes in CSF proved target engagement. A recently identified CSF biomarker for tau tangles, MTBR-tau-243 fragment, decreased in AD patients by 30% to 70%. The study is scheduled to be completed in 2027.

## 5. Conclusion

Alzheimer's disease is a neurological disorder that affects tens of millions of people, causing slow progression of dementia that has a devastating impact on both patients and their families. The two most common biomarkers of AD are Aβ plaques and tau tangles. Aβ plaques are formed from amyloid precursor protein cleavage by β-secretase and γ-secretase and are proposed to cause neurotoxicity and inflammation, driving AD progression. Additionally, aggregation of tau protein to form tau tangles in the neuron has also been associated with AD progression. Recent developments in anti-amyloid monoclonal antibodies have proven their effectiveness in AD treatment. The anti-amyloid mAb's aducanumab, lecanemab, and donanemab have received approval from the FDA to treat AD and are marketed as Aduhelm, Leqembi, and Kisunla, respectively. Furthermore, new anti-amyloid mAb treatments, remternetug, have shown promise in phase 3 clinical trials. While Biogen and Eisai were first to market with aducanumab, followed by lecanemab, Eli Lilly's donanemab has demonstrated superior efficacy. This difference in efficacy is proposed to be attributed to Eli Lilly's mAbs targeting the matured pyroglutamate Aβ (Aβ(p3-42)) plaques, as opposed to the soluble Aβ peptide. Additionally, Eisai is developing E2814, an MTBR-targeting mAb that aims to prevent tau tangle formation. The rapid development of mAbs to treat AD has brought treatment to a large group of patients who were previously without treatment, and the field's fast progression brings hope to finding more treatments for the disease.

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